SYNTHESIS, STRUCTURAL AND BIOLOGICAL STUDIES OF POTENTIAL 5-HT3 RECEPTOR ANTAGONISTS.

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SYNTHESIS, STRUCTURAL AND BIOLOGICAL STUDIES OF POTENTIAL 5-HT$_3$ RECEPTOR ANTAGONISTS.

by

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A Thesis presented to Dublin City University for the degree of Doctor of Philosophy.

This work was carried out under the supervision of

Dr. Paraic James at Dublin City University, Dublin and
Dr. Enrique Gálvez at Universidad de Alcalá de Henares, Madrid.

December 1994

To my wife Pilar and my parents
Jimmy and Kathleen.

I hereby certify that this material, which I now submit for assessment on the programme of study leading to the award of PhD is entirely my own work and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my own work

Signed: Brendan Whelan Date: 11 Nov. 1994

Candidate

Date: 11 Nov. 1994

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Abstract

This thesis involves the syntheses of new compounds as potential antagonists of the 5-HT_3 receptor, a sub-group of the serotonin receptors.

The objective of the work can be considered two fold: The primary aim, which can be regarded as the principal goal, was the design and chemical synthesis of new molecules which could antagonise the 5-HT_3 receptor and thus lead to new drug substances which could be effective in the treatment of illnesses associated with this receptor, among which may be included the control of emesis in cancer patients receiving chemotherapy. Secondly, by carrying out the structural and conformational studies of the synthesised compounds and relating these to the biological studies it was hoped to elucidate more information on the nature of the 5-HT_3 receptor, the structure of which is unknown.

Three series of potential antagonists were synthesised. The first series involves a tropane spiroimidazoline molecule with various aromatic substituents in the 2' position of the imidazoline ring (the final compounds of this series have been numbered **I a-g** throughout the text, the number **I** referring to the number of the series and the letters **a-g** to the individual final products within the series) The structure represents a novel feature within the known 5-HT_3 antagonists. A second series of products (**II a-g**) was synthesised in which the tropane function of the molecule was replaced by a bicyclic quinuclidine system. The synthetic method developed for the syntheses of these 2'-aryl-8-methyl-8-azabicyclo[3.2.1]octane-3-spiro-4'(5')-imidazolines and 2'-aryl-1-azabicyclo[2.2.2]octane-3-spiro-4'(5')-imidazo-lines takes place *via* the reaction of an azabicyclic 1,2-diamines with aryl imidate salts. Competing reactions in the syntheses of the 1,2-diamines such as the reduction of aminonitriles with $LiAlH_4$ lead to some anomalous products. In the Pinner synthesis of the imidates, unstable pyridine type imidates were stabilised as their *N*-oxide derivatives.

A third series of tropane 1,2,4-oxadiazoles (**III a-g**) was synthesised *via* the reaction of exo-3-carbomethoxy-8-methyl-8-azabicyclo[3.2.1]octane with aryl amidoximes. The former tropinone carbomethoxy ester was synthesised in a high yielding stereospecific

synthesis from tropinone, *via* the intermediacy of 3-(1,3-dithiane-2-ylidene)-8-methyl-8-azabicyclo[3.2.1]octane.

The structural and conformational analysis of the compounds shows that in solution the tropinone moiety in both the tropinone spiroimidazolines and the tropinone oxadiazoles adopts a chair-envelope conformation for the piperidine and pyrrolidine rings respectively, with the piperidine ring in a slightly flattened disposition. The N-methyl group adopts an equatorial position with respect to the six membered piperidine ring. X-ray structural analysis for one compound in each of the tropinone series showed that a similar conformation was observed for the tropinone systems in the solid state. In the tropinone imidazoline series the aromatic indole group attached to the imidazoline ring was conjugated with the latter thus forming an almost planar structure, a phenomenon which was also observed in solution, and thus provides an important feature for 5-HT_3 antagonists.

Pharmacological and biochemical studies indicated that one compound in each of the spiroimidazoline series (those containing the dichlorophenyl aromatic substituent) displayed 5-HT_3 antagonistic properties comparable to MDL 72222 a potent 5-HT_3 receptor antagonist. These activity results, combined with the structural analysis, led to the conclusion that the imidazoline group was acting as an bioisosteric replacement for a carbonyl function and as such is the first time this system has been reported in 5-HT_3 antagonists.

The oxadiazole series likewise displayed several biologically active molecules of which the most active was again that containing the dichlorophenyl substituent as the aromatic portion of the molecule.

List of Abbreviations

δ	Chemical Shift
λ	Wavelength
ν	Stretching Frequency
Δ	heat
Ac:	$COCH_3$
tBOC:	$OCOC(CH_3)_3$
b.p.:	boiling point
iBu:	$CH_2CH(CH_3)_2$
tBU:	$C(CH_3)_3$
Bz:	$CH_2C_6H_5$
DMF	dimethylformamide
Et:	C_2H_5
5HT:	5-hydroxytryptamine
h.	hours
IR	infra-red
Me	CH_3
mp:	melting point
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Ph.:	C_6H_5
ppm:	parts per million
iPr:	$CH(CH_3)_2$
r.t.:	room temperature
S.A.R.	structure-activity-relationship
THF:	tetrahydrofuran
TLC:	thin layer chromatography
TMS:	trimethylsilyl
UV:	ultra-violet

CHAPTER I

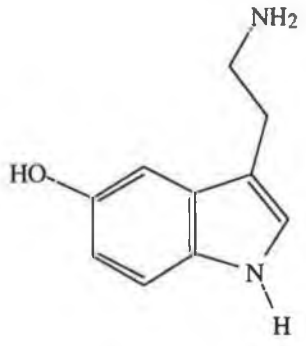
Literature Review

1.1 5-HT_3 Antagonists

1.1.1 Review

Not since the pioneering days of serotonin research in the late 1950s, have we enjoyed such excitement in this field as we are experiencing today. Since the isolation of serotonin from blood in 1948, the whole area has been fraught with controversy, and it is only in recent years, with the advent of specific potent antagonists, that huge inroads have been made into this fascinating subject.

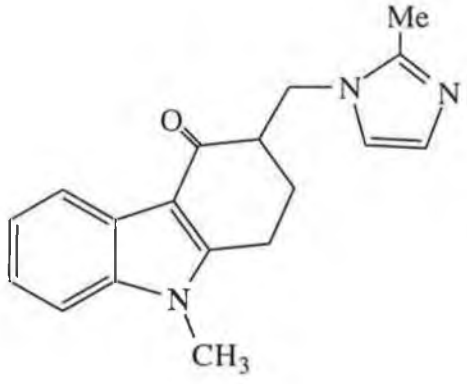
Shortly after its isolation, it was recognised in 1957 by Gaddum and Picarelli[1] that serotonin, identified as 5-hydroxytryptamine (5-HT) (**1**) might act on multiple types of 5-HT receptors and divided them into two sub divisions, namely D and M receptors. Later Bradley *et al.*[2] divided the classification into three categories; 5-HT_1, 5-HT_2, and 5-HT_3 receptors. Currently, four broad classes are characterised with a fourth group, 5-HT_4, being added to the above three already mentioned.[3-6] Further subdivisions of some of these sub classes have also been proposed.[7]



(1)

It is in the area of 5-HT_3 research that we have focused our attention, with the hope of shedding some new light on the efforts to further understand and classify this receptor, through the design and synthesis of potential antagonists.

Recently, the 5-HT_3 receptor has attracted considerable attention and its understanding has dramatically increased over the past few years due to the discovery and widespread availability of potent and selective antagonists such as Ondansetron[8] **(2)**, Granisetron[9] **(3)**, Zacopride[10] **(4)**, and ICS 205-930[11] **(5)**.



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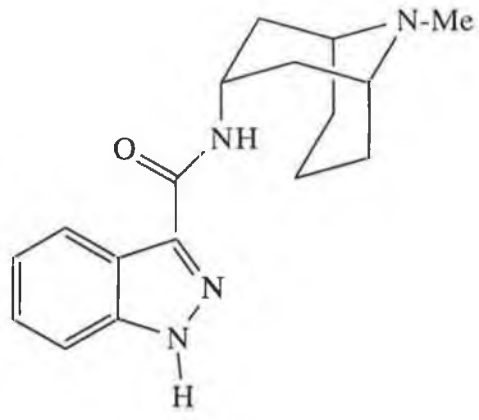

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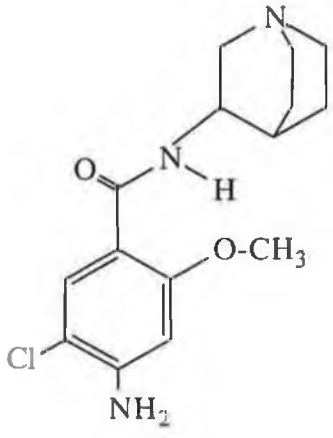

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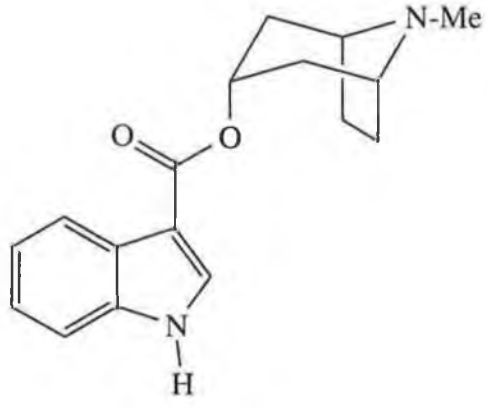


(5)

This interest is in grand part due to the effectiveness of these compounds in the control of emesis induced by cancer chemotherapy, an event suggested to be modulated by the 5-HT_3 receptors in the *area postrema*.[12] In addition, evidence has been presented for the therapeutic roles of 5-HT_3 receptor antagonists in migraine,[13] schizophrenia,[14] and anxiety.[15]

In an effort to qualitatively account for the activity of existing 5-HT_3 antagonists, in 1990, Hibert[16] carried out a structure-activity relationship (SAR) study of existing 5-HT_3 receptor antagonists using molecular modelling techniques in order to define a pharmacophore and receptor map for these compounds. According to the model defined, the basic pharmacophore consisted essentially of a carbonyl group coplanar to an aromatic ring and a basic centre in the relative positions illustrated in Figure **1.1.**

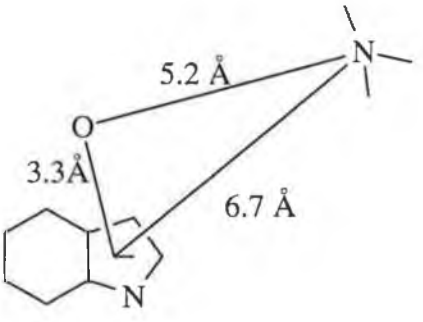
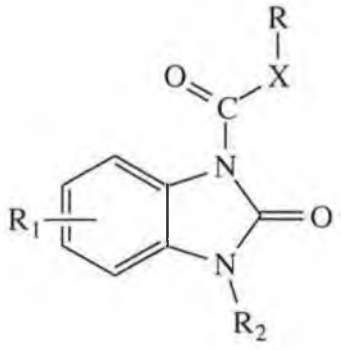


Figure 1.1

In 1990 Turconi *et al.*[17] designed and synthesised a series of 2,3-dihydro-2-oxo-1*H*-benzimidazole-1-carboxylic acid esters and amides containing a basic azacyclo or azabicycloalkyl moiety (Figure **1.2**).



X = O, NH

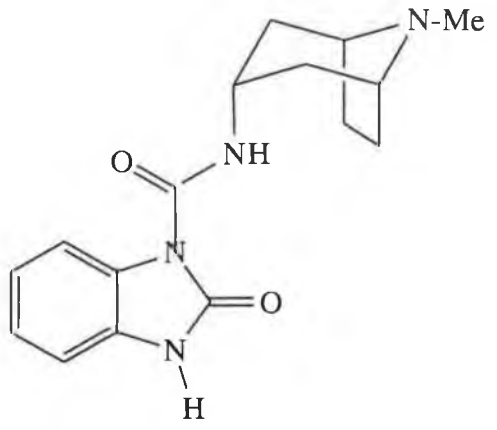
R = azabicyclo or azabicycloalkyl moiety

R_1 = H, OCH_3, Cl, F, CF_3, $COCH_3$

R_2 = H, CH_3, C_2H_5

Figure 1.2

A selected member of this series (**6**), R = azabicyclo, R_1 = H, R_2 = H, which displayed high 5-HT_3 antagonistic ability, was subjected to molecular modelling studies to ascertain how it might fit the model proposed by Hibert. They found that compound (**6**) fitted the model quite well, as measured by the root mean square (R.M.S.) index when superimposed on the reference compound (**7**) (one of the antagonists used to define the 5-HT_3 pharmacophore[16]).



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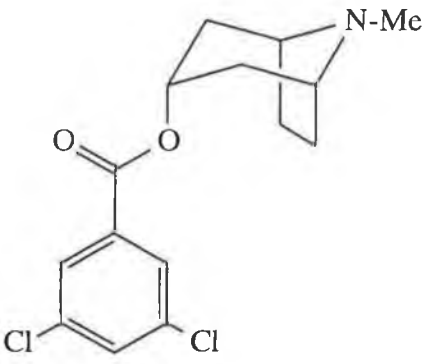
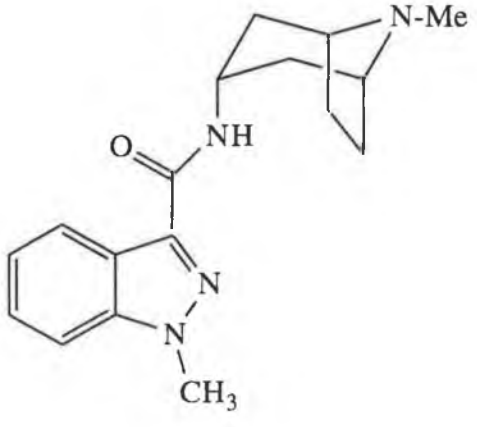


(7)

Coplanarity was again emphasised as being important as indicated from the torsional angles between the imidazole ring and the amide group. This planarity was assisted by an intramolecular H-bond between the imidazole oxygen and the amide nitrogen.

In a communication published in 1990 by Nagel *et al.*[18] the then existing 5-HT_3 antagonists were classified into two broad structural classes: the aromatic ester/amide series represented by ICS-205-930 (**5**), MDL 72222[19] (**7**), BRL-43694[20](**3**), LY-278,584[21] (**8**) and Zacopride (**4**), and the indole-3-ketone series typified by the carbazole derivatives Ondansetron (**2**) and GR-65-630[22] (**9**).



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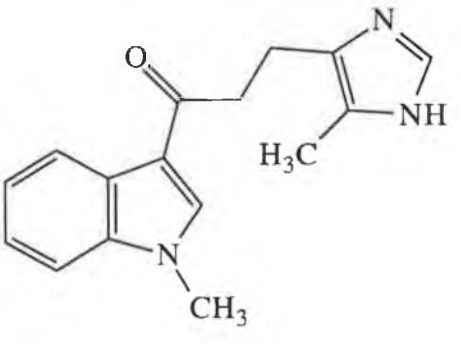
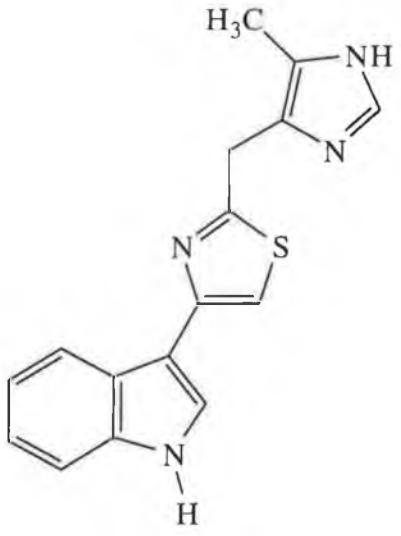


(9)

Nagel presented in this paper a new series of potent 5-HT_3 antagonists where the amide/ester function of the ICS-205-930 series and the ketone functionality in the ondansetron series were replaced by a thiazole ring system, best represented by compounds **(10)** and **(11)**.



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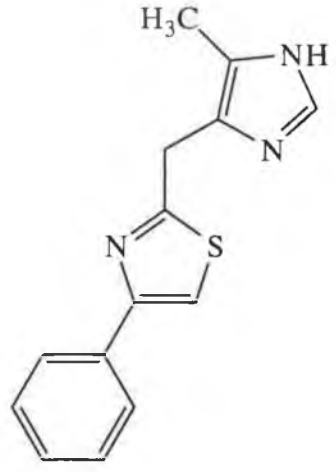
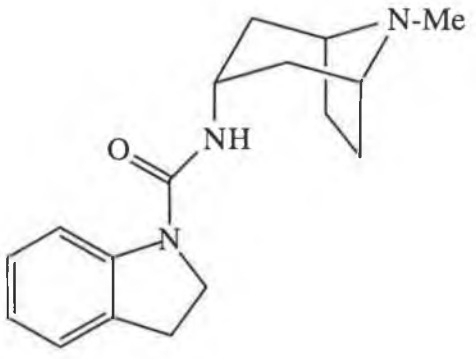


(11)

As such, this series of compounds represented the first group of potent and selective 5-HT_3 receptor antagonists lacking a carbonyl-containing side chain between the aryl and basic portions of the molecule. The same authors concurrently published[23] molecular modelling studies whereby they proposed a hypothetical model for specific 5-HT_3 receptor binding based on the structures of known potent 5-HT_3 antagonists. The ability of their new thiazole series to fit the model was then examined. The pharmacophore model defined by Rizzi and Nagel involved three components. Optimal binding required two key electrostatic interactions: a hydrogen bond accepting interaction and a hydrogen bond donating interaction. The third component of the model involves the occupancy of

a plane by a lipophilic ring. This model avoided the perception that molecules should overlap on an atom for atom basis. On the basis of this model Rizzi found that the thiazole nitrogen in this new series of compounds was acting as a replacement for the carbonyl portions of previously reported 5-HT_3 antagonists. As the pKa of a thiazole ring is generally between 3 and 4 and therefore in the unprotonated form at physiological pH, it was expected that this system would act as a weak proton acceptor, similar to a carbonyl oxygen, rather than a basic nitrogen which would be protonated at physiological pH. This suggested that the thiazole moiety might represent a bioisostere for a carbonyl oxygen in the 5-HT_3 series.

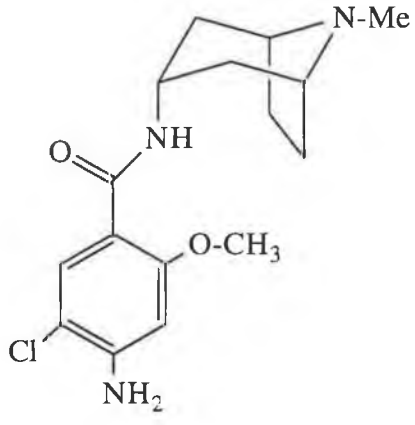
King *et al.*[24] published an article in which they also classified the existing 5-HT_3 antagonists, this time into three structural classes. In the first class they included the benzoate esters in which the carbonyl group is attached to a six membered aromatic ring and is typified by MDL 72222 (**7**). In the second group are the 6,5-heterobicyclic esters and amides in which the carbonyl is connected to a six membered aromatic ring via an sp^2 hybridised N or C atom, for example ICS 205-930 (**5**), granisetron (**3**), and indoline (**12**).



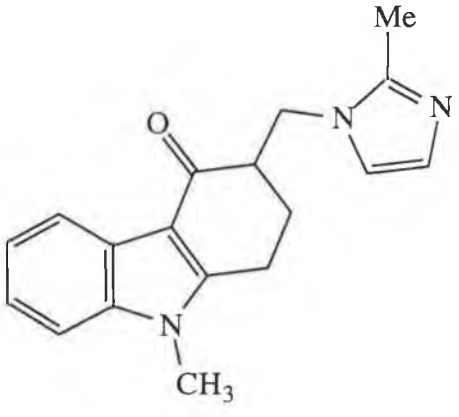
(12)

In the third class are the carbazoles such as ondansetron (**2**) in which the basic side chain nitrogen is provided by an aromatic imidazole.

The above authors reiterated the importance of maintaining coplanarity between the carbonyl group and the aromatic moiety in order to confer 5-HT_3 antagonism on these compounds.[25] They suggested that in benzamide compounds such as BRL 24682 (**13**) that potency was in large part due to the formation of a planar "virtual ring"[26] resulting from the hydrogen bond between the amidic N-H and the ortho methoxy group, thus holding the amide system in the same plane, and hence in conjugation with the aromatic ring. Similarly, the carbonyl group in (**2**) would also be held in plane by its inclusion in a fused 6-membered ring.

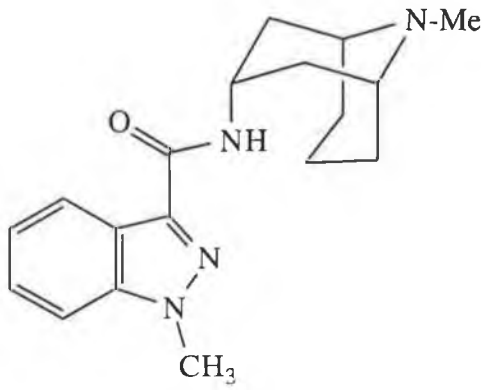


(**13**)



(**2**)

Bermudez and co-workers thus concluded that the active compounds (**14**) and ICS 205-930 (**5**) probably adopt an "in plane" orientation of the carbonyl group at the 5-HT_3 receptor. This necessity for co-planarity, they argued, would account for the lack of 5-HT_3 antagonism of the methyl isomer (**15**) in which steric interactions would destabilise the "in plane" orientation.



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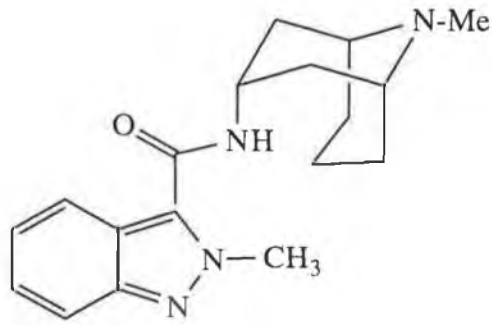
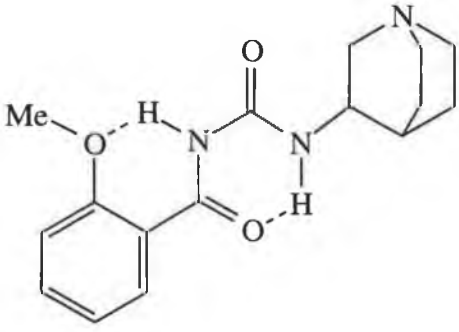


(15)

Similar results were reported by Bradley *et al.* in 1992[27] for 5-HT_3 antagonists derived from (2-alkoxybenzoyl)ureas. Structure-activity relationship studies performed on compound (**16**) suggested that the potency-enhancing effect of 2-methoxy substitution might be due to conformational restriction induced by intramolecular hydrogen-bond formation between the methoxy substituent and the benzamide N-H, a phenomenon well known for 2-alkoxybenzamides.[28] ^1H NMR studies also supported the existence of an intramolecular H-bond. 2,6-Dimethoxy substitution (**17**) reduced activity however, possibly reflecting non-planarity arising from steric effects. Similarly, replacement of an ortho methoxy substituent by an ortho phenol reduced activity, consistent with the expected hydrogen bond weakening effect of this modification.



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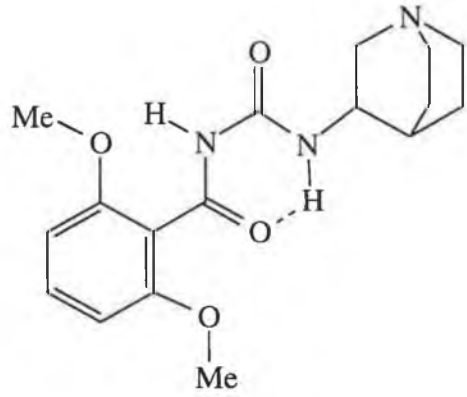
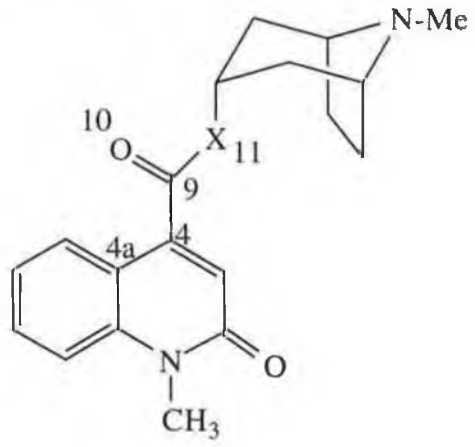


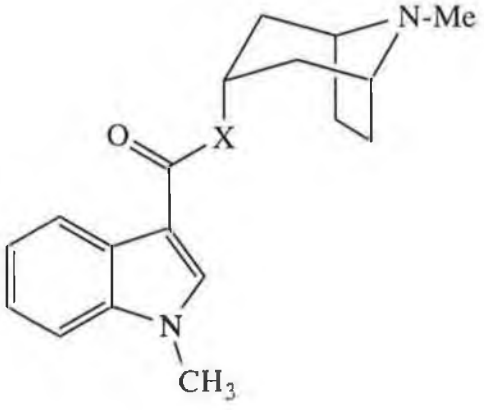
(17)

Hayashi *et al.*[29], in their search for new 5-HT_3 antagonists developed a new series of esters and amides of 1-alkyl-2-oxo-1,2-dihydroquinoline-4-carboxylic acid or 2-alkoxy quinoline-4-carboxylic acid containing a basic azabicycloalkyl moiety. In this study Hayashi took two potent antagonists **(18)** and **(19)** which they synthesised and compared them to two known antagonists **(20)** and **(21)** in order to examine the co-planarity of these compounds using molecular modelling techniques.



(18) X = O

(19) X =NH

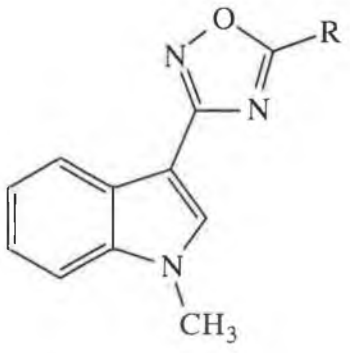


(20) X = O

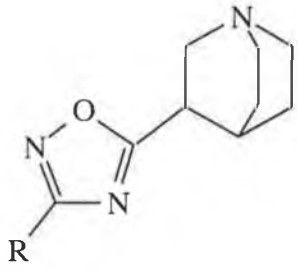
(21) X =NH

They showed that for (**20**) and (**21**), coplanarity existed between the aromatic and carbonyl functions of these molecules and that this was important for 5-HT_3 binding affinity, as had previously been shown to be the case.[30-32] However, they found for compounds (**18**) and (**19**), that the dihedral angles C(4a)-C(4)-C(9)-O(N)(11) in the minimum energy conformations were 156.0° and 149.2° respectively. This was a surprising result, because the carbonyl moiety was estimated to deviate more than 20° from the plane of the aromatic ring. However, the energy difference between the co-planar configuration of (**20**), which is not a stable one, and the minimum-energy conformation was calculated to be ca. 0.5 Kcal. Thus, they felt it reasonable to suppose that the molecule could take up the planar configuration on interacting with the 5-HT_3 receptor, as the energy compensation from binding can be up to 30 Kcal mol^{-1}, [33] much greater than that required for the increase in conformational energy.

In 1991 Swain *et al.*[34] in an effort to find new bioisosteric replacements for the carbonyl functionality, investigated the possibility of a number of five-membered heterocyclic rings as potential candidates. Based on comparisons of their electrostatic maps the 1,2,4-oxadiazole group was selected as offering considerable similarity with known systems. It had been previously demonstrated in both the cholinomimetic system[35] and the benzodiazepines[36] that the 1,2,4-oxadiazole was an excellent bioisosteric replacement for esters. Since most of the known 5-HT_3 receptor antagonists up to then were ester or amide derivatives and were thus potentially susceptible to hydrolysis, they speculated that this unwanted side property could be obviated by incorporation of H-bond acceptors within a five-membered heteroaromatic ring, namely 1,2,4-oxadiazole. Swain synthesised several derivatives based on this system with various aromatic and basic functionalities (**22**) and (**23**), mainly indole and quinuclidine derivatives.



(22)



(23)

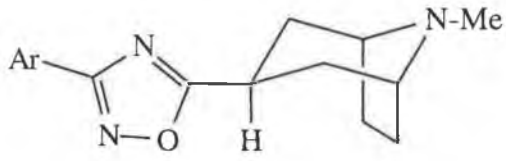
They found that these compounds displayed high affinity for 5-HT_3 receptors and reported a number of S.A.R's. The effect of substitution on the aromatic indole ring served to emphasise the steric restrictions of the aromatic binding site. Substitution at the 5 or 7 positions caused a reduction in binding affinity while groups any larger than methyl in the 1 position decreased potency. The authors claimed that the environment of the basic nitrogen was optimum when constrained within an azabicylic system.

1.1.2 **Research Plan**

With a thorough literature search of 5-HT_3 antagonists completed, the following project was designed with the aim of developing new possible antagonists of this receptor. The plan was to synthesise series of compounds and to measure their biological activity by means of *in vitro* binding studies and *in vivo* pharmacological tests. This in conjunction with NMR and X-ray studies should assist in determining a structure activity relationship.

Our investigation took two basic approaches. Firstly, we proposed to further the studies carried out by Swain *et al.*[34] Their work centred mainly on the use of quinuclidine and 1-azabicyclic systems to provide the nitrogen function, and indole derivatives for the

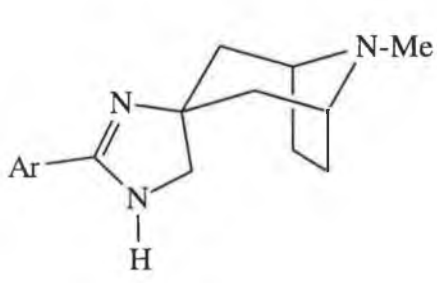
aromatic portion of the molecule. Due to the successful employment of tropinone as the nitrogen source in other 5-HT_3 antagonists with amine or ester linking groups, we proposed to investigate its use with the 1,2,4-oxadiazole ring as the linking function with the aromatic moiety being provided by several substituted phenyl groups (Series **III**, Figure **1.3**).



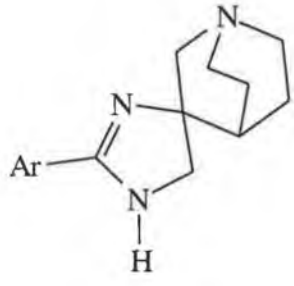
(III)

Figure 1.3

Secondly, a series of compounds was designed which incorporated the novel spiroimidazoline structure in figure **1.4**. Two series of these compounds were proposed: one containing the tropinone azabicyclic system **I** and the other with the quinuclidine structure **II**.



I



II

Figure 1.4

The imidazoline system is unknown in 5-HT_3 antagonists but has been employed on a_2 adrenergic central receptors.[37-41] Because the azabicyclic system is attached to the

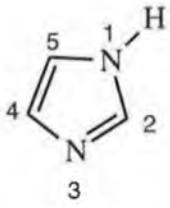
imidazoline ring *via* a spiro carbon, a planar rigid structure is obtained which should assist in the S.A.R. study.

Our hope was that the C=N of the imidazoline ring would act like a carbonyl group at the 5-HT_3 receptor thus providing a bioisosteric replacement for this functionality. Conjugation of the aromatic function with the N-C-N of the imidazoline ring should assist in maintaining co-planarity between these two groups thus forming a completely planar structure.

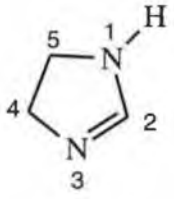
1.2 **2-IMIDAZOLINES**

Before expounding the development of the synthesis of imidazolines, it is appropriate to give a brief description of the naming and numbering of these compounds and related chemical systems.

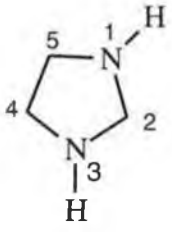
Imidazole (**24**), imidazoline (**25**), and imidazolidine (**26**) are all related structures, the latter two being dihydroimidazoles and tetrahydroimidazoles, respectively.



(**24**)



(**25**)



(**26**)

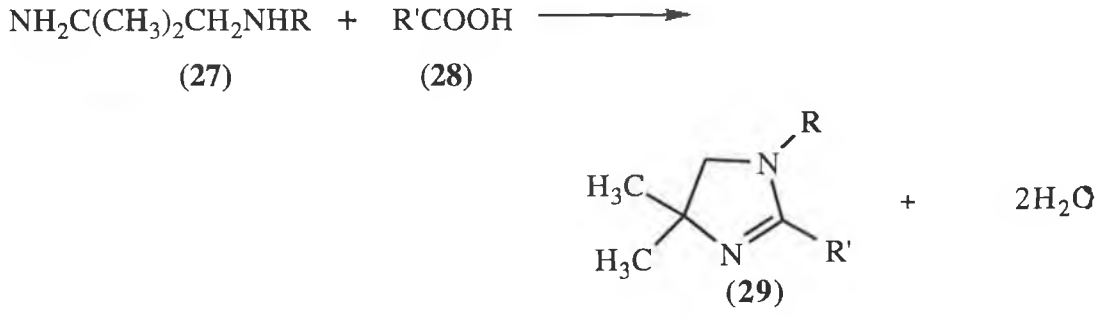
The number 1 position is assigned to the nitrogen connected through single bonds to two carbon atoms of the ring, and the number 3 position to the nitrogen connected to one carbon atom by a double bond. Due to possible tautomerism the alternate numbering is sometimes designated in parenthesis, as for example 4(5)-methylimidazole.

The oldest and most generally used method of entering the imidazoline series is that which was first reported in 1875 involving the dry distillation of a suitable acid derivative of a 1,2-diamine.[42] In general the yields were very poor. While ring closure of 1,2-diamine derivatives of carboxylic acid is a common method of forming this heterocyclic ring system, it may be formed by several other synthetic approaches.

1.2.1 From 1,2-diamines

1.2.1.1 *By reaction with monocarboxylic acids:*

In 1935 Chitwood and Reid[43] reported the synthesis of 2-methyl-2-imidazoline by the reaction of ethylenediamine with acetic acid, though a yield of only 19% was obtained. Riebsomer, in 1948[44] found that with diamines such as 2,3-dimethyl-2,3-butanediamine or 1,2-butanediamine with acetic acid, that the diacetyl derivatives of the respective diamines were isolated in yields between 10-15% with little or none of the 2- imidazoline being obtained. Earlier reports[45-47] employing the distillation of ethylene diamine hydrochloride with an excess of sodium acetate furnished 2-methyl-2-imidazoline in only 8% yield. Waldmann and Chwala[48] made an extensive study of the preparation of 2-imidazolines from high molecular weight carboxylic acids and free aliphatic amines. These reactions were carried out by heating the reactants at 200-300 °C. Condensing agents such as aluminium chloride, phosphorous trichloride, stannic chloride, and phosphorous pentoxide were employed. A number of 1,2-substituted-4,4-dimethyl-2-imidazolines (**29**) have been prepared by heating 1,2-diamines containing one secondary and one primary group (**27**) with organic acids (**28**) in the presence of benzene as shown in scheme[1.1]. The mixtures were heated under conditions to remove water by azeotropic distillation.[44]



Scheme [1.1]

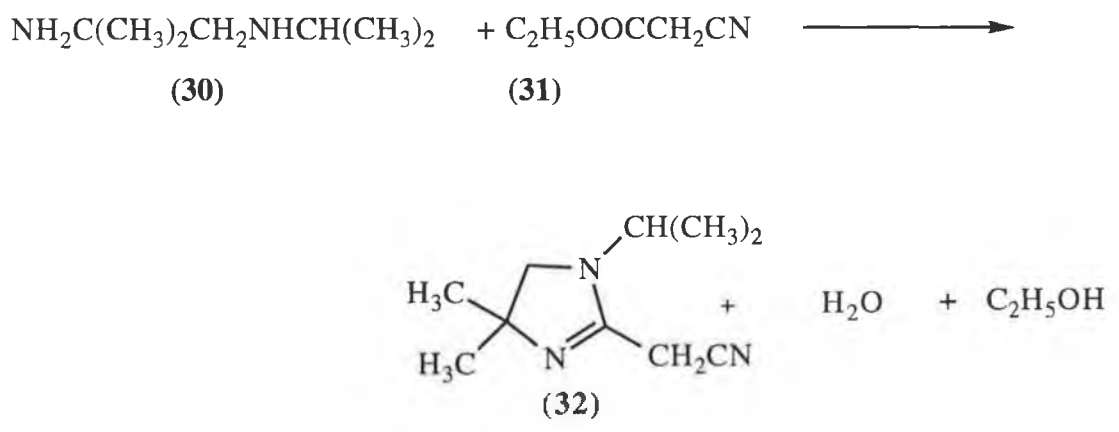
In 1975 Bespalyi reported a similar synthesis of 2-imidazolines by treating fatty acids with diamines in a 1:3 acid/amine ratio in BuOH initially at 130-130 °C then at 250-270 °C.[49]

1.2.1.2 *By reaction with dicarboxylic acids:*

1,2-diamines containing one primary and one secondary amino group react with dibasic acids containing four or more carbon atoms giving bisimidazolines.[50] Chwala reported that di- or polycarboxylic acids react at temperatures of about 280 °C with a mixture of 1,2-diamines and their salts in the presence of strong mineral acids to yield more than one 2-imidazoline per molecule.[51]

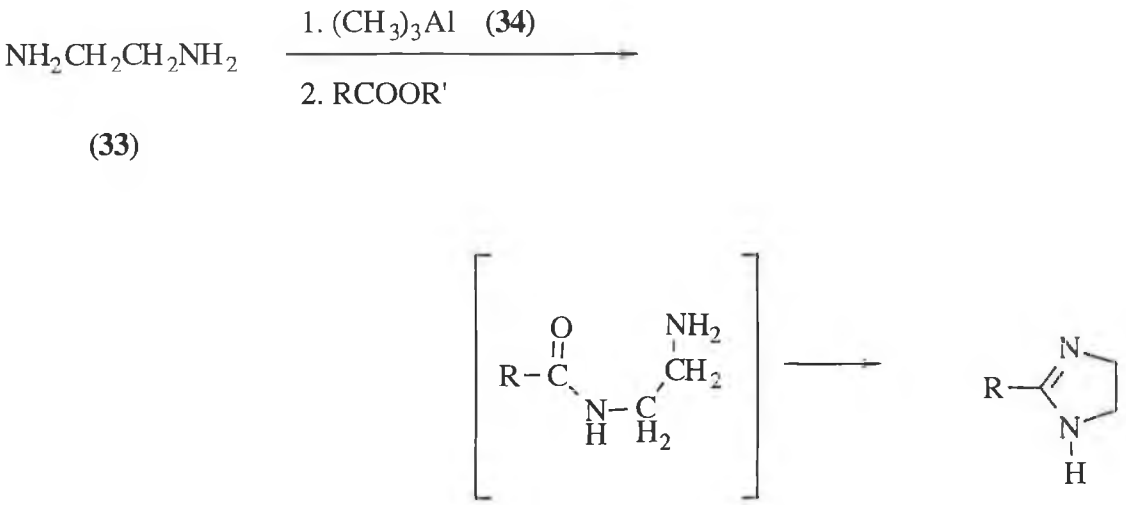
1.2.1.3 *By reaction with esters:*

In 1950 Morrill[52] disclosed in a U.S. patent, a preparation of 2-imidazolines by refluxing ethylene diamine with an ester and removing the alcohol and water formed by distillation. The reaction was proposed to proceed via initial amide formation followed by loss of water and cyclisation to the imidazoline. Pachter and Riebsomer[53] found that cyanoacetic ester **(31)** reacts with N-(2-aminoisobutyl)isopropylamine **(30)** to produce 2-cyanomethyl-2-imidazoline **(32)** (Scheme 1.2).



Scheme [1.2]

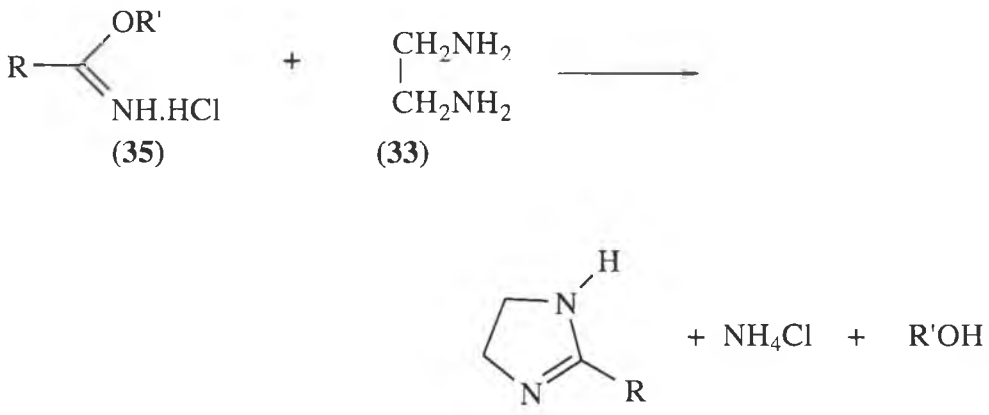
In 1981 Neef and co-workers[54] presented a variation of this synthesis claiming that the original method was very limited in its usefullness, often requiring drastic reaction conditions to effect conversion (sealed tube, 160-300 °C). They reported that bifunctional units such as 1,2-diaminoethane (**33**) could be coupled with trimethyl aluminium (**34**) to produce reagents that could be treated with a wide variety of esters to give 2-imidazolines under mild reaction conditions according to scheme [1.3].



Scheme [1.3]

1.2.1.4 *By reaction with imino ethers:*

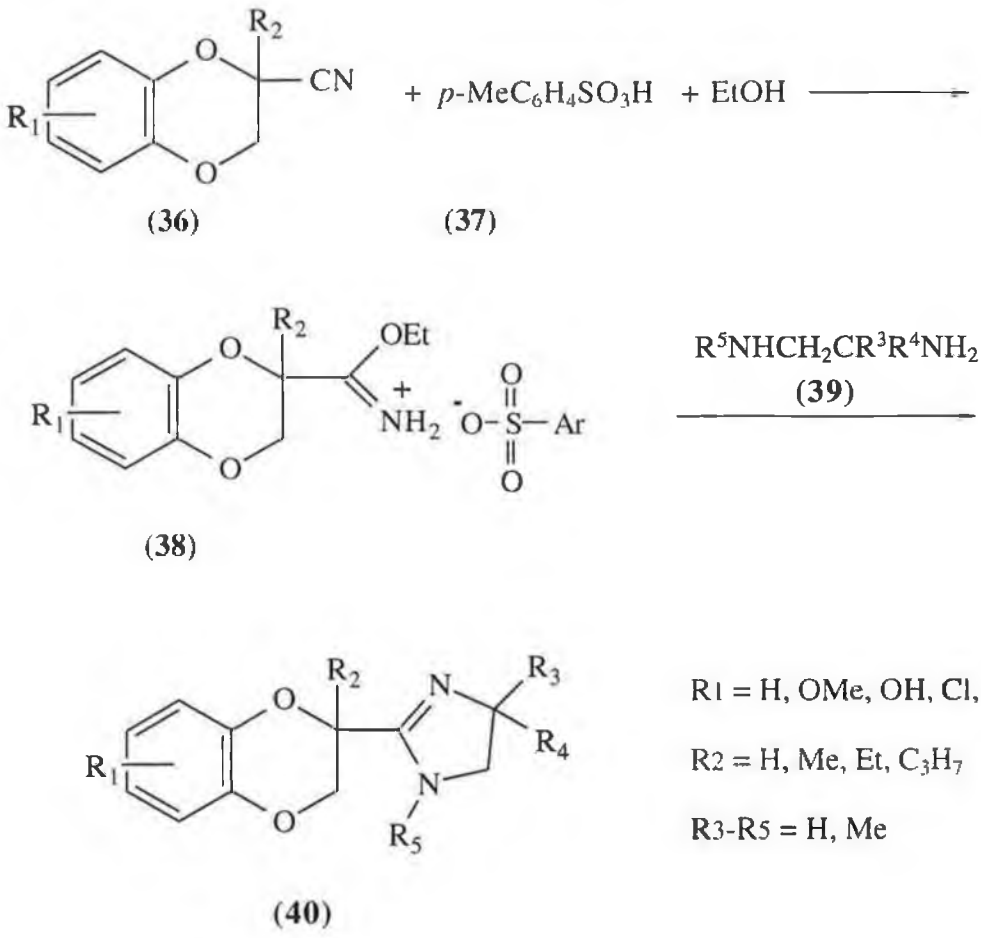
In 1935 Sonn[55] obtained a patent for the preparation of 2-substituted imidazolines by the action of aliphatic 1,2-diamines (**33**) on imido ester (imino ether) hydrochlorides (**35**) derived from aryl, aryloxy or carboxyalkyl substituted products (Scheme 1.4). The reaction of imino ethers or their hydrochlorides with 1,2-diamines is a satisfactory method of preparing 2-imidazolines.



R = Aryl, aryloxy or carboxyalkyl substituted products

Scheme [1.4]

R' may be an alkyl group but generally is ethyl. Several authors have synthesised in this manner using various R groups; $ClCH_2$,[56] $Cl(CH_2)_3$,[57] $HOCH_2$,[58] $C_6H_5CONH(CH_2)_2$,[59] C_6H_5NH,[60] C_6H_5.[61] Other variations of this synthesis have been described where the imino ether or imidate, as it may be alternatively named, was prepared as the tosylate rather than the hydrochloride salt. In 1987 Lopez Calahorra[62] reported the preparation of 2-(benzo-1,4-dioxan-2-yl)-4,5-dihydro-imidazoles (**40**) by treatment of benzodioxanecarbonitriles (**36**) with a strong acid such as *p*-$MeC_6H_4SO_3H$ (**37**) in EtOH, thus forming ethyl(benzo-1,4-dioxane-2-yl) formidate as the tosylate salt (**38**), which was subsequently treated with an alcoholic solution of KOH and the diamine (**39**).



Scheme [1.5]

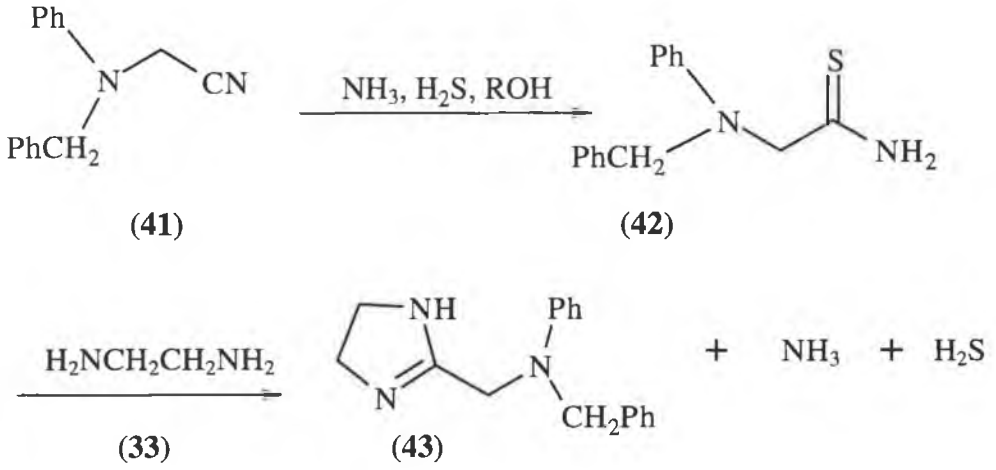
1.2.1.5 *By reaction with nitriles:*

The heating of aromatic or aliphatic nitriles and the salts of 1,2 diamines at 140-250 °C was shown to be a very effective method of preparing 2-imidazolines[63] as depicted in scheme [1.6].

Scheme [1.6]

While the free base was found to react with some reactive nitriles, in general this reaction was found to be too slow to be useful. The mono or di sulphonic acid salts of 1,2-diamines are preferred over the hydrochloride salts as they produce a homogenous reaction mixture. A variation of this method was described by Borisova *et al.*[64] in 1975 where imidazolines were produced by treating RCN with $H_2NCR_3R_4(CR'R_2)_nOH$ at 40-120 °C in AcOH using either $HClO_4$ or H_2SO_4 in catalytic amounts.

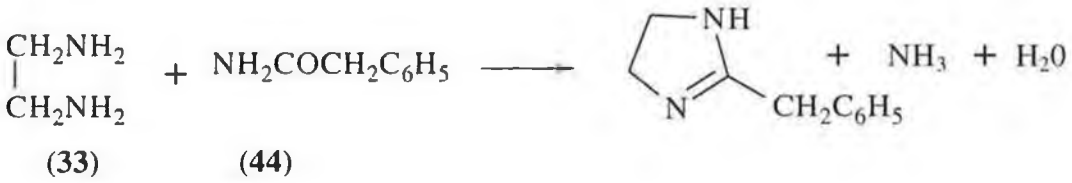
The presence of H_2S was found to be advantageous in the preparation of 2-imidazolines from 1,2-diamines and aliphatic or aromatic nitriles.[65-67] In some instances these reactions are carried out under conditions in which hydrogen sulfide is formed by hydrolysis of a sulfide.[68] A U.S. patent[69] describes the formation of imidazoline **(43)** from $Ph(PhCH_2)NCH_2CSNH_2$ **(42)** and diamine **(33)**, the former being generated from the action H_2S and NH_3 on $Ph(PhCH_2)NCH_2CN$ **(41)**. The beneficial uses of H_2S is again shown by Nakata and co-workers in the synthesis of imidazoline derivatives from nitriles[70] (Scheme 1.7).



Scheme [1.7]

1.2.1.6 *By reaction of amides:*

Aryl acetamides (**44**) have been treated in the absence of mineral acids or condensing agents, with an excess of ethylene diamine at 150-200 °C to yield 2-imidazolines[71] according to scheme [1.8].

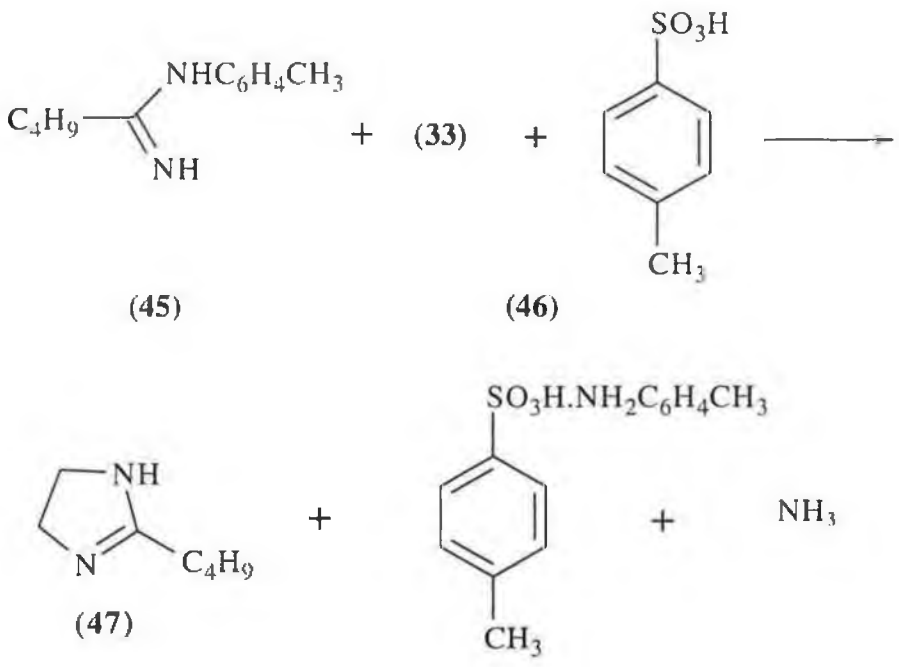


(**33**) (**44**)

Scheme [1.8]

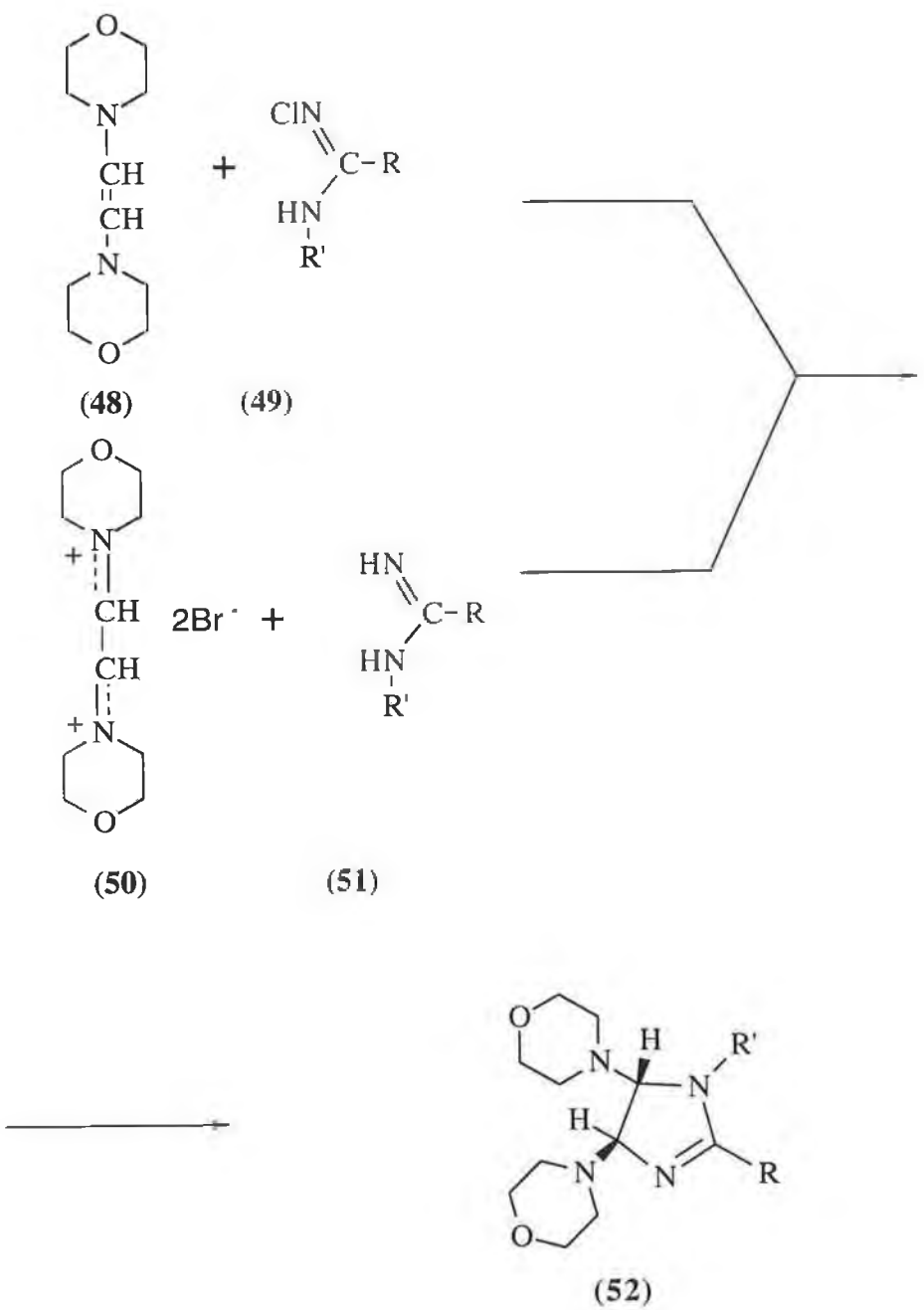
1.2.1.7 *By reaction of amidines and guanidines:*

It has been shown that N-substituted amidine salts prepared from the free bases (**45**) and *p*-toluene sulphonic acid (**46**) may be heated with 1,2-diamines (**33**) to yield 2-imidazolines (**47**) and ammonia[72] as outlined in scheme [1.9]. This is in accord with the suggestion that amidines may be intermediates in some of the reactions of nitriles and salts of 1,2-diamines to form 2-imidazolines.[63]



Scheme [1.9]

As given in scheme [1.10] Citerio *et al.*[73] reported the reaction of N-chloroamidines (**49**) with 1,2-amino ethenes (**48**) or with amidines (**51**) and a diimmonium bromide derivative (**50**) to give 4,5 substituted 2-imidazolines (**52**).



Scheme [1.10]

1.2.2 **From monoacyl and diacyl derivatives**

Hill and Aspinall[74] found that many aromatic and aliphatic monoacyl ethylene diamines undergo dehydration and cyclisation to 2-imidazolines, with the addition of lime being necessary for the reaction of the latter. Their preparation from diacetyl ethylene diamine was thoroughly investigated by Chitwood and Reid[75] who found that the highest yields were obtained when diacetyl ethylene diamine was heated with magnesium powder.

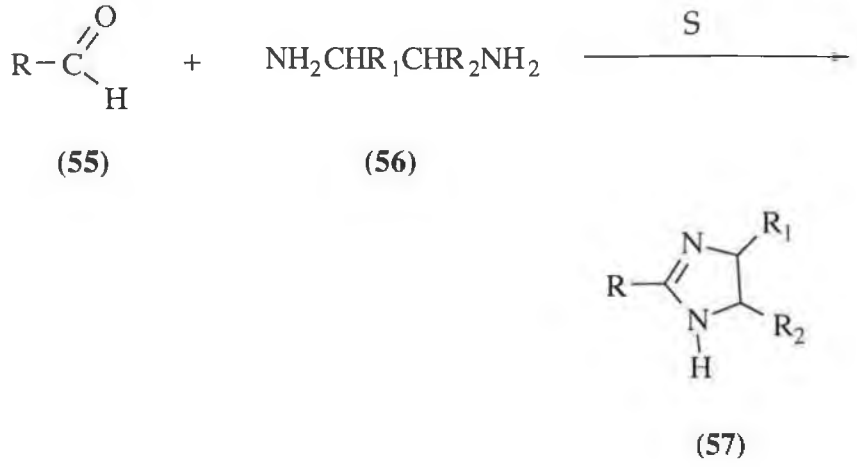
1.2.3 **From carbonyl containing compounds:**

Aromatic aldehydes react with ammonia to yield hydroamides (**53**) which may be cyclised on heating to 2,4,5-triaryl-2-imidazolines (**54**)[76,77] as shown in scheme [1.11].

(53) **(54)**

Scheme [1.11]

Hagen *et al.* in a patent application described in 1973 the synthesis of 2-imidazolines (**57**) by reaction of aldehydes (**55**) with R_1, R_2 substituted diamino alkanes (**56**) and sulphur[78] (Scheme 1.12).

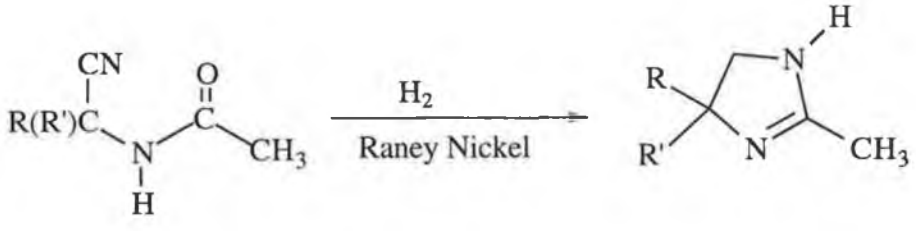


(55) **(56)** **(57)**

Scheme [1.12]

1.2.4 **Miscellaneous Syntheses:**

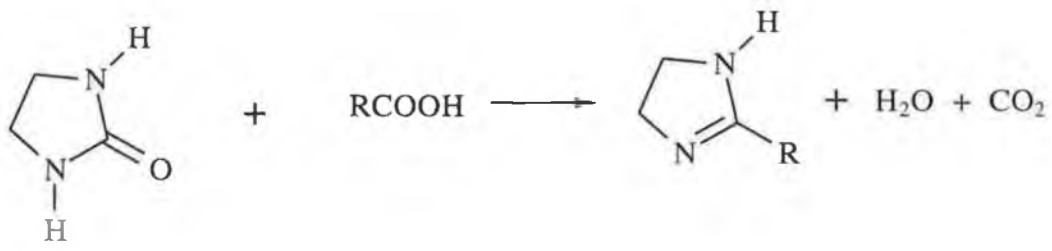
2-Imidazolines have been prepared in yields as high as 94% by reducing the monoacetyl derivatives of amino nitriles **(58)**[79,80] (Scheme 1.13).



(58)

Scheme [1.13]

An unusual method of forming imidazolines shown in scheme [1.14] consists of heating to a high temperature a mixture of 2-imidazolidone (**59**) and a carboxylic acid (**60**) other than formic acid.[81]

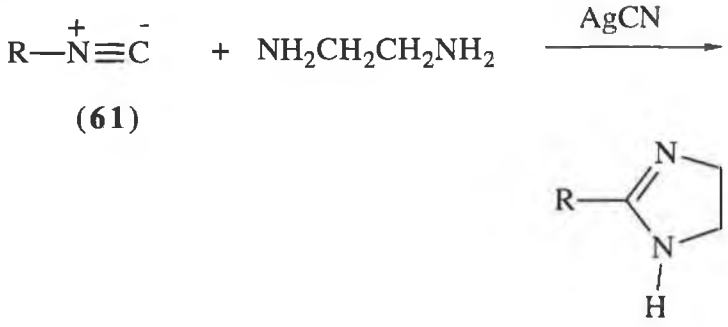


(**59**) (**60**)

R ≠ H

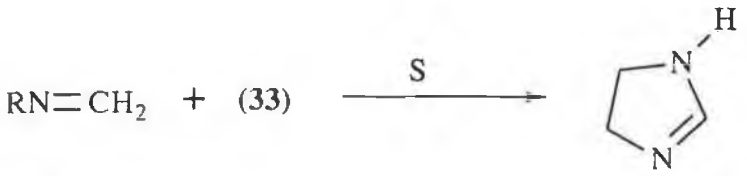
Scheme [1.14]

In 1973 Yoshihiko and co-workers[82] prepared imidazolines in a single reaction of an isonitrile (**61**) with the diamine (**33**) (Scheme 1.15) assumed to proceed *via* a carbene coordinated silver complex intermediate. Hagen *et al.*[83] simultaneously reported the synthesis of imidazolines by the reaction of $RN{:}CH_2$ (**62**) with an appropriate diamine and sulphur giving yields of 86% (Scheme 1.16).



(**61**)

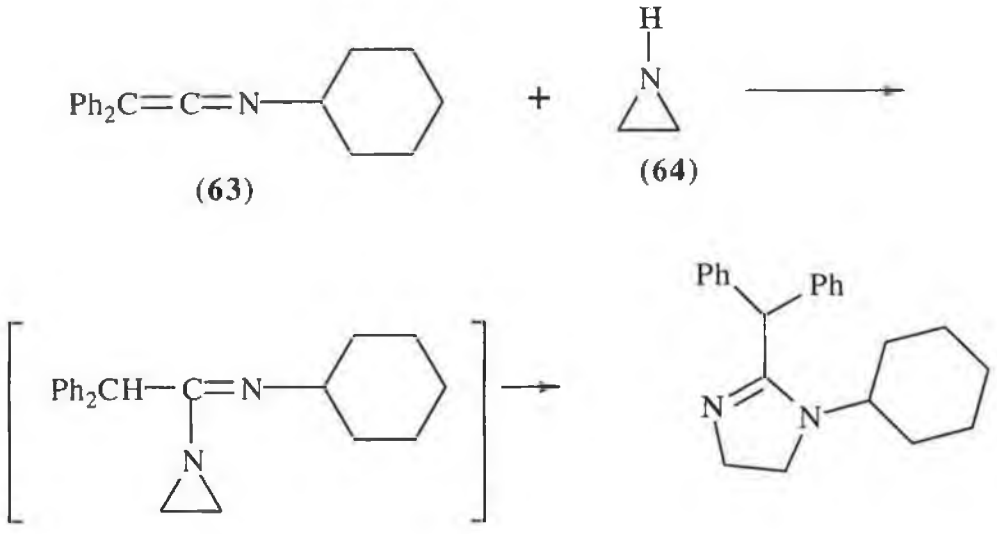
Scheme [1.15]



(62)

Scheme [1.16]

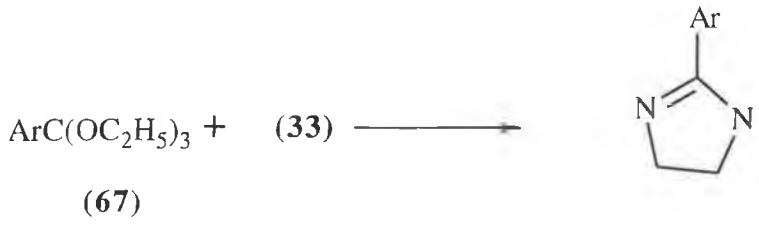
A very elegant synthesis of imidazolines **(66)** outlined in scheme [1.17] was reported by Murai[84] where keteneimines **(63)** reacted with aziridines **(64)** giving imidoylaziridines **(65)** which subsequently rearranged to imidazolines in good yields.



(63) **(64)** **(65)** **(66)**

Scheme [1.17]

Hill and Johnson[85] successfully formed imidazolines from the reaction of diamines **(33)** with orthoesters **(67)**, using mainly aromatic derivatives due to the difficulty of obtaining aliphatic orthoesters (Scheme 1.18).

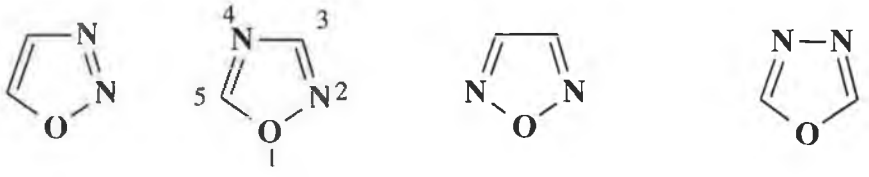


Scheme [1.18]

1.3 1,2,4-OXADIAZOLES

1.3.1 Introduction

1,2,4-Oxadiazoles have been known since the last century with the first report being made by Tiemann and Kruger[86] in 1884 who proposed the name "azoximes" for these compounds. Oxadiazoles are five membered heterocyclic compounds containing one oxygen and two nitrogen atoms. Four oxadiazole isomers are possible depending on the relative positions of the oxygen and nitrogen atoms in the heterocyclic ring.



1,2,3-	1,2,4-	1,2,5-	1,3,4-
(68)	**(69)**	**(70)**	**(71)**

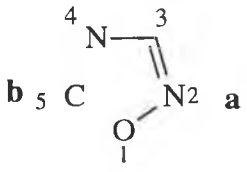
Scheme [1.19]

In older French literature, oxadiazoles are considered as a furan nucleus in which two CH groups are replaced by nitrogen atoms and therefore are sometimes termed furadiazoles or furodiazoles. When these latter names are used, the relative positions of the nitrogen atoms are indexed by the letters α and β' for the 1,2,4-oxadiazoles for example. In the old German literature, the carbon atoms in the ring are considered as part of the substituent and thus 1,2,4-oxadiazole would be named as dimethenylazoxim.

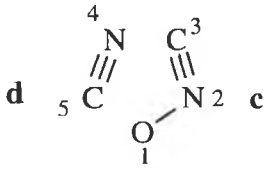
The greatest part of the work carried out in the field of 1,2,4-oxadiazoles is due to Tiemann and his co- workers.[87-90] All the compounds they prepared were substituted in the 3- and 5- positions, by two hydrocarbon radicals, at least one of which was an

aromatic radical.[91] Compounds with only aliphatic substituents were mentioned for the first time in 1959.[92-93]

Two widely used methods of synthesising 1,2,4-oxadiazoles embrace 95% of the practical preparations of these compounds: the conversion of amidoximes[94] by means of carboxylic derivatives to the cyclic structure [shown schematically as the combination of two skeletons] (**72 a,b**) and the cycloaddition of nitrile oxides[95] to nitrile (**73c,d**).



(**72**)



(**73**)

Scheme [1.20]

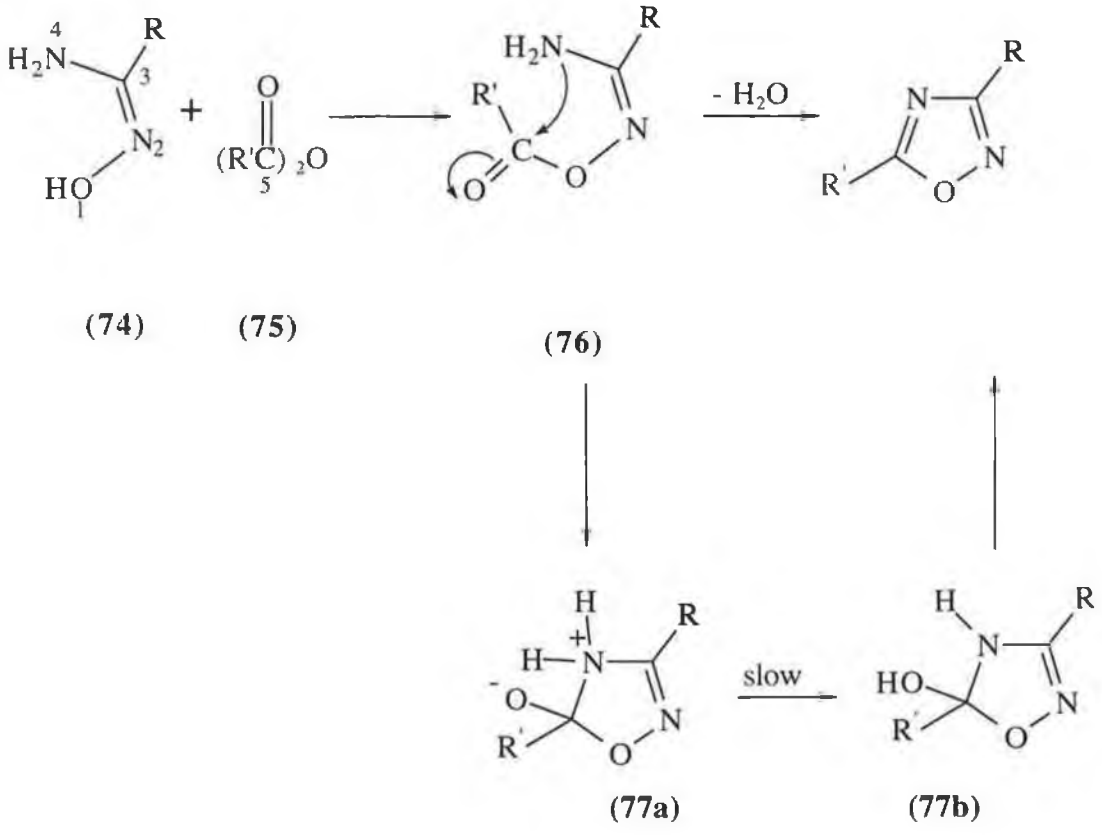
The fragments making up the moieties (**72a**), (**72b**), (**73c**) and (**73d**) can be disguised in a variety of ways. The carbon atom C5 in (**72b**) can be in the oxidation state +4, +3, or +2 to give oxadiazoles or the reduced ring oxadiazolines. The sp^2 carbon at C-3 is commonly in an amidoxime or an iminoether. The fragments (**73c**) and (**73d**) may be triple bonds as shown, but double bonds in either moiety give Δ^2 or Δ^4-oxadiazolines, or oxadiazolidine derivatives.

1.3.2 **Ring Closure on Carbon**

1.3.2.1 *From O-Acylamidoximes*

An amidoxime **(74)** is a good starting point for a suitable reagent containing an sp^2 carbon (C-3) with two nitrogen atoms attached. The carbon to end up as C-5 in the +3 oxidation state may be furnished by an anhydride **(75)**. This is the most frequently used preparation of these oxadiazoles since the work of Tiemann.[86]

The amidoxime which is usually made by heating a nitrile with hydroxylamine in acid solution[96-98] is converted to the O-acyl derivative **(76)**, as indicated in scheme [1.21], long assumed to be intermediates in the pathways to oxadiazoles[86,99] but only proven to be the case in 1963.[100]

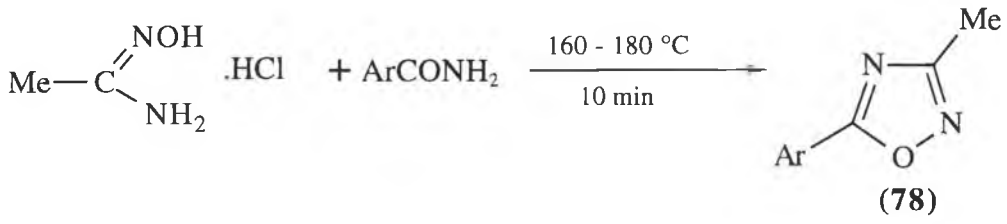


(74) **(75)** **(76)** **(77a)** **(77b)**

Scheme [1.21]

The O-acyl derivatives are not often isolated, and indeed cannot often be isolated if the acylation is carried out above 100 °C. A kinetic study suggests that the rate determining step is the proton transfer (**77a**) → (77**b**) following cyclisation.[101] In addition to the anhydride[102-105] many other sources for the C-5 carbon can be employed. Ketenes,[106] reactive acids such as formic[107] and acrylic,[108] acid chlorides,[109] esters,[110] ortho esters,[111] ethyl oxylate,[112] amides,[112] and iminoethers[113] may also furnish the C-5 carbon.

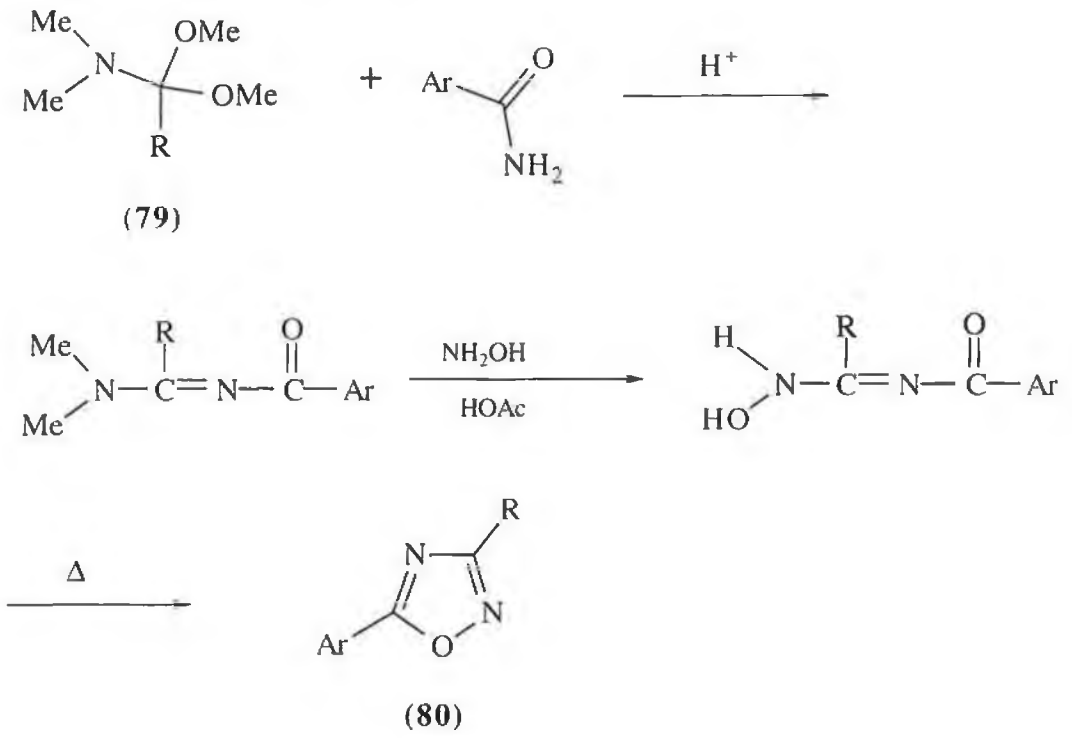
The reaction of amides[112] with an amidoxime salt to give oxadiazoles (**78**) (Scheme 1.22) is especially felicitous because no solvent is needed and recovery is simple. The two components are melted together at 160-180 °C for 10 minutes, and water is lost at the elevated temperature. Both aromatic and aliphatic (di- and monosubstituted) amidoximes give yields in the range of 60-90%.



(78)

Scheme [1.22]

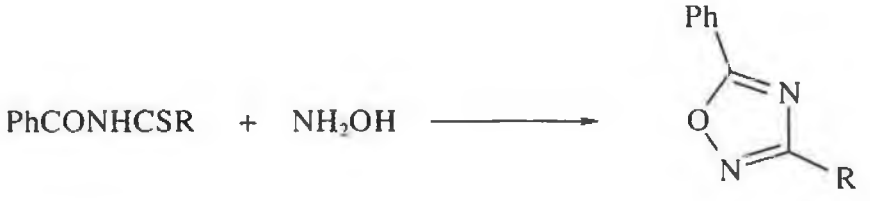
A successful innovation of this method outlined in scheme [1.23], with yields of oxadiazoles (**80**) of 81-95% is the use of the fragment (**72a**) as an N,N-dimethylalkanamide dimethyl acetal (**79**).[114]



(79) **(80)**

Scheme [1.23]

Still another variation of this method[115] is the reaction of a mixed imide **(81)** with hydroxylamine shown below in which the R group takes the C-3 position as in **(82)**.

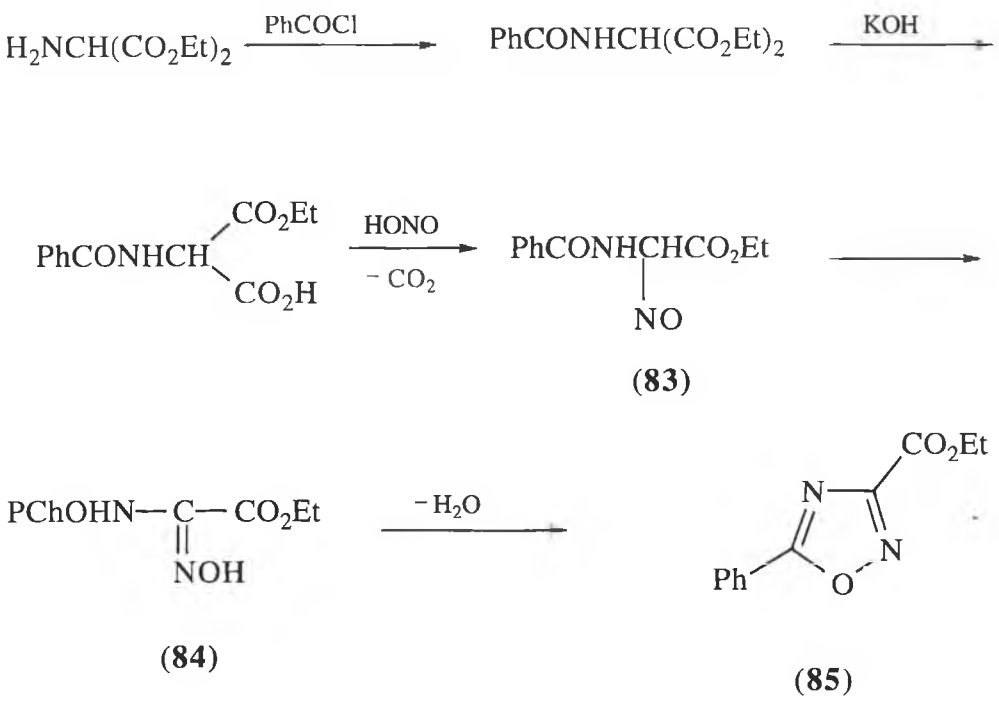


(81) **(82)**

Scheme [1.24]

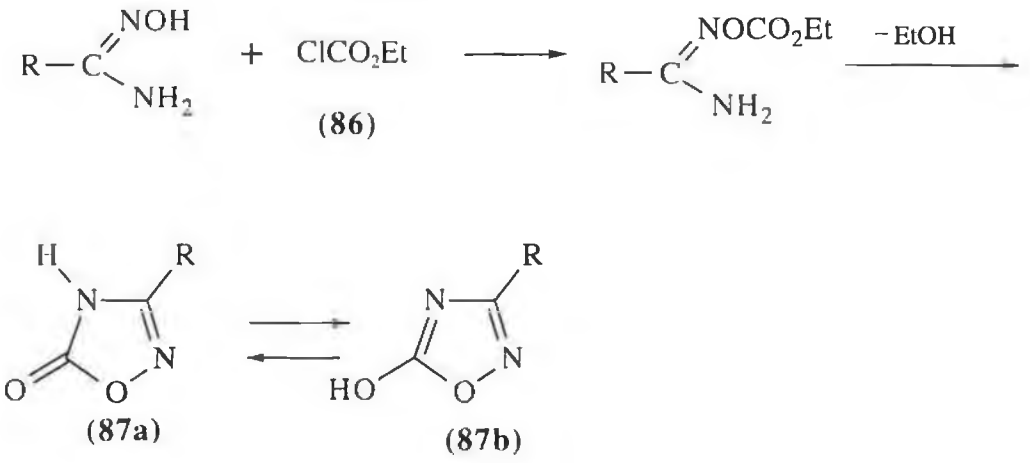
The oximino group in **(72)** can be introduced through nitrosation on carbon if there is an active hydrogen at that carbon atom. For example in scheme [1.25], nitrosation of the

acylamino half ester of malonic acid gives an intermediate (**83**) that can isomerise to an oxime (**84**) and then cyclise to a 3-ethoxycarbonyloxadiazole (**85**).



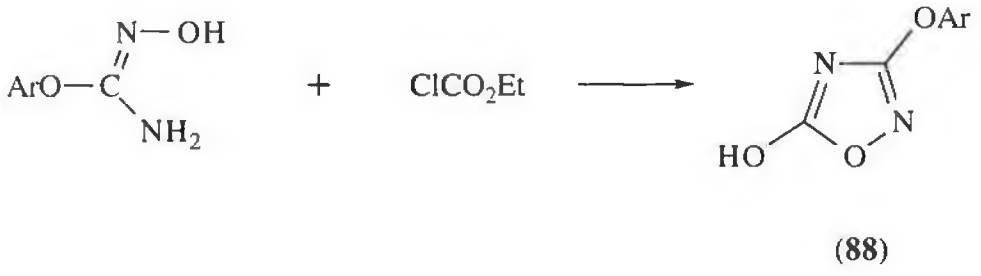
Scheme [1.25]

When the (**72b**) fragment is a carbonic acid derivative[116] i.e. of oxidation state +4, a hydroxy group may be introduced at C-5. Chloroethyl formate (**86**) reacts with amidoximes to give a carbonate ester that loses a molecule of ethanol in the cyclisation shown in scheme [1.26]. The expected oxadiazolone (**87a**) is a tautomer of the 5-hydroxy form (**87b**).



Scheme [1.26]

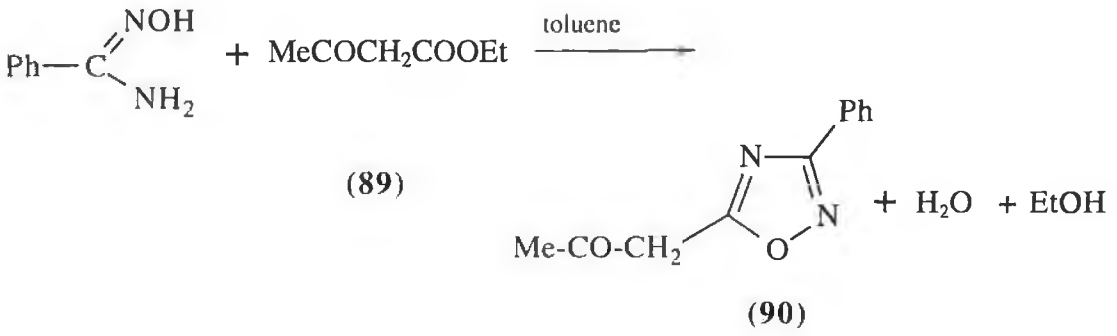
In 1965 Grigat *et al.*[117] obtained compound **(88)** (Scheme 1.27) with an ArO group at C-3, made using ArO-C(=NOH)NH_2 in place of amidoxime employed in scheme [1.26]. The aryloxy amidoxime was synthesised from ArOCN, unknown until 1964.[118]



(88)

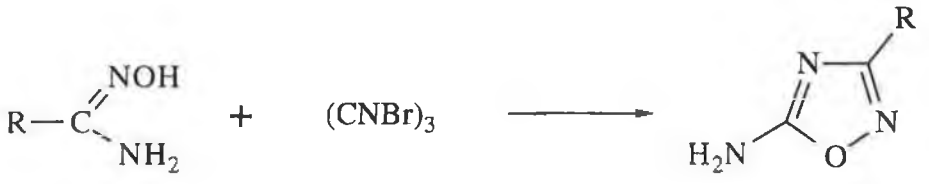
Scheme [1.27]

β-Ketoesters[119] **(89)** are sufficiently activated to react with amidoximes, particularly at the boiling point of toluene,[120] to cyclise with the loss of azeotropic water and ethanol yielding the oxadiazole **(90)** as indicated in the scheme below. O-acylamidoximes were proposed as intermediates.



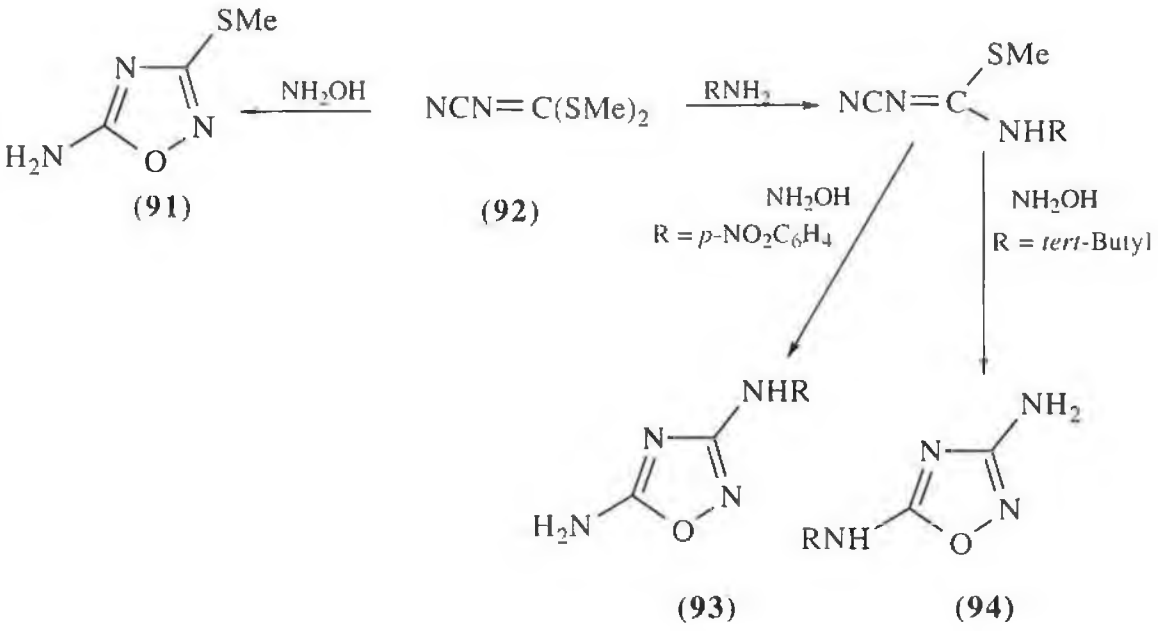
Scheme [1.28]

Cyanuric bromide with an amidoxime gives the 5-amino oxadiazole derivative delineated in scheme [1.29].[121]



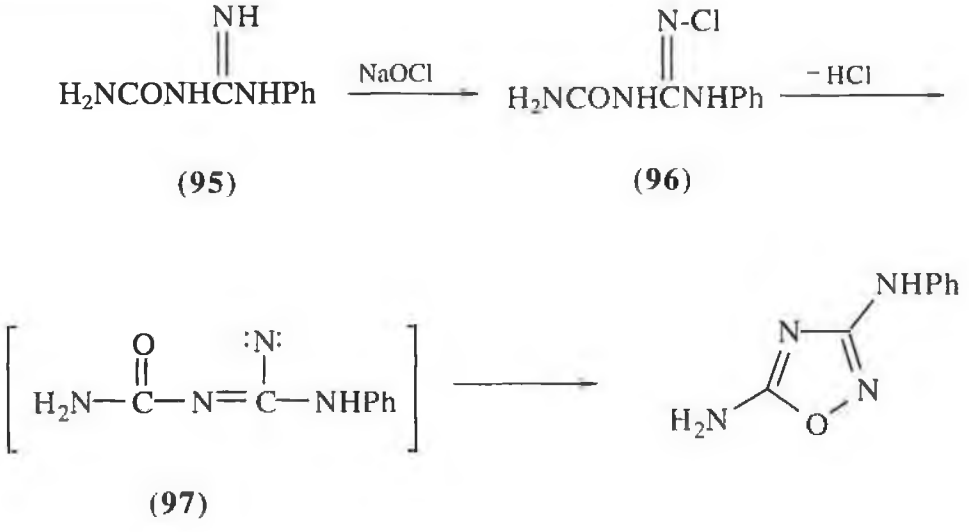
Scheme [1.29]

5-Amino-3-methylthiooxadiazole **(91)**[122] and 3,5-diamino derivatives[123] **(93)** and **(94)** have been synthesised from the cyanoimino compound **(92)**. When the amine was *p*-nitroaniline, **(93)** was obtained in 68% yield and with *tert*-butylamine **(94)** was formed in 52% yield (Scheme 1.30).



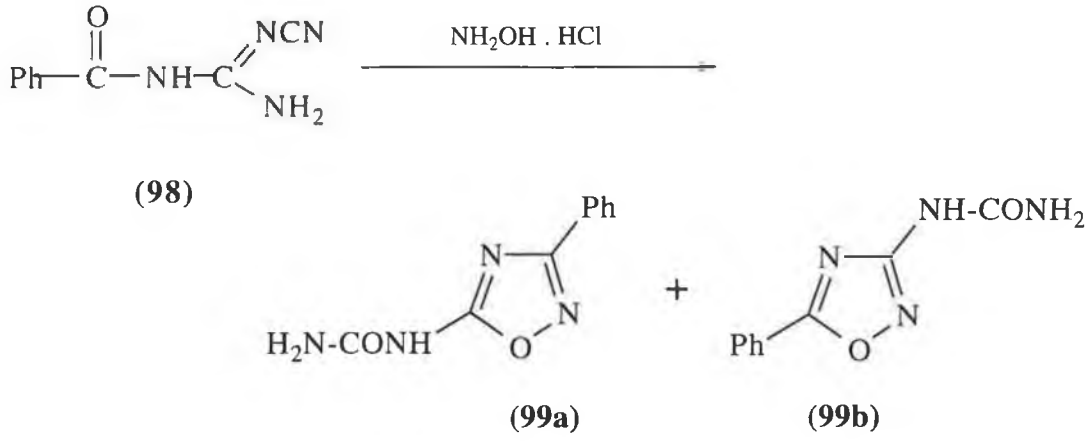
Scheme [1.30]

A new variation represented in scheme [1.31] is the activation of the oximino group in the amidoxime by replacement with =N-Cl (**96**). This was accomplished by oxidation of an imino group in a guanidine derivative **(95)** with sodium hypochlorite. A nitrene **(97)** was suggested as an intermediate.[124]



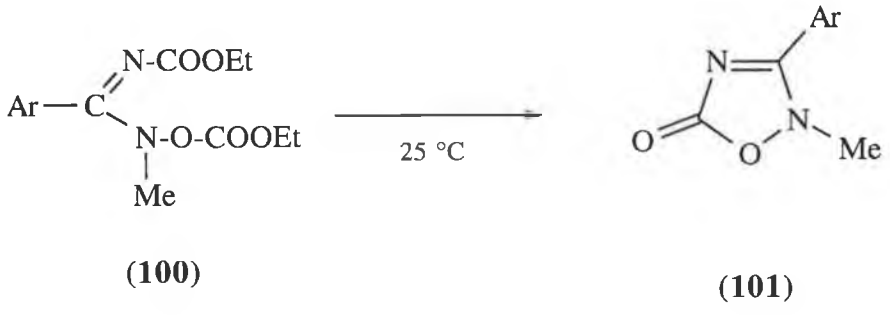
Scheme [1.31]

When employing amidoximes as starting materials in the synthesis of 1,2,4-oxadiaxoles it should not be taken for granted that the amidoxime carbon always becomes the C-3 carbon in the oxadiazole. Warburton[125] for example, demonstrated that benzoyldicyandiamide **(98)** gave a mixture of two ureido derivatives **(99a)** and **(99b)**, the first predominating.



Scheme [1.32]

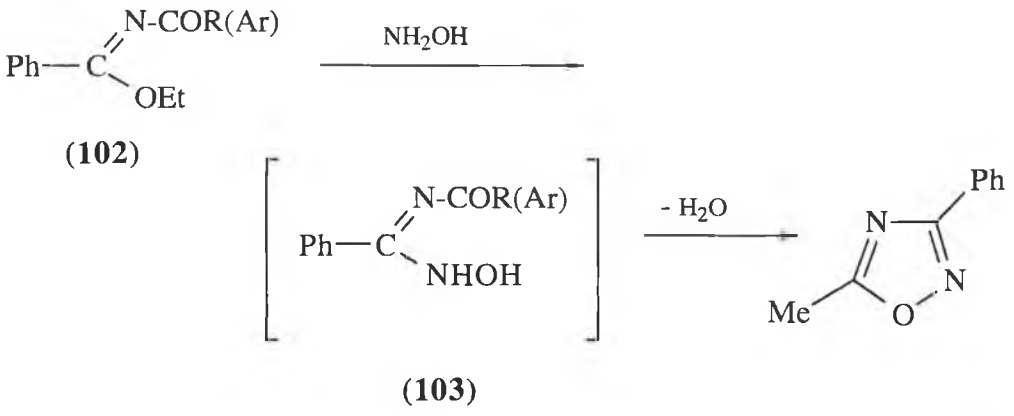
Dimsdale[126] in 1981 made a similar caveat when he showed that mistakes in structure have been made by assuming that the anhydride carbon atom always takes the C-5 position as opposed to the C-3 position (See scheme 1.21). Warburton and co-workers[127] destroyed another unstated tenet of diazole chemistry, namely that only monoacylated amidoximes cyclise, when they found that **(100)** slowly cyclised to **(101)** merely on standing for 27 days.



Scheme [1.33]

1.3.2.2 *From N-acylimino ethers*

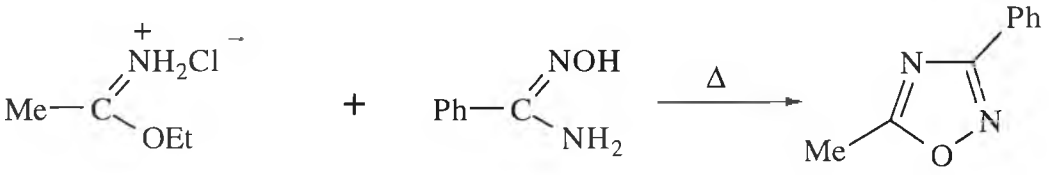
Another source of the sp^2 carbon at C-3 is an N-acylimino ether. The iminoether (**102**) reacts with hydroxylamine to give the intermediate (**103**) which has not been isolated,[128] and then cyclises to the oxadiazole (Scheme 1.34).



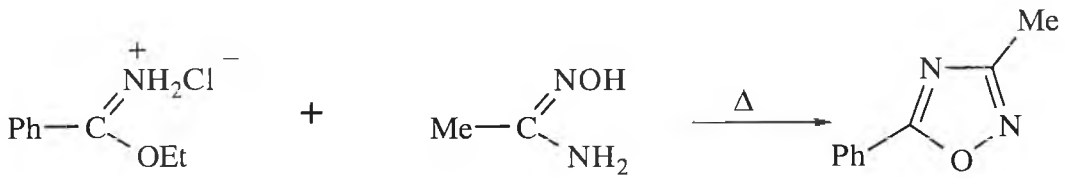
Scheme [1.34]

Earlier Beckman and Sandel[129] had used N-acyliminochlorides and N-acylbenzamidine in the same way with hydroxylamine, but these starting compounds are less stable and not so easily obtained as the N-acyliminoethers.

An iminoether may also be used as the source of the C-5 carbon in the final product if an amidoxime furnishes the one at C-3. Weidinger and Kranz[113] prepared 3-phenyl-5-methyloxadiazole (**104**) in 87% yield and 5-phenyl-3-methyloxadiazole (**105**) in 68% yield by this variation (Scheme 1.35).



(104)



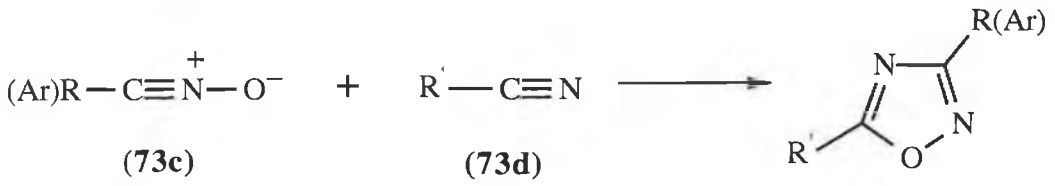
(105)

Scheme [1.35]

1.3.3 **Dipolar Cycloadditions**

1.3.3.1 *Reaction of nitrile oxides with nitriles*

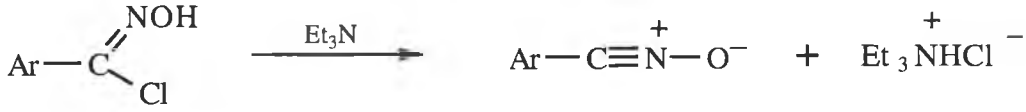
The second general method of generating the oxadiazole ring is to add the fragments **(73c)** a nitrile oxide to the nitrile **(73d)** in a 1,3-dipolar cycloaddition. This method has been widely exploited[130-137] since Leandri[95] first suggested the idea (Scheme 1.36).



(73c) **(73d)**

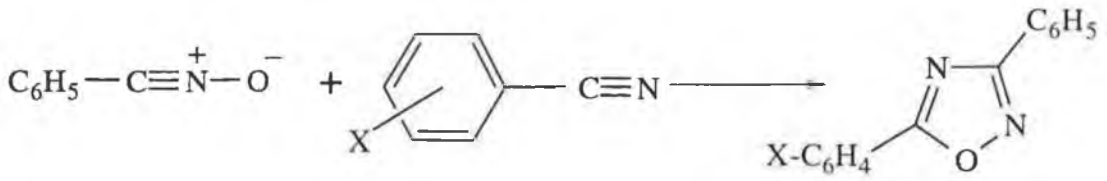
Scheme [1.36]

Aliphatic nitrile oxides are usually generated *in situ* from a primary nitroalkane with phenylisocyanate as dehydrating agent.[138,139] Aromatic nitrile oxides are much less reactive and can be isolated but again are more often generated in the presence of the nitrile by the action of a base or heat on hydroxamic acid[140,141] according to scheme [1.37].



Scheme [1.37]

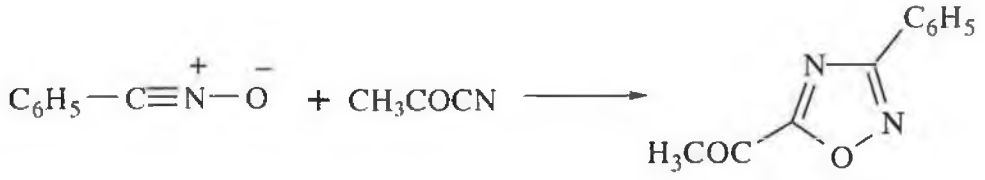
In 1957 Leandri[142] reported the condensation of aromatic nitriles with benzonitrile oxide with yields of the oxadiazole **(106)** varying from 0.2 to 29% depending on the substituent X linked to the aromatic nitrile. The yield increases when X is electron withdrawing and decreases when X is electron donating (Scheme 1.38).



(106)

Scheme [1.38]

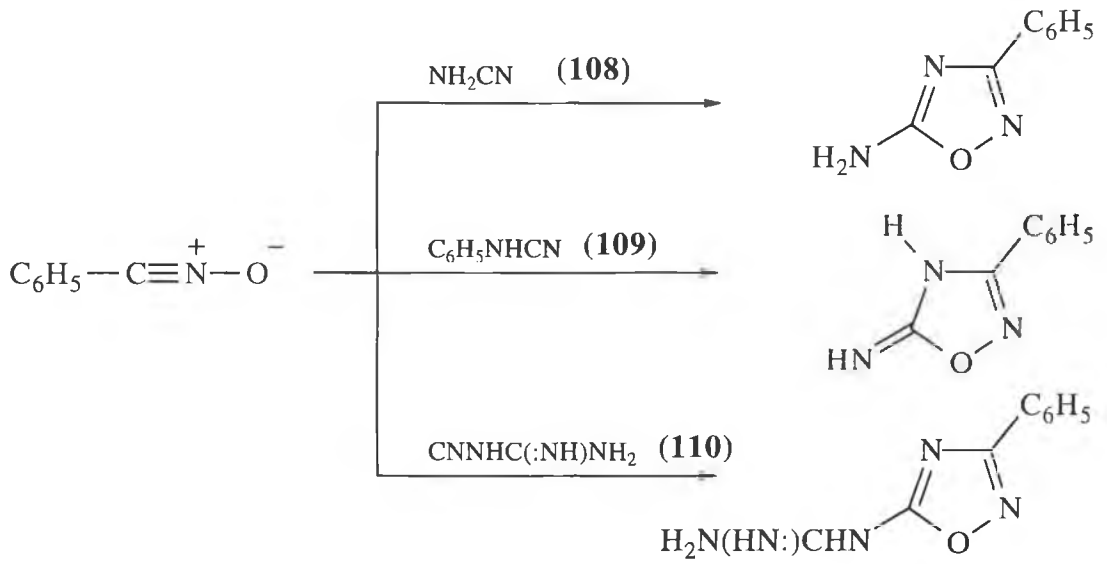
Aliphatic nitriles were found not to react with benzonitrile oxide unless activated by an electron withdrawing group.[143] For example, acetylcyanide gives 3-phenyl-5-acetyoxadiazole **(107)** in a yield of 60%.[144]



(107)

Scheme [1.39]

Cyanamide **(108)**, phenylcyanamide **(109)** and cyanoguanidine **(110)** are also reported to form oxadiazoles when treated with benzonitrile oxide in accord with scheme [1.40].[145]

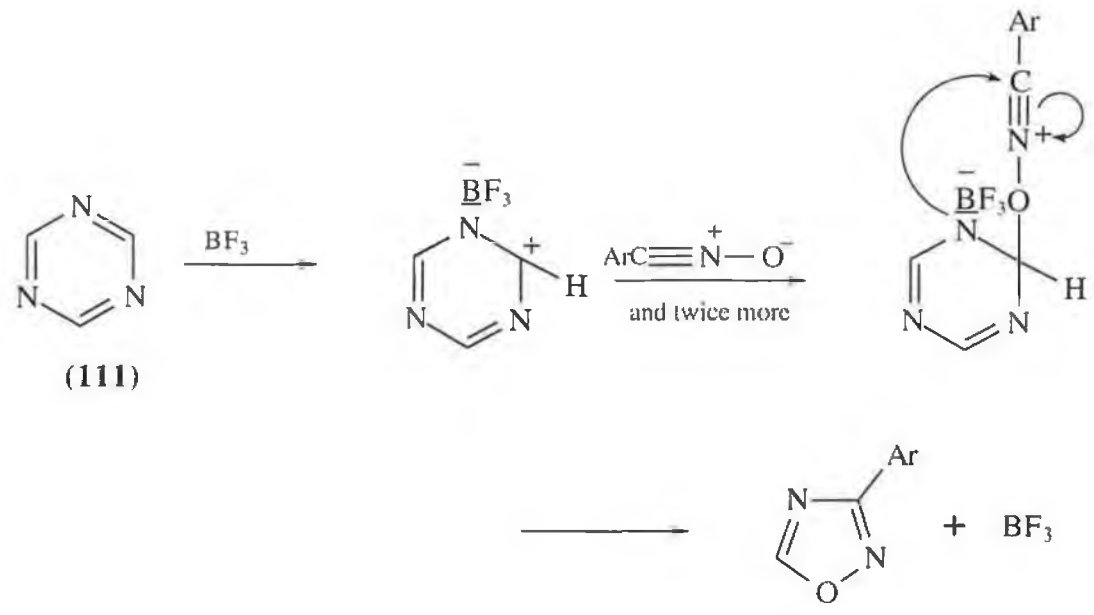


Scheme [1.40]

The reaction is considered as a 1,3-dipolar addition to a mesomeric form of the nitrile oxide.[146,143]

Scheme [1.41]

Bast *et al.*[130] reported yields as high as 88% for aryl nitrile oxides with aryl or negatively substituted alkyl cyanides. Yields of 35-40% were reported[131] for four aliphatic nitriles with benzonitrile oxide, but boron trifluoride etherate was needed as catalyst. A novel use of the general method outlined is the addition of an aromatic nitrile oxide to the nitrile equivalent tied up in the triazine[147] (**111**). The reaction occurs to give good yield but again only in the presence of boron trifluoride etherate whose role is illustrated in scheme [1.42].

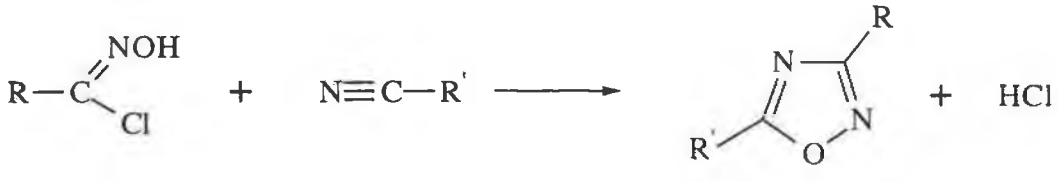


(111)

Scheme [1.42]

1.3.3.2 *Reaction of hydroxamyl chlorides with nitriles*

It has been found[148] that the formation of nitrile oxides from hydroxamyl chlorides is not always necessary. When heated in an inert solvent without any base, an equimolar mixture of a nitrile and a hydroxamyl chloride produces the expected oxadiazole with evolution of HCl (Scheme 1.43).

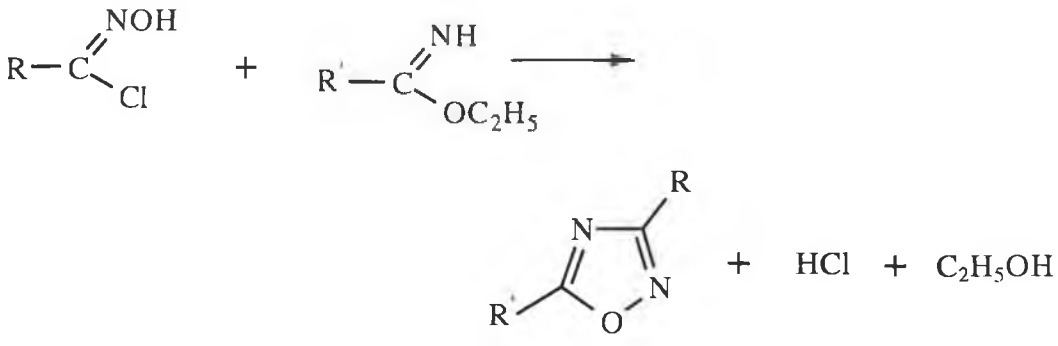


Scheme [1.43]

The advantage of this method is its applicability to some hydroxamyl chlorides such as dichloroglyoxime, the nitrile oxide of which is unknown, and ethyl α-chloro-α-isonitrosoacetate which immediately dimerises in the presence of a base.

1.3.3.3 *Reaction of hydroxamyl chlorides with iminoethers.*

The process consists in condensing a hydroxamyl chloride with an iminoether at comparatively low temperature (Scheme 1.44).

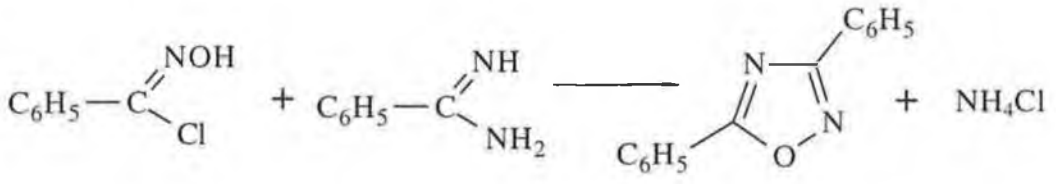


Scheme [1.44]

The reaction occurs in one step, but an equivalent excess of imino-ether must be used as HCl scavenger. The process is limited by the choice of reagents, but when hydroxamyl chlorides and iminoethers are easily available, their condensation is the most practical way to obtain oxadiazoles.[149] The condensation is particularly suited to aromatic and heterocyclic derivatives.

1.3.3.4 *Reaction of hydroxamyl chlorides with amidines.*

Diphenyloxadiazole has been prepared in almost quantitative yields from benzhydroxamyl chloride and benzamidine at room temperature in accord with scheme [1.45]. The reaction occurs apparently in one step as no intermediate product is isolated.[150] However as amidines are derived from iminoethers, this method presents only little interest.



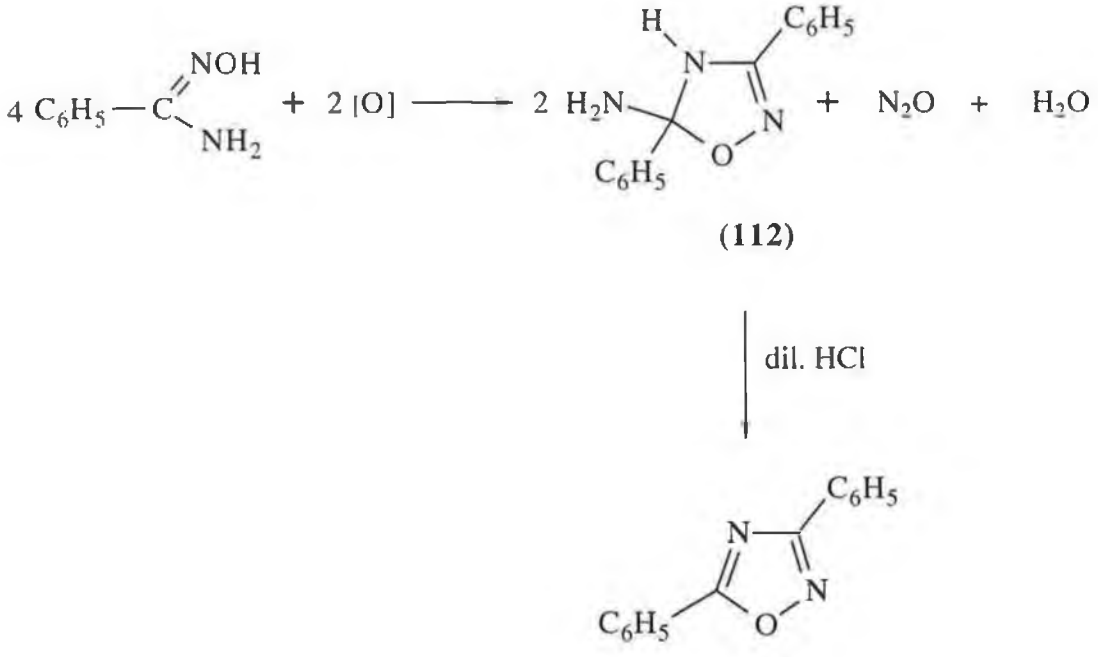
Scheme [1.45]

1.3.4 FROM OXIDATIONS

A less common and in general a less satisfactory method of entering the oxadiazole series is through the oxidation of compounds such as aromatic aldoximes, amidoximes and oxadiazolines.

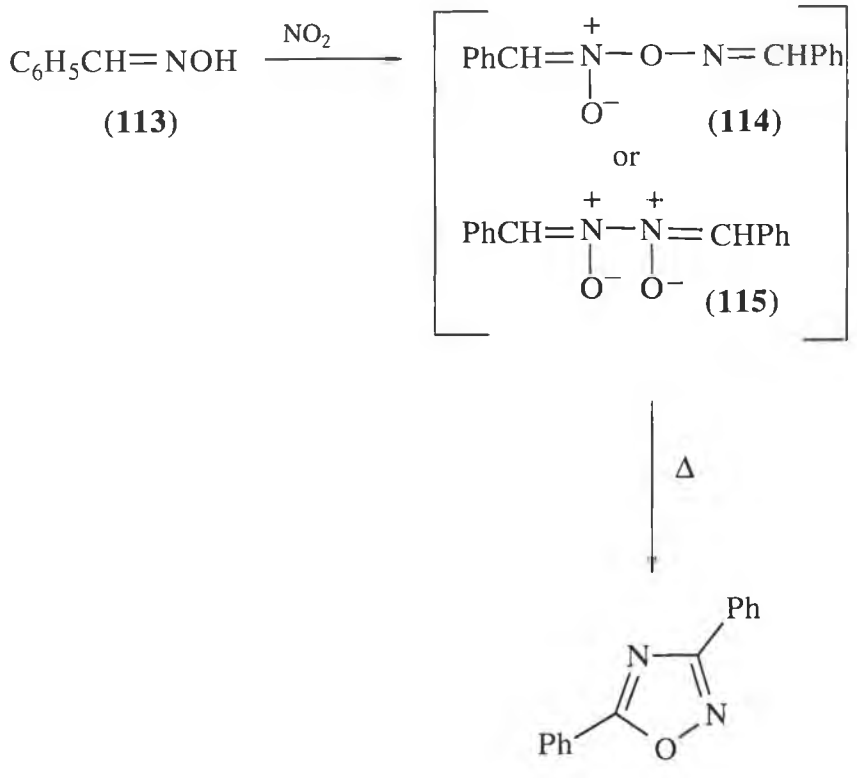
1.3.4.1 *From the oxidation of amidoximes and oximes.*

The action of bromine, ferricyanide,[151] and other mild oxidizing agents[152] directly on benzamidoxime has been reported to give 3,5-diphenyl-5-amino-dihydroxadiazole (**112**) which on subsequent heating in dilute mineral acid readily loses NH_3 to yield diphenyl oxadiazole (Scheme 1.46).



Scheme [1.46]

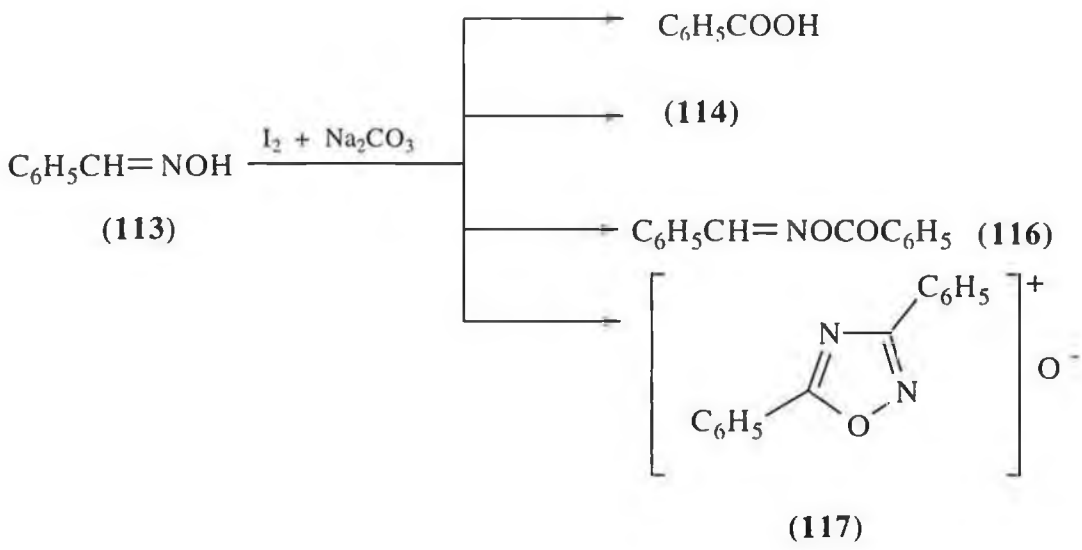
Benzaldoxime (**113**) can be oxidized with nitrogen dioxide in ether to a dimer that thermally decomposes to an oxadiazole as outlined in scheme [1.47].[153] Boyer[154] proposed the intermediate dimer structure (**114**) as benzaldoxime anhydride *N*-oxide but an alternative (**115**) offered by Horner *et al.*[155] could not be excluded. The dimer is converted to the oxadiazole in chloroform or benzene.



Scheme [1.47]

The oxidation of benzaldoxime (**113**) with iodine and sodium carbonate yields, besides benzoic acid, at least four substances identified as benzoyl-benzaldoxime (**116**), benzaldoxime peroxide (**114**), and two distinct oxides of diphenyloxadiazole (**117**)

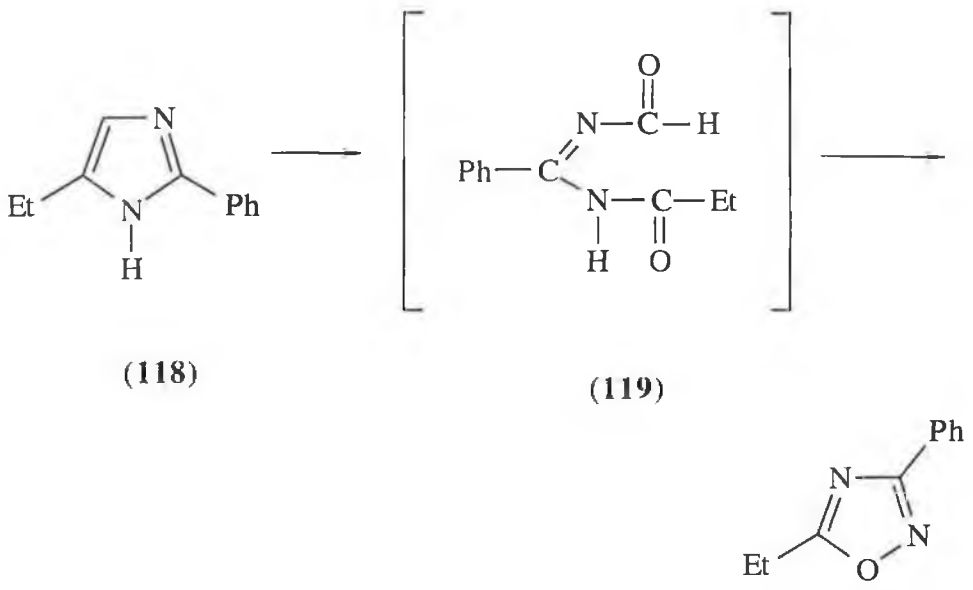
depicted in scheme [1.48]. The oxides (**117**) are easily reduced to diphenyl oxadiazole with zinc and acetic acid.[156,157]



(**117**)

Scheme [1.48]

Van Meeteren and van der Plas[158] oxidised several imidazoles (**118**) to oxadiazoles. They proposed the formylamidine intermediate (**119**) shown in scheme [1.49], since alkaline oxidation of imidazoles is known to produce such derivatives.[159] An additional fact supporting the intermediate was that imidazoles disubstituted at C-4, C-5 could not be oxidised to oxadiazoles.

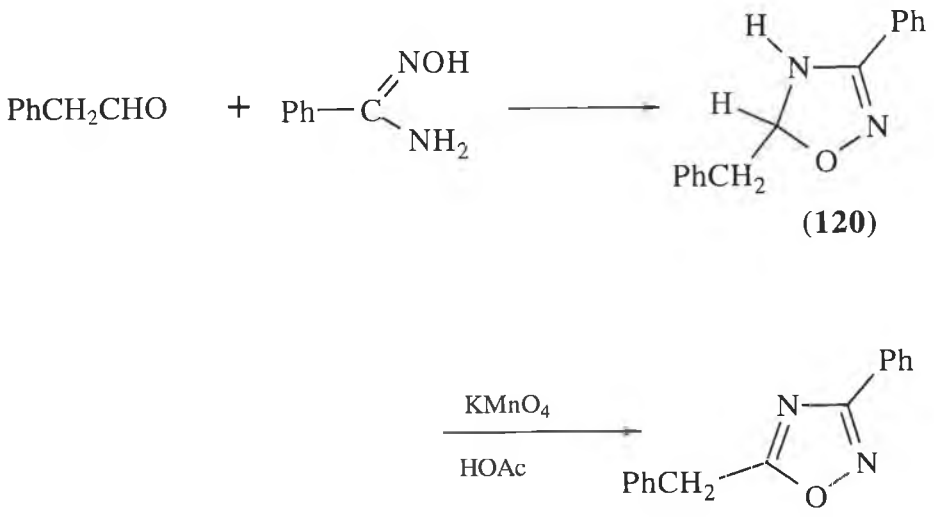


(118) **(119)**

Scheme [1.49]

1.3.4.2 *Oxidation of oxadiazolines*

Amidoximes readily condense with aliphatic aldehydes in aqueous solution to form 4,5-dihydro-1,2,4-oxadiazolines **(120)** represented pictorially in scheme [1.50]. This partially reduced ring can then be oxidised to an oxadiazole by various oxidising agents such as potassium permanganate,[160] nitrogen dioxide in ether,[161] sodium hypochlorite,[161] and N-chlorosuccinimide.[161]


PhCH2CHO
+
Ph—C
NOH
NH2
H
N
Ph
H
N
O
PhCH2
(120)
KMnO4
HOAc
Ph
N
N
O
PhCH2

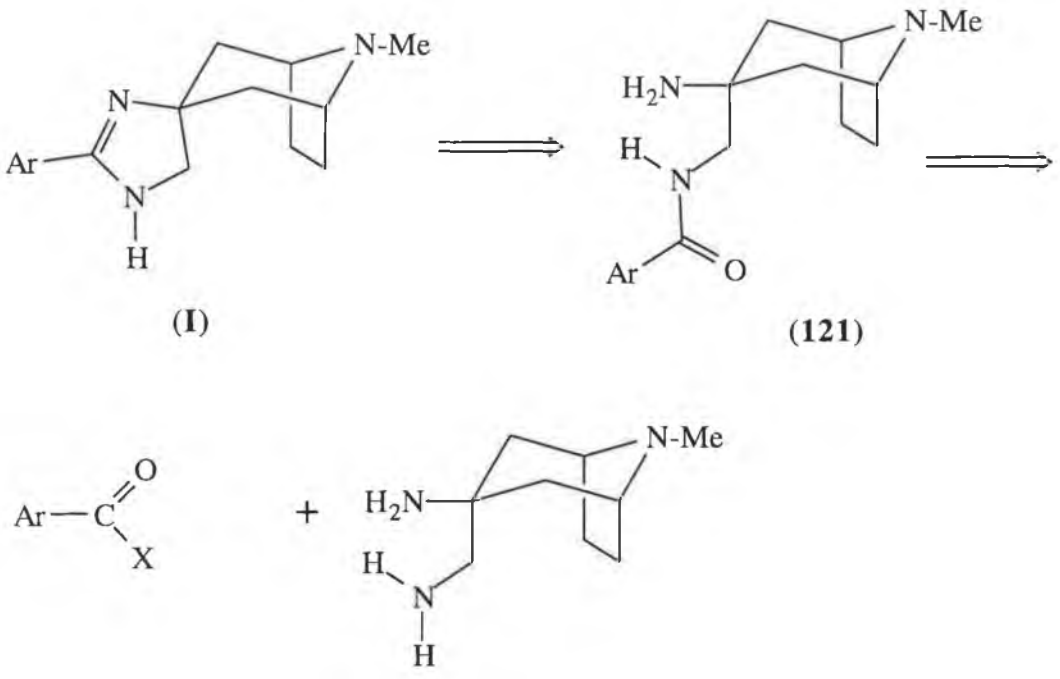
Scheme [1.50]

CHAPTER II

Synthesis of 2'Aryl-tropane-3-spiro-4'(5')-imidazolines.

2.1 **Introduction.**

Retrosynthetic analysis (Scheme 2.1) indicated that the spirofused imidazoline **(I)** could be prepared in a number of ways, all encompassing the key diamine intermediate **(122)**. At first examination the monoacylation of the diamine to give compound **(121)**, followed by cyclisation with the concurrent loss of water looked an attractive approach.



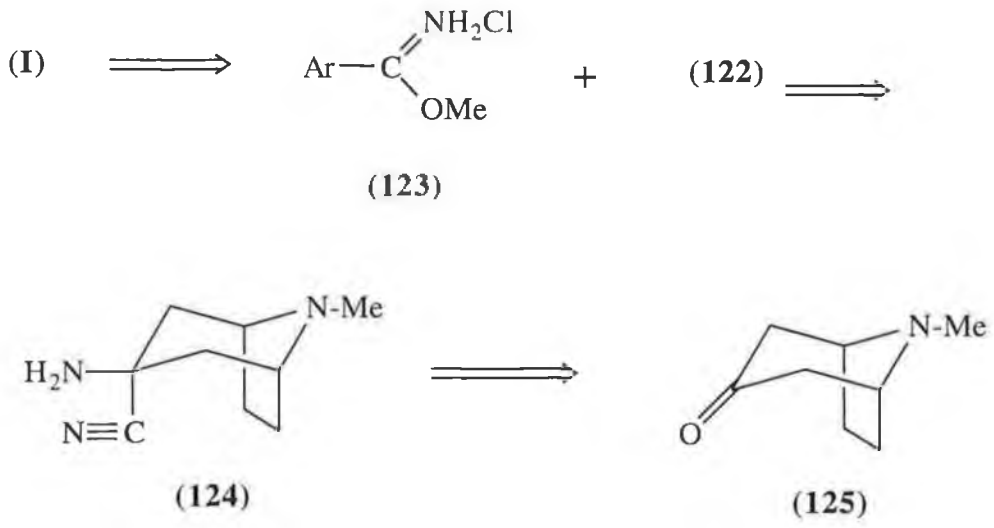
(I) **(121)** **(122)**

X = OH, OR, NH_2

Scheme [2.1]

Preliminary investigations to form the amide by condensation of the diamine **(122)** with carboxylic acids, esters or amides however proved unsuccessful due to the high temperature required and consequent rupture of the tropinone ring system. Attempts to condense the diamine directly with an aromatic nitrile proved unfruitful, again resulting in decomposition of the tropinone ring system as a result of the high temperature needed.[63]

The most successful synthesis of the spiroimidazolines, was found to be that where the tropinone diamine was condensed with the hydrochloride salt of an aryl imidate (**123**) as outlined in scheme [2.2].

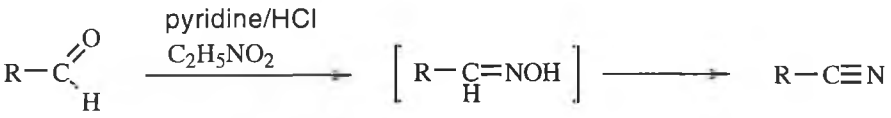


Scheme [2.2]

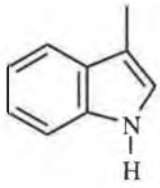
The imidates were prepared from the corresponding aryl nitriles which were either commercially available or were synthesised from the aldehyde. It was proposed that the key diamine intermediate (**122**) could be prepared by reduction of the amino nitrile (**124**) which in turn could be made from readily obtainable tropinone (**125**).

2.2. **Preparation of 1*H*-indole-3-carbonitrile (126)**

Several methods for the conversion of aldehydes into nitriles are known.[162-167] A method published by Dauzonne *et al.*[168] in 1981 using inexpensive reagents, was reported to give high yields of nitriles in one step from aromatic and certain heteroaromatic aldehydes *via* reaction with pyridine hydrochloride and a nitroalkane, preferentially nitroethane.



R =



(126)

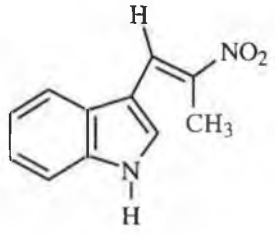
Scheme [2.3]

The method was reported to be less efficient with aliphatic aldehydes because of partial hydrolysis of the product nitriles or incomplete reaction. A typical procedure involves mixing the aldehyde with a 15% excess of pyridine hydrochloride in nitroethane and heating under reflux for one hour. Work-up involves cooling the reaction to room temperature, adding chloroform and 0.1 normal hydrochloric acid followed by separation and washing of the organic phase. The product is isolated pure by column chromatography.

The title compound was prepared by the above authors in 70% yield, requiring a reaction time of 30 min. Using the conditions described we successfully synthesised the 1*H*-indole-3-carbonitrile, though the reaction conditions and yields were somewhat at variance with those of the published method. Under the conditions described we found

than only about 15-20% conversion to the nitrile could be achieved in the time outlined in the published procedure. Reaction times of six to seven hours were required to achieve full conversion of the aldehyde. On thin layer chromatographic plates an intense yellow spot was observed as well as the product nitrile. The intensity of this spot reached a maximum during the course of the reaction and on continued heating of the mixture (after the disappearance of the starting aldehyde) no variation of its intensity was observed. This seemed to indicate that, firstly, the compound was not an intermediate of the reaction and secondly that the impurity was not derived from decomposition or rearrangement of the product nitrile.

The yellow impurity was isolated by column chromatography on silica gel and was obtained in 15 % yield as a fine yellow powder. The required nitrile was isolated in 32 % yield. NMR analysis of the yellow compound in CD_3OD showed, as well as the aromatic protons of the indole system, a singlet integrating for 3 protons at $\delta = 2.50$ ppm and a singlet at $\delta = 7.76$ ppm integrating for 1 proton. Based on this information the structure **(127)** was proposed.

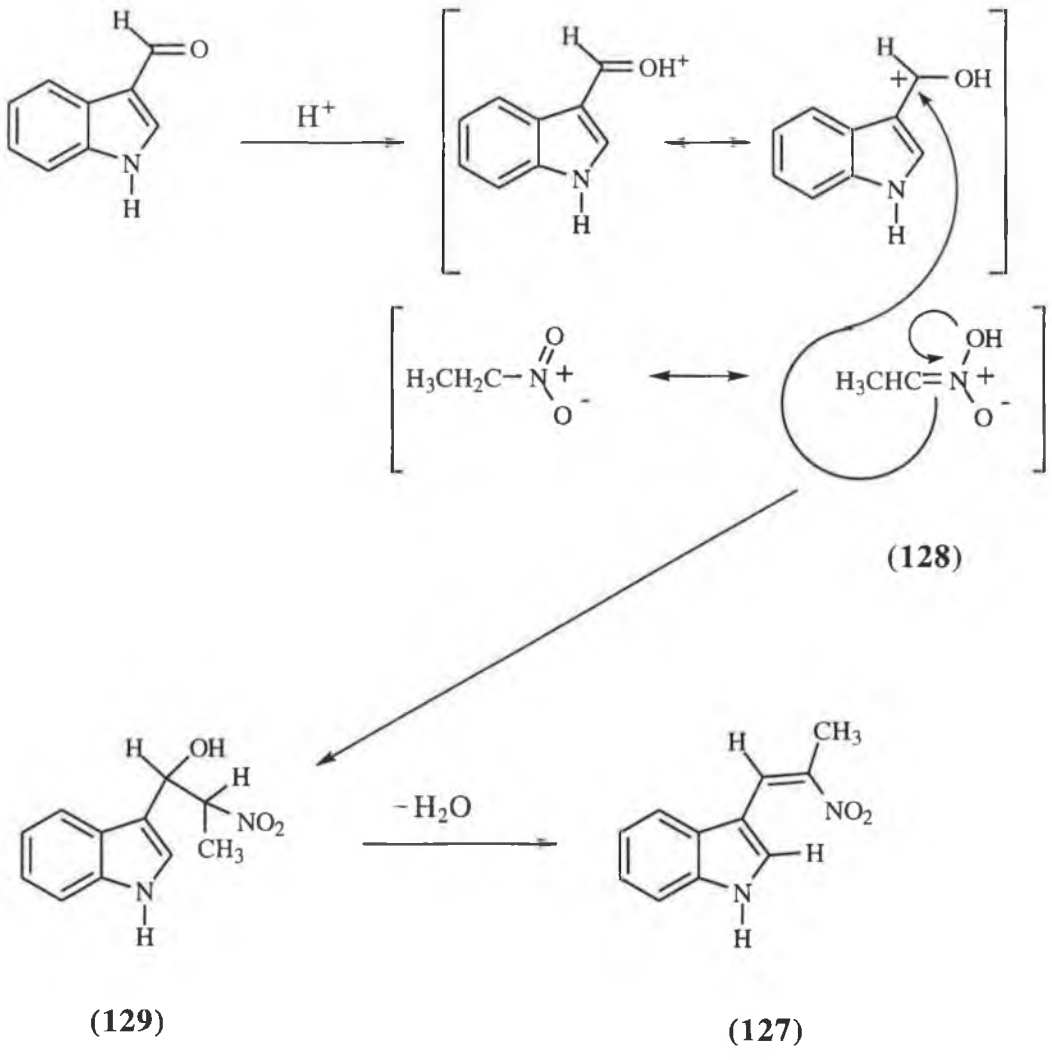


(127)

Mass spectrometry supported the structure, since electron impact gave a mass ion of 202 and a base peak of 154 corresponding to the loss of HNO_2.

The formation of this 1-indole-2-nitropropene probably takes place via the mechanism given in scheme [2.4]. Nucleophilic attack of the α carbon of the nitronic acid intermediate **(128)** on the protonated carbonyl group leads to the intermediate **(129)**

which on loss of H_2O gives the proposed compound which from its extended conjugated system probably accounts for the intense yellow colour of the product.



(128)

(129) **(127)**

Scheme [2.4]

This side reaction was not reported by Dauzonne *et al.* in their published synthesis of nitriles. However a subsequent report by Karmarkar and coworkers[169] employing a variation of the Dauzonne synthesis, using NaOAc/AcOH and NH_4OAc/AcOH in place of pyridine hydrochloride, showed that while the sodium acetate mixture led exclusively

to the nitrile the latter gave the aryl nitropropene as the only product. Also noteworthy was the fact that when they used nitromethane instead of nitroethane 1-aryl-2-nitroethylenes (ω-nitrostyrenes) were always isolated even when sodium acetate was used.

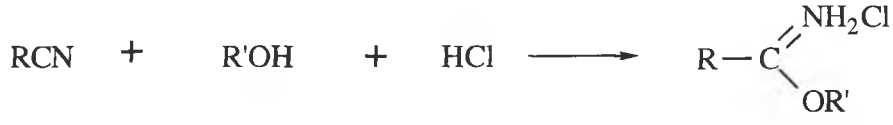
The mechanism of formation of nitriles from aldehydes is somewhat obscure and difficult to elucidate. Dauzonne[168] made the assumption that in their reaction using pyridine hydrochloride and nitroethane, the reaction proceeded via the intermediacy of aldoximes (Scheme 2.3). They based their assumption on the fact that nitroalkanes are capable of generating aldoximes under the action of pyridinium halides[170] and that pyridinium halides can dehydrate aldoximes to nitriles.[171] However no clear mechanism was outlined. Similarly, Karmarkar and coworkers[169] were unable to present a definitive mechanism for the conversion of aldehydes to nitriles with nitroalkanes. They reiterated the idea of an intermediate aldoxime which could be cleaved to give the nitrile in the presence of sodium acetate. As evidence for the formation of the aldoxime they cited a report[172] which claimed that nitroethane reacts with concentrated sulfuric acid to give ethanehydroxamic acid. The presence of an intermediate of this type, they claimed, could presumably convert the aldehyde into the oxime derivative. To substantiate the proposed mechanism they showed that under the conditions used in the reaction in question, that the oxime acetate prepared from 2-methoxy-1-naphthaldehyde was converted to the same nitrile which was obtained directly from the aldehyde.

2.3. **Imidate salts.**

2.3.1 *Introduction.*

The chemistry of imidates and their salts is well documented and it is proposed that only a brief outline of their synthesis plus some practical considerations be given here. The first major work on the subject was described by Pinner in his book *Die Imidoäther und ihre Derivate,*[173] a work which is however difficult to obtain. A more recent and accesible review of imidates was carried out by Roger and Neilson[174] and provides a comprehensive covering of imidate synthesis.

Imidates may be synthesised in several ways, among which include the condensing of a nitrile and an alcohol under anhydrous conditions, known as the Pinner synthesis,[173] the synthesis of imidates via imino chlorides (Hoesch reaction),[175] from amides,[176] orthoesters,[177] aldehydes and ketones,[178,179] unsaturated systems[180] and by transesterifications.[181] Probably the most widely used method of imidate synthesis is that of the Pinner synthesis, and it is this method which was exploited to form the imidate intermediates required for this project. The method is outlined in scheme [2.5].



Scheme [2.5]

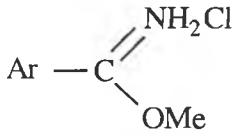
The nitrile is reacted with the alcohol under anhydrous conditions in the presence of hydrogen chloride or hydrogen bromide.[182] The reaction is normally carried out at 0 °C and anhydrous chloroform,[183] nitrobenzene,[183] dioxane,[184,185] dimethyl

Cellosolve,[186] and in particular benzene[187] and ether[188] have been used as diluents. It was established however, that the use of solvent may be detrimental to the yield and that better results accrue in certain cases when the anhydrous diluent is added after several days or when the imidate is on the point of crystallisation.[189] Excess alcohol has also found use as diluent,[190] but this can be conducive to the formation of ortho esters in certain cases. However this problem does not generally exist when the reaction is carried out at 0 °C.

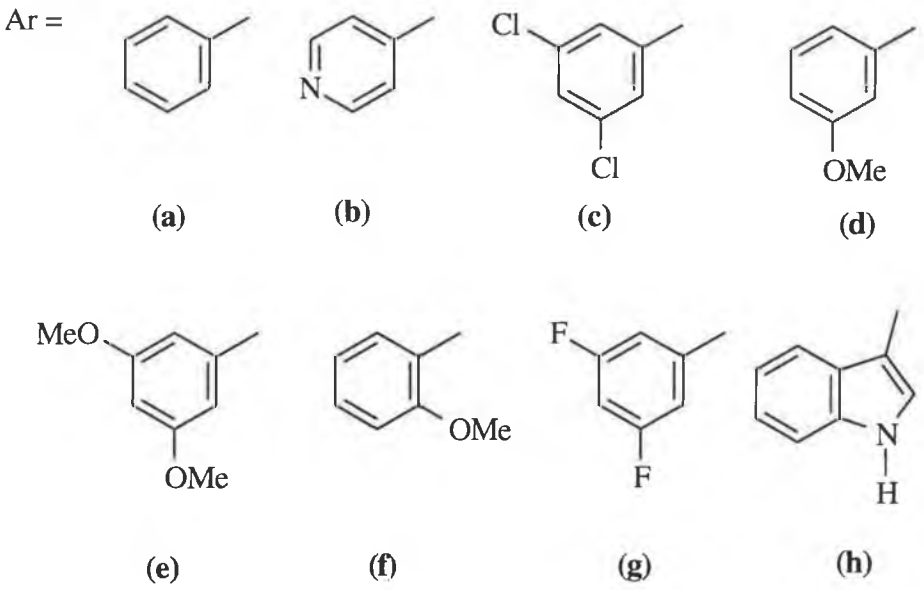
Of the alcohols, methanol and ethanol are the most used and in general give satisfactory yields of imidate hydrochlorides in the Pinner synthesis, but propyl,[191] isopropyl,[192] butyl,[191] isobutyl,[193] *sec*-butyl,[194] and benzyl alcohols,[195] among the simpler members have all been used.

2.3.2. *Preparation of Imidate salts (123 a-h) using the Pinner synthesis.*

The following imidate salts were required as intermediates in the synthesis of the desired imidazolines.



(123)



(a) **(b)** **(c)** **(d)**

(e) **(f)** **(g)** **(h)**

Figure [2.1]

In general the imidate hydrochlorides outlined were synthesised by passing a stream of HCl gas through a solution of the nitrile in anhydrous methanol at 0-5 °C and the reaction mixtures were then stored under refrigeration at 0 °C for 24 hours. The progress of the reactions were monitored by taking samples of the reaction mixture and evaporating them to dryness *in vacuo*. IR spectroscopy was then performed on the

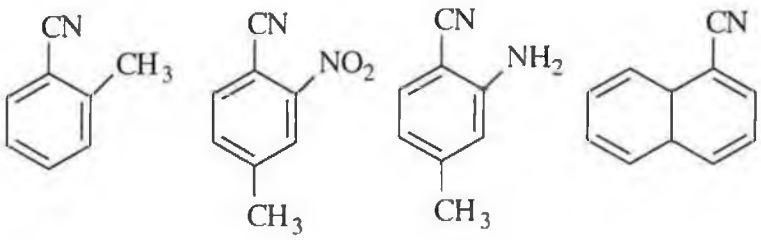
samples to monitor them for the disappearance of the nitrile stretching band at c. 2231 cm^{-1} and the development of the C=N stretching band of the imidate at c.1651-1680 cm^{-1}. The reaction could also be followed by thin layer chromatography. The imidate hydrochlorides were then isolated by precipitation from the methanol solution with anhydrous diethyl ether, followed by filtration and washing with several aliquots of anhydrous ether. Due to the sensitive nature of imidate hydrochlorides to moisture they were stored *in vacuo* over solid sodium hydroxide, which removes any excess hydrogen chloride and also maintains anhydrous conditions.

Depending however on the nature of the starting nitrile, variations in the reaction conditions had to be made in order to effect formation of some of the imidates. It was found for example that with 1*H*-indole-3-carbonitrile, the reaction had to be carried out at a higher temperature than usual to give conversion. At 20 °C complete conversion to the imidate salt was observed. Despite the high temperature employed in the reaction, none of the competing orthoester formation was observed. In other instances the reaction success was found to be very sensitive to the concentration of the nitrile in the methanol. The 3-methoxyphenyl imidate (**123d**) failed to form in solutions of 0.6 molar concentration, and could only be achieved when the concentration was increased to 1.9 molar. A similar problem was encountered with 3,5-dimethoxybenzonitrile where, because of the low solubility of the nitrile, high dilutions of the starting material in methanol had to be employed. The problem was overcome in this case by carrying out the imidate formation in a 50:50 mixture of methanol and diethylether in which the starting material was much more soluble and hence higher concentrations of nitrile could be used.

The extreme sensitivity of some of the imidate hydrochloride products also required the employment of a variation in the general work-up procedure. On working up the imidate of 3,5-dichlorobenzene in the usual manner by precipitation with diethyl ether and

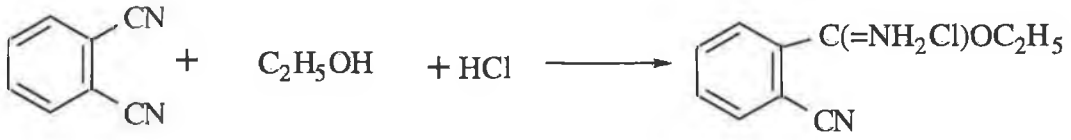
filtration, a second product was observed to form as monitored by TLC. From IR spectroscopy a strong band at 1731 cm^{-1} was observed as well as the band corresponding to the imidate C=N at 1651 cm^{-1} . The band at 1731 cm^{-1} was tentatively assigned to the carbonyl stretching frequency of an ester presumably formed during work up of the reaction mixture by hydrolysis of the imidate with atmospheric moisture. The same band could be seen when a sample of the pure imidate (showing only one band at 1651 cm^{-1} on IR) was stirred in methanol spiked with a few drops of water thus reinforcing the idea that the side product formed on work-up was the ester derivative. The most successful method of working up the reaction was by evaporating the reaction mixture under vacuum leaving a white solid product which was then used directly for the next reaction without further purification. The only contaminant in the product was traces of the starting nitrile which caused no interference in the next stage of the reaction sequence and could easily be recovered by acid extraction of the product.

A similar work up procedure had to be applied in the case of the ortho methoxyphenyl imidate hydrochloride **(123f)**. The formation of this imidate was found to be extremely slow and showed only about 25 % conversion from the nitrile after 72 hours at 0-5 °C plus 24 hours at room temperature. The addition of diethyl ether to the reaction mixture failed to precipitate any product. On evaporating the reaction mixture to dryness and using it directly in the subsequent reaction again no interference was caused by the ortho methoxybenzonitrile which could be recovered in almost quantitative yield. This difficulty in synthesising benzimidates containing ortho substituents has been observed by several authors. The proximity effect was first observed by Pinner[196] who was unable to obtain imidates in the normal way from *o*-substituted benzonitriles **(130)**, **(131)**, **(132)**, and from α-cyanonaphthalene **(134)** although the other positional isomers readily yielded imidates.[197]



(130) **(131)** **(132)** **(133)**

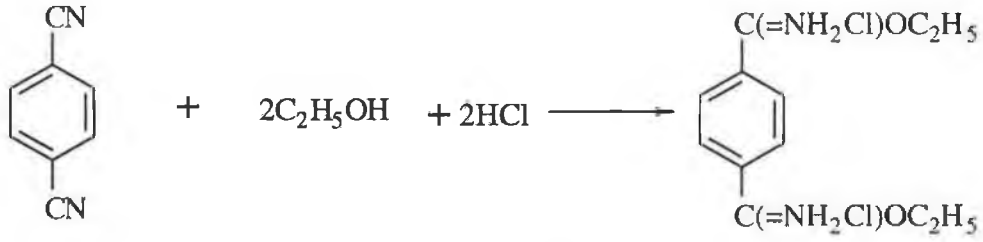
Extending his investigations, Pinner[196] discovered that phthalonitrile **(134)** gave rise to a mono imidate salt only Scheme [2.6].



(134)

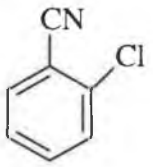
Scheme [2.6]

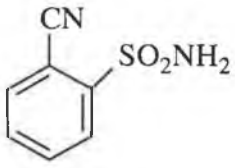
whereas the iso- and terephthalonitriles furnished diimidate salts (Scheme 2.7).



Scheme [2.7]

Other examples of this proximity effect were discovered by Lander and Jewson,[198] who failed to convert *o*-chlorobenzonitrile into an imidate, and by Guy and Paris,[199] who were similarly unsuccessful in the case of *o*-cyanobenzenesulfonamide.





Moreover, steric inhibition of imidate formation of a similar character has been noted with 3-chloro- and 3-bromo-1,1-diphenylpropyl cyanides **(135)** (X = Cl or Br) which failed to give imidates *via* the Pinner method within forty-four days.[200]

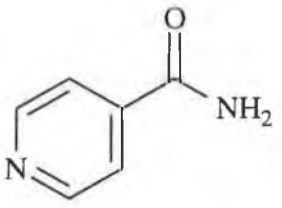
$$XCH_2CH_2C(C_6H_5)_2CN$$

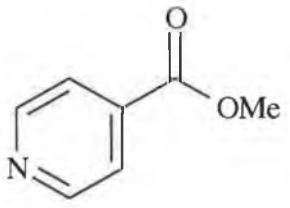
(135)

The extent of the limitations of this proximity effect has never been fully studied, but it is of interest to note that *o*-ethoxybenzonitrile[201] and α-naphthylacetonitrile[202] form imidates using the Pinner synthesis.

It was with the synthesis of the pyridine imidate hydrochloride **(123b)** that a lot of difficulty was encountered. At first sight it seemed as if this compound presented no difficulties in its preparation using the standard procedure. The 4-pyridine nitrile was dissolved in methanol and HCl gas was passed through the solution at 0-5 °C. After refrigeration for 20 hours a white crystalline solid was precipitated on addition of diethyl ether. TLC indicated one clean spot with an R_f value distinct from that of the starting material. From infrared spectroscopy no nitrile stretching band could be seen and a strong absorbtion at 1668 cm^{-1} seemed to indicate the required product. When attempts to condense this product with tropinone diamine in the subsequent reaction failed, the identity of the "imidate" was called into question. Closer examination of the IR spectrum revealed the presence of two bands at 3340 cm^{-1} and 3151 cm^{-1} possibly the stretching frequencies of the NH_2 group of a primary amide. The suspicion of the

presence of an amide was substantiated by the evidence provided from mass spectroscopy. A strong mass ion of 122 corresponded to the amide (**136**).





(136) **(137)**

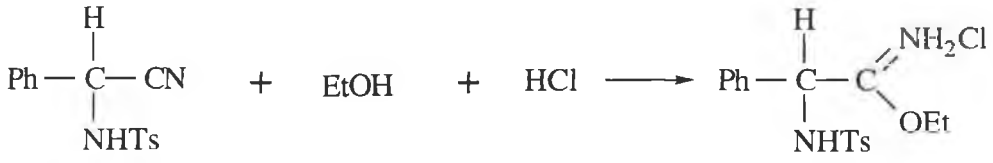
In some of the cases where the reaction was left for longer periods of time, of up to four days, the amide was accompanied by the presence of a high ester content, (**137**) presumably formed from methanolysis of the amide in the acid medium. As with 4-cyanopyridine, when attempts were made to convert 3-cyanopyridine or 3-cyanoquinoline to their respective imidate hydrochlorides only amides and esters of these compounds could be isolated.

An explanation for the failure of these reactions is as follows. It has previously been reported that imidate hydrochlorides of some compounds containing strongly electronegative substituents have been observed to decompose spontaneously to the corresponding amide. Steinkopf and Malinowski[203] found that acetonitriles substituted with either two or more chlorine atoms or with a nitro group tended to give amides under the Pinner synthesis (Scheme 2.8).

$$CCl_3CN + EtOH + HCl \longrightarrow CCl_3CONH_2 + EtCl$$

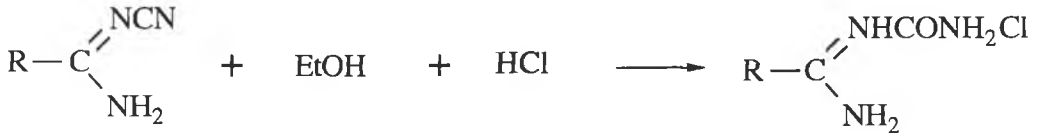
Scheme [2.8]

When protonated, α-aminonitriles act as an electron sink and spontaneous decomposition of the imidate salt takes place giving α-aminoamides[204] often in excellent yield and in a high state of purity. However, as outlined in scheme [2.9] tosylation or acylation of the amino function permits the formation of stable imidate salts.[205]



Scheme [2.9]

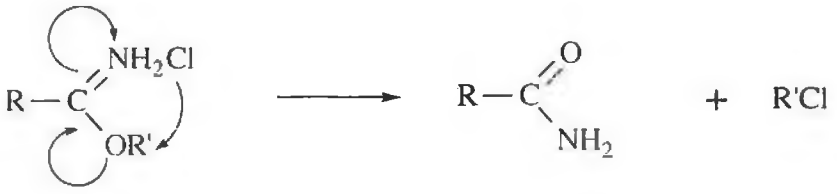
Neilson and Watson[206] noted that although mandelimidate salts derived from primary alcohols are stable, decomposition to mandelamide takes place readily when secondary alcohols are employed. Similarly, attempts to convert *N*-cyanoamidines into imidates gave only the *N*-carboxamidoamidines **(138)**.[207]



(138)

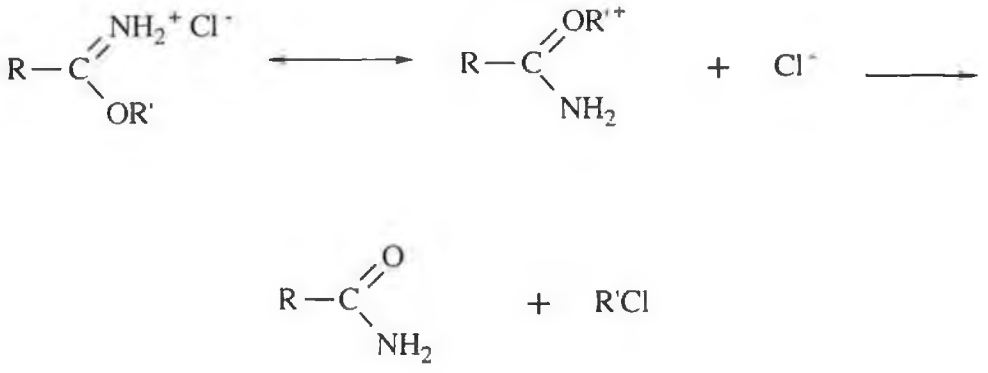
Scheme [2.10]

The decomposition of several imidate hydrochlorides to amides in chloroform and *tert*-butyl alcohol solutions at 60 °C was studied by McElvain and Tate.[208] These decompositions follow first order kinetics with respect to the disappearance of the halide ion, giving straight line plots of log [Cl^-] *vs.* time. Thus, either an intramolecular attack by the halogen (Scheme 2.11),



Scheme [2.11]

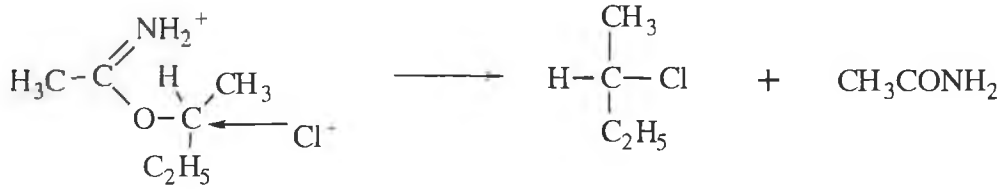
or a bimolecular process (Scheme 2.12) (wherein the ionisation of the imidate salt is considered to be slight) are feasible reaction mechanisms.



Scheme [2.12]

Support for the S_N2 mechanism (Scheme 2.12) was established when it was found that the rates of decomposition of alkyl acetimidate salts were of the same order as for other recognised S_N2 reactions.[208]

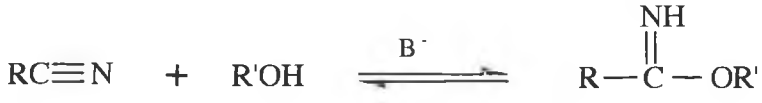
Subsequently, Stevens, Morrow and Lawson[194] obtained *sec*-butyl chloride of high optical purity but with inverted configuration from the thermal decomposition of optically active *sec*-butyl acetimidate hydrochloride, thereby confirming the S_N2 mechanism (Scheme 2.13).



Scheme [2.13]

In an attempt to overcome the inherent instability of the pyridine imidate hydrochlorides several alternative synthetic approaches were adopted.

Schaefer and Peters[209] reported that the free bases of certain imidates containing electronegative substituents, which are more stable than their hydrochloride salt counterparts, could be readily prepared by the base catalysed reaction of nitriles with alcohols (Scheme 2.14). They pointed out that those nitriles which were unsuited for the base-catalysed reaction usually gave excellent results in the Pinner synthesis and conversely, the nitriles which were most reactive in the base catalysed process often gave unstable imidate hydrochlorides. Thus the two processes complement each other very agreeably.



Scheme [2.14]

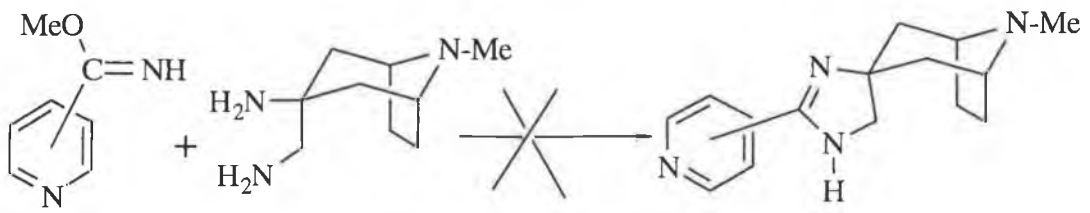
The method described is simple and usually high yielding. A solution of the nitrile and sodium methoxide in methanol (not necessarily anhydrous), is left to stand overnight at room temperature and the product is isolated by distillation.

Using this method the imidate free bases of the three isomers of cyano pyridine were prepared by stirring the respective nitriles in NaOMe/MeOH at room temperature for 24 hours. The absence of the nitrile spot on TLC (plus the appearance of a new spot ;

Silica/Hexane/EtOH) and the non-appearance of the stetching band at 2242 cm^{-1} indicated complete conversion of the pyridine nitrile. A new band at 1651 cm^{-1} plus the lack of any NH_2 stretching bands at 3000-3500 cm^{-1} strongly indicated that the compound present was the imidate base. NMR analysis confirmed the presence of the OMe protons as a singlet appearing at δ = 3.98 ppm. Mass spectroscopy showed a mass ion of 136 corresponding to the imidate and the absence of any peak at 122 for the amide product (The above data refers to the 2-cyano isomer).

It should be noted that on evaporating the methanol under vacuum during work up, reversal of the imidate to the starting nitrile occurred to the extent of about 70 %. The phenomenon was not observed when the imidate was refluxed in methanol and thus the reversal is not due to thermal decomposition of the imidate to the nitrile. The reversal of the reaction is a result of removing the methanol from the equilibrium, thus favouring the displacement of the reaction towards the left (Scheme 2.14) according to the Le Chatelier principle. On re-dissolving the "reversed" sample in methanol complete rereversal to the imidate occured on standing overnight. The problem of reaction reversal was avoided by adding acetic acid to the reaction mixture on work up. Thus, employing this synthesis pyridine imidate bases were obtained which were relatively stable, showing only slight decomposition to ester on standing for three weeks. When methanol HCl was added to the imidate bases immediate decomposition to the expected amides was observed thus confirming the compounds as being the required imidates.

Efforts to condense any of the isomers of pyridine imidate free bases with tropinone diamine **(122)** to form the imidazolines **(139)** were relatively unsuccessful (scheme 2.15). The only imidate to show any sign of an "imidazoline" product was 2-pyridyl imidate free base which after one week at room temperature plus 48 hours at reflux in the presence of the diamine in methanol showed only traces of a new product according to TLC.

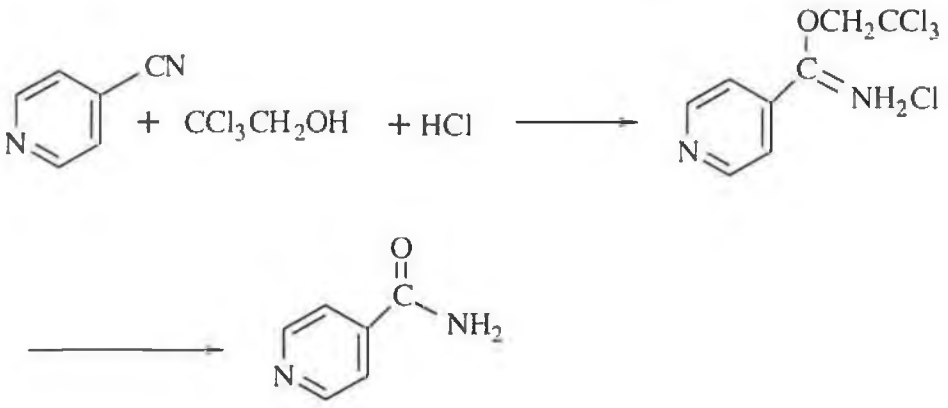


(122) **(139)**

Scheme [2.15]

It was thus concluded that the pyridine imidate free bases, though stable to decomposition were too unreactive to react with the tropinone diamine. It would seem that the protonation of the C=NH of the imidate confers increased reactivity on this functional group making it a more effective electrophile. With these results in hand an alternative approach was taken.

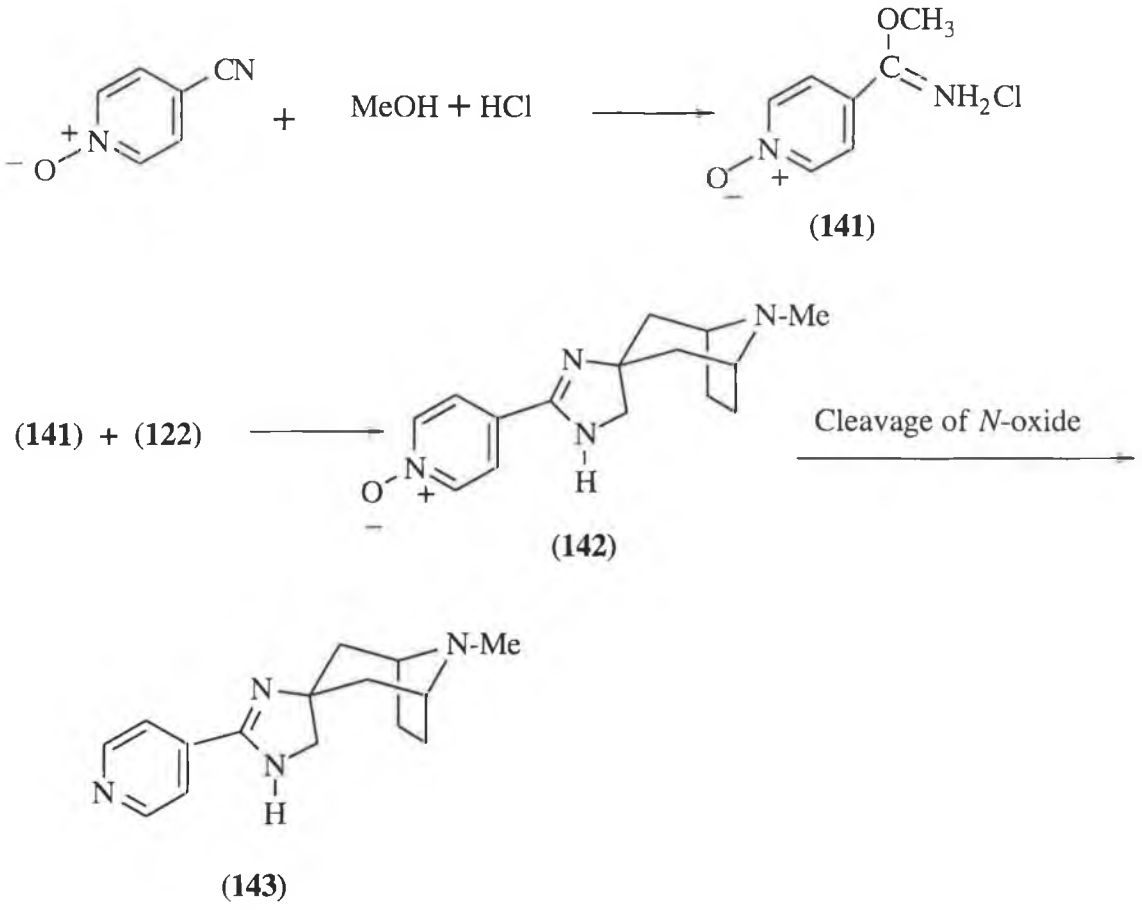
It has been demonstrated that in the case of some nitriles with powerful electron-withdrawing groups, the imidate salts of which decomposed with simple alcohols, that stable imidate hydrochlorides can be formed using 2,2,2-trichloroethanol[210] and some 2-nitroalkanols in place of simple alcohols. Accordingly the Pinner synthesis was carried out by dissolving 500 mgs of 4-cyanopyridine in Cl_3CCH_2OH (10 mL) through which was passed HCl gas at 0 °C. The reaction was maintained at 0-5 °C for 24 hours as normal and the product was precipitated with dry diethylether. Infrared spectroscopy on the product revealed it to be isonicotinamide (**136**).



(136)

Scheme [2.16]

With the failure of 2,2,2-trichloroethanol to stabilise the imidate hydrochloride an alternative strategy was proposed. If the reason for the instability of the pyridine imidate salts was the electron deficient pyridine ring system then increasing the electron density of the ring by forming the *N*-oxide derivative **(141)** should give a more stable imidate salt. Condensation of the pyridine *N*-oxide imidate salt with the tropinone diamine in the subsequent reaction would give **(142)** which should be easily cleaved to give the desired pyridine imidazoline **(143)** (Scheme 2.17).



Scheme [2.17]

With this strategy in mind, the Pinner reaction was performed on 4-cyanopyridine-*N*-oxide. The starting material however was quite insoluble in methanol but when HCl gas was bubbled into the suspension of alcohol and nitrile, a clear solution formed as the reaction progressed. After 24 hours at 0 °C a white solid was precipitated with diethylether. The product was pure on TLC and had a lower R_f value than the starting nitrile (Silica/EtOH). From IR spectroscopy the product had a band at 1652 cm^{-1} possibly corresponding to the C=N stretching frequency, and no bands could be seen in the 3100-3400 cm^{-1} region for the NH_2 of an amide. The mass spectrum of the product gave a mass ion of 152 which represents the molecular weight of the correct product. In the subsequent condensation reaction with the diamine the pyridine *N*-oxide imidate salt reacted smoothly to give the required imidazoline product (See section 2.5). It should be

pointed out that although this imidate salt is fairly stable it does gradually decompose in the solid state to the amide with about 50 % conversion taking place after three months at room temperature.

The attempted synthesis of the imidate salt from 3,5-difluorobenzonitrile proved unsuccessful using all of the variations developed for the other imidates of the series.

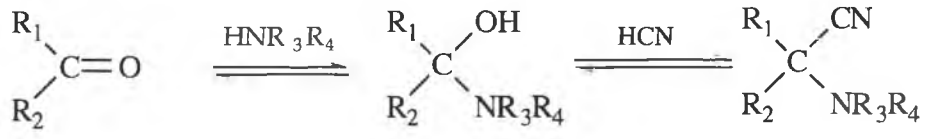
2.4 Synthesis of α-aminonitriles

2.4.1 *Introduction.*

Several reviews on the syntheses of α-aminonitriles have been published, the most recent of which are as follows. In 1962 a review was published in Danish but is however difficult to access as a literature source.[211] The use of α-aminonitriles in organic synthesis is the topic of another review which appeared in a Japanese journal which unfortunately also has a limited availibility.[212] The most recent and accessible review of α-aminonitriles appeared in Russian in 1989,[213] the English translation of which appeared in the same year.[214]

By far the most widely studied and used method of α-aminonitrile synthesis is that known as the Strecker synthesis.

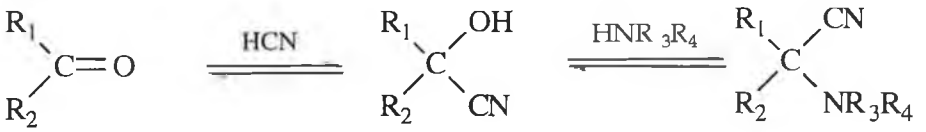
In 1850 Strecker[215] carried out the synthesis of glycine and alanine by treatment of formaldehyde and acetaldehyde with aqueous solutions of ammonia and hydrocyanic acid followed by hydrolysis of the α-aminoacetonitrile formed. This reaction was subsequently extended to ketones and amines and became known as the Strecker reaction (Scheme 2.18).



Scheme [2.18]

The replacement of volatile hydrocyanic acid and ammonia by a mixture of potassium or sodium cyanide and ammonium salts was proposed by Zelinskii and Stadnikov.[216] In this case ammonium chlorides or sulphates are reacted directly or are prepared *in situ*.

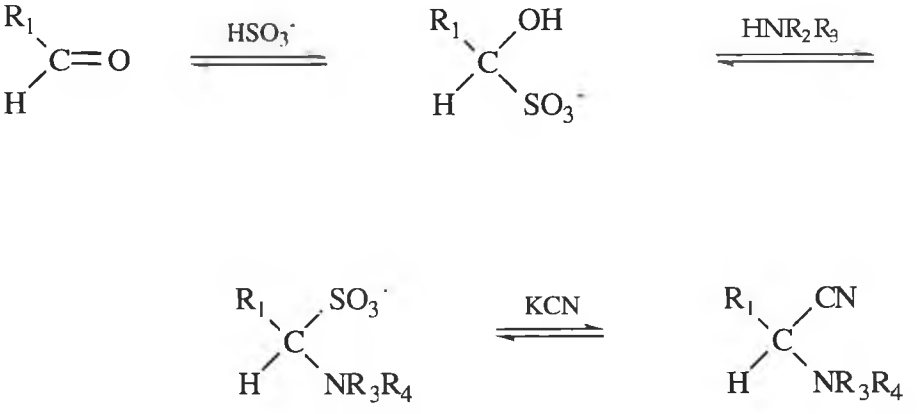
A modification of the Strecker synthesis proposed by Tiemann[216] involves changing the order of mixing the reagents as outlined in scheme [2.19]. It is suggested that the increase in yields of α-aminonitriles that often occurs in this case is due to participation of α-hydroxynitriles (cyanohydrins) **(144)** in the reaction.



(144)

Scheme [2.19]

When aldehydes have low reactivity, their bisulphite adducts are subjected to the Strecker reaction. For primary and secondary α-aminonitriles, the reaction is carried out in water with ammonium or alkylammonium salts in the presence of excess free base. This form of the Strecker reaction has become known as the Knoevenagel-Bucherer method[217]Scheme [2.20].

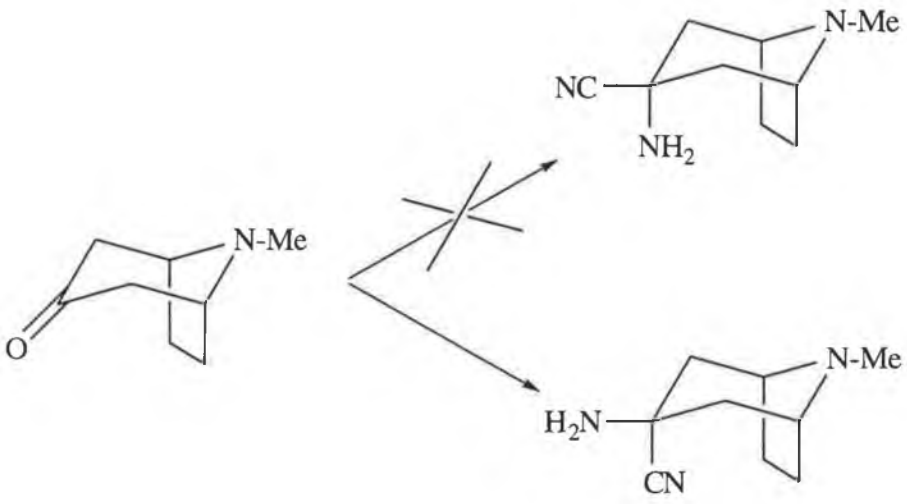


Scheme [2.20]

A number of synthesis of α-aminonitriles have been carried out under non-aqueous conditions; in alcohols, THF, benzene, in excess amine, and also without any solvent. The most significant development of the Strecker synthesis has been the introduction of new sources of cyano groups into synthetic use. Acetone cyanohydrin, isobutyrl cyanohydrin, benzoyl cyanide, diethylphosphonocyanide, and trimethylsilylcyanide (TMSCN) have been used for this.[214]

2.4.2 *Synthesis of 3β-Amino-8-methyl-azabicyclo[3.2.1]octane-3α-carbonitrile (124)*

The desired aminonitrile isomer (**124**) was synthesised using a variation of the Strecker synthesis described by Fernandez *et al.*[218] According to the method described a mixture of KCN, NH_4Cl, and *N*-methylnortropane, in equivalent molar proportions, is stirred at room temperature for 48 hours in an aqueous solution. After this period a white inorganic solid precipitates from the reaction which is then filtered off. The aqueous filtrate is then cooled to -5 °C until crystallisation of the aminonitrile takes place.



(124)

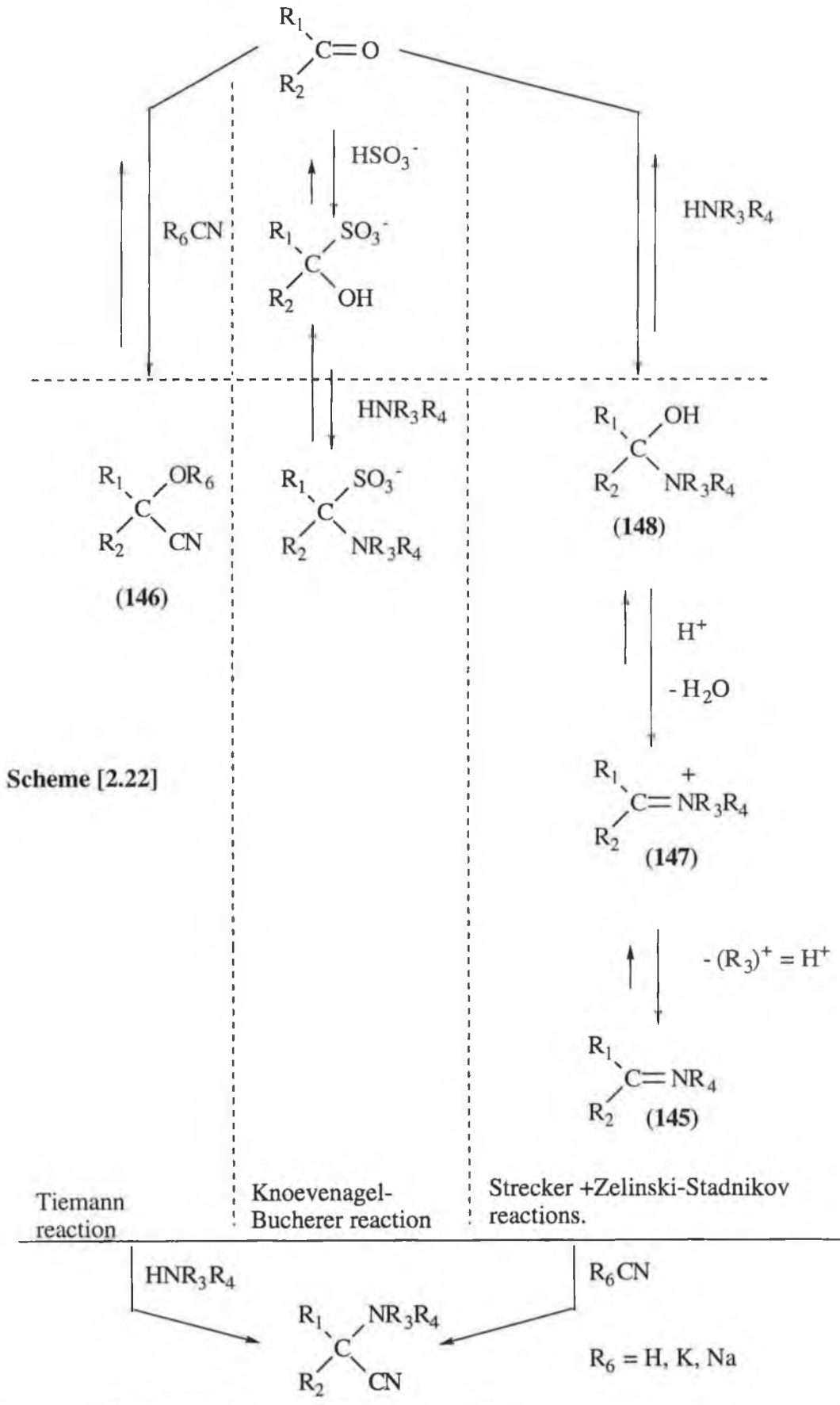
Scheme [2.21]

Our initial attempts to form the aminonitrile using the above method resulted in extremely low yields (less than 10 %). It was found that the product co-crystallised out of the reaction mixture with the inorganic materials and consequently very little product was obtained from the aqueous filtrate. The use of larger amounts of H_2O in the reaction mixture, though successful in preventing precipitation of the product from the reaction medium, also resulted in very low yields due to the difficulty in precipitating the product.

A more successful and consistent procedure was developed whereby on completion of the reaction, the products were deliberately caused to precipitate from the reaction medium by cooling and were then purified by selective extraction into ethyl acetate. The full procedure is as follows: The reagents were mixed in equimolar proportions and stirred in an aqueous solution. It was found to be beneficial to leave the reaction mixture stirring for a period of 90 hours to improve the degree of conversion. Towards the end of the reaction the addition of CH_2Cl_2 helped to mobilise the reaction and improve stirring. The reaction was worked up by cooling to 0-10 °C for 1 hour which caused the solid products in the reaction to precipitate. The white solids were then filtered off and refluxed with ethyl acetate. This served to dissolve the aminonitrile product while leaving an insoluble inorganic solid out of solution, which was removed by filtration. The product was then isolated by precipitation from the ethyl acetate with petroleum ether.

The mechanism of the formation of α-aminonitriles by the Strecker method has been widely investigated but the results obtained have been ambiguous. We can propose that the synthesis of α-aminonitriles may involve the formation of a cyanohydrin followed by substitution by an amino group (S_N2 mechanism) or else by initial formation of the imine which then undergoes attack by the cyanide ion.

A scheme for the extended Strecker reaction is shown below outlining the possible routes of formation. Scheme [2.22]


R1 C=O R2
HSO3-
R6CN
R1 SO3- C OH R2
HNR3R4
HNR3R4
R1 OR6 C CN R2
(146)
R1 SO3- C NR3R4 R2
R1 OH C NR3R4 R2
(148)
H+
- H2O
R1 + C=NR3R4 R2
(147)
- (R3)+ = H+
R1 C=NR4 R2
(145)
Tiemann reaction
Knoevenagel-Bucherer reaction
Strecker +Zelinski-Stadnikov reactions.
HNR3R4
R6CN
R1 NR3R4 C CN R2
R6 = H, K, Na

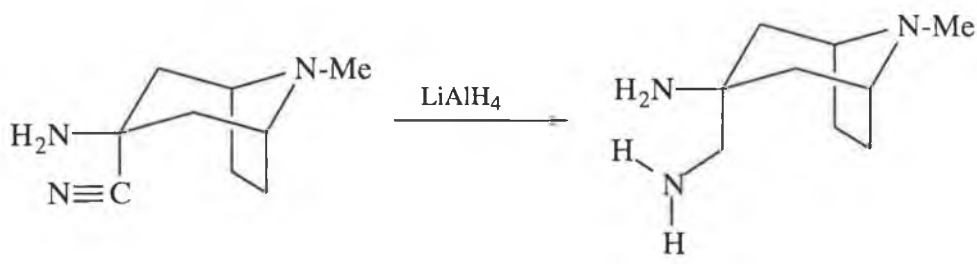
Scheme [2.22]

Ogata and Kawasaki[219] carried out a study in 1971 on the kinetics of the reaction and concluded that the most likely intermediate was an imine type compound **(145)** rather than a cyanohydrin **(146)**. Other authors[220-221] endorsed this opinion of the intervention of an imine in the Strecker reaction. However, several other investigators claimed the cyanohydrin to be the most likely intermediate. Studies by Stewart[222] favoured the formation of the cyanohydrin, while Mowry[223] considered that imines and their corresponding ions would have no possibility of forming in aqueous solution from the three reagents employed. In another major study[224] α-aminonitriles obtained by the Strecker and Tiemann reactions had the same optical purity. On the basis of this experiment the author rejected a mechanism involving stereocontrol of the reaction, due to steric hindrance in attack on cyanohydrins **(146),** and considered the stereoselective addition of HCN to geometric isomers of Schiff bases of the type **(145)** more likely. In another study[225] it was concluded that cyanide ions most probably add to ketiminium cations of the type **(147)**, the presence of which in the reaction mixture was reliably detected. Moreover, the authors did not rule out the possibility of α-aminonitriles being formed by S_N2 attack of CN^- on aminoalcohols such as **(148)**.

In the synthesis of 3β-amino-8-methyl-azabicyclo[3.2.1]octane-3α-carbonitrile **(124)** a ketimine type intermediate is proposed.[226] It is interesting to note however that in one reaction where the reaction was worked up after 18 h reaction time, we obtained 40% of a product which was identified as the cyanohydrin. This may indicate that this compound is the precursor to the aminonitrile but is not conclusive. The reversal of the cyanohydrin to the ketone under aqueous conditions and subsequent ketimine formation can not be ruled out as a possibility. In conclusion it seems that the mechanism of the aminonitrile formation is not definitive. Shafran and Bakulev[214] state that by and large the mechanism of the Strecker reaction is not universal and depends on the nature of the solvent and the reagents and also the order in which they are mixed.

2.5 Synthesis of 3α-Aminomethyl-8-methyl-8-azabicyclo[3.2.1]octyl-3β-amine (122).

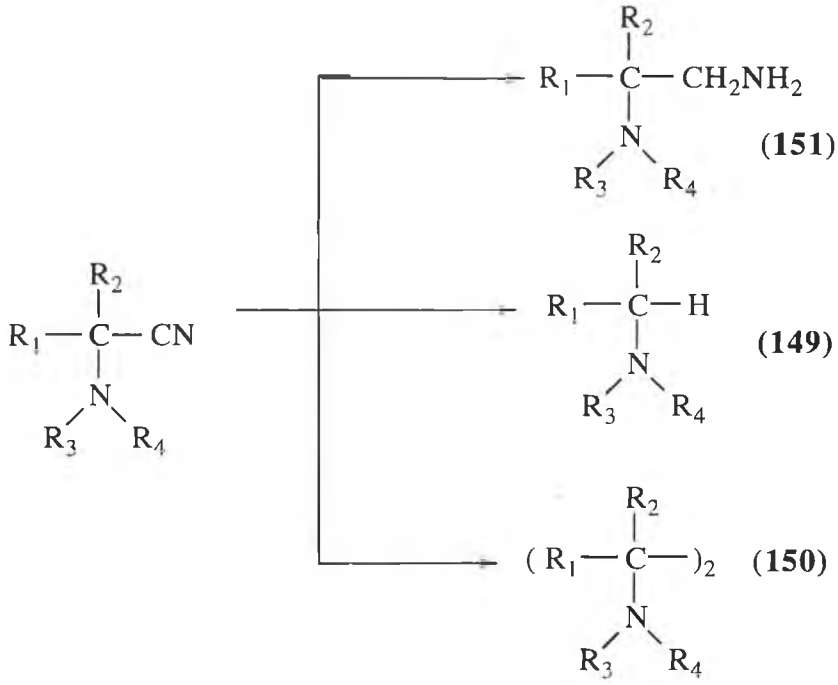
The diamine (**122**) was obtained by reduction of the aminonitrile (**124**) according to the scheme given below.



(124) **(122)**

Scheme [2.23]

The cyano group in α-aminonitriles has been reduced using various reducing agents. Thus for example, α-aminonitriles were reduced with sodium in a water-ether emulsion and boiling toluene,[227-228] with hydrogen on Raney nickel, platinum, and palladium.[229] However, major by-products formed when using these reagents are the decyanated and dimeric products (**149**) and (**150**) shown in scheme [2.24].



Scheme [2.24]

At the same time there have been reports of the reduction of α-aminonitriles with Raney nickel,[229] platinum, and palladium,[229] lithium aluminium hydride,[230] and also diborane and diisopropylbutylaluminium[231] giving exclusively "normal" ethylenediamine products (**151**).

The choice of reagent for the reduction of the aminonitrile (**124**) was lithium aluminium hydride. It is a reagent which is cheap and relatively easy to handle, taking the appropriate precautions in manipulation and in storing. Different solvents were explored as reaction media, the choice solvent being diethyl ether. THF was also found to be an effective solvent, considerably reducing the reaction time as compared to diethyl ether. However a purer product was obtained when using ether. The reduction procedure involved adding the solid aminonitrile in portions to a suspension of $LiAlH_4$ in anhydrous ether at 0-10 °C then heating at reflux for a further 48 hours. The reaction was worked up by quenching with H_2O, NaOH followed by more H_2O then filtering off the aluminium salts and working up the filtrate. In the initial experiments very low

yields of the diamine were obtained, some of which were as low as 20 %. It was found that in order to obtain good yields of the diamine, simply washing the aluminium salts with large quantities of ether was insufficient. It was detected that up to 70 % of the product could be retained on the aluminium salts and the only effective method of liberating the product from these was by extraction of the diamine with a Soxhlet apparatus. Thus after filtration of the quenched reaction mixture, the aluminium salts were placed in a Soxhlet finger and extracted with refluxing ether for 5 hours. The extract and the reaction filtrate were then combined and worked up and the product was purified by high vacuum distillation.

The product obtained from distillation showed only one spot on TLC, and IR spectroscopy indicated no nitrile stretching peak. The melting point of the distilled product however was not sharp and melted over a range of 28 °C (55-83 °C) implying that the product was possibly impure. On analysing the compound by high resolution ^{1}H NMR there seemed to be two compounds present in the product (Figure 2.2). Two singlets at δ = 2.30 and 2.67 ppm were tentatively assigned to the N-CH_3 and the CH_2NH_2 respectively. Two more singlets with the same relative proportions were present at δ = 2.35 and 2.97 ppm. The broad singlet at δ = 3.15 corresponding to H 1(5) and integrating for two protons had an intergal equal to the sum of the integrations for the two peaks at δ = 2.97 and 2.67 and likewise the two peaks at δ = 2.30 and 2.35 gave a total integral of 3 protons compared to the broad singlet at δ = 3.15. This implied that the broad singlet possibly contained the H 1(5) protons of a mixture of compounds.

On the basis of the above data we postulated that there might have been two isomers of the diamine present, namely the required 3α-aminomethyl-8-methyl-8-azabicyclo-[3.2.1]octyl-3β-amine and 3β-aminomethyl-8-methyl-8-azabicyclo[3.2.1]-octyl-3α-amine. The origin of these two isomers we speculated could have arose from an isomeric starting aminonitrile, or else as a result of epimerisation of the aminonitrile

under the basic reaction conditions, thus giving a mixture of diamine isomers on subsequent reduction.

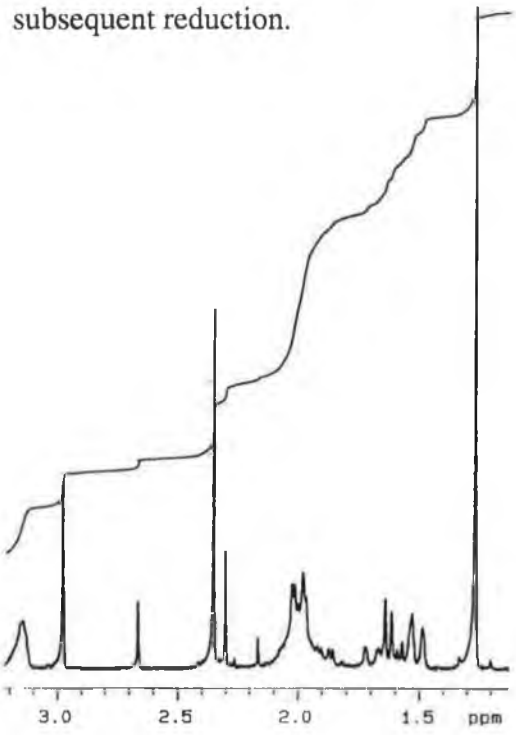


Figure 2.2 ^{1}H NMR of the mixture isolated from the $LiAlH_4$ reduction of **(124)**.

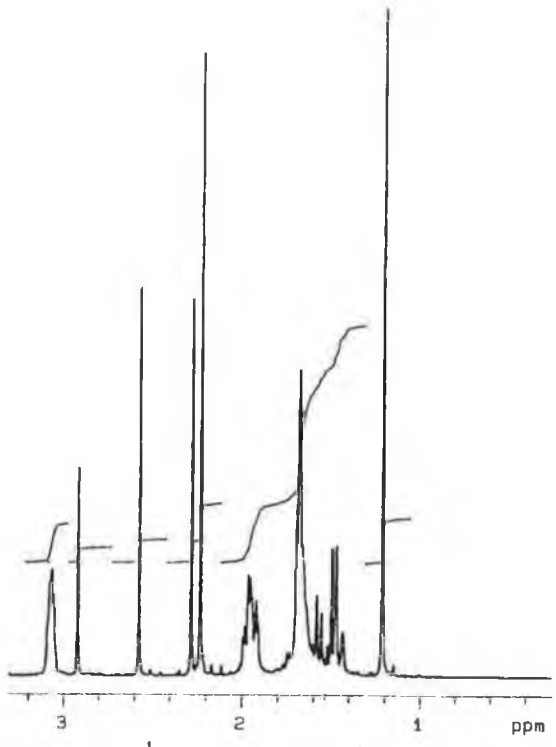


Figure 2.3 ^{1}H NMR of the mixture in fig. 2.2 after two days refluxing in MeOH

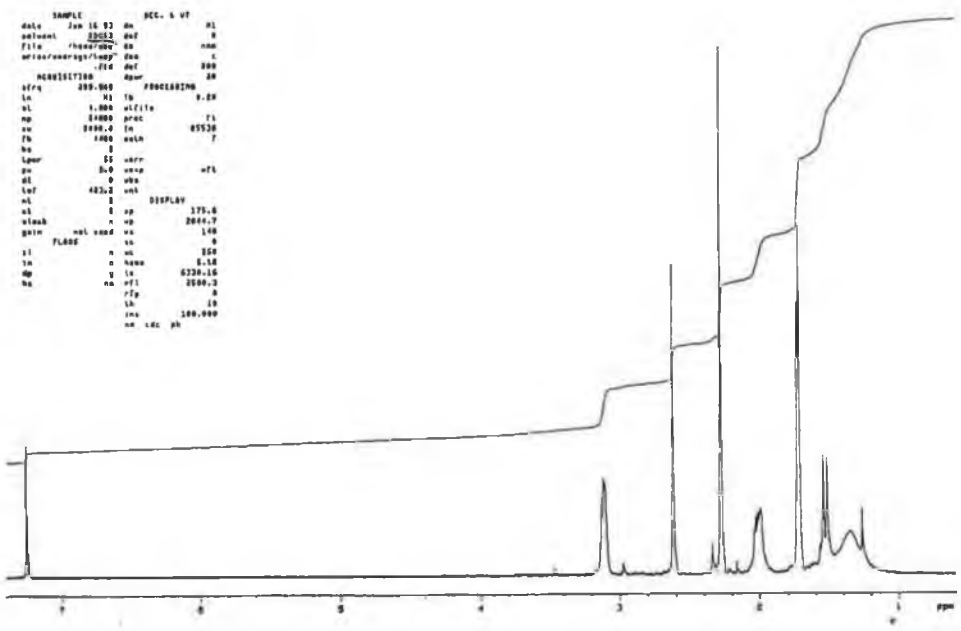
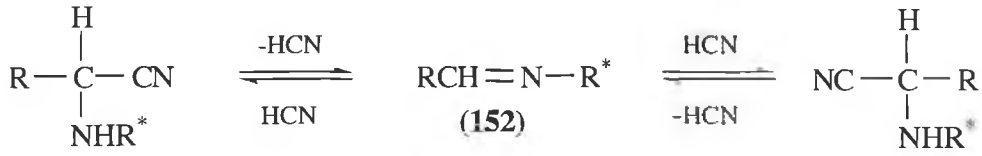


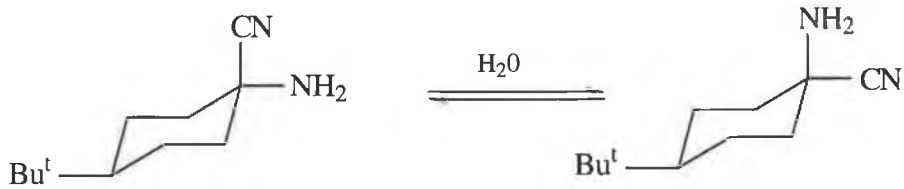
Figure 2.4 ^{1}H NMR of the mixture in Fig. 2.2 after 2 hours refluxing in MeOH containing a catalytic amount of aq. HCl (free diamine **122**)

We found an example of such epimerisation in the published literature in the synthesis of chiral aminonitriles.[224] The authors found that optical purities of 100 % could be achieved in the addition reaction of HCN to preformed imines (**152**). A thermodynamic equilibrium was suggested as outlined in scheme [2.25]. Preferential crystallisation of one of the diastereoisomers shifts the equilibrium, resulting in high optical yields.



Scheme [2.25]

Geneste *et al.*[225] also observed the epimerisation of α-aminonitriles in the presence of one equivalent of H_2O. Scheme [2.26]

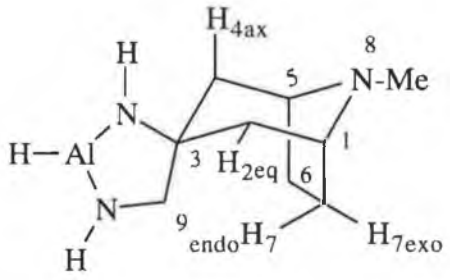


Scheme [2.26]

The epimeric starting material was ruled out after a thorough reinvestigation of the amino nitrile showed it to contain only one isomer. The epimerisation of the aminonitrile was later disfavoured as a possibility when subsequent analysis of the product mixture of the reduction by mass spectroscopy using electron impact ionisation, displayed a peak at 195 mass units along with abundant peaks at 194 and 82 mass units. No peak was observed at 169 mass units corresponding to the tropinone diamine (**122**) (the pure diamine was later found to be unstable under electron impact conditions and no

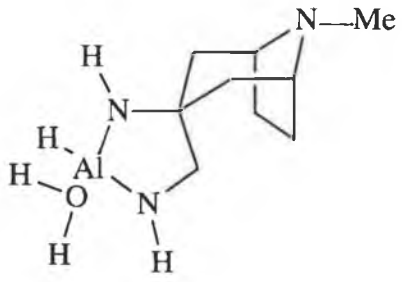
molecular ion is observed. It is however stable under chemical ionisation and the mass ion shows up as the base peak).

Based on the mass spectroscopy data the following structure **(153)** was tentatively proposed which has a molecular weight of 195. The intense peak at 194 could result from loss of the aluminium proton.



(153)

From the ^1H NMR spectrum (Figure 2.2) a sharp peak at $\delta = 1.27$ ppm integrated for a total of four protons. Taking this into consideration a more probable structure **(154)** given below was postulated.



(154)

In this structure a molecule of water is coordinated to the aluminium atom, the two protons of which could give a chemical displacement similar to the two nitrogen protons thus accounting for the integration of four protons. This structure containing the aluminium covalently bonded to nitrogen is more probable than a coordinated complex

which, like boron complexes of nitrogen compounds would show up as the free base under mass spectroscopy.[231]

It was observed that a sample of the proposed diamine complex which was left in a solution of methanol over a period of 2 weeks, yielded a white solid (when the methanol had evaporated off) which was more crystalline in nature than the original sample. The solid had a melting point which ranged from 155 °C, when the sample initially began to melt, to 190 °C when complete melting was observed. This compared to a melting point of 55-83 °C for the original sample isolated from the distillation of the reaction mixture. It was suggested that the proposed aluminium complex of the diamine had been decomplexed by the methanol leaving the free diamine and an aluminium methoxide.

In an attempt to benefit from this observation, we refluxed the product obtained from the distillation, in methanol for 2 days in an attempt to liberate the diamine from the supposed aluminium complex. A product was obtained which by ^{1}H NMR had a profile as seen in Figure 2.3. It was found that the signals tentatively assigned to the NCH_3 protons (as with the H9 methylene protons) had changed from a ratio of 3:1 (Complex : free diamine) in the distilled sample to a ratio of 1:1.5 in the sample refluxed in methanol. Complete liberation of the diamine from its complex could be achieved within three to five hours by adding a drop of dilute HCl to the methanolic solution of the complex.

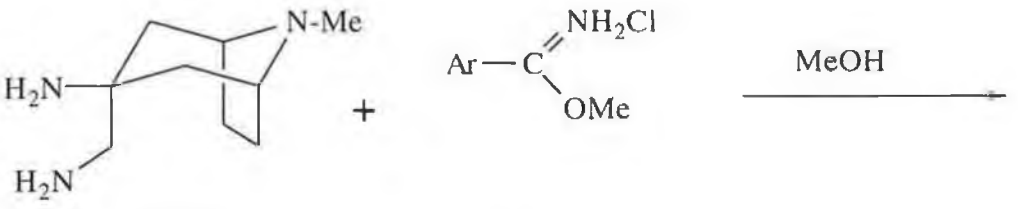
Thus on filtering the methanolic solution and evaporating the solvent a compound was obtained which indicated a single compound by ^{1}H NMR analysis and corresponded to the required diamine (Figure 2.4). Examination by mass spectroscopy using the chemical ionisation technique gave an abundant peak for 170 corresponding to the M^++1

signal for the free base of the diamine while no peak for the complexed compound could be observed.

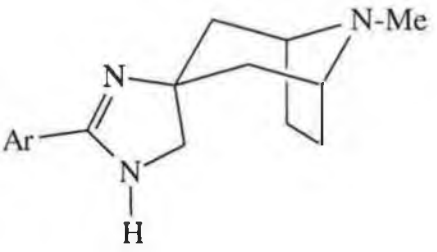
The change in chemical shifts and peak profiles in the ^1H NMR spectra is perfectly compatible with complexation at the site indicated. From the spectrum (Fig 2.4) it can be seen that the H9 methylene protons (δ = 2.67 ppm) are those which experience the largest downfield shift of 0.34 ppm on complexation, while little or no shift is noted for the H6(7) endo or exo protons (δ = 1.51 and 2.0 ppm respectively) or the bridge head protons H1(5) at δ = 3.15 ppm. A very slight downfield shift of 0.06 ppm is observed for the methyl group while two of the H2(4) (either the axial or equatorial protons) experience a shift from δ = 1.73 in the free base to δ = 2.0 ppm in the complex. The profile of the NH_2 protons also changes, from being a broad singlet centered at δ = 1.36 ppm in the free base to a very sharp singlet at δ = 1.21 ppm in the complexed amine. This is consistent with the protons being more tightly bound to the nitrogen as a result of complexation, resulting in a slower interchange of the protons with consequent sharpening of the NMR signal.

2.6 Synthesis of 2'-Aryl-8-methyl-8-azabicyclo[3.2.1]octane-3-spiro-4'(5')-imidazolidines (Ia-g)

The tropinone imidazolines (**I**) were formed by condensation of the diamine (**122**) with the aryl imidates (**123**) in a methanolic solution [Scheme 2.27].

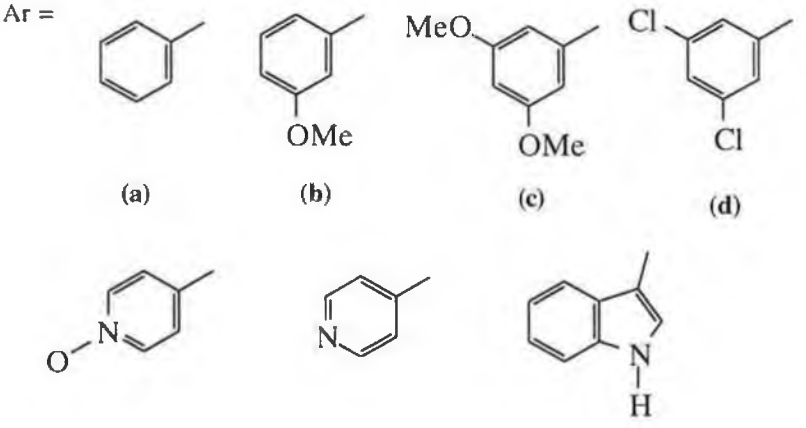


(122) (123)



(I)

Ar =



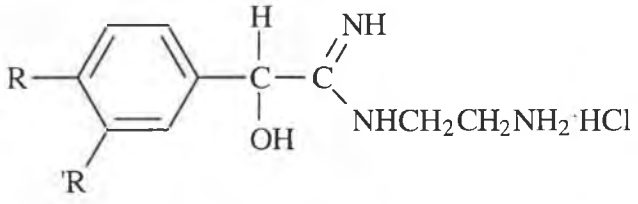
(a) (b) (c) (d)

(e) (f) (g)

Scheme [2.27]

The condensations took place at room temperature over a period of about 24 h but in some cases it was more favourable to carry out the reaction at reflux. The solvent was then removed under reduced pressure and the product was isolated as the free base on a basic alumina column. For compounds (**Ie, Ig**) the products were isolated directly from the reaction medium as the dihydrochloride salts by adding a methanolic HCl solution which precipitated the pure product salt.

The intermediate amidine of the type (**155**) reportedly isolated by Bristow[232] was not observed in any of the reactions even when the reaction was carried out at 10 °C. Presumably the reaction proceeds *via* this amidine type intermediate but immediately cyclises with loss of ammonia.



(155)

An interesting aside reported by Neilson *et al.*[233] in the synthesis of some imidazolines with chiral imidates as starting materials, was the observation that racemisation tended to occur on forming the imidazolines, either due to the diamine or the ammonia liberated in the cyclisation reaction. In an endeavour to avoid this they added HCl at intervals to neutralise the liberated ammonia.

The only by-products isolated from the interaction of the tropinone diamine with the imidate salts were aryl amides resulting from the decomposition of the imidates as described in section (2.3.2). The highest amount of amide was isolated from the reaction with the imidate salt of 4-pyridine *N*-oxide, amounting to 18 % of the isolated product. 2'-(4-pyridyl)-8-methyl-8-azabicylclo[3.2.1]octane-3-spiro-4'(5')-imidazoline (**If**) was synthesised from the corresponding *N*-oxide derivative (**Ie**) by cleavage of the oxygen

with PCl_3 in $CHCl_3$. The cleavage failed to take place when the dihydrochloride derivative was used as substrate and thus had to be liberated from its salt. The free base was thus obtained by liberation with K_2CO_3, and on subsequent reaction with PCl_3 gave a product which by ^1H NMR was indicative of the product required i.e. there was a large downfield displacement of 0.44 ppm for the H3'(5') protons of the aromatic ring and very little difference (0.02 ppm) in the H2'(6') shift position as to be expected.

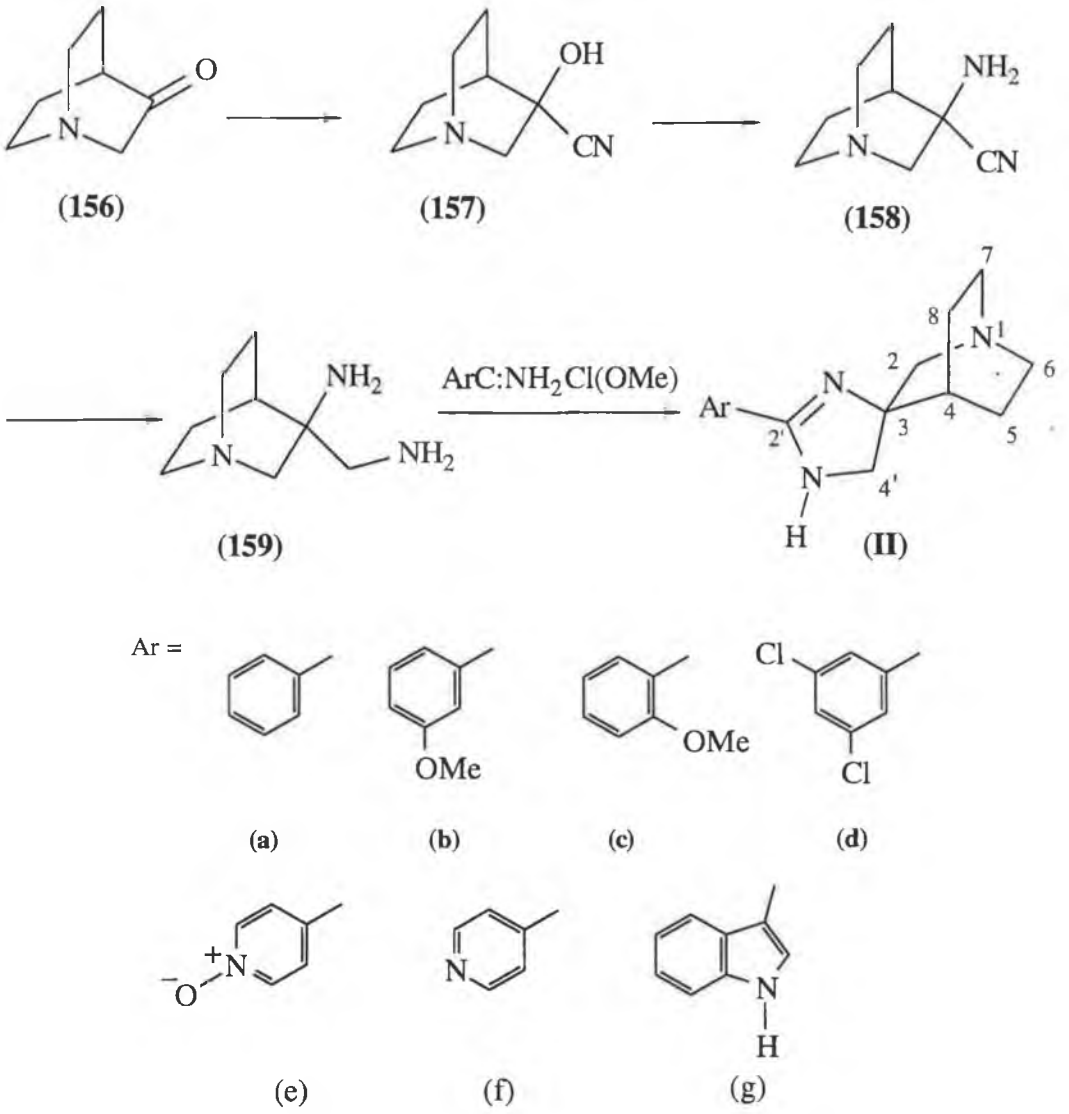
CHAPTER III

Synthesis of 2'Aryl-1-azabicyclo[2.2.2]-

octane-3-spiro-4'(5')-imidazolines

3.1 **Introduction.**

The chemical synthesis of the quinuclidine imidazolines followed an analagous route to that employed for the tropinone series, taking advantage of the developments already made for this series. Some notable differences however were observed especially in the synthesis of the quinuclidine diamine (**159**). The overall synthetic pathway is outlined in scheme[3.1].

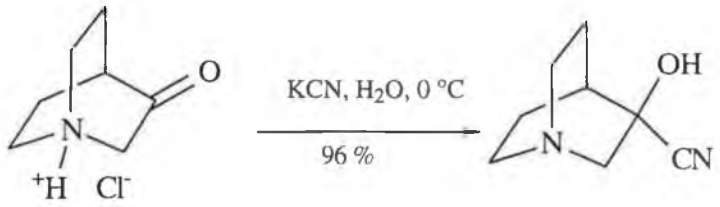


Scheme [3.1]

Unlike the synthesis of the tropinone aminonitrile **(124)** the quinuclidine homolog was prepared by initially forming the cyanohydrin followed by subsequent nucleophilic substitution with ammonia.

3.2 Synthesis of 3-hydroxy-1-azabicyclo[2.2.2]octane-3-carbonitrile (157)

The synthesis of this intermediate was carried out using a slight variation of a method described by Grob[234] employing KCN in place of NaCN as the nitrile source.

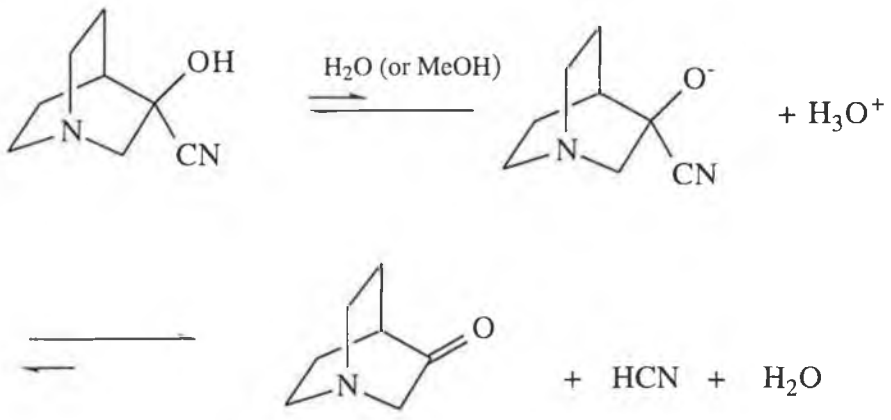


(156) **(157)**

Scheme [3.2]

The reaction is simple and high yielding, and is achieved by adding an aqueous solution of the cyanide salt to the hydrochloride salt of 3-quinuclidinone pre-dissolved in H_2O and stirred for 3 hours at 0-5 °C. Filtration and washing of the precipitated solid with water affords the title compound as the free base.

The reaction proceeded very well giving yields of the crude product greater than 90 % which showed only small traces of starting material on TLC (basic alumina). However on attempting to recrystallise the product from either ethanol or methanol very low yields (30 %) of the cyanohydrin were obtained. Examination of the mother-liquors on TLC showed it not to contain aminonitrile but some impurity of lower R_f value than the cyanohydrin which corresponded exactly with that of 3-quinuclidinone. Isolation of the impurity and analysis by IR spectroscopy conclusively showed it to be quinuclidinone formed by dehydrocyanation of the cyanohydrin as outlined in scheme [3.3].

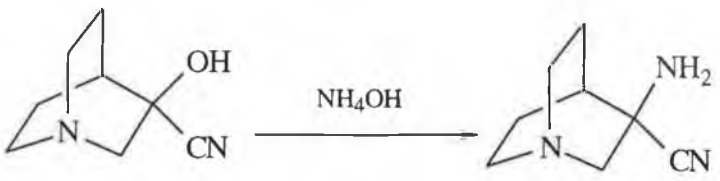


Scheme [3.3]

A sample of the cyanohydrin which was left in laboratory grade methanol for 5 hours transformed completely into the ketone, as did a similar sample in dry methanol. In dry THF no reversal was found to occur. Similarly, a sample of the cyanohydrin in H_2O-methanol containing a drop of acetic acid showed no reversal to the starting material, consistent with displacement of the equilibrium in scheme[3.3] towards the left. It was later discovered that on basic alumina TLC plates, the cyanohydrin decomposes to the ketone to a slight extent. Re-examination of samples of cyanohydrin which earlier showed up traces of ketone, were seen to be pure when examined on silica plates. Thus the product of the crude reaction was found to be sufficiently pure to enter the following reaction without recrystallisation. It may be possible however that in the event of recrystallisation being necessary, it could be carried out in ethanol or methanol in the presence of acetic acid.

3.3 Synthesis of 3-Amino-1-azabicyclo[2.2.2]octane-3-carbonitrile (158).

The synthesis of the amino carbonitrile (**158**) was carried out by nucleophilic substitution of the hydroxyl group in (**157**) with aqueous ammonia.



(157) **(158)**

Scheme [3.4]

The reported synthesis of this compound[218] describes a method where the cyanohydrin is stirred at room temperature for 48 h in a solution of ethanol/aqueous ammonia which on work up yielded 63 % of an aminonitrile that melted at 85 °C. We found that by following this procedure the starting material was insoluble in the reaction medium and the yields quoted could not be obtained. Also, the product obtained was impure, containing traces of starting material. It was observed that when the reaction was carried out at 50 °C greater conversion and isolated yields could be achieved. The isolated product however, still contained traces of cyanohydrin after work up and subsequent recrystallisation from acetone. Attempts to eliminate the starting material from the aminonitrile by recrystallising from MeCN, acetone/petroleum ether, EtOH, toluene and Et_2O were likewise unsuccessful due the similar solubilities of the two compounds. With the failure of recrystallisation to remove the starting material two other options were considered; chromatography or complete conversion of the cyanohydrin. The latter was chosen as the most feasible, as the resolution of the two compounds was thought

not to be sufficient enough to give success by column chromatography. Thus attempts were made to completely convert the cyanohydrin to the aminonitrile by longer reaction times at 50 °C. This proved to be unsuccessful however, and in fact some rereversal of the aminonitrile to the cyanohydrin was observed. It was discovered however that towards the end of the reaction (after about 90 % conversion), if the reaction temperature was lowered to 20 °C for 12 hours, then the remaining traces of starting material could be converted. This result can be rationalised in terms of the equilibrium reaction involved.

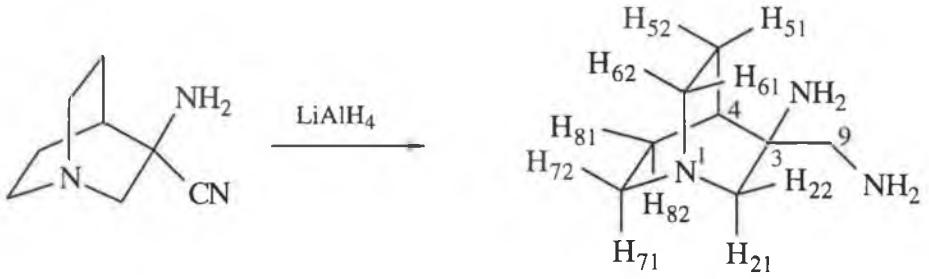
Scheme [3.5]

The reaction can be considered as an exothermic reaction since there is no net change in entropy. The input of heat into this equilibrium reaction thus favours displacement of the equilibrium towards the starting material and conversely removal of heat from the reaction by cooling should drive the reaction further towards the aminonitrile.

Employing this variation in the synthesis, yields of 85-89 % could be achieved and a pure product was obtained. The melting point of the aminonitrile isolated (after recrystallisation from acetone) was 111-113 °C, 26 °C higher than the quoted literature value.

3.4 Synthesis of 3-Aminomethyl-1-azabicyclo[2.2.2]octyl-3-amine (159).

The synthesis of the quinuclidine diamine **(159)** was similar to that employed for the preparation of the tropinone diamine **(122)**.

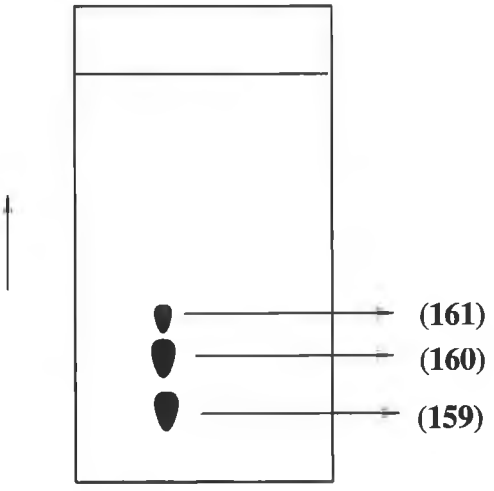


(158) **(159)**

Scheme [3.6]

The reduction was carried out by adding solid aminonitrile **(158)** to a suspension of $LiAlH_4$ in Et_2O at 0-10 °C then heated to reflux for 48 h. However the product profile obtained in this reaction, presented a significant difference over that of the tropinone counterpart.

TLC analysis of the isolated reaction mixture on basic alumina plates (MeOH, developed in I_2) indicated that there were at least three major products present.



Attempts were made to isolate them by column chromatography but pure fractions could not be obtained due to the poor resolution of the components. High vacuum distillation proved to be the method of choice in obtaining all the components in a pure state.

At the initial stages of the distillation (60-70 °C; 0.1 mmHg) a white solid appeared in the condenser which was removed by dissolving in MeOH. This solid, which corresponded to the middle spot on TLC, was estimated to be about 95% pure and was further purified by column chromatography on basic alumina. A second fraction which distilled at 80-100 °C was then isolated pure and corresponded to the lowest of the three spots on TLC, remaining almost on the baseline. Finally, a third product which distilled over at c.190 °C was obtained in approximately 80 % purity and was further purified on basic alumina. The compound corresponded to the least polar of the three components present on TLC. All three compounds were analysed by high resolution ^{1}H NMR and mass spectrometry.

The ^{1}H NMR spectra of the quinuclidine system present a somewhat complicated pattern which makes a complete analysis difficult. However, an interpretation can be made within reasonable confidence limits. The identification of the diamine could be observed by ^{1}H NMR analysis where the appearance of a pair of doublets centered at δ = 2.78 and δ = 2.56 ppm, each displaying a coupling constant of -12.8 Hz corresponding to geminal coupling (Figure 3.1). These signals which integrate for a total of two protons were assigned to 2 H9 protons arising from the reduction of the nitrile function. They appear as an AB system because of their position alpha to the chiral center C 3.

A pair of double doublets centered at δ = 2.64 and δ = 2.52 ppm were assigned to the protons H21 and H22 and can be considered as part of the three spin ABX systems formed by H21, H22, H62 and H21, H22 and H72 respectively. The primary AB coupling between the H21 and H22 proton is split by long distance coupling with the H62 and H72 respectively in the form of W coupling[235,236] frequently observed in rigid bicyclic systems.

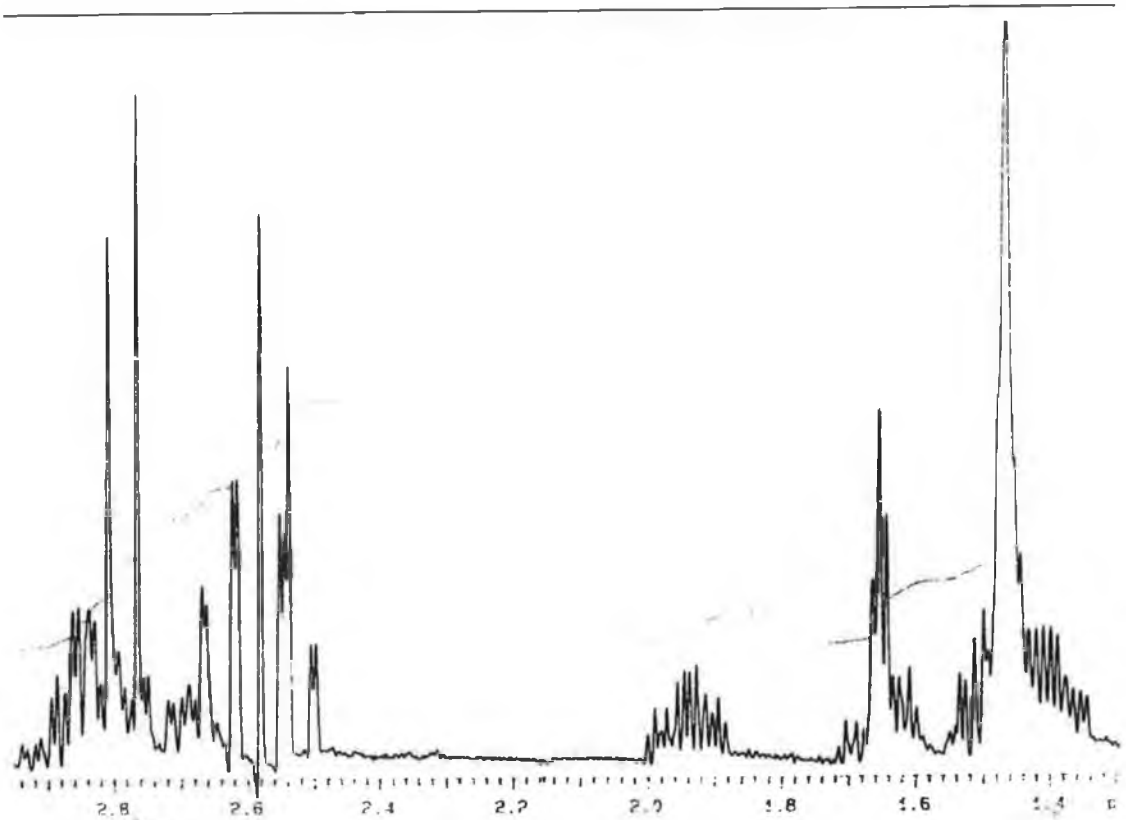


Figure 3.1 ^{1}H NMR of quinuclidine diamine (**159**, 300 MHz, $CDCl_3$)

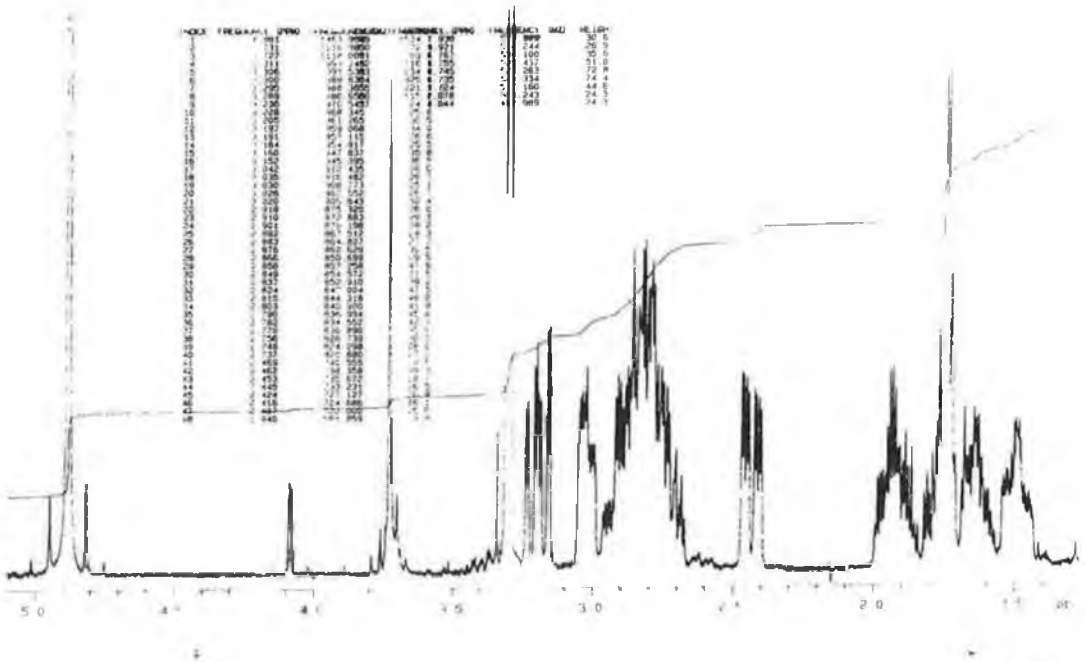


Figure 3.2 ^{1}H NMR of impurity (**160**) isolated from the reduction of quinuclidine aminonitrile (CD_3OD).

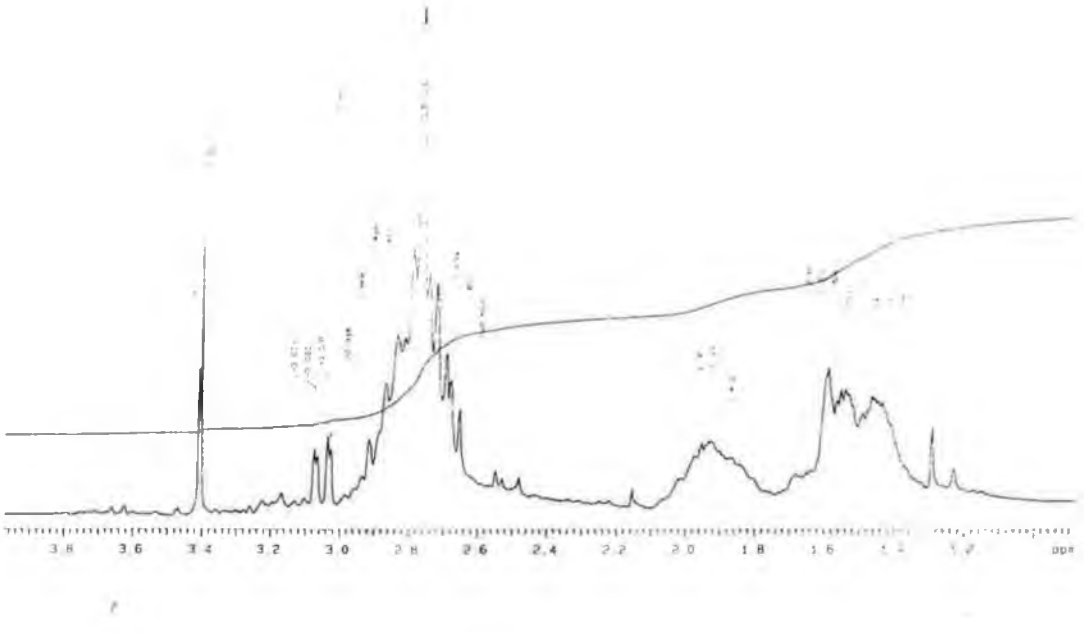


Figure 3.3 ^{1}H NMR of impurity (**161**) isolated from the reduction of quinuclidine aminonitrile.

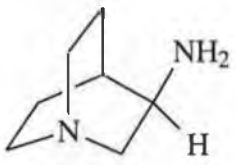
Analysis of the system using first order rules allowed for the establishment of ^{2}J(H-21, H-22), ^{4}J(H-21, H62), and ^{4}J(H-22, H-72) giving -13.7, and 2.5 and 2.5 Hz respectively. Apart from the protons mentioned, a multiplet integrating for a further 4 protons is observed between δ = 2.64 and 2.94 ppm corresponding to the remaining two CH_2N groups H61, H62, H71 and H72. The corresponding coupling constant of 2.5 Hz for the W coupling with H21 and H22 is observed. Three further multiplets centered at δ = 1.94, 1.64 and 1.43 ppm can be attributed to the H52, H52, H41, H81 and H82 protons. A broad singlet integrating for 4 protons and which was interchangeable in D_2O was assigned to the amine protons.

An analysis of this compound by chemical ionisation mass spectrometry gave a M^{+}+1 peak of 156 along with M^{+}+29 and M^{+}+41 peaks, and was thus confidently assigned

as the required quinuclidine diamine (Spectrum 24). The compound corresponded to the baseline spot on TLC and was obtained in a yield of 40 %.

With the quniclidine diamine confidently assigned there remained the task of identifying the two remaining reaction products. The unequivocal identification of these major by products, it was felt, would lend to a better understanding of the reaction and thus possibly lead to their elimination and improvement in yield of the diamine.

The solid impurity isolated from the first distillation fraction gave a ^{1}H NMR spectrum which though quite complex, was resolvable (Figure 3.2). The most striking observation about the spectrum was the absence of any obvious AB system corresponding to the H9 methylene protons. IR analysis indicated that the nitrile group was absent from the molecule. The total integration indicated the presence of 12 protons, the nitrogen protons not being visible as the spectrum was recorded in deuterated methanol. The molecule was suspected as being the amine (**160**) resulting from hydrogenolysis of the aminonitrile with $LiAlH_4$. The CI mass spectrum of the impurity gave the expected M^++1, M^++29 and M^++41 peaks, thus confirming the structure (Spectrum 25).

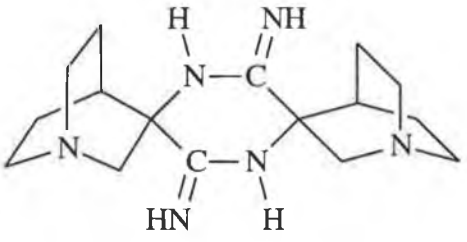


(160)

As further conclusive evidence, the trihydrochloride salt of the amine was synthesised and had a melting point identical to that of a commercial sample (321- 323 °C).

The second impurity isolated from the reaction and which corresponding to the least polar of the components on TLC gave a ^{1}H NMR spectrum which displayed three series

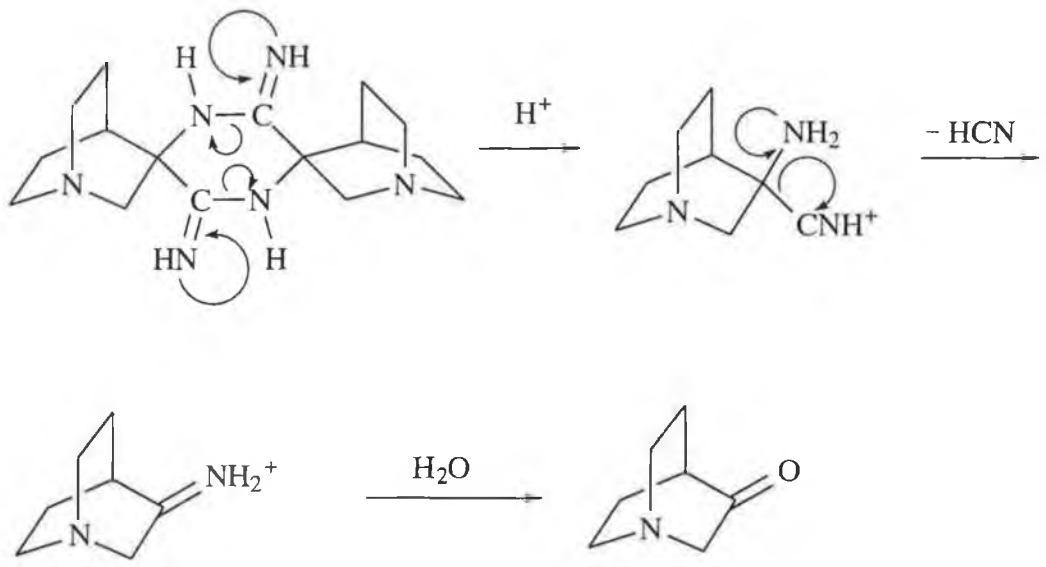
of totally unresolvable multiplets in the ratio of 6:2:3 at chemical shifts centred at δ = 2.78, 1.92 and 1.5 ppm respectively, as depicted in figure 3.3. Mass spectrometry gave a weak M^++1 peak for 303 mass units (Spectrum 26). Based on this piece of evidence a dimeric structure (**161**) having a molecular weight of 302 was considered as a possible candidate.



(161)

The structure would be entirely in keeping with the NMR results for 12 downfield protons for the 6 CH_2N groups and the 10 remaining more shielded protons corresponding to the upfield values of 1.92 and 1.5 ppm.

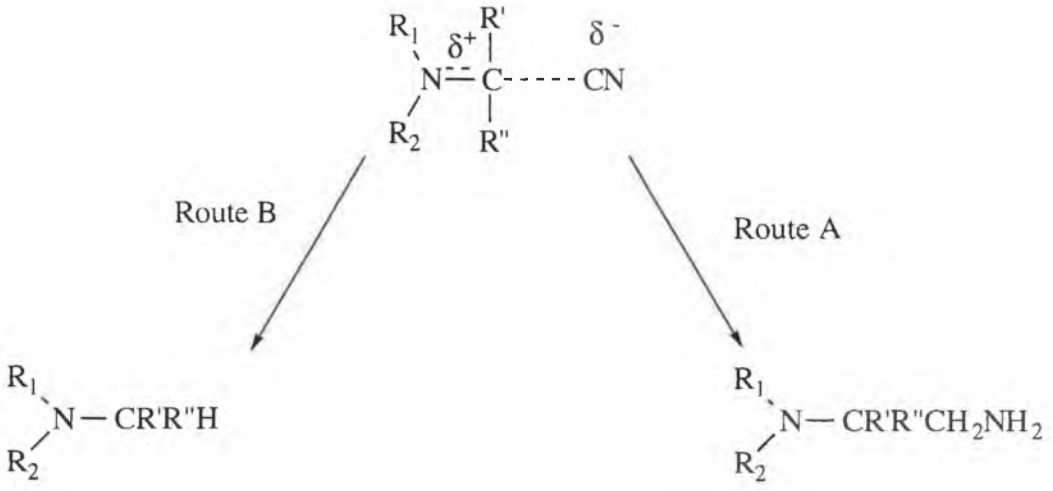
In an attempt to form a hydrochloride of the impurity in methanol or in aqueous HCl, decomposition to an almost pure compound occurred. The decomposition product was identified as quinuclidine hydrochloride whose formation from the dimeric product could theoretically be as outlined in scheme [3.7].



Scheme [3.7]

Support for the formation of the dimeric structure, which can be considered as a cyclic amidine, is found in the fact that amines can condense with nitriles to form amidines when there are electron withdrawing groups α to the nitrile and in the absence of this requisite may form in the presence of aluminium trichloride.[237] No report of the formation of such a dimeric compound in the reduction of α-aminonitriles with $LiAlH_4$ could be found in the literature.

The formation of hydrogenolysis products (**149**) have previously been reported in reductions of aminonitriles with $LiAlH_4$.[238] Welwart carried out a study of the factors governing the preference for formation of the reduction product to give diamines or the hydrogenolysis product to give the monoamine. Such behaviour of α-aminonitriles can be explained as follows.



Scheme [3.8]

Due to the electron donating effect of the lone pair of electrons in the nitrogen, coupled with the electron attracting effect of the nitrile group acting on the same α carbon, the bond between this carbon and the nitrile function simultaneously presents both electrovalent and covalent caracter. The relative reactivities of the two carbons in question depends on the nature of the α-aminonitriles.

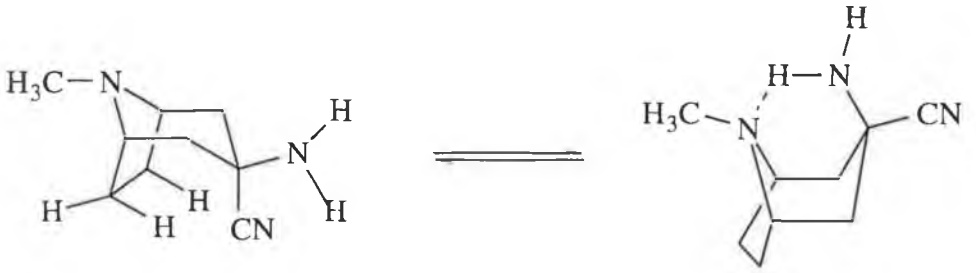
The authors report that if the α-carbon is monosubstituted the reduction compound is obtained as the exclusive product (Route A). However if the α-carbon is disubstituted then the reaction may proceed via either reduction or hydrogenolysis (Route A or B) the direction being governed by the substituents on the nitrogen group. If the amine is unsubstituted or substituted with methyl groups then normal reduction occurs whereas substitution with more sterically demanding groups such as ethyl or butyl functions leads to hydrogenolysis. The nature of the substituents on the α-carbon may also exercise a certain influence over the nature of the products.

The observations noted may be explained by the steric effect influenced over the nitrile group. Thus in the case of the larger diethylamino substituent the attack of the incoming $LiAlH_4$ on the nitrile may be impeded while simultaneously the sterically hindered

environment around the α-carbon may provoke the weakening of the C_α-CN bond which would favour the formation of a proposed immonium intermediate which is thought to favour the hydrogenolysis product.

By considering the results of the investigation of Welwart[238] we attempted to rationalise why a hydrogenolysis product was obtained in the reduction of the quinuclidine aminonitrile, while none of this by-product was observed in the corresponding reduction of the tropinone compound.

Firstly, it is noteworthy that contrary to the findings of Welwart, hydrogenolysis was observed in the quinuclidine aminonitrile even though the amine was unsubstituted. We could find no other reports of unsubstituted aminonitriles which gave hydrogenolysis with $LiAlH_4$ and may thus be the first reported case. On initial examination, an explanation of the result is not obvious based on steric differences between the tropinone and quinuclidine aminonitriles. In fact the steric impediment to reduction of the nitrile group seems to be greater in the case of the tropinone where the approach of the reducing agent would be hindered by the methylene protons of the C6(7) atoms. Indeed, on looking at a model of the two compounds, access to the nitrile group in tropinone was seen to be severely impeded when in the chair conformation. The quinuclidine nitrile however, is much more accessible to attack and therefore should be less susceptible to hydrogenolysis which was not the case. It was then attempted to explain the more selective reduction in the tropinone by supposing that the reduction takes place with the tropinone in a boat conformation, where the nitrile function is much more exposed and available for reduction. It seems reasonable to assume that the tropinone aminonitrile will exist in a state of dynamic equilibrium between the chair **(124)** and the boat **(162)** conformation with probably the chair in the major amount. Reduction of the compound in the boat conformation would thus remove it from the equilibrium thus assisting complete reduction of the aminonitrile.

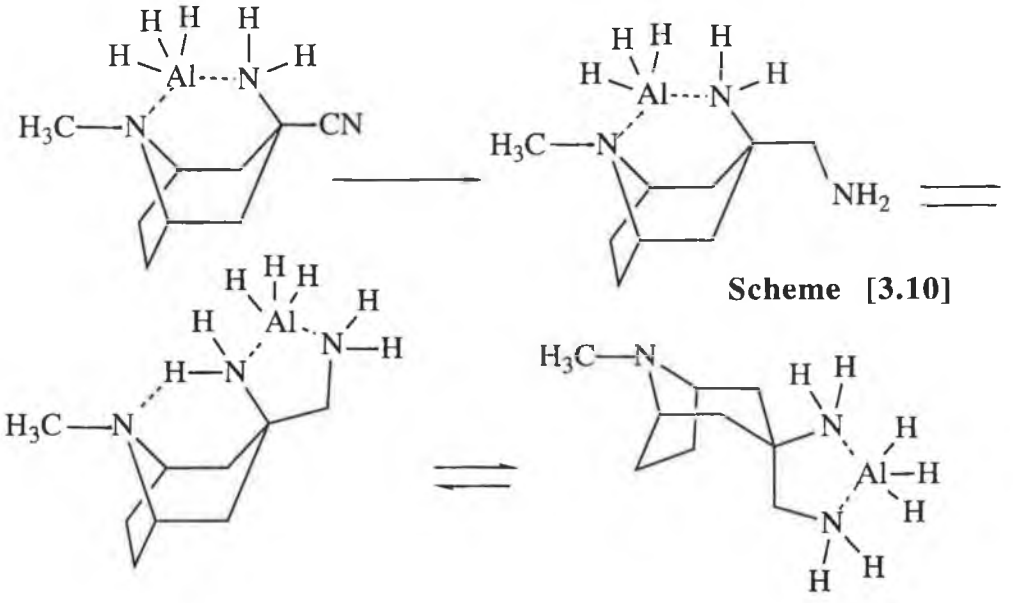


(124) **(162)**

Scheme [3.9]

However, it is very probable that the aminonitrile in a boat conformation would form an internal hydrogen bond shown in scheme [3.9]. This would have the result of increasing the charge density on the primary amine thus assisting the formation of the immonium type structure which reportedly leads to the hydrogenolysis product.

An alternative theory involving intermediate complex type structures was then considered. It is not an unreasonable assumption to suppose that some type of aluminium complex initially forms at the azabicyclic nitrogen (formally shown as a trihydride of the aluminium but in reality may be a more complex species).



Scheme [3.10]

It can be seen that such a complex has the possibility of coordinating aluminium with both nitrogens of the tropinone when it is present in the boat conformation and thus forms a stable six membered ring species. The effect of this is to "tie up" the lone pair of electrons of the primary amine consequently reducing the polarity of the C_{α}-CN bond by hindering the immonium ion formation which in turn would favour reduction over hydrogenolysis. In the quinucludine system, any complexation would probably take place at the tertiary azabicyclic nitrogen which is highly nucleophilic and does not have the possibility of forming the same internal cyclic structure as tropinone does. Thus a plausible explanation for the distinct behaviours of the two aminonitriles is presented.

Some efforts were spent in attempting to increase the yield of the quinuclidine reduction product. The reaction was performed in THF at various temperatures ranging from 0 °C to reflux and no improvement in the reaction profile was observed and in fact gave an inferior yield of the diamine. Reduction of the aminonitrile in Et_2O at room temperature proved to be very sluggish and contained c.95 % starting material after 5 hours reaction time. The reduction was carried out in THF with BH_3·THF as the reducing agent. Following hydrolysis of the borane complex after reduction, an array of products could be seen on TLC. In addition, difficulty in isolating the reaction products from the aqueous phase, after hydrolysis of the complex, was encountered. Complete saturation of the aqueous phase failed to liberate the product into diethyl ether or methylene chloride.

3.5 Preparation of 2'Aryl-1-azabicyclo[2.2.2]octane-3-spiro-4'(5')-imidazolines (IIa-g)

The quinuclidine imidazolines were generally formed by the same procedure developed for the tropinone homologs, by condensation of the quinuclidine diamine **(159)** with the corresponding imidate hydrochloride in dry methanol (Scheme 3.1). A notable feature of this reaction was the greater reactivity of the quinuclidine diamine over the corresponding tropinone derivative towards the imidate hydrochlorides. In general, complete consumption of the quinuclidine diamine to form the imidazoline took place within 2 hours at room temperature. This augmentation in reactivity can possibly be rationalised by the steric impediment to the approach of the imidate caused by the C6 and C7 protons in the tropinone system.

The reactions were either worked up by column chromatography purification or by directly precipitating the hydrochloride salt of the product from the reaction. In the case of the pyridine *N*-oxide imidazoline **(IIe)** which was isolated as its dihydrochloride salt, the compound was found to be extremely hygroscopic and was seen to be more manageable in its mono hydrochloride or free base form.

As with the tropinone series, the pyridyl imidazoline **(IIf)** was obtained by cleavage of the *N*-oxide group from the free base of **(IIe)**. Some unexpected difficulty was encountered however in the procedure. In an attempt to liberate the free base of **(IIe)**, a solution in H_2O was basified to pH 10 with K_2CO_3 as in the case of the tropinone equivalent. The free base which was later found to be very soluble in H_2O failed to extract into methylene chloride, ethyl acetate or toluene and so the "liberated" product was isolated by removing the water azeotropically with toluene and then extracting the base from the residue with MeOH. The "free base" was subsequently reacted with PCl_3, the product of which on examination by ^1H NMR showed a displacement of the azabicyclic protons (compared to an authentic sample of the free base) but no significant change in the chemical shift in the aromatic region which should be expected on

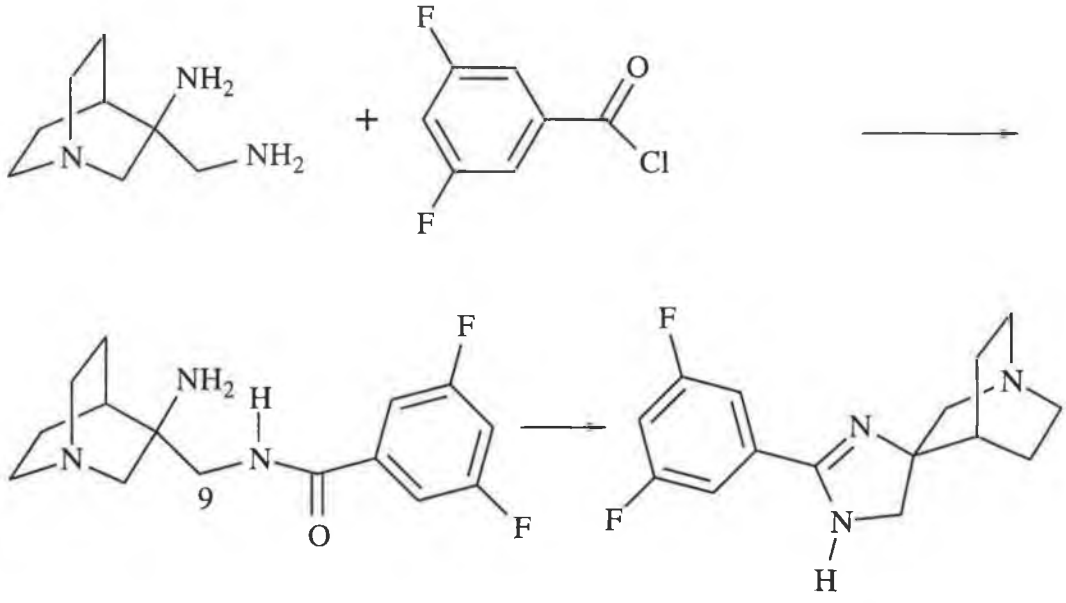
converting from a pyridine *N*-oxide to a pyridyl group. On further investigation the compound transpired to be the mono hydrochloride salt of the *N*-oxide imidazoline **(IIe)** which failed to completely liberate with K_2CO_3 and passed through the next reaction unchanged. Similarly, only the monohydrochloride salt was obtained on attempting to liberate with NaOH. This lack of success in completely liberating the free base from its dihydrochloride salt is due to the high basicity of the quinuclidine nitrogen combined with the fact that the *N*-oxide free base is very soluble in H_2O and thus cannot be removed from the protonated-free base imidazoline equilibrium by extraction into an organic solvent. The simplest and highest yielding method of completely liberating the free base was by "flashing" the dihydrochloride salt down a basic alumina column with CH_2Cl_2-EtOH.

For the preparation of compounds **(IIc)** and **(IId)** the starting imidates were used in their unpurified form, i.e. they contained considerable amounts of the corresponding nitrile, which however caused no interference in the reaction. The offending nitrile could easily be removed and recovered by acidification of the imidazoline reaction mixture and extracting with methylene chloride.

3.6 Preparation of 2'(3,5-Difluorophenyl)-1-azabicyclo[2.2.2]octane-3-spiro-4'(5')-imidazoline (IIh).

Because of the biologically interesting results found for the dichlorophenyl derivative of the quinuclidine imidazoline (**IId**) (see chapter VI) the synthesis of the difluoro congener was considered to be of special interest. As the standard synthesis *via* the imidate failed for this compound due to the increased electronegativity of the fluoro group, an alternative synthesis was investigated.

The acylation of the quinuclidine diamine with a suitable acylating agent followed by cyclisation was considered as a possibility although previous attempts with the tropinone system were unsuccessful. A more reactive acylating agent such as an acid chloride was considered more suitable than an ester, carboxylic acid or amide (Scheme 3.11).

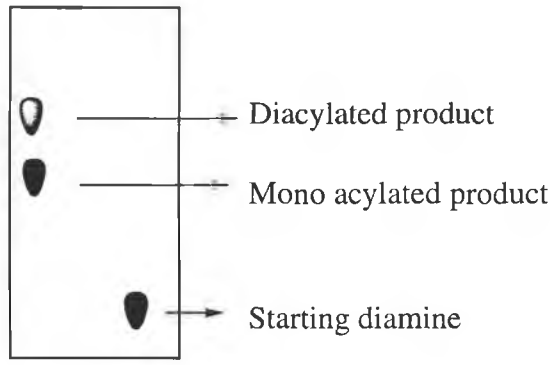


(II h)

Scheme [3.11]

The acylation was carried out by adding a dry toluene solution of the difluorobenzoyl chloride dropwise at room temperature to a toluene solution of the diamine. A white

solid precipitated immediately and after 30 minutes the reaction was worked up by evaporating the reaction mixture to dryness, adding CH_2Cl_2 and H_2O, and then acidifying. The aqueous solution was then washed with CH_2Cl_2, basified with K_2CO_3 and extracted into fresh CH_2Cl_2. On evaporating the solvent a clear oil was obtained which contained two spots on TLC.



It was considered probable that the top spot was the less polar diacylated product. The presence of diacylated product was supported by both the ^1H NMR results and mass spectra which indicated approx. 30 % of this impurity (See figures 3.4 to 3.7).

Although the ^1H NMR spectrum of the crude isolated reaction mixture presents a very complex pattern the side-chain methylene protons H9 can readily be distinguished and provides a useful diagnostic tool to determine the ratio of diacyl to mono acyl product in the reaction mixture.

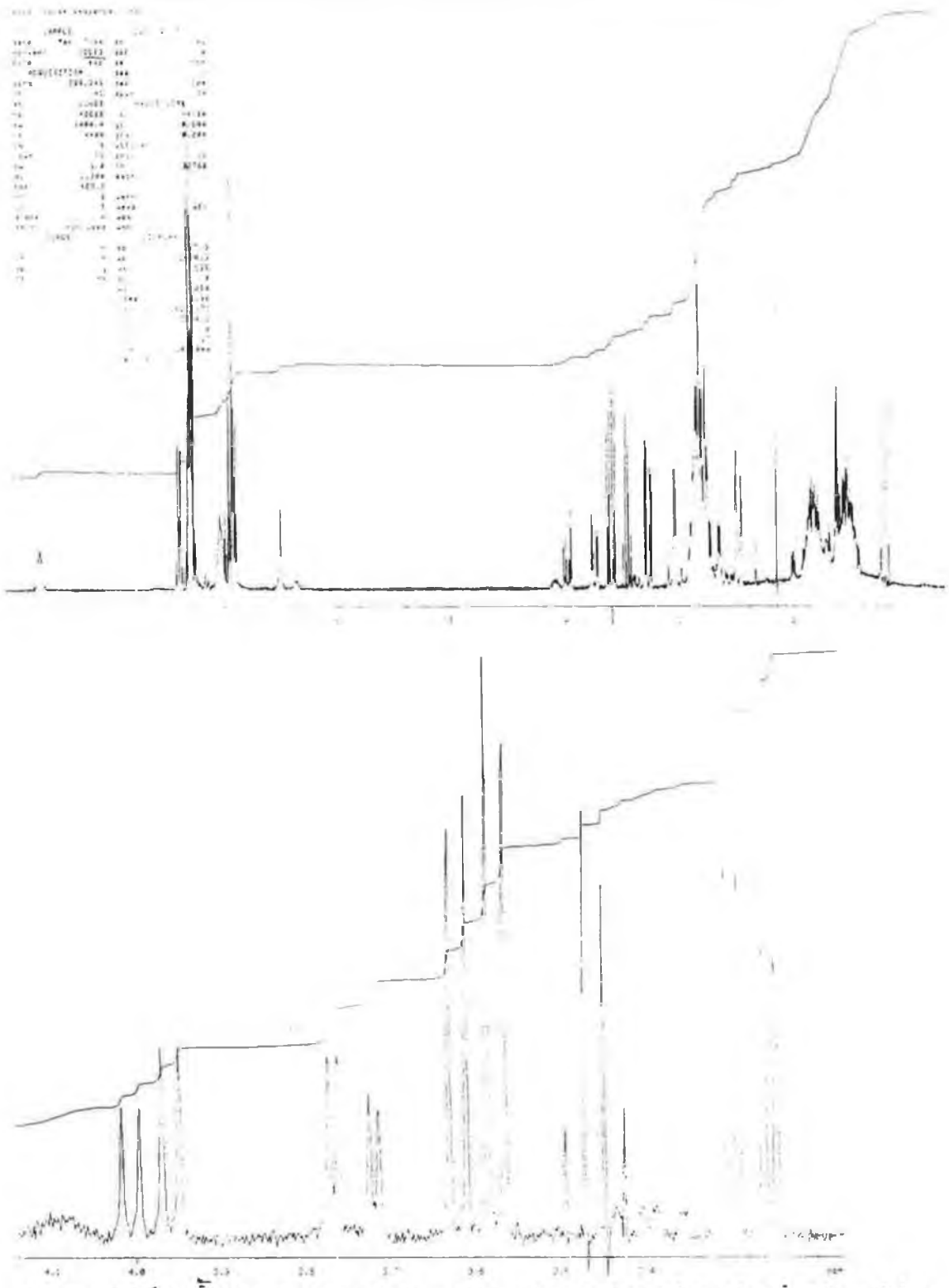


Figure 3.4 ^{1}H NMR spectrum of the crude product isolated from the reaction of the quinuclidine diamine (**159**) with 3,5-diflouorobenzoyl chloride ($CDCl_3$).

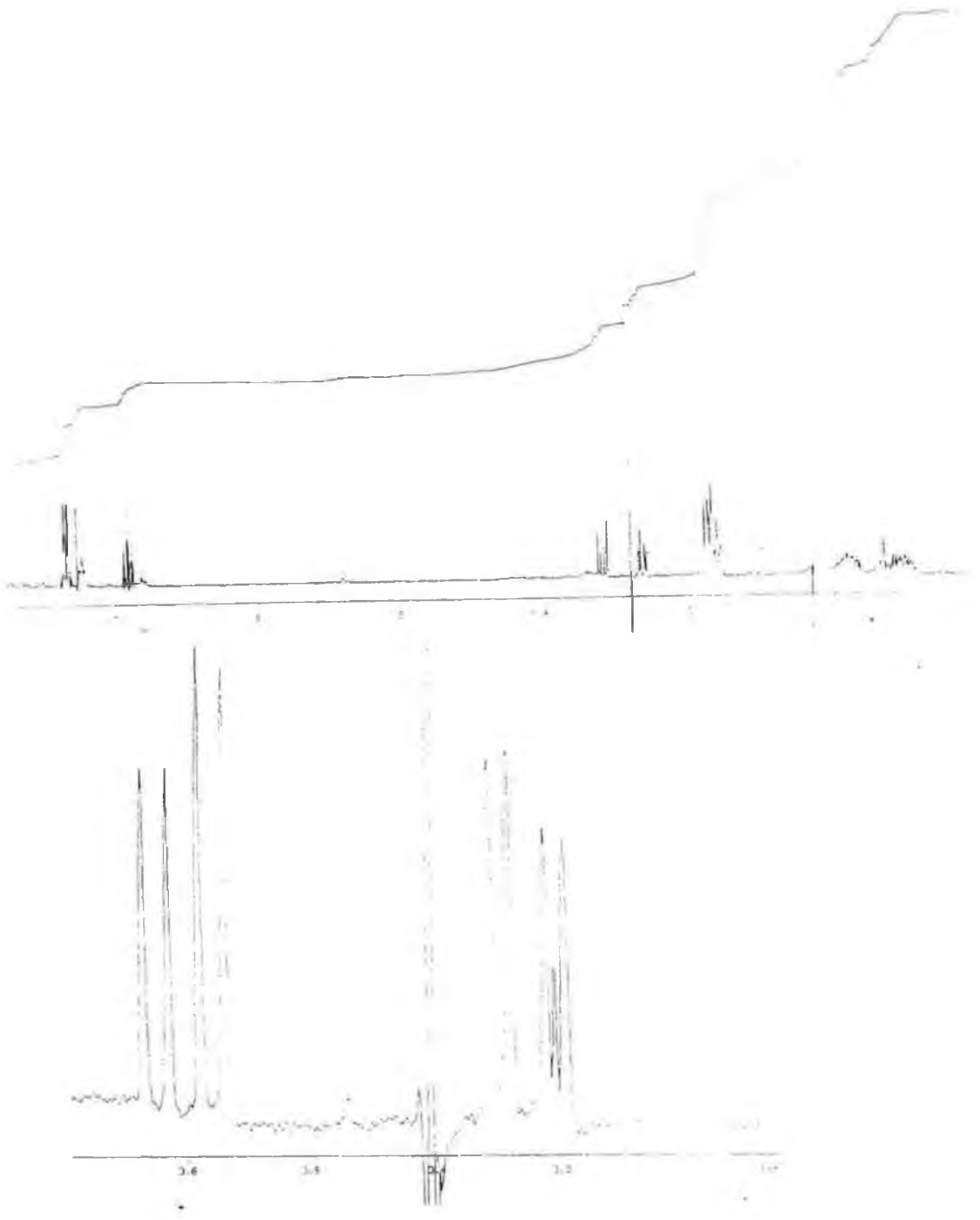


Figure 3.5 ^{1}H NMR spectrum of the purified monoacyldiamine isolated from the reaction of the quinuclidine diamine (**159**) with 3,5-difluorobenzoyl chloride ($CDCl_3$).

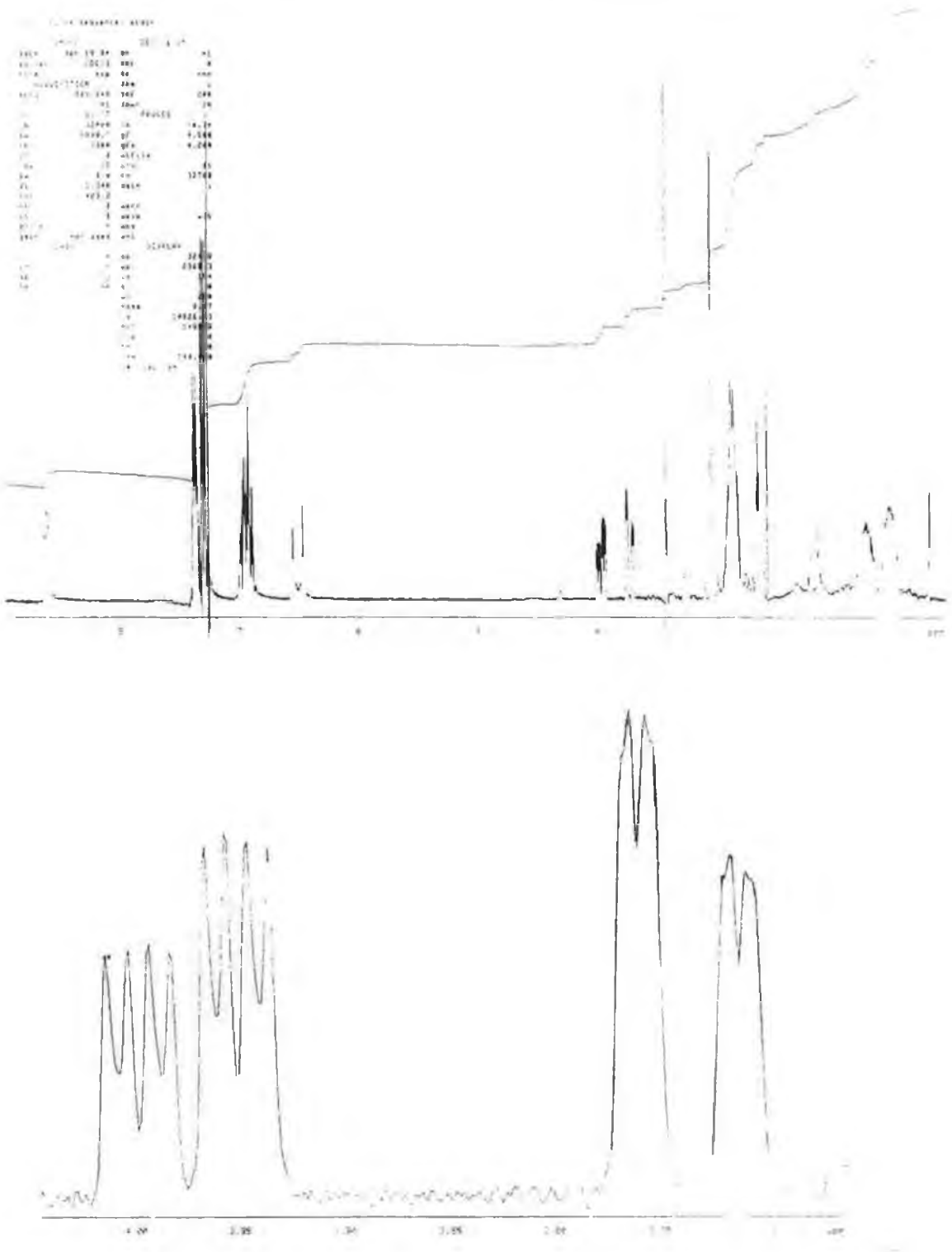


Figure 3.6 ^{1}H NMR spectrum of the purified diacyldiamine isolated from the reaction of the quinuclidine diamine (**159**) with 3,5-diflouorobenzoyl chloride ($CDCl_3$).

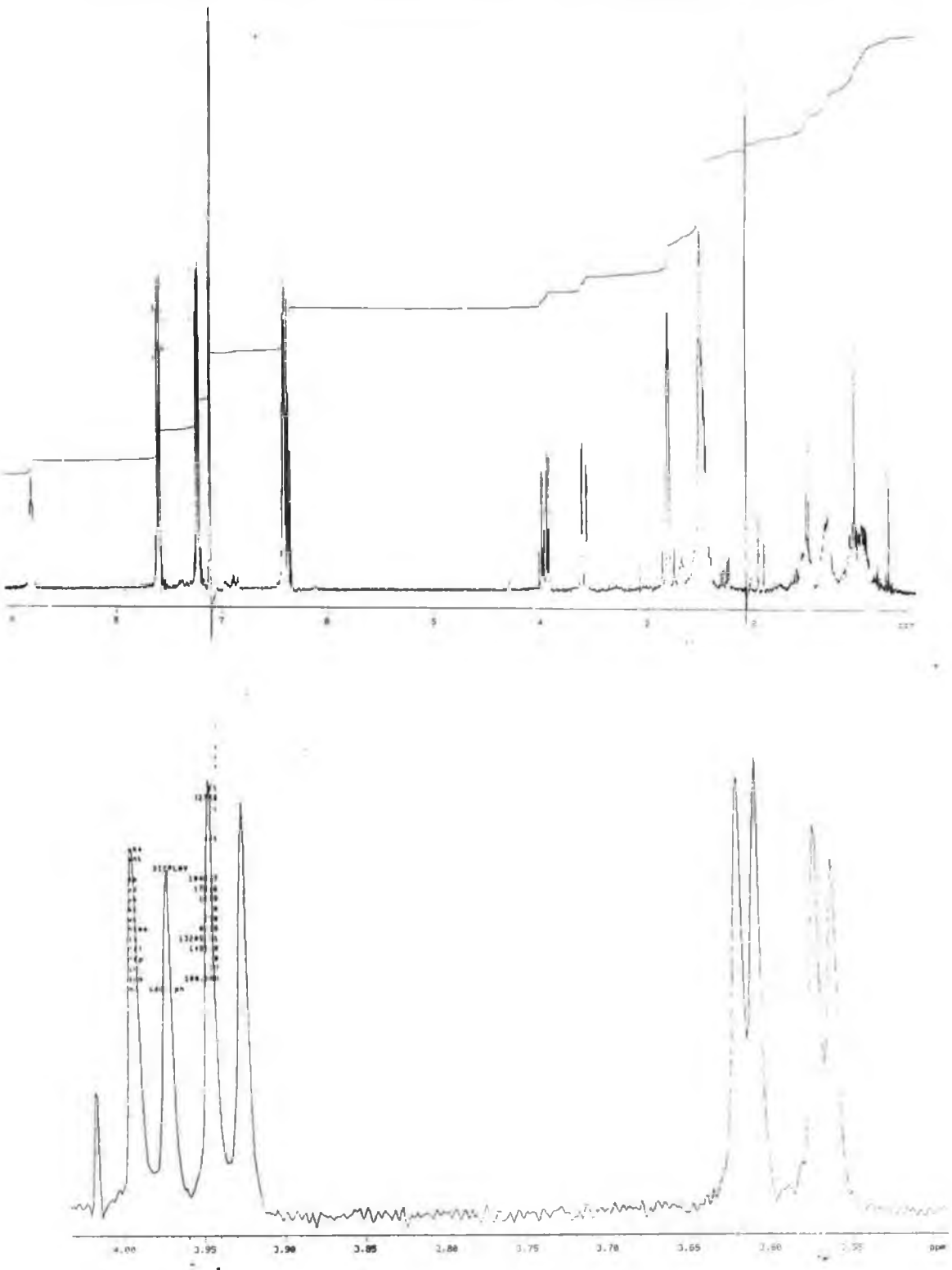


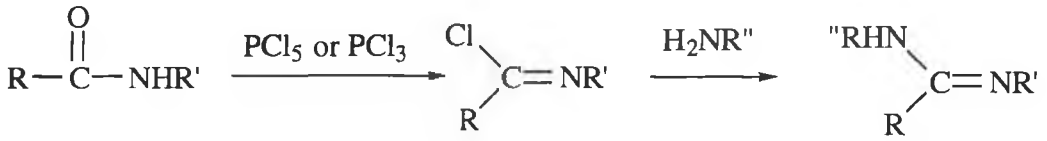
Figure 3.7 ^{1}H NMR spectrum of the purified diacyldiamine isolated from the reaction of the quinuclidine diamine (**159**) with 3,5-diflouorobenzoyl chloride (C_6D_6).

As can be seen from the ^1H NMR spectrum in figure (3.4) two sets of peaks between δ = 3.2 and δ = 3.4 ppm corresponding to the methylene protons in two different AMX systems can be visualised which may be assigned to the side chain methylene protons H9 of the monoacylated and the diacylated product. The CH_2 protons appear as an AMX system due to their position α to the chiral C3 centre (see full assignment of quinuclidine protons in section 3.4.) and the amide nitrogen which can couple with these methylene protons. The AM part of the system centred at δ = 3.98 ppm and δ = 3.74 ppm was assigned to the diacylated product due to their downfield position, while the AM part of the second AMX system centred at δ = 3.6 ppm and δ = 3.28 ppm should correspond to the monoacylated product.

The appearance of the side-chain methylene protons as an AMX system in the precursor to **(II h)** is proof that the monoacylation takes place at the NH_2 attached to the secondary carbon rather than at the amine attached to the quaternary carbon (Scheme 3.11). The geminal coupling for the diacylated product is -14.7 Hz while that of the monoacylated compound is -13.4Hz. The two halves of the AM systems for the diacyl are 6.43 Hz and 3.75 Hz while the mono compound has vicinal coupings of 6.03 Hz and 4.40 Hz. This significant difference in vicinal coupling between both parts of each AM system indicates that there is probably restricted rotation of the amide group.

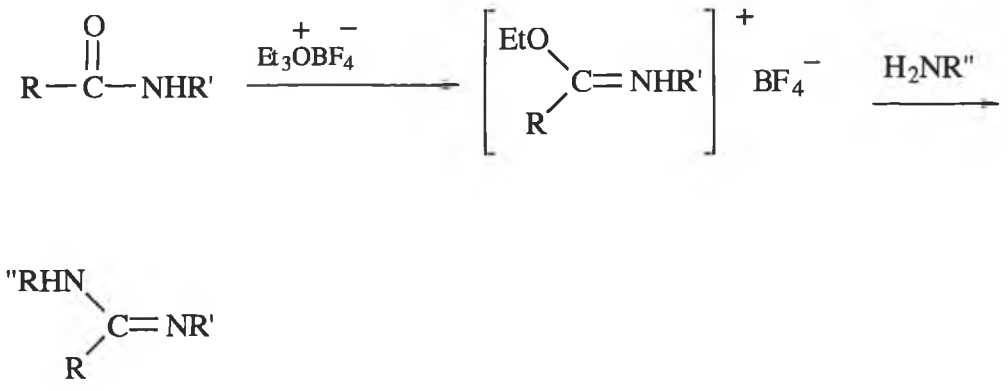
In an initial attempt to investigate the cyclisation of the amino amide, the crude reaction mixture containing the diacylated and monoacylated compounds was used. At first the thermal cyclisation with the elimination of H_2O was investigated. Heating the crude oil in toluene at reflux resulted in no change in the starting material after 6 hours reflux. On changing the solvent to xylene to increase the reflux temperature, decomposition of the starting materials occurred and the reaction mixture of TLC plates showed an array of spots. The ^1H NMR likewise indicated that the bicyclic system was not intact.

It was obvious that some milder method of cyclising the amide was required. With this aim some condensating agents were considered. Several methods were examined but the two which seemed the more attractive were the following: The first involves the use of a method for the condensation of amides with amines in the presence of halogenating agents to form amidines.[239] The reaction involves the intermediacy of an imido chloride which subsequently reacts with an amine (Scheme 3.12). Since the imidazoline is a cyclic amidine this was obviously a method worth considering.



Scheme [3.12]

The second option considered the use of triethyloxonium fluoroborate (Scheme 3.13) to give an imido ester fluoroborate which on reacting with an amine yields amidines as reported by Weintraub and co-workers.[240]



Scheme [3.13]

On considering this latter method the possibility of methylating the free amine or the bridgehead quinuclidine nitrogen with the very powerful alkylating agent was regarded as a serious likelyhood. Because of this the first method was investigated.

Preliminary attempts to cyclise the crude mixture of mono and diamide isolated from the aforementioned procedure, with PCl_3 in toluene proved unsuccessful. However subsequent use of one equivalent of pyridine (after the PCl_3 addition) gave some reaction in which indications were that some of the cyclised product had been formed. On examination by mass spectroscopy, using the electron impact technique, a weak mass ion of 277 was observed which corresponds to the molecular weight of the cyclised product while under chemical ionisation conditions an intense M^++1 peak of 278 m.u. was seen though other extraneous peaks of higher m.u. were also observed which did not correspond to the usual M^++29 or M^++41 peaks (Figures 3.8 and 3.9).

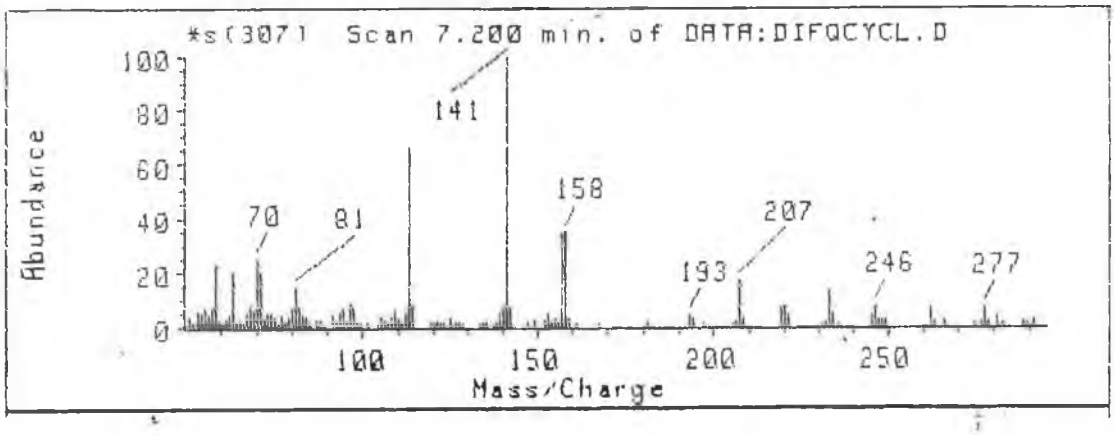


Figure 3.8 Mass spectrum (EI) of the crude (**II h**) cyclisation product.

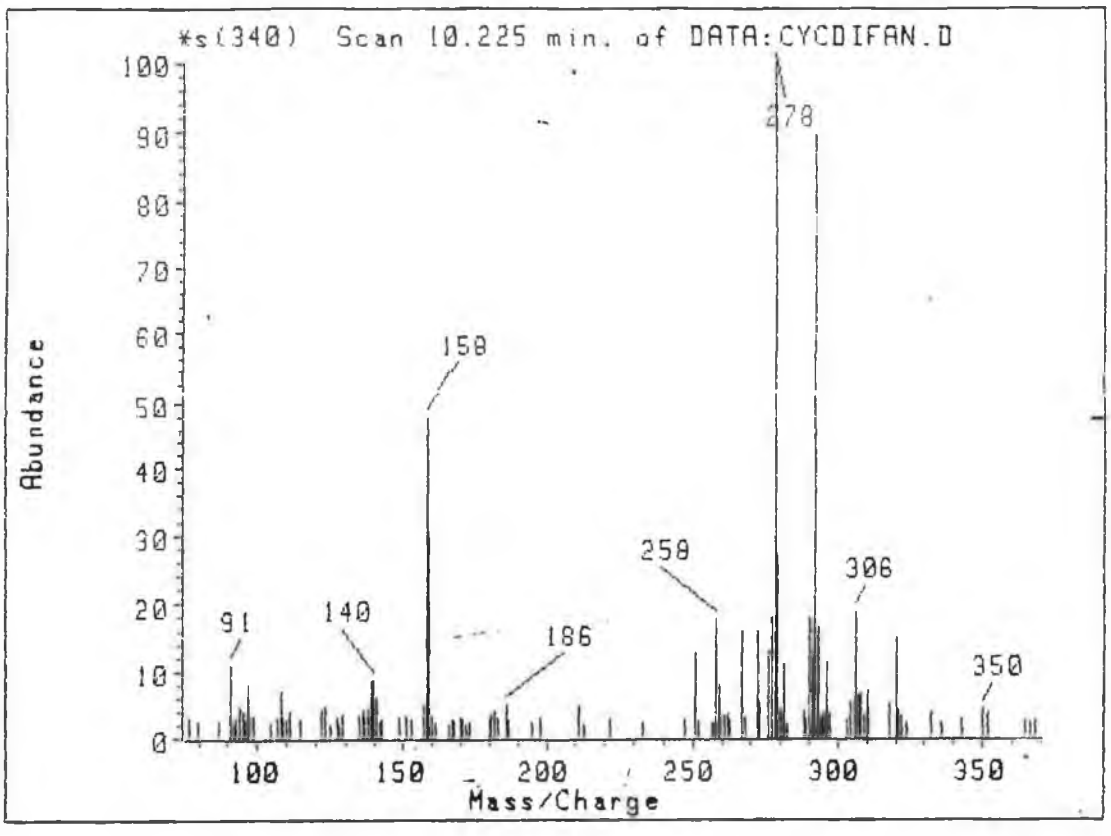


Figure 3.9 Mass spectrum (CI) of the crude (**II h**) cyclisation product.

With this preliminary success it was decided to purify the amino amide by column chromatography on basic alumina. Both the mono and diacylated diamine compounds were isolated relatively pure and were analysed by ^{1}H NMR and mass spectrometry. The tentative assignation made for the methylene side chains of the mono acylated and the diacylated amine in the crude sample were shown to be correct. ^{1}H NMR spectra of both the purified monoacyl and diacyl compounds are shown in figures (3.5 and 3.6). An interesting observation was made regarding the splitting pattern of the side-chain methylene in the diacylated compound. It has been mentioned that the signals corresponding to these protons in the crude reaction mixture, show up as two pairs of double doublets centred at $\delta = 3.98$ and $\delta = 3.74$ ppm. However when in the pure state,

each of these peaks in the down field half of the system was further split into two signals with a coupling constant of 2.9 Hz, while the upfield half showed only a very slight broadening of the peaks (see figure 3.6). This result was curious and is believed to result from the following. It is thought that when in the pure state, intramolecular π-π interactions were taking place between the phenyl rings of the diacyl product as depicted in figure 3.10. This would have the effect of "locking" the amide methylene into a fixed ring. Because of this forced rigidity it is possible that one of these methylene protons could occupy a position in which it can undergo long-range coupling with a proton of the quinuclidine ring, for example W coupling with the bridgehead H4 proton [the protons involved are shown as broken lines in the quinuclidine structure in figure 3.10] The coupling constant of 2.9 Hz is consistent with ^4J coupling in these systems.

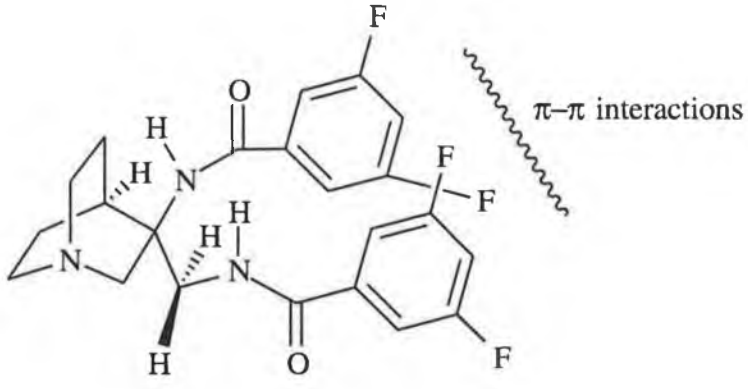
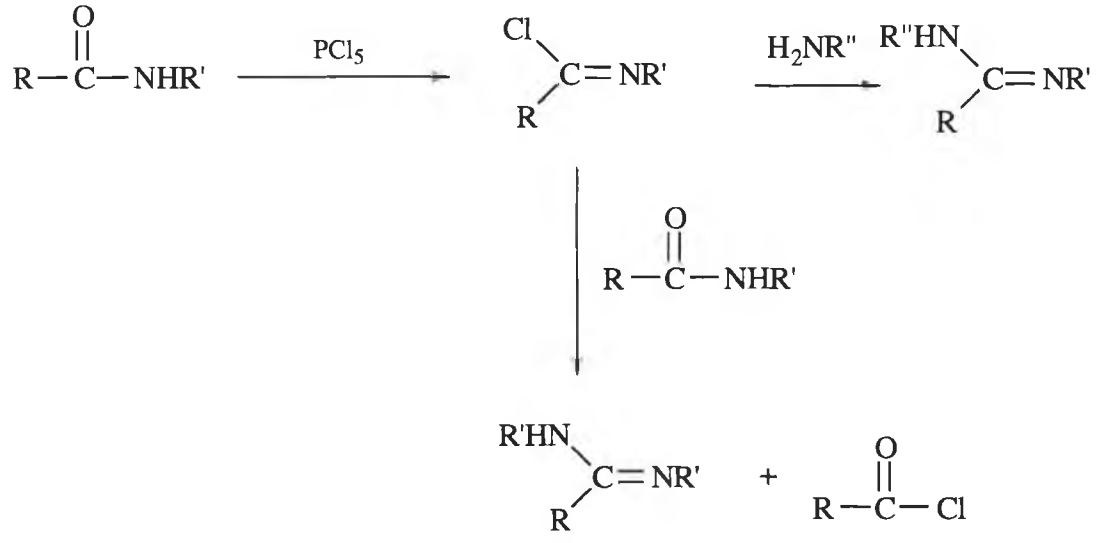


Figure 3.10

It may be that in the impure sample the aromatic portion of the monoacylated amine causes the rupture of the π-π interactions in the diacylated molecule. To test this postulation the ^1H NMR of the pure diamine was carried out in deuterated benzene which is known to break up such π-π interactions. As expected the spectrum (see figure 3.7) did not show the additional coupling and the methylene splitting pattern looked similar to that in the impure sample.

With a sample of the reasonably pure monoacylated amine in hand, the cyclisation experiments with the PCl_3 were repeated under the conditions developed for the crude sample. Surprisingly however it was found that no cyclisation took place even on repeated runs. Hence a new batch of amide was synthesised which again contained c.30 % diacylated impurity. The cyclisation was repeated on this sample and, as found initially, a new product was formed which according to mass spectrometry and ^1H NMR contained the desired cyclised imidazoline.

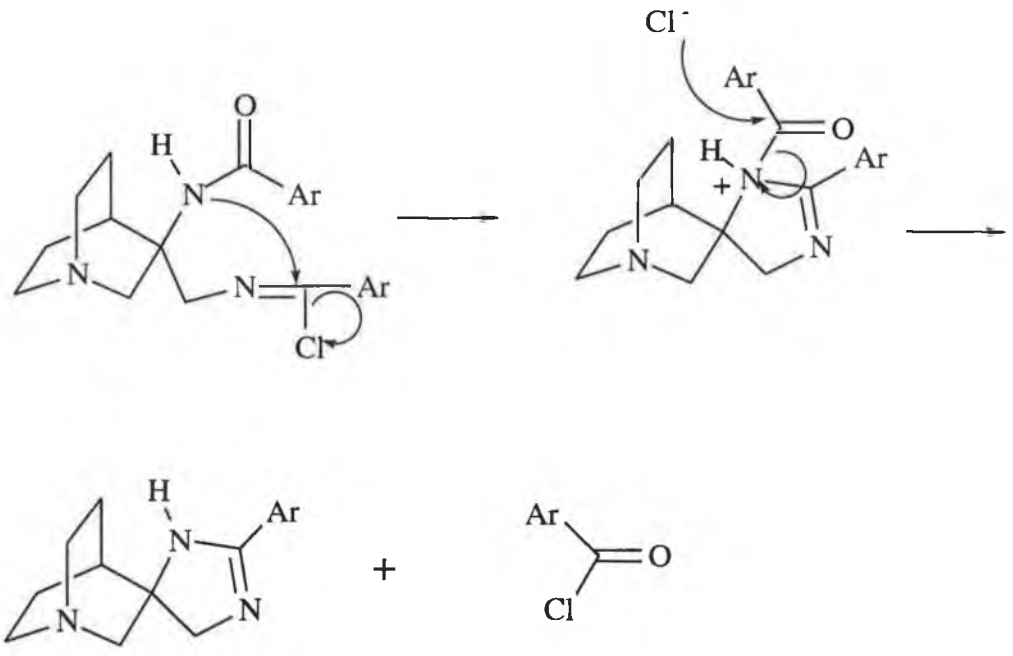
To explain this strange observation a literature search for some possible answer was performed. It was reported by Delaby and co-worker[239] that in the synthesis of amidines from the reaction of amides with amines using halogenating agents, side reactions involving the reaction of a molecule of amide on the intermediate imido chloride were observed.



Scheme [3.14]

Likewise in the absence of an amine the heating of an amide in the presence of a halogenating agent gives amidines in high yields.[241] Taking these facts into account it was thought possible that the compound which was cyclising in the impure reaction

mixture was the diacylated compound and not the monoacyl derivative as expected, as illustrated in scheme[3.15].



Scheme [3.15]

The difluorobenzoyl chloride formed as a result of the cyclisation could theoretically acylate more monoacylated starting material which could then cyclise to form more imidazoline and benzoyl chloride thus acting as a form of catalyst in the cyclisation reaction.

In order to test the hypothesis that the diacylated compound was cyclising, a large sample of the pure compound was isolated by chromatography and this was used as the substrate for the cyclisation reaction. However, on reacting the pure diacylated compound with PCl_3 in toluene, none of the required imidazoline was obtained but rather a mixture of other products was isolated, none of which could be identified by ^1H NMR or mass spectroscopy. This result was surprising and showed that when using either pure monoacylated starting material or pure diacylated compound no cyclisation

could be achieved. However, when the starting material contained a mixture of the two compounds, cyclised product could be obtained. This observed fact is not easy to explain but it is of interest to note that Aspinall reported that in the cyclisation of monoacetylenediamines to imidazolines, if a mixture of monoamide and diamide from the reaction of ethylenediamine and an ester, is cyclised with lime the yields are much higher than those obtained by dehydrating the pure monoamide with lime.[242] However no explanation as to the reason for this effect was offered.

If the failure of the pure diamide to cyclise is to be rationalised, perhaps the π-π interactions observed in the pure sample by ^{1}H NMR could offer a clue. If we suppose that under the conditions of the reaction the pure diacyl compound exists in the "locked" form (figure 3.10) already described, then the intramolecular cyclisation may be made difficult because of this. If the imido chloride does form, then attack from another molecule of diamide might be more favourable giving rise to intermolecular reactions.

In conclusion, the cyclisation of the mixture of mono- and diamides proved the most efficient mixture for the cyclisation. While the required difluoro product was obtained, it was never isolated in a pure state and thus requires further development in order to optimise the yields and the purity. The method however does provide a possible alternative route to the synthesis of 2-substituted imidazolines and may be useful in the synthesis of ortho substituted phenyl imidazoline derivatives which in most cases are not formed *via* the imidate route due to the problem of synthesising ortho substituted imidates.[196]

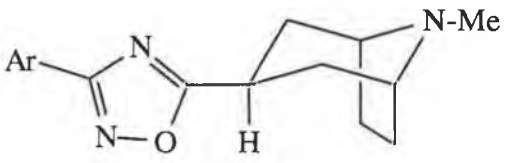
CHAPTER IV

Synthesis of exo-5'-(8-Methyl-8-azabicyclo[3.2.1]-

octan-3-yl)-3'-(aryl)-1,2,4-oxadiazoles.

4.1. **Introduction.**

In an attempt to expand the work carried out by Swain *et al.*[34] who prepared 1,2,4 oxadiazole derivatives of principally quinuclidine and 1-azabicyclo[2.2.1]heptane azabicyclic systems, we focused our attention on the synthesis of a series of 5'-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-3'-(aryl)-1,2,4-oxadiazoles (**IIIa-g**).



(III)

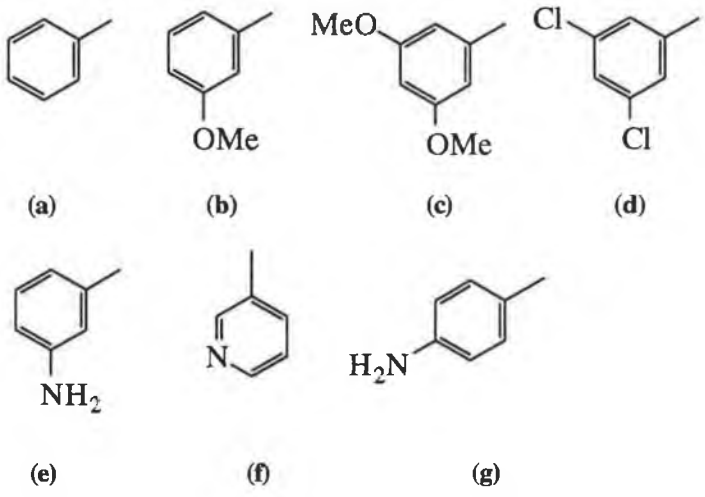
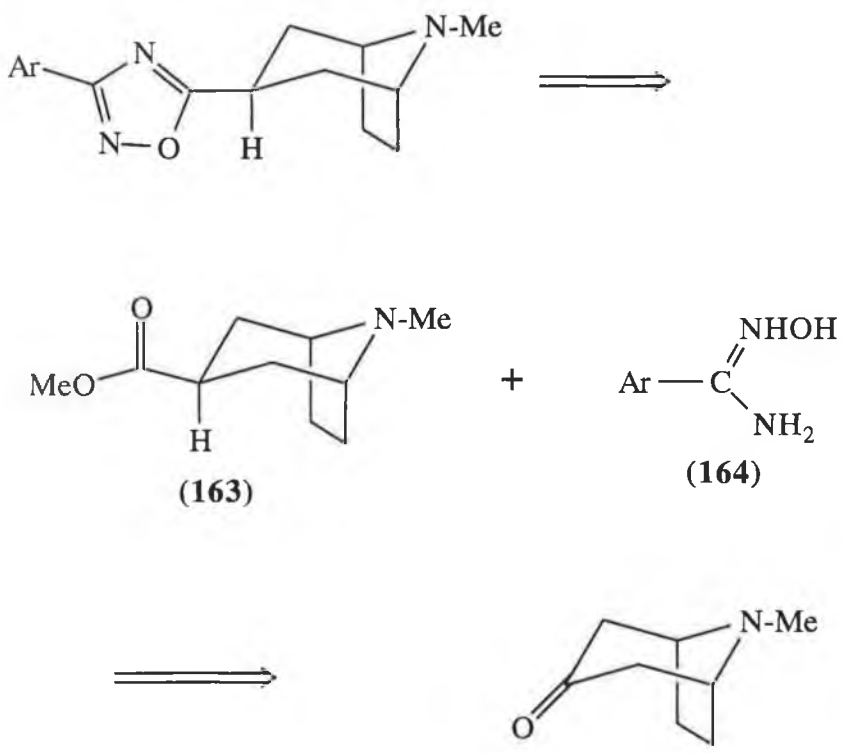


Figure 4.1

As was stated in the introduction (section 1.3.2) a very successful method of arriving at 1,2,4-oxadiazoles is by acylation of an amidoxime with ensuing cyclisation and concurrent loss of H_2O. The acylating agent can take the form of an acid anhydride,

ester, carboxylic acid or acid chloride among others.[102-113] From a synthetic standpoint an ester or carboxylic acid derivative of tropinone seemed the agent of choice.

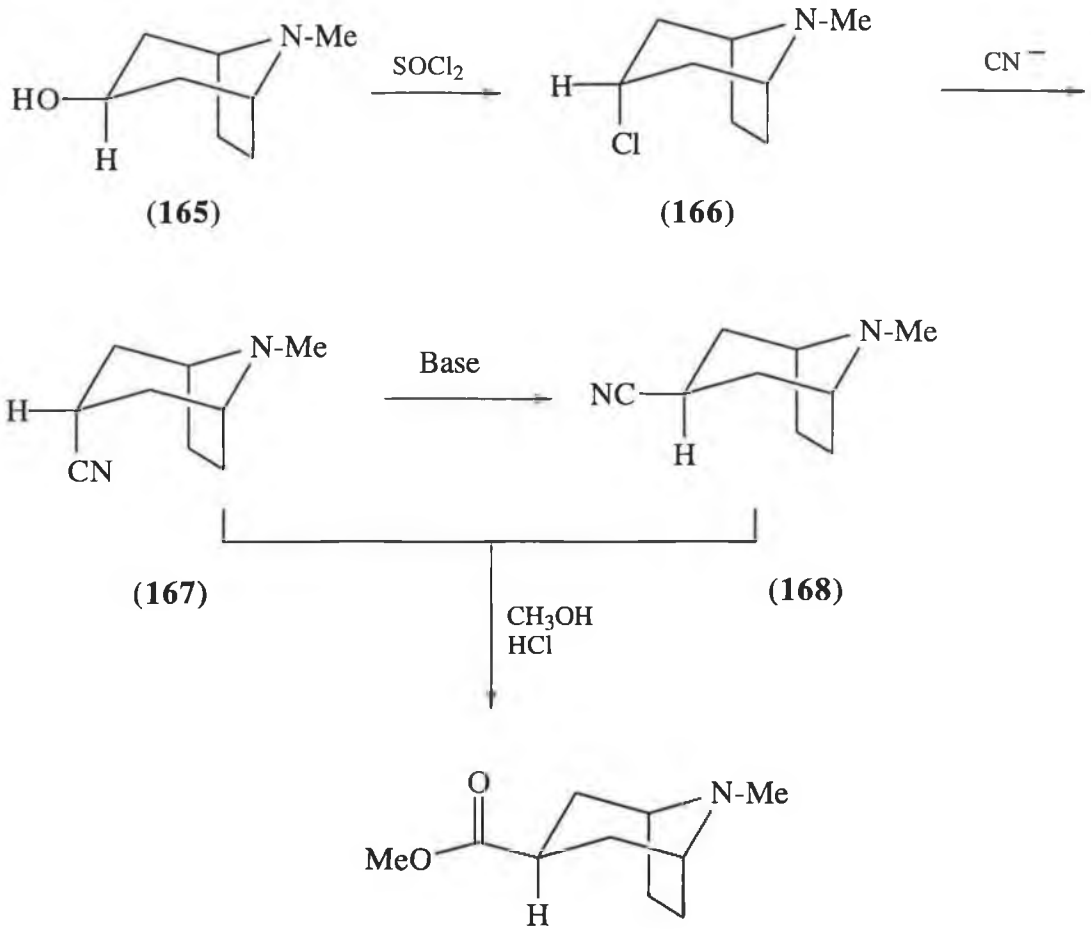
A retrosynthetic synthesis of the oxadiazoles from readily available tropinone was thus proposed which incorporates the β-tropinone ester (**163**) as a key intermediate. Scheme [4.1].



Scheme [4.1]

It was found that the success of the synthetic route proposed was highly dependant on encountering an efficient synthesis of the tropinone ester (**163**). A complete search of the literature revealed two reported synthesis of this compound with the ester functionality in the desired exo disposition. The method described by Archer *et al.*[243] involves the nucleophilic substitution of pseudotropinone (**165**) with thionyl chloride giving the chlorotropane (**166**) with inversion of configuration. This compound is then

subjected to a further substitution with a cyanide ion furnishing the nitrile (**167**) which may be epimerised to (**168**), both of which can then yield the desired tropane ester on acidic methanolysis (Scheme 4.2).



Scheme [4.2]

Before venturing into the synthesis described, which required the use of pseudotropine as starting material we speculated that the endo tropinone alcohol (tropine) which is commercially available, could be employed as starting material since the final exo or β-ester can be formed regardless of the stereochemistry of the nitrile precursor (Scheme 4.2). Though such systems with certain substituents in the exo orientation have been reported to ring open in the presence of cyanide ions,[244] we hoped that by careful choice

of solvent and mild reaction conditions, substitution without ring opening could be achieved.

Thus, the substitution of tropine with thionyl chloride was successfully carried out though in poor yield. The subsequent attempts at nucleophilic substitution of the 3β-chlorotropane with both potassium and sodium cyanide under various conditions of solvent and temperature failed to yield the desired tropanyl nitrile. IR and ^{1}H NMR analysis indicated that ring opening to a mixture of 2-allyl-4-cyano-1-methylpyrrolidines shown in figure 4.2 had ocurred (See spectrum 38).

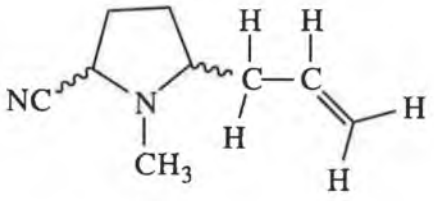
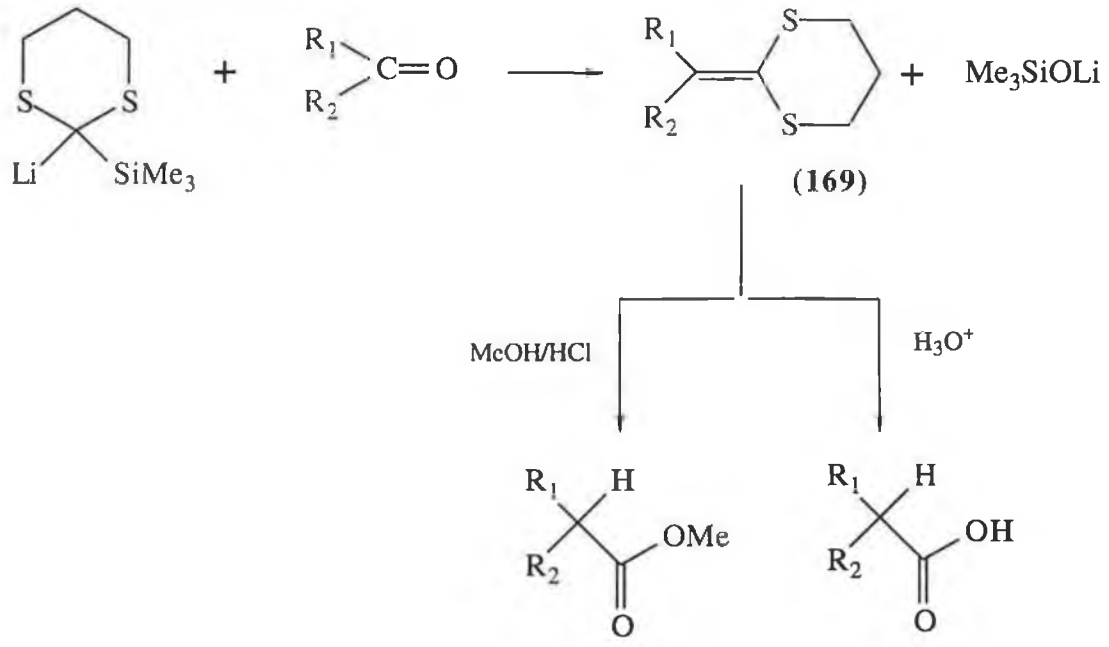


Figure 4.2

The failure of the synthesis using tropine as starting material obliged us to carry out the preparation commencing with pseudotropine. Accordingly, pseudotropine was obtained by equilibrating tropine in Na/*n*-pentanol by the method described by Beckett *et al.*[245] yielding a mixture which contained 90 % of the more thermodynamically stable pseudotropine and 10 % of the tropine isomer. After purification by column chromatography the pure isomer was obtained in 80 % yield. Chlorination of this compound with thionyl chloride gave the chlorotropane (**166**) though the reaction product was difficult to purify and yields were variable. The subsequent cyanation occurred smoothly and on methanolysis, the more thermodynamically stable exo ester was obtained whose physical characteristics corresponded to those described.[243]

However, the overall yields obtained by this method proved to be very disappointing, ranging from 5-10% and in some cases total failure, the chief losses being observed in the chlorination step. Nevertheless sufficient ester was obtained to successfully acylate benzamidoxime which gave the desired oxadiazole on cyclisation (see section 4.5). This success spurred us to search for a more efficient method of forming the ester and consequently improve the overall yield of oxadiazoles. Examination of the only alternative method, described by Zirkle *et al.*[246] though quoting higher overall yields of 23% revealed the procedure to be very laborious and required the use of very expensive α-ecgonine as starting material.

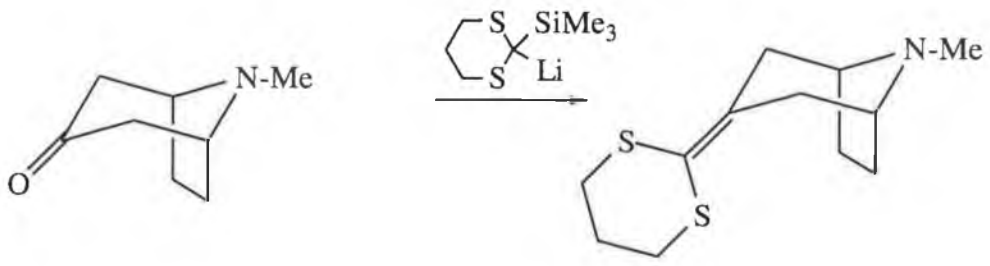
Once again the literature was resorted to, in an endeavour to find a more satisfactory method of forming the required ester. The possibility of synthesising the ester in question *via* the intermediacy of a ketene dithiane was presented as an interesting prospect. As a result of the pioneering work carried out by Corey and Seebach[247] on 2-lithio-1,3-dithiane derivatives, ketene dithioacetals (**169**) have proved to be very useful synthetic intermediates for the introduction of a range of functional groups, some of which include, carboxylic acids, esters, and aldehydes. Thus for example Seebach[248] converted ketones to ketene thioacetals which on subsequent hydrolysis yielded carboxylic acids. Snow *et al.*[249] similarly formed esters by methanolysis of the ketene dithiane intermediate (Scheme 4.3).



Scheme [4.3]

The ketene thioacetals have been synthesised using various R_1 and R_2 substituents ranging from aromatic groups to simple alkyl functions to bicyclic systems.[250] Bearing the above findings in mind we designed a synthesis of the exo-tropinone ester using the methodology described.

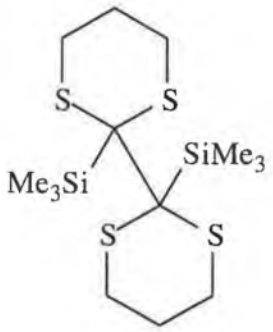
4.2 Synthesis of 3-(1,3-dithiane-2-ylidene)-8-methyl-8-azabicyclo-[3.2.1]octane (170)



(170)

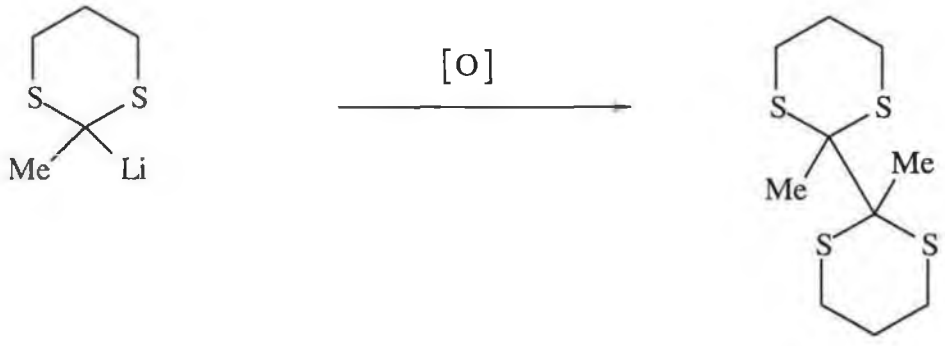
Scheme[4.4]

The reaction was carried out by preforming the carbanion of 2-(trimethylsilyl)-1,3-dithiane with n-butyllithium in hexane at -40 °C. The tropinone was then added to the dithiane salt at -50 °C following which, the reaction was allowed to warm to room temperature and quenched with H_2O. The product was isolated by extraction into methylene chloride furnishing a white semi-solid on removing the solvent. The final product was isolated by purification on a basic alumina column and was obtained in 94 % yield. Mass spectroscopy showed an M^+ of 241 corresponding to the tropinone dithiane (Spectrum 29) while ^1H NMR (Spectrum 9) clearly indicated the identity of the desired compound. Small quantities of an impurity (2-4%) were isolated by column chromatography (not in every reaction) from the reaction mixture, though not in a pure state. Mass spectrometry showed a molecular ion of 382 which could possibly correspond to the dimeric structure **171** (Spectrum 30).



(171)

Such oxidative dimerisation of anions of 1,3-dithiane has been observed[251] where the dimeric structure (**172**) was formed by coupling of (**173**) under the influence of oxidising agents such as 1,2-dibromomethane, Cu(II) or I_2.

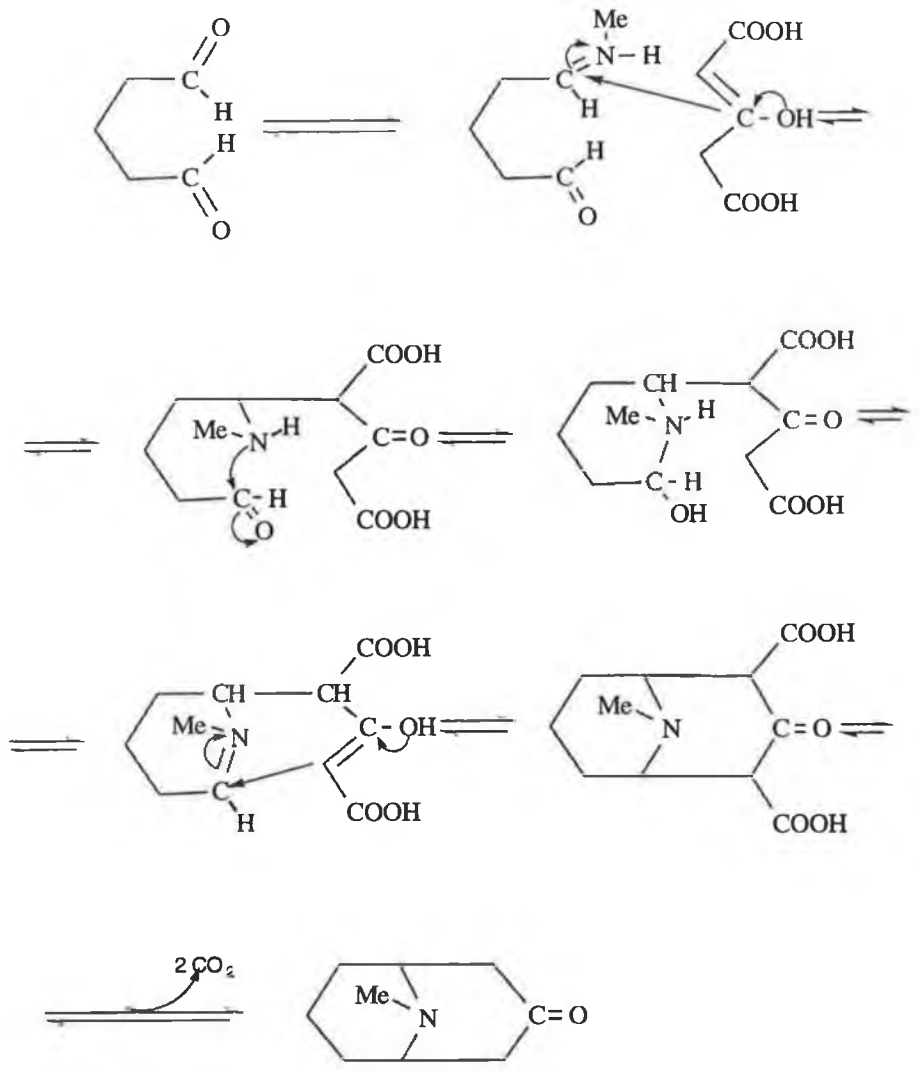


(173) **(172)**

Scheme [4.5]

Following the successful formation of the ketene thioacetal from tropinone, which represents the first reported synthesis of this compound, we sought to explore the possibility of a similar synthesis on the related granatanone system, a compound of particular interest in 5-HT_3 chemistry. The ketone (**174**) was synthesised following a procedure described by Robinson-Schöpf and modified by Ballesteros.[252] The synthesis of this amino ketone basically involved reacting glutaraldehyde,

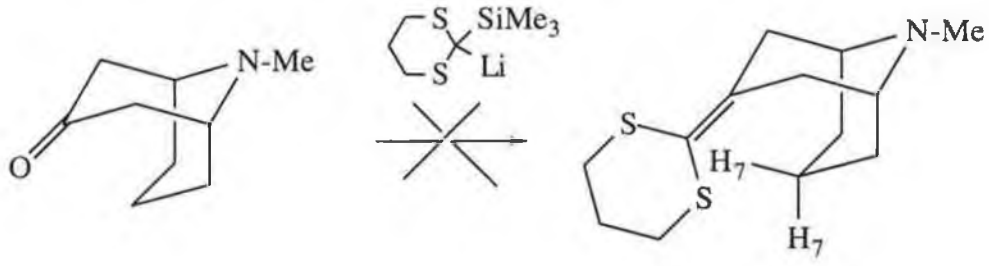
acetonedicarboxylic acid and methylamine hydrochloride at room temperature and buffering the reaction with sodium acetate/hydrochloric acid at pH 3. The mechanistic representation of the reaction is outlined in scheme [4.6].



Scheme [4.6]

The aminoketone (granatanone) thus obtained was reacted with the lithium salt of the dithiane in the manner described for tropinone (Scheme 4.7).

The reaction failed however, under various conditions of temperature and solvent and can be rationalised by the steric impediment caused by the H7 protons to the formation of the ketene structure **(175)**, thus demonstrating the steric limitations to the preparation of such compounds.

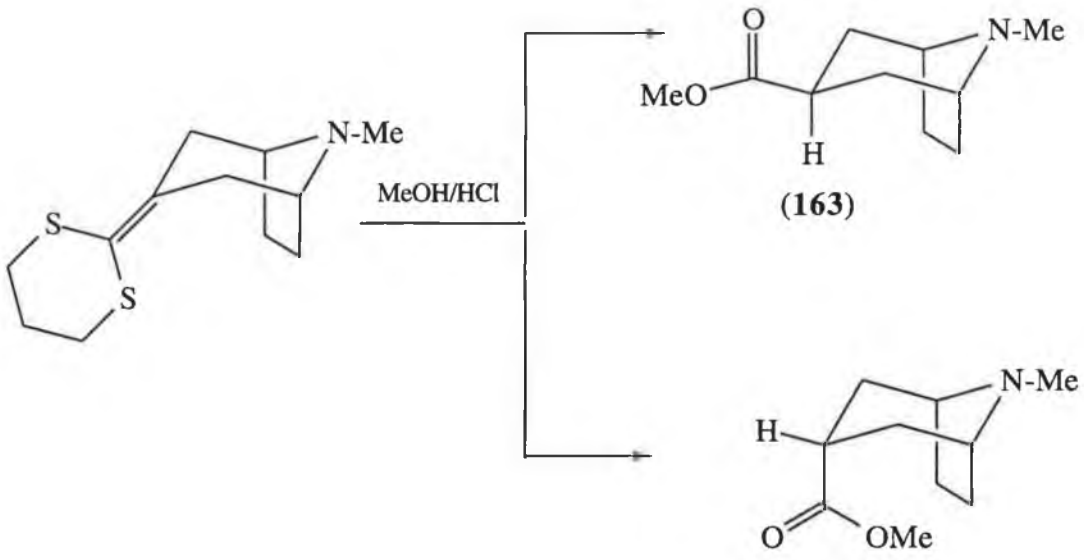


(174) **(175)**

Scheme [4.7]

4.3. Synthesis of exo-3-Carbomethoxy-8-methyl-8-azabicyclo[3.2.1]-octane (163)

The methanolyis of the tropinone ketene dithioacetal could theoretically lead to either the α (176) or β esters **(163)** of tropinone as outlined in scheme [4.8].



Scheme [4.8]

The acidic methanolysis of the dithiane was examined under various conditions of temperature and acid concentration in order to determine firstly, if these variables had any bearing on the isomeric ratio of esters formed on methanolysis, and secondly to find the conditions which gave the best yields of the exo ester.

The degree of conversion was measured by examination on TLC and a qualitative analysis of the product was made using ^{1}H NMR and IR spectroscopy.(Zirkle *et al.*[246] showed that the two isomers could readily be identified by IR analysis by observing distinctive peaks in the fingerprint region of the spectrum). It was seen that under all the conditions employed, only one isomer was obtained. However in reactions carried out at

0 °C the methanolysis was found to be very slow and complete conversion to the ester was not achieved within 72 hours. The reactions at 30 ° C and 50 °C were found to proceed much more rapidly, the best conditions being when a saturated solution of HCl in MeOH was use. The optimum conditions were thus found to be as follows. The dithiane was stirred in a saturated solution of HCl in dry MeOH at room temperature for 48 hours after which time the solvent was removed by distillation. The product was then dissolved in H_2O, neutralised with K_2CO_3 and extracted into methylene chloride. The crude oil obtained after concentration was purified under high vacuum distillation giving a product with a boiling point corresponding well to the quoted literature value for the exo ester.[246] The NMR and mass spectra (Spectra 10 and 30) confirmed the tropinone ester as the sole product while IR showed peaks at υ = 1736, 1302, 1007, 931, 848, 798, 762 cm^{-1} which are distinctive for the product with the ester group in the equatorial position.[246]

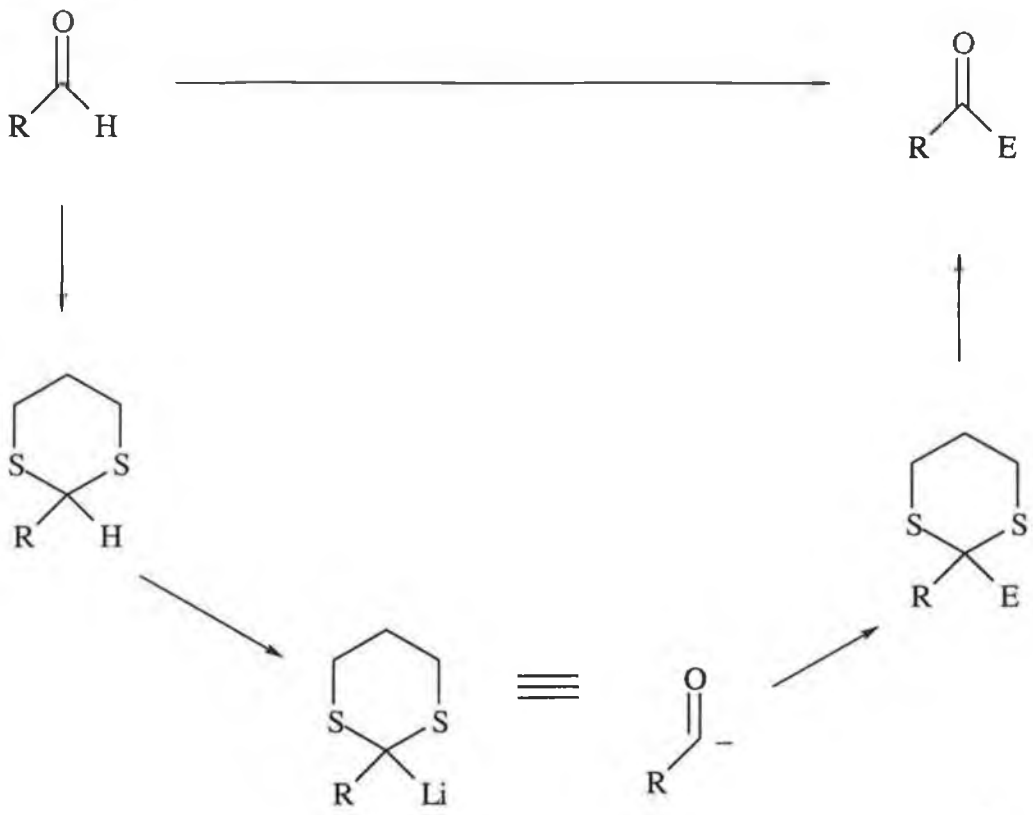
As conclusive evidence of the β disposition a sample of the product was refluxed in NaOMe /MeOH for 8 hours and no change in the compound structure was observed. It has been shown[242] that for the α isomer such treatment results in almost complete epimerisation to the more thermodynamically stable β epimer.

Noteworthy of mention is the fact that during workup of the reaction, the tropinone ester should not be left standing in the aqueous solution and should be extracted with methylene chloride as promptly as possible after quenching the reaction with H_2O. This is because the ester is quite soluble in H_2O and in aqueous solution can easily hydrolyse, especially at higher temperatures. Thus for example if the ester is left in the aqueous solution over the weekend at room temperature a 40% drop in yield is observed while if refluxed in H_2O, complete hydrolysis to the corresponding acid takes place within 3 hours.

In conclusion, a facile synthesis of the exo ester from tropinone in two steps, reported here for the first time, has been developed giving an overall yield of 94 X 65% = 61 %. The stereoselectivity in the hydrolysis is absolute, while the methodology is much simpler than either of the reported methods whose syntheses are long and laborious and in one case necessitates the formation and recrystallisation of the oxalate salts of the epimeric ester mixture in order to obtain the required pure exo ester. The yield obtained represents a significant improvement over the available methods, where quoted yields range from 15-22% and whose starting materials are considerably more expensive.

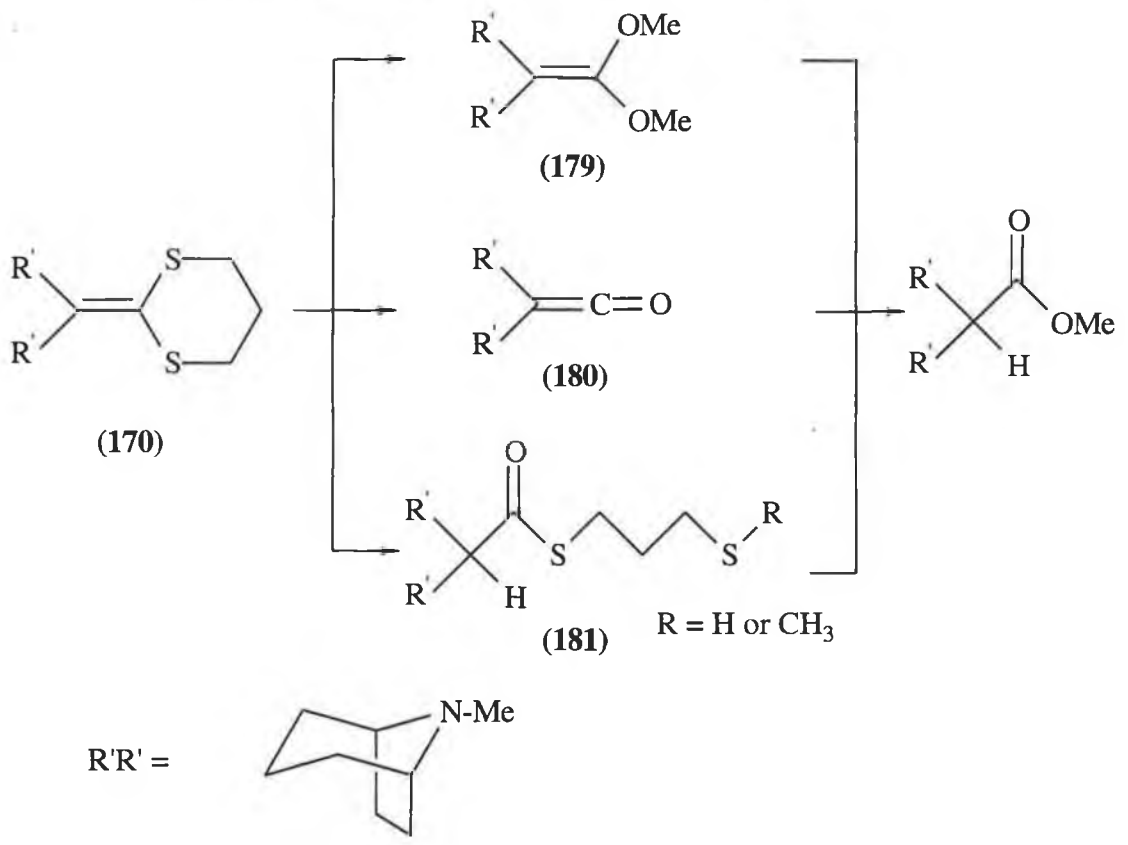
At this point it is interesting to consider the mechanisms implicated in the synthesis of the ester in both the ketene dithiane formation and in the methanolysis reaction.

The sulphur stabilised anion **(177)** shown in scheme [4.9] directly reverses the normal pattern of reactivity of the carbonyl group and thus is the equivalent of an acyl anion **(178)**. After reaction with and electrophile the dithioacetal moiety may be hydrolysed to provide the corresponding ketone. The term *Umpolung* was coined by Corey and Seebach[247] to describe the temporary reversal of the characteristic reactivity pattern of a functional group. The overall effect is the addition of an acyl function to an electrophilic carbonyl group.



Scheme [4.9]

The mechanism of the hydrolysis of the ketene dithiane provides some interesting discussion. An *a priori* examination of the mechanism of methanolysis indicates the existence of several feasible intermediates.



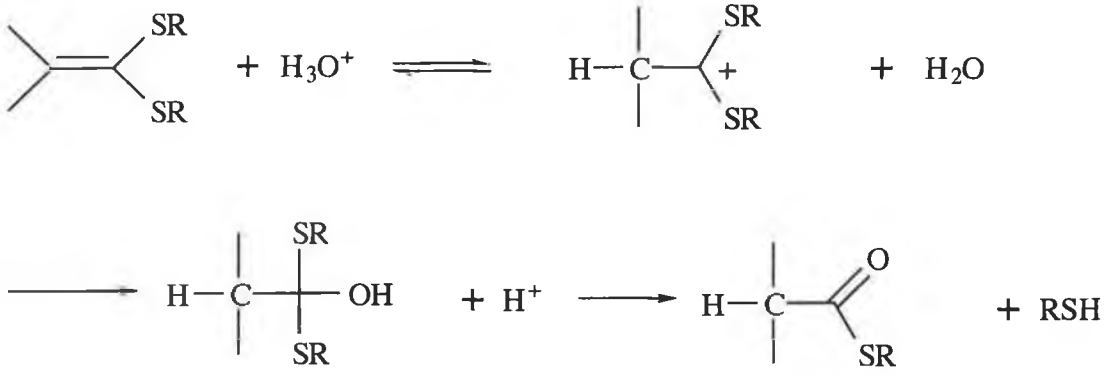
Scheme [4.10]

Protonation of one of the sulphur atoms followed by nucleophilic attack at the 2 position of the dithiane ring with ensuing ring opening, succeeded by a second similar substitution could give the ketene acetal (**179**) whose mechanism of acid catalysed hydrolysis to the ester has been studied.[253] A second possibility which exists is the attack of the methanol as described, which then, rather than being attacked by a second molecule of methanol, eliminates $CH_3S(CH_2)_3SH$ or $HS(CH_2)_3SH$ giving rise to the ketene **(180)** which on subsequent nucleophilic attack by methanol could give the ester. A third candidate is the thiol ester **(181)**.

A literature search was performed to find some evidence to substantiate one or other of the proposed mechanisms. After a detailed investigation however no study on the acidic methanolysis of ketene dithianes could be found. Nevertheless some Japanese researchers have carried out detailed kinetic and mechanistic studies of the acidic

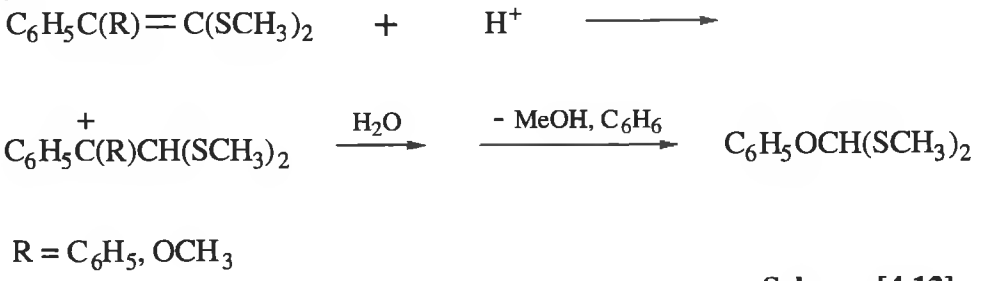
hydrolysis of ketene dithioacetals the findings of which could possibly be extrapolated to the corresponding methanolysis.

Okuyama *et al.*[254] found that ketene dithioacetals underwent acid catalysed hydrolysis to give thiol esters in a stepwise manner in a similar mechanism to ketene acetals. They found hydration of the double bond to be the primary reaction which proceeds through carbon protonation and ensuing water attack on the intermediate carbocation (Scheme 4.11).



Scheme [4.11]

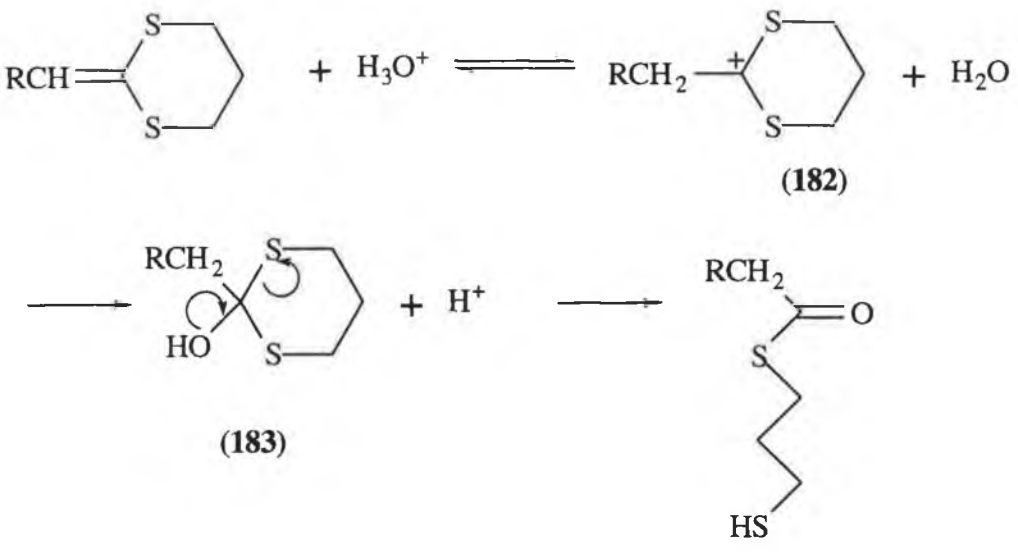
They found that in constrast to the hydrolysis of ketene acetals, the initial protonation which is reversible, was not the rate determining step in the hydrolysis of ketene dithioacetals. It should be noted at this stage that the carbocation formation does not always take place at the position α to the sulphur atoms. Russel and Ochrymowycz[255] in their studies on the hydration of vinyl sulphides found products in the protonation of ketene mercaptals which were consistent with protonation at the other carbon. Scheme [4.12].



Scheme [4.12]

This result can be explained by considering the increased stability conferred on the carbonium ion by the two phenyl substituents or the methoxy group.

Expanding their studies on hydrolysis of acyclic ketene dithioacetals, Okuyama *et al.*[256] investigated the hydrolysis of the cyclic counterparts, namely 2-methylene-1,3-dithiane and its derivatives and found a similar stepwise hydrolysis of initial protonation to form the carbocation, succeeded by hydration and decay of the 2-hydroxy-1,3-dithiane giving the thiol ester. Scheme [4.13]



Scheme [4.13]

As with the acyclic compounds, further hydrolysis to the acid was found to be quite slow in acidic solutions. The hydrolysis reactivity of the cyclic compound was found to be similar to the acyclic analogue but the reversibility of the protonation step was much smaller and was ascribed to the ease of hydration of the carbocation. This acceleration of the hydration in the cyclic dithiane carbocation was rationalised by the change in hybridisation on going from **(182)** to **(183)**. The 2-carbon is sp^2 hybridised in **(182)** and so are the two adjacent sulphur atoms. However, these three atoms become sp^3 hybridised in **(183)** and consequently, the forced planarity involving the C-S-S triad induces a considerable strain on the dithiane ring of **(182)**, but such a strain does not

occur in **(183)**. Thus the hydration step relieves the strain in the molecule making this step much faster than that of the acyclic analogue.

In conclusion, can any parallel be drawn from these hydrolysis studies to provide a mechanism for the methanolysis of the tropinone dithiane **(170)** ?

It was observed that when the methanolysis of the tropinone dithiane was performed at 0 °C not only was the reaction much slower than at room temperature as already stated, but also an additional spot could be seen on TLC which diminished with time, and can probably be considered as an intermediate product. Examination of the IR spectra of the low temperature methanolysis reactions all showed, apart from the ester carbonyl at 1735 cm^{-1} and the distinctive peaks in the fingerprint region for the alpha ester, additional bands at 1692, 1351, 1128 and 913 cm^{-1} (Figure 4.5). The band at 1692 cm^{-1} could be assigned to the stretching frequency of the carbonyl group of a thiol ester which are characterised by carbonyl bands lower than normal esters due to increased resonance from the more polarisable sulphur atom. For aliphatic thiol esters the carbonyl normally shows up between 1700-1680 cm^{-1}. The bands at 1128 and 913 cm^{-1} may correspond to the C-C and C-S stretches respectively. These additional bands do not correspond to a ketene carbonyl or a ketene diacetal and so the intermediate **(181)** seems to be a more likely candidate as the intermediate in the methanolysis reaction. It is not unreasonable therefore to assume a mechanism for the methanolysis of the tropinone dithiane similar to that outlined in scheme [4.13]. However in the case of the methanolysis of compound **(170)** the reaction goes further and the thiol ester **(181)** undergoes nucleophilic attack by another molecule of MeOH to give the ester **(163)** with liberation of the mercaptan $HS(CH_2)_3SR$ where R could be either H or CH_3. The methanol is probably a better nucleophile than H_2O towards the carbonyl group of the thiol ester under the acidic reaction conditions and hence the reaction doesn't tend to stop at the thiol ester as in the case of the hydrolysis with H_2O.

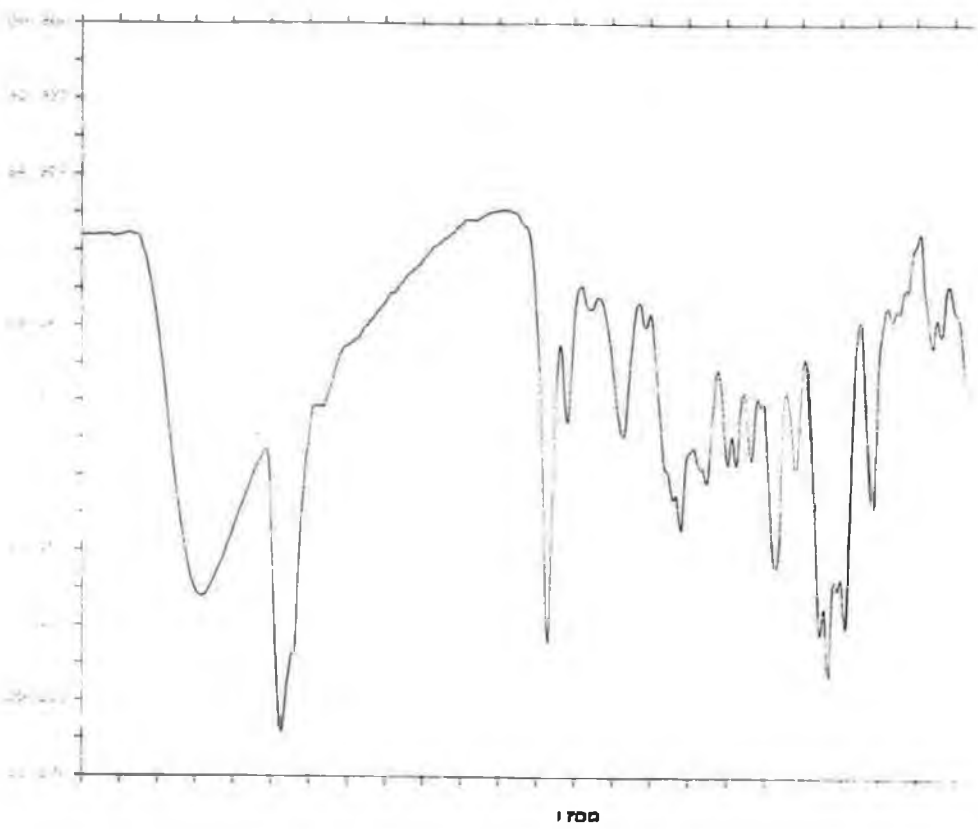


Figure [4.3] IR spectrum of the tropinone ketenedithioacetal **170** (KBr)

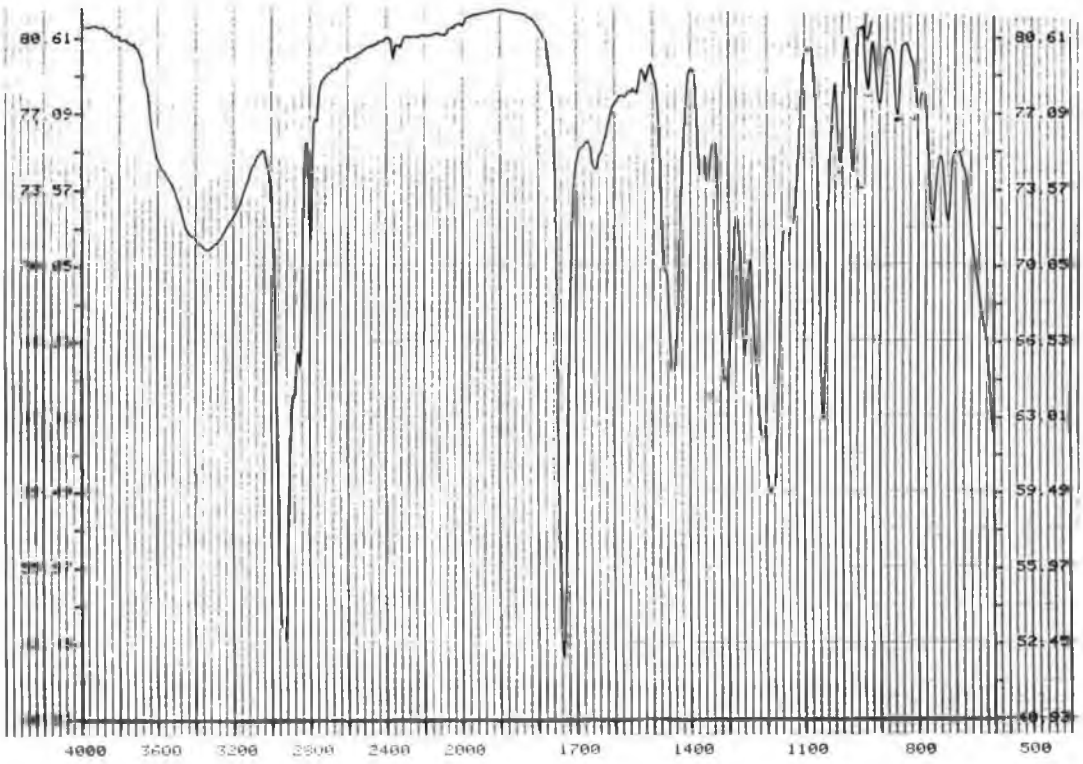


Figure [4.4] IR spectrum of the tropinone ester **163** following acidic methanolysis of 170 at **40** °C.

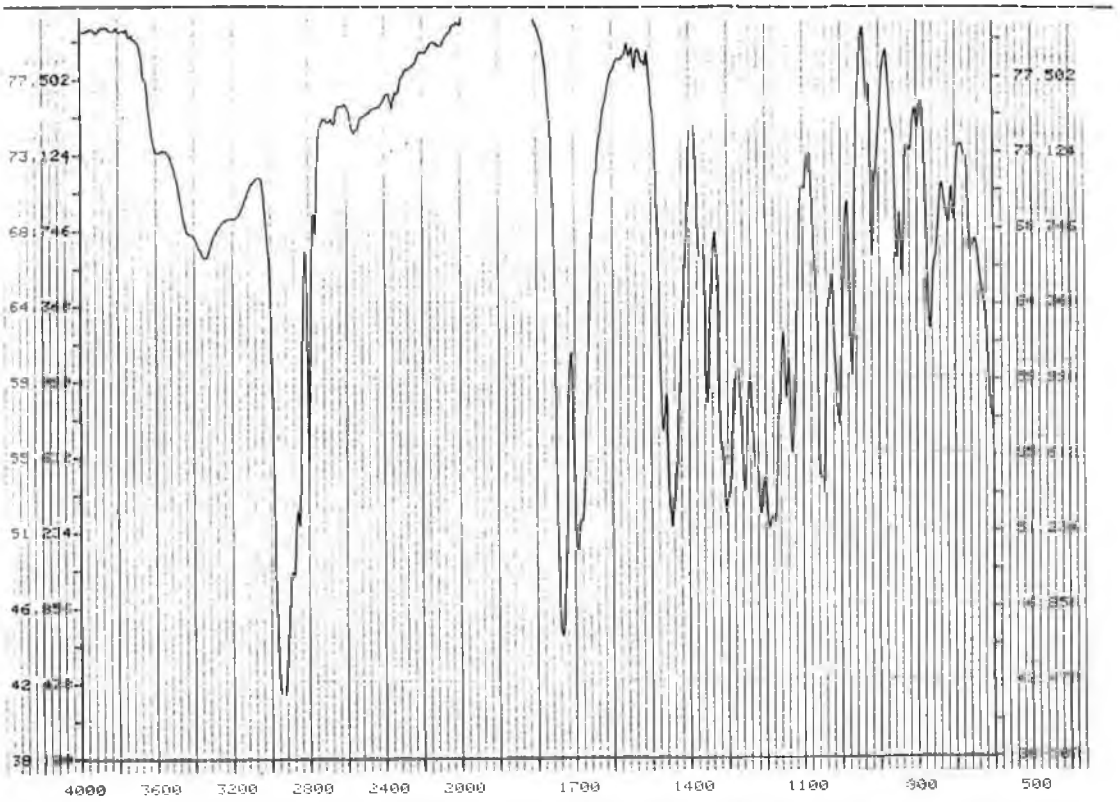


Figure [4.5] IR spectrum of the tropinone ester **163** following acidic methanolysis of 170 at **0** °C.

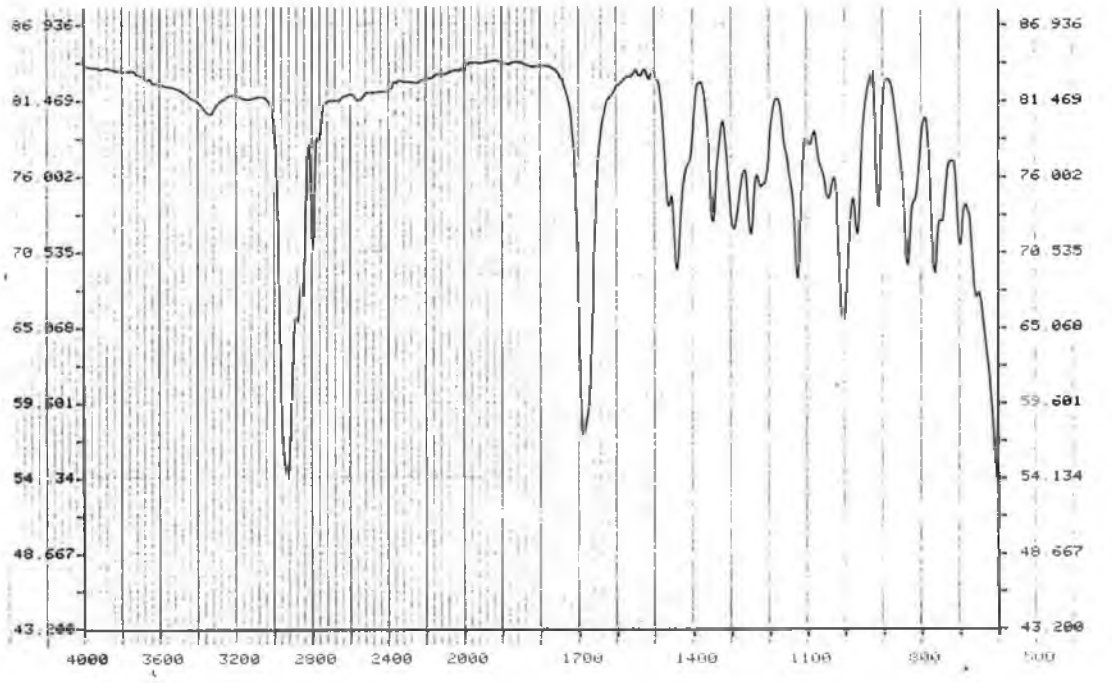


Figure [4.6] IR spectrum of the tropinone thiol ester **181** following aqueous acidic hydrolysis of 170 at **40** °C.

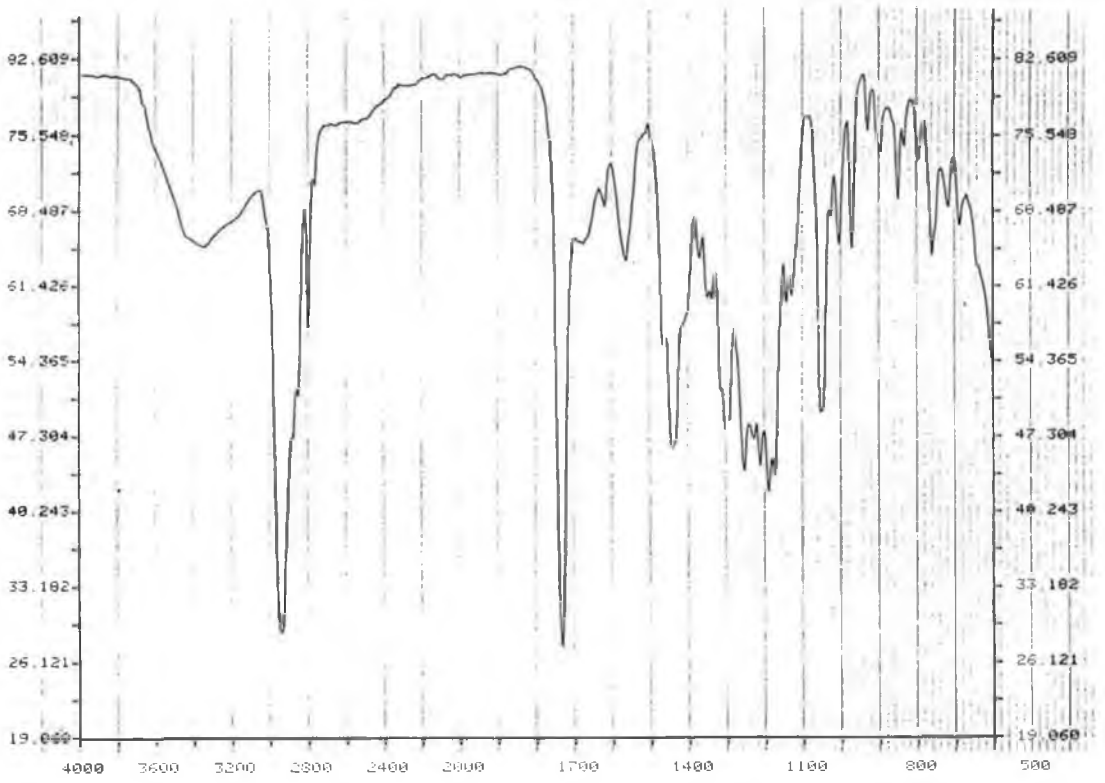


Figure [4.7] IR spectrum of the tropinone thiol ester **181** after stirring in MeOH for 12 h.

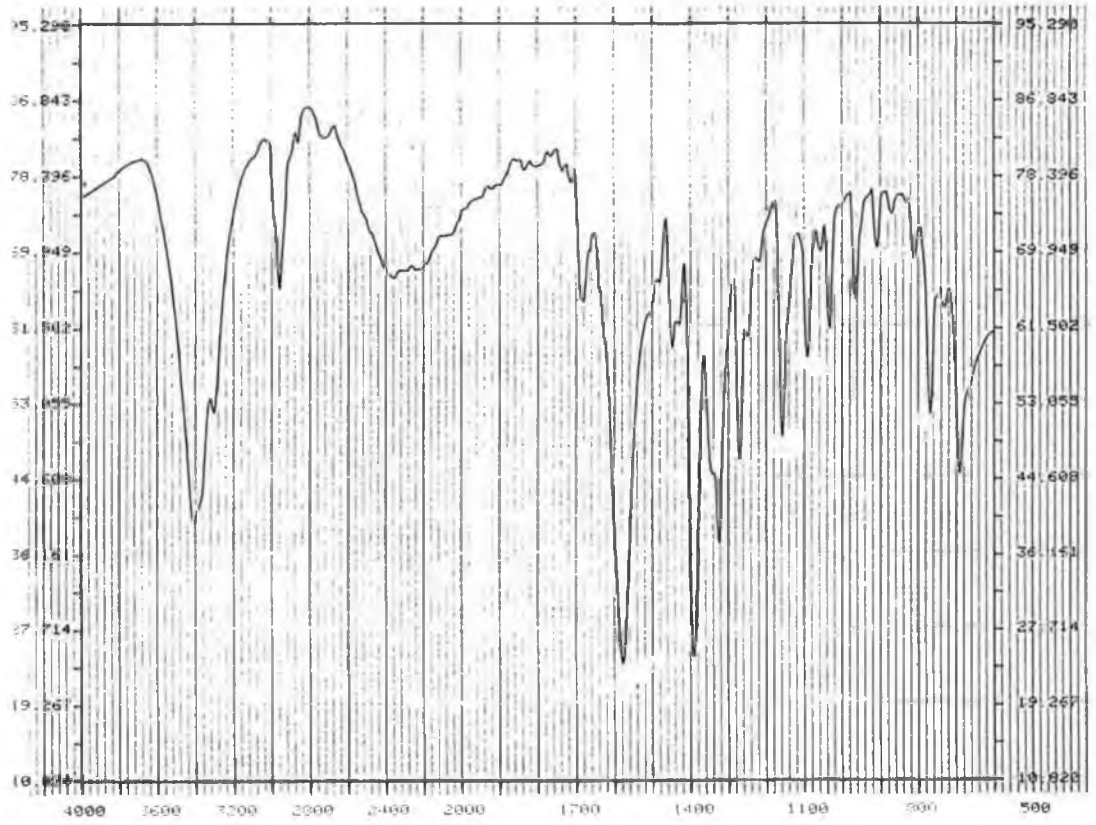
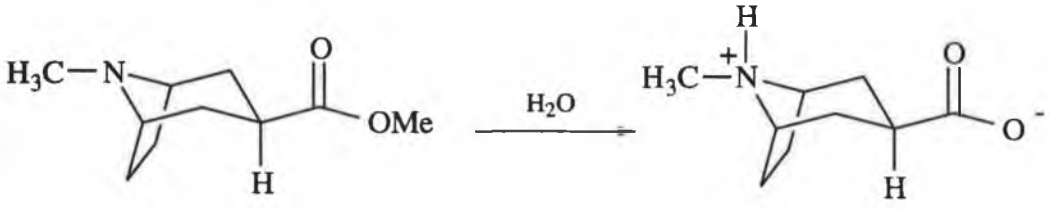


Figure [4.8] IR spectrum of the tropinone 3β carboxylic acid zwitterion **184**.

To corroborate this supposition the hydrolysis of the ketene dithiane **(170)** was carried out in aqueous hydrochloric acid which should yield the thiol ester **(181)** where R = H. A compound was obtained which had a strong adsorption on IR at 1692 cm^{-1} probably corresponding to the carbonyl of the expected thiol ester, plus a weak band at 913 cm^{-1} and a weak adsorption at 2560 cm^{-1} corresponding to S-H deformation and S-H stretching frequencies respectively (see ir spectrum figure 4.6). All three bands were present in the product from the methanolysis of the ketene dithiane carried out at 0°C (figure 4.5) implying that the methanolysis intermediate **(181)** has R = H and not CH_3. The methanolysis and hydrolysis reaction thus have a common intermediate.

In order to unequivocally confirm that the carbonyl frequency from the 0 °C methanolysis resulted from a thiol ester carbonyl and not from any possible carboxylic acid whose adsorption frequencies can be very similar, a sample of the tropinone ester was hydrolysed to the acid by refluxing in water and studied by IR spectroscopy.

Surprisingly it was found not only did the aminoacid carbonyl have a different adsorption from the thiol ester but that it appeared a full 110 cm^{-1} below the thiol carbonyl at 1580 cm^{-1} (figure 4.8) This value being excessively low for a carboxylic acid even in an associated state, indicated that the tropane amino acid probably existed in its zwitterionic form **184** (Scheme 4.14).



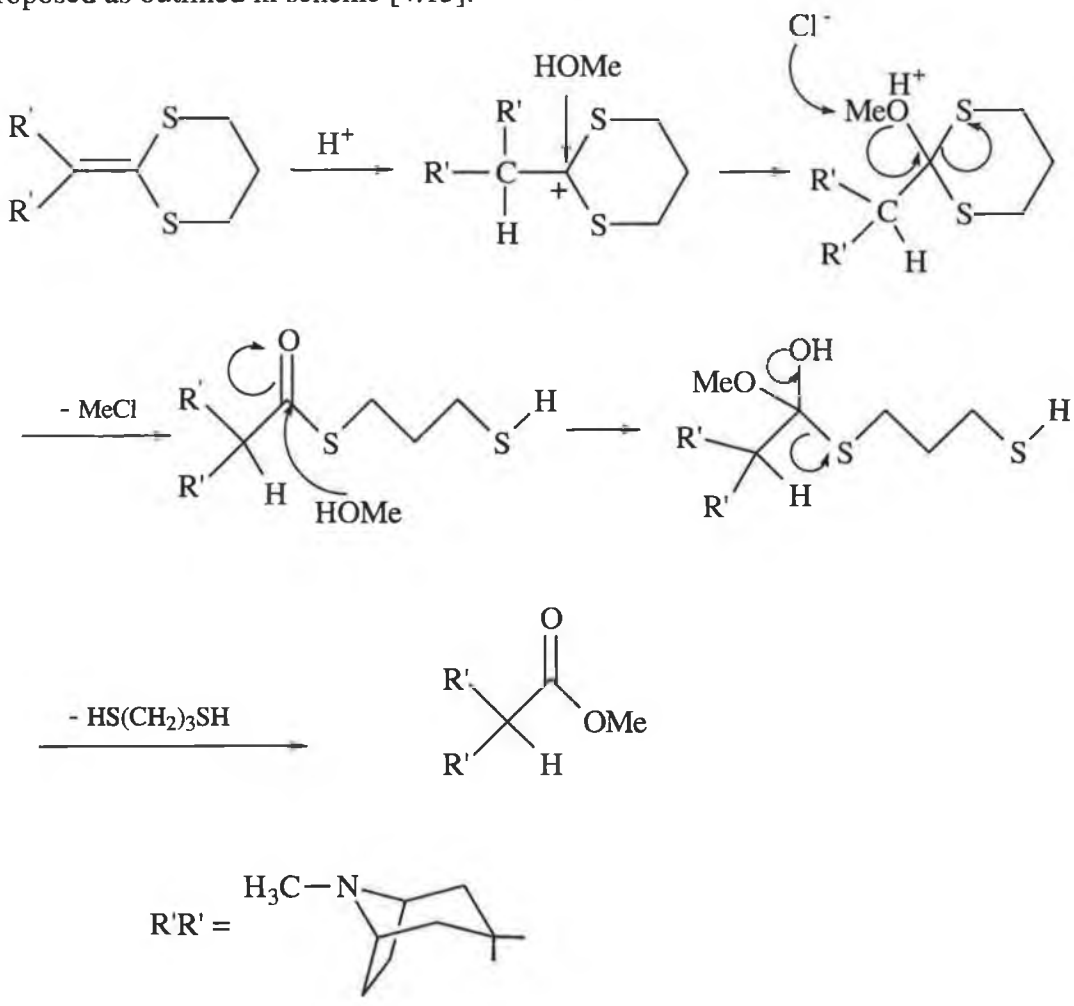
(163) **(184)**

Scheme [4.14]

This being the case, the carbonyl frequency perfectly matches the published figures for the anionic form of an acid. Confirmatory evidence should be provided by the chemical

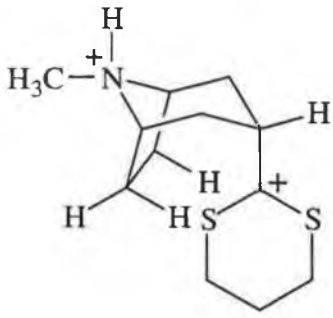
shift of the N-CH_3 group by ^1H NMR. Hence the δ value at 2.74 ppm for a tropinone methyl group in deuterated methanol corresponded perfectly to a protonated N-CH_3 rather than the free base.[257] This is the first time that this observation has been reported for this compound.

If the thiol ester (**181**) is, as already stated, common to both the methanolysis and hydrolysis reactions then addition of methanol to the isolated aqueous hydrolysis product should yield the tropane ester (**163**). This indeed was found to be the case. When the thiol ester was stirred overnight in methanol a product was obtained which gave an IR spectrum identical to that of the tropinone ester (figure 4.7). On considering such evidence an overall reaction mechanism for the acidic methanolysis can be proposed as outlined in scheme [4.15].



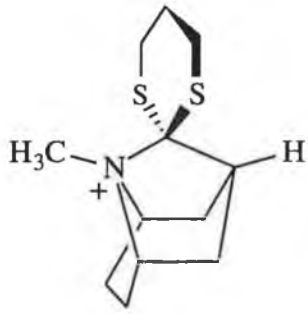
Scheme [4.15]

Presuming the mechanism outlined is correct, it is not altogether surprising that the only isomer obtained from the reaction was the exo ester. From a steric point of view the presence of the sterically demanding dithiane carbocation group in the endo orientation (**185**) would seem highly unfavourable, the exo position probably being more thermodynamically stable and hence after hydration (which unlike the protonation is usually irreversible) would lead ultimately to the exo ester formation.



(185)

Apart from the unfavourable steric impediment to the dithiane in the endo position an electronic stabilising effect of the exo carbocation **(186)** is not to be ruled out.

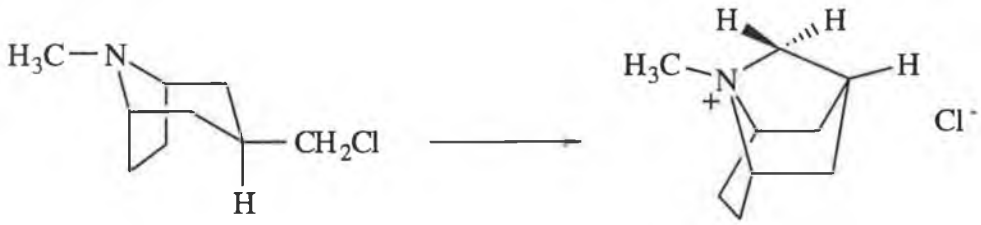


(186)

It can be seen that the nitrogen could donate its lone pair of electrons* to the cationic centre of the dithiol thus stabilising the positive charge. This would also have a stability effect in that the 2-position of the dithiane would then be an sp^3 rather than an sp^2 centre

thus relieving ring strain alluded to earlier. Such 5 membered systems are known, which lend support to the structure. For example, Zirkle *et al.*[246] formed the tricyclic quaternary ammonium chloride **(187)** by heating the base at reflux for 2 hours. Scheme [4.16]

*It is true however that under the acidic hydrolysis of the tropinone ketene dithioacetal, the nitrogen is primarily in the protonated state. It is reasonable to presume however that a certain amount exists in equilibrium as the free base at any particular time thus allowing for the formation of intermediate (**186**).



(187)

Scheme [4.16]

Attempts were made to synthesise and identify the hypothesised intermediate **(186)** by stirring the tropinone dithane in HCl dissolved in a non nucleophilic medium. However, only the hydrochloride salt of the starting material was obtained from reactions using CH_2Cl_2, MeCN and acetone as solvents. It may be that these solvents are insufficiently polar to favour the formation of the carbocation.

4.4 Synthesis of aryl amidoximes (164)

Amidoximes are well known and widely used compounds and were first described at the end of the ninteenth century. A comprehensive review of amidoximes has been published by Eloy and Lenares[258] so a minimal coverage of their synthesis and properties is given here.

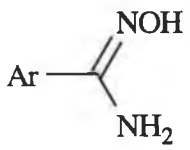
Amidoximes can be synthesised by several synthetic approaches which among others include, the action of hydroxylamine on nitriles, amides, thioamides, imino ethers or amidine hydrochlorides, the reduction of nitrosolic and nitrolic acids or oxyamidoximes, the action of ammonia on hydroximic acid chlorides, glyoxime peroxides or oximinoethers, and the reaction of formamidoxime with aromatic aldehydes.[258] By far the most used process and the one which was used in the preparation of the amidoximes for this project, is that which reacts hydroxylamine with nitriles.

$$RCN \quad + \quad NH_2OH \longrightarrow \quad RC(=NOH)NH_2$$

Scheme [4.17]

The method usually consists in liberating the hydroxylamine from its hydrochloride with potassium of sodium carbonate and adding an equivalent amount of nitrile and enough alcohol to obtain a clear solution, and keeping the mixture at 60-80 °C for a few hours.

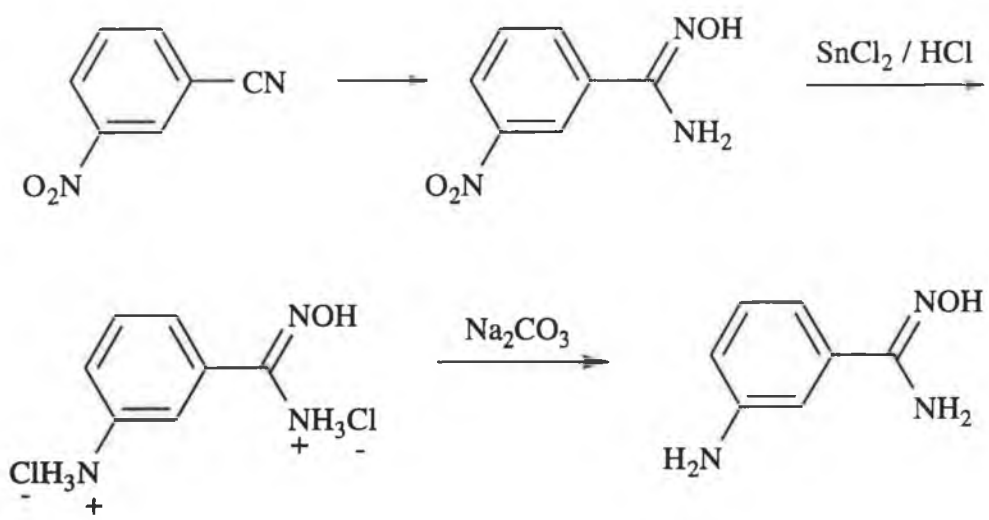
In order to synthesise the required oxadiazoles the following amidoximes were prepared.



(164 a-h)

For **164 a-g** Ar- refers to the series of aryl groups which are given in figure 4.1. **164 h** refers to the 4-pyridine *N*-oxide derivative.

Though some of the amidoximes prepared here have been previously reported, considerable comment will be made regarding the methods of preparing the amidoximes in question as they represent significant advances over existing methods. Thus for example the only reported synthesis of the *meta* and *para* amino phenyl amidoxime[259,260] employs a method whereby the corresponding nitro amidoxime derivative was initially prepared by the action of hydroxylamine on nitrobenzonitrile. The nitro compound was subsequently reduced with $SnCl_2$ in dilute HCl to yield after precipitation of the tin salts, the dihydrochloride salt of the desired aniline amidoxime. Liberation of the salt with sodium carbonate thus yielded the aniline amidoxime which in the case of the meta isomer, according to the authors couldn't be obtained in a crystalline state but rather as a semi solid. No melting point is consequently quoted.



Scheme [4.18]

We found that for conversion of the aminobenzonitriles to the corresponding amidoximes it wasn't necessary to proceed *via* the intermediacy of the nitroamidoxime. It was discovered that very reasonable conversion of the aminonitriles to the free base of

the amidoximes could be achieved directly by reaction with hydroxylamine under the conditions described. Thus for the synthesis of 3-aminophenyl amidoxime the method involves mixing the nitrile with an equivalent of the hydrochloride salt of hydroxylamine and 1.35 equivalents of K_2CO_3 in absolute ethanol and heating to reflux for 12 hours. After this period of time about 60-70% conversion, as monitored by TLC was achieved. Unlike the amidoximes (**164 a,b,c,d,f**) the aminophenyl derivatives were soluble in H_2O and hence their work-up procedure had to be varied. Thus the reaction mixture after 12 h refluxing was cooled to 20 °C and the inorganic salts were filtered off. The reaction mixture was then dissolved in H_2O and stirred with 3 x CH_2Cl_2 which selectively extracted the unreacted starting material leaving solely the amidoxime in the aqueous phase. Most of the water was then removed by azeotropic distillation with toluene until 1-2 volumes of H_2O remained from which the amidoxime crystallised in a pure crystalline form in 40 % yield giving a sharp melting point of 125-127 °C and the required mass spectroscopic analysis.

Under similar reaction conditions the 4-amino benzonitrile failed to give more than c. 5% conversion after 12 hours reflux. It was found that by adding H_2O to the reaction about 60% conversion could be achieved after 3 hours at reflux temperature. On further heating no further conversion could be achieved. The reaction at this stage formed a cream coloured paste from which the supernatent liquid was decanted. The liquid was then evaporated to dryness and partitioned between CH_2Cl_2/H_2O at 40 °C which like the previous case resulted in selective partitioning of the product into the aqueous phase and the starting material into the methylene chloride. The water volume was reduced as described and the product was obtained in 48 % yield as a pure crystalline solid on crystalliation from H_2O.

With the remaining amidoximes variations in the work-up procedure were made depending on the solubilities of the products. Thus for compounds (**164 a,b,c**) the reaction products were obtained by filtering off the inorganic products and evaporating

the filtrate to dryness. Any remaining inorganic salts were then removed by dissolving the residue in methylene chloride followed by filtration of the resulting cloudy solution. In the case of compound (**164 f**) the residue was redissolved in ethanol rather than CH_2Cl_2 due to its insolubility in the latter.

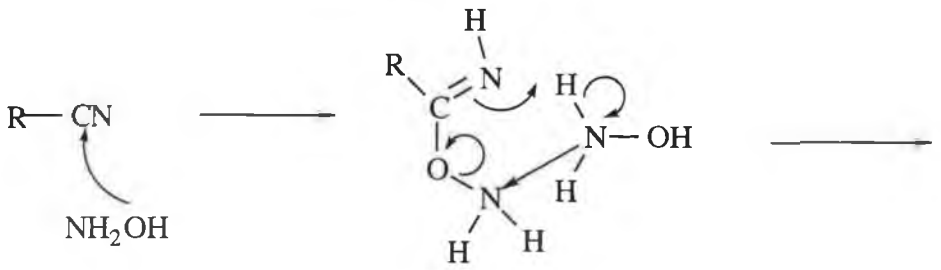
Special difficulty was encountered in the case of the pyridine *N*-oxide amidoxime (**164 h**) which proved to be extremely insoluble in all the organic solvents tried. It was found that the amidoxime, as soon as it formed, immediately precipitated from the reaction medium and thus the solids filtered from the reaction contained a mixture of inorganic salts and amidoxime. Attempts to selectively extract the product with MeOH, CH_2Cl_2, EtOAc, acetone or nitromethane all proved unsuccessful. As the amidoxime was also found to be insoluble in H_2O it was isolated from the inorganic salts by refluxing the solid mixture in H_2O for two hours which on filtration left the highly insoluble amidoxime. The product was then stirred in hot methanol to remove any traces of starting material or impurities that might have been present.

The identity of the amidoxime was confirmed by the two typical sharp NH_2 bands at 3418, and 3296 cm^{-1}, the broad OH band at 3160 cm^{-1} and the C=N stretching frequency at 1644 cm^{-1}. MS also gave a strong M^+ of 153 corresponding to the amidoxime along with a perfect elemental analysis. Consistent with the amphoteric properties of amidoximes, compound (**164 h**) was found to be soluble in both dilute mineral acid and basic solutions. What was unusual about the pyridine *N*-oxide compound was that, unlike the remaining amidoximes prepared which could only be dissolved in KOH or NaOH solutions, (**164 h**) was soluble in aqueous K_2CO_3 solutions. Moreover, on dissolving in aqueous potassium carbonate, an intense yellow solution formed which on acidification with HCl reverted to a colourless solution. Rebasification with K_2CO_3 again produced the yellow colour. The colour produced on basifying was thought to be due to a potassium complex of the deprotonated amidoxime, since it is known that amidoximes form coloured crystalline compounds with the salts of

some metals.[258] Werner,[261] prepared a great number of such compounds with different amidoximes and proved that they are internal complexes in which the metal atom is linked to the oxime group as well as to the amino group. Certain amidoximes have been used as analytical reagents for various cations, such as the quantitative analysis of Ni^{2+}, Cu^{2+}, Ag^{+}, Co^{2+} and for the spectrophotometric determination of uranium.[258] The synthesis of amidoxime (**164 f**) has not previously been described in the literature and it is quite possible that it may serve as a useful agent in qualitative analysis.

All the amidoximes synthesised were identified by IR spectroscopy (Spectrum 39), mass spectroscopy and elemental analysis. A positive identification by all three methods was obtained for all the amidoximes except the 3,5-dichlorophenyl amidoxime (**164 d**). This compound though conforming to the required structure by IR and mass spectra analysis and which according to TLC analysis seemed to contain only one compound, failed to give an accurate elemental analysis even on repeated synthesis.

At this stage the literature was resorted to in an effort to find a solution to the problem. It was found that the only reported synthesis of the amidoxime in question was carried out by Stephenson *et al.*[262] in 1969. The authors reported a study on the effects of electron withdrawing substituents when aromatic nitriles were treated with hydroxylamine in anhydrous methanol. They found that when 4-cyanopyridine or nitriles of the type $X{\cdot}C_6H_4CN$ (X= *o*-NO_2, *p*-CN, *p*-Cl *p*-CF_3) were treated with an excess of hydroxylamine in methanol, the resultant amidoximes were contaminated with substantial amounts (17-55 %) of the corresponding amides. The following mechanism was proposed to explain the observations. Scheme [4.19]



$$RCONH_2 \quad + \quad [\ H_2N{\cdot}NH{\cdot}OH\ ]$$

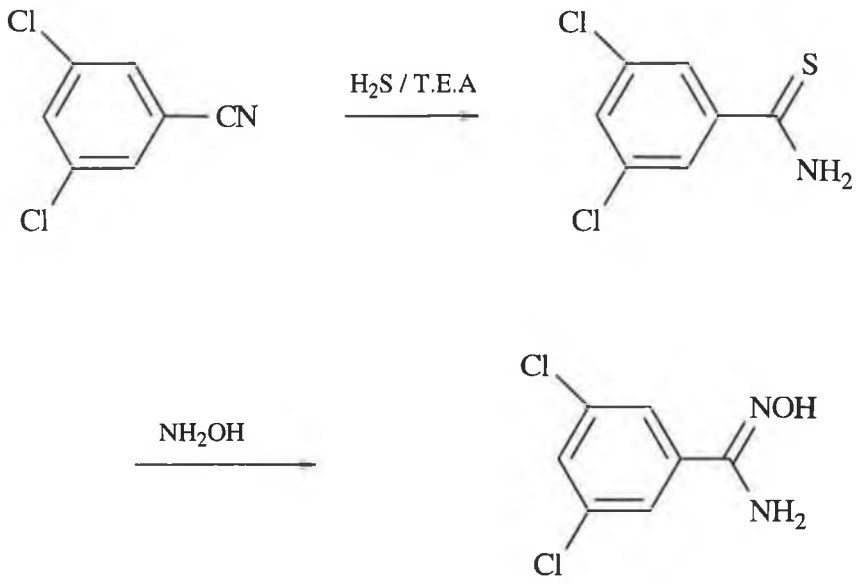
$$\downarrow NH_2OH$$

$$2\,H_2O \quad + \quad NH_3 \quad + \quad N_2$$

Scheme [4.19]

They based their proposal on the fact that hydroxylamine can react as an ambident nucleophile in displacement and addition reactions and on reports of nucleophilic attack by the nitrogen atom of hydroxylamine on other nitrogen atoms bearing electron withdrawing groups. The authors proposed that the initial attack at the nitrile by the hydroxyl amine could take place at the nitrogen of the hydroxylamine to give the normal amidoxime, or attack of the oxygen to give the amide product. An increase in the positive charge at the nitrile carbon, they claimed, presumably induces some attack by the more electronegative element of the ambident nucleophile hydroxylamine. The observation correlated well with the observed proportions of *o*-, *p*-, and *m*-nitrobenzamide formed with consideration of the inductive effect of the nitro-group in the three positions.

In order to prepare amide free amidoximes containing electron withdrawing substituents such as 3,5 dichlorobenzamidoxime, Stephenson used an alternative route whereby the nitrile was first converted to the corresponding thioamide which was subsequently converted to the amidoxime by reaction with hydroxylamine.[262] Scheme [4.20]



Scheme [4.20]

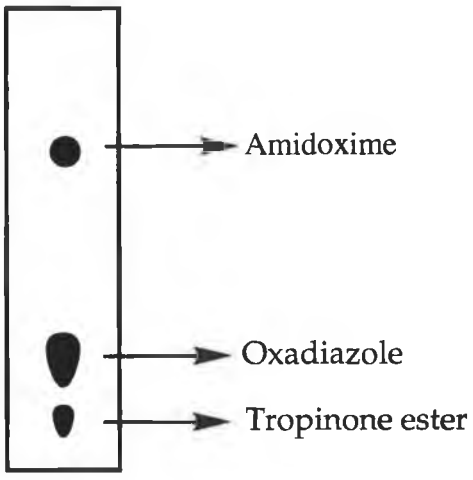
It seemed clear that a posible impurity in the dichlorobenzamidoxime (**164 c**) was the corresponding amide. Considering that amidoximes are acid soluble, the best way of isolating any possible amide present was by dissolving the amidoxime in dilute HCl. On doing this some of the solid failed to go into solution and was filtered off. The insoluble solid was shown to be the amide as expected and amounted to 5% of the total product isolated. After liberating the amidoxime from its HCl salt a pure white solid was obtained which gave a perfect result on elemental analysis and a melting point 20 °C higher than the original sample. In conclusion, it is certain that the electronegative substituents on 3,5-dichlorocyanobenzene leads to some amide formation on reacting with hydroxylamine. However the amount of amide formed is small (5 %) and could easily be removed by acid extraction giving yields equivalent to the overall yield reported by Stephenson *via* the thioamide route and would seem therefore to be a much more practical synthesis as it involves only a single step. It may be that the different reaction conditions employed by us (ethanol instead of methanol and the presence of K_2CO_3 in

the reaction) gave rise to the lower presence of amide in the reaction product but no attempts were made to prove this.

4.5 Synthesis of exo-5'-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-3'-(aryl)-1,2,4-oxadiazoles III a-g.

Having developed efficient methods for the syntheses of the tropinone ester **(163)** and the amidoximes **(164)** an effective method for the condensation of these two moieties to give the required oxadiazoles was investigated. Due to the fact that amidoximes are indifferent towards non activated esters the presence of a strong base such as NaH to increase the nucleophilic nature of the isonitroso group in the amidoxime has previously been employed.[263]

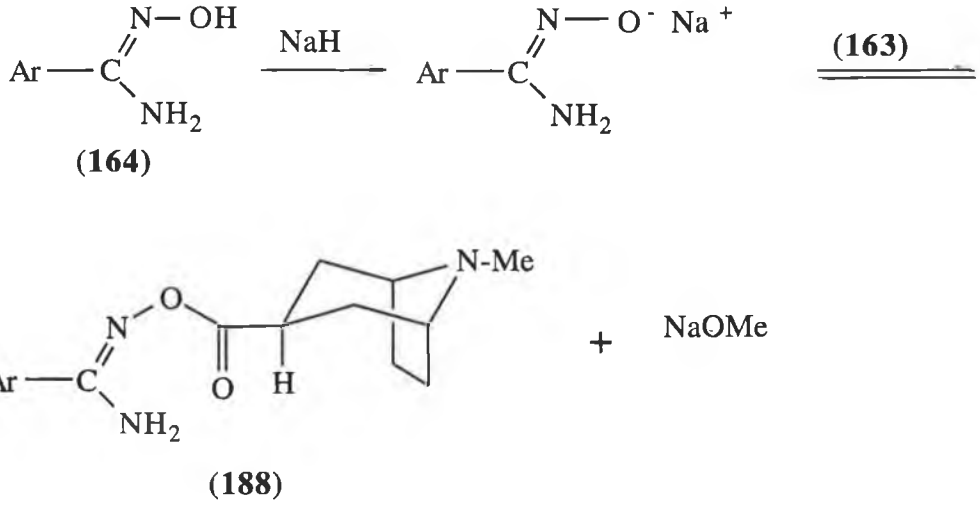
The general method employed for the synthesis of oxadiazoles **III a-g**, involved the initial formation of the sodium salt of the amidoxime in anhydrous THF using NaH as base whereupon the reaction appearance changes from a fine greyish suspension of NaH to a coarser white suspension on addition of the amidoxime. On termination of the evolution of hydrogen, to this mixture was added a solution of the tropinone ester **(163)** in dry THF solution (c. 30 % excess) which was then refluxed until no ester remained (c. 3-6 hrs). The reaction mixture at this stage forms a thick cream paste, the stirring of which in some cases had to be assisted by the addition of extra THF. The progress of the reactions were monitored on TLC using silica gel and 10:1 CH_2Cl_2/THF as developing solvent. A typical reaction profile is shown below .



On completion of the reaction, the product was isolated by filtering off the very fine suspension and purifying the filtrate by column chromatography on silica gel (8:2 CH_2Cl_2/ THF). The colourless oil obtained was converted to its hydrochloride salt in ethanol/HCl and crystallised from an appropriate solvent. During the development of the reaction procedure the following observations were made.

1) As H_2O is eliminated in the reaction (see scheme [4.22]) the presence of *in situ* molecular sieves to remove the water was investigated but was found not to have any significant effect on the reaction.

2) It was discovered that in order to fully convert the tropinone ester to the oxadiazole, an excess of amidoxime had to be used, it being found that a 30 % excess was sufficient for complete conversion. When equivalent molar amounts of ester and amidoxime were used the reaction only proceeded to about 50% conversion. This may be because the formation of the intermediate acylated product (**188**) is a reversible reaction with the intermolecular nucleophilic attack of the NaOMe formed in the reaction competing with the intramolecular nucleophilic attack of the NH_2 group. Scheme [4.21]



Scheme [4.21]

3) With regards to the synthesis of the dichlorophenyl derivative **III d** a large excess of NaH had to be used in order to fully convert the ester to the oxadiazole. Attempts to

carry out the reaction using the standard conditions gave only 20 % conversion after several hours refluxing. On addition of a further equivalent of NaH to the reaction mixture followed by further heating (Note: newly purchased NaH was used) conversion to c.50% was obtained which remained unchanged on continued refluxing. Addition of one equivalent more NaH gave 80% conversion with a further equivalent being necessary for complete conversion. The reaction was then worked up in the standard fashion and isolated as usual.

4) When the 4-pyridin *N*-oxide amidoxime **164 h** was used to react with the ester using the standard procedure, no oxadiazole could be obtained even with large excesses of NaH. The amidoxime was found to be highly insoluble in the common organic solvents tested (THF, DMF etc.). This insolubility was judged to be cause of the reaction failure. Several other mixtures were tested including MeOH/NaOMe and EtOH/ NaOMe none of them however being successful. As the amidoxime **164 h** was found to be completely soluble in H_2O/K_2CO_3 it was attempted to react the tropinone ester in this solution. After 8 hours at r.t. only starting materials were observed. On heating the reaction to reflux the ester completely converted to the tropinone acid as had been feared. Continued reflux failed to produce any reaction of the amidoxime salt (complex) with the acid which is probably to be expected as the tropinone acid probably existed in its zwitterionic form as had previously been shown (Sec. 4.3).

It should be pointed out that like **164 h** the 4-aminophenyl amidoxime was similarly insoluble in the reaction solvent (THF) which in the latter case however posed no problems as complete conversion to the oxadiazole was obtained. This may suggest that the failure of the *N*-oxide amidoxime to condense with the ester may not be due to a solubility problem but may be a result of electronic effects.

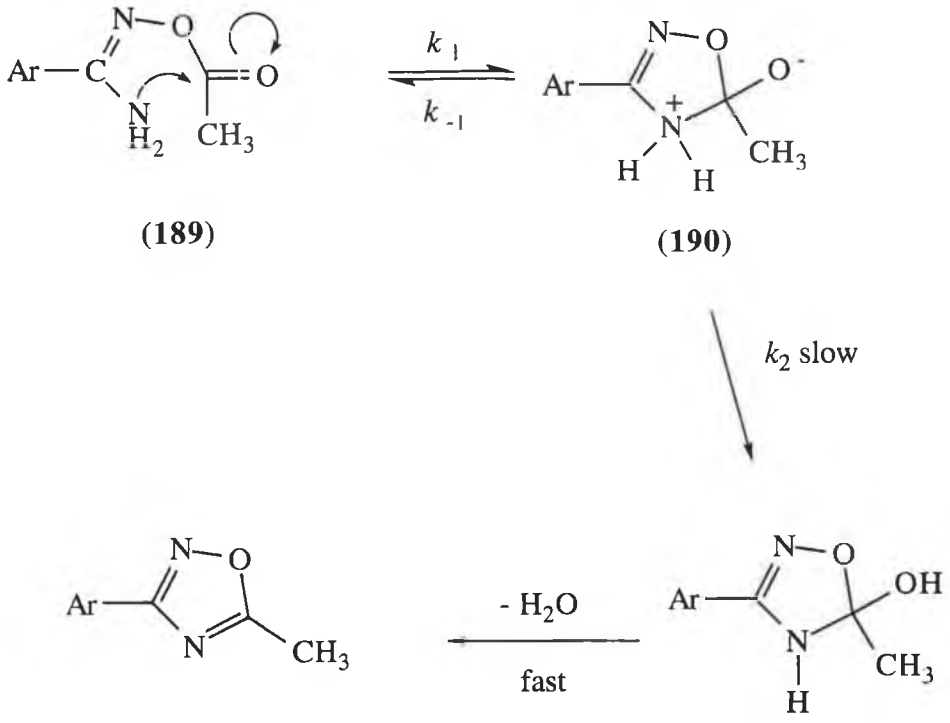
5) In the preparation of **III g,** although complete conversion of the tropinone ester was apparently achieved, very low yields of the oxadiazole were attained (c.5%). Subsequent examination of the tropinone ester used in the reaction showed that on

standing at room temperature over a period of 1 month it had decomposed to a by-product which had a similar R_f value on TLC as the amidoxime. The ester was purified by column chromatography using silica gel and MeOH: THF (8:2). The ester was found to have been only 12% pure, the remainder being a decomposition product which seemed to be a single product on TLC. Due to the complex spectrum of the isolated impurity a positive identification of its structure was not feasible. Subsequent to this the tropinone ester was stored at 0 °C which avoided the aforementioned decomposition. On repeating the oxadiazole formation with the repurified ester normal yields of the oxadiazole were obtained.

6) Although, generally the work-up of the reaction mixture was by filtration and purification of the filtrate by column chromatography, it was also possible to isolate the oxadiazole product in reasonable purity by evaporating the solvent from the filtrate then partitioning the resulting oil between CH_2Cl_2 and H_2O, then basifying with NaOH and, washing the seperated organic layer with H_2O followed by drying and concentration. The free base obtained was slightly less pure than that obtained by chromatography, however on subsequent HCl salt formation an equally pure oxadiazole salt was isolated.

As outlined in scheme [4.21] the synthetic route to the formation of oxadiazoles occurs through acylation of the isonitroso group to give the O-acylated amidoxime which subsequently cyclises to the oxadiazole. Though the acylated intermediate can normally be isolated none was observed in the synthesis of the oxadiazoles **III a-g**.

The thermal cyclisation of acylated amidoximes has been known since 1884 and widely used for the formation of 1,2,4-oxadiazoles but the mechanism was not studied until 1980.[264] In this investigation Sim Ooi and Wilson carried out a mechanistic study on the formation of 3,5-disubstituted 1,2,4-oxadiazoles from O-acetylarylamidoximes and O-aroylacetamidoximes in which the following conclusions were reached. They concluded that the cyclisation followed the mechanistic pathway outlined in scheme [4.22].



(189) **(190)**

Scheme [4.22]

The equilibrium **(189)** to **(190)** was found to lie well to the left and the second step, the proton transfer, was the rate determining step with the observed rate constant being the product k_1k_2/k_{-1}.

That these cyclisations do indeed form polar species was shown by Hammett correlations. The effect of ring substitution in **(189)** (ρ – 0.79) is in accord with the amidoxime NH_2 group acting as nucleophile, with decrease of electron density at the amidoxime carbon. The rate constants for cyclisations of **(189)** with various aromatic substituents is given in Table (4.1) along with the σ values for the various substituents. From these results some conclusions may be made for the formation of oxadiazoles **III a-g**.

Table [4.1]

Compound **189**	$10^4 k/s^{-1}$	Hammett correlation [a]
Ar = C_6H_5	2.1	
Ar = *p*-$Me_2NC_6H_4$	9.0	
Ar = *p*-$MeOC_6H_4$	3.4	ρ - 0.79 (σ)
Ar = *p*- BrC_6H_4	1.35	
Ar = *m*-ClC_6H_4	1.2	
Ar =*p*-$NO_2C_6H_4$	0.46	

[a] Using σ values *p* -Me_2N, - 0.83; *p*- -MeO, -0.27; *p* -Br, 0.23; *m* -Cl, 0.37; *p* -NO_2, -O.78;

As can be seen from the table the electron donating group such as *p*-Me_2N has a definite positive effect on the increase in reaction rate while electron attracting groups such as *m*-Cl, *p*-Br or *p*-NO_2 considerably decrease the reaction rate. As was previously stated the formation of the dichloro oxadiazole (**IIId**) was much slower than any of the other products containing electron donating substituents or the *m*-OMe substituted amidoximes which, while being electron attracting substituents when in this position are much less so than *m*-Cl. A full explanation is given as follows; If we suppose that the formation of the acylated amidoxime **(188)** is an equilibrium reaction (Scheme 4.21) which from previous evidence seems to be the case (i.e. the beneficial use of an excess of amidoxime in the reaction) then the acylated amidoxime can either undergo reversal to the amidoxime or alternatively cyclise to a polar intermediate similar to **(190)** which according to Sim Ooi and Wilson[264] is also reversible. Therefore if the rate of cyclisation is disfavoured by the two *meta* chloro substituents, reversal to the starting amidoxime would predominate.

It has been mentioned that the rate of this reaction was substantially increased by the addition of a large excess of NaH to the reaction mixture. This observation is not entirely unusual as it has previously been observed that the rate of cyclisation of acylated amidoximes can be considerably increased by the presence of NaH.[264] The effect of

sodium hydride in these cyclisations is to form an anion at the NH_2 of the acylated amidoxime which far more readily ring-closes by nucleophilic addition to the carbonyl than does the poorly nucleophilic neutral derivative itself.

CHAPTER V

Structural and conformational study of

Imidazolines and Oxadiazoles.

5.1 Introduction

All the potential 5-HT_3 antagonists synthesised have been studied by ^{1}H and ^{13}C NMR while a representative compound of the tropane imidazoline and the tropane oxadiazole series has been studied by X-ray diffraction. In the case of the series of compounds containing the tropinone moiety, a conformational analysis in solution was of particular interest since the spatial position of the moieties attached to this bicyclic group is dependent on the conformation adopted by the tropane. The quinuclidine series, being a more rigid molecule did not necessitate such a conformational analysis in order to determine the geometric positions of the groups attached. Thus in order to assist in the structure-activity relationship the preferred conformations of series **I** and **III** were determined in solution and in the solid state.

5.2 Study of Tropane spiroimidazolines (I).

5.2.1 *X-ray study of 2'(1H-indol-3-yl)-8-methyl-8-azabicyclo[3.2.1]octane-3- spiro-4'(5')-imidazoline dihydrochloride (I g).*

The X-ray crystal structure of **(I g)** was obtained, verifying the proposed structure for this series of compounds. The crystals used for the analysis were developed by slow recrystallisation from methanol. The full experimental and structural determination procedures and crystallographic data are given in Appendix 1. Selected bond distances, bond angles, torsional angles and interatomic distances are shown in Tables 5.1-5.4. Figures 5.1 and 5.2 represent the PLUTO view of **(Ig)** showing atomic numbering and the molecular packing diagram for **(Ig)** respectively. Full crystallographic data has been deposited at the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB21EW, U.K.

Table [5.1]

Selected Bond Lengths (Å) for I g

Bond	Length /A	Bond	Length /A
O25 - C26	1.43 (2)	C4 - C13	1.60 (2)
N1 - C2	1.50 (2)	C5 - C6	1.52 (2)
N1 - C6	1.50 (2)	C6 - C7	1.52 (2)
N1 - C9	1.51 (2)	C7 - C8	1.55 (2)
N10 - C4	1.50 (1)	C11 - C14	1.38 (1)
N10 - C11	1.36 (2)	C14 - C15	1.39 (2)
N12 - C11	1.34 (1)	C14 - C18	1.44 (2)
N12 - C13	1.45 (2)	C17 - C18	1.40 (1)
N16 - C15	1.35 (2)	C17 - C22	1.40 (2)
N16 - C17	1.37 (2)	C18 - C19	1.38 (2)
C2 - C3	1.54 (2)	C19 - C20	1.37 (2)
C2 - C8	1.52 (2)	C20 - C21	1.37 (2)
C3 - C4	1.53 (2)	C21 - C22	1.38 (2)
C4 - C5	1.53 (2)		

Table [5.2]

Selected Bond Angles (°) for I g

Atoms	Angle (°)	Atoms	Angle (°)
C6 - N1 - C9	112 (1)	C6 - C7 - C8	105 (1)
C2 - N1 - C9	114 (1)	C2 - C8 - C7	105 (1)
C2 - N1 - C6	102 (1)	N10 - C11 - N12	109 (1)
C4 - N10 - C11	113 (1)	N12 - C11 - C14	127 (1)
C11 - N12 -C13	114 (1)	N10 - C11 - C14	124 (1)
C15 - N16 - C17	110 (1)	N12 - C13 - C4	103 (1)
N1 - C2 - C8	102 (1)	C11 - C14 - C18	130 (1)
N1 - C2 - C3	109 (1)	C11 - C14 - C15	123 (1)
C3 - C2 - C8	115 (1)	C15 - C14 - C18	106 (1)
C2 - C3 - C4	112 (1)	N16 - C15 - C14	109 (1)
N10 - C4 - C3	108 (1)	N16 - C17 - C22	129 (1)
C3 - C4 - C13	114 (1)	N16 - C17 - C18	108 (1)
C3 - C4 - C5	112 (1)	C18 - C17 - C22	123 (1)
N10 - C4 - C13	100 (1)	C14 - C18 - C17	106 (1)
N10 - C4 - C5	109 (1)	C17 - C18 - C19	118 (1)
C5 - C4 - C13	112 (1)	C14 - C18 - C19	135 (1)
C4 - C5 - C6	115 (1)	C18 - C19 - C20	119 (1)
N1 - C6 - C5	106 (1)	C19 - C20 - C21	122 (1)
C5 - C6 - C7	114 (1)	C20 - C21 - C22	121 (1)
N1 - C6 - C7	102 (1)	C17 - C22 - C21	116 (1)

Table [5.3]

Selected Torsion Angles (°) for I g

Atoms	Angle (°)
C2 - C3 - C4 -N10	- 158 (1)
C2 - C3 - C4 - C13	91 (1)
N10 - C4 - C5 - C6	159 (1)
C13 - C4 - C5 - C6	- 90 (1)
N12 - C11 - C14 - C15	- 154 (1)
N10 - C11 - C14 - C15	27 (2)
N12 - C11 - C14 - C18	21 (2)
N10 - C11 - C14 - C18	- 157 (1)

Table [5.4]

Interatomic Bond Distances and Angles for Ig

N1-H1	H1...025	N1...025	N1-H1...025
1.0 (1) Å	1.7 (1) Å	2.72 (1) Å	164 (1) °
Cl23-H23	H23...025	Cl23...025	Cl23-H23...025
1.7 (2) Å	2.5 (1) Å	3.04 (1) Å	92 (1)°
N10-H10	H10...Cl23	N10...Cl23	N10-H10...Cl23
1.0 (1) Å	2.3 (1) Å	3.24 (1) Å	168 (1) °
N12-H12	H12...Cl24	N12...Cl24	N12-H12...Cl24
1.0 (1) Å	2.2 (1) Å	3.15 (1) Å	165 (1) °
N16-H16	H16...Cl24[1]	N16...Cl24[1]	N16-H16...Cl24[1]
0.7 (2) Å	2.5 (2) Å	3.18 (1) Å	165 (1) °

[1] -X, 1-Y, -Z

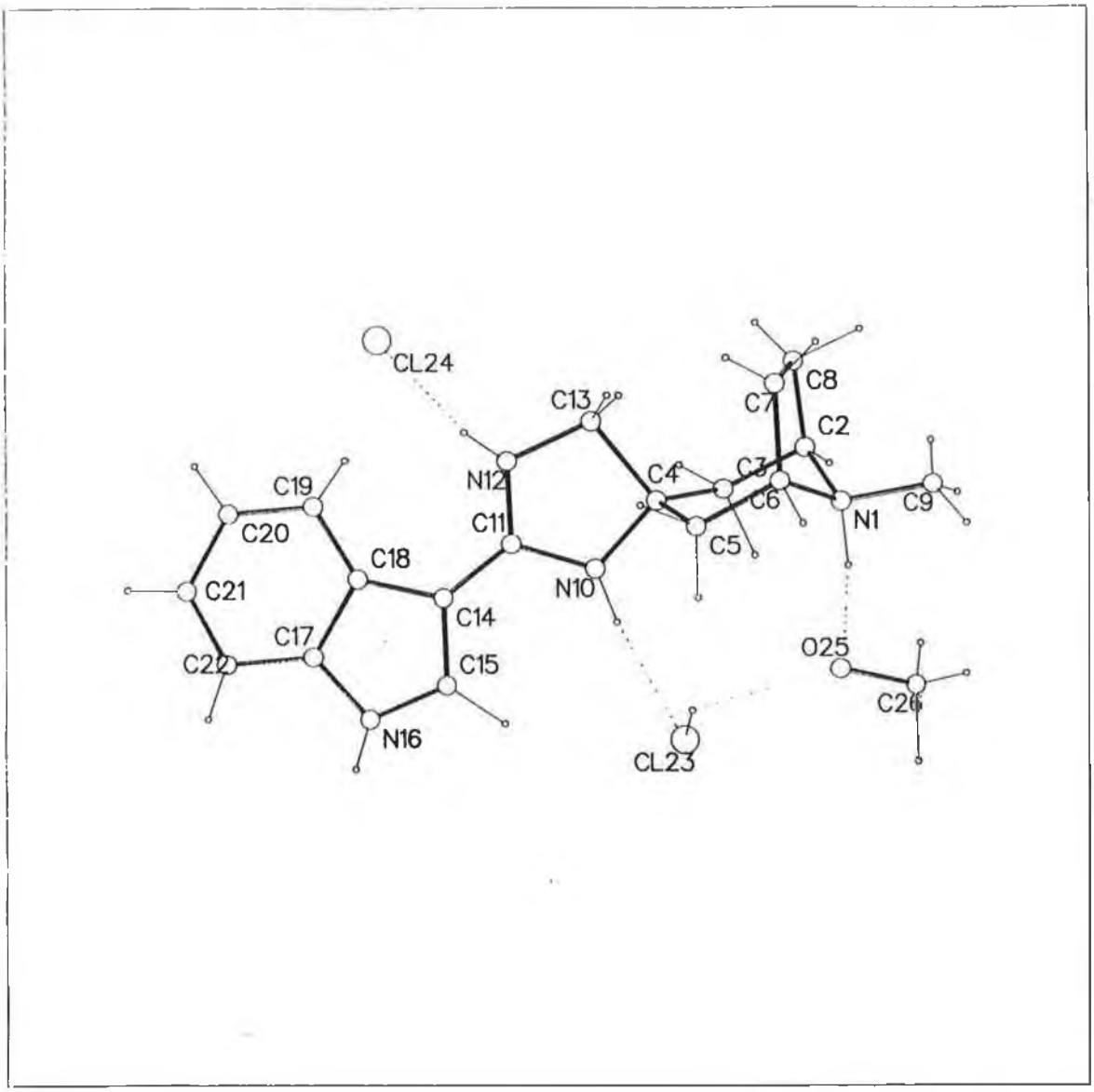


Figure 5.1 Pluto view of **I g** showing atomic numbering

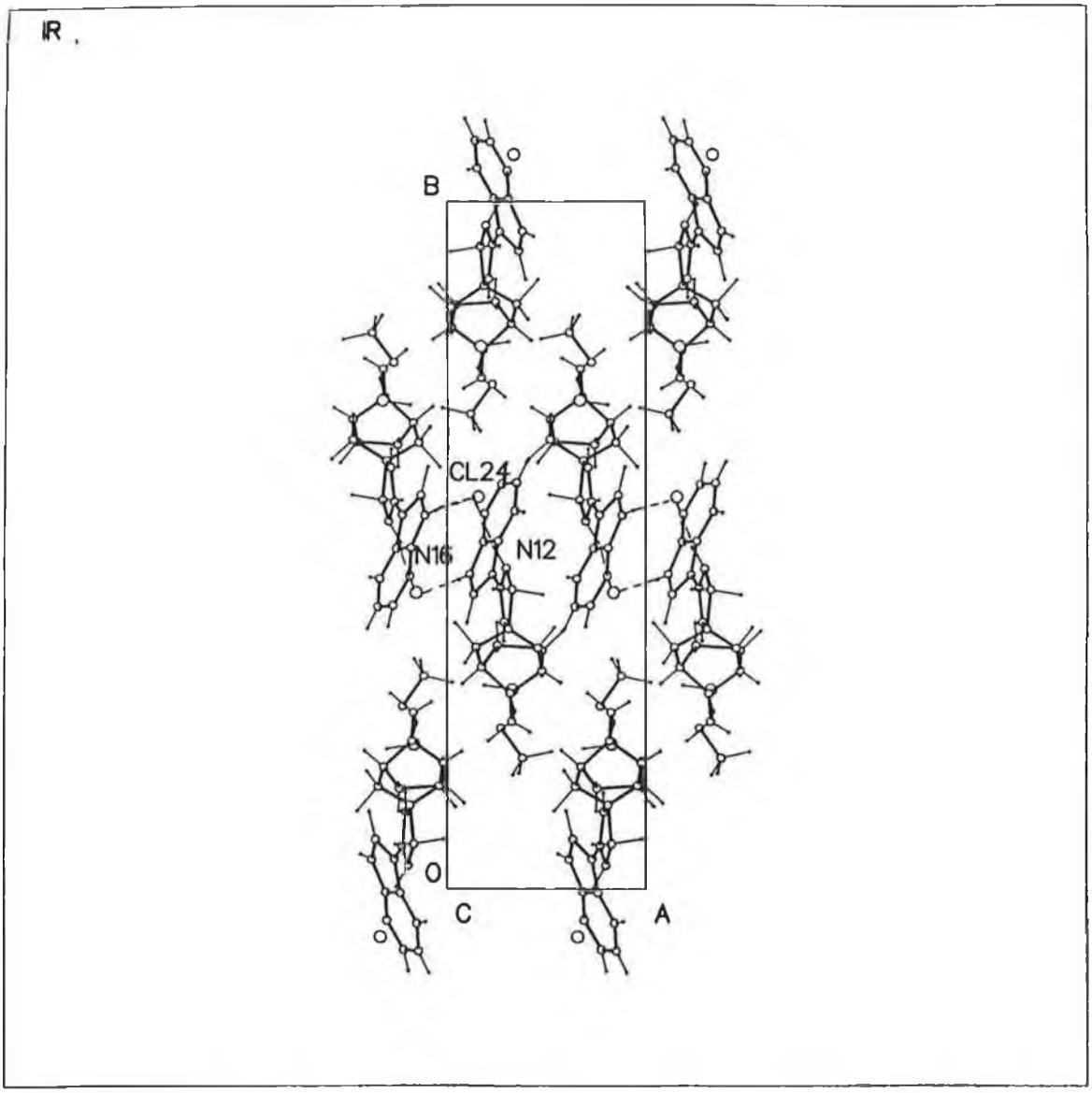


Figure 5.2 Crystal Packing of **I g** showing the intermolecular hydrogen bonds.

As can be seen from the PLUTO view of the compound (Figure 5.1), a molecule of methanol is incorporated into the crystal structure. The bicyclic system is in the chair-envelope conformation commonly found in these kind of compounds. The chair is flattened at the C4 atom to release steric hindrance, C4 and N1 being 0.49(1) and 0.86(1)Å, respectively, from the mean plane defined by the other four atoms. N1, on the other hand, is in the flap of the envelope, 0.70(1)Å away from the plane defined by the rest of the atoms in this ring.

The molecule presents a pseudo-mirror plane, passing through the N1, C4, and C9 atoms. The imidazoline ring is almost in this plane with an interplanar angle of only 5°. The indole moiety deviates from this symmetry defining an interplanar angle of 24°. Cl23 and Cl24 are in opposite positions with respect to the pseudo-mirror plane, being 0.639(4) and 1.472(3)Å respectively out of this plane.

As indicated by the bond lengths (Table 5.1), the electrons are delocalised along N10-C11-N12 and the indole moiety, which maintains the interplanar angle of 24° between the indole and the imidazoline ring. Consequently, there is no difference between the N10, N12 atoms or the C11-N12 and the C11-N10 bond lengths. Both N atoms of the imidazoline ring form hydrogen bonds with the two chlorine atoms. However, one of them acts as the counter chloride ion (Cl24), while the other seems to be present as a hydrochloride of crystallisation and also interacts with the CH_3-O group of the solvent, which in turn interacts with the bicyclic N1 atom. The hydrogen bonding pattern is completed by a hydrogen bond between the indole N16 and the Cl24 atom from a different asymmetric unit. Two molecules related by a center of symmetry form a dimer through two hydrogen bonds: N12-H12....Cl24 and N16-H16....Cl24. These dimers form isolated units stacked along the "a" axis. The first hydrogen bond links the Cl24 atom to the N12 one in the same molecule (x,y,z) and the second links the Cl24 to the N16 of a different asymmetric unit (-x,1-y, -z), the Cl atom acting as the nexus between the two molecules (see figure 5.2).

5.2.2 NMR study of 2'(aryl)-8-methyl-8-azabicyclo[3.2.1]octane-3-spiro-4'(5')-imidazolines (I a-g).

The ^{1}H and ^{13}C NMR data of compounds **I a-g** show great similarity between compounds. The assignment of proton and carbon resonances has been made on the basis of double resonance experiments on compound **Ic** and previous studies of tropane compounds.[265-267] In CD_3OD and $CDCl_3$ all the proton resonances could be assigned. Figure 5.3 indicates the numbering system used for the assignation of the carbons and protons and two typical ^{1}H NMR sprectra are given in Appendix 3 (Spectra 4 and 5)

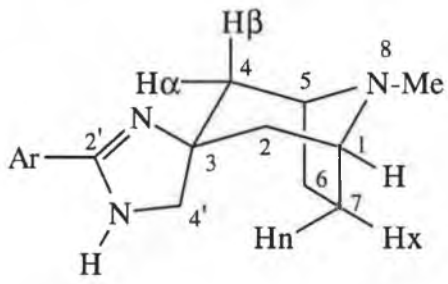


Figure 5.3

The long range couplings between the protons in the W disposition, ^{4}J H2α-H4α, ^{4}J H2β-H7x or ^{4}J H4β-H6x have not been observed under the conditions used to record the spectra. As is frequently observed in tropane systems,[267] the protons situated at the bridge-head carbon atoms H1(5) appear as a non-resolvable broad singlet, the medium width at half height being in the range $W_{1/2}$ = 9-11 Hz. It was therefore not possible to measure the coupling constants for these protons. The H2(4)α and H2(4)β signals were assigned on the basis of the values of the corresponding couplings with H1(5) protons for related systems. The H1, H2α and H2β (or H5, H4α and H4β) atoms form a three spin AMX system whose analysis leads to the establishment of their proton magnetic parameters. The protons H2(4)β appear as double doublets as a consequence of the geminal coupling with H2(α) and the smaller coupling with the vicinal H1(5) proton. The geminal couplings ^{2}J H2(4)α-H2(4)β are generally in the range -14 to -16 Hz,

while the vicinal coupling ^3J H2(4)β-H1(5) average around 3-4 Hz. The H2(4)α protons present a similar appearance though the vicinal coupling with H1(5) is smaller, being on average 2.0 Hz. The assignment of the H6(7)n and H6(7)x signals was carried out from analysis of their shapes: the simpler signal being attributed to H6(7)n since ^3J H6(7)n-H1(5) is very small (0.5Hz) in tropane derivatives i.e. practically unobserved.[267]

As with the ^{1}H-NMR spectra the ^{13}C NMR spectra all show great similarity between each other (See spectrum 13 in Appendix 4 for a representative ^{13}C NMR profile). In order to assign the ^{13}C signals steric and electronic effects were taken into consideration and a proton-carbon coupled spectrum was carried out on **Ic** (spectrum 14) to confirm the assignation. Previous studies on related systems were also used to aid in the designation of signals.[265-267]

The coupling constants deduced from first-order analysis of the ^{1}H-NMR are compiled in Table [5.5] while the ^{1}H and ^{13}C NMR data of **I a-g** are summarised in table [5.6].

Table [5.5] Coupling constants deduced from the first-order analysis of the ^{1}H-NMR spectra of compounds **Ia-g**. (CD_3OD: 300 MHz)

Coupling Constant *J* (Hz)	**I a**	**Ib**	**Ic**	**Id**	**Ie**	**If**	**Ig**
H2(4)α-H2(4)β	-14.7	-13.9	-14.4	-13.4	-13.0	-14.2	-16.3
H2(4)α-H1(5)	2.4	2.4	1.9	2.6	a	2.5	2.5
H2(4)β-H1(5)	3.4	3.4	3.4	3.4	2.9	3.1	3.0

a ^{3}J H1(5)-H2(4)α could not be established, only a slight broadening of the H2(4)α signal was observed.

Table [5.5] ^{13}C and ^{1}H NMR data for compounds **I a-g** (ppm)

Atoms	Ia	Ib	Ic	Id	Ie[a]	If[a]	Ig[b]
H1(5)brs	3.30	3.24	3.22	3.38	3.18	3.39	4.08
C1(5)	61.95	61.85	61.85	61.83		61.56	59.86
W1/2(Hz)		9.40	9.79	9.70	11.40	10.9	11.8
H2(4)α dd	1.96	1.87	1.86	1.94	2.01	1.92	2.55
C2(4)	42.50	42.58	42.54	42.46		41.96	41.0
H2(4)β dd	2.12	2.08	2.08	2.12	2.07	2.46	2.65
C3	62.67	62.50	62.47			60.3	
H6(7)x m	2.12	2.08	2.08	2.12	1.80	2.10	2.42
C6(7)	25.99	26.25	26.26	26.21		24.84	24.04
H6(7)n m	1.86	1.84	1.83	1.90	1.69	1.86	2.28
CH_3N s	2.39	2.37	2.37	2.46	2.28	2.42	2.86
CH_3N	38.96	38.83	38.83	38.89		38.66	
C2'	164.49	164.22	164.22	161.67		160.0	161.91
H4' s	3.97	3.89	3.88	3.91	3.87	3.91	4.33
C4'	65.11	67.29	67.26			67.87	64.36
CH_3O s		3.82	3.80				
CH_3O		55.83	55.94				
C1"	124.75	132.97	132.79	134.37		136.9	
H2"	7.77	7.32	6.95	7.72	7.61	7.63	8.83
C2"	129.83	113.49	106.26	126.92		124.15	132.3
H4"	7.50	7.03	6.58	7.60			7.93
C4"	133.10	117.94	104.07	131.49			120.2
H5"	7.50	7.32	162.3		8.14	8.58	7.34
C5"	128.54	130.55		136.40		150.10	123.9
H6"	7.77	7.32	6.95	7.72	7.61	7.63	7.34
C6"	129.83	132.95	106.26	126.92		124.15	125.11
H7"							7.57
C7"							114.05
C7a"							138.44

[a] In $CDCl_3$; [b] Dihydrochloride salt

5.2.3 *Conformational study of tropane spiroimidazolines* ***I a-g.***

From the ^{1}H and ^{13}C NMR data, it can be proposed that compounds **I a-g** adopt a preferred conformation in solution similar to that observed for compound **I g** in the crystalline state:

a) The pyrrolidine and piperidine rings adopt a flattened N8 envelope and distorted chair conformation puckered at N8 and flattened at C3 as evidenced by the ^{1}H NMR spectra where the $W_{1/2}$ values for the H1(5) signals of 9-12 Hz correspond to a tropane system with the piperidine ring in a chair conformation. This is supported by the vicinal coupling values for ^{3}J H2(4)β-H1(5) which do not correspond to dihedral angles of 0 °, typical of a boat conformation. In compounds **I a-g** ^{3}J H2(4)β-H1(5) is always greater than ^{3}J H2(4)α-H1(5), consequently, the dihedral angle H2(4)α-C-C-H1(5) is greater than H2(4)β-H1(5). From the ^{13}C NMR spectra the chair conformation adopted by the piperidine ring is confirmed by the δC2(4) values. For a boat conformation, these carbon signals would be shifted to higher fields as a result of the steric compressing effect due to the eclipsing between the C2(4)β and the C1(5) hydrogen atoms.[266,268]

b) The δ of the N-substituent is in agreement with an equatorial position for this group.[269]

c) The groups linked to the imidazoline ring are nearly coplanar with respect to this ring, i.e. partial conjugation between these groups is observed as indicated by the $\delta^{1}H$ and $\delta^{13}C$ values for the aromatic groups in **Ia-g.**

It is worth pointing out that **I g**, which is a dihydrochloride salt, has a similar conformational behaviour as that deduced for the free bases. The deshielding observed for the proton and carbon signals of the protonated derivatives can be mainly ascribed to the field effect exerted by the positively charged nitrogen atom. The ^{3}J H2(4)β-H1(5) and ^{3}J H2(4)α-H1(5) as well as the $W_{1/2}$ of the H1(5) protons remain practically unchanged as a result of protonation. Consequently, it seems obvious that the protonated forms, which predominate in a physiological medium, and the free base must

exibit the same predominant chair-envelope conformation of the tropane system slightly flattened at C3 and puckered at N8, with the N-methyl group in an equatorial position.

5.3 Structural and Conformational Study of tropane oxadiazoles (III).

5.3.1 X-ray study of exo-5'-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-3'-(3,5-dimethoxyphenyl)-1,2,4-oxadiazole hydrochloride **III c.**

An X-ray crystal structure of **(III c)** was obtained which confirmed the proposed exo structure for this series of compounds. The crystal used for the analysis was obtained by slow recrystallisation from methanol. The experimental and structural determination procedures and full crystallographic data are given in Appendix II. Figures 5.4 and 5.5 represent the PLUTO view of **(III c)** showing atomic numbering used in the crystallographic study and the molecular packing diagram for **(III c)** respectively. Selected bond distances, bond angles and torsion angles are given in tables 5.7 - 5.9. The crystallographic data is to be deposited at the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rosd, Cambridge CB21EW, U.K.

Table [5.7] Selected Bond distances(Å) for **IIIc**.

Bond	Length (Å)	Bond	Length (Å)
C1-C2	1.54(1)	C11-N12	1.29(1)
C1-C6	1.53(1)	C11-C14	1.47(1)
C1-C9	1.48(1)	N12-O13	1.409(5)
C2-C3	1.53(1)	C14-C15	1.39(1)
C3-N4	1.508(5)	C14-C19	1.40(1)
C3-C7	1.52(1)	C15-C16	1.39(1)
N4-C5	1.51(1)	C16-C17	1.38(1)
C5-C6	1.53(1)	C17-C18	1.39(1)
C5-C8	1.53(1)	C18-C19	1.39(1)
C7-C8	1.52(1)	C18-O22	1.377(5)
C9-N10	1.291(5)	O20-C21	1.41(1)
C9-O13	1.342(4)	O22-C23	1.42(1)
N10-C11	1.384(5)		

Table [5.8] Selected Bond Angles (degrees) for **IIIc**.

Bonds	Angle (°)	Bonds	Angle (°)
C6 - C1 - C9	111.9 (3)	N10 - C11 - C14	124.6 (4)
C2 - C1 - C9	109.6 (4)	N10 - C11 - N12	114.2 (4)
C2 - C1 - C6	111.3 (3)	N12 - C11 - C14	121.2 (4)
C1 - C2 - C3	111.4 (4)	C11 - C12 - O13	103.5 (3)
C2 - C3 - C7	113.3 (4)	C9 - O13 - N12	106.5 (3)
C2 - C3 - N4	107.1 (3)	C11 - C14 - C19	118.1 (4)
N4 - C3 - C7	102.8 (4)	C11 - C14 - C15	119.9 (4)
C3 - N4 - C24	113.4 (3)	C15 - C14 - C19	122.0 (4)
C3 - N4 - C5	101.2 (3)	C14 - C15 - C16	118.8 (4)
C5 - N4 - C24	113.6 (3)	C15 - C16 - O20	124.3 (5)
N4 - C5 - C8	102.4 (4)	C15 - C16 - C17	120.3 (4)
N4 - C5 - C6	107.2 (4)	C17 - C18 - O20	115.4 (4)
C6 - C5 - C8	114.0 (4)	C16 - C17 - C18	120.2 (5)
C1 - C6 - C5	110.7 (3)	C17 - C18 - O22	115.1 (4)
C3 - C7 - C8	105.5 (4)	C17 - C18 - C19	120.9 (5)
C5 - C8 - C7	105.5 (5)	C19 - C18 - O22	123.9 (4)
C1 - C9 - O13	115.5 (4)	C14 - C19 - C18	117.6 (4)
C1 - C9 -N10	131.7 (4)	C16 - O20 - C21	117.2 (40
N10 - C9 - O13	112.7 (4)	C18 - O22 - C23	118.8 (4)
C9 - N10 - C11	130.0 (3)		

Table [5.9] Selected Torsion Angles (degrees) for **IIIc**.

Bonds	Angle (°)	Bonds	Angle (°)
C2 - C1 - C6 - C5	-46.5 (5)	C8 - C5 - C6 - C1	-50 (1)
C6 - C1 - C2 - C3	46.1 (5)	C6 - C5 - C8 - C7	88 (1)
C1 - C2 - C3 - N4	-61.3 (4)	C3 - C7 - C8 - C5	-0 (1)
C1 - C2 - C3 - C7	51 (1)	C6 - C1 - C9 - N10	-9 (1)
C2 - C3 - C7 - C8	-87 (1)	C2 - C1 - C9 - N10	-132.9(5)
C2 - C3 - N4 - C5	74.2 (4)	C6 - C1 - C9 - O13	170.8 (4)
N4 - C3 - C7 - C8	28.2 (5)	C2 - C1 - C9 - O13	46.8 (5)
C7 - C3 - N4 - C5	-45.5 (4)	N10 - C11 - C14 - C15	-8 (1)
C3 - N4 - C5 - C6	-75.2 (4)	N10 - C11 - C14 - C19	171.9 (4)
C3 - N4 - C5 - C8	45.1 (4)	N12 - C11 - C14 - C15	172.8 (4)
N4 - C5 - C6 - C1	62.6 (4)	N12 - C11 - C14 - C19	- 7 (1)
N4 - C5 - C8 - C7	- 27.5 (5)		

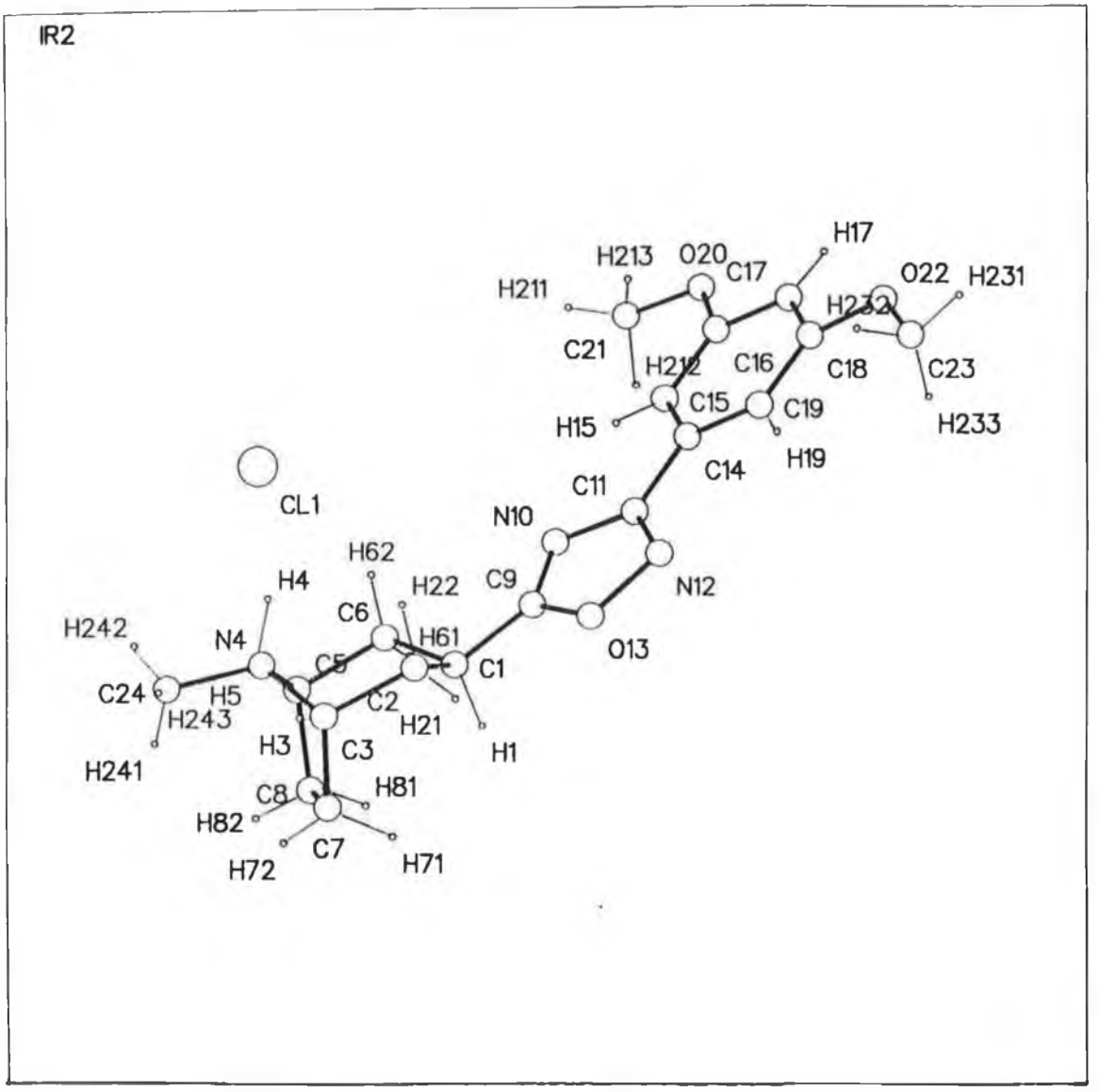


Figure 5.4 Pluto view of **IIIc** showing atomic numbering.

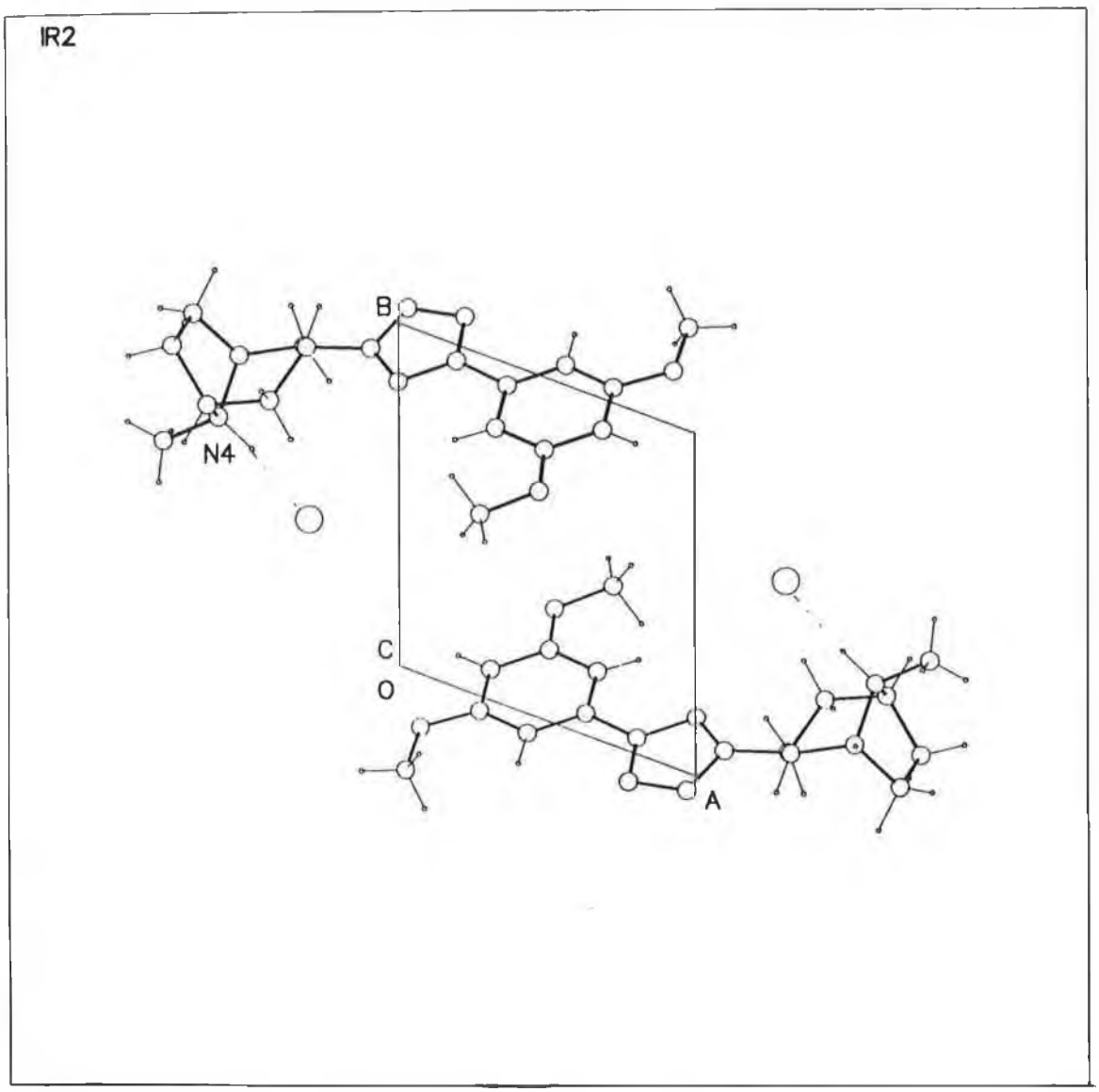


Figure 5.5 Unit cell packing of **IIIc** viewed down the c axis.

The bicyclic system consists of two rings, one of five and the other of six atoms. The five membered ring has an envelope conformation with N4 at the flap and at a distance of 0.689(3)Å from the plane defined by the other four atoms C3, C5, C7 and C8, while the six membered ring has a chair conformation with C1 and N4 out of the plane defined by C2, C3, C5 and C6 by -0.586(4) Å and 0.885(3) Å respectively. Rings 3 and 4 are planar, forming an angle of 7.4°(1) between them. They are in the equatorial position with respect to the bicylic ring system. The two methoxy groups are also coplanar to the phenyl ring.

The H atom of the Cl migrates towards N4 and forms an intramolecular hydrogen bond between N4.....Cl (see Appendix II) ; their is also an intramolecular short contact between C2....O13. Figure 5.5 shows the molecular packing viewed down the c axis. The molecules are held together by van der Waals forces.

5.3.2 *NMR and conformational study of exo-5'-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-3'-(aryl)-1,2,4-oxadiazole hydrochlorides III a-g.*

^{1}H nmr (300 MHz) and ^{13}C nmr (75 MHz) spectroscopy was performed on all the samples in the series using deuterated methanol as solvent. From the ^{1}H NMR spectra all the signals could be assigned, although the resolution of the signals in the tropinone moiety was not as good as for the series of imidazolines. Because of this it was difficult to measure some of the coupling constants, but nevertheless the chair conformation of the tropinone could be deduced.

All the compounds show very similar NMR profiles with respect to the tropinone moiety. Compound **III d** is thus taken as a typical example. The ^{1}H NMR and ^{13}C NMR spectra are to be found in Appendixes III and IV respectively (Spectra 12, 16 and 17) In the ^{1}H NMR spectrum the aromatic portion of this molecule shows a doublet at δ = 7.98 ppm integrating for 2 protons and a triplet centered at δ = 7.65 ppm corresponding to 1 proton. Only *meta* coupling i.e.2 Hz can be observed which is in accord with the structure of the aromatic portion of the molecule. The signals can thus be assigned as the doublet corresponding to the H"2 and H"6 protons and the triplet to the H"4 proton.

At δ = 4.06 ppm the protons corresponding to the bridge-head carbons H1(5) appear as a broad non-resolvable singlet with $W_{1/2}$ = 10.0 Hz. This is again indicative of the tropinone system with the piperidine ring in a chair conformation. This was supported by the chemical shift displacement of the C2(4) and the C1(5) carbons in the ^{13}C spectra.[265-268] The signal centered at δ = 2.40 ppm integrating for 6 protons was assigned to the H2(4) α and β protons and the H6(7) exo protons. The multiplet showed a complex pattern which did not permit the extraction of any coupling constants. H2(4) α and H2(4) β may be considered as the AB part of an ABXY system which between them display geminal coupling and vicinal coupling with both H1(5) and H3

giving rise to the complicated pattern. The 2 protons corresponding to the H6(7) endo protons are centered at δ = 2.21 ppm. A multiplet centered at δ = 3.77 ppm and integrating for 1 proton was assigned to the endo H3 proton of the tropinone and whose spin-spin splitting provides valuable information as regards to the orientation of the oxadiazole with respect to the bicyclic system as well as giving evidence as to the piperidine ring conformation .

The H3 proton can be considered as the X part of two ABX systems. As already mentioned the $W_{1/2}$ of the peak for H1(5) and the ^{13}C NMR shift values indicate that the tropinone six membered ring is in a chair conformation. Using this knowledge we can examine the following two situations;

For a compound in the chair conformation and with the oxadiazole in the endo position at C3 the exo H3 proton would have a dihedral angle of 60 ° with respect to the H2(4) alpha and beta protons thus giving rise to a quintuplet with coupling constants of about 1.5 - 2.0 Hz according to the Karplus equation. If on the other hand the oxadiazole is in the exo position then we should be able to see a large splitting corresponding to axial-axial coupling of the H3 endo proton with the H2(4) β or axial protons thus giving a triplet. Each of these signals should then be split into a further triplet with a smaller splitting (c.2Hz) arising from the axial-equatorial coupling between H3 and H2(4) α.

On examination of the multiplet at δ = 3.75 ppm for H3 we can observe 9 signals with two large coupling constants of 10.8 Hz for the axial axial coupling and 6 smaller splittings of 6.5 Hz corresponding to the axial-equatorial coupling (Figure 5.6).

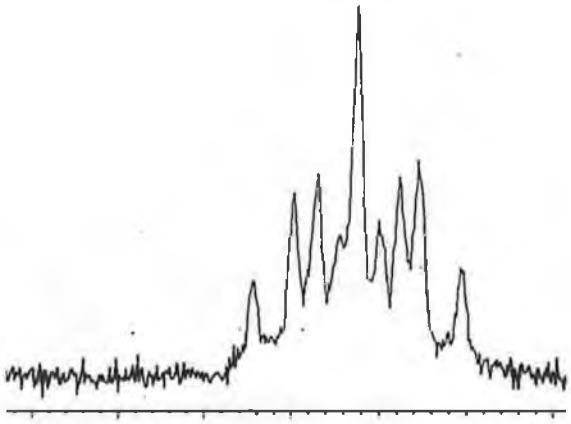


Figure 5.6 Multiplet coresponding to H3 of III d under 300 Mz ^{1}H NMR.

The fact that the a-e coupling is 6.5 Hz implies a dihedral angle of 35-40 ° and would thus indicate that the piperidine ring exists in a slightly flattened chair rather than in a perfectly non distorted chair conformation.

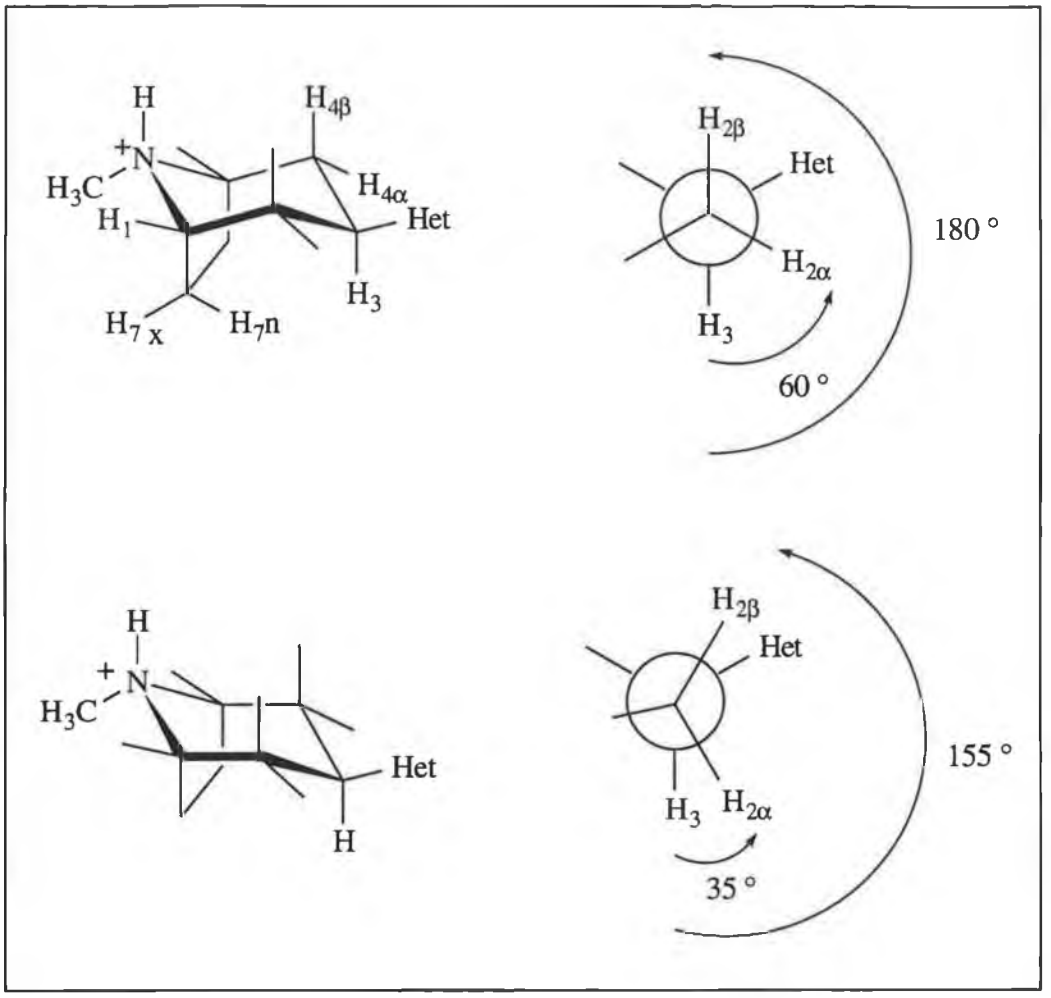


Figure 5.7

In order to confirm the conformation of the bicyclic system and the oxadiazole orientation, double resonance and NOE experiments were performed. By saturating the signal for the H3 proton at $\delta = 3.77$ ppm the multiplet at $\delta = 2.2$ ppm simplified to the more familiar ABX system seen in the tropinone imidazoline series. A coupling constant of 3.6 Hz for ^3J H2(4)β-H1(5) was obtained while ^3J H2(4)α-H1(5) could not be measured, a slight broadening of the signals only being observed. These coupling constants are again confirmation of the the chair conformation of the piperidine ring.

Nuclear Overhauser effect (N.O.E.) experiments were performed to confirm the exo orientation of the oxadiazole group with respect to the piperidine ring. Irradiation of the signal corresponding to the H6(7)endo protons caused a 22 % enhancement in the signal for the H3 proton thus confirming their spatial proximity and consequently the axial orientation of H3 while simultaneously lending support to the chair conformation of the piperidine ring. Similarly, irradiating H3 resulted in 9.8% enhancement of the H6(7) endo signal.

The singlet at δ = 2.84 ppm integrating for three protons is in accord with an N-methyl group in the protonated form.[257] From the displacements of the protons in the aromatic portions of molecules **III e, III f,** and **III g** it can be seen that the pyridine and aniline moities of these groups exist in their protonated state. This was confirmed by the elemental analysis where the compounds were found to be dihydrochloride salts.

The ^{13}C NMR spectra all display a similar appearance. The signals for the C3'and C5' of the oxadiazole appear well downfield at c.167 ppm and 182 ppm. The C5' peak was assigned to that appearing at 182 ppm as it is situated between the nitrogen and the more electronegative oxygen atom. The signals for the tropinone fraction appear similar to those found in the imidazoline series[257] except for carbon C3 which changes from approximately 62 ppm in the imidazolines to about 27.0 ppm in the oxadiazole series probably arising from the lower electronegativity of the oxadiazole function. The C2(4) carbons also experience a slight upfield shift of c. 6.6 ppm again probably due to the smaller electron withdrawing effect of the oxadiazole group. The assignment of the ^{13}C signals was confirmed by double resonance techniques where the coupling with the hydrogens gave the expected multiplicities (Spectrum 17).

CHAPTER VI

Pharmacology, Biochemical Studies and Structure-Activity Relationship

6.1 Introduction.

The importance of serotonin (5-hydroxytryptamine) as a neurotransmitter stems from its role as a mediator in numerous physiological processes including eating behaviour, sexual behaviour, pain and stress. Thus there has been an explosion of research aimed at characterising serotonin receptors, identifying receptor subtypes and utilising the functional information as a basis for targeting specific therapeutic disorders at the receptor level. As is the case with many areas of pharmaceutical research, the serotonergic field has been enormously facilitated by the development of radioligand binding techniques.

What is now classified as the 5-HT_3 receptor has been known to exist in the periphery since the late 1950s.[1] However, the recent discovery of 5-HT_3 receptors in the brain has stimulated great excitement in this field. Selective ligands for the receptor have become available only very recently, so the majority of potential indications for these compounds, based on behavioural, electrophysiological and anatomical evidence have yet to be validated clinically.[270] The one indication for which the class of agents has demonstrated efficacy is the blockade of chemotherapy-induced emesis (nausea and vomiting), an event suggested to involve activation of 5-HT_3 receptors in the *area postrema*.[12]

There exists very little basic research into the mechanisn by which cancer chemotherapy and radiation produce vomiting and nausea. The most accepted theory is that cytotoxic drugs and radiation cause cellular lesions probably in the enterocromaffin cells in the cells of the gut mucosa, producing the liberation of serotonin which activates 5-HT_3 receptors in the afferent vagus nerve which produces the vomiting reflex.[271] This theory is supported by studies which show a marked increase of the plasma concentration of serotonin in patients undergoing chemotherapy[272] and a significant rise in the urinary level of 5-hydroxyindoleacetic acid,[273] the principal metabolite of serotonin. The 5-HT_3

antagonists function as anti-emetics in cancer patients by competing with serotonin and blocking the 5-HT_3 receptors thus inhibiting the actions of the serotonin.

Another possible site of action is the 5-HT_3 receptors located centrally in the NTS (nucleus of the solitary tract) or the *area subpostrema* in the brain stem. If 5-HT is involved in the central processing of information in vomiting, blocking 5-HT_3 receptors would effectively prevent this and control vomiting. It is quite possible that 5-HT_3 receptor antagonists are acting at both sites (Figure 6.1, Taken from Glaxo training manual for nurses, 1991).

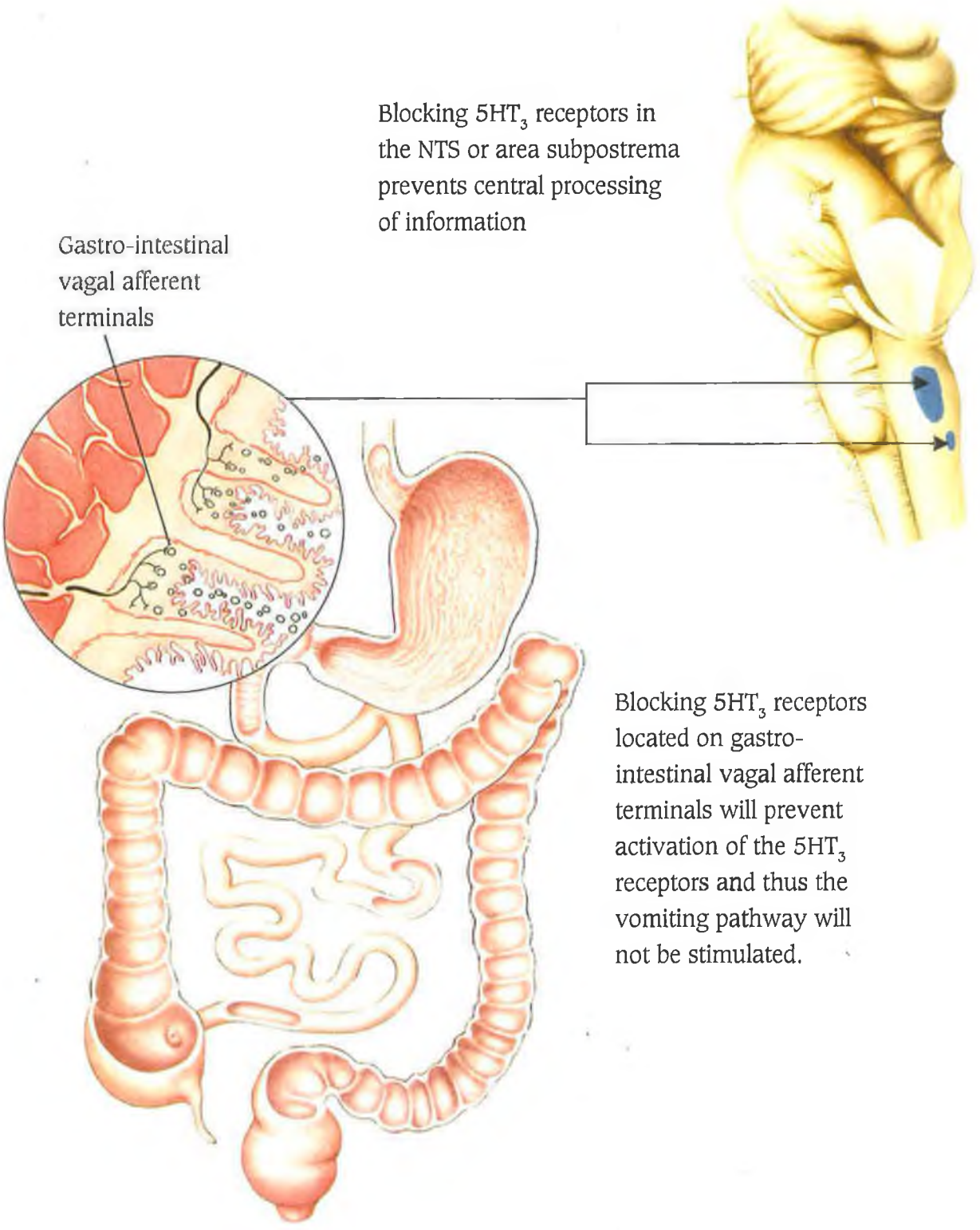


Figure [6.1] Possible sites of 5-HT$_3$ antagonist action.

6.2 **Pharmacological Studies of Series I, II, and III *(in vivo)*.**

The method employed to provide an *in vivo* measure of a drug's functional activity at the 5-HT_3 receptor was a method known as the von Bezold-Jarish (B-J) reflex.[274] Administration of serotonin to rat (or several other species, including man) results in a rapid and transient reflex bradycardia (decrease in heart rate), an event mediated by reflex stimulation of the vagus nerve following activation of the sensory nerve located in the right ventricle wall. Prior treatment with a 5-HT_3 antagonist will block this effect. A compound's potency is defined by its ability to inhibit (% inhibition) this response (bradycardia) at a given dose. The evaluation of the antagonistic properties of **I, II** and **III** were carried out and compared to known potent antagonists using a modified version of the von Bezold-Jarish reflex test described by Saxena and Lewang.[275] Basically the method involved orally administering mice with the potential antagonists, followed 45 minutes later by an intravenous injection of serotonin. The % inhibition of the bradycardia produced is measured by comparing to a standard. The results are displayed in table [6.1] for the three series of compounds.

Table [6.1]

Product	Dose (mg/kg)	Inhibition (%)	
Metaclopramide	10	66.61	S ($p < 0.001$)
Zacopride	1	76.74	S ($p < 0.001$)
MDL 72222	5	66.74	S ($p < 0.001$)
	1	66.03	S ($p < 0.010$)
I b	25	- 7.55	NS
I c	25	7.55	NS
I d	25	63.97	S ($p < 0.001$)
	10	63.85	S ($p < 0.001$)
	5	- 0.01	NS
I e	25	- 3.05	NS
I f	25	5.01	NS
I g	25	11.43	NS
II a	25	13.11	NS
II b	25	- 12.53	NS
***II c**			
II d	25	74.81	S ($p < 0.001$)
	10	59.44	S ($p < 0.010$)
	5	61.61	S ($p < 0.001$)
	1	5.21	NS
II e	25	0.06	NS
II f	25	3.98	NS
II g	25	7.59	NS
III a	25	70.00	S ($p < 0.001$)
	10	70.01	S ($p < 0.001$)
	5	20.83	NS
III b	25	71.79	S ($p < 0.001$)
	10	79.69	S ($p < 0.001$)
	5	48.26	S ($p < 0.001$)
	1	14.09	NS
III c	25	64.60	S ($p < 0.001$)
	10	52.34	S ($p < 0.001$)
	5	30.66	S ($p < 0.001$)
	1	12.22	NS
III d	25	71.27	S ($p < 0.001$)
	10	53.69	S ($p < 0.001$)
	5	55.58	S ($p < 0.001$)
	1	30.49	S ($p < 0.001$)
III e	25	69.0	S ($p < 0.001$)
	10	68.0	S ($p < 0.001$)
	5	50.0	S ($p < 0.001$)
	1	10.2	S ($p < 0.001$)
III f	25	9.06	NS
III g	25	4.01	NS

*B-J results were not available at the time of writing.

S = significant result ; NS = non significant result

6.3. **Binding studies on compounds I, II and III *(in vitro).***

The compounds synthesised were evaluated for 5-HT_3 receptor binding affinity by determining their affinity to displace the radioligand [^{3}H]GR65630 bound to membranes from the brain stem *area postrema.*[276] In three duplicate experiments, the binding of increasing concentrations of [^{3}H]GR65630 was measured in order to produce a saturation equilibrium curve (Figure 6.2). From this a dissociation constant, K_D = 1.39 ± 0.5. 10^{-9} M and the maximum number of binding sites B_{max} = 84.32± 21.9 fmol. mg prot $^{-1}$ was obtained. In the initial screening, displacement of [^{3}H]-GR65630 binding by the compounds **I, II** and **III** was studied at two concentrations of each compound, 30 μM and 3μM (Figures 6.3-6.5). For series **I** a full concentration-displacement curve was performed on compounds **I d,** MDL 72222, metoclopramide and zacopride in order to determine the IC_{50}, and the K_i values (Figure 6.6).

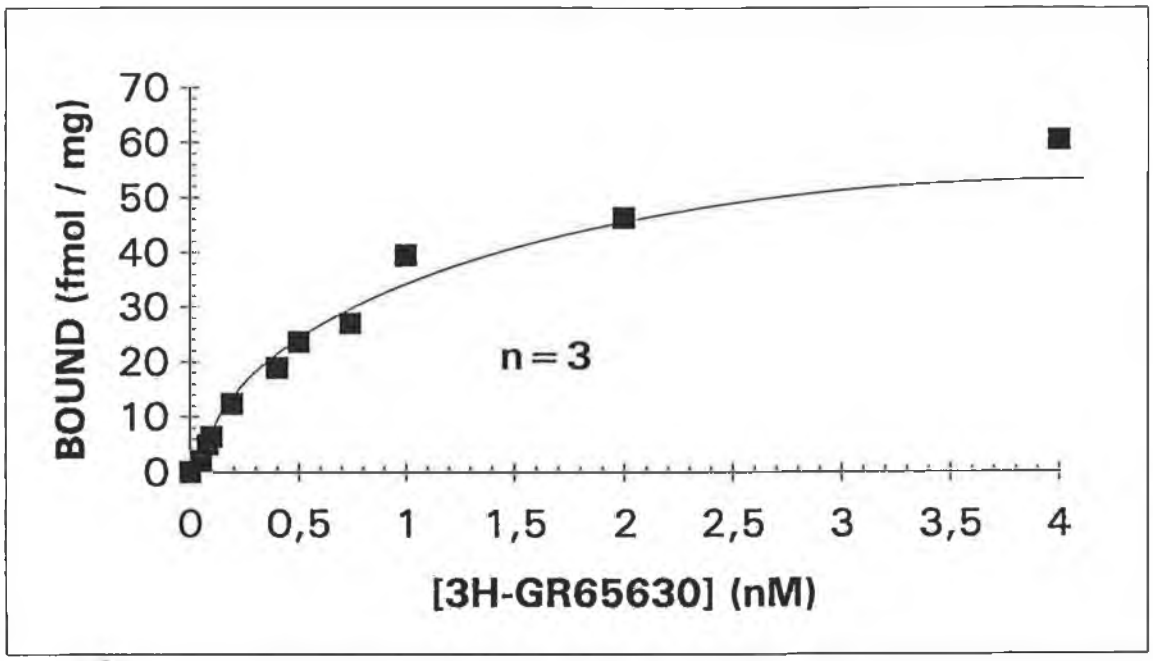


Figure [6.2] Saturable specific binding of [^{3}H]GR65630 to membranes of bovine *area postrema* (2 mg wet weight, 174.62 µg protein) using filtration binding methodology.

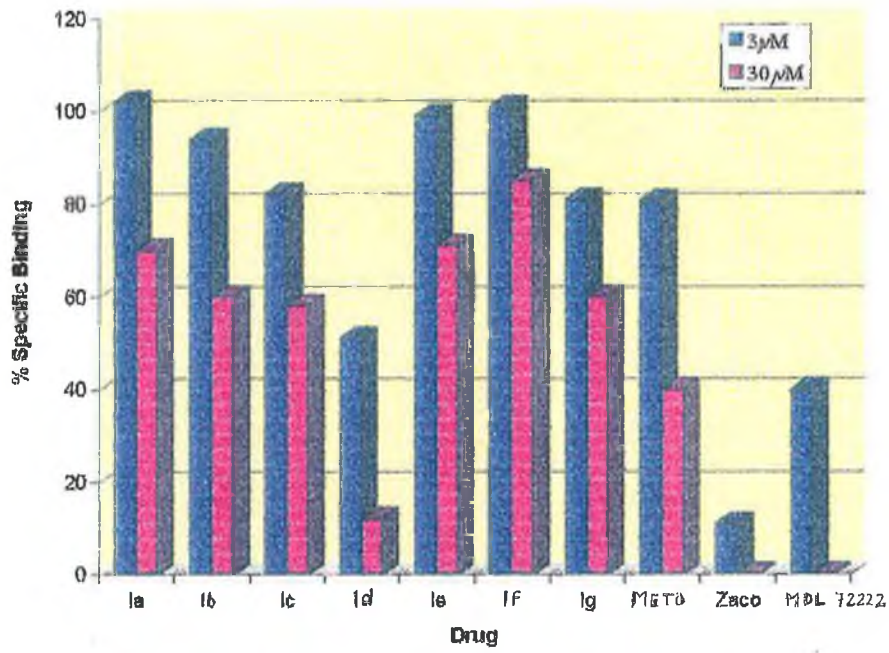


Figure [6.3] Competition experiments at two concentrations of compounds **I a-g**, MDL 72222, zacopride and metoclopramide using [^{3}H]GR65630 at 1nM. Data are normalised as percentage specific binding; the non specific binding was obtained in the presence of 30 μM MDL 72222. They are the means of three triplicate experiments.

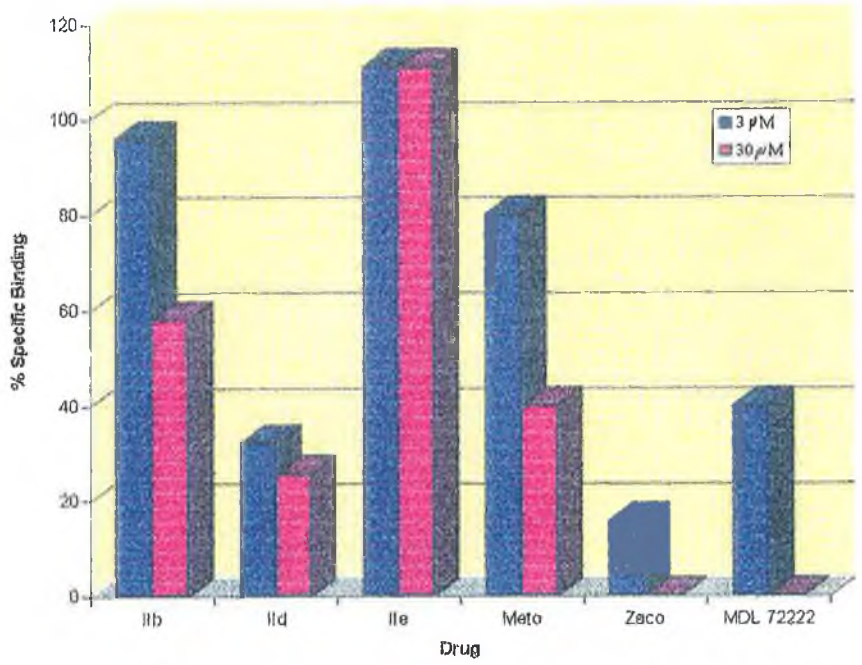


Figure [6.4] Competition experiments at two concentrations of compounds **IIb**, **IId**, **IIe**, MDL 72222, zacopride and metoclopramide using [^{3}H]GR65630 at 1nM. Data are normalised as percentage specific binding; the non specific binding was obtained in the presence of 30 µM MDL 72222. They are the means of three triplicate experiments.

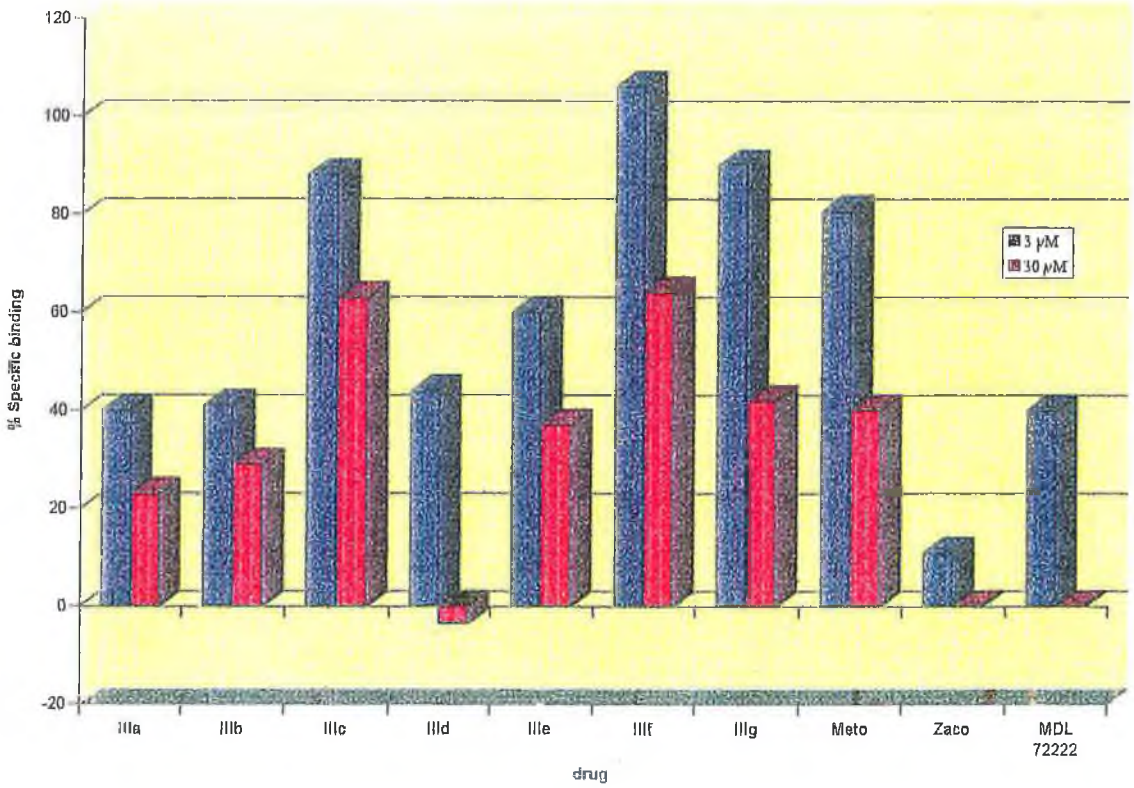


Figure [6.5] Competition experiments at two concentrations of compounds **IIIa-g**, MDL 72222, zacopride and metoclopramide using [^{3}H]GR65630 at 1nM. Data are normalised as percentage specific binding; the non specific binding was obtained in the presence of 30μM MDL 72222. They are the means of three triplicate experiments.

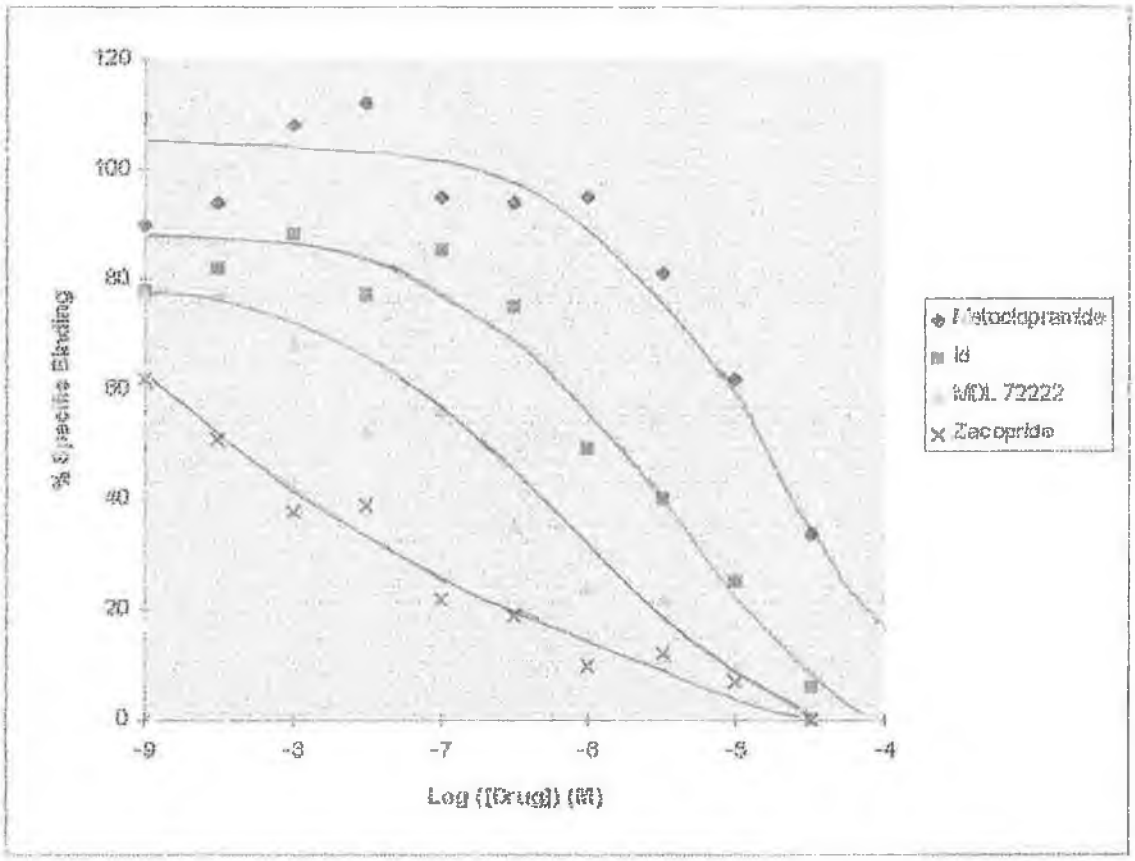


Figure [6.6] Representative competition curves for MDL 72222, metoclopramide, zacopride and compound **Id**, using [^{3}H]GR65630 (1nM) as radioligand. Data are means (SEM) of the number of experiments shown in parentheses.

6.4 Discussion of Biological results.

The *in vivo* and *in vitro* data presented above show some very interesting results. Considering those of the tropinone imidazolines **I a-g** the following observations can be made. In the binding studies, at 3 μM concentrations, compounds **I a, Ib, I e** and **If** which correspond to tropane spiroimazolines with phenyl, 3-methoxy, 4-pyridine-N-oxide and 4-pyridyl aromatic substituents respectively, none show any ability to displace the binding of [^{3}H]GR65630. The 3-indoyl (**I g**) and 3,5 dimethoxy (**I c**) congeners displaced binding by 20 %, while the dichloro compound (**I d**) showed the greatest displacement of 50 %. This is comparable to that exibited by the potent selective 5-HT_3 atagonist MDL 72222 (60%) and much greater than that of metoclopramide which displaced binding by 20%. These figures collate well with the *in vivo* von Bezold-Jarish (B-J) studies where the most active compound was found to be (**I d**) which at a concentration of 10 mg/kg inhibited the induced bradycardia by 64 %. None of the other compounds in the series showed any significant inhibitory effect.

In the quinuclidine imidazoline series the same pattern is repeated. Of the products tested, (Note: biological results for the ortho substituted derivatives are awaiting finalisation) the only compound showing significant activity both in the *in vivo* and the *in vitro* studies was the dichlorophenyl compound (**II d**). At 3μM this compound displaces binding by 68 % which is greater than either MDL 72222 or Metoclopramide and less than the very potent antagonist Zacopride which diplaced binding by 90 %. The B-J *in vivo* studies confirm the potency of the dichloro compound which demonstrated the ability to inhibit the bradycardia reflex by 75 % at a dosage level of 25 mg/kg.

In the oxadiazole series (**III**) several compounds showed antagonistic properties. Compounds (**III a**), (**III b**) and (**III d**) which correspond to phenyl, 3-methoxyphenyl and 3,5 dichlorophenyl substituents respectively, were able to displace binding by 50-60 % while the analogue with the meta aniline substituent displaced c.40 % binding. Again the *in vivo* studies support these findings. Compounds (**III f**) and (**III g**) which refer to the the 3-pyridyl and 4-aminophenyl derivatives respectively demonstrate almost no ability to displace binding or likewise any reduction in the induced bradycardia. The 3,5 dimethoxy congener (**IIIc**) which gave 65 % inhibition in the von Bezold-Jarish test showed very little capacity to displace the binding (10 %) of the radioligand [^{3}H]-GR65630.

6.5 Structure-Activity Relationship (SAR)

The selective 5-HT_3 receptor antagonists reported to date may generally be represented by the structure Ar-(Carbonyl)-N in which an aromatic group is linked by a carbonyl-containing moiety to a basic amine. This simple model can be further refined by considering the three-dimensional aspects of the pharmacophore. The carbonyl group is coplanar to an aromatic group, and the interatomic distances in the 5-HT_3 receptor antagonist pharmacophore are in adequate ranges (carbonyl oxygen-an aromatic centre, ca.3-4 Å; carbonyl oxygen -basic nitrogen centre, ca.5Å: basic nitrogen centre-aromatic centre, ca.7-8Å[27-30]. One of the most important structural factors is the coplanarity between the aromatic ring and the carbonyl moiety. Bearing in mind that, as deduced from conformational studies using ^{1}H and ^{13}C NMR the more stable conformation of the tropane imidazoline compounds **Ia-g** in solution is similar to that found for **Ig** in the

solid state, and by considering the interatomic distances (Table 6.2) deduced from the X-ray data in compound **Ig** it can be seen that the C=N group of the imidazoline ring closely approximates the position of the ester or amide carbonyl group of the pharmacophore model.

Table [6.2] Selected Interatomic Distances for **Ig** in the solid state.

Atom [a] 1	Atom 2	Interatomic distance Å
N8	X[b]	9.2
N8	Y[c]	7.6
N8	N3'	4.1
N8	N1'	5.3
N3'	X	5.2
N1'	X	4.4
N3'	Y	3.5
N1'	Y	3.6

[a] The numeration of the atoms is based on the NMR numbering system
[b] X=Gravimetric center of the indol six membered aromatic ring.
[c] Y= Gravimetric center of the indol five membered ring.

Given that compound **Id** demonstrates 5-HT_3 receptor antagonism comparable to that of MDL72222 and metoclopramide, it is likely that the imidazoline ring may provide a useful bioisosteric replacement for the carbonyl group in 5-HT_3 antagonists. The ability of the imidazoline group to act as a biosteric replacement for a carbonyl group is supported by the biological activity of the corresponding analogue in the quinuclidine

series. This is the first time[277] that such a functionality has been employed in 5-HT_3 antagonists and to the best of our knowledge represents the first reported case of imidazolines acting as bioisosteric replacements for a carbonyl group. It is very interesting to note that the only compounds showing 5-HT_3 antagonism in the imidazoline series were those carrying a dichlorophenyl group as the aromatic moiety. The slightly better potency of the quinuclidine derivative over the tropane equivalent is consistent with previously reported results where highest activity was found in systems having the nitrogen at the bridgehead position within the azabicyclic system.[34]

The results of the oxadiazole series also provided several biologically interesting compounds. The use of an unsubstituted phenyl group (**IIIa**) as the lipophilic aromatic moiety afforded a compound which displayed binding abilities similar to that of MDL 72222 and gave B-J inhibition similar to that of Metoclopramide. This finding is very interesting given that several investigators have noted that as in the case of the imidazolines **Ia** and **IIa**, an unsubstituted phenyl derivative results in significant drops in binding abilities. Thus for example replacement of indole in ICS 205-930 (**5**) with a phenyl group resulted in a 100 fold drop in binding affinity.[270] Swain *et al.*[34] also noted a dramatic drop in affinity when they introduced an unsubstituted benzene into the quinuclidine oxadiazole series. However Rosen *et al* .[278] did have a similar finding to ours when a phenyl group was employed in 5-HT_3 derivatives containing the thiazole function. They found a significant increase over the indole derivative in both binding and B-J inhibition when an unsubstituted phenyl was present as the aromatic function.

In order to increase the electron density of the aromatic centre, thus mimicking the electron rich indole nucleus, a methoxy substituent (**IIIb**) was introduced. This had no significant effect on the binding ability, compared to the unsubstituted phenyl substituent. However, some slight increase in the inhibition of the B-J reflex was observed. Further enhancement of of the electron density in the aromatic nucleus by

replacing the 3-methoxy group with a 3-NH_2 (**IIIe**) function resulted in a reduction in binding affinity and B-J antagonism. An NH_2 group (**IIIg**) in the *para* position caused an almost complete loss of activity possibly arising from steric limitations in this position and may also account for the complete inactivity of the 4-pyridyl *N*-oxides in the imidazoline series, though in these cases the deleterious effect may also arise from the reduction in the lipophilic nature of the *N*-oxide. This *para* effect has previously been observed by other authors.[34,270] The introduction of a π deficient pyridine system (**IIIf**) into the molecule also causes a lack of activity, a fact which is repeated with the imidazoline series.

On going from mono- to disubstituted derivatives such as 3,5 dichlorophenyl (**IIId**), this compound was shown to have the highest activity of the series based on both the *in vivo* and *in vitro* studies. Changing the dichloro for the corresponding dimethoxy caused a drop in the binding ability so that only 10 % of the radioligand was displaced compared to 58 % for the mono methoxy compound and thus again may reflect a possible steric interaction in this region with the receptor. However, an interesting fact is that in the B-J reflex studies the dimethoxy compound was found to be a moderately potent antagonist, comparable to the monomethoxy at low dosage levels. This is somewhat surprising, as Turconi *et al.*[17] described good correlation between ligand binding studies and *in vivo* B-J experiments for 5-HT_3 antagonism. There have been some cases reported however where compounds display the ability to effectively displace binding and are inactive in the Bezold-Jarish test. Thus for example Hayashi *et al.*[29] showed two of their compounds to have higher activity than the reference compound Ondansetron in binding studies while giving much lower activity in the *in vivo* studies. This observation can be explained by considering that either the compounds are not stable *in vivo* or else they are acting as partial agonists of the 5-HT_3 receptor. This however is the opposite to what was found for the dimethoxy phenyl

oxadiazole **III c** where the higher activity was found in the *in vivo* studies. The correlation of the binding of 5-HT_3 antagonists with their abilities to inhibit 5-HT-induced depolarisations of rat isolated vagus nerve was tested by Kilpatrick *et al.*[22] They again found good correlation (correlation efficient = 0.92) but found that it was not absolute. They found that two of their compounds mCPP and MDL 72222 were equipotent in the binding model but 20 fold different in the functional model. They attributed the anomaly to either simple experimental error or, alternatively, to the fact that the two antagonists might have different affinities for the putative subtypes of the 5-HT_3 receptor, as proposed by Richardson and Engel.[3]

This anomalous result found for **III c** is very interesting but would have to be repeated to eliminate the possibility of experimental error. It may be a that the inhibition of the bradycardia took place *via* some other receptor type or maybe by interacting with a hypothesised subgroup of the 5-HT_3 receptor. Caution should however be taken in such an interpretation and further studies will have to be carried out.

CHAPTER VII

Experimental

7.1 Materials and methods.

Except where otherwise stated, the following procedures were adopted throughout. ^{1}H NMR (600 MHz) were recorded on a Bruker AM-600 spectrometer in perdeuteriomethanol. Spectral parameters included sweep widths of 7000Hz in 16K memory and acquisition times of 1 min 32 s over 32 transients. The ^{13}C NMR (75.429 MHz) and ^{1}H NMR (300 MHz) spectra were obtained on a Varian UNITY 300 spectrometer in perdeuteriomethanol or deuterated chloroform. Chemical shifts are reported in ppm relative to methanol or chloroform. Coupling constants were evaluated by first order rules with an estimated accuracy of 0.5Hz. Mass spectra were recorded on a Hewlett-Packard 5890 mass spectrometer and elemental analyses were performed on a Perkin-Elmer Elemental Analyzer model 2409E. The IR spectra were recorded on a Perkin Elmer 883 spectrophotometer. Organic solvents were purified when necessary by the methods described by Perrin (*Purification of Laboratory Chemicals;* Pergamon: Oxford 1986) or were purchased from Aldrich Chemical Co. Thin layer and preparative chromatography were performed on basic alumina or silica gel plates and gravity columns. Melting points were taken in open capillary tubes on an Electrothermal IA6304 apparatus, and are uncorrected.

7.2 1*H*-indole-3-carbonitrile (126).

A mixture of 1*H*-indole-3-carboxaldehyde (10.0g, 69.0 mmol), pyridine hydrochloride (79.7 mmol) and $EtNO_2$ (6 g, 80.0 mmol) was heated at reflux for 7 h. CH_2Cl_2 (50 mL) and 0.1N HCl (120 mL) were then added and the organic layer was separated. The aqueous layer was then extracted with CH_2Cl_2 (3 X 50 mL) and the combined organic phases were washed with H_2O and dried ($MgSO_4$). The solvent was evaporated and the

residue was purified by column chromatography (Silica; CH_2Cl_2) yielding the nitrile (**126**) (3.12 g) as an off-white solid, and a yellow impurity (**127**) (2 g).

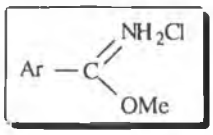
Yield 32%, mp 178 °C, (Lit. mp,[168] 178 °C)

IR (KBr): $\upsilon = 2210\ cm^{-1}$

Compound **127** ^1H NMR (300 MHz, CD_3OD): δ = 2.50 (3H, s, CH_3), 7.21 (2 H, m, H5, H6), 7.45 (1H, dd, H7), 7.74 (1H, dd, H4), 7.77 (1H, s, H_{vinyl}), 8.51 (1H, s, H2)

MS (EI): *m/z* (%) = 202 (M^+, 65), 155 (73), 154 (100), 145 (52), 144 (52), 128 (97).

7.3 Synthesis of carboximidate hydrochlorides (123 a, c-f, h, 141).



Phenyl carboximidate hydrochloride (123a)

Dry hydrogen chloride gas was bubbled through a solution of benzonitrile (1.0 g, 9.7 mmol) in dry MeOH (5.0 mL) at 0 °C. The solution was allowed to stand at 0 °C for 24 h. Addition of dry Et_2O (15 mL) precipitated the title compound which was filtered and washed with dry Et_2O.

Yield 82 %

3,5-Dichlorophenyl carboximidate hydrochloride (123c)

Dry hydrogen chloride gas was bubbled through a solution of dichlorobenzonitrile (0.25 g, 1.45 mmol) in dry MeOH (5.0 mL) at 0 °C. The solution was allowed to stand at 0 °C for 24 h. The solvent was then evaporated from the reaction mixture *in vacuo* at 35 °C and the crude reaction mixture was used directly in the subsequent reaction.

IR (KBr): $\upsilon = 1651\ cm^{-1}$

3-Methoxyphenyl carboximidate hydrochloride (123d)

Dry hydrogen chloride gas was bubbled through a solution of 3-methoxybenzonitrile (2.0 g, 15.0 mmol) in dry MeOH (8.0 mL) at 0 °C. The solution was allowed to stand at

0 °C for 24 h. Addition of dry Et_2O (15 mL) precipitated the title compound which was filtered and washed with dry Et_2O.

Yield 54 %

IR (KBr): $\upsilon = 1640\ cm^{-1}$

3,5-Dimethoxyphenyl carboximidate hydrochloride (123e).

Dry hydrogen chloride gas was bubbled through a solution of 3,5-dimethoxybenzonitrile (1.50 g, 9.2 mmol) in dry MeOH (15.0 mL) and dry Et_2O (15 mL) at 0 °C. The solution was allowed to stand at 0 °C for 36 h. Addition of dry Et_2O (20 mL) precipitated the title compound which was filtered and washed with dry Et_2O.

Yield 54 %

IR (KBr): $\upsilon = 1642\ cm^{-1}$

2-Methoxyphenyl carboximidate hydrochloride (123f).

Dry hydrogen chloride gas was bubbled through a solution of 2-methoxybenzonitrile (2.0 g, 15.0 mmol) in dry MeOH (8.0 mL) at 0 °C. The solution was allowed to stand at 0 °C for 72h then 24 h at r.t. The solvent was then evaporated from the reaction mixture *in vacuo* at 35 °C and the crude reaction mixture was used directly in the subsequent reaction.

1H-indole-3-carboximidate hydrochloride (123h).

Dry hydrogen chloride gas was bubbled through a solution of 1H-indole-3-carbonitrile (0.5 g, 3.52 mmol) in dry MeOH (20 mL). The solution was allowed to stand at r. t. for 24 h. Addition of dry Et_2O (15 mL) precipitated the title compound which was filtered and washed with dry Et_2O.

Yield 65 %. mp 176-177 °C.

IR (KBr): $\upsilon = 1677\ cm^{-1}$

N-oxido 4-Pyridyl carboximidate hydrochloride (141).

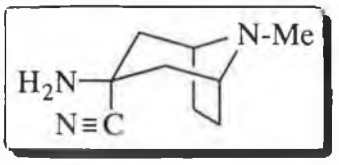
Dry hydrogen chloride gas was bubbled through a suspension of 4-cyanopyridine *N*-oxide (2.0 g, 16.7 mmol) in dry MeOH (150.0 mL) at 0 °C. On addition of the HCl gas a complete solution eventually formed. The solution was allowed to stand at 0 °C for 24 h. Addition of dry Et_2O (80 mL) precipitated the title compound which was filtered and washed with dry Et_2O.

Yield 96 %

IR (KBr): $\upsilon = 1652\ cm^{-1}$

MS (EI); *m/z* (%) = 152 (100, M^+), 121 (99), 104 (32), 94 (12)

7.4 3β-Amino-8-methyl-8-azabicyclo[3.2.1]octane-3α-carbonitrile (124)

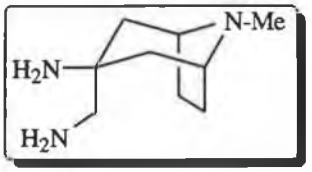


A mixture of potassium cyanide (4.48g, 68.9 mmol), ammonium chloride (3.69g, 68.9mmol) and *N*-methyltropinone (10.0g, 68,9mmol) was added to H_2O (14.0 mL) and agitated at 20 °C for 48 h in a stoppered flask. The suspension was then cooled to 0-5 °C for 1 h and filtered. The resulting solid was taken up into EtOAc (100 mL), filtered and dried ($MgSO_4$). The amino nitrile was then precipitated from solution with petroleum ether (50 mL).

Yield: 83% mp 72-74 °C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.8 (2 H, bs, NH_2), 1.6-1.88 (2 H, m), 2.06-2.16 (6 H, m), 2.29 (3 H, s, CH_3), 3.2 [2H, bs, H1(5)]

7.5. 3α-Aminomethyl-8-methyl-8-azabicyclo[3.2.1]octyl-3β-amine (122)



The amino nitrile (**124**) (4.5 g, 27.3 mmol) was added in portions over 0.5 h to a suspension of $LiAlH_4$ (2.5 g, 67.5 mmol) in anhydrous Et_2O (30.0 mL) at 0-10 °C under N_2. The reaction was refluxed for 48h and then quenched at 0-10 °C with H_2O

(2.5 mL), followed by 4N NaOH (2.5mL) then H_2O (2.5 mL). The inorganic salts were filtered off and extracted with refluxing Et_2O (80 mL) in a Soxhlet apparatus for 5 h then refiltered. The filtrates were combined, dried over $MgSO_4$ and stripped to dryness. The residue was then distilled under high vacuum (90-100°C, 0.5 mm Hg) and the product was refluxed in methanol (50 mL) containing a drop of dilute HCl for 24 h to give the required product as a low melting solid.

Yield: 85%

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (4 H, br s, $2NH_2$), 1.52 [2 H, m, H6(7)$_{endo}$], 1.72 [4 H, m, H2(4)$_{ax,eq}$], 2.00 [2 H, m, H6(7)$_{exo}$], 2.28 (3 H, s, Me), 2.62 (2 H, s, $C\underline{H}_2NH_2$), 3.12 [2 H, br s, H1(5)]

IR (film): υ = 3300, 2940, cm^{-1}

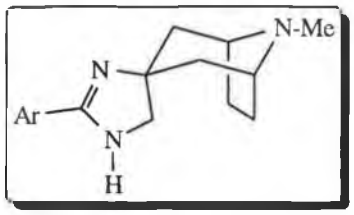
MS:(CI) *m/z* (%) = 170 (M^++1, 100), 198 (M^++29, 2), 210 (M^++41, 5), 153 (25), 139 (10), 122 (10)

Compound **(154)** : ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (4H, s, $2NH_2$) 1.41-1.60 (2 H, m, H6(7)$_{endo}$), 1.90-2.11 [6 H, m, H6(7)$_{exo}$, H2(4)$_{ax,\ eq}$] 2.29 (3 H, s, Me), 2.98 (2 H, s, $C\underline{H}_2NH$), 3.15 [2 H, br s, H1(5)]

IR (film):υ = 3320, 2960, cm^{-1}

MS:(EI) *m/z* (%) = 194 (M^+, 69), 177 (11), 163 (4), 139 (8), 122 (22)

7.6. Synthesis of 2'Aryl-8-methyl-8-azabicyclo[3.2.1]octane-3-spiro-4'(5)-imidazolines (I a-g)



2'-Phenyl-8-methyl-8-azabicyclo[3.2.1]octane-3-spiro-4'(5')-imidazoline (Ia).

The carboximidate **(123a)** (1.03 g, 6.0 mmol) and the tropinone 1,2-diamine (**122**) (1.01 g, 6.0 mmol) were added to dry methanol (25.0 mL) and stirred at room temperature for 24 h under Ar. The solvent was removed under reduced pressure and the residue purified by column chromatography using basic alumina and CH_2Cl_2 : EtOH as eluent. Trituration of the resulting oil with Et_2O afforded a white solid which was recrystallised from acetone (5.0 mL).

Yield 43%, mp 175-177°C

MS (EI): *m/z* (%) = 255 (25, M^+), 227 (3), 185 (6), 174 (35), 173 (44), 158 (100), 104 (35), 82 (67)

^{1}H NMR (300 MHz, CD_3OD): δ = 3.30 [2H, bs, H1(5)] 1.96 [2 H, dd, H2(4)$_\alpha$], 2.12 [2 H, dd, H2(4)β], 2.12 [2H, m, H6(7)$_{exo}$] 1.86 (2 H, m, H6(7)$_{endo}$), 2.39 (3 H, s, CH_3,), 3.97 (H, s, H4'), 7.77 (1H, H2"), 7.50 (1H, H3"), 7.50 (1H, H4"), 7.50 (1H, 7.50, H5"), 7.77 (1H, H6").

^{13}C NMR (75.429 MHz, CD_3OD) δ = 25.99 (C6,7), 38.96 (NCH_3), 42.50 (C2,4), 61.95 (C1,5), 62.67 (C3), 65.11 (C4'), 124.75 (C1"), 128.54 (C3"), 128.54 (C5"), 129.83 (C2"), 129.83 (C6"), 133.10 (C4"), 164.49 (C2')

Anal. $C_{16}H_{21}N_3$: Calc. C, 75.26; H, 8.29; N, 16.46.

Found: C, 75.46; H, 8.49; N, 16.51.

2'-(3-Methoxyphenyl)-8-methyl-8-azabicyclo[3.2.1]octane-3-spiro 4'(5')-imidazoline (Ib)

The carboximidate **(123d)** (0.5 g, 2.5 mmol) and the tropinone 1,2-diamine (**122**) (0.42 g, 2.5 mmol) were added to dry MeOH (10.0 mL) and stirred at r.t. for 24 h under Ar. The solvent was removed under reduced pressure and the residue purified by column chromatography using basic alumina and CH_2Cl_2 : EtOH as eluent. Trituration of the resulting oil with Et_2O afforded a pure white solid.

Yield 41%, mp 152-154°C (from acetone)

MS (EI): *m/z* (%) = 285 (34, M^+), 230 (5), 203 (37), 189 (66), 188 (100), 147 (7), 134 (16), 98 (26), 82 (54), 70 (13)

^{1}H NMR (300 MHz, CD_3OD): δ = 3.24 [2H, bs, H1(5), $W_{1/2}$ = 9.40] 1.87 [2 H, dd, H2(4)$_\alpha$], 2.08 [2 H, dd, H2(4)β], 2.08 [2H, m, H6(7)$_{exo}$] 1.84 (2 H, m, H6(7)$_{endo}$), 2.37 (3 H, s, CH_3), 3.89 (1 H, s, H4'), 3.82 (3 H, s, OCH_3) 7.32 (1H, H2"), 7.03 (1H, H4"), 7.32 (1H, H5"), 7.32 (1H, H6").

^{13}C NMR (75.429 MHz, CD_3OD) δ = 61.85 (C1,5), 42.58(C2,4), 62.50 (C3), 26.25 (C6,7), 38.83 (NCH_3), 164.22 (C2'), 67.29 (C4'), 55.83 (OCH_3), 132.97 (C1"), 113.49 (C2"), 161.5 (C3"), 117.94 (C4"), 130.55 (C5"), 132.95 (C6")

Anal. $C_{17}H_{23}N_3O$: Calc. C, 71.55; H, 8.12; N, 14.72.

Found C, 71.46; H, 8.32; N, 14.67.

2'-(3,5-Dimethoxyphenyl)-8-methyl-8-azabicyclo[3.2.1]octane-3-spiro-4'(5')-imidazoline (Ic)

The carboximidate (**123e**) (0.4 g, 1.7 mmol) and the tropinone 1,2-diamine (**122**) (0.29 g, 0.17 mmol) were added to dry MeOH (8.0 mL) and stirred at r.t. for 48 h under Ar. The solvent was removed under reduced pressure and the residue purified by column chromatography using basic alumina and CH_2Cl_2 : EtOH as eluent. Trituration of the resulting oil with Et_2O afforded a pure white solid.

Yield 48%, mp 167-168 °C (from acetone)

MS (EI): *m/z* (%) = 315 (40, M^+), 260 (5), 233 (32), 219 (60), 218 (100), 164 (14), 122 (3), 98 (36), 82 (81)

^{1}H NMR (300 MHz, CD_3OD): δ = 3.22 [2H, bs, H1(5), $W_{1/2}$ = 9.79] 1.86 [2 H, dd, H2(4)$_\alpha$], 2.08 [2 H, dd, H2(4)β], 2.08 [2H, m, H6(7)$_{exo}$] 1.83(2 H, m, H6(7)$_{endo}$), 2.37 (3 H, s, CH_3,), 3.88 (1 H, s, H4'), 3.80 (6 H, s, 2 OCH_3) 6.95 (1H, H2"), 6.58 (1H, H4"), 6.95 (1H, H6").

^{13}C NMR (75.429 MHz, CD_3OD) δ = 26.26 (C6,7), 38.83 (NCH_3), 42.54 (C2,4), 55.94 (OCH_3), 61.85 (C1,5), 62.47 (C3), 67.26 (C4'), 104.07 (C4"), 106.26 (C2"), 106.26 (C6"), 132.79 (C1"), 162.3 (C3"), 162.3 (C5"), 164.22 (C2')

Anal. $C_{18}H_{23}N_3O_2$: Calc. C, 68.54; H, 7.99 N, 13.20.

Found C, 68.30 H, 8.30 N, 13.21.

2'-(3,5-Dichlorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-3-spiro-4'(5')-imidazoline (Id)

The crude carboximidate (**123c**) (0.36 g,) and the tropinone 1,2-diamine (**122**) (0.24 g, 0.145 mmol) were added to dry MeOH (8.0 mL) and stirred at r.t. for 48 h under Ar. The solvent was removed under reduced pressure and the residue purified by column chromatography using basic alumina and CH_2Cl_2 : EtOH as eluent. Trituration of the resulting oil with Et_2O afforded a pure white solid.

Yield 38%, mp 139 -140 °C (from acetone)

^{1}H NMR (300 MHz, CD_3OD): δ = 3.38 [2H, bs, H1(5), $W_{1/2}$ = 9.70] 1.94 [2 H, dd, H2(4)$_\alpha$], 2.12 [2 H, dd, H2(4)β], 2.12 [2H, m, H6(7)$_{exo}$] 1.90 (2 H, m, H6(7)$_{endo}$), 2.46 (3 H, s, CH_3), 3.91 (1 H, s, H4'), 7.72 (1H, H2"), 7.60 (1H, H4"), 7.72 (1H, H6").

^{13}C NMR (75.429 MHz, CD_3OD) δ = 26.21 (C6,7), 38.89 (NCH_3), 42.46 (C2,4), 55.94 (OCH_3), 61.83 (C1,5), 67.26 (C4'), 126.92 (C2"), 126.92 (C6"), 131.49 (C4"), 134.37(C1"), 136.4 (C3"), 136.4 (C5"), 161.67 (C2')

MS (EI): *m/z* (%) = 323 (1, M^+, Cl^{35}), 229 (1), 227 (4), 225 (1), 147 (2), 147 (6), 145 (9), 100 (5), 98 (19), 96 (24), 82 (100)

Anal. $C_{16}H_{19}Cl_2N_3$:H_20 Calc. C, 56.14; H, 6.14 N, 12.28

Found C, 56.02, H, 6.10 N, 12.18

2'-(N-oxido-4-pyridyl)-8-methyl-8-azabicyclo[3.2.1]octane-3-spiro-4'(5')-imidazoline dihydrochloride (Ie)

The crude carboximidate (**141**) (1.0 g, 6.6 mol) and the tropinone 1,2-diamine (**122**) (1.1 g, 6.6 mmol) were added to dry MeOH (30.0 mL) and stirred at reflux for 3 h under Ar. The reaction mixture was cooled to r.t. and 5 mL saturated methanolic HCl was added to the reaction mixture. The reaction was then stirred for 1 h , cooled to 0-5 °C for a further 1 h and the precipitated HCl salt was filtered and washed with MeOH.

Yield 29%, mp 232 °C (Dec.) (from methanol)

MS: (EI) *m/z* (%) = 272 (40, M^+), 256 (5), 191 (50), 175 (100), 160 (50), 105 (20), 98 (40), 82 (65)

^{1}H NMR Free base.(300 MHz, $CDCl_3$): δ = 3.18 [2H, bs, H1(5), $W_{1/2}$ = 11.40] 2.01[2 H, dd, H2(4)$_\alpha$], 2.07 [2 H, dd, H2(4)β], 1.80 [2H, m, H6(7)$_{exo}$] 1.69 (2 H, m, H6(7)$_{endo}$), 2.28 (3 H, s, CH_3), 3.87 (1 H, s, H4'), 7.61 (1H, m, H2"), 8.14 (1H, m, H3"), 8.14 (1H, m, H5"), 7.61 (1H, m, H6").

Anal. $C_{15}H_{22}Cl_2N_4O$: Calc. C, 52.18; H, 6.42 N, 16.23.

Found: C, 52.18, H, 6.48 N, 16.44.

2'-(1H-indol-3-yl)-8-methyl-8-azabicyclo[3.2.1]octane-3-spiro-4'(5')-imidazoline dihydrochloride (Ig)

The crude carboximidate (**123h**) (0.5 g, 1.61 mol) and the tropinone 1,2-diamine (**122**) (0.27 g, 1.61 mmol) were added to dry MeOH (6.0 mL) and stirred at r.t. for 24 h then at reflux for 3 h under Ar. The reaction mixture was cooled to r.t. and 5 mL saturated methanolic HCl was added to the reaction mixture. The reaction was then stirred for 1 h , cooled to 0-5 °C for a further 3 h and the precipitated HCl salt was filtered and washed with MeOH.

Yield 52%, mp 255-257 °C (from methanol)

MS: (EI) *m/z* (%) = 294 (30, M^+), 266 (5), 212 (20), 197 (90), 142 (30), 115 (10), 82 (100), 55 (35)

^{1}H NMR (300 MHz, CD_3OD): δ = 4.08[2H, bs, H1(5), $W_{1/2}$ = 11.8] 2.55 [2 H, dd, $H2(4)_\alpha$], 2.65 [2 H, dd, H2(4)β], 2.42 [2H, m, $H6(7)_{exo}$] 2.28 (2 H, m, $H6(7)_{endo}$), 2.86 (3 H, s, CH_3), 4.33 (1 H, s, H4'), 8.83 (1H, m, H2"), 7.93 (1H, m, H4"), 7.34 (1H, m, H5"), 7.34 (1H, m, H6"), 7.57 (1H, m, H7")

^{13}C NMR (75.429 MHz, CD_3OD) δ = 24.04 (C6,7), 41.0 (C2,4), 59.85 (C1,5), 64.36 (C4'), 99.34 (C3"), 114.05 (C7"), 120.2 (C4"), 123.9 (C5"), 125.11 (C6"), 132.3(C2"), 138.44 (C7a"), 161.91 (C2')

Anal. $C_{18}H_{24}Cl_2N_4$·MeOH: Calc. C, 57.14; H, 7.04, N, 14.03.

Found C, 57.39, H, 7.14, N, 14.06.

2'-(4-pyridyl)-8-methyl-8-azabicyclo[3.2.1]octane-3-spiro-4'(5')-imidazoline (If)

Compound **(Ie)** (0.5 g, 1.83 mmol) was liberated from its hydrochloride salt by dissolving in H_2O (2 mL), basifying to pH 10 and extracting with CH_2Cl_2. The organic solution was then dried and concentrated to dryness. The free base was dissolved in $CHCl_3$ (3.0 mL) and PCl_3 (0.28 g, 2.0 mmol) was added dropwise while maintaining the temperature between 0-10 °C . The reaction was heated to reflux for 2 h then carefully quenched with H_2O (1.0 mL), basified to pH 10 with NaOH (10%) and extracted with $CHCl_3$ (5.0 ml). The organic solution was dried (Na_2SO_4) and evaporated to dryness to give a low melting solid which was sufficiently pure for characterisation.

Yield : 91%

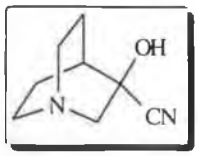
^{1}H NMR Free base.(300 MHz, $CDCl_3$): δ = 3.39 [2H, bs, H1(5), $W_{1/2}$ = 10.90] 1.92[2 H, dd, H2(4)$_\alpha$], 2.46 [2 H, dd, H2(4)$_\beta$], 2.10 [2H, m, H6(7)$_{exo}$] 1.86 (2 H, m, H6(7)$_{endo}$), 2.42 (3 H, s, CH_3), 3.91 (1 H, s, H4'), 7.63 (1H, m, H2"), 8.58 (1H, m, H3"), 8.58 (1H, m, H5"), 7.63 (1H, m, H6").

^{13}C NMR (75.429 MHz, $CDCl_3$) δ = 61.56 (C1,5), 41.96 (C2,4), 24.84 (C6,7), 38.66 (NCH_3), 160.0 (C2'), 67.87 (C4'), 136.9 (C1"), 124.15 (C2"), 150.1 (C3"), 150.1 (C5"), 124.15 (C6")

Anal. $C_{15}H_{20}N_4$: Calc. C, 70.31; H,7.81, N, 21.88.

Found C, 69.70, H, 8.56, N, 21.67.

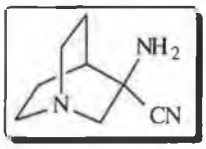
7.7 **3-Hydroxy-1-azabicyclo[2.2.2]octane-3-carbonitrile (157)**



3-Quinuclidinone hydrochloride (0.186 mol) was dissolved in water (40 mL) and the solution was cooled to 0 °C. Potassium cyanide (0.186 mol) in water (40 mL) was added dropwise to this solution, and the contents were stirred at 0 °C for 3 h. The resulting solid was isolated by filtration, washed with water, and dried under vacuum to afford the title compound as the free base.

Yield: 99%, mp. 153-156 °C, Lit.[234] mp 152-155 °C

7.8 **3-Amino-1-azabicyclo[2.2.2]octane-3-carbonitrile (158)**



To a solution of 3-cyano-3-hydroxyquinuclidine (8.0g, 42.0 mmol) in absolute ethanol (40.0mL) was added a solution of 28% aqueous ammonia (6.0mL). The mixture was stirred at 50°C for 72h then for a further 12h at 20°C. The solvent was then removed under reduced pressure and the residue was recrystallised from acetone (30mL).

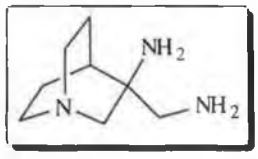
Yield: 89%, mp. 111-113°C, Lit. mp.[218] 85°C

IR (KBr): $\upsilon_{max.=}$ 3348, 3242, 2202 cm^{-1}

$C_8H_{13}N_3$	Calc.	C, 63.55; H, 8.66; N, 27.79.
	Found	C, 63.50; H, 8.56; N, 27.72.

MS: (EI) *m/z* (%) = 151 (35, M^+), 136 (5), 125 (4), 107 (6), 94 (10), 81 (20), 70 (100), 58 (85)

7.9 **3-Aminomethyl-1-azabicyclo[2.2.2]octyl-3-amine (159)**



The procedure for the synthesis of **(159)** is identical to that for the preparation of the diamine **(122)** with the exception that the final step of heating the distilled base under reflux in methanol is not required. The crude oil obtained on concentrating the solvent was distilled under high vacuum (0.1 mmHg). A first fraction which appears between 60-70 °C condenses in the condenser and can be removed by dissolving in methanol and corresponds to the impurity **(160)**. A second fraction distilling at 80-100 °C is the required diamine **(159)** while the third fraction at c.190 °C corresponds to the impurity **(161)**.

Yield: 40%

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30-1.70 (4 H, m, 2 x CH_2), 1.46 (4 H, br s, 2 x NH_2), 1.94 (1 H, m, CH), 2.56 (1 H, d, C<u>H</u>HNH_2, *J* = 12.8 Hz), 2.78 (1 H, d,CH<u>H</u>NH_2, *J* = 12.8 Hz), 2.64 (1 H, dd, C<u>H</u>HN, J_1 = 13.6 Hz, J_2 = 2.5 Hz), 2.52 (1 H, dd, CH<u>H</u>N, J_1 = 13.6 Hz, J_2 = 2.5 Hz), 2.64-2.94 (4 H, m, 2 x CH_2N)

IR(film): $u_{max.=}$ 3200, 2936, 1594, 1456 cm^{-1}

MS:(CI) *m/z* (%) = 156 (M^++1, 100), 184 (M^++29, 5), 196 (M^++41, 2), 138 (25), 96(4)

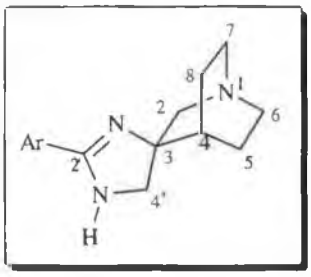
Compound (**161**) :^{1}H NMR (300 MHz, CD_3OD): δ = 1.35-1.61 (6 H, m), 1.80-2.01 (4 H, m), 2.62-3.0 (12 H, m)

MS:(CI) *m/z* (%) = 303 (M^++1, 5), 263 (14), 229 (17), 201 (100)

Compound (**160**) : ^{1}H NMR (300 MHz, CD_3OD): δ = 1.42-1.55 (1 H, m), 1.55-1.70 (1 H, m), 1.7-1.82 (2 H, m), 1.82-2.0 (1 H, m) 2.38-2.48 (1H, m) 2.68-2.97 (4H, m), 2.98-3.6 (1H, m)

MS:(CI) *m/z* (%) = 127 (M^++1, 100), 155 (M^++29, 14), 167 (M^++41, 3), 111 (49)

7.10 2'-Aryl-1-azabicyclo[2.2.2]octane-3-spiro-4'(5')-imidazolines (IIa-g).



2'-Phenyl-1-azabicyclo[2.2.2]octane-3-spiro-4'(5')-imidazoline (IIa).

A solution of the imidate hydrochloride **(123a)** (0.5 g, 2.87 mmol) in dry methanol (2.0mL) was added to a solution of the diamine **(159)** (0.45 g, 2.87 mmol) in dry methanol (3.0 mL) at ambient temperature under argon and stirred for 2 hours. The solvent was then removed under vacuum and the product was isolated by column chromatography using basic silica and CH_2Cl_2 :MeOH (9:1) as eluting solvent. Yield 71%, mp 162-164 °C

MS:(EI) *m/z* (%) = 241 (15, M^+), 226 (21), 213 (11), 185 (14), 171 (100), 145 (9), 104 (28), 71 (33), 70 (25)

^{1}H NMR (300 MHz, CD_3OD): δ = 1.50-1.70 (2 H, m, CH_2), 1.70-1.90 (2 H, m CH_2), 2.10-2.24 (1 H, m, CH), 2.72-2.90 (3 H, m), 2.90-3.10 (3H, m), 3.55 (1H, d, C**H**H $_{imidazoline}$), 3.95 (1H, d, CH**H** $_{imidazoline}$)

^{13}C NMR (300 MHz, CD_3OD): δ = 22.64 (C5), 23.25 (C8) 32.8 (C4), 47.0 (C7 or C6), 47.2 (C7 or C6), 62.3 (C3), 64.7 (C2) 66.5 (C4'$_{imidazoline}$,weak), 128.3 (C3",C5"), 129.2 (C2",C6"), 131.1 C(C1"), 131.8 (C4), 165.0 (C2', $_{imidazoline}$)

Anal. $C_{15}H_{19}N_3$: Calc. C,74.69; H,7.90, N,17.4.

Found: C,74.19, H,7.71, N,17.3.

2'-(3-Methoxyphenyl)-1-azabicyclo[2.2.2]octane-3-spiro-4'(5')-imidazoline dihydrochloride (IIb).

A solution of the imidate hydrochloride (**123d**) (0.5 g, 2.5 mmol) in dry methanol (2.0mL) was added to a solution of the diamine (**159**) (0.39 g, 2.5 mmol) in dry methanol (2.0 mL) at ambient temperature under argon and stirred for 2 hours. HCl gas was bubbled through the reaction solution until the solvent was saturated. The solvent was then removed and replaced with EtOH (5 mL). Some undissolved grey solid was removed by filtration and the product was allowed to crystallise from the filtrate by standing at 10 °C overnight. The product was filtered and washed with ice-cold EtOH and dried under vacuum.

Yield 59%, mp 270-272°C

MS: (EI) *m/z* (%) = 271 (13, M^+), 256 (19), 243 (12), 201 (100), 134 (15), 77 (21), 71 (67), 70 (55)

^{1}H NMR (300 MHz, CD_3OD): δ = 2.05-2.18 (3 H, m), 2.38-2.45 (1H, m), 2.50 (1H, m), 3.35 (2H, m), 3.45 (1H, m), 3.55 (1H, m), 3.88 (3H, s, CH_3), 3.70 (1H, dd, CHHN, J_1=14.5 Hz, J_2=1.74 Hz), 3.79 (1H, dd, CHHN, J_1=14.5 Hz, J_2=1.74 Hz), 4.15 (1H, d, CHH $_{imidazoline}$, J=12.4 Hz), 4.40 (1H, d, CHH $_{imidazoline}$, J=12.4 Hz), 7.32 (1H), 7.55 (3H)

Anal. $C_{17}H_{23}N_3O_2 \cdot 2HCl$: Calc. C, 54.55; H, 6.73; N, 11.23.

Found: C, 54.54; H, 6.72; N, 11.38.

2'-(2-Methoxyphenyl)-1-azabicyclo[2.2.2]octane-3-spiro-4'(5')-imidazoline (IIc)*

A solution of the crude imidate hydrochloride (**123f**) (2.5 g; contains c. 20% imidate) in dry methanol (4.0mL) was added to a solution of the diamine (0.93 g, 6.0 mmol) in dry methanol (5.0 mL) at ambient temperature under argon and stirred for 2 hours. The solvent was removed under reduced pressure, then dissolved in H_2O (5mL) and acidified to to pH 2. Unreacted starting nitrile was then extracted with 3 x 10 mL CH_2Cl_2 and the required product was isolated by liberating into CH_2Cl_2 with K_2CO_3. The solvent was removed under reduced pressure leaving the product as a viscous oil.

Yield 20 %, mp-viscous oil

MS: (EI) *m/z* (%) = 271 (13, M^+), 256 (19), 243 (12), 201 (100), 134 (15), 77 (21), 71 (67), 70 (55)

MS:(CI) *m/z* (%) = 272 (M^++1, 100), 300 (M^++29, 11), 312 (M^++41, 1.8)

*On standing for a period of time at room temperature this compound was found to decompose to a new compound. According to mass spectrometry the compound seemed to have hydrolysed to the corresponding 2-hydroxy compound by cleavage of the OMe bond.

2'-(3,5-Dichlorophenyl)-1-azabicyclo[2.2.2]octane-3-spiro-4'(5')-imidazoline (IId).

A solution of the crude imidate hydrochloride **(123c)** (2.0 g) in dry methanol (4.0mL) was added to a solution of the diamine (0.46 g, 3.0 mmol) in dry methanol (5.0 mL) at ambient temperature under argon and stirred for 2 hours. The solvent was removed under reduced pressure, then the residue was dissolved in H_2O (5mL) and acidified to pH 2. Unreacted starting nitrile was then extracted with 3 x 10 mL CH_2Cl_2 and the required product was isolated by liberating into CH_2Cl_2 with NaOH. The organic phase was dried over $MgSO_4$ and the solvent was removed under vacuum giving a white solid which was recrystallised in ethanol.

Yield 56%, mp 103-106°C

MS:(EI) *m/z* (%) = 311 (M^+,Cl^{37},11), 309 (M^+,Cl^{35},17), 296 (21), 294 (28), 243 (12), 242 (14), 241 (70), 240 (18), 239 (95), 149 (8), 147 (20), 145 (38), 99 (16), 98 (12), 97 (61), 96 (60), 71 (100), 70 (90)

^{1}H NMR (300 MHz, CD_3OD): d = 1.54-1.72 (2H, m, CH_2), 1.72-1.90 (2 H, m, CH_2), 2.10-2.22 (1 H, m, CH), 2.75-2.95 (3 H, m, CH_2N), 2.95-3.10 (3H, m, CH_2N), 3.58 (1H, d, C<u>H</u>H $_{imidazoline}$, J=12.7Hz), 3.98 (1H, d, CH<u>H</u> $_{imidazoline}$, J=12.7Hz), 7.57 (1H, t), 7.76 (2H, d)

^{13}C NMR (300 MHz, CD_3OD): δ = 22.79 (C5), 23.30 (C8) 32.97 (C4), 47.18 (C7), 47.46 (C6), 62.7 (C3)weak, 64.84 (C4'$_{imidazoline}$,weak), 127.15 C2"(C6"), 131.49(C4"), 136.65 (C1"), 136.33, C3"(5"), 162.50 (C2'$_{imidazoline}$)

Anal. $C_{15}H_{17}N_3Cl_2$: Calc. C,58.08; H, 5.52; N, 13.54.

Found C,58.01; H, 5.58; N, 13.48.

2'-(N-oxido-4-pyridyl)-1-azabicyclo[2.2.2]octane-3-spiro-4'(5')-imidazoline (IIe)

A solution of the imidate hydrochloride (**141**) (0.5 g, 2.87 mmol) in dry methanol (2.0mL) was added to a solution of the diamine (**159**) (0.45 g, 2.87 mmol) in dry methanol (3.0 mL) at ambient temperature under argon and stirred for 2 hours. The solvent was then removed under vacuum and the product was isolated by column chromatography using basic silica and CH_2Cl_2 :MeOH (75:25) as eluting solvent.

Yield 31%, mp 60-62 °C

MS:(EI) *m/z* (%) = 258 (17, M^+), 243 (18), 227 (7), 188 (46), 172 (33), 145 (5), 105(14), 97 (27), 71 (98), 70 (100)

^{1}H NMR (300 MHz, CD_3OD): δ = 1.57-1.75 (2 H, m, CH_2), 1.75-1.90 (2 H, m CH_2), 2.10-2.24 (1 H, m, CH), 2.78-2.95 (3 H, m), 2.96-3.10 (3H, m), 3.62 (1H, d, *J* = 12.5 Hz, C<u>H</u>H $_{imidazoline}$), 4.00 (1H, d, *J* = 12.5 Hz, CH<u>H</u> $_{imidazoline}$)

^{13}C NMR (300 MHz, CD_3OD): δ = 22.80 (C5), 23.24 (C8) 33.0 (C4), 47.13 (C7), 47.45 (C6), C3(absent), 67.5 (C4',weak), 123.3 C2"(C6"), 140.0 (C1"), 150.7 C3"(C5"), 161.1 (C2'$_{,imidazoline}$)

Anal. $C_{14}H_{18}N_4O$: Calc. C, 65.09; H, 7.07; N, 21.69.

Found: C, 65.41; H, 7.14; N, 21.15.

2'-(4-pyridyl)-1-azabicyclo[2.2.2]octane-3-spiro-4'(5')-imidazoline (IIf)

The free base of **IIe** (0.47g, 1.83 mmol) was dissolved in $CHCl_3$ (3.0 mL) and PCl_3 (0.28 g, 2.0 mmol) was added dropwise while maintaining the temperature between 0-10 °C . The reaction was heated to reflux for 2 h then carefully quenched with H_2O (1.0 mL), basified to pH 10 with NaOH (10%) and extracted with $CHCl_3$ (5.0 ml). The organic solution was dried (Na_2SO_4) and evaporated to dryness to give a low melting solid which was purified on basic alumina using CH_2Cl_2:MeOH (9:1) as the eluting solvent.

Yield 93% (oil)

^1H NMR (300 MHz, CD_3OD): δ = 1.54-1.72 (2 H, m, CH_2), 1.74-1.90 (2 H, m CH_2), 2.08-2.22 (1 H, m, CH), 2.76-2.94 (3 H, m), 2.94-3.05 (3H, m), 3.62 (1H, d, C<u>H</u>H $_{imidazoline}$, J= 12.0 Hz), 4.01 (1H, d, CH<u>H</u> $_{imidazoline}$, J= 12.0 Hz), 7.78 (2H, dd, H2"(6"), 8.65 (2H, dd, H3"(5").

^{13}C NMR (300 MHz, CD_3OD): δ = 22.85 (C5), 23.31 (C8) 33.0 (C4), 47.18 (C7), 47.47 (C6), C3(absent), 64.90 (C2), 67.5 (C4',weak), 126.3 C2"(C6"), 131.5(C1"), 140.5 (C3"), 161.1 ($C2'_{,imidazoline}$)

Anal. $C_{14}H_{18}N_4$: Calc. C, 69.39; H, 7.49; N, 23.12.

Found C, 69.01; H, 7.44; N, 23.15.

2'-(1H-Indol-3-yl)-1-azabicyclo[2.2.2]octane-3-spiro-4'(5')-imidazoline (IIg)

A solution of the imidate hydrochloride (**123h**) (0.6 g, 2.87 mmol) in dry methanol (2.0mL) was added to a solution of the diamine (**159**) (0.45 g, 2.87 mmol) in dry methanol (3.0 mL) at ambient temperature under argon and stirred for 2 hours. The solvent was then removed under vacuum and the product was isolated by column chromatography using basic silica and CH_2Cl_2 :MeOH (9:1) as eluting solvent. The dihydrochloride salt was then formed by dissolving the residue in ethanol and saturating with dry HCl gas. The product was slowly precipitated with acetone then filtered and washed with ethanol.

Yield 65 %, mp 263-265 °C

MS: (free base)(CI) *m/z* (%) = 281 (15, M^++1), 309 (15, M^++29), 321 (2, M^++41),

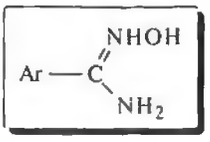
^{1}H NMR (300 MHz, CD_3OD): δ = 2.05-2.25 (3 H, m), 2.40-2.58 (2H, m), 3.35-3.68 (6H, m), 3.74 (1H, d, CHHN, J_1=14.6 Hz), 3.84 (1H, d, CHHN, J_1=14.6 Hz, 4.15 (1H, d, $CHH_{imidazoline}$, J=11.9 Hz), 4.36 (1H, d, $CHH_{imidazoline}$, J=11.9 Hz), 8.49 (1H, H2"), 7.93 (1H, m, H4"), 7.34 (1H, m, H5"), 7.34 (1H, m, H6"), 7.56 (1H, m, H7")

^{13}C NMR (300 MHz, CD_3OD): δ = 19.4 (C5), 20.0 (C8) 31.5 (C4), 46.9 (C7 or C6), 47.3 (C7 or C6), 56.6 (C3), 59.3 (C2) 62.7 ($C4'_{imidazoline}$,weak), 162.0 ($C2'_{imidazoline}$), 99.36 (C3"), 120.2 (C4"), 123.9 (C5"), 125.11 (C6"), 114.05 (C7"), 138.43 (C7a"),

Anal. $C_{17}H_{20}N_4 \cdot 2HCl$ Calc. C, 57.95; H, 6.25; N,15.90

Found C, 57.83; H, 6.25; N,15.93.

7.11. **Synthesis of amidoximes (164a-h)**



Benzamidoxime (164a).

To a solution of hydroxylamine hydrochloride (0.83 g, 12.0 mmol) in H_2O (4.0 mL) was slowly added potassium carbonate (1.67 g, 12.1 mmol), followed by a solution of benzonitrile (1.0 g, 9.7 mmol) in abs. EtOH (30 mL). The reaction mixture was refluxed for 18 h then the solution was cooled to r.t., filtered and the filtrate concentrated under vacuum. The residue was dissolved in CH_2Cl_2 (50 mL) and then washed with water. The organic layer was dried ($MgSO_4$) and concentrated to dryness to give an oily residue which was recrystallised from H_2O.

Yield: 93 %, mp 79-81 °C Lit.[258] mp 79-80 °C

IR (KBr): υ = 3455, 3363 (NH_2), 3150 (OH), 1648 (C=N), cm^{-1}

MS (EI): *m/z* (%) = 136 (100, M^+), 121 (38), 120 (10), 119 (85), 106 (54), 105 (100), 104 (76), 103 (12), 91 (28), 77 (91)

Anal. $C_7H_8N_2O$ Calc. C, 61.75; H, 5.92 ; N, 20.57

Found C, 61.55; H, 5.89; N, 20.57

3-Methoxyphenyl-carboxamide Oxime (164b)

A suspension of hydroxylamine hydrochloride (1.30g, 18.0 mmol), potassium carbonate (2.5g, 18.0 mmol), and 3-methoxybenzonitrile (1.70g, 12.8 mmoL) in abs. EtOH (100 mL) was stirred at r.t. for 12 h. The reaction mixture was cooled to 0-5 °C and the inorganic solids were filtered off. The resulting cloudy solution was concentrated under vacuum to give a clear oil to which was added CH_2Cl_2 (30 mL), causing any remaining inorganic salts to precipitate. The solution was refiltered and the solvent evaporated to dryness, affording a residue which was purified by column chromatography (Silica Gel; CH_2Cl_2-EtOH; 9:1). The amidoxime obtained was slurried in diethyl ether (20 mL), filtered and dried, yielding the required compound as a pure white solid.

Yield: 70 %, mp 103-105 ^oC

IR (KBr): υ = 3470, 3360 (NH_2), 3190 (OH), 1643 (C=N) cm^{-1}

MS (EI): *m/z* (%) = 166 (100, M^+), 151 (13), 150 (11), 149 (81), 136 (7), 135 (22), 134 (68), 133 (7), 119 (10), 107 (15), 92 (18), 91 (18), 77 (15), 63 (11)

^1H NMR (300 MHz, $CDCl_3$): δ = 3.83 (3 H, s, OMe), 4.90 (2 H, bs, NH_2), 6.97 (1 H, m, H4'), 7.19 (2H, m, H2',6'), 7.31 (1 H, m, H5')

Anal. $C_8H_{10}N_2O_2$ Calc. C, 57.81; H, 6.07; N, 16.86

Found C, 57.56; H, 6.17; N, 16.63

3,5-Dimethoxyphenyl-carboxamide Oxime (164c)

Potassium carbonate (1.80 g, 12.6 mmol), hydroxylamine hydrochloride (0.65 g, 8.2 mmol), and 3,5-dimethoxybenzonitrile (1.04 g, 6.4 mmol) in abs. EtOH (50 mL) were reacted as in the preparation of (**164b**) affording the required product as a white solid. Yield: 65 %, mp 135-137 ^{o}C

IR (KBr): υ = 3455, 3354 (NH_2), 3200 (OH), 1679 (C=N), cm^{-1}

MS (EI): *m/z* (%) = 196 (96, M^+), 179 (62), 164 (100), 149 (25), 137 (25), 122 (41).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.81 (6 H, s, 2OMe), 4.83 (2 H, bs, NH_2), 6.51 (1 H, t, H4', *J* = 2.5 Hz), 6.77 (2H, d, H2',6', *J* = 2.5 Hz), 7.31 (1H, dd, H5')

Anal. $C_9H_{12}N_2O_3$ Calc. C, 55.09; H, 6.16 ; N, 14.28

Found: C, 54.81; H, 6.14; N, 14.02

3,5-Dichlorophenyl-carboxamide Oxime (164d).

Potassium carbonate (0.436 g, 3.2 mmol), hydroxylamine hydrochloride (0.227 g, 0.326 mmol), and 3,5-dichlorobenzonitrile (0.386 g, 2.24 mmol) in abs. EtOH (20 mL) were stirred at r.t. for 3 h. The reaction mixture was cooled to 0-5° C and filtered to remove the inorganic solids and the solution was concentrated to dryness under vacuum. The residue was dissolved in 2N HCl (25 mL), stirred for 1 h and the undissolved amide remaining was filtered off. The filtrate was basified (K_2CO_3) to pH 10 and the liberated amidoxime was filtered and washed with hot water, then ethanol.Yield: 89 %, mp 194-195 °C Lit. mp[21] 195 °C

IR (KBr): υ = 3487, 3387 (NH_2), 3120 (OH), 1664 (C=N), cm^{-1}

MS (EI): *m/z* (%) = 204 (M^+, Cl^{35}, 82), 206 (M^+, $Cl^{35,37}$, 55), 208 (M^+, Cl^{37} 10), 191 (14), 189 (71), 187 (100), 176 (11), 174 (56), 172 (75), 149 (7), 147 (32), 145 (46)

Anal. $C_7H_6Cl_2N_2O$ Calc. C, 41.18; H, 2.96 ; N, 13.73

Found: C, 41.17; H, 2.90; N, 13.70

3-Aminophenyl-carboxamide Oxime (164e).

Potassium carbonate (3.6 g, 26.1 mmol), hydroxylamine hydrochloride (1.30 g, 18.7 mmol), and 3-aminobenzonitrile (1.5 g, 13.0 mmol) in abs. EtOH (100 mL) were refluxed for 15 h. The reaction mixture was cooled to 0-5 °C, filtered and the filtrate concentrated to dryness under vacuum. The resulting oil was partitioned between CH_2Cl_2 (100 mL) and H_2O (30 mL) at 35° C, resulting in the organic phase selectively extracting the unreacted starting material. The aqueous phase was extracted with CH_2Cl_2 (2 x 20mL) and the volume of the aqueous solution was then reduced to 5 mL under vacuum and the product was allowed to crystallise overnight giving the amidoxime after filtration and washing with diethyl ether.

Yield: 40 %, mp 125-127 °C

IR (KBr): υ = 3489, 3389 (NH_2), 3170 (OH), 1648 (C=N), cm^{-1}

MS (EI): *m/z* (%) = 151 (100, M^+), 135 (14), 134 (95), 120 (13), 119 (76), 118 (24), 105 (16), 94 (22), 93 (13), 92 (43), 91 (19), 80 (17), 79 (20), 65 (51)

Anal. $C_7H_9N_3O$ Calc. C, 55.62; H,6.00 ; N, 27.80

Found C, 55.60; H, 5.98; N, 27.77

3-Pyridyl-carboxamide Oxime (164f).

Potassium carbonate (3.60 g, 26.0 mmol), hydroxylamine hydrochloride (18.7 mmol), and 3-cyanopyridine (1.33 g, 13.0 mmol) in abs. EtOH (100 mL) were stirred at reflux for 4 h. The reaction mixture was cooled to 0-5° C and filtered to remove the inorganic solids and the solution was concentrated to dryness under vacuum. EtOH (30 mL) was added to the residue and the resulting cloudy solution was refiltered to remove any remaining traces of inorganic material. The filtrate was evaporated to dryness to give an oil which on trituration with CH_2Cl_2 (40 mL) gave a white product which was filtered to yield pure (**4e**).

Yield: 90 %, mp 128-129 °C Lit.[258] mp 128 °C

IR (KBr): υ = 3420, 3250 (NH_2), 3180 (OH), 1645 (C=N) cm^{-1}

MS (EI): *m/z* (%) = 137 (99, M^+), 122 (5), 121 (9), 120 (38), 106 (12), 105 (100), 92 (14), 78 (69), 76 (31), 66 (15)

Anal. $C_6H_7N_3O$ Calc. C, 52.55; H, 5.14 ; N, 30.64

Found: C, 52.25; H, 5.04; N, 30.55

4-Aminophenyl-carboxamide Oxime (164g).

Potassium carbonate (6.0 g, 43.4 mmol), hydroxylamine hydrochloride (2.17 g, 31.2 mmol), and 4-aminobenzonitrile (2.5 g, 24.0 mmol) in abs. EtOH (160 mL) were refluxed for 12 h. H_2O (20 mL) was then added and the reaction was refluxed for a further 12 h. The liquid was decanted from the tacky solid and concentrated to dryness. The resulting oil was partitioned between CH_2Cl_2 (100 mL) and H_2O (100 mL) at 40° C, and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The volume of the aqueous phase was then reduced to about 15 mL and the product was allowed to

crystallise overnight giving the product amidoxime after filtration and washing with methanol. Yield: 48 %, mp 166-168 °C Lit.[258] mp 160-174 °C

IR (KBr): υ = 3464, 3389 (NH_2), 3210 (OH), 1651 (C=N), cm^{-1}

MS (EI): *m/z* (%) = 151 (100, M^+), 135 (8), 134 (79), 133 (11), 120 (11), 119 (39), 118 (19), 105 (21), 92 (27), 91 (11), 79 (19), 65 (33)

^1H NMR (300 MHz, CD_3OD): δ = 6.67 [2 H, m, H3'(5')], 7.35 [2 H, m, H2'(6')]

Anal. $C_7H_9N_3O$ Calc. C, 55.62; H,6.00 ; N, 27.80

Found: C, 55.39; H, 6.04; N, 27.71

N-Oxido-4-pyridyl-carboxamide Oxime (164h)

Potassium carbonate (3.5 g, 25.3 mmol), hydroxylamine hydrochloride (1.3 g, 18.7 mmol), and 4-cyanopyridine *N*-oxide (1.53 g, 18.7 mmol) in abs. EtOH were stirred at r.t. for 48 h. The reaction mixture was concentrated under vacuum and the resulting solid residue was stirred at 50 °C in H_2O (100 ml). The undissolved solid remaining was refluxed in MeOH for 20 min. then filtered, yielding a white solid which was insoluble in MeOH, DMF, THF and soluble in dil. HCl and aq. K_2CO_3. Yield: 95 %, mp 260-262 °C

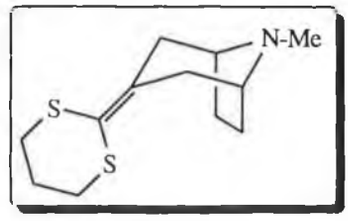
IR (KBr): υ = 3418, 3296 (NH_2), 3160 (OH), 1644 (C=N), cm^{-1}

MS (EI): *m/z* (%) = 153 (M^+,19), 136 (60), 121 (330), 105 (13), 94 (150), 77 (21), 63 (64), 52 (100).

Anal. $C_7H_9N_3O$ Calc. C, 47.06; H, 4.61; N, 27.44

Found: C, 46.81; H, 4.60; N, 27.71

7.12 3-(1,3-dithiane-2-ylidene)-8-methyl-8-azabicyclo[3.2.1]octane (170)



A solution of *n*-butyllithium in hexane (1.6 M, 21.1 mL, 34.6 mmol) was added to a stirred solution of 2-(trimethylsilyl)-1,3-dithiane (6.8 mL, 34.9 mmoL) in dry THF (128 mL), at -40 to -35 °C under N_2. After 1 h, a solution of tropinone (**125**) (4.0 g) in THF (25 mL) was added dropwise at -50 C° and stirred for 1 h. The solution was warmed to 25 C° and stirred for a further 1 h, and then quenched with H_2O (30 mL). The aqueous solution was extracted with CH_2Cl_2 (6 x 30 mL) and the combined organic phases were dried ($MgSO_4$), and concentrated to dryness under vacuum. The residue obtained was chromatographed on basic alumina in CH_2Cl_2/EtOH (95:5) to give the intermediate 3-(1,3-dithiane-2-ylidene)-8-methyl-8-azabicyclo[3.2.1]octane (**170**).

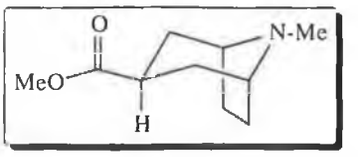
Yield: 94 %, mp 63-64 ° C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40-1.48 [2 H, m, H6(7)$_{endo}$], 1.88-1.94 [2 H, m, H6(7)$_{exo}$], 2.08-2.18 [2 H, m, $CH_{2(dithiane)}$], 2.20-2.28 (2 H, dd, H2(4)$_{eq}$.*J* 1 = 14.7 Hz, *J* 2 = 2.8 Hz)] 2.32 (3 H, s, NCH_3), 2.76-2.94 [6 H, m, 2 X CH_2S, H2(4)$_{ax}$], 3.18 [2 H, bs, H2(4)].

IR (Film): υ = 1771 cm^{-1}

MS (EI): *m/z* (%) = 241 (11, M^+), 184 (3), 160 (19), 82 (100)

7.13 **exo-3-Carbomethoxy-8-methyl-8-azabicyclo[3.2.1]octane (163)**



A solution of **(170)** (1.0 g, 4.2 mmol) in a saturated solution of methanolic HCl (25 mL) was stirred at 30 °C for 24 h. The solvent was removed under vacuum in a fumehood then the residue was taken up into H_2O (5 mL) and washed with CH_2Cl_2 (5 mL). The aqueous phase was basified with K_2CO_3, and extracted (6x) with CH_2Cl_2. The extracts were dried ($MgSO_4$) then concentrated to a colourless liquid which was purified by high vacuum distillation affording the pure exo ester **(163)**.

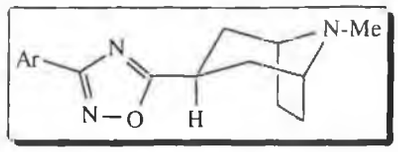
Yield: 65 %, bp 82 °C (2.0 mm Hg)

IR (Film): υ = 1736, 1302, 1007, 931, 848, 798, 762 cm^{-1} Lit [246] 1302, 1004, 929, 849, 796, 762 cm^{-1}.

MS (EI): *m/z* (%) = 183 (M^+,19), 152 (8), 124 (47), 96 (93), 83 (51), 82 (100).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.50-1.58 [2 H, m, $H6(7)_{endo}$], 1.59-1.68 [2 H, ddd, $H2(4)_{eq}$], 1.84-1.95 [2 H, m, $H2(4)_{ax}$], 2.00-2.08 [2 H, m, $H6(7)_{exo}$] 2.28 [3 H, s, NCH_3], 2.54-2.66 (1 H, m, H3), 3.18 [2 H, bs, H1(5)]

7.14. **Synthesis of tropane 1,2,4-oxadiazoles (III)**



exo-5'-(8-Methyl-8-azabicyclo[3.2.1]octane-3-yl)-3'-phenyl-1,2,4-oxadiazole Hydrochloride (IIIa)

Sodium hydride (80% dispersion in oil, (56.0 mg, 1.86 mmol) was added to dry THF (5 mL) containing 4 Å powdered molecular sieves (0.3 g) and stirred for 10 min. under N_2. The amidoxime **164a** (0.231 g, 1.70 mmol) was dissolved in anhydrous tetrahydrofuran (10 mL) and the mixture was added dropwise to the NaH suspension and stirred at r.t. until the hydrogen evolution had subsided. The reaction mixture was heated to 50 °C for 0.5 h then cooled to 20 °C. A solution of the tropinone ester **(163)** (0.237 g, 1.3 mmol) in dry tetrahydrofuran (2 mL) was then added dropwise. The resulting mixture was heated at reflux for 2 h, cooled and filtered and the filtrate concentrated under vacuum. The residue was partitioned between CH_2Cl_2 (10 mL) and H_2O (5 mL) and basified to pH 10 with 2N NaOH. The aqueous phase was removed and the organic layer was washed with 2 x 10 mL H_2O. The organic layer was thyen dried over Na_2SO_4 and concentrated to dryness. The residue was dissolved in EtOH and HCl gas was bubbled through this mixture at 0 ° C until saturation. The hydrochloride salt was allowed to crystallise overnight at 0-5 ° C. The white solid was filtered and washed with Et_2O.

Yield 37%, mp 246-248 °C

IR (KBr): υ = 1591 (Ar), 1567 (C=N), cm^{-1}

MS (EI): *m/z* (%) = 269 (25, M^+), 240 (3), 174 (5), 149 (6), 121 (45), 119 (20), 96 (70), 83 (82), 82 (100).

^{1}H NMR (300 MHz, CD_3OD) δ = 2.22 [2 H, m, $H(6)7_{endo}$], 2.39 [6 H, m, $H2(4)_{\alpha,\beta}$,$H6(7)_{exo}$], 2.84 (3 H, s, NCH_3), 3.74 (1 H, m, $H3_{endo}$), 4.08 [2 H, bs, H1(5) , $W_{1/2}$ = 10.1 Hz], 7.51 (3 H, m, H3",4",5") 8.04 (2 H, d, H2",6")

^{13}C NMR (75.429 MHz, CD_3OD) δ = 24.89 (C6,7), 27.21 (C3), 34.59, (C2,4), 39.69 (NCH_3), 64.75 (C1,5), 127.90 (C1"), 128.29 (C2"), 128.29 (C6"), 130.05 (C3"), 130.05 (C5"), 132.51 (C4'), 169.54 (C3'), 181.75 (C5')

Anal. $C_{16}H_{19}N_3O{\cdot}HCl{\cdot}H_2O$ Calc. C, 59.35; H, 6.85; N, 12.98

Found C, 59.36; H, 6.82; N, 12.91

exo-5'-(8-Methyl-8-azabicyclo[3.2.1]octane-3-yl)-3'-(3-methoxy-phenyl)-1,2,4-oxadiazole Hydrochloride (IIIb)

Sodium hydride (60% dispersion in oil, (86 mg, 2.15 mmol) was added to dry THF (10 mL) containing 4 Å powdered molecular sieves (0.4 g) and stirred for 10 min.under N_2. The amidoxime **164b** (0.327 g, 1.96 mmol) was dissolved in anhydrous tetrahydrofuran (10 mL) and the mixture was added dropwise to the NaH suspension and stirred at r.t. until the hydrogen evolution had subsided, the grey NaH giving way to a white precipitate. A solution of the tropinone ester **(163)** (0.250 g, 1.37 mmol) in dry tetrahydrofuran (2 mL) was then added dropwise. The resulting mixture was heated at reflux for 5 h, then cooled and filtered through celite and the filtrate concentrated under vacuum. The residue was purified by column chromatography [silica gel; MeOH-THF; 8:2], affording a colourless oil which was converted to its hydrochloride salt in an EtOH-HCl solution and allowed to crystallise from the alcoholic solution overnight. The

product was filtered off and washed with ice cold EtOH to give a white crystalline compound.

Yield 41% , mp 233-234 °C

IR (KBr): υ = 1604 (Ar), 1574 (C=N), cm^{-1}

MS (EI): *m/z* (%) = 299 (15, M^+), 270 (2), 204 (2), 149 (12), 134 (7), 133 (5), 122 (14), 121 (28), 97 (22), 96 (60), 95 (21), 94 (48), 93 (17), 83 (72), 82 (100).

^1H NMR (300 MHz, CD_3OD) δ = 2.21 [2 H, m, $H(6)7_{endo}$], 2.39 [6 H, m, $H2(4)_{\alpha,\beta}$,$H6(7)_{exo}$], 2.84 (3 H, s, NCH_3), 3.74 (1 H, m, $H3_{endo}$), 3.85 (3 H, s, OCH_3), 4.03 (2 H, bs, H1,5, $W_{1/2}$ = 11.0 Hz), 7.10 (1 H, m, H4"), 7.42 (1 H, t, H5"), 7.56 (1 H, dd, H2"), 7.62 (1 H, m, H6")

^{13}C NMR (75.429 MHz, CD_3OD) δ = 24.87 (C6,7), 27.21 (C3), 34.65 (C2,4), 39.68 (NCH_3), 55.92 (OMe), 64.78 (C1,5), 113.54 (C2"), 118.26 (C4"), 120.61 (C6"), 129.01(C1"), 131.25 (C5"), 161.54 (C3'), 169.51 (C3'), 181.72 (C5').

Anal. $C_{17}H_{21}N_3O_2 \cdot HCl$. Calc. C, 60.80; H, 6.60 ; N, 12.51

Found: C, 60.52; H, 6.44; N, 12.45

exo-5'-(8-Methyl-8-azabicyclo[3.2.1]octane-3-yl)-3'-(3,5-dimethoxy-phenyl)-1,2,4-oxadiazole Hydrochloride (IIIc)

Sodium hydride (60% dispersion in oil, (68.8 mg, 1.72 mmol) was added to dry THF (10 mL) containing 4 Å powdered molecular sieves (0.3 g) and stirred for 10 min. under N_2. The amidoxime **164c** (0.309 g, 1.57 mmol) was dissolved in anhydrous tetrahydrofuran (8 mL) and the mixture was added dropwise to the NaH suspension and stirred at r.t. until the hydrogen evolution had subsided, the grey NaH giving way to a white precipitate. A solution of the tropinone ester **(163)** (0.20 g, 1.10 mmol) in dry tetrahydrofuran (2 mL) was then added dropwise. The resulting mixture was heated at reflux for 5 h, then cooled and filtered through celite and the filtrate concentrated under vacuum. The residue was purified by column chromatography [silica gel; MeOH-THF; 8:2], affording a colourless oil which was converted to its hydrochloride salt in an EtOH-HCl solution to which was added Et_2O and allowed to crystallise overnight. The product was filtered off and washed with ice cold EtOH to give a white crystalline compound.

Yield, 48% mp 255-256 °C

IR (KBr): υ = 1614 (Ar), 1572 (C=N), cm^{-1}

MS (EI): *m/z* (%) = 329 (31, M^+), 300 (2), 207 (4), 234 (3), 179 (5), 147 (9), 121 (34), 96 (66), 82 (100).

^1H NMR (300 MHz, CD_3OD) δ = 2.21 [2 H, m, $H(6)7_{endo}$], 2.40 [6 H, m, $H2(4)_{\alpha,\beta}$,$H6(7)_{exo}$], 2.84 (3 H, s, NCH_3), 3.74 (1 H, m, $H3_{endo}$), 3.83 (6 H, s, OCH_3), 4.06 [2 H, bs, H1(5) , $W_{1/2}$ = 9.08 Hz], 6.66 (1 H, t, H4") 7.17 [2 H, d, H2"(6")]

^{13}C NMR (75.429 MHz, CD_3OD) δ = 24.85 (C6,7), 27.19 (C3), 29.50 (C1'), 34.68 (C2,4), 39.64 (NCH_3), 56.01 (OMe), 64.72 (C1,5), 104.35 (C4"), 106.20 (C2"), 106.20 (C6"), 162.80 (C3"), 162.80 (C5"), 169.10 (C3'), 181.72 (C5')

Anal. $C_{18}H_{23}N_3O_3 \cdot HCl \cdot H_2O$ Calc. C, 56.32; H, 6.83 ; N, 10.95

Found: C, 56.61; H, 6.75; N, 11.04

exo-5'-(8-Methyl-8-azabicyclo[3.2.1]octane-3-yl)-3'-(3,5-dichloro-phenyl)-1,2,4-oxadiazole Hydrochloride (IIId)

Sodium hydride (60% dispersion in oil, (74.5 mg, 1.86 mmol) was added to dry THF (10 mL) containing 4 Å powdered molecular sieves (0.3 g) and stirred for 10 min. under N_2. The amidoxime **164d** (0.35 g, 1.7 mmol) was dissolved in anhydrous tetrahydrofuran (10 mL) and the mixture was added dropwise to the NaH suspension and stirred at r.t. then at reflux for 1 h until the hydrogen evolution had subsided. The reaction was then cooled to r.t. A solution of the tropinone ester **(163)** (0.237 g, 1.30 mmol) in dry tetrahydrofuran (2 mL) was then added dropwise. The resulting mixture was heated at reflux for 3 h, after which time there was about 20 % reaction which did not increase on further refluxing. A second addition of NaH (1.86 mmol) was made and the reaction was stirred for a further 3 hours. A third addition of NaH (1.86 mmol) was then made and the reaction was refluxed for a further 4 h at which point there only remained c. 5 % starting ester. The remainder of the experimental procedure was similar to that for compound (**IIIc**).

Yield 61%, mp 272-274 °C

IR (KBr): υ = 1586 (Ar), 1562 (C=N), cm^{-1}

MS (EI): *m/z* (%) = 337 (M^+, Cl^{35},10), 339 (M^+, $Cl^{35,37}$, 6), 341 (M^+, Cl^{37} 1), 308 (2), 189 (2), 187 (3), 149 (3), 121 (19), 96 (41), 83 (74), 82 (100),

^1H NMR (300 MHz, CD_3OD) δ = 2.21 [2 H, m, $H(6)7_{endo}$], 2.40 [6 H, m, $H2(4)_{\alpha,\beta}$, $H6(7)_{exo}$], 2.84 (3 H, s, NCH_3), 3.76 (1 H, m, $H3_{endo}$), 4.06 [2 H, bs, H1(5), $W_{1/2}$ = 10.0 Hz], 7.65 (1 H, t, H4") 7.97 (2 H, d, H2",6")

^{13}C NMR (75.429 MHz, CD_3OD) δ = 24.84 (C6,7), 27.24 (C3), 34.60 (C2,4), 39.65 (NCH_3), 64.74 (C1,5), 126.70 (C2"), 126.70 (C6"), 131.1 (C1"), 132.18 (C4"), 137.03 (C3"), 137.03 (C5"), 167.65 (C3'), 182.50 (C5').

Anal. $C_{16}H_{17}N_3OCl_2 \cdot HCl \cdot 0.5\ H_2O$ Calc. C, 50.08; H, 5.01 ; N, 10.95

Found: C, 50.16; H, 4.99; N, 10.76

exo-5'-(8-Methyl-8-azabicyclo[3.2.1]octane-3-yl)-3'-(3-aminophenyl)-1,2,4-oxadiazole Dihydrochloride (IIIe).

Sodium hydride (80% dispersion in oil, (47 mg, 1.56 mmol) was added to dry THF (10 mL) and stirred for 10 min. under N_2. The amidoxime **164e** (0.196 g, 1.3 mmol) was dissolved in anhydrous tetrahydrofuran (8 mL) and added dropwise to the NaH suspension and stirred at reflux until the hydrogen evolution had subsided. A solution of the tropinone ester **(163)** (0.20 g, 1.10 mmol) in dry tetrahydrofuran (2 mL) was then added dropwise. The resulting mixture was heated at reflux for 2 h, then cooled and filtered through celite and the filtrate concentrated under vacuum. The residue was purified by column chromatography [silica gel; MeOH-THF; 8:2], affording a colourless oil which was converted to its hydrochloride salt in an Acetone/EtOH-HCl solution and allowed to crystallise overnight. The product was filtered off and washed with ice cold EtOH to give a white crystalline compound.

Yield 68% , mp 268-270 °C

IR (KBr): υ = 1605 (Ar), 1570 (C=N), cm^{-1}

MS (EI): *m/z* (%) = 284 (6, M^+), 202 (6), 202 (1), 189 (2), 149 (2), 134 (12), 121 (18), 96 (46), 94 (43), 83 (59), 82 (100).

^1H NMR (300 MHz, CD_3OD) δ = 2.22 [2 H, m, $H(6)7_{endo}$], 2.42 [6 H, m, $H2(4)_{\alpha,\beta}$,$H6(7)_{exo}$], 2.84 (3 H, s, NCH_3), 3.77 (1 H, m, $H3_{endo}$), 4.08 [2 H, bs, H1(5), $W_{1/2}$ = 9.2 Hz], 7.6 [1 H, H6" or (H4")], 7.72 (1 H, t, H5"), 8.11 (1 H, t, H2"), 8.17, [1 H, m, H4"or (H6")]

^{13}C NMR (75.429 MHz, CD_3OD) δ = 24.65 (C6,7), 27.03 (C3), 34.31 (C2,4), 39.47 (NCH_3), 64.51 (C1,5), 122.58 (C5"), 126.70 (C6"), 128.51 (C4"), 129.84 (C1"), 131.93 (C2"), 132.91 (C3"), 168.12 (C3'), 182.15 (C5')

Anal. $C_{16}H_{20}N_4O{\cdot}2HCl{\cdot}0.5\ H_2O$ Calc. C, 52.47; H, 6.33 ; N, 15.30

Found C, 52.10; H, 6.40; N, 15.41

exo-5'-(8-Methyl-8-azabicyclo[3.2.1]octane-3-yl)-3'-(3-pyridyl)-1,2,4-oxadiazole Dihydrochloride (IIIf)

Sodium hydride (80% dispersion in oil, (70.6 mg, 2.30 mmol) was added to dry THF (13 mL) and stirred for 10 min. under N_2. The amidoxime **164f** (0.295 g, 2.15 mmol) was dissolved in anhydrous tetrahydrofuran (8 mL) and the mixture was added dropwise to the NaH suspension and stirred at r.t. for 1 h until the hydrogen evolution had subsided, the grey NaH giving way to a white precipitate. A solution of the tropinone ester **(163)** (0.30 g, 1.65 mmol) in dry tetrahydrofuran (2 mL) was then added dropwise. The resulting mixture was heated at reflux for 1 h after which time

more THF (10mL) was added to improve stirring. The reaction was refluxed for a further 3 h then cooled and filtered through celite and the filtrate concentrated under vacuum. The residue was purified by column chromatography [silica gel; MeOH-THF; 8:2], affording a colourless oil which was converted to its hydrochloride salt in an Acetone/EtOH-HCl solution and allowed to crystallise overnight. The product was filtered off and washed with ice cold EtOH to give a white crystalline compound.

Yield 29% , mp 213-215 °C

IR (KBr): υ = 1613 (Ar), 1568 (C=N), cm^{-1}

MS (EI): *m/z* (%) = 270 (5, M^+), 241 (1), 174 (3), 149 (2), 121 (18), 120 (9), 96 (47), 83 (74), 82 (100).

^1H NMR (300 MHz, CD_3OD) δ = 2.25 [2 H, m, $H(6)7_{endo}$], 2.46 [6 H, m, $H2(4)_{\alpha,\beta}$,$H6(7)_{exo}$], 2.85 (3 H, s, NCH_3), 3.85 (1 H, m, $H3_{endo}$), 4.10 [2 H, bs, H1(5) , $W_{1/2}$ = 12.9 Hz], 8.29 (1 H, m, H5"), 9.07 (1 H, m, H4"), 9.22 (1 H, m, H6"), 9.50 (1 H, m, H2")

^{13}C NMR (75.429 MHz, CD_3OD) δ = 24.80 (C6,7), 27.40 (C3), 34.38 (C2,4), 39.72 (NCH_3), 64.71 (C1,5), 128.48 (C1"), 129.28 (C5"), 142.02 (C2"), 145.25 (C4"), 145.25 (C6"), 165.42 (C3'), 183.56 (C5')

Anal. $C_{15}H_{18}N_4O{\cdot}2HCl{\cdot}H_2O$ Calc. C, 49.87; H, 6.14 ; N, 15.51

Found C, 49.65; H, 6.21; N, 15.50

exo-5'-(8-Methyl-8-azabicyclo[3.2.1]octane-3-yl)-3'-(4-aminophenyl)-1,2,4-oxadiazole Dihydrochloride (IIIg).

Sodium hydride (80% dispersion in oil, (47 mg, 1.56 mmol) was added to dry THF (10 mL) and stirred for 10 min. under N_2. The amidoxime **164g** (0.196 g, 1.3 mmol) was slurried in anhydrous tetrahydrofuran (8 mL) and the slurry was added dropwise to the NaH suspension and stirred at reflux until the hydrogen evolution had subsided. A solution of the tropinone ester **(163)** (0.20 g, 1.10 mmol) in dry tetrahydrofuran (2 mL) was then added dropwise. The resulting mixture was heated at reflux for 5 h, then cooled and filtered through celite and the filtrate concentrated under vacuum. The residue was purified by column chromatography [silica gel; MeOH-THF; 8:2], affording a colourless oil which was converted to its hydrochloride salt in an Acetone/EtOH-HCl solution and allowed to crystallise overnight. The product was filtered off and washed with ice cold EtOH to give a white crystalline compound. Yield 51%, mp 275-277 °C

IR (KBr): υ = 1614 (Ar), 1580 (C=N), cm^{-1}

MS (EI): *m/z* (%) = 284 (97, M^+), 255 (6), 202 (20), 189 (17), 149 (7), 134 (42), 121 (52), 96 (100), 83 (64), 82 (89).

^1H NMR (300 MHz, CD_3OD) δ = 2.21 [2 H, m, $H(6)7_{endo}$], 2.41 [6 H, m, $H2(4)_{\alpha,\beta}$,$H6(7)_{exo}$], 2.84 (3 H, s, NCH_3), 3.75 (1 H, m, $H3_{endo}$), 4.08 (2 H, bs, H1,5 , $W_{1/2}$ = 10.0 Hz), 7.56 [2 H, m, H3"(5")], 8.20 [2 H, m, H2"(6")]

^{13}C NMR (75.429 MHz, CD_3OD) δ = 24.90 (C6,7), 27.27 (C3), 34.58 (C2,4), 39.72 (NCH_3), 64.77 (C1,5), 124.73 (C2"), 124.73 (C6"), 128.48 (C1"), 130.13 (C3"), 130.13 (C5"), 135.37 (C4"), 168.52 (C3'), 182.23 (C5').

Anal. $C_{16}H_{20}N_4O \cdot 2HCl$ Calc. C, 53.91; H,6.23 ; N, 15.73

Found: C, 53.76; H, 6.23; N, 15.71

7.15 Pharmacological Methods.

7.16 *Serotonin-Induced von Bezold-Jarisch Reflex in mice.*

The compounds were evaluated for antagonism of the Bezold-Jarisch reflex evoked by serotonin (5-HT) in anaesthetized mice by a modification of the method of Saxena and Lawang.[275] Female Swiss CD-1 mice (23-28 g, Charles River) were fasted for 15 h before the experiment, but water was freely available. The compounds to be examined (20mg/Kg) were suspended in 0.25% aqueous Xanthan gum (Sanofi) solution and were given orally. Metoclopramide (Sigma) and Zacopride (Glaxo) were used as reference compounds. One group received only vehicle and was used as control.

Forty five minutes later, the mice were anaesthetized with urethane (Aldrich) (1.25g/Kg, i.p.) and electrocardiogram and heart rate were continuously monitored and recorded (Hugo Sachs Electronik: HSE-571, HSE-567, HSE-WR3310). Fifteen minutes later (1 hour after oral treatment) serotonin (Sigma) (0.25 mg/Kg) was given intravenously and changes in heart rate were quantified.

On injection of the serotonin an intense transitory reflex is induced; the initial cardio frequency value (CF_0) and the minimum value in the reflex (CF) were measured.

With the values of CF_0 and CF the percentage reflex (R) was calculated as

$$R\ (\%) = \frac{CFo - CF}{CFo} \cdot 100$$

The average intensity of the reflex calculated for each experimental group (R) was compared with the corresponding average for the control group (R_C): the activity for

each product and dosage is expressed as the percentage inhibition in relation to the aforementioned control.

$$\text{Inhibition (\%)} = \frac{Rc - R \cdot 100}{Rc}$$

Statistical significance was determined by Student's t test for non-paired data. Significance level was considered as $Ps < 0.05\%$.

7.17. *[^{3}H]-GR65630 Binding.*

[^{3}H]-GR65630 (63.74 Ci/mmol) was obtained from Dupont. MDL 72222 was purchased from Research Biochemicals Inc. Calf brains were obtained in ice from a local slaughterhouse and dissected on ice, using a procedure adapted from the method of Glowinsky and Iverson.[279] The *area postrema* was scraped away from the surrounding tissues and placed in cold buffer. Approximately 100mg of wet weight tissue was dissected per brain. The tissue was homogenized in ice-cold 50 mM Tris-HCl, 0.5 mM EDTA, 10mM $MgSO_4$, at pH 7.4 and centrifuged at 30,000*g* for 15 min. The pellet was resuspended in buffer (in a homogenizer), incubated at 37 °C for 15 min, and then recentrifuged twice at 30,000*g* for 15 min (with a resuspension between each centrifuging). The final pellet was resuspended in 50 mM Tris-HCl, 0.5 mM EDTA, 10 mM $MgSO_4$, 0.1% ascorbate, 10^{-5} M paragyline, and 140 mM NaCl, aliquoted and frozen.

Assays were performed three times, with sets of tubes in triplicate in competition experiments, and in duplicate in saturation experiments, in a 2.0 ml volume containing 2 mg of wet weight tissue (added last).

Tubes were incubated at room temperature for 30 minutes, filtered on glass microfibre filters (Whatman GF/C) and washed three times with 7 ml of ice-cold buffer. The filters were counted in a liquid scintillation analyzer (Packard Tri-carb 1500) in 4 ml of aqueous counting scintillation fluid (Beckman Ready Micro), following 12 h of equilibration.

Kinetic saturation constants and competition experiments were analyzed by a computer program. Protein determinations were performed following the method of Lowry *et al.*[280] using bovine serum albumin (BSA) as a standard.

SUMMARY AND CONCLUSIONS

1) A series of 2'aryl-tropane-3-spiro-4'(5')-imidazolines, which have not previously been reported, were synthesised *via* the condensation of aryl imidate hydrochlorides (**129**) with 3α-aminomethyl-8-methyl-8-azabicyclo[3.2.1]octane-3β-amine (**122**). The condensation occurs smoothly in anhydrous methanol, and generally requires heating to complete the reactions. The crude reaction products which were present as the mono hydrochloride salts were purified and simultaneously liberated by column chromatography on basic alumina.

2) The preparation of the tropinone diamine precursor (**122**) was carried out by performing the Strecker synthesis on *N*-methyl tropinone (**125**) to give the tropinone aminonitrile (**124**) followed by reduction. The synthesis of the aminonitrile leads exclusively to a single isomer with the nitrile function in the axial position with respect to the piperidine ring. The reduction of this compound with $LiAlH_4$ to give the diamine gave rise to the isolation of an interesting intermediate where both nitrogens of the 1,2-diamine were complexed with aluminium thus forming a five membered cyclic structure (154). This complex was easily converted to the free diamine by refluxing in methanol containing a catalytic amount of HCl.

3) A series of imidate salts were synthesised as precursors to the tropinone imidazoles. The optimal experimental conditions for the synthesis of each imidate were developed, it being found that the reaction was particularly sensitive to the nature of both the starting nitrile and to the nature of the product. In particular, the synthesis of imidate salts with pyridine substituents proved fruitless. Because of the electronegative nature of the pyridine ring, the imidate salt derivatives, on formation, immediately decomposed to the corresponding amides. The problem was overcome indirectly by stabilising the pyridine imidate salt as the *N*-oxide derivative which after subsequent condensation with the diamine was cleaved with PCl_3.

4) The aforementioned work comprised part of an article published in the chemical journal *Synthesis* **1994**, 832-836.

5) A series of 2'Aryl-1-azabicyclo[2.2.2]octane-3-spiro-4'(5')-imidazolines was synthesised (**IIa-g**) using a similar synthetic route to that developed for the tropinone imidazole series (**I**). The condensation reaction of the quinuclidine diamine with the imidate salts was much faster than with the tropinone congener. The increased reactivity was thought to be due to steric factors.

6) The formation of the quinuclidine diamine (**159**) by the reduction of the corresponding aminonitrile (**158**) with $LiAlH_4$ did not give rise to the isolation of the aluminium complex described for the tropine diamine. This reaction proved to be especially troublesome and two major side products were isolated from the reaction resulting from hydrogenolysis and dimerisation of the aminonitrile under the reaction conditions to give the impurities (**160**) and (**161**) respectively. The difference in behaviour of the tropinone and quinuclidine aminonitriles under the reduction conditions has been rationalised.

7) The work described for this series of compounds made up part of an article published in *Synthesis* **1994**, 832-836.

8) Due to the difficulty of forming stable imidate salts from difluorobenzonitrile an alternative synthetic route was investigated for the synthesis of the quinuclidine spiro-imidazoline with the difluorophenyl substituent in the 2 position of the imidazoline ring. The alternative route involved the acylation of the diamine (**159**) with difluorobenzoyl chloride followed by cyclisation to the imidazoline using PCl_3 as condensing agent. It was discovered that when pure mono acylated diamine was used as the starting material for cyclisation none of the required product was obtained. Only when the starting material was contaminated with diacylated diamine was there any cyclisation to the desired product. The cyclisation precursor was found to be the diacylated compound which however also failed to give the required imidazoline when attempting to cyclise in

the pure state. It was thought that π-π interactions of the two difluorophenyl rings of the diacylated compound in the pure state prevented the cyclisation while the rupture of these interactions in the sample contaminated with monoacylated compound permitted the desired cyclisation.

The required compound was isolated though not in a pure state and the reaction requires further optimisation. It may provide a useful alternative route to imidazolines which are not available via the imidate route such as in the case of ortho substituted phenyl derivatives.

9) A convenient synthesis of exo-5'-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-3'-(aryl)-1,2,4-oxadiazoles (**III**) from tropinone has been developed. The method involves the intermediacy of the hitherto unreported compound 3-(1,3-dithiane-2-ylidene)-8-methyl-8-azabicyclo[3.2.1]octane (**170**) which on acidic methanolysis lead exclusively to exo-3-carbomethoxy-8-methyl-8-azabicyclo[3.2.1]octane (**163**). The condensation of this tropinone ester (**163**) with aryl amidoximes (**164**) gave rise to the exo-5'-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-3'-(aryl)-1,2,4-oxadiazoles (**III**) again as the exclusive isomer.

10) A series of aryl amidoximes (**164**) were synthesised as precursors to the oxadiazoles, the synthesis of which were carried out by the action of hydroxylamine on aryl nitriles. Although some of the aminonitriles described have previously been reported the methods described herein show some considerable advances over existing methods. Thus for example the synthesis of the 3-aminophenyl (**164e**) and 4-aminophenyl amidoximes (**164g**) which to date have been formed by the action of hydroxylamine on the nitrophenyl nitrile followed by subsequent reduction to the amine derivative, were synthesised here directly in one step from the aniline nitrile. Likewise the 3,5-dichlorophenyl amidoxime (**164d**), whose literature synthesis takes place by converting the nitrile to the thioamide which was then succeeded by reaction with hydroxylamine, has been prepared here directly in one step from the nitrile.

11) An in depth sructural and conformational analysis has been performed on both the tropane spiro-imidazolines (**I**) and on the tropane oxadiazoles (**III**) series.

X-ray analysis of the spiroimidazoline (Ig) revealed that the bicyclic system is in the chair-envelope conformation commonly found in these kinds of compounds while the chair is flattened at the C4 atom. The aromatic indole moiety has its electrons delocalised along the N10-C11-N12 of the imidazoline ring thus helping to maintain an interplanar angle of 24 °. From high resolution ^{1}H and ^{13}C NMR the tropane imidazolines display in CD_3OD solution the same preferred conformation as that found in the solid state. The pyrrolidine and piperidine rings adopt an envelope conformation flattened at N8 and a distorted chair conformation puckered at C3 respectively, with the N-substituent in the equatorial position with respect to the piperidine ring.

X-ray analysis and NMR studies of the tropane oxadiazoles demonstrate that the tropane system adopts a similar conformation to that found in the imidazoline series. The oxadiazole ring was shown by both X-ray and NMR analysis to be in the exo position with respect to the piperidine ring.

12) The *in vivo* pharmacological studies and the *in vitro* binding tests of the two imidazoline series showed that the dichlorophenyl derivative of each of these series have 5-HT_3 antagonistic activity comparable to metochlopramide or to the potent antagonist MDL 72222. Structure-activity relationship studies have shown that the C=N of the imidazoline function in these compounds was mimicking the function of the carbonyl group present in most 5-HT_3 receptor antagonists. Thus the imidazoline was found to be a biosteric replacement for the carbonyl and is the first time that such a group has been employed in 5-HT_3 antagonists.

13) These findings have been published in the American *Journal of Pharmaceutical Sciences* (in press; planned for November 1994)

14) The *in vivo* pharmacological studies and the *in vitro* binding tests of the series of oxadiazoles (III) showed several of these compounds to have potent 5-HT_3

antagonistic activity (In preparation for publication). The results of this series as well as the imidazolines clearly demonstrate the sensitivity of the antagonistic properties of the molecule to changes in the aromatic moiety. In all cases, those molecules containing the 3,5-dichlorophenyl group as the lipophilic aromatic function were shown to demonstrate highest antagonism of the 5-HT_3 receptor. The replacement of the chlorine atoms with bulkier groups such as OMe, or compounds with para substitution, causes a reduction in activity. It was thus felt that the difluoro counterpart which could offer similar electronic characteristics but with less steric requirements could offer some interesting results. Efforts to acquire a sufficient amount of this product in the pure state are on-going.

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APPENDIXES

Appendix I

Crystal Structure Data for 2'-(1H-indol-3-yl)-8-methyl-8-azabicyclo-[3.2.1]octane-3-spiro-4'(5')-imidazoline dihydrochloride (Ig).

Table A Experimental Data and Structural Refinement Procedure for (Ig)

PARAMETER	VALUE
Crystal data	
Formula	C_{19} H_{28} N_4 O Cl_2
Symmetry	Monoclinical, $P2_1/n$
Unit cell determinations:	Least squares fit from 60 reflections (θ <15°)
Unit cell dimensions (Å)	7.661 (1), 26.432 (4), 9.986 (2), 90.0, 98.43(1) , 90.0
Packing: V(A^3), Z	2000.3(6), 4
Dc ($g.cm^{-3}$), M, F (000)	1.3261, 399.36, 848
μ (cm^{-1})	3.389
Experimental data	
Technique	Four circle difractometer: Enraf-Nonius, Cad-4. Bisecting geometry. Grafite orientated monochromator :MoKa ω scans, scan width : 1° up max. 28°
Number of reflections:	
Measured	4773
Observed	1026 (2σ (I) criterion)
Range of hkl	0 10, 0 34, -13 13
Value of Rint	0.01
Max.- min. transmission factors	1.244, 0.555
Solution and refinement	
Solution	Direct methods and Fourier synthesis
Refinement	Full-matrix L.S. on Fobs. Anisotropic thermal paramaters of C6 fixed
H atoms	Difference synthesis. H52, H92, H93 and H262 not refined
w-scheme	Empirical as to give no trends in <wΔF> vs. <Fobs> and <sin θ/λ>
Final ΔF peaks	0.3 e/A^3
Final R and Rw	0.054, 0.013
Computer and programs	Vax 6410, Difabs, Multan80 Dirdif, Xray System, Pesos, Parst

Scattering factors	Int.Tables for X-Ray Crystallography
Anomalous dispersion	Int.Tables for X-Ray Crystallography

Atomic parameters for non H-Atoms for (**Ig**).

Atom	x	y	z	Ueq
CL23	0.3296(5)	0.2900(1)	0.0439(3)	50(1)
CL24	0.1582(4)	0.5693(1)	0.4115(3)	39(1)
O25	0.2725(13)	0.2338(3)	0.3002(8)	50(3)
C26	0.3802(24)	0.1896(6)	0.3161(17)	62(6)
N1	0.3190(12)	0.2848(3)	0.5396(10)	31(3)
N10	0.2882(15)	0.3882(4)	0.2318(10)	41(4)
N12	0.2993(14)	0.4655(4)	0.3139(10)	38(3)
N16	0.1148(16)	0.4572(5)	-0.1490(10)	48(4)
C2	0.4798(16)	0.3176(5)	0.5513(12)	36(4)
C3	0.4789(17)	0.3466(4)	0.4169(11)	35(4)
C4	0.3120(15)	0.3783(4)	0.3807(10)	29(4)
C5	0.1478(17)	0.3514(5)	0.4166(12)	40(4)
C6	0.1752(15)	0.3228(5)	0.5501(11)	36
C7	0.2556(16)	0.3543(6)	0.6709(14)	44(5)
C8	0.4579(17)	0.3505(6)	0.6727(13)	43(5)
C9	0.3277(25)	0.2443(6)	0.6464(15)	66(6)
C11	0.2693(14)	0.4381(5)	0.2001(11)	31(4)
C13	0.3283(24)	0.4352(5)	0.4367(13)	53(5)
C14	0.2296(16)	0.4563(4)	0.0693(11)	33(4)
C15	0.1362(16)	0.4287(5)	-0.0361(12)	39(4)
C17	0.1864(16)	0.5044(5)	-0.1220(10)	34(4)
C18	0.2599(15)	0.5056(5)	0.0147(10)	31(4)
C19	0.3443(20)	0.5494(5)	0.0649(13)	43(5)
C20	0.3535(23)	0.5895(6)	-0.0209(17)	55(6)
C21	0.2785(21)	0.5879(7)	-0.1545(16)	57(6)
C22	0.1910(17)	0.5455(6)	-0.2093(12)	44(5)

Coordinates and thermal parameters as
Ueq=(1/3).Sum[Uij.ai*.aj*.ai.aj.cos(ai,aj)].10**3

Thermal parameters for (**Ig**).

Atom	U11	U22	U33	U12	U13	U23
CL23	58(2)	43(2)	50(2)	-3(2)	10(2)	-5(2)
CL24	37(2)	40(2)	39(2)	2(2)	0(1)	-9(1)
O25	51(6)	42(6)	56(5)	-5(5)	4(4)	-3(4)
C26	51(10)	52(10)	79(11)	7(9)	-5(9)	-15(8)
N1	29(5)	34(5)	28(4)	1(5)	2(4)	3(4)
N10	68(8)	26(6)	31(5)	12(5)	13(5)	2(5)
N12	35(6)	41(6)	38(6)	15(5)	7(5)	1(5)
N16	49(7)	63(9)	31(6)	15(6)	5(5)	-6(6)
C2	28(7)	42(7)	34(7)	5(7)	-10(5)	7(5)
C3	36(7)	40(7)	30(6)	-3(7)	9(5)	3(6)
C4	34(7)	29(6)	24(6)	-2(6)	4(5)	-5(5)
C5	32(8)	53(7)	33(6)	5(7)	-1(6)	-9(6)
C6	26	42	34	4	-13	8
C7	23(8)	57(9)	53(9)	15(7)	7(6)	-10(8)
C8	37(8)	51(9)	37(7)	2(7)	-8(6)	2(7)
C9	70(12)	58(10)	65(9)	-7(9)	-6(8)	17(8)
C11	23(6)	39(8)	34(6)	-6(5)	6(5)	-10(6)
C13	78(12)	40(8)	40(7)	1(8)	1(7)	4(6)
C14	36(8)	34(7)	29(7)	16(6)	8(6)	4(6)
C15	35(7)	52(8)	33(6)	13(7)	12(5)	-3(7)
C17	30(7)	41(8)	37(7)	14(6)	22(6)	-3(6)
C18	30(7)	39(8)	24(6)	10(6)	-2(5)	-7(5)
C19	57(10)	44(7)	27(7)	0(7)	4(6)	-5(6)
C20	58(11)	47(8)	65(11)	3(8)	30(9)	14(8)
C21	44(9)	62(10)	66(11)	20(8)	17(8)	2(9)
C22	37(8)	73(10)	30(7)	6(8)	26(6)	-1(7)

Thermal parameters as exp[-2.pi**2.Sum(Uij.ai*.aj*.hi.hj) .10**3]

Coordinates and thermal parameters for H-atoms in (**Ig**)

Atom	x	y	z	U
H23	0.171(22)	0.303(5)	0.137(16)	52
H261	0.524(28)	0.196(6)	0.344(18)	68
H262	0.333	0.165	0.215	68
H263	0.370(25)	0.174(7)	0.403(18)	68
H1	0.322(18)	0.263(6)	0.457(14)	36
H10	0.282(20)	0.360(6)	0.172(14)	41
H12	0.238(20)	0.497(6)	0.331(13)	36
H16	0.060(23)	0.446(7)	-0.208(17)	48
H2	0.610(21)	0.298(6)	0.590(14)	35
H31	0.588(20)	0.365(5)	0.389(14)	36
H32	0.479(19)	0.315(5)	0.339(14)	36
H51	0.108(20)	0.331(6)	0.347(15)	42
H52	0.040	0.387	0.424	42
H6	0.058(21)	0.303(6)	0.529(14)	43
H71	0.225(21)	0.390(6)	0.657(15)	40
H72	0.241(19)	0.346(6)	0.769(16)	40
H81	0.528(19)	0.334(6)	0.750(15)	47
H82	0.506(21)	0.386(6)	0.674(15)	47
H91	0.215(24)	0.220(7)	0.639(17)	66
H92	0.420	0.228	0.631	66
H93	0.349	0.258	0.752	66
H131	0.447(24)	0.442(6)	0.461(15)	58
H132	0.215(22)	0.443(6)	0.505(16)	58
H15	0.104(19)	0.384(6)	-0.035(13)	40
H19	0.359(21)	0.553(6)	0.145(16)	42
H20	0.410(25)	0.621(7)	0.011(17)	59
H21	0.280(22)	0.620(7)	-0.213(18)	54
H22	0.195(21)	0.535(6)	-0.288(15)	40

Coordinates and thermal parameters as
exp[-8.pi**2.U.(sin(theta)/lambda)**2 .10**3]

Crystal data

a =	7.6610(0.0010)	alpha=	90.000(0.000)
b =	26.4320(0.0040)	beta =	98.430(0.010)
c =	9.9860(0.0020)	gamma=	90.000(0.000)
V =	2000.27(0.57) cubic-Angstrom		

Niggli reduced cell: 7.661 9.986 26.432 90.00 90.00 98.43

Niggli matrix:

58.6909	99.7202	698.6506
0.0000	0.0000	-11.2154

Transformation matrix:

-1.00	0.00	0.00
0.00	0.00	1.00
0.00	1.00	0.00

H 28. C 19. N 4. O 1. CL 2.

M	=	399.362	(Atomic weights 1977)
Z	=	4.00	
D(calc.)	=	1.3261	Mg/m**3
F(000)	=	848.0	
mu	=	3.389	cm**-1 (Int.Tab.Vol.IV,p.55)
Lambda	=	0.7107000	Angstrom

Number of atoms: 54

Atomic coordinates

Atom	X/a	Y/b	Z/c
CL23	0.32960(51)	0.29001(13)	0.04386(33)
H23	0.17117(2228)	0.30265(523)	0.13658(1565)
CL24	0.15818(42)	0.56931(11)	0.41147(28)
O25	0.27245(126)	0.23384(34)	0.30017(83)
C26	0.38023(238)	0.18962(60)	0.31607(167)
H261	0.52430(2782)	0.19631(636)	0.34432(1771)
H262	0.33280(0)	0.16530(0)	0.21480(0)
H263	0.37026(2452)	0.17368(727)	0.40326(1758)
N1	0.31897(124)	0.28485(34)	0.53958(95)
H1	0.32226(1822)	0.26299(573)	0.45728(1364)
N10	0.28818(150)	0.38820(40)	0.23179(96)
H10	0.28232(1979)	0.35981(615)	0.17157(1423)
N12	0.29926(144)	0.46551(41)	0.31389(97)
H12	0.23829(1987)	0.49684(606)	0.33062(1295)
N16	0.11478(161)	0.45725(47)	-0.14905(105)
H16	0.05958(2275)	0.44582(683)	-0.20751(1720)
C2	0.47979(160)	0.31763(48)	0.55129(117)
H2	0.61021(2066)	0.29827(551)	0.59021(1405)
C3	0.47892(165)	0.34658(45)	0.41690(105)
H31	0.58799(1992)	0.36477(537)	0.38888(1364)
H32	0.47874(1872)	0.31524(502)	0.33863(1376)
C4	0.31198(154)	0.37829(40)	0.38072(101)
C5	0.14778(166)	0.35137(47)	0.41657(121)
H51	0.10826(1976)	0.33072(564)	0.34684(1481)
H52	0.03968(0)	0.38700(0)	0.42352(0)
C6	0.17516(153)	0.32278(50)	0.55009(112)
H6	0.05799(2115)	0.30319(564)	0.52919(1412)
C7	0.25563(164)	0.35430(59)	0.67091(144)
H71	0.22523(2079)	0.38981(647)	0.65709(1460)
H72	0.24132(1854)	0.34578(565)	0.76947(1573)
C8	0.45792(166)	0.35053(56)	0.67275(126)
H81	0.52833(1904)	0.33408(552)	0.74975(1490)
H82	0.50611(2142)	0.38624(649)	0.67392(1520)
C9	0.32766(249)	0.24431(61)	0.64644(153)
H91	0.21484(2356)	0.21983(700)	0.63904(1729)
H92	0.41980(0)	0.22760(0)	0.63120(0)
H93	0.34850(0)	0.25790(0)	0.75190(0)
C11	0.26930(141)	0.43809(45)	0.20005(106)
C13	0.32835(240)	0.43520(51)	0.43672(129)

H131	0.44667(2351)	0.44152(614)	0.46068(1469)
H132	0.21504(2239)	0.44254(647)	0.50487(1610)
C14	0.22957(160)	0.45631(45)	0.06928(107)
C15	0.13617(160)	0.42875(50)	-0.03611(115)
H15	0.10415(1917)	0.38377(602)	-0.03460(1334)
C17	0.18642(156)	0.50439(50)	-0.12201(101)
C18	0.25990(151)	0.50561(47)	0.01466(97)
C19	0.34432(196)	0.54939(49)	0.06486(128)
H19	0.35950(2080)	0.55252(585)	0.14483(1571)
C20	0.35346(225)	0.58951(59)	-0.02086(169)
H20	0.40960(2520)	0.62144(703)	0.01121(1710)
C21	0.27851(211)	0.58792(66)	-0.15446(165)
H21	0.28004(2177)	0.62024(693)	-0.21306(1806)
C22	0.19098(170)	0.54546(59)	-0.20930(124)
H22	0.19520(2052)	0.53504(562)	-0.28778(1537)

Orthogonal coordinates (Angstrom)
Orthogonalization matrix:

a	b cosgamma	c cosbeta	7.66100	0.00000	-1.46396
0	b singamma	-c sinbeta cosalpha*	0.00000	26.43200	0.00000
0	0	c sinbeta sinalpha*	0.00000	0.00000	9.87811

Atom	X	Y	Z
CL23	2.4609(0.0040)	7.6655(0.0035)	0.4333(0.0033)
H23	1.1114(0.1722)	7.9996(0.1382)	1.3492(0.1546)
CL24	0.6094(0.0033)	15.0480(0.0029)	4.0645(0.0028)
O25	1.6478(0.0097)	6.1809(0.0090)	2.9651(0.0082)
C26	2.4502(0.0184)	5.0120(0.0159)	3.1222(0.0165)
H261	3.5126(0.2147)	5.1889(0.1681)	3.4012(0.1749)
H262	2.2351(0.0004)	4.3692(0.0004)	2.1218(0.0005)
H263	2.2462(0.1896)	4.5907(0.1922)	3.9834(0.1737)
N1	1.6537(0.0096)	7.5292(0.0090)	5.3300(0.0094)
H1	1.7994(0.1410)	6.9514(0.1515)	4.5171(0.1347)
N10	1.8684(0.0116)	10.2609(0.0106)	2.2896(0.0095)
H10	1.9117(0.1530)	9.5105(0.1626)	1.6948(0.1406)
N12	1.8331(0.0111)	12.3044(0.0108)	3.1006(0.0096)
H12	1.3415(0.1534)	13.1325(0.1602)	3.2659(0.1279)
N16	1.0975(0.0124)	12.0860(0.0124)	-1.4723(0.0104)
H16	0.7602(0.1761)	11.7839(0.1805)	-2.0498(0.1699)
C2	2.8686(0.0124)	8.3956(0.0127)	5.4457(0.0116)
H2	3.8108(0.1596)	7.8839(0.1456)	5.8302(0.1388)
C3	3.0587(0.0127)	9.1608(0.0119)	4.1182(0.0104)
H31	3.9353(0.1539)	9.6416(0.1419)	3.8414(0.1347)
H32	3.1719(0.1448)	8.3324(0.1327)	3.3450(0.1359)
C4	1.8327(0.0119)	9.9990(0.0106)	3.7608(0.0100)
C5	0.5223(0.0128)	9.2874(0.0124)	4.1149(0.0120)
H51	0.3216(0.1529)	8.7416(0.1491)	3.4261(0.1463)
H52	-0.3160(0.0004)	10.2292(0.0004)	4.1836(0.0005)
C6	0.5366(0.0118)	8.5317(0.0132)	5.4338(0.0111)
H6	-0.3305(0.1633)	8.0139(0.1491)	5.2274(0.1395)
C7	0.9762(0.0127)	9.3649(0.0156)	6.6273(0.0142)
H71	0.7635(0.1607)	10.3035(0.1710)	6.4908(0.1442)
H72	0.7223(0.1439)	9.1397(0.1493)	7.6009(0.1554)
C8	2.5232(0.0129)	9.2652(0.0148)	6.6455(0.0125)
H81	2.9499(0.1475)	8.8304(0.1459)	7.4061(0.1472)
H82	2.8907(0.1656)	10.2091(0.1715)	6.6571(0.1501)
C9	1.5638(0.0192)	6.4576(0.0161)	6.3856(0.0151)
H91	0.7104(0.1823)	5.8105(0.1850)	6.3125(0.1708)
H92	2.2920(0.0004)	6.0159(0.0004)	6.2351(0.0005)
H93	1.5691(0.0004)	6.8168(0.0004)	7.4273(0.0005)
C11	1.7702(0.0109)	11.5796(0.0119)	1.9761(0.0105)
C13	1.8761(0.0185)	11.5032(0.0135)	4.3140(0.0128)
H131	2.7475(0.1814)	11.6703(0.1623)	4.5506(0.1451)
H132	0.9083(0.1731)	11.6972(0.1710)	4.9872(0.1590)
C14	1.6573(0.0124)	12.0612(0.0119)	0.6844(0.0106)
C15	1.0961(0.0124)	11.3327(0.0132)	-0.3567(0.0114)
H15	0.8485(0.1482)	10.1438(0.1591)	-0.3418(0.1318)
C17	1.6068(0.0121)	13.3320(0.0132)	-1.2052(0.0100)

C18	1.9696(0.0117)	13.3643(0.0124)	0.1448(0.0096)
C19	2.5429(0.0151)	14.5215(0.0130)	0.6407(0.0127)
H19	2.5421(0.1610)	14.6042(0.1546)	1.4306(0.1552)
C20	2.7384(0.0174)	15.5819(0.0156)	-0.2061(0.0167)
H20	3.1215(0.1947)	16.4259(0.1858)	0.1107(0.1689)
C21	2.3598(0.0164)	15.5399(0.0174)	-1.5258(0.0163)
H21	2.4573(0.1689)	16.3942(0.1832)	-2.1046(0.1784)
C22	1.7695(0.0132)	14.4176(0.0156)	-2.0675(0.0123)
H22	1.9167(0.1588)	14.1422(0.1485)	-2.8427(0.1518)

Bond distances (Angstrom)

		Distance	e.s.d.
CL23	- H23	1.6648	0.1751
O25	- C26	1.4264	0.0189
C26	- H261	1.1125	0.2069
C26	- H262	1.2084	0.0160
C26	- H263	0.9803	0.1832
N1	- H1	1.0080	0.1431
N1	- C2	1.4967	0.0155
N1	- C6	1.5046	0.0157
N1	- C9	1.5068	0.0183
N10	- H10	0.9586	0.1553
N10	- C4	1.4947	0.0139
N10	- C11	1.3590	0.0158
N12	- H12	0.9771	0.1593
N12	- C11	1.3393	0.0147
N12	- C13	1.4546	0.0163
N16	- H16	0.7338	0.1642
N16	- C15	1.3461	0.0163
N16	- C17	1.3723	0.0178
C2	- H2	1.1390	0.1498
C2	- C3	1.5440	0.0163
C2	- C8	1.5215	0.0183
C3	- H31	1.0374	0.1546
C3	- H32	1.1388	0.1362
C3	- C4	1.5275	0.0165
C4	- C5	1.5326	0.0176
C4	- C13	1.6033	0.0170
C5	- H51	0.9015	0.1444
C5	- H52	1.2627	0.0127
C5	- C6	1.5201	0.0167
C6	- H6	1.0308	0.1563
C6	- C7	1.5204	0.0181
C7	- H71	0.9720	0.1702
C7	- H72	1.0310	0.1604
C7	- C8	1.5504	0.0181
C8	- H81	0.9745	0.1399
C8	- H82	1.0130	0.1713
C9	- H91	1.0735	0.1828
C9	- H92	0.8649	0.0186
C9	- H93	1.1019	0.0152
C11	- C14	1.3832	0.0150
C13	- H131	0.9183	0.1752
C13	- H132	1.1948	0.1794
C14	- C15	1.3890	0.0158
C14	- C18	1.4445	0.0170
C15	- H15	1.2145	0.1593
C17	- C18	1.3983	0.0135
C17	- C22	1.3959	0.0189
C18	- C19	1.3833	0.0176
C19	- H19	0.7943	0.1557
C19	- C20	1.3710	0.0209
C20	- H20	0.9795	0.1833
C20	- C21	1.3736	0.0224
C21	- H21	1.0365	0.1837
C21	- C22	1.3789	0.0221
C22	- H22	0.8358	0.1559

Number of bond distances: 55

Bond angles (degrees)
(e.s.d. following Cruickshank, Internat. Tables, II, 1959, p.331)

			Angle	e.s.d.
O25	- C26	- H263	109.38	10.86
O25	- C26	- H262	104.16	1.21
O25	- C26	- H261	115.76	8.91
H262	- C26	- H263	117.49	11.31
H261	- C26	- H263	92.68	13.88
H261	- C26	- H262	117.53	9.18
C6	- N1	- C9	112.41	0.98
C2	- N1	- C9	113.95	0.99
C2	- N1	- C6	102.22	0.89
H1	- N1	- C9	99.55	8.31
H1	- N1	- C6	123.02	8.09
H1	- N1	- C2	106.07	8.16
C4	- N10	- C11	113.29	0.89
H10	- N10	- C11	128.30	8.90
H10	- N10	- C4	118.34	8.90
C11	- N12	- C13	113.81	1.02
H12	- N12	- C13	109.91	7.70
H12	- N12	- C11	125.24	7.78
C15	- N16	- C17	110.32	1.00
H16	- N16	- C17	134.23	13.94
H16	- N16	- C15	114.92	13.88
N1	- C2	- C8	101.98	0.95
N1	- C2	- C3	108.69	0.93
N1	- C2	- H2	115.94	7.38
C3	- C2	- C8	115.00	1.04
H2	- C2	- C8	100.27	7.13
H2	- C2	- C3	114.27	7.32
C2	- C3	- C4	111.98	0.92
C2	- C3	- H32	103.62	6.75
C2	- C3	- H31	124.27	7.99
H32	- C3	- C4	108.67	7.16
H31	- C3	- C4	111.19	8.02
H31	- C3	- H32	94.13	10.43
N10	- C4	- C3	107.90	0.87
C3	- C4	- C13	114.35	0.99
C3	- C4	- C5	112.17	0.93
N10	- C4	- C13	100.05	0.85
N10	- C4	- C5	109.22	0.89
C5	- C4	- C13	112.27	1.00
C4	- C5	- C6	115.04	1.00
C4	- C5	- H52	103.53	0.92
C4	- C5	- H51	107.15	9.53
H52	- C5	- C6	109.26	0.95
H51	- C5	- C6	111.35	9.48
H51	- C5	- H52	110.20	9.68
N1	- C6	- C5	106.16	0.94
C5	- C6	- C7	114.29	1.08
C5	- C6	- H6	93.90	8.11
N1	- C6	- C7	101.81	0.94
N1	- C6	- H6	106.02	8.33
H6	- C6	- C7	132.51	8.03
C6	- C7	- C8	105.22	1.09
C6	- C7	- H72	123.39	8.30
C6	- C7	- H71	110.83	8.83
H72	- C7	- C8	102.75	8.11
H71	- C7	- C8	106.38	9.59
H71	- C7	- H72	106.84	12.10
C2	- C8	- C7	104.71	1.04
C7	- C8	- H82	107.59	9.62
C7	- C8	- H81	118.34	8.73
C2	- C8	- H82	117.34	8.87
C2	- C8	- H81	105.13	8.68
H81	- C8	- H82	104.36	12.52

N1	- C9	- H93		115.48	1.27
N1	- C9	- H92		101.01	1.34
N1	- C9	- H91		115.36	9.45
H92	- C9	- H93		109.09	1.78
H91	- C9	- H93		105.35	9.28
H91	- C9	- H92		110.47	9.92
N10	- C11	- N12		109.15	0.98
N12	- C11	- C14		126.84	1.10
N10	- C11	- C14		124.00	1.06
N12	- C13	- C4		103.19	0.93
C4	- C13	- H132		108.95	8.30
C4	- C13	- H131		106.58	10.59
N12	- C13	- H132		110.89	8.26
N12	- C13	- H131		98.21	10.10
H131	- C13	- H132		126.44	12.18
C11	- C14	- C18		130.18	1.02
C11	- C14	- C15		123.39	1.10
C15	- C14	- C18		106.29	0.95
N16	- C15	- C14		109.10	1.10
C14	- C15	- H15		125.91	6.56
N16	- C15	- H15		123.93	6.51
N16	- C17	- C22		128.99	1.06
N16	- C17	- C18		107.77	1.07
C18	- C17	- C22		123.24	1.11
C14	- C18	- C17		106.48	1.03
C17	- C18	- C19		118.22	1.03
C14	- C18	- C19		135.26	1.01
C18	- C19	- C20		118.99	1.24
C18	- C19	- H19		116.31	11.33
H19	- C19	- C20		122.26	11.26
C19	- C20	- C21		122.03	1.46
C19	- C20	- H20		121.50	10.06
H20	- C20	- C21		116.42	10.15
C20	- C21	- C22		121.35	1.49
C20	- C21	- H21		119.04	10.06
H21	- C21	- C22		119.45	9.92
C17	- C22	- C21		116.12	1.21
C21	- C22	- H22		123.86	10.64
C17	- C22	- H22		109.71	10.29

Number of angles: 102

Torsion angles (degrees)
(right-hand rule, Klyne & Prelog.(1960). Experientia,16,521)
(e.s.d. following Stanford & Waser, Acta Cryst.(1972).A28,213)

				Angle	e.s.d.
C6	-N1	-C9	-H91	65.44	10.73
C2	-N1	-C9	-H91	-178.86	10.67
H1	-N1	-C9	-H91	-66.41	13.50
C6	-N1	-C9	-H92	-175.45	1.21
C2	-N1	-C9	-H92	-59.75	1.63
H1	-N1	-C9	-H92	52.70	8.35
C6	-N1	-C9	-H93	-57.95	1.65
C2	-N1	-C9	-H93	57.75	1.67
H1	-N1	-C9	-H93	170.20	8.31
C2	-N1	-C6	-H6	172.18	8.78
H1	-N1	-C6	-H6	53.59	13.10
C2	-N1	-C6	-C7	-46.72	1.09
H1	-N1	-C6	-C7	-165.31	9.72
C9	-N1	-C6	-C5	-164.26	1.04
C2	-N1	-C6	-C5	73.16	1.06
H1	-N1	-C6	-C5	-45.43	9.76
H1	-N1	-C2	-H2	-74.84	11.89
H1	-N1	-C2	-C3	55.48	8.51
H1	-N1	-C2	-C8	177.34	8.48
C6	-N1	-C2	-C8	47.36	1.07
C6	-N1	-C2	-C3	-74.51	1.06
C6	-N1	-C2	-H2	155.17	8.35
C9	-N1	-C2	-C8	-74.18	1.23

C9	-N1	-C2	-C3	163.96	1.04
C9	-N1	-C2	-H2	33.64	8.42
C9	-N1	-C6	-C7	75.87	1.22
C9	-N1	-C6	-H6	-65.23	8.83
C4	-N10	-C11	-C14	-173.86	1.05
H10	-N10	-C11	-C14	2.89	11.77
C4	-N10	-C11	-N12	7.58	1.34
H10	-N10	-C11	-N12	-175.67	11.66
H10	-N10	-C4	-C5	-66.02	10.43
H10	-N10	-C4	-C13	175.98	10.40
C11	-N10	-C4	-C3	-126.74	1.03
H10	-N10	-C4	-C3	56.16	10.43
C11	-N10	-C4	-C13	-6.92	1.23
C11	-N10	-C4	-C5	111.08	1.09
H12	-N12	-C11	-N10	-144.80	10.67
C13	-N12	-C11	-N10	-4.66	1.44
C11	-N12	-C13	-H131	109.46	10.39
H12	-N12	-C13	-H131	-104.37	13.89
C11	-N12	-C13	-H132	-116.32	8.70
H12	-N12	-C13	-H132	29.85	12.71
C11	-N12	-C13	-C4	0.20	1.39
H12	-N12	-C13	-C4	146.37	9.27
H12	-N12	-C11	-C14	36.69	10.79
C13	-N12	-C11	-C14	176.83	1.19
C15	-N16	-C17	-C18	1.08	1.43
H16	-N16	-C17	-C18	171.96	19.20
C15	-N16	-C17	-C22	-179.12	1.28
H16	-N16	-C17	-C22	-8.24	19.32
H16	-N16	-C15	-H15	16.31	17.39
C17	-N16	-C15	-C14	-2.05	1.47
H16	-N16	-C15	-C14	-174.85	15.17
C17	-N16	-C15	-H15	-170.89	8.42
N1	-C2	-C8	-H81	96.28	9.02
N1	-C2	-C8	-H82	-148.32	10.42
N1	-C2	-C8	-C7	-29.14	1.20
N1	-C2	-C3	-H31	-164.18	9.67
N1	-C2	-C3	-H32	-59.42	7.23
N1	-C2	-C3	-C4	57.51	1.21
C3	-C2	-C8	-H81	-146.31	9.01
H2	-C2	-C8	-H81	-23.26	11.80
C3	-C2	-C8	-H82	-30.91	10.49
H2	-C2	-C8	-H82	92.15	12.91
C3	-C2	-C8	-C7	88.27	1.24
H2	-C2	-C8	-C7	-148.67	7.64
H2	-C2	-C3	-H31	-32.95	12.73
H2	-C2	-C3	-H32	71.80	10.93
H2	-C2	-C3	-C4	-171.26	8.24
C8	-C2	-C3	-C4	-56.04	1.35
C8	-C2	-C3	-H32	-172.97	7.21
C8	-C2	-C3	-H31	82.27	9.72
C2	-C3	-C4	-N10	-158.49	0.93
H32	-C3	-C4	-N10	-44.64	7.42
H31	-C3	-C4	-N10	57.63	8.60
C2	-C3	-C4	-C5	-38.15	1.29
C2	-C3	-C4	-C13	91.17	1.20
H32	-C3	-C4	-C5	75.70	7.42
H31	-C3	-C4	-C5	177.97	8.57
H32	-C3	-C4	-C13	-154.97	7.39
H31	-C3	-C4	-C13	-52.70	8.62
N10	-C4	-C13	-N12	3.77	1.18
C3	-C4	-C13	-N12	118.78	1.09
C5	-C4	-C13	-N12	-111.94	1.11
C3	-C4	-C13	-H131	15.90	10.78
N10	-C4	-C13	-H131	-99.11	10.73
C3	-C4	-C13	-H132	-123.33	8.58
N10	-C4	-C13	-H132	121.66	8.58
C3	-C4	-C5	-H51	-84.42	10.02
N10	-C4	-C5	-H51	35.15	10.04

C3	-C4	-C5	-H52	159.10	0.87
N10	-C4	-C5	-H52	-81.33	1.04
C3	-C4	-C5	-C6	39.96	1.36
N10	-C4	-C5	-C6	159.53	0.97
C5	-C4	-C13	-H131	145.18	10.72
C5	-C4	-C13	-H132	5.94	8.64
C13	-C4	-C5	-C6	-90.44	1.24
C13	-C4	-C5	-H52	28.70	1.24
C13	-C4	-C5	-H51	145.18	10.00
C4	-C5	-C6	-N1	-58.15	1.25
H52	-C5	-C6	-N1	-174.05	0.86
H51	-C5	-C6	-N1	64.00	10.29
C4	-C5	-C6	-H6	-166.07	8.47
C4	-C5	-C6	-C7	53.23	1.43
H52	-C5	-C6	-H6	78.03	8.48
H51	-C5	-C6	-H6	-43.93	13.29
H52	-C5	-C6	-C7	-62.67	1.32
H51	-C5	-C6	-C7	175.37	10.26
C5	-C6	-C7	-H71	28.28	10.17
N1	-C6	-C7	-H71	142.25	10.10
C5	-C6	-C7	-H72	156.74	10.04
N1	-C6	-C7	-H72	-89.29	10.07
C5	-C6	-C7	-C8	-86.32	1.27
N1	-C6	-C7	-C8	27.66	1.22
H6	-C6	-C7	-H71	-92.71	15.27
H6	-C6	-C7	-H72	35.74	15.30
H6	-C6	-C7	-C8	152.69	11.46
C6	-C7	-C8	-C2	0.80	1.33
H72	-C7	-C8	-C2	131.06	8.60
H71	-C7	-C8	-C2	-116.85	9.85
C6	-C7	-C8	-H81	-115.84	9.90
C6	-C7	-C8	-H82	126.34	9.72
H72	-C7	-C8	-H81	14.42	13.11
H71	-C7	-C8	-H81	126.51	13.92
H72	-C7	-C8	-H82	-103.40	12.94
H71	-C7	-C8	-H82	8.69	13.83
N12	-C11	-C14	-C15	-154.29	1.22
N10	-C11	-C14	-C15	27.41	1.85
N12	-C11	-C14	-C18	20.82	2.05
N10	-C11	-C14	-C18	-157.48	1.20
C11	-C14	-C15	-N16	178.26	1.13
C11	-C14	-C18	-C19	5.06	2.33
C11	-C14	-C18	-C17	-177.21	1.21
C11	-C14	-C15	-H15	-13.18	8.77
C18	-C14	-C15	-N16	2.14	1.38
C15	-C14	-C18	-C19	-179.19	1.39
C15	-C14	-C18	-C17	-1.46	1.30
C18	-C14	-C15	-H15	170.70	8.62
N16	-C17	-C18	-C14	0.27	1.32
N16	-C17	-C22	-H22	-31.10	11.35
N16	-C17	-C22	-C21	-177.70	1.35
N16	-C17	-C18	-C19	178.46	1.12
C22	-C17	-C18	-C14	-179.55	1.16
C18	-C17	-C22	-H22	148.67	11.23
C18	-C17	-C22	-C21	2.08	1.96
C22	-C17	-C18	-C19	-1.36	1.84
C17	-C18	-C19	-H19	162.37	12.70
C14	-C18	-C19	-H19	-20.09	12.86
C17	-C18	-C19	-C20	-0.35	1.90
C14	-C18	-C19	-C20	177.19	1.39
C18	-C19	-C20	-H20	178.53	12.67
C18	-C19	-C20	-C21	1.24	2.32
H19	-C19	-C20	-H20	16.89	18.58
H19	-C19	-C20	-C21	-160.40	13.50
C19	-C20	-C21	-H21	174.98	11.28
C19	-C20	-C21	-C22	-0.47	2.55
H20	-C20	-C21	-H21	-2.44	16.59
H20	-C20	-C21	-C22	-177.89	12.08

C20	-C21	-C22	-C17	-1.15	2.24
H21	-C21	-C22	-C17	-176.57	11.31
C20	-C21	-C22	-H22	-142.53	12.76
H21	-C21	-C22	-H22	42.05	17.10

Number of torsion angles: 163

Weighted least-squares planes through the starred atoms
(Nardelli, Musatti, Domiano & Andreetti Ric.Sci.(1965),15(II-A),807).
Equation of the plane: m1*X+m2*Y+m3*Z=d

Plane 1
m1 = -0.99813(0.00033)
m2 = 0.05170(0.04244)
m3 = -0.03249(0.06162)
D = -1.43449(0.65244)

Atom		d	s	d/s	(d/s)**2
C4	*	0.0000	0.0119	0.000	0.000
N1	*	0.0000	0.0096	0.000	0.000
C9	*	0.0000	0.0192	0.000	0.000
C2		-1.1716	0.0124	-94.602	8949.527
C6		1.1635	0.0118	98.213	9645.768
C3		-1.2786	0.0127	-100.387	10077.644
C5		1.2597	0.0128	98.064	9616.529
C7		0.7290	0.0128	57.145	3265.511
C8		-0.8209	0.0129	-63.818	4072.775
C13		0.0165	0.0185	0.891	0.794
N10		0.0257	0.0116	2.220	4.928
C11		0.2021	0.0109	18.498	342.161
N12		0.1403	0.0111	12.603	158.829
CL23		-0.6395	0.0040	-161.524	26089.934
CL24		1.4722	0.0033	449.975	202477.672
O25		0.0130	0.0097	1.336	1.786
C26		-0.8535	0.0184	-46.400	2152.970
C14		0.3817	0.0124	30.873	953.134
C15		0.9380	0.0124	75.758	5739.256
N16		1.0117	0.0124	81.360	6619.462
C17		0.5592	0.0121	46.400	2152.925
C18		0.1548	0.0117	13.274	176.202
C19		-0.3736	0.0151	-24.694	609.813
C20		-0.4864	0.0174	-27.934	780.322
C21		-0.0678	0.0164	-4.149	17.213
C22		0.4809	0.0132	36.535	1334.770
					==========
			Sum((d/s)**2) for starred atoms		0.000

Plane 2
m1 = -0.04487(0.00501)
m2 = -0.86475(0.00418)
m3 = -0.50019(0.00722)
D = -10.11617(0.00915)

Atom		d	s	d/s	(d/s)**2
C2	*	0.0035	0.0124	0.280	0.078
C3	*	-0.0028	0.0115	-0.239	0.057
C5	*	0.0032	0.0123	0.258	0.067
C6	*	-0.0037	0.0127	-0.290	0.084
N1		0.8651	0.0091	95.079	9040.105
C4		-0.4938	0.0104	-47.307	2237.972
C7		-1.3408	0.0153	-87.843	7716.375
C8		-1.3332	0.0143	-93.545	8750.726
					==========
			Sum((d/s)**2) for starred atoms		0.286

Chi-squared at 95% for 1 degrees of freedom: 3.84
The group of atoms does not deviate significantly from planarity

Plane 3
m1 = 0.05252(0.00647)

m2 = 0.81289(0.00539)
m3 = -0.58005(0.00756)
D = 3.81410(0.09335)

Atom		d	s	d/s	(d/s)**2
C2	*	0.0024	0.0123	0.197	0.039
C6	*	-0.0025	0.0125	-0.201	0.040
C7	*	0.0055	0.0151	0.366	0.134
C8	*	-0.0048	0.0141	-0.339	0.115
N1		-0.6986	0.0091	-76.483	5849.616
C4		2.2287	0.0104	214.532	46023.793
C3		1.4045	0.0114	123.034	15137.310
C5		1.3761	0.0123	112.101	12566.552
			Sum((d/s)**2) for starred atoms		0.327

Chi-squared at 95% for 1 degrees of freedom: 3.84
The group of atoms does not deviate significantly from planarity

Plane 4
m1 = 0.99968(0.00016)
m2 = 0.01261(0.00596)
m3 = -0.02172(0.00724)
D = 1.90605(0.07167)

Atom		d	s	d/s	(d/s)**2
C4	*	-0.0294	0.0119	-2.475	6.124
N10	*	0.0415	0.0116	3.582	12.829
C11	*	-0.0332	0.0109	-3.040	9.244
N12	*	0.0144	0.0111	1.290	1.665
C13	*	0.0209	0.0185	1.133	1.283
CL23		0.6413	0.0040	161.918	26217.596
CL24		-1.1952	0.0033	-365.208	133376.984
C3		1.1778	0.0127	92.448	8546.595
C5		-1.3561	0.0128	-105.559	11142.621
C14		-0.1120	0.0124	-9.056	82.018
			Sum((d/s)**2) for starred atoms		31.146

Chi-squared at 95% for 2 degrees of freedom: 5.99
The group of atoms deviates significantly from planarity

Plane 5
m1 = 0.90561(0.00236)
m2 = -0.34707(0.00580)
m3 = -0.24377(0.00545)
D = -2.88727(0.08713)

Atom		d	s	d/s	(d/s)**2
C17	*	0.0090	0.0121	0.746	0.557
C18	*	-0.0027	0.0116	-0.229	0.052
C19	*	-0.0060	0.0148	-0.409	0.167
C20	*	0.0094	0.0172	0.547	0.299
C21	*	0.0028	0.0165	0.170	0.029
C22	*	-0.0102	0.0134	-0.759	0.576
C14		0.0352	0.0122	2.886	8.329
C15		0.0336	0.0124	2.701	7.297
N16		0.0454	0.0123	3.684	13.574
			Sum((d/s)**2) for starred atoms		1.681

Chi-squared at 95% for 3 degrees of freedom: 7.81
The group of atoms does not deviate significantly from planarity

Plane 6
m1 = 0.91305(0.00263)
m2 = -0.32977(0.00585)
m3 = -0.24000(0.00609)
D = -2.63864(0.07639)

Atom		d	s	d/s	(d/s)**2
C14	*	0.0102	0.0122	0.837	0.701

C15	*	-0.0121	0.0124	-0.978	0.956
N16	*	0.0085	0.0123	0.692	0.479
C17	*	-0.0015	0.0121	-0.124	0.015
C18	*	-0.0048	0.0116	-0.415	0.173
C19		0.0180	0.0148	1.214	1.475
C20		0.0500	0.0172	2.908	8.455
C21		0.0349	0.0165	2.118	4.487
C22		-0.0040	0.0134	-0.295	0.087
					==========
			Sum((d/s)**2) for starred atoms		2.324

Chi-squared at 95% for 2 degrees of freedom: 5.99
The group of atoms does not deviate significantly from planarity

Plane 7
m1 = 0.90955(0.00153)
m2 = -0.33700(0.00283)
m3 = -0.24319(0.00446)
D = -2.73216(0.03977)

Atom		d	s	d/s	(d/s)**2
C14	*	0.0085	0.0122	0.695	0.482
C15	*	-0.0033	0.0124	-0.269	0.072
N16	*	0.0154	0.0123	1.253	1.570
C17	*	-0.0062	0.0121	-0.516	0.266
C18	*	-0.0154	0.0116	-1.321	1.746
C19	*	-0.0046	0.0148	-0.308	0.095
C20	*	0.0218	0.0172	1.270	1.613
C21	*	0.0126	0.0165	0.762	0.581
C22	*	-0.0144	0.0134	-1.072	1.150
C11		-0.0406	0.0110	-3.691	13.623
N10		0.4168	0.0114	36.686	1345.843
N12		-0.5012	0.0110	-45.504	2070.655
					==========
			Sum((d/s)**2) for starred atoms		7.576

Chi-squared at 95% for 6 degrees of freedom: 12.60
The group of atoms does not deviate significantly from planarity

Dihedral angles formed by LSQ-planes

Plane	- plane	angle (e.s.d.)
1	2	89.06(2.81)
1	3	89.52(2.82)
1	4	175.18(2.83)
1	5	156.06(2.80)
1	6	157.01(3.19)
1	7	156.55(2.96)
2	3	114.53(0.55)
2	4	92.57(0.44)
2	5	67.58(0.41)
2	6	68.64(0.40)
2	7	68.15(0.34)
3	4	85.68(0.52)
3	5	95.35(0.48)
3	6	94.64(0.48)
3	7	94.88(0.46)
4	5	25.01(0.53)
4	6	23.96(0.48)
4	7	24.45(0.40)
5	6	1.10(0.42)
5	7	0.62(0.35)
6	7	0.50(0.35)

Interatomic contacts greater than 1.50 and less than 3.30 Angstrom, involving atoms of the original set.

		Distance	e.s.d.
CL23	...H23	1.6648	0.1751
CL23	...O25	3.0456	0.0094
CL23	...N10	3.2455	0.0110

N10	...C3	2.4435	0.0145
N10	...H31	2.6577	0.1388
N10	...H32	2.5558	0.1326
N10	...C5	2.4681	0.0169
N10	...H51	2.4480	0.1565
N10	...H52	2.8913	0.0113
N10	...C13	2.3751	0.0162
N10	...H131	2.8056	0.1486
N10	...H132	3.2033	0.1688
N10	...C14	2.4213	0.0151
N10	...C15	2.9578	0.0147
N10	...H15	2.8246	0.1278
H10	...N12	3.1286	0.1589
H10	...C3	2.7038	0.1357
H10	...H31	2.9530	0.1914
H10	...H32	2.3873	0.1929
H10	...C4	2.1244	0.1429
H10	...C5	2.7995	0.1529
H10	...H51	2.4733	0.2230
H10	...C11	2.0929	0.1627
H10	...C13	3.2912	0.1497
H10	...C14	2.7553	0.1595
H10	...C15	2.8626	0.1473
H10	...H15	2.3831	0.1887
N12	...C4	2.3981	0.0150
N12	...H52	3.1777	0.0111
N12	...H131	1.8278	0.1492
N12	...H132	2.1870	0.1711
N12	...C14	2.4348	0.0142
N12	...C18	3.1431	0.0140
N12	...H19	2.9293	0.1587
H12	...C4	3.2102	0.1593
H12	...C11	2.0637	0.1507
H12	...C13	2.0097	0.1500
H12	...H131	2.4011	0.2142
H12	...H132	2.2826	0.2216
H12	...C14	2.8128	0.1357
H12	...C18	3.1921	0.1331
H12	...C19	3.2038	0.1442
H12	...H19	2.6411	0.2212
N16	...C14	2.2283	0.0145
N16	...H15	2.2611	0.1540
N16	...C18	2.2382	0.0152
N16	...C22	2.4984	0.0197
N16	...H22	2.6032	0.1547
H16	...C14	2.8909	0.1634
H16	...C15	1.7841	0.1667
H16	...H15	2.3696	0.2269
H16	...C17	1.9562	0.1736
H16	...C18	2.9625	0.1667
H16	...C22	2.8205	0.1807
H16	...H22	2.7436	0.2379
C2	...C3	1.5440	0.0163
C2	...H31	2.2944	0.1478
C2	...H32	2.1234	0.1394
C2	...C4	2.5461	0.0155
C2	...C5	2.8410	0.0166
C2	...H51	3.2689	0.1403
C2	...C6	2.3360	0.0171
C2	...H6	3.2291	0.1623
C2	...C7	2.4325	0.0193
C2	...H71	3.0271	0.1680
C2	...H72	3.1313	0.1611
C2	...C8	1.5215	0.0183
C2	...H81	2.0097	0.1467
C2	...H82	2.1810	0.1656
C2	...C9	2.5183	0.0215
C2	...H92	2.5726	0.0127

C2	...H93	2.8475	0.0126
H2	...C3	2.2643	0.1387
H2	...H31	2.6571	0.1989
H2	...H32	2.6049	0.1889
H2	...C7	3.2960	0.1601
H2	...C8	2.0568	0.1555
H2	...H81	2.0299	0.2154
H2	...H82	2.6338	0.2267
H2	...C9	2.7187	0.1592
H2	...H92	2.4413	0.1530
H2	...H93	2.9521	0.1595
C3	...C4	1.5275	0.0165
C3	...C5	2.5395	0.0181
C3	...H51	2.8542	0.1481
C3	...C6	2.9134	0.0177
C3	...C7	3.2671	0.0190
C3	...C8	2.5855	0.0168
C3	...H82	2.7519	0.1551
C3	...C13	2.6313	0.0190
C3	...H131	2.5654	0.1630
H31	...H32	1.5947	0.1939
H31	...C4	2.1342	0.1534
H31	...C8	3.1620	0.1469
H31	...H82	3.0563	0.2145
H31	...C13	2.8158	0.1514
H31	...H131	2.4555	0.2233
H32	...C4	2.1780	0.1403
H32	...C5	2.9198	0.1481
H32	...H51	2.8806	0.2112
C4	...C5	1.5326	0.0176
C4	...H51	1.9941	0.1490
C4	...H52	2.2020	0.0120
C4	...C6	2.5752	0.0167
C4	...H6	3.2819	0.1595
C4	...C7	3.0582	0.0181
C4	...H71	2.9477	0.1541
C4	...C8	3.0556	0.0157
C4	...H82	3.0906	0.1453
C4	...C11	2.3848	0.0151
C4	...C13	1.6033	0.0170
C4	...H131	2.0625	0.1610
C4	...H132	2.2897	0.1731
C5	...C6	1.5201	0.0167
C5	...H6	1.8938	0.1545
C5	...C7	2.5542	0.0181
C5	...H71	2.5953	0.1475
C5	...C8	3.2262	0.0164
C5	...C13	2.6043	0.0195
C5	...H131	3.2893	0.1698
C5	...H132	2.5917	0.1691
H51	...H52	1.7870	0.1523
H51	...C6	2.0301	0.1445
H51	...H6	2.0492	0.2136
H51	...C13	3.2911	0.1477
H52	...C6	2.2741	0.0121
H52	...H6	2.4489	0.1474
H52	...C7	2.8963	0.0133
H52	...H71	2.5484	0.1391
H52	...C13	2.5389	0.0173
H52	...H132	2.0736	0.1649
C6	...C7	1.5204	0.0181
C6	...H71	2.0755	0.1638
C6	...H72	2.2584	0.1534
C6	...C8	2.4399	0.0165
C6	...H81	3.1310	0.1368
C6	...H82	3.1387	0.1595
C6	...C9	2.5026	0.0205
C6	...H91	2.8648	0.1837

C6	...H92	3.1706	0.0125
C6	...H93	2.8251	0.0116
C6	...H132	3.2184	0.1717
H6	...C7	2.3435	0.1445
H6	...H71	2.8346	0.2176
H6	...H72	2.8300	0.2006
H6	...C9	2.7114	0.1499
H6	...H91	2.6675	0.2311
H6	...H93	3.1434	0.1416
C7	...C8	1.5504	0.0181
C7	...H81	2.1881	0.1407
C7	...H82	2.0926	0.1668
C7	...C9	2.9759	0.0225
C7	...H93	2.7357	0.0152
C7	...C13	3.2763	0.0205
C7	...H132	2.8521	0.1675
H71	...H72	1.6089	0.2205
H71	...C8	2.0490	0.1626
H71	...H81	2.7907	0.2112
H71	...H82	2.1358	0.2285
H71	...C13	2.7232	0.1597
H71	...H131	3.0933	0.2376
H71	...H132	2.0554	0.2292
H72	...C8	2.0426	0.1568
H72	...H81	2.2574	0.2089
H72	...H82	2.5955	0.2297
H72	...C9	3.0624	0.1534
H72	...H93	2.4785	0.1493
C8	...C9	2.9784	0.0219
C8	...H92	3.2833	0.0148
C8	...H93	2.7416	0.0146
C8	...C13	3.2960	0.0187
C8	...H131	3.1973	0.1568
H81	...H82	1.5702	0.2214
H81	...C9	2.9314	0.1437
H81	...H92	3.1186	0.1444
H81	...H93	2.4417	0.1465
H82	...C13	2.8625	0.1510
H82	...H131	2.5676	0.2168
H82	...H132	2.9888	0.2224
H91	...H92	1.5968	0.1834
H91	...H93	1.7300	0.1706
H92	...H93	1.6080	0.0002
C11	...C13	2.3415	0.0164
C11	...H131	2.7553	0.1435
C11	...H132	3.1342	0.1666
C11	...C15	2.4408	0.0150
C11	...H15	2.8781	0.1364
C11	...C18	2.5649	0.0158
C11	...H19	3.1688	0.1564
H131	...H132	1.8905	0.2551
C14	...H15	2.3202	0.1506
C14	...C17	2.2777	0.0156
C14	...C19	2.6152	0.0178
C14	...H19	2.7941	0.1538
C15	...C17	2.2312	0.0183
C15	...C18	2.2676	0.0177
C17	...C19	2.3872	0.0166
C17	...H19	3.0726	0.1499
C17	...C20	2.7094	0.0200
C17	...C21	2.3547	0.0218
C17	...H22	1.8530	0.1551
C18	...H19	1.8758	0.1510
C18	...C20	2.3732	0.0202
C18	...H20	3.2713	0.1874
C18	...C21	2.7706	0.0207
C18	...C22	2.4584	0.0163
C18	...H22	3.0876	0.1516

C19	...H20	2.0597	0.1876
C19	...C21	2.4009	0.0206
C19	...C22	2.8184	0.0171
H19	...C20	1.9166	0.1580
H19	...H20	2.3230	0.2431
H19	...C21	3.1063	0.1547
C20	...H21	2.0841	0.1764
C20	...C22	2.3999	0.0203
C20	...H22	3.1145	0.1474
H20	...C21	2.0108	0.1694
H20	...H21	2.3130	0.2365
H20	...C22	3.2567	0.1739
C21	...H22	1.9709	0.1480
H21	...C22	2.0932	0.1825
H21	...H22	2.4307	0.2332

Number of contacts: 290

Equivalent positions:
X,Y,Z
1/2+X,1/2-Y,1/2+Z
plus the centrosymmetric ones

Maximum translation by 2 unit cell

Intermolecular contacts less than 3.30 Angstrom

			Distance	e.s.d.
CL23	...H261	+X-1/2,-Y+1/2,+Z-1/2	2.8645	0.1845
CL23	...H2	+X-1/2,-Y+1/2,+Z-1/2	2.9516	0.1523
CL23	...H6	+X+1/2,-Y+1/2,+Z-1/2	3.0375	0.1546
CL23	...H72	+X,+Y,+Z-1	3.0976	0.1522
CL23	...H91	+X+1/2,-Y+1/2,+Z-1/2	2.9764	0.1739
CL23	...H93	+X,+Y,+Z-1	3.0603	0.0034
CL23	...H20	-X+1,-Y+1,-Z	3.1772	0.1917
H23	...H261	+X-1/2,-Y+1/2,+Z-1/2	2.9701	0.2280
H23	...H263	+X-1/2,-Y+1/2,+Z-1/2	3.0918	0.2263
H23	...H2	+X-1/2,-Y+1/2,+Z-1/2	2.7358	0.2010
H23	...C9	+X-1/2,-Y+1/2,+Z-1/2	2.9244	0.1683
H23	...H92	+X-1/2,-Y+1/2,+Z-1/2	2.0785	0.1671
H23	...H93	+X-1/2,-Y+1/2,+Z-1/2	3.2913	0.1686
CL24	...H262	-X+1/2,+Y+1/2,-Z+1/2	2.8386	0.0029
CL24	...N16	-X,-Y+1,-Z	3.1822	0.0108
CL24	...H16	-X,-Y+1,-Z	2.4688	0.1605
CL24	...H31	-X+1,-Y+1,-Z+1	3.1073	0.1362
CL24	...H52	-X,-Y+1,-Z+1	2.6606	0.0032
CL24	...H71	-X,-Y+1,-Z+1	3.1104	0.1574
CL24	...H82	-X+1,-Y+1,-Z+1	3.0602	0.1702
CL24	...H131	-X+1,-Y+1,-Z+1	3.1214	0.1692
CL24	...H132	-X,-Y+1,-Z+1	3.1099	0.1777
CL24	...H22	+X,+Y,+Z+1	3.1098	0.1527
O25	...H2	+X-1/2,-Y+1/2,+Z-1/2	2.4284	0.1364
O25	...H81	+X-1/2,-Y+1/2,+Z-1/2	2.5881	0.1441
O25	...H92	+X-1/2,-Y+1/2,+Z-1/2	3.1382	0.0088
O25	...H93	+X-1/2,-Y+1/2,+Z-1/2	3.2202	0.0096
C26	...H2	+X-1/2,-Y+1/2,+Z-1/2	2.8462	0.1383
C26	...H72	+X+1/2,-Y+1/2,+Z-1/2	3.0203	0.1493
C26	...H81	+X-1/2,-Y+1/2,+Z-1/2	2.7524	0.1435
C26	...H15	+X+1/2,-Y+1/2,+Z+1/2	2.8600	0.1454
H261	...CL23	+X+1/2,-Y+1/2,+Z+1/2	2.8645	0.1845
H261	...H23	+X+1/2,-Y+1/2,+Z+1/2	2.9701	0.2280
H261	...H6	+X+1/2,-Y+1/2,+Z-1/2	3.1950	0.2334
H261	...C7	+X+1/2,-Y+1/2,+Z-1/2	2.9713	0.2028
H261	...H72	+X+1/2,-Y+1/2,+Z-1/2	2.2192	0.2563
H261	...H93	+X+1/2,-Y+1/2,+Z-1/2	3.0261	0.2102
H261	...H15	+X+1/2,-Y+1/2,+Z+1/2	2.4697	0.2269
H262	...CL24	-X+1/2,+Y-1/2,-Z+1/2	2.8386	0.0029
H262	...C2	+X-1/2,-Y+1/2,+Z-1/2	2.9814	0.0114
H262	...H2	+X-1/2,-Y+1/2,+Z-1/2	2.1820	0.1429

H82	...C19	-X+1,-Y+1,-Z+1	3.1837	0.1538
H82	...H19	-X+1,-Y+1,-Z+1	2.5318	0.2169
H82	...H20	-X+1,-Y+1,-Z+1	3.1224	0.2243
C9	...H23	+X+1/2,-Y+1/2,+Z+1/2	2.9244	0.1683
H91	...CL23	+X-1/2,-Y+1/2,+Z+1/2	2.9764	0.1739
H91	...H32	+X-1/2,-Y+1/2,+Z+1/2	3.0266	0.2400
H91	...H20	-X+1/2,+Y-1/2,-Z+1/2	3.0829	0.2537
H91	...H21	-X+1/2,+Y-1/2,-Z+1/2	2.7329	0.2597
H92	...H23	+X+1/2,-Y+1/2,+Z+1/2	2.0785	0.1671
H92	...O25	+X+1/2,-Y+1/2,+Z+1/2	3.1382	0.0088
H92	...H51	+X+1/2,-Y+1/2,+Z+1/2	2.8612	0.1417
H93	...CL23	+X,+Y,+Z+1	3.0603	0.0034
H93	...H23	+X+1/2,-Y+1/2,+Z+1/2	3.2913	0.1686
H93	...O25	+X+1/2,-Y+1/2,+Z+1/2	3.2202	0.0096
H93	...H261	+X-1/2,-Y+1/2,+Z+1/2	3.0261	0.2102
H93	...H51	+X+1/2,-Y+1/2,+Z+1/2	3.1293	0.1464
H131	...CL24	-X+1,-Y+1,-Z+1	3.1214	0.1692
H131	...H131	-X+1,-Y+1,-Z+1	3.2640	0.2281
H132	...CL24	-X,-Y+1,-Z+1	3.1099	0.1777
H132	...H16	+X,+Y,+Z+1	3.2678	0.2504
H132	...H22	+X,+Y,+Z+1	3.2219	0.2269
C15	...H72	+X,+Y,+Z-1	3.1123	0.1566
H15	...C26	+X-1/2,-Y+1/2,+Z-1/2	2.8600	0.1454
H15	...H261	+X-1/2,-Y+1/2,+Z-1/2	2.4697	0.2269
H15	...H262	+X-1/2,-Y+1/2,+Z-1/2	3.2773	0.1335
H15	...H263	+X-1/2,-Y+1/2,+Z-1/2	2.3613	0.2374
H15	...H72	+X,+Y,+Z-1	2.5580	0.2182
C19	...H82	-X+1,-Y+1,-Z+1	3.1837	0.1538
H19	...H81	-X+1,-Y+1,-Z+1	3.2505	0.2108
H19	...H82	-X+1,-Y+1,-Z+1	2.5318	0.2169
C20	...H263	-X+1/2,+Y+1/2,-Z+1/2	3.1395	0.1947
H20	...CL23	-X+1,-Y+1,-Z	3.1772	0.1917
H20	...H263	-X+1/2,+Y+1/2,-Z+1/2	2.7874	0.2760
H20	...H10	-X+1,-Y+1,-Z	3.2266	0.2525
H20	...C8	-X+1,-Y+1,-Z+1	3.2558	0.1670
H20	...H81	-X+1,-Y+1,-Z+1	2.6408	0.2252
H20	...H82	-X+1,-Y+1,-Z+1	3.1224	0.2243
H20	...H91	-X+1/2,+Y+1/2,-Z+1/2	3.0829	0.2537
C21	...H31	-X+1,-Y+1,-Z	2.9651	0.1481
H21	...C3	-X+1,-Y+1,-Z	3.0700	0.1866
H21	...H31	-X+1,-Y+1,-Z	2.1868	0.2402
H21	...H32	-X+1,-Y+1,-Z	2.9283	0.2336
H21	...H52	-X,-Y+1,-Z	2.9906	0.1595
H21	...H91	-X+1/2,+Y+1/2,-Z+1/2	2.7329	0.2597
C22	...H52	-X,-Y+1,-Z	3.1269	0.0131
H22	...CL24	+X,+Y,+Z-1	3.1098	0.1527
H22	...H52	-X,-Y+1,-Z	2.9337	0.1467
H22	...H132	+X,+Y,+Z-1	3.2219	0.2269

Number of contacts: 157

Possible hydrogen bonds

Donor-H	Donor...Acceptor	H...Acceptor	Donor-H.....Acceptor

Appendix II

Crystal Structure Data for exo-5'-(8-Methyl-8-Azabicyclo[3.2.1]-octan-3-yl)-3'-(3,5-Dimethoxyphenyl)-1,2,4-oxadiazoles (III c).

Table A Experimental Data and Structural Refinement Procedure for (III c)

PARAMETER	VALUE
Crystal data	
Formula	$C_{18}H_{23}N_3O_3.HCl$
Crystal size (mm)	0.38x0.24x0.21
Symmetry	Triclinical, P-1
Unit cell determinations:	Least squares fit from 37 reflections ($5<\theta<35°$)
Unit cell dimensions	7.113(1), 7.719(1), 18.467 (2), Å 78.10(2) 102.09(1), 112.32(1)°
Packing: V(A^3), Z	908.1(1), 2
Dc ($g.cm^{-3}$), M, F (000)	1.3380, 365.859, 388.0
μ (cm^{-1})	20.562
Experimental data	
Technique	Four circle difractometer: Seifert XRD 3000s Bisecting geometry Grafite orientated monochromator: Cu Kα 1.5418 Å w/2Θ scan
Scanning range for Θ	$2<2\Theta<120°$
Number of reflections:	
Measured	2672
Observed	1589 ($I>2\sigma$ (I) criterion)
Range of hkl	-7/7 -8/8 0/20
Absorption	Correction applied
Solution and refinement	
Solution	Direct methods
Refinement	L.S. on Fobs
H atoms	Fourier Synthesis
Variables	298
w-scheme	Empirical as to give no trends in $\langle w\Delta^2F\rangle$ vs. <Fobs> and $\langle \sin\theta/l\rangle$
Final max. shift /error	0.192
Final av.shift / error	0.018
final R and Rw	0.041, 0.049
Computer and programs	Vax 11/750 , Multan80 ,Difabs, XRAY80, PESOS, PARST Parst
Scattering factors	Int.Tables for X-Ray Crystallography
Anomalous dispersion	Int.Tables for X-Ray Crystallography

Atomic parameters for non H-atoms in (**IIIc**).

Coordinates and thermal parameters as
Ueq=(1/3).Sum[Uij.ai*.aj*.ai.aj.cos(ai,aj)].10**4

Atom	x	y	z	Ueq
CL1	-0.30490(17)	0.33107(15)	0.62472(6)	407(5)
C1	-0.31243(61)	0.83005(55)	0.69537(22)	318(17)
C2	-0.31977(69)	0.83171(65)	0.61124(23)	377(18)
C3	-0.53871(63)	0.73468(56)	0.57392(25)	373(18)
N4	-0.60904(49)	0.53223(43)	0.61120(17)	280(13)
C5	-0.64702(63)	0.55516(59)	0.68566(23)	340(17)
C6	-0.43731(66)	0.63428(61)	0.73253(23)	354(18)
C7	-0.69356(79)	0.80842(70)	0.58989(33)	544(23)
C8	-0.76383(79)	0.69232(77)	0.66284(33)	541(24)
C9	-0.09551(61)	0.89536(53)	0.73178(22)	313(17)
N10	-0.00293(49)	0.82813(45)	0.79236(18)	332(15)
C11	0.19778(61)	0.95290(54)	0.79440(23)	337(18)
N12	0.22658(55)	1.08978(52)	0.73932(22)	494(17)
O13	0.03070(43)	1.05243(40)	0.69616(17)	491(13)
C14	0.36859(63)	0.93566(56)	0.85248(23)	352(18)
C15	0.32967(72)	0.80030(63)	0.91512(24)	385(19)
C16	0.49266(72)	0.78939(61)	0.96985(24)	424(21)
C17	0.69030(76)	0.91036(68)	0.96146(28)	471(22)
C18	0.72732(67)	1.04378(63)	0.89819(26)	422(20)
C19	0.56745(68)	1.05816(61)	0.84208(26)	397(19)
O20	0.47375(50)	0.66365(48)	1.03398(17)	562(16)
C21	0.27464(91)	0.53278(83)	1.04357(33)	585(26)
O22	0.92991(47)	1.15759(48)	0.89617(20)	606(16)
C23	0.98101(87)	1.29976(85)	0.83378(33)	587(26)
C24	-0.79420(71)	0.40514(65)	0.56778(28)	393(19)

Thermal parameters for non H-atoms in (**IIIc**).

Thermal parameters as exp[-2.pi**2.Sum(Uij.ai*.aj*.hi.hj) .10**4]

Atom	U11	U22	U33	U12	U13	U23
CL1	438(6)	423(6)	424(7)	203(5)	96(5)	-65(5)
C1	338(23)	254(21)	345(25)	87(18)	50(18)	-36(18)
C2	409(26)	326(23)	286(25)	39(20)	67(20)	37(19)
C3	377(25)	278(22)	333(25)	28(19)	15(19)	30(19)
N4	309(18)	261(17)	262(18)	74(15)	70(14)	-44(14)
C5	355(24)	339(23)	317(23)	62(19)	121(19)	-73(19)
C6	389(26)	366(24)	264(23)	77(20)	72(19)	-35(19)
C7	447(30)	376(28)	778(40)	191(24)	-133(27)	-147(27)
C8	381(28)	561(32)	801(39)	172(25)	98(26)	-329(30)
C9	377(24)	230(20)	311(24)	88(19)	41(19)	-43(18)
N10	352(20)	334(19)	284(20)	82(16)	42(16)	-64(16)
C11	369(25)	264(23)	388(25)	97(19)	47(20)	-105(20)
N12	345(22)	396(22)	576(26)	72(17)	-66(18)	42(20)
O13	365(18)	373(17)	532(20)	43(14)	-60(15)	81(15)
C14	389(25)	317(23)	371(25)	123(20)	24(19)	-126(19)
C15	423(26)	388(25)	367(26)	146(21)	39(21)	-112(21)
C16	552(32)	399(26)	367(27)	241(24)	-8(22)	-84(21)
C17	430(31)	478(29)	505(32)	191(25)	-56(23)	-133(24)
C18	388(27)	402(25)	477(28)	146(21)	-14(21)	-132(22)
C19	446(28)	330(24)	414(28)	139(21)	39(22)	-72(20)
O20	583(22)	622(22)	410(20)	204(18)	33(16)	23(17)
C21	684(37)	590(34)	474(33)	238(30)	183(28)	69(27)
O22	342(19)	610(22)	721(25)	73(17)	-20(16)	-64(19)
C23	466(32)	660(37)	587(37)	81(28)	153(27)	-136(30)
C24	380(26)	317(24)	398(27)	13(20)	48(20)	-91(20)

Atomic parameters for H-atoms in (**IIIc**).

Coordinates and thermal parameters as
exp[-8.pi**2.U.(sin(theta)/lambda)**2 .10**3]

Atom	x	y	z	U
H1	-0.364(7)	0.934(7)	0.702(3)	30(0)
H21	-0.270(8)	0.961(8)	0.589(3)	38(0)
H22	-0.236(8)	0.755(8)	0.605(3)	38(0)
H3	-0.542(8)	0.738(7)	0.522(3)	34(0)
H4	-0.498(8)	0.474(7)	0.621(3)	27(0)
H5	-0.726(8)	0.422(7)	0.709(3)	33(0)
H61	-0.465(8)	0.652(7)	0.783(3)	36(0)
H62	-0.365(8)	0.545(8)	0.738(3)	36(0)
H71	-0.619(9)	0.957(9)	0.593(3)	53(0)
H72	-0.802(10)	0.789(9)	0.553(3)	53(0)
H81	-0.723(8)	0.772(8)	0.707(3)	50(0)
H82	-0.911(10)	0.614(8)	0.658(3)	50(0)
H15	0.191(9)	0.722(8)	0.921(3)	38(0)
H17	0.800(9)	0.906(8)	0.998(3)	47(0)
H19	0.598(8)	1.157(8)	0.797(3)	37(0)
H211	0.215(9)	0.453(9)	1.000(4)	55(0)
H212	0.181(9)	0.614(9)	1.044(3)	55(0)
H213	0.291(9)	0.457(9)	1.094(4)	55(0)
H231	1.131(10)	1.352(8)	0.842(3)	57(0)
H232	0.935(9)	1.238(9)	0.782(4)	57(0)
H233	0.917(9)	1.392(9)	0.833(3)	57(0)
H241	-0.916(9)	0.421(8)	0.579(3)	37(0)
H242	-0.810(8)	0.279(8)	0.591(3)	37(0)
H243	-0.769(8)	0.441(7)	0.515(3)	37(0)

IR2 COORD. FINALES. R=0.0 RW=0.0
P-1

Crystal data

a =	7.1130(0.0010)	alpha=	78.100(0.020)
b =	7.7190(0.0010)	beta =	102.090(0.010)
c =	18.4670(0.0020)	gamma=	112.320(0.010)
V =	908.13(0.22) cubic-Angstrom		

Niggli reduced cell: 7.113 7.719 18.347 93.46 100.19 112.32

Niggli matrix:	50.5948	59.5830	336.6005
	-8.5419	-23.0826	-20.8519
Transformation matrix:	-1.00	0.00	0.00
	0.00	-1.00	0.00
	-1.00	0.00	1.00

C 18. O 3. N 3. CL 1. H 24.

M	=	365.859	(Atomic weights 1977)
Z	=	2.00	
D(calc.)	=	1.3380	Mg/m**3
F(000)	=	388.0	
mu	=	20.562	cm**-1 (Int.Tab.Vol.IV,p.55)
Lambda	=	1.5418000	Angstrom

Number of atoms: 49

Atomic coordinates

Atom	X/a	Y/b	Z/c
CL1	-0.30490(17)	0.33107(15)	0.62472(6)
C1	-0.31243(61)	0.83005(55)	0.69537(22)
H1	-0.36364(723)	0.93420(706)	0.70156(263)
C2	-0.31977(69)	0.83171(65)	0.61124(23)
H21	-0.26964(789)	0.96133(817)	0.58855(296)
H22	-0.23612(798)	0.75484(757)	0.60543(288)
C3	-0.53871(63)	0.73468(56)	0.57392(25)
H3	-0.54178(756)	0.73805(714)	0.52164(302)
N4	-0.60904(49)	0.53223(43)	0.61120(17)
H4	-0.49803(762)	0.47430(694)	0.62105(264)
C5	-0.64702(63)	0.55517(59)	0.68566(23)
H5	-0.72572(752)	0.42224(747)	0.70909(277)
C6	-0.43731(66)	0.63428(61)	0.73253(23)
H61	-0.46479(758)	0.65228(713)	0.78261(305)
H62	-0.36539(790)	0.54491(753)	0.73788(286)
C7	-0.69356(79)	0.80842(70)	0.58989(33)
H71	-0.61912(867)	0.95731(878)	0.59347(312)
H72	-0.80162(957)	0.78881(852)	0.55320(349)
C8	-0.76383(79)	0.69232(77)	0.66284(33)
H81	-0.72292(843)	0.77238(813)	0.70692(333)
H82	-0.91136(966)	0.61439(837)	0.65830(320)
C9	-0.09551(61)	0.89536(53)	0.73178(22)
N10	-0.00293(49)	0.82813(45)	0.79236(18)
C11	0.19778(61)	0.95290(54)	0.79440(23)
N12	0.22658(55)	1.08978(52)	0.73932(22)
O13	0.03070(43)	1.05243(40)	0.69616(17)
C14	0.36859(63)	0.93566(56)	0.85248(23)
C15	0.32967(72)	0.80030(63)	0.91512(24)
H15	0.19131(857)	0.72220(772)	0.92054(293)
C16	0.49266(72)	0.78939(61)	0.96985(24)
C17	0.69030(76)	0.91036(68)	0.96146(28)
H17	0.80007(890)	0.90567(782)	0.99768(336)
C18	0.72732(66)	1.04378(63)	0.89819(26)
C19	0.56745(68)	1.05816(61)	0.84208(26)
H19	0.59824(774)	1.15715(753)	0.79741(306)
O20	0.47375(50)	0.66365(48)	1.03398(17)
C21	0.27464(91)	0.53278(83)	1.04357(33)
H211	0.21548(891)	0.45304(862)	1.00023(353)
H212	0.18054(893)	0.61373(860)	1.04356(321)

H213	0.29135(882)	0.45717(861)	1.09392(361)
O22	0.92991(47)	1.15759(48)	0.89617(20)
C23	0.98101(87)	1.29976(85)	0.83378(32)
H231	1.13134(1019)	1.35182(845)	0.84247(336)
H232	0.93479(915)	1.23828(878)	0.78163(363)
H233	0.91680(948)	1.39153(906)	0.83300(349)
C24	-0.79420(71)	0.40514(65)	0.56778(28)
H241	-0.91639(874)	0.42138(750)	0.57868(292)
H242	-0.80956(790)	0.27890(819)	0.59072(303)
H243	-0.76888(762)	0.44101(727)	0.51473(318)

Orthogonal coordinates (Angstrom)
Orthogonalization matrix:

a	b cosgamma	c cosbeta	7.11300	-2.93151	-3.86787
0	b singamma	-c sinbeta cosalpha*	0.00000	7.14067	2.52848
0	0	c sinbeta sinalpha*	0.00000	0.00000	17.87950

Atom	X	Y	Z
CL1	-5.5556(0.0015)	3.9437(0.0014)	11.1697(0.0011)
C1	-7.3452(0.0048)	7.6853(0.0041)	12.4329(0.0039)
H1	-8.0387(0.0564)	8.4447(0.0509)	12.5435(0.0470)
C2	-7.0769(0.0054)	7.4845(0.0048)	10.9287(0.0041)
H21	-7.0125(0.0621)	8.3527(0.0588)	10.5230(0.0529)
H22	-6.2341(0.0620)	6.9209(0.0546)	10.8248(0.0515)
C3	-8.2054(0.0049)	6.6973(0.0042)	10.2614(0.0045)
H3	-8.0349(0.0589)	6.5891(0.0516)	9.3267(0.0540)
N4	-8.2564(0.0038)	5.3459(0.0032)	10.9279(0.0031)
H4	-7.3350(0.0588)	4.9571(0.0500)	11.1041(0.0472)
C5	-8.8818(0.0049)	5.6980(0.0044)	12.2593(0.0041)
H5	-9.1425(0.0588)	4.8080(0.0538)	12.6782(0.0495)
C6	-7.8033(0.0052)	6.3814(0.0045)	13.0973(0.0041)
H61	-8.2453(0.0590)	6.6365(0.0515)	13.9927(0.0545)
H62	-7.0505(0.0614)	5.7567(0.0543)	13.1929(0.0511)
C7	-9.5848(0.0062)	7.2642(0.0052)	10.5469(0.0059)
H71	-9.5056(0.0679)	8.3364(0.0632)	10.6109(0.0558)
H72	-10.1540(0.0738)	7.0314(0.0615)	9.8909(0.0624)
C8	-10.0265(0.0062)	6.6196(0.0056)	11.8512(0.0059)
H81	-10.1407(0.0658)	7.3027(0.0587)	12.6394(0.0595)
H82	-10.8298(0.0740)	6.0517(0.0603)	11.7701(0.0572)
C9	-6.1346(0.0047)	8.2438(0.0039)	13.0839(0.0039)
N10	-5.5133(0.0039)	7.9169(0.0034)	14.1670(0.0032)
C11	-4.4593(0.0048)	8.8130(0.0040)	14.2035(0.0041)
N12	-4.4426(0.0043)	9.6511(0.0039)	13.2187(0.0039)
O13	-5.5595(0.0034)	9.2753(0.0030)	12.4470(0.0031)
C14	-3.4184(0.0049)	8.8367(0.0042)	15.2419(0.0041)
C15	-3.5407(0.0056)	8.0285(0.0046)	16.3619(0.0043)
H15	-4.3169(0.0660)	7.4846(0.0556)	16.4588(0.0524)
C16	-2.5611(0.0056)	8.0890(0.0045)	17.3404(0.0043)
C17	-1.4774(0.0059)	8.9316(0.0050)	17.1904(0.0050)
H17	-0.8230(0.0686)	8.9897(0.0565)	17.8380(0.0601)
C18	-1.3605(0.0052)	9.7243(0.0046)	16.0592(0.0047)
C19	-2.3228(0.0053)	9.6852(0.0045)	15.0560(0.0047)
H19	-2.2212(0.0605)	10.2791(0.0543)	14.2573(0.0547)
O20	-2.5750(0.0039)	7.3533(0.0036)	18.4870(0.0031)
C21	-3.6447(0.0071)	6.4430(0.0061)	18.6585(0.0059)
H211	-3.6641(0.0696)	5.7641(0.0622)	17.8836(0.0631)
H212	-4.5513(0.0695)	7.0211(0.0620)	18.6583(0.0574)
H213	-3.4990(0.0691)	6.0305(0.0622)	19.5587(0.0645)
O22	-0.2453(0.0038)	10.5319(0.0036)	16.0231(0.0036)
C23	-0.0573(0.0068)	11.3894(0.0062)	14.9076(0.0057)
H231	0.8258(0.0777)	11.7831(0.0609)	15.0629(0.0601)
H232	-0.0041(0.0714)	10.8185(0.0634)	13.9752(0.0649)
H233	-0.7800(0.0737)	12.0427(0.0653)	14.8936(0.0624)
C24	-9.0329(0.0056)	4.3286(0.0048)	10.1516(0.0050)
H241	-9.9918(0.0669)	4.4721(0.0541)	10.3465(0.0522)
H242	-8.8608(0.0622)	3.4852(0.0590)	10.5618(0.0542)
H243	-8.7528(0.0595)	4.4506(0.0525)	9.2031(0.0569)

Bond distances (Angstrom)

			Distance	e.s.d.
C1	- H1		1.0343	0.0639
C1	- C2		1.5411	0.0061
C1	- C6		1.5335	0.0052
C1	- C9		1.4837	0.0053
C2	- H21		0.9605	0.0540
C2	- H22		1.0192	0.0701
C2	- C3		1.5292	0.0055
C3	- H3		0.9563	0.0575
C3	- N4		1.5077	0.0048
C3	- C7		1.5184	0.0087
N4	- H4		1.0154	0.0620
N4	- C5		1.5124	0.0060
N4	- C24		1.4969	0.0051
C5	- H5		1.0176	0.0466
C5	- C6		1.5272	0.0054
C5	- C8		1.5252	0.0083
C6	- H61		1.0306	0.0631
C6	- H62		0.9829	0.0675
C7	- H71		1.0770	0.0618
C7	- H72		0.8992	0.0585
C7	- C8		1.5204	0.0079
C8	- H81		1.0492	0.0662
C8	- H82		0.9872	0.0579
C9	- N10		1.2908	0.0050
C9	- O13		1.3418	0.0043
N10	- C11		1.3839	0.0046
C11	- N12		1.2933	0.0052
C11	- C14		1.4705	0.0057
N12	- O13		1.4086	0.0045
C14	- C15		1.3865	0.0056
C14	- C19		1.3981	0.0056
C15	- H15		0.9528	0.0526
C15	- C16		1.3860	0.0063
C16	- C17		1.3808	0.0063
C16	- O20		1.3624	0.0050
C17	- H17		0.9225	0.0577
C17	- C18		1.3863	0.0063
C18	- C19		1.3907	0.0062
C18	- O22		1.3774	0.0049
C19	- H19		1.0005	0.0505
O20	- C21		1.4150	0.0062
C21	- H211		1.0305	0.0668
C21	- H212		1.0752	0.0781
C21	- H213		1.0010	0.0607
O22	- C23		1.4195	0.0063
C23	- H231		0.9793	0.0656
C23	- H232		1.0946	0.0700
C23	- H233		0.9744	0.0822
C24	- H241		0.9890	0.0708
C24	- H242		0.9535	0.0590
C24	- H243		0.9965	0.0588

Number of bond distances: 51

Bond angles (degrees)
(e.s.d. following Cruickshank, Internat. Tables, II, 1959, p.331)

				Angle	e.s.d.
C6	- C1	- C9		111.94	0.34
C2	- C1	- C9		109.59	0.36
C2	- C1	- C6		111.35	0.34
H1	- C1	- C9		102.94	2.91
H1	- C1	- C6		112.19	2.88
H1	- C1	- C2		108.47	2.63
C1	- C2	- C3		111.38	0.36
C1	- C2	- H22		108.39	3.03
C1	- C2	- H21		107.83	3.39

H22	- C2	- C3	106.33	3.15
H21	- C2	- C3	109.30	3.48
H21	- C2	- H22	113.67	4.92
C2	- C3	- C7	113.34	0.39
C2	- C3	- N4	107.06	0.35
C2	- C3	- H3	110.68	3.43
N4	- C3	- C7	102.76	0.36
H3	- C3	- C7	112.83	3.47
H3	- C3	- N4	109.68	3.11
C3	- N4	- C24	113.42	0.33
C3	- N4	- C5	101.21	0.30
C3	- N4	- H4	112.90	3.09
C5	- N4	- C24	113.59	0.34
H4	- N4	- C24	107.49	2.83
H4	- N4	- C5	108.16	2.69
N4	- C5	- C8	102.45	0.36
N4	- C5	- C6	107.17	0.36
N4	- C5	- H5	105.35	2.99
C6	- C5	- C8	113.98	0.39
H5	- C5	- C8	116.51	3.31
H5	- C5	- C6	110.27	3.01
C1	- C6	- C5	110.72	0.35
C5	- C6	- H62	108.05	3.15
C5	- C6	- H61	106.54	3.27
C1	- C6	- H62	110.72	3.47
C1	- C6	- H61	107.10	2.90
H61	- C6	- H62	113.66	4.34
C3	- C7	- C8	105.48	0.45
C3	- C7	- H72	109.95	4.08
C3	- C7	- H71	108.43	3.58
H72	- C7	- C8	109.40	4.16
H71	- C7	- C8	113.10	3.04
H71	- C7	- H72	110.34	5.20
C5	- C8	- C7	105.53	0.46
C7	- C8	- H82	114.19	3.47
C7	- C8	- H81	113.58	3.26
C5	- C8	- H82	106.56	3.53
C5	- C8	- H81	105.91	3.40
H81	- C8	- H82	110.35	5.25
C1	- C9	- O13	115.52	0.36
C1	- C9	- N10	131.73	0.39
N10	- C9	- O13	112.75	0.38
C9	- N10	- C11	102.99	0.34
N10	- C11	- C14	124.62	0.36
N10	- C11	- N12	114.16	0.40
N12	- C11	- C14	121.21	0.40
C11	- N12	- O13	103.54	0.35
C9	- O13	- N12	106.55	0.32
C11	- C14	- C19	118.07	0.38
C11	- C14	- C15	119.91	0.42
C15	- C14	- C19	122.02	0.42
C14	- C15	- C16	118.85	0.44
C14	- C15	- H15	119.13	3.47
H15	- C15	- C16	121.93	3.26
C15	- C16	- O20	124.29	0.46
C15	- C16	- C17	120.31	0.43
C17	- C16	- O20	115.40	0.45
C16	- C17	- C18	120.25	0.49
C16	- C17	- H17	121.26	3.69
H17	- C17	- C18	118.49	3.76
C17	- C18	- O22	115.15	0.43
C17	- C18	- C19	120.94	0.46
C19	- C18	- O22	123.91	0.42
C14	- C19	- C18	117.61	0.42
C18	- C19	- H19	119.27	3.37
C14	- C19	- H19	123.09	3.34
C16	- O20	- C21	117.20	0.41
O20	- C21	- H213	105.31	3.87

O20	- C21	- H212		106.95	3.34
O20	- C21	- H211		110.30	3.71
H212	- C21	- H213		110.15	4.92
H211	- C21	- H213		114.05	5.02
H211	- C21	- H212		109.77	5.11
C18	- O22	- C23		118.82	0.41
O22	- C23	- H233		108.54	3.98
O22	- C23	- H232		111.15	3.36
O22	- C23	- H231		103.75	3.76
H232	- C23	- H233		111.93	5.29
H231	- C23	- H233		113.68	5.37
H231	- C23	- H232		107.52	5.13
N4	- C24	- H243		105.34	3.22
N4	- C24	- H242		106.53	3.44
N4	- C24	- H241		107.59	3.15
H242	- C24	- H243		117.84	4.63
H241	- C24	- H243		116.26	4.53
H241	- C24	- H242		102.63	4.73

Number of angles: 95

Torsion angles (degrees)
(right-hand rule, Klyne & Prelog.(1960). Experientia,16,521)
(e.s.d. following Stanford & Waser, Acta Cryst.(1972).A28,213)

				Angle	e.s.d.
C6	-C1	-C9	-N10	-8.90	0.66
C2	-C1	-C9	-N10	-132.95	0.49
H1	-C1	-C9	-N10	111.78	2.97
C6	-C1	-C9	-O13	170.84	0.36
C2	-C1	-C9	-O13	46.79	0.49
H1	-C1	-C9	-O13	-68.48	2.97
C2	-C1	-C6	-H61	-162.27	3.23
H1	-C1	-C6	-H61	-40.47	4.48
C2	-C1	-C6	-H62	73.32	3.51
H1	-C1	-C6	-H62	-164.88	4.66
C9	-C1	-C6	-C5	-169.56	0.36
C2	-C1	-C6	-C5	-46.49	0.49
H1	-C1	-C6	-C5	75.30	3.12
H1	-C1	-C2	-H21	42.05	4.75
H1	-C1	-C2	-H22	165.50	4.50
H1	-C1	-C2	-C3	-77.86	3.05
C6	-C1	-C2	-C3	46.06	0.50
C6	-C1	-C2	-H22	-70.58	3.36
C6	-C1	-C2	-H21	165.97	3.66
C9	-C1	-C2	-C3	170.46	0.36
C9	-C1	-C2	-H22	53.82	3.37
C9	-C1	-C2	-H21	-69.63	3.67
C9	-C1	-C6	-H62	-49.74	3.51
C9	-C1	-C6	-H61	74.67	3.24
C1	-C2	-C3	-H3	179.20	3.54
C1	-C2	-C3	-N4	-61.30	0.45
C1	-C2	-C3	-C7	51.28	0.53
H22	-C2	-C3	-H3	-62.91	4.84
H21	-C2	-C3	-H3	60.16	5.11
H22	-C2	-C3	-N4	56.59	3.32
H21	-C2	-C3	-N4	179.67	3.69
H22	-C2	-C3	-C7	169.17	3.32
H21	-C2	-C3	-C7	-67.75	3.71
C2	-C3	-C7	-H71	34.50	3.56
C2	-C3	-C7	-H72	155.22	4.51
C2	-C3	-C7	-C8	-86.93	0.51
C2	-C3	-N4	-H4	-41.22	3.23
C2	-C3	-N4	-C5	74.17	0.39
C2	-C3	-N4	-C24	-163.79	0.36
N4	-C3	-C7	-H71	149.68	3.53
H3	-C3	-C7	-H71	-92.29	5.03
N4	-C3	-C7	-H72	-89.61	4.51
H3	-C3	-C7	-H72	28.43	5.77
N4	-C3	-C7	-C8	28.25	0.50

H3	-C3	-C7	-C8	146.28	3.60
H3	-C3	-N4	-H4	78.92	4.76
H3	-C3	-N4	-C5	-165.69	3.51
H3	-C3	-N4	-C24	-43.65	3.53
C7	-C3	-N4	-C24	76.58	0.44
C7	-C3	-N4	-C5	-45.46	0.41
C7	-C3	-N4	-H4	-160.84	3.22
C3	-N4	-C24	-H241	-81.44	3.56
C3	-N4	-C24	-H242	169.10	3.69
C3	-N4	-C24	-H243	43.19	3.40
C3	-N4	-C5	-H5	167.39	3.18
C3	-N4	-C5	-C6	-75.18	0.39
C3	-N4	-C5	-C8	45.07	0.41
C5	-N4	-C24	-H241	33.42	3.57
H4	-N4	-C24	-H241	153.04	4.71
C5	-N4	-C24	-H242	-76.04	3.70
H4	-N4	-C24	-H242	43.57	4.82
C5	-N4	-C24	-H243	158.05	3.38
H4	-N4	-C24	-H243	-82.34	4.59
H4	-N4	-C5	-H5	-73.76	4.45
H4	-N4	-C5	-C6	43.68	3.13
H4	-N4	-C5	-C8	163.93	3.12
C24	-N4	-C5	-C8	-76.84	0.44
C24	-N4	-C5	-C6	162.91	0.36
C24	-N4	-C5	-H5	45.47	3.20
N4	-C5	-C6	-C1	62.59	0.44
H5	-C5	-C6	-C1	176.76	3.27
N4	-C5	-C8	-H81	-148.27	3.51
N4	-C5	-C8	-H82	94.21	3.92
N4	-C5	-C8	-C7	-27.54	0.50
N4	-C5	-C6	-H61	178.71	3.21
N4	-C5	-C6	-H62	-58.81	3.45
C8	-C5	-C6	-C1	-50.01	0.52
C6	-C5	-C8	-H81	-32.86	3.54
H5	-C5	-C8	-H81	97.34	4.91
C6	-C5	-C8	-H82	-150.38	3.92
H5	-C5	-C8	-H82	-20.18	5.22
C6	-C5	-C8	-C7	87.86	0.51
H5	-C5	-C8	-C7	-141.94	3.44
H5	-C5	-C6	-H61	-67.12	4.59
H5	-C5	-C6	-H62	55.36	4.75
C8	-C5	-C6	-H62	-171.41	3.44
C8	-C5	-C6	-H61	66.11	3.24
C3	-C7	-C8	-C5	-0.35	0.55
H72	-C7	-C8	-C5	117.88	4.50
H71	-C7	-C8	-C5	-118.69	3.65
C3	-C7	-C8	-H81	115.23	3.70
C3	-C7	-C8	-H82	-117.04	4.13
H72	-C7	-C8	-H81	-126.55	5.80
H71	-C7	-C8	-H81	-3.12	5.20
H72	-C7	-C8	-H82	1.19	6.11
H71	-C7	-C8	-H82	124.62	5.49
C1	-C9	-O13	-N12	-179.98	0.35
C1	-C9	-N10	-C11	179.34	0.45
N10	-C9	-O13	-N12	-0.19	0.47
O13	-C9	-N10	-C11	-0.41	0.47
C9	-N10	-C11	-N12	0.95	0.50
C9	-N10	-C11	-C14	-178.36	0.41
N10	-C11	-C14	-C15	-7.89	0.67
N10	-C11	-C14	-C19	171.90	0.42
N10	-C11	-N12	-O13	-1.04	0.49
N12	-C11	-C14	-C15	172.84	0.44
N12	-C11	-C14	-C19	-7.36	0.65
C14	-C11	-N12	-O13	178.29	0.37
C11	-N12	-O13	-C9	0.73	0.44
C11	-C14	-C19	-H19	0.61	3.93
C11	-C14	-C19	-C18	178.46	0.42
C11	-C14	-C15	-H15	-1.95	4.08

C11	-C14	-C15	-C16	-178.66	0.43
C15	-C14	-C19	-H19	-179.60	3.90
C15	-C14	-C19	-C18	-1.74	0.70
C19	-C14	-C15	-C16	1.55	0.71
C19	-C14	-C15	-H15	178.26	4.04
C14	-C15	-C16	-C17	-0.65	0.73
C14	-C15	-C16	-O20	179.52	0.44
H15	-C15	-C16	-C17	-177.26	4.16
H15	-C15	-C16	-O20	2.90	4.21
C15	-C16	-O20	-C21	1.96	0.70
C15	-C16	-C17	-H17	179.27	4.53
C15	-C16	-C17	-C18	0.00	0.77
C17	-C16	-O20	-C21	-177.88	0.47
O20	-C16	-C17	-C18	179.85	0.45
O20	-C16	-C17	-H17	-0.88	4.57
C16	-C17	-C18	-C19	-0.22	0.77
C16	-C17	-C18	-O22	179.50	0.45
H17	-C17	-C18	-C19	-179.50	4.40
H17	-C17	-C18	-O22	0.22	4.44
C17	-C18	-C19	-C14	1.06	0.72
C17	-C18	-O22	-C23	-179.18	0.47
C17	-C18	-C19	-H19	179.00	3.74
O22	-C18	-C19	-C14	-178.64	0.43
C19	-C18	-O22	-C23	0.53	0.71
O22	-C18	-C19	-H19	-0.70	3.79
C16	-O20	-C21	-H211	58.53	3.91
C16	-O20	-C21	-H212	-60.80	3.57
C16	-O20	-C21	-H213	-177.98	3.90
C18	-O22	-C23	-H231	-174.50	4.04
C18	-O22	-C23	-H232	-59.23	3.80
C18	-O22	-C23	-H233	64.29	4.23

Number of torsion angles: 143

Weighted least-squares planes through the starred atoms
(Nardelli, Musatti, Domiano & Andreetti Ric.Sci.(1965),15(II-A),807).
Equation of the plane: m1*X+m2*Y+m3*Z=d

Plane 1
m1 = 0.62519(0.00239)
m2 = -0.76097(0.00180)
m3 = -0.17336(0.00232)
D = -12.00956(0.02161)

Atom		d	s	d/s	(d/s)**2
C2	*	-0.0049	0.0050	-0.979	0.959
C3	*	0.0043	0.0045	0.954	0.911
C5	*	-0.0045	0.0046	-0.979	0.958
C6	*	0.0044	0.0048	0.932	0.869
C1		-0.5863	0.0044	-134.601	18117.301
N4		0.8852	0.0035	254.266	64651.355
C9		-0.3672	0.0043	-85.921	7382.428
C24		1.3085	0.0051	256.100	65587.023
			Sum((d/s)**2) for starred atoms		3.697

Chi-squared at 95% for 1 degrees of freedom: 3.84
The group of atoms does not deviate significantly from planarity

Plane 2
m1 = -0.41674(0.00294)
m2 = -0.74914(0.00205)
m3 = -0.51489(0.00218)
D = -6.88025(0.04218)

Atom		d	s	d/s	(d/s)**2
C3	*	-0.0009	0.0044	-0.206	0.042
C5	*	0.0009	0.0044	0.206	0.042
C7	*	0.0022	0.0055	0.399	0.159
C8	*	-0.0024	0.0058	-0.417	0.174

N4	0.6895	0.0033	208.548	43492.391
C24	2.1749	0.0050	435.809	189929.313
C2	-1.4045	0.0047	-297.149	88297.414
C6	-1.3920	0.0045	-307.681	94667.805

Sum((d/s)**2) for starred atoms 0.418

Chi-squared at 95% for 1 degrees of freedom: 3.84

The group of atoms does not deviate significantly from planarity

Plane 3

m1 = 0.56815(0.00202)

m2 = -0.63705(0.00160)

m3 = -0.52094(0.00185)

D = -15.55324(0.01501)

Atom		d	s	d/s	(d/s)**2
C9	*	0.0004	0.0042	0.084	0.007
N10	*	-0.0027	0.0035	-0.758	0.575
C11	*	0.0063	0.0043	1.468	2.154
N12	*	-0.0052	0.0041	-1.275	1.626
O13	*	0.0017	0.0032	0.538	0.290
C1		0.0074	0.0043	1.726	2.979
C2		1.0714	0.0048	222.249	49394.824
C6		0.2317	0.0046	50.092	2509.231
C14		0.0416	0.0044	9.443	89.175
C15		-0.0965	0.0049	-19.791	391.688
C19		0.2204	0.0048	45.746	2092.687

Sum((d/s)**2) for starred atoms 4.652

Chi-squared at 95% for 2 degrees of freedom: 5.99

The group of atoms does not deviate significantly from planarity

Plane 4

m1 = 0.50172(0.00187)

m2 = -0.73153(0.00143)

m3 = -0.46167(0.00181)

D = -15.20860(0.02183)

Atom		d	s	d/s	(d/s)**2
C14	*	-0.0076	0.0043	-1.744	3.043
C15	*	0.0052	0.0048	1.075	1.157
C16	*	0.0007	0.0047	0.144	0.021
C17	*	-0.0028	0.0052	-0.525	0.275
C18	*	-0.0017	0.0048	-0.361	0.131
C19	*	0.0073	0.0048	1.536	2.359
C11		-0.0330	0.0042	-7.793	60.723
O20		0.0025	0.0036	0.706	0.498
C21		0.0525	0.0063	8.340	69.559
O22		-0.0163	0.0036	-4.477	20.045
C23		-0.0342	0.0063	-5.458	29.791

Sum((d/s)**2) for starred atoms 6.985

Chi-squared at 95% for 3 degrees of freedom: 7.81

The group of atoms does not deviate significantly from planarity

Dihedral angles formed by LSQ-planes

Plane	- plane	angle (e.s.d.)
1	2	66.50(0.20)
1	3	21.52(0.18)
1	4	18.13(0.17)
2	3	59.42(0.18)
2	4	54.79(0.21)
3	4	7.44(0.13)

Ring puckering coordinates

following Cremer D. & Pople J.A., JACS (1975).97,1354

```
Ring  1
Atom            Internal cartesian coordinates
                X                Y                Z
C1        0.0000(0.0000)   1.4914(0.0040) -0.1353(0.0034)
C2        1.2712(0.0046)   0.6848(0.0052)  0.1937(0.0037)
C3        1.1675(0.0043)  -0.7524(0.0049) -0.3184(0.0033)
N4       -0.0044(0.0041)  -1.3891(0.0033)  0.3847(0.0029)
C5       -1.1664(0.0039)  -0.7321(0.0049) -0.3263(0.0032)
C6       -1.2679(0.0045)   0.6974(0.0052)  0.2016(0.0033)
q2  =  0.2161(0.0044)
q3  = -0.6369(0.0044)
phi2  =    2.11(  1.36)
Total puckering amplitude:  QT =  0.6726(0.0042)
Spherical polar angles:
Theta2  =  161.26(  0.39)

Asymmetry parameters
Following Nardelli M., Acta Cryst.(1983).C39,1141

C1    C2    C3    N4    C5    C6

DS(C1    )=0.0062(0.0024)        DS(C1    -C6    )=0.3763(0.0019)
D2(C1    )=0.2996(0.0016)        D2(C1    -C6    )=0.0676(0.0020)

DS(C2    )=0.1310(0.0023)        DS(C2    -C1    )=0.3777(0.0019)
D2(C2    )=0.2886(0.0015)        D2(C2    -C1    )=0.0590(0.0019)

DS(C3    )=0.1371(0.0024)        DS(C3    -C2    )=0.3608(0.0019)
D2(C3    )=0.2880(0.0016)        D2(C3    -C2    )=0.1264(0.0019)


Ring  2
Atom            Internal cartesian coordinates
                X                Y                Z
C3        0.0000(0.0000)   1.2353(0.0044)  0.2323(0.0053)
N4        1.1441(0.0038)   0.4041(0.0060) -0.2903(0.0027)
C5        0.7778(0.0054)  -0.9652(0.0047)  0.2373(0.0053)
C7       -1.2119(0.0050)   0.3805(0.0066) -0.0937(0.0079)
C8       -0.7101(0.0048)  -1.0547(0.0056) -0.0857(0.0078)
q2  =  0.4590(0.0043)
phi2  =   36.83(  1.61)

Asymmetry parameters
Following Nardelli M., Acta Cryst.(1983).C39,1141

C3    N4    C5    C7    C8

DS(C3    )=0.2188(0.0052)        D2(C3    )=0.2139(0.0036)
DS(N4    )=0.0050(0.0058)        D2(N4    )=0.2664(0.0033)
DS(C5    )=0.2108(0.0051)        D2(C5    )=0.2183(0.0036)
DS(C7    )=0.3460(0.0041)        D2(C7    )=0.0862(0.0040)
DS(C8    )=0.3491(0.0041)        D2(C8    )=0.0794(0.0040)

Ring  3
Atom            Internal cartesian coordinates
                X                Y                Z
C9        0.0000(0.0000)   1.1119(0.0039)  0.0006(0.0024)
N10       1.0948(0.0035)   0.4282(0.0045) -0.0037(0.0024)
C11       0.6443(0.0040)  -0.8803(0.0049)  0.0053(0.0025)
N12      -0.6436(0.0039)  -0.9969(0.0039) -0.0050(0.0024)
O13      -1.0955(0.0032)   0.3372(0.0043)  0.0027(0.0025)
q2  =  0.0086(0.0037)
phi2  =   83.89( 24.01)

Asymmetry parameters
Following Nardelli M., Acta Cryst.(1983).C39,1141

C9    N10   C11   N12   O13
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```
DS(C9    )=0.0075(0.0021)        D2(C9    )=0.0007(0.0016)
DS(N10   )=0.0056(0.0021)        D2(N10   )=0.0038(0.0017)
DS(C11   )=0.0015(0.0021)        D2(C11   )=0.0053(0.0016)
DS(N12   )=0.0031(0.0021)        D2(N12   )=0.0051(0.0017)
DS(O13   )=0.0066(0.0021)        D2(O13   )=0.0027(0.0016)

Ring  4
Atom            Internal cartesian coordinates
                X                Y                Z
C14       0.0000(0.0001)  1.3711(0.0048) -0.0084(0.0032)
C15       1.2107(0.0051)  0.6955(0.0051)  0.0046(0.0037)
C16       1.2032(0.0050) -0.6905(0.0059)  0.0007(0.0035)
C17       0.0073(0.0062) -1.3808(0.0052) -0.0023(0.0038)
C18      -1.1962(0.0049) -0.6928(0.0065) -0.0015(0.0040)
C19      -1.2251(0.0054)  0.6975(0.0073)  0.0069(0.0034)
q2  =  0.0095(0.0049)
q3  = -0.0075(0.0043)
phi2  =  166.27( 31.14)
Total puckering amplitude:  QT =  0.0121(0.0043)
Spherical polar angles:
Theta2  =  128.15( 23.18)

Asymmetry parameters
Following Nardelli M., Acta Cryst.(1983).C39,1141

C14   C15   C16   C17   C18   C19

DS(C14   )=0.0016(0.0026)        DS(C14   -C19   )=0.0070(0.0020)
D2(C14   )=0.0052(0.0016)        D2(C14   -C19   )=0.0016(0.0022)

DS(C15   )=0.0066(0.0025)        DS(C15   -C14   )=0.0060(0.0020)
D2(C15   )=0.0037(0.0017)        D2(C15   -C14   )=0.0039(0.0021)

DS(C16   )=0.0050(0.0026)        DS(C16   -C15   )=0.0046(0.0021)
D2(C16   )=0.0044(0.0017)        D2(C16   -C15   )=0.0055(0.0021)


Interatomic contacts greater than 0.50 and less than 3.50 Angstrom,
involving atoms of the original set.
                              Distance    e.s.d.
CL1   ...H22                    3.0730    0.0588
CL1   ...N4                     3.0527    0.0043
CL1   ...H4                     2.0488    0.0641
CL1   ...H62                    3.1009    0.0659
CL1   ...H242                   3.3918    0.0569
C1    ...H1                     1.0343    0.0639
C1    ...C2                     1.5411    0.0061
C1    ...H21                    2.0503    0.0520
C1    ...H22                    2.0988    0.0650
C1    ...C3                     2.5360    0.0056
C1    ...H3                     3.3654    0.0527
C1    ...N4                     2.9271    0.0047
C1    ...H4                     3.0346    0.0522
C1    ...C5                     2.5181    0.0049
C1    ...H5                     3.4014    0.0441
C1    ...C6                     1.5335    0.0052
C1    ...H61                    2.0840    0.0510
C1    ...H62                    2.0938    0.0544
C1    ...C7                     2.9580    0.0065
C1    ...H71                    2.9001    0.0618
C1    ...C8                     2.9433    0.0065
C1    ...H81                    2.8290    0.0635
C1    ...C9                     1.4837    0.0053
C1    ...N10                    2.5332    0.0050
C1    ...O13                    2.3910    0.0044
H1    ...C2                     2.1107    0.0594
```

H1	...H21	2.2681	0.0803
H1	...H22	2.9211	0.0928
H1	...C3	2.8791	0.0505
H1	...C5	2.8872	0.0454
H1	...C6	2.1493	0.0514
H1	...H61	2.3264	0.0658
H1	...H62	2.9366	0.0818
H1	...C7	2.7875	0.0435
H1	...H71	2.4287	0.0708
H1	...C8	2.7859	0.0422
H1	...H81	2.3940	0.0710
H1	...C9	1.9895	0.0554
H1	...N10	3.0483	0.0523
H1	...O13	2.6164	0.0498
C2	...H21	0.9605	0.0540
C2	...H22	1.0192	0.0701
C2	...C3	1.5292	0.0055
C2	...H3	2.0702	0.0486
C2	...N4	2.4423	0.0048
C2	...H4	2.5465	0.0477
C2	...C5	2.8670	0.0056
C2	...C6	2.5392	0.0057
C2	...H61	3.3871	0.0552
C2	...H62	2.8483	0.0490
C2	...C7	2.5463	0.0077
C2	...H71	2.5934	0.0736
C2	...H72	3.2789	0.0663
C2	...C8	3.2092	0.0076
C2	...C9	2.4717	0.0054
C2	...O13	2.7955	0.0047
H21	...H22	1.6574	0.0921
H21	...C3	2.0571	0.0469
H21	...H3	2.3636	0.0679
H21	...N4	3.2790	0.0495
H21	...H4	3.4600	0.0726
H21	...C6	3.3374	0.0505
H21	...C7	2.7932	0.0526
H21	...H71	2.4947	0.0923
H21	...H72	3.4662	0.0800
H21	...C9	2.7094	0.0506
H21	...O13	2.5815	0.0483
H22	...C3	2.0624	0.0567
H22	...H3	2.3659	0.0709
H22	...N4	2.5653	0.0479
H22	...H4	2.2686	0.0624
H22	...C5	3.2502	0.0548
H22	...C6	2.8139	0.0564
H22	...H62	2.7622	0.0706
H22	...C7	3.3797	0.0634
H22	...C9	2.6198	0.0547
H22	...O13	2.9377	0.0514
C3	...H3	0.9563	0.0575
C3	...N4	1.5077	0.0048
C3	...H4	2.1203	0.0548
C3	...C5	2.3340	0.0058
C3	...H5	3.2075	0.0470
C3	...C6	2.8816	0.0059
C3	...H62	3.2882	0.0501
C3	...C7	1.5184	0.0087
C3	...H71	2.1212	0.0781
C3	...H72	2.0115	0.0746
C3	...C8	2.4186	0.0083
C3	...H81	3.1251	0.0714
C3	...H82	3.0952	0.0695
C3	...C24	2.5114	0.0055
C3	...H241	2.8548	0.0481
C3	...H242	3.2920	0.0536
C3	...H243	2.5430	0.0514

H3	...N4	2.0393	0.0489
H3	...H4	2.5124	0.0706
H3	...C5	3.1799	0.0536
H3	...C7	2.0849	0.0671
H3	...H71	2.6202	0.1018
H3	...H72	2.2371	0.1026
H3	...C8	3.2157	0.0617
H3	...C24	2.6051	0.0445
H3	...H241	3.0580	0.0676
H3	...H242	3.4413	0.0686
H3	...H243	2.2592	0.0648
N4	...H4	1.0154	0.0620
N4	...C5	1.5124	0.0060
N4	...H5	2.0342	0.0514
N4	...C6	2.4461	0.0051
N4	...H61	3.3254	0.0568
N4	...H62	2.5987	0.0484
N4	...C7	2.3643	0.0072
N4	...H71	3.2564	0.0719
N4	...H72	2.7418	0.0728
N4	...C8	2.3681	0.0084
N4	...H81	3.2107	0.0753
N4	...H82	2.7982	0.0798
N4	...C24	1.4969	0.0051
N4	...H241	2.0281	0.0541
N4	...H242	1.9904	0.0522
N4	...H243	2.0057	0.0543
H4	...C5	2.0678	0.0639
H4	...H5	2.4015	0.0817
H4	...C6	2.4941	0.0552
H4	...H61	3.4631	0.0835
H4	...H62	2.2547	0.0704
H4	...C7	3.2702	0.0620
H4	...C8	3.2505	0.0660
H4	...C24	2.0457	0.0478
H4	...H241	2.8049	0.0799
H4	...H242	2.1883	0.0635
H4	...H243	2.4249	0.0678
C5	...H5	1.0176	0.0466
C5	...C6	1.5272	0.0054
C5	...H61	2.0714	0.0514
C5	...H62	2.0564	0.0551
C5	...C7	2.4247	0.0067
C5	...H71	3.1729	0.0620
C5	...H72	3.0009	0.0619
C5	...C8	1.5252	0.0083
C5	...H81	2.0747	0.0743
C5	...H82	2.0394	0.0740
C5	...C24	2.5180	0.0067
C5	...H241	2.5285	0.0498
C5	...H242	2.7890	0.0610
C5	...H243	3.3034	0.0599
H5	...C6	2.1082	0.0437
H5	...H61	2.4242	0.0672
H5	...H62	2.3541	0.0693
H5	...C7	3.2819	0.0507
H5	...C8	2.1788	0.0584
H5	...H81	2.6873	0.0916
H5	...H82	2.2844	0.0943
H5	...C24	2.5740	0.0518
H5	...H241	2.5042	0.0690
H5	...H242	2.5116	0.0831
C6	...H61	1.0306	0.0631
C6	...H62	0.9829	0.0675
C6	...C7	3.2338	0.0069
C6	...C8	2.5596	0.0074
C6	...H81	2.5538	0.0699
C6	...H82	3.3211	0.0661

C6	...C9	2.5007	0.0051
C6	...N10	2.9574	0.0049
H61	...H62	1.6856	0.0971
H61	...C8	2.7854	0.0507
H61	...H81	2.4224	0.0831
H61	...H82	3.4586	0.0773
H61	...C9	2.8043	0.0483
H61	...N10	3.0222	0.0491
H62	...C8	3.3766	0.0606
H62	...H81	3.4994	0.0968
H62	...C9	2.6526	0.0471
H62	...N10	2.8245	0.0457
C7	...H71	1.0770	0.0618
C7	...H72	0.8992	0.0585
C7	...C8	1.5204	0.0079
C7	...H81	2.1654	0.0636
C7	...H82	2.1252	0.0575
C7	...C24	3.0131	0.0077
C7	...H241	2.8287	0.0516
C7	...H243	3.2271	0.0629
H71	...H72	1.6254	0.0775
H71	...C8	2.1811	0.0540
H71	...H81	2.3635	0.0786
H71	...H82	2.8839	0.0742
H72	...C8	2.0071	0.0604
H72	...H81	2.7618	0.0873
H72	...H82	2.2243	0.0821
H72	...C24	2.9377	0.0711
H72	...H241	2.6046	0.0819
H72	...H243	3.0161	0.1004
C8	...H81	1.0492	0.0662
C8	...H82	0.9872	0.0579
C8	...C24	3.0207	0.0090
C8	...H241	2.6224	0.0574
H81	...H82	1.6721	0.0755
H82	...C24	2.9694	0.0781
H82	...H241	2.2855	0.0977
H82	...H242	3.4531	0.1064
C9	...N10	1.2908	0.0050
C9	...C11	2.0938	0.0054
C9	...N12	2.2049	0.0048
C9	...O13	1.3418	0.0043
N10	...C11	1.3839	0.0046
N10	...N12	2.2479	0.0043
N10	...O13	2.1922	0.0041
N10	...C14	2.5278	0.0050
N10	...C15	2.9531	0.0054
N10	...H15	2.6212	0.0521
C11	...N12	1.2933	0.0052
C11	...O13	2.1236	0.0049
C11	...C14	1.4705	0.0057
C11	...C15	2.4734	0.0058
C11	...H15	2.6213	0.0503
C11	...C19	2.4601	0.0058
C11	...H19	2.6761	0.0477
N12	...O13	1.4086	0.0045
N12	...C14	2.4095	0.0055
N12	...C19	2.8054	0.0058
N12	...H19	2.5314	0.0508
C14	...C15	1.3865	0.0056
C14	...H15	2.0289	0.0495
C14	...C16	2.3870	0.0058
C14	...C17	2.7519	0.0064
C14	...C18	2.3855	0.0058
C14	...C19	1.3981	0.0056
C14	...H19	2.1173	0.0478
C15	...H15	0.9528	0.0526
C15	...C16	1.3860	0.0063

C15	...C17	2.3998	0.0066
C15	...H17	3.2387	0.0567
C15	...C18	2.7786	0.0059
C15	...C19	2.4358	0.0058
C15	...H19	3.3519	0.0488
C15	...O20	2.4300	0.0053
C15	...C21	2.7927	0.0069
C15	...H211	2.7311	0.0576
C15	...H212	2.7037	0.0575
H15	...C16	2.0556	0.0545
H15	...C17	3.2698	0.0536
H15	...C19	3.2843	0.0501
H15	...O20	2.6768	0.0539
H15	...C21	2.5249	0.0519
H15	...H211	2.3273	0.0833
H15	...H212	2.2600	0.0769
C16	...C17	1.3808	0.0063
C16	...H17	2.0198	0.0554
C16	...C18	2.3994	0.0058
C16	...C19	2.7970	0.0059
C16	...O20	1.3624	0.0050
C16	...C21	2.3708	0.0067
C16	...H211	2.6301	0.0525
C16	...H212	2.6151	0.0602
C16	...H213	3.1683	0.0574
C17	...H17	0.9225	0.0577
C17	...C18	1.3863	0.0063
C17	...C19	2.4163	0.0065
C17	...H19	3.3124	0.0521
C17	...O20	2.3188	0.0054
C17	...O22	2.3328	0.0054
H17	...C18	1.9982	0.0567
H17	...C19	3.2362	0.0575
H17	...O20	2.4837	0.0529
H17	...O22	2.4507	0.0538
C18	...C19	1.3907	0.0062
C18	...H19	2.0725	0.0524
C18	...O22	1.3774	0.0049
C18	...C23	2.4077	0.0066
C18	...H231	3.1640	0.0593
C18	...H232	2.7166	0.0636
C18	...H233	2.6590	0.0575
C19	...H19	1.0005	0.0505
C19	...O22	2.4430	0.0052
C19	...C23	2.8388	0.0067
C19	...H232	2.7980	0.0635
C19	...H233	2.8221	0.0543
H19	...O22	2.6620	0.0510
H19	...C23	2.5176	0.0484
H19	...H231	3.4922	0.0801
H19	...H232	2.2991	0.0870
H19	...H233	2.3648	0.0704
O20	...C21	1.4150	0.0062
O20	...H211	2.0189	0.0523
O20	...H212	2.0114	0.0661
O20	...H213	1.9370	0.0557
C21	...H211	1.0305	0.0668
C21	...H212	1.0752	0.0781
C21	...H213	1.0010	0.0607
H211	...H212	1.7226	0.1097
H211	...H213	1.7042	0.0898
H212	...H213	1.7028	0.0951
O22	...C23	1.4195	0.0063
O22	...H231	1.9064	0.0579
O22	...H232	2.0819	0.0650
O22	...H233	1.9606	0.0653
C23	...H231	0.9793	0.0656
C23	...H232	1.0946	0.0700

C23	...H233	0.9744	0.0822
H231	...H232	1.6740	0.0802
H231	...H233	1.6354	0.1098
H232	...H233	1.7159	0.1128
C24	...H241	0.9890	0.0708
C24	...H242	0.9535	0.0590
C24	...H243	0.9965	0.0588
H241	...H242	1.5164	0.0987
H241	...H243	1.6861	0.0917
H242	...H243	1.6702	0.0729

Number of contacts: 308

Equivalent positions:
X,Y,Z
plus the centrosymmetric ones

Maximum translation by 2 unit cell

Intermolecular contacts less than 3.50 Angstrom

			Distance	e.s.d.
CL1	...H1	+X,+Y-1,+Z	3.0094	0.0500
CL1	...H21	+X,+Y-1,+Z	3.1709	0.0704
CL1	...H3	-X-1,-Y+1,-Z+1	2.7744	0.0540
CL1	...H71	+X,+Y-1,+Z	2.9834	0.0550
CL1	...H82	+X+1,+Y,+Z	2.8610	0.0534
CL1	...H19	+X-1,+Y-1,+Z	3.3014	0.0547
CL1	...H232	+X-1,+Y-1,+Z	3.1334	0.0609
CL1	...H241	+X+1,+Y,+Z	2.8499	0.0642
CL1	...H243	-X-1,-Y+1,-Z+1	2.8282	0.0529
C1	...H232	+X-1,+Y,+Z	3.4996	0.0655
H1	...CL1	+X,+Y+1,+Z	3.0094	0.0500
H1	...C19	+X-1,+Y,+Z	3.1309	0.0585
H1	...H19	+X-1,+Y,+Z	2.8249	0.0912
H1	...H232	+X-1,+Y,+Z	2.9213	0.0745
H21	...CL1	+X,+Y+1,+Z	3.1709	0.0704
H21	...H3	-X-1,-Y+2,-Z+1	3.2555	0.0814
H21	...C7	-X-1,-Y+2,-Z+1	3.4151	0.0515
H21	...H71	-X-1,-Y+2,-Z+1	3.2729	0.0752
H21	...H72	-X-1,-Y+2,-Z+1	2.9258	0.0774
H21	...H241	+X+1,+Y+1,+Z	3.4792	0.0693
H21	...H242	+X+1,+Y+1,+Z	3.2577	0.0660
H22	...H72	+X+1,+Y,+Z	3.3286	0.0981
H22	...C8	+X+1,+Y,+Z	3.4887	0.0603
H22	...H82	+X+1,+Y,+Z	2.8259	0.0965
H22	...H243	-X-1,-Y+1,-Z+1	2.9441	0.0920
H3	...CL1	-X-1,-Y+1,-Z+1	2.7744	0.0540
H3	...H21	-X-1,-Y+2,-Z+1	3.2555	0.0814
H3	...H4	-X-1,-Y+1,-Z+1	3.4867	0.0879
H3	...H71	-X-1,-Y+2,-Z+1	2.8760	0.0718
H3	...H243	-X-1,-Y+1,-Z+1	3.2510	0.0952
H4	...H3	-X-1,-Y+1,-Z+1	3.4867	0.0879
H4	...N12	+X-1,+Y-1,+Z	3.4813	0.0439
H4	...H243	-X-1,-Y+1,-Z+1	3.2702	0.0835
C5	...N12	+X-1,+Y-1,+Z	3.3387	0.0056
C5	...H231	+X-2,+Y-1,+Z	3.3902	0.0636
H5	...N12	+X-1,+Y-1,+Z	2.4165	0.0568
H5	...O13	+X-1,+Y-1,+Z	2.7493	0.0494
H5	...C23	+X-2,+Y-1,+Z	3.1881	0.0558
H5	...H231	+X-2,+Y-1,+Z	2.7337	0.0879
H5	...H232	+X-2,+Y-1,+Z	2.7583	0.0815
C6	...H213	-X,-Y+1,-Z+2	3.1745	0.0618
H61	...C14	+X-1,+Y,+Z	3.4100	0.0679
H61	...C19	+X-1,+Y,+Z	3.4412	0.0623
H61	...C21	-X,-Y+1,-Z+2	3.4542	0.0515
H61	...H213	-X,-Y+1,-Z+2	2.5007	0.0792
H61	...H231	+X-2,+Y-1,+Z	3.1727	0.0761
H62	...H19	+X-1,+Y-1,+Z	2.8997	0.0790

H62	...H213	-X,-Y+1,-Z+2	3.0375	0.0848
H62	...H233	+X-1,+Y-1,+Z	2.8261	0.0886
C7	...H21	-X-1,-Y+2,-Z+1	3.4151	0.0515
H71	...CL1	+X,+Y+1,+Z	2.9834	0.0550
H71	...H21	-X-1,-Y+2,-Z+1	3.2729	0.0752
H71	...H3	-X-1,-Y+2,-Z+1	2.8760	0.0718
H71	...H242	+X,+Y+1,+Z	3.2362	0.1055
H72	...H21	-X-1,-Y+2,-Z+1	2.9258	0.0774
H72	...H22	+X-1,+Y,+Z	3.3286	0.0981
H72	...C24	-X-2,-Y+1,-Z+1	3.3042	0.0564
H72	...H241	-X-2,-Y+1,-Z+1	3.1142	0.0785
H72	...H242	-X-2,-Y+1,-Z+1	3.3737	0.0763
H72	...H243	-X-2,-Y+1,-Z+1	3.0414	0.0713
C8	...H22	+X-1,+Y,+Z	3.4887	0.0603
H81	...C9	+X-1,+Y,+Z	3.2766	0.0729
H81	...N10	+X-1,+Y,+Z	2.9815	0.0733
H81	...C11	+X-1,+Y,+Z	2.6032	0.0747
H81	...N12	+X-1,+Y,+Z	2.8023	0.0727
H81	...O13	+X-1,+Y,+Z	3.2153	0.0731
H81	...C14	+X-1,+Y,+Z	3.0461	0.0659
H81	...C19	+X-1,+Y,+Z	3.4659	0.0583
H81	...H19	+X-1,+Y,+Z	3.4823	0.0764
H82	...CL1	+X-1,+Y,+Z	2.8610	0.0534
H82	...H22	+X-1,+Y,+Z	2.8259	0.0965
H82	...H232	+X-2,+Y-1,+Z	3.2737	0.0789
C9	...H81	+X+1,+Y,+Z	3.2766	0.0729
C9	...H232	+X-1,+Y,+Z	2.8964	0.0758
N10	...H81	+X+1,+Y,+Z	2.9815	0.0733
N10	...H213	-X,-Y+1,-Z+2	3.1519	0.0588
N10	...H232	+X-1,+Y,+Z	3.3209	0.0751
N10	...H233	+X-1,+Y-1,+Z	3.1499	0.0678
C11	...H81	+X+1,+Y,+Z	2.6032	0.0747
C11	...H232	+X-1,+Y,+Z	3.3374	0.0790
N12	...H4	+X+1,+Y+1,+Z	3.4813	0.0439
N12	...C5	+X+1,+Y+1,+Z	3.3387	0.0056
N12	...H5	+X+1,+Y+1,+Z	2.4165	0.0568
N12	...H81	+X+1,+Y,+Z	2.8023	0.0727
N12	...H231	+X-1,+Y,+Z	3.3688	0.0796
N12	...H232	+X-1,+Y,+Z	3.0146	0.0814
N12	...H242	+X+1,+Y+1,+Z	2.8399	0.0523
O13	...H5	+X+1,+Y+1,+Z	2.7493	0.0494
O13	...H81	+X+1,+Y,+Z	3.2153	0.0731
O13	...H232	+X-1,+Y,+Z	2.6726	0.0815
O13	...C24	+X+1,+Y+1,+Z	3.2532	0.0052
O13	...H241	+X+1,+Y+1,+Z	3.1526	0.0506
O13	...H242	+X+1,+Y+1,+Z	2.4805	0.0514
C14	...H61	+X+1,+Y,+Z	3.4100	0.0679
C14	...H81	+X+1,+Y,+Z	3.0461	0.0659
H15	...H17	-X+1,-Y+2,-Z+2	3.4860	0.0975
H15	...C21	-X,-Y+1,-Z+2	3.2749	0.0541
H15	...H211	-X,-Y+1,-Z+2	3.2136	0.0874
H15	...H212	-X,-Y+1,-Z+2	2.9959	0.0707
H15	...H213	-X,-Y+1,-Z+2	3.1516	0.0794
H15	...H231	+X-1,+Y-1,+Z	3.3091	0.0974
H15	...H233	+X-1,+Y-1,+Z	3.0879	0.0816
C16	...H211	-X+1,-Y+1,-Z+2	3.1876	0.0755
C16	...H213	-X+1,-Y+1,-Z+2	3.3574	0.0810
C17	...H17	-X+2,-Y+2,-Z+2	3.3336	0.0562
C17	...H211	-X+1,-Y+1,-Z+2	3.0379	0.0721
C17	...H212	-X+1,-Y+2,-Z+2	3.4175	0.0655
C17	...H213	-X+1,-Y+1,-Z+2	3.2627	0.0767
C17	...O22	-X+2,-Y+2,-Z+2	3.4666	0.0059
H17	...H15	-X+1,-Y+2,-Z+2	3.4860	0.0975
H17	...C17	-X+2,-Y+2,-Z+2	3.3336	0.0562
H17	...H17	-X+2,-Y+2,-Z+2	2.6497	0.0782
H17	...C18	-X+2,-Y+2,-Z+2	3.4287	0.0578
H17	...C21	-X+1,-Y+1,-Z+2	3.4416	0.0660
H17	...H211	-X+1,-Y+1,-Z+2	2.7213	0.0964

H17	...H213	-X+1,-Y+1,-Z+2	3.3524	0.0991
H17	...O22	-X+2,-Y+2,-Z+2	2.5516	0.0584
H17	...H231	-X+2,-Y+2,-Z+2	3.2582	0.0805
C18	...H17	-X+2,-Y+2,-Z+2	3.4287	0.0578
C18	...H212	-X+1,-Y+2,-Z+2	2.8526	0.0696
C19	...H1	+X+1,+Y,+Z	3.1309	0.0585
C19	...H61	+X+1,+Y,+Z	3.4412	0.0623
C19	...H81	+X+1,+Y,+Z	3.4659	0.0583
C19	...H212	-X+1,-Y+2,-Z+2	3.3555	0.0610
H19	...CL1	+X+1,+Y+1,+Z	3.3014	0.0547
H19	...H1	+X+1,+Y,+Z	2.8249	0.0912
H19	...H62	+X+1,+Y+1,+Z	2.8997	0.0790
H19	...H81	+X+1,+Y,+Z	3.4823	0.0764
O20	...O20	-X+1,-Y+1,-Z+2	3.2122	0.0060
O20	...C21	-X+1,-Y+1,-Z+2	3.4034	0.0090
O20	...H211	-X+1,-Y+1,-Z+2	2.9032	0.0782
O20	...H231	-X+2,-Y+2,-Z+2	3.2509	0.0635
C21	...H61	-X,-Y+1,-Z+2	3.4542	0.0515
C21	...H15	-X,-Y+1,-Z+2	3.2749	0.0541
C21	...H17	-X+1,-Y+1,-Z+2	3.4416	0.0660
C21	...O20	-X+1,-Y+1,-Z+2	3.4034	0.0090
C21	...H211	-X,-Y+1,-Z+2	3.4485	0.0667
C21	...H212	-X,-Y+1,-Z+2	3.1840	0.0544
C21	...H233	-X+1,-Y+2,-Z+2	3.1377	0.0793
H211	...H15	-X,-Y+1,-Z+2	3.2136	0.0874
H211	...C16	-X+1,-Y+1,-Z+2	3.1876	0.0755
H211	...C17	-X+1,-Y+1,-Z+2	3.0379	0.0721
H211	...H17	-X+1,-Y+1,-Z+2	2.7213	0.0964
H211	...O20	-X+1,-Y+1,-Z+2	2.9032	0.0782
H211	...C21	-X,-Y+1,-Z+2	3.4485	0.0667
H211	...H211	-X,-Y+1,-Z+2	3.4054	0.1044
H211	...H212	-X,-Y+1,-Z+2	2.6400	0.0852
H211	...O22	+X-1,+Y-1,+Z	3.1102	0.0601
H211	...C23	+X-1,+Y-1,+Z	3.3887	0.0628
H211	...H231	+X-1,+Y-1,+Z	3.0511	0.0944
H211	...H233	+X-1,+Y-1,+Z	3.3714	0.0831
H212	...H15	-X,-Y+1,-Z+2	2.9959	0.0707
H212	...C17	-X+1,-Y+2,-Z+2	3.4175	0.0655
H212	...C18	-X+1,-Y+2,-Z+2	2.8526	0.0696
H212	...C19	-X+1,-Y+2,-Z+2	3.3555	0.0610
H212	...C21	-X,-Y+1,-Z+2	3.1840	0.0544
H212	...H211	-X,-Y+1,-Z+2	2.6400	0.0852
H212	...H212	-X,-Y+1,-Z+2	2.8769	0.0738
H212	...O22	-X+1,-Y+2,-Z+2	2.6836	0.0784
H212	...C23	-X+1,-Y+2,-Z+2	3.0322	0.0738
H212	...H231	-X+1,-Y+2,-Z+2	3.4722	0.1086
H212	...H233	-X+1,-Y+2,-Z+2	2.5058	0.0983
H213	...C6	-X,-Y+1,-Z+2	3.1745	0.0618
H213	...H61	-X,-Y+1,-Z+2	2.5007	0.0792
H213	...H62	-X,-Y+1,-Z+2	3.0375	0.0848
H213	...N10	-X,-Y+1,-Z+2	3.1519	0.0588
H213	...H15	-X,-Y+1,-Z+2	3.1516	0.0794
H213	...C16	-X+1,-Y+1,-Z+2	3.3574	0.0810
H213	...C17	-X+1,-Y+1,-Z+2	3.2627	0.0767
H213	...H17	-X+1,-Y+1,-Z+2	3.3524	0.0991
H213	...H233	-X+1,-Y+2,-Z+2	2.8597	0.1159
O22	...C17	-X+2,-Y+2,-Z+2	3.4666	0.0059
O22	...H17	-X+2,-Y+2,-Z+2	2.5516	0.0584
O22	...H211	+X+1,+Y+1,+Z	3.1102	0.0601
O22	...H212	-X+1,-Y+2,-Z+2	2.6836	0.0784
C23	...H5	+X+2,+Y+1,+Z	3.1881	0.0558
C23	...H211	+X+1,+Y+1,+Z	3.3887	0.0628
C23	...H212	-X+1,-Y+2,-Z+2	3.0322	0.0738
H231	...C5	+X+2,+Y+1,+Z	3.3902	0.0636
H231	...H5	+X+2,+Y+1,+Z	2.7337	0.0879
H231	...H61	+X+2,+Y+1,+Z	3.1727	0.0761
H231	...N12	+X+1,+Y,+Z	3.3688	0.0796
H231	...H15	+X+1,+Y+1,+Z	3.3091	0.0974

H231	...H17	-X+2,-Y+2,-Z+2	3.2582	0.0805
H231	...O20	-X+2,-Y+2,-Z+2	3.2509	0.0635
H231	...H211	+X+1,+Y+1,+Z	3.0511	0.0944
H231	...H212	-X+1,-Y+2,-Z+2	3.4722	0.1086
H232	...CL1	+X+1,+Y+1,+Z	3.1334	0.0609
H232	...C1	+X+1,+Y,+Z	3.4996	0.0655
H232	...H1	+X+1,+Y,+Z	2.9213	0.0745
H232	...H5	+X+2,+Y+1,+Z	2.7583	0.0815
H232	...H82	+X+2,+Y+1,+Z	3.2737	0.0789
H232	...C9	+X+1,+Y,+Z	2.8964	0.0758
H232	...N10	+X+1,+Y,+Z	3.3209	0.0751
H232	...C11	+X+1,+Y,+Z	3.3374	0.0790
H232	...N12	+X+1,+Y,+Z	3.0146	0.0814
H232	...O13	+X+1,+Y,+Z	2.6726	0.0815
H233	...H62	+X+1,+Y+1,+Z	2.8261	0.0886
H233	...N10	+X+1,+Y+1,+Z	3.1499	0.0678
H233	...H15	+X+1,+Y+1,+Z	3.0879	0.0816
H233	...C21	-X+1,-Y+2,-Z+2	3.1377	0.0793
H233	...H211	+X+1,+Y+1,+Z	3.3714	0.0831
H233	...H212	-X+1,-Y+2,-Z+2	2.5058	0.0983
H233	...H213	-X+1,-Y+2,-Z+2	2.8597	0.1159
C24	...H72	-X-2,-Y+1,-Z+1	3.3042	0.0564
C24	...O13	+X-1,+Y-1,+Z	3.2532	0.0052
C24	...H241	-X-2,-Y+1,-Z+1	3.4079	0.0553
H241	...CL1	+X-1,+Y,+Z	2.8499	0.0642
H241	...H21	+X-1,+Y-1,+Z	3.4792	0.0693
H241	...H72	-X-2,-Y+1,-Z+1	3.1142	0.0785
H241	...O13	+X-1,+Y-1,+Z	3.1526	0.0506
H241	...C24	-X-2,-Y+1,-Z+1	3.4079	0.0553
H241	...H241	-X-2,-Y+1,-Z+1	3.0865	0.0722
H241	...H243	-X-2,-Y+1,-Z+1	2.9238	0.0824
H242	...H21	+X-1,+Y-1,+Z	3.2577	0.0660
H242	...H71	+X,+Y-1,+Z	3.2362	0.1055
H242	...H72	-X-2,-Y+1,-Z+1	3.3737	0.0763
H242	...N12	+X-1,+Y-1,+Z	2.8399	0.0523
H242	...O13	+X-1,+Y-1,+Z	2.4805	0.0514
H243	...CL1	-X-1,-Y+1,-Z+1	2.8282	0.0529
H243	...H22	-X-1,-Y+1,-Z+1	2.9441	0.0920
H243	...H3	-X-1,-Y+1,-Z+1	3.2510	0.0952
H243	...H4	-X-1,-Y+1,-Z+1	3.2702	0.0835
H243	...H72	-X-2,-Y+1,-Z+1	3.0414	0.0713
H243	...H241	-X-2,-Y+1,-Z+1	2.9238	0.0824

Number of contacts: 225

Possible hydrogen bonds

Donor-H	Donor...Acceptor	H...Acceptor	Donor-H.....Acceptor
C2 -H21	C2 ....O13 (0)	H21 ...O13 (0)	C2 -H21 ...O13 (0)
0.960(.054)	2.795(.005)	2.582(.048)	92.63(3.72)
1.080		2.579	89.98 (**)
N4 -H4	N4 ....CL1 (0)	H4 ...CL1 (0)	N4 -H4 ...CL1 (0)
1.015(.062)	3.053(.004)	2.049(.064)	169.42(4.11)
1.030		2.034	169.34 (**)
C5 -H5	C5 ....N12 (1)	H5 ...N12 (1)	C5 -H5 ...N12 (1)
1.018(.047)	3.339(.006)	2.417(.057)	150.30(4.41)
1.080		2.363	149.55 (**)
C24 -H242	C24 ....O13 (1)	H242...O13 (1)	C24 -H242...O13 (1)
0.954(.059)	3.253(.005)	2.480(.051)	138.12(4.75)
1.080		2.388	136.09 (**)
C17 -H17	C17 ....O22 (2)	H17 ...O22 (2)	C17 -H17 ...O22 (2)
0.923(.058)	3.467(.006)	2.552(.058)	171.50(4.89)
1.080		2.396	170.95 (**)

Number of possible hydrogen bonds 5

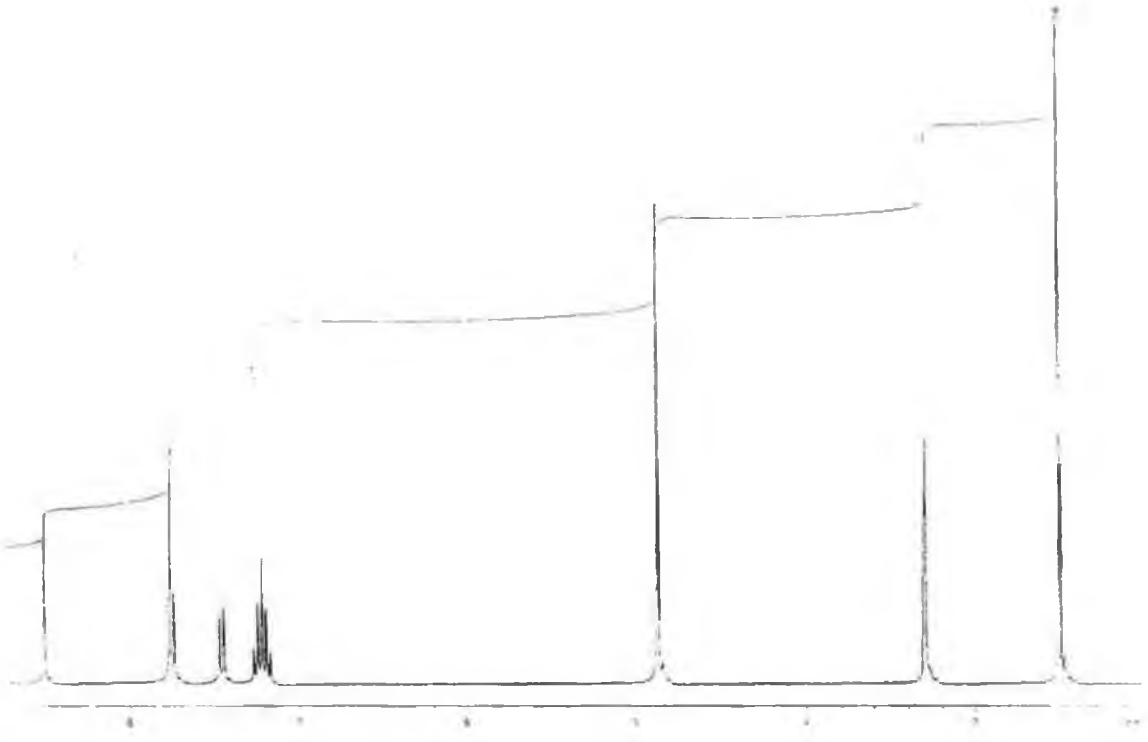
(**) Values normalized following G.A.Jeffrey & L.Lewis, Carbohydr.Res. (1978).60,179; R.Taylor, O.Kennard, Acta Cryst.(1983).B39,133.

Equivalent positions:
(0) X,Y,Z
(1) +X-1,+Y-1,+Z
(2) -X+2,-Y+2,-Z+2

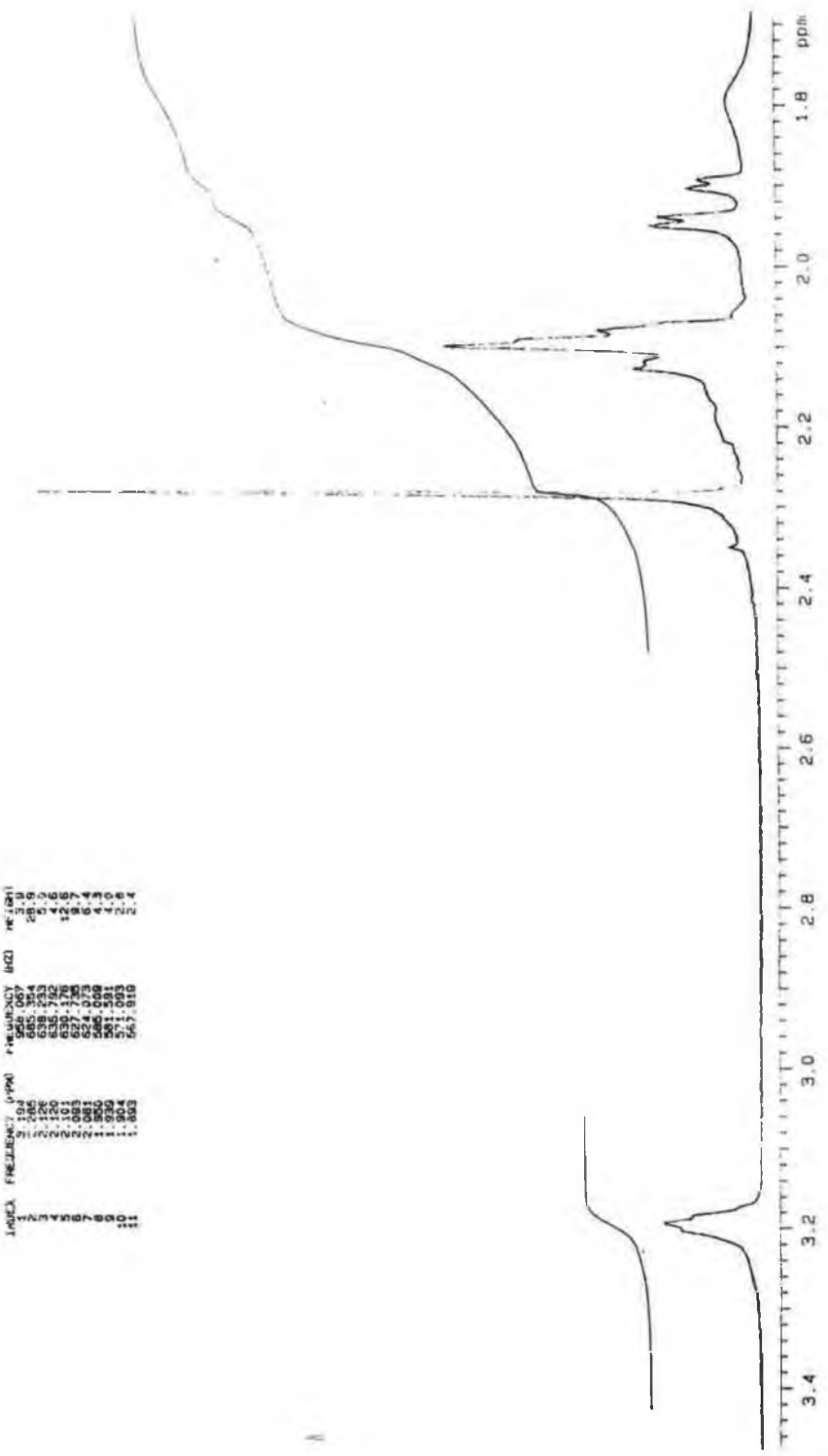
Reference for the program:
Parst: a system of computer routines for calculating molecular parameters from results of crystal structure analyses
Computer and Chemistry (1983) 7, 95-98

Appendix III

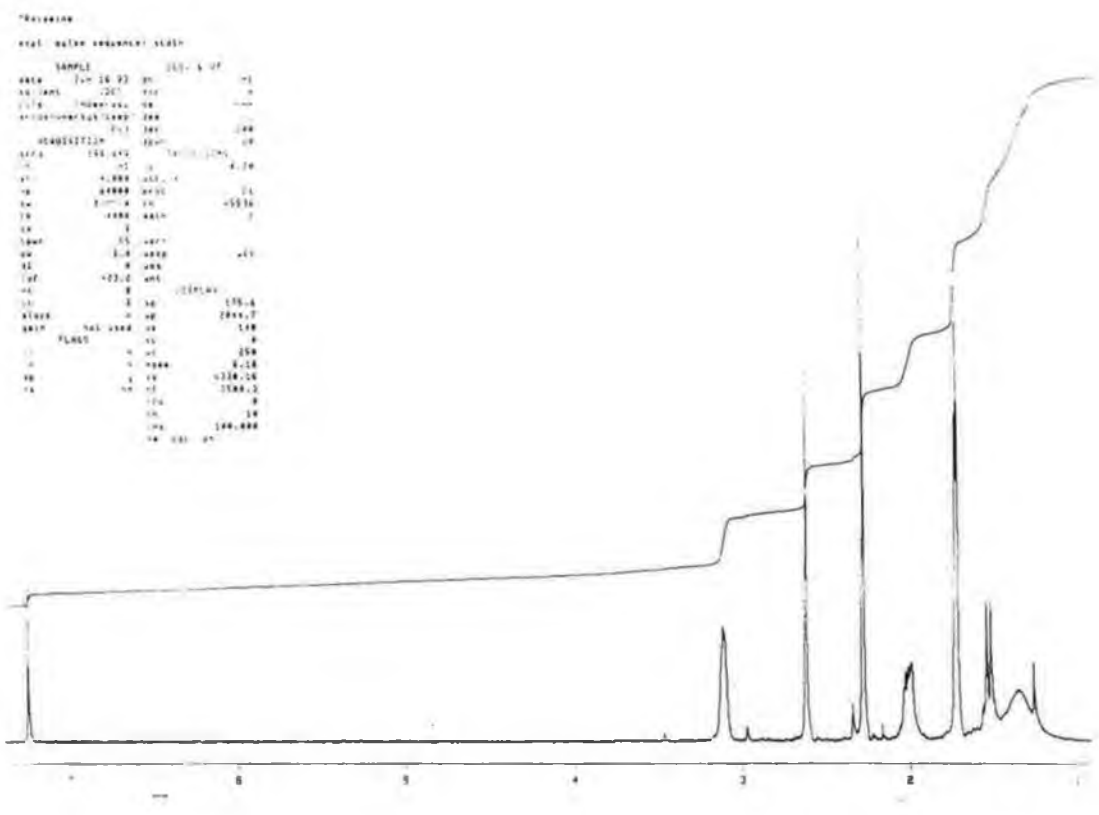
^1H NMR Spectra



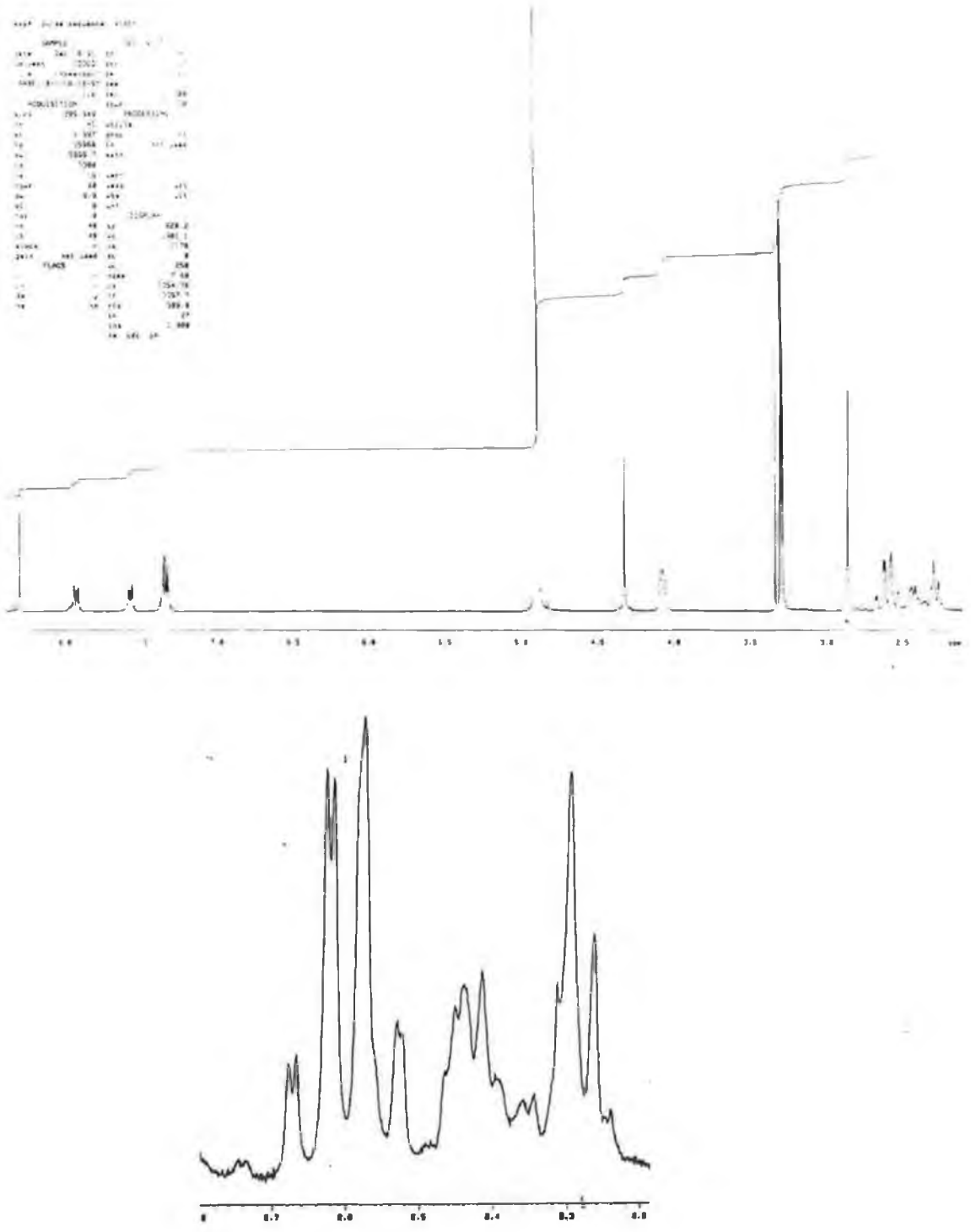
Spectrum 1 ^{1}H NMR of the impurity isolated from the synthesis of 1*H*-indole-3-carbonitrile (**126a**, CD_3OD, 300 MHz).



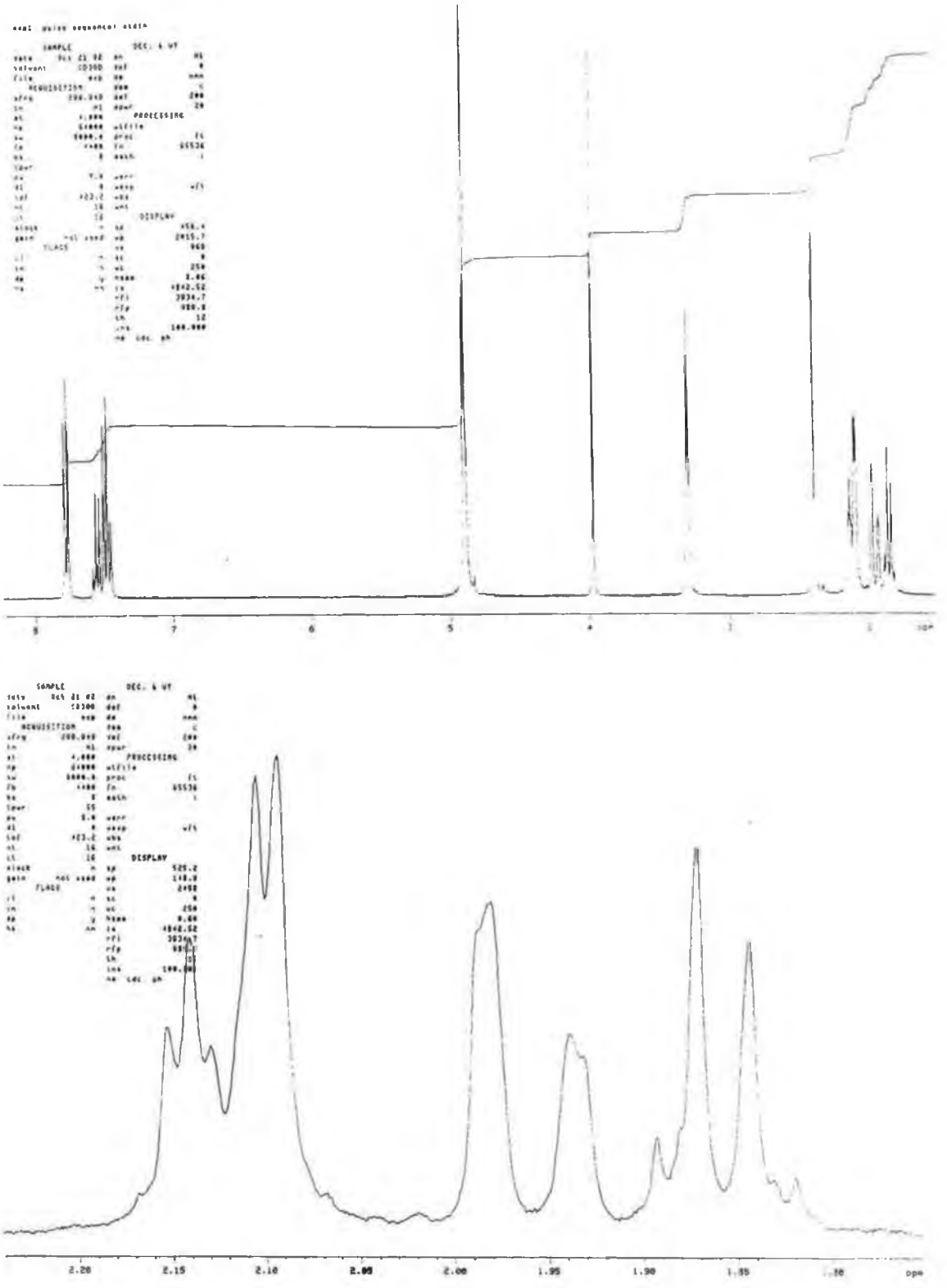
Spectrum 2 ^{1}H NMR of β-Amino-8-methyl-8-azabicyclo[3.2.1]octane-3α-carbonitrile (**124**, $CDCl_3$, 300 MHz).



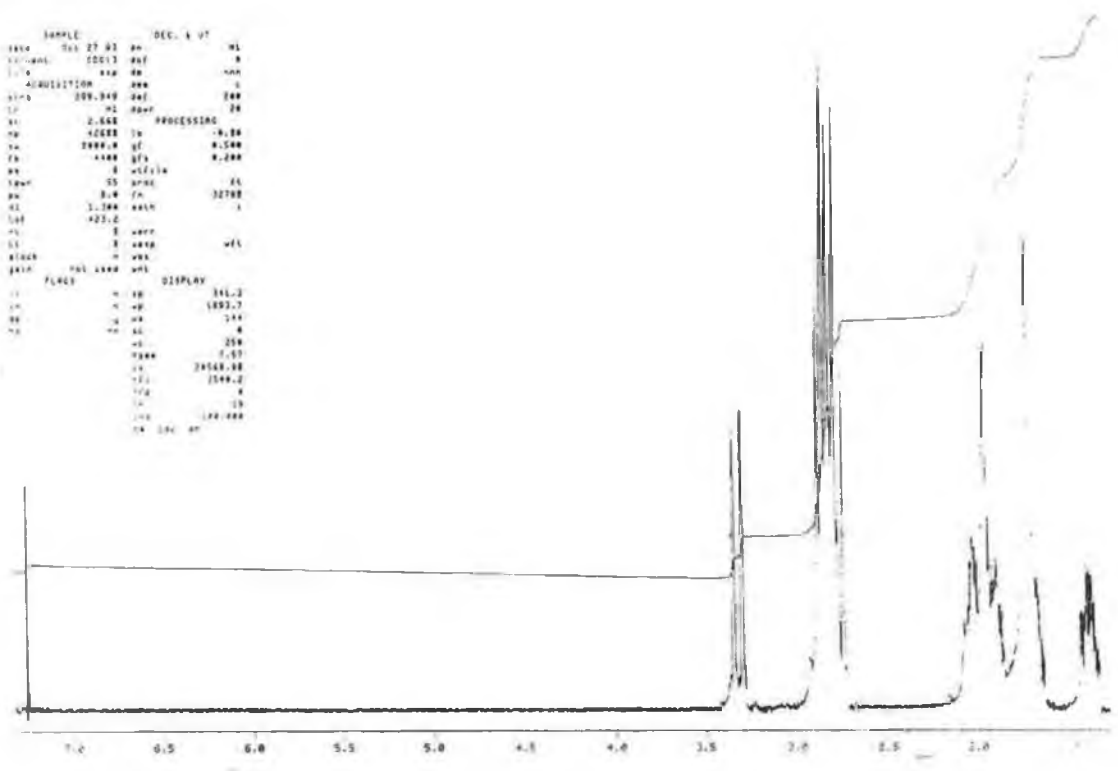
Spectrum 3 ^{1}H NMR of 3α-Aminomethyl-8-methyl-8-azabicyclo[3.2.1]-octane-3β-amine (**122**, $CDCl_3$, 300 MHz)



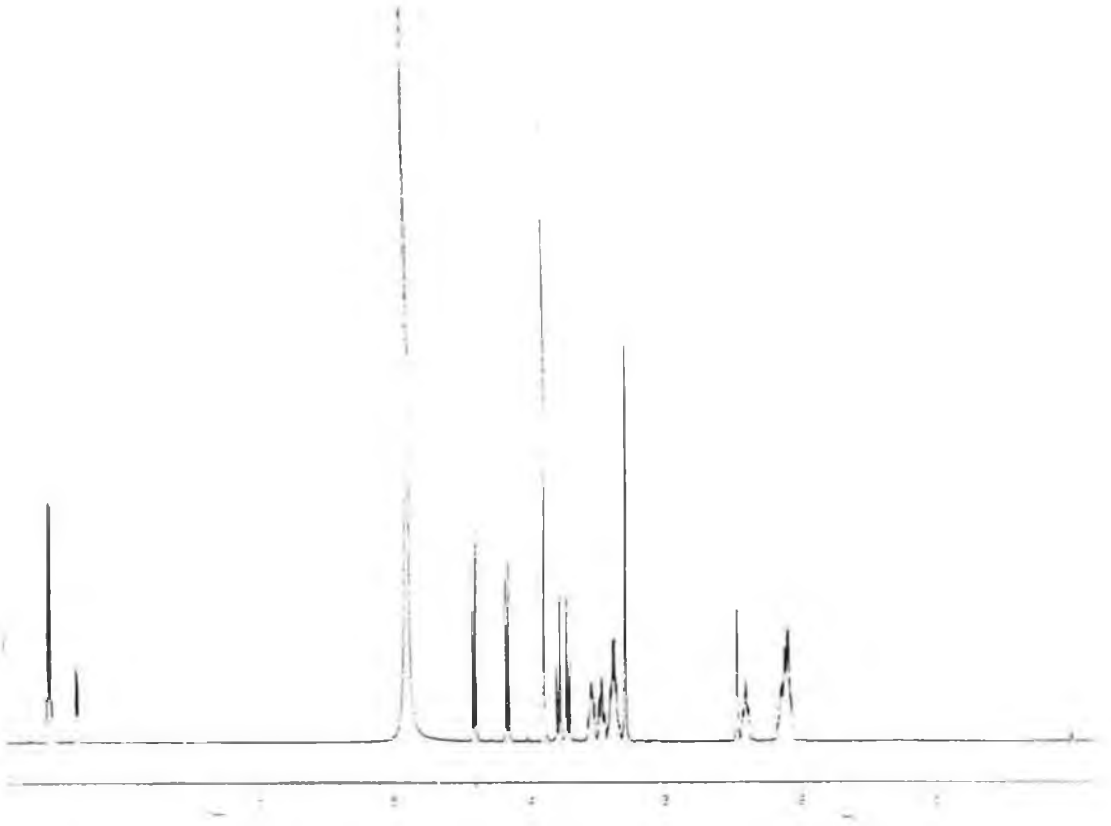
Spectrum 4 ^{1}H NMR of 2'(1*H*-indol-3-yl)-8-methyl-8-azabicyclo[3.2.1]octane-3-spiro-4'(5)-imidazoline dihydrochloride (above) and the expansion of section δ = 2.2-2.8 ppm. (**Ig**, CD_3OD, 300 MHz).



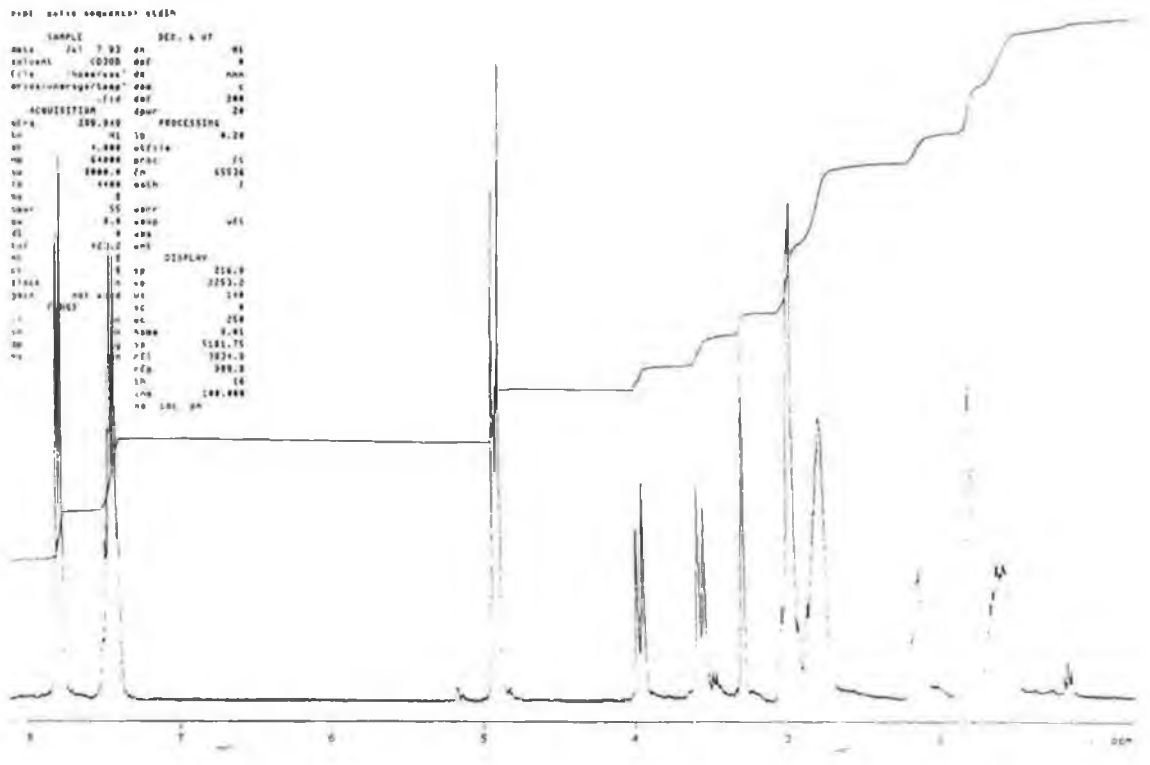
Spectrum 5 ^{1}H NMR of 2'-Phenyl-8-methyl-8-azabicyclo[3.2.1]octane-3-spiro-4'(5)-imidazoline (above) and the expansion of section δ = 1.80 - 2.20 ppm (**Ia**, CD_3OD, 300 MHz).



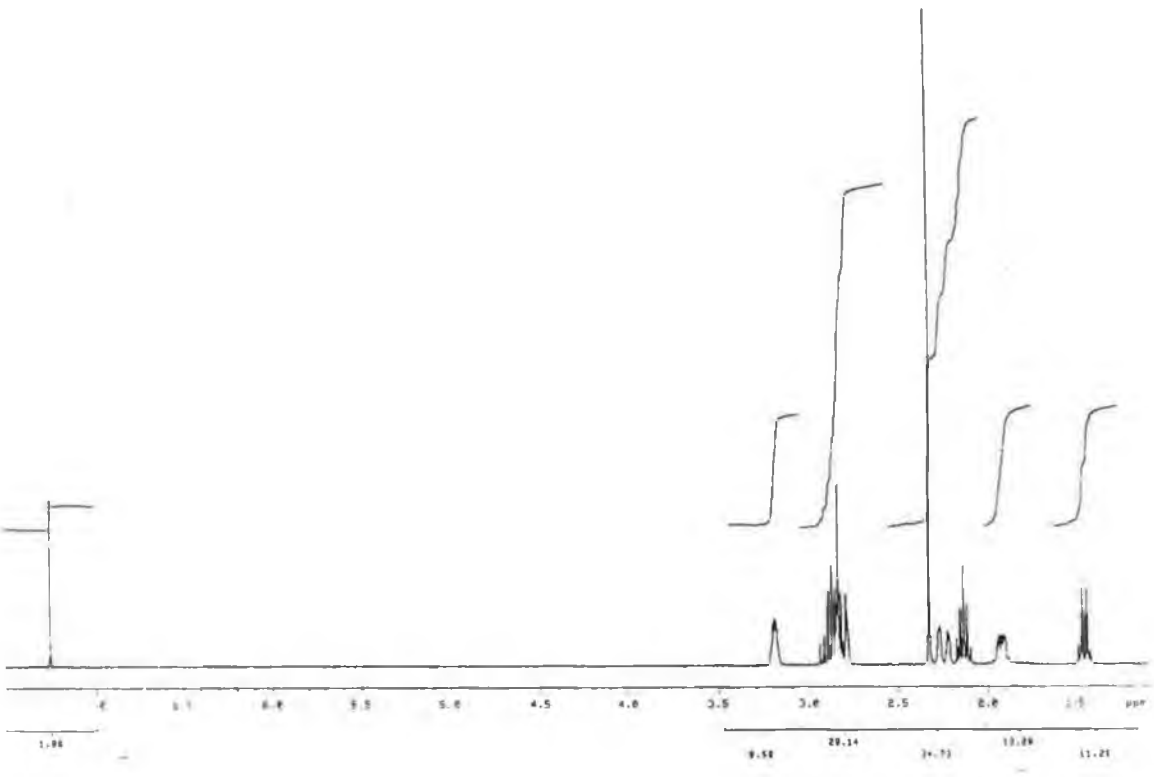
Spectrum 6 ^{1}H NMR of 3-amino-1-azabicyclo[2.2.2]octane-3-carbonitrile (**158** $CDCl_3$, 300 MHz).



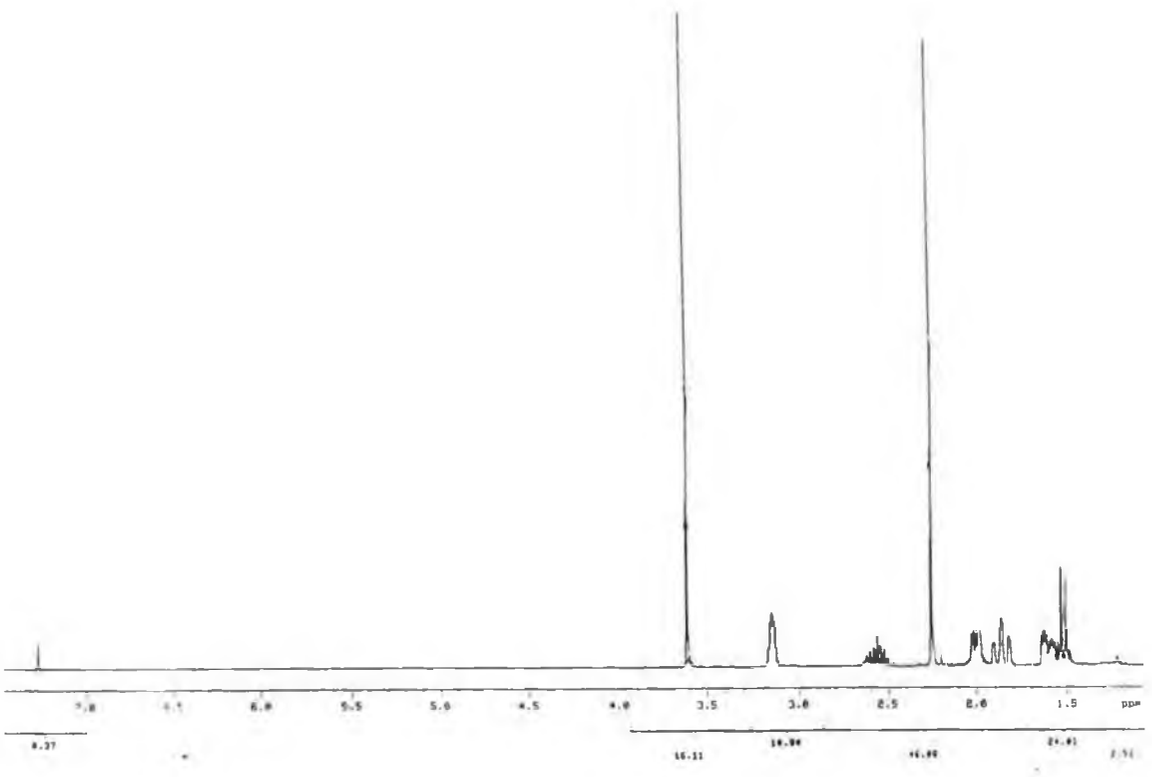
Spectrum 7 ^{1}H NMR of 2'(3-methoxyphenyl)-1-azabicyclo[2.2.2]octane-3-spiro-4'(5')-imidazoline dihydrochloride (**IIb**, CD_3OD, 600 MHz).



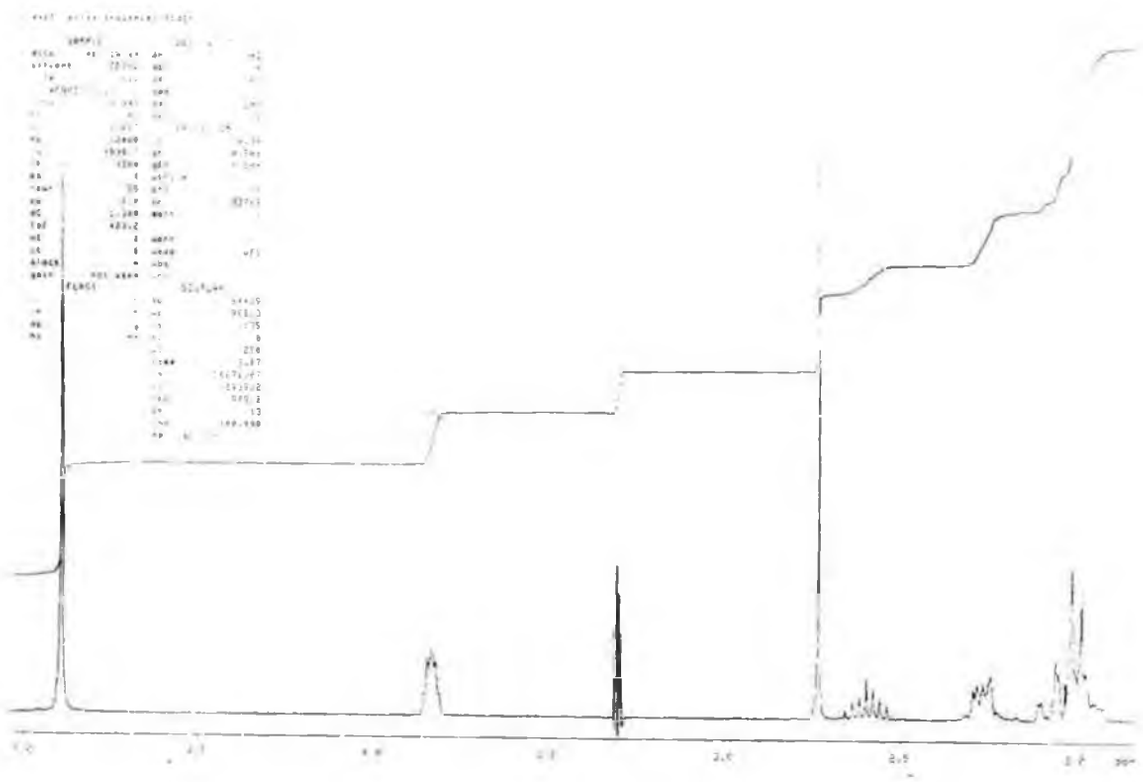
Spectrum 8 ^{1}H NMR of 2'-Phenyl-1-azabicyclo[2.2.2]octane-3-spiro-4'(5')-imidazoline (**IIa**, CD_3OD, 300 MHz).



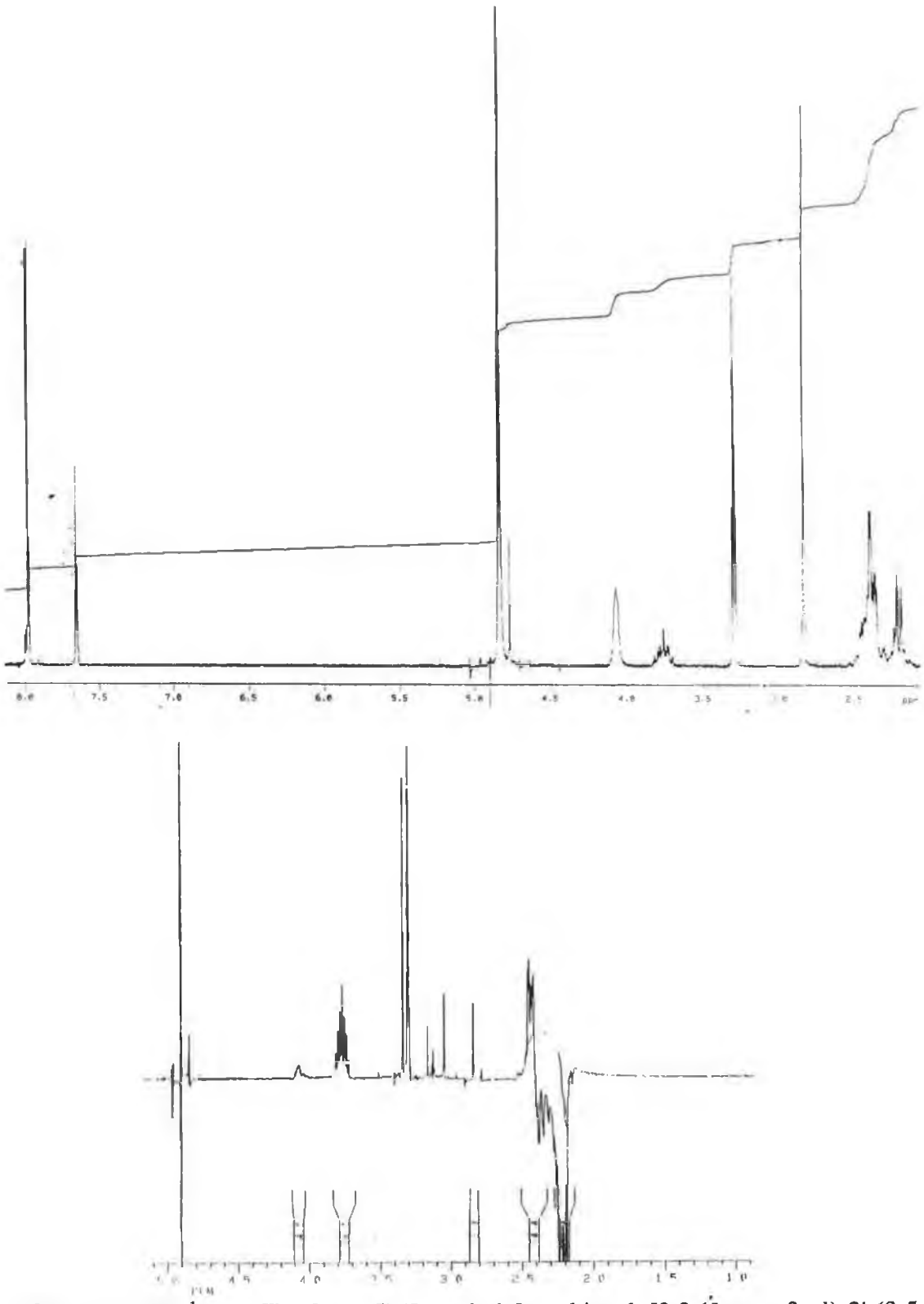
Spectrum 9 ^{1}H NMR of 3-(1,3-dithiane-2-ylidene)-8-methyl-8-azabicyclo[3.2.1]-octane (**170**, $CDCl_3$, 300 MHz).



Spectrum 10 ^{1}H NMR of exo-3-carbomethoxy-8-methyl-8-azabicyclo[3.2.1]octane (**163**, $CDCl_3$, 300 MHz).



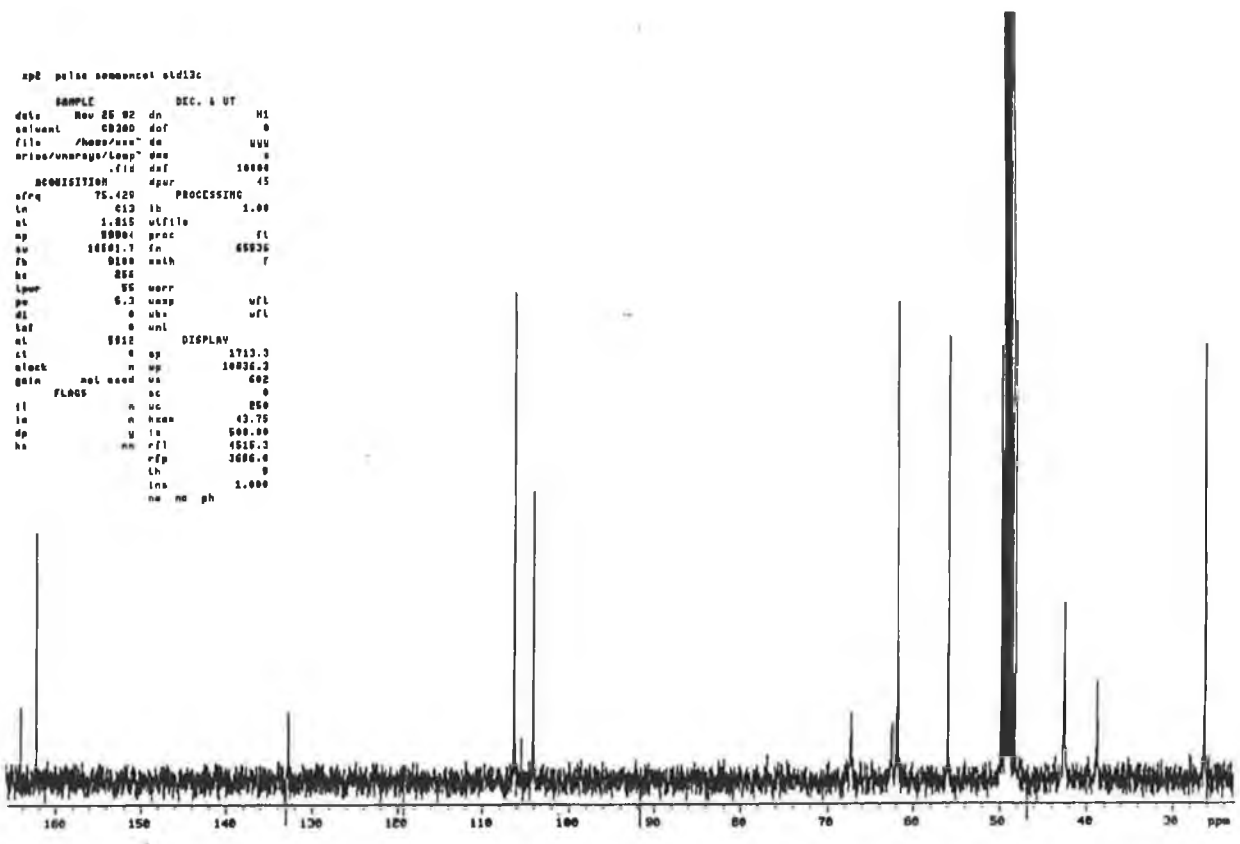
Spectrum 11 ^{1}H NMR of tropane-3β-carboxylic acid zwitterion (**184**, CD_3OD, 300 MHz).



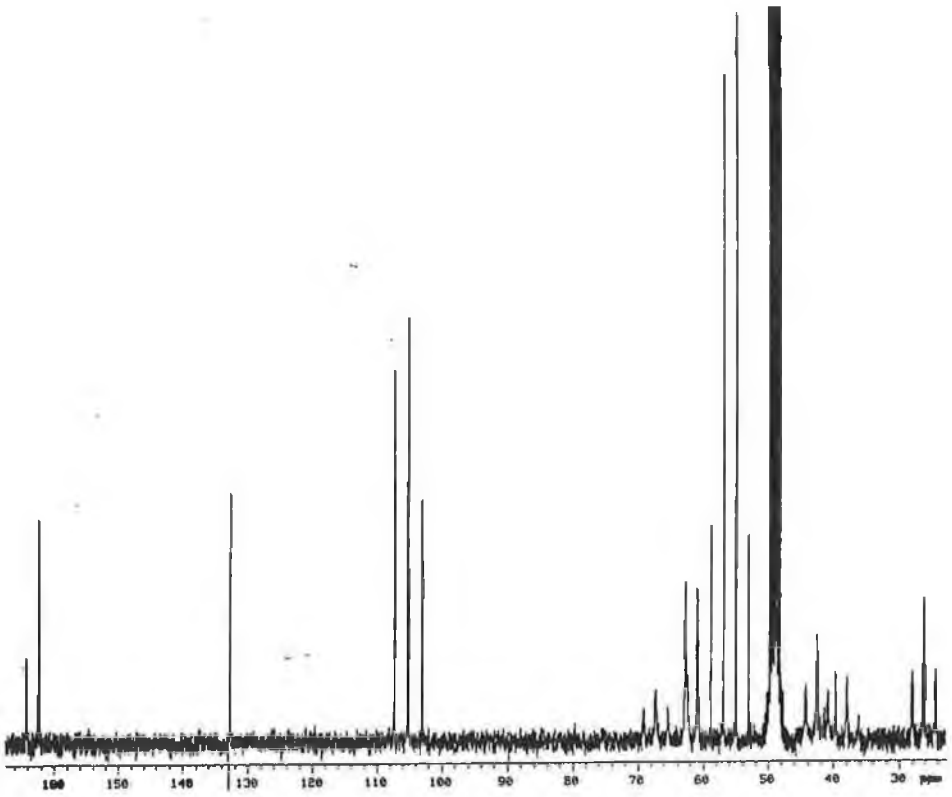
Spectrum 12 ^{1}H NMR of exo-5'-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-3'-(3,5-dichlorophenyl)-1,2,4-oxadiazole hydrochloride and the corresponding NOE spectrum (**IIId**, CD_3OD, 300 MHz).

Appendix IV

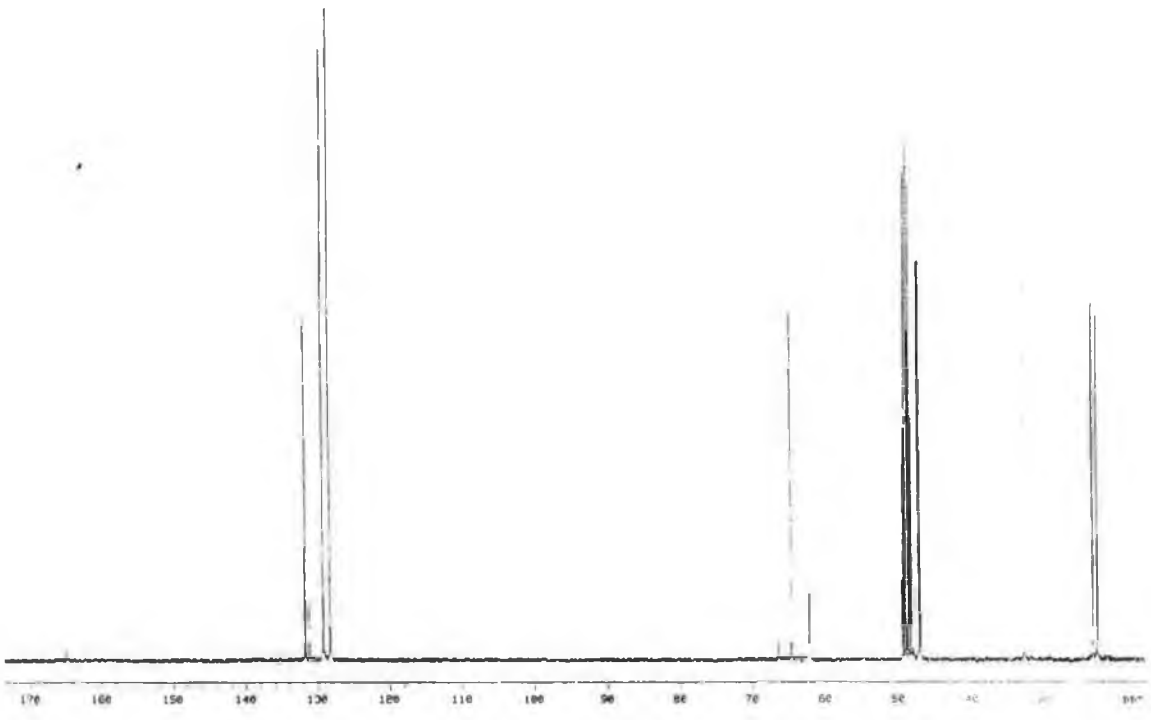
^{13}C NMR Spectra.



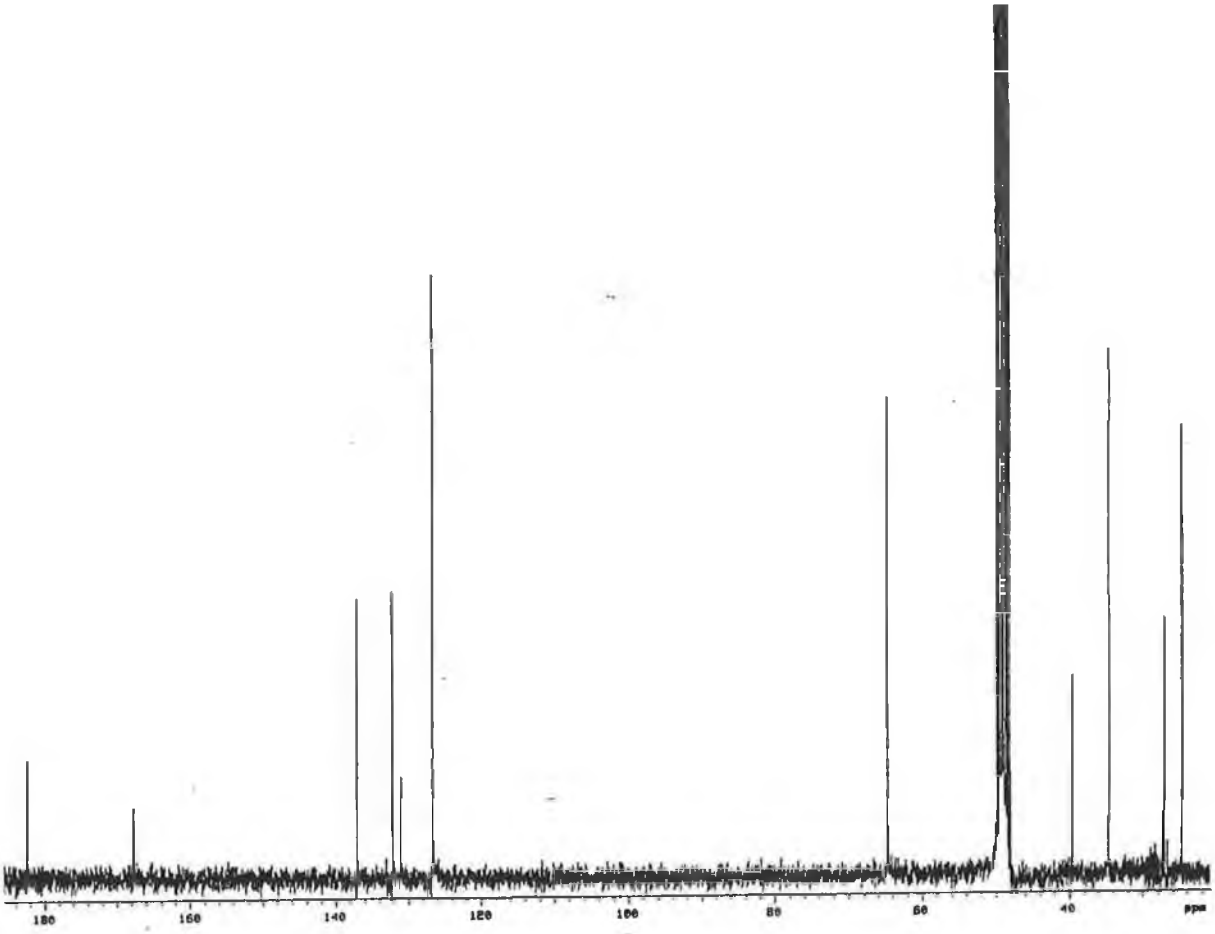
Spectrum 13 ^{13}C NMR of 2'-(3,5-dimethoxyphenyl)-8-methyl-8-azabicyclo[3.2.1]-octane-3-spiro-4'(5)-imidazoline (**Ic**, CD_3OD, 75.4 MHz)



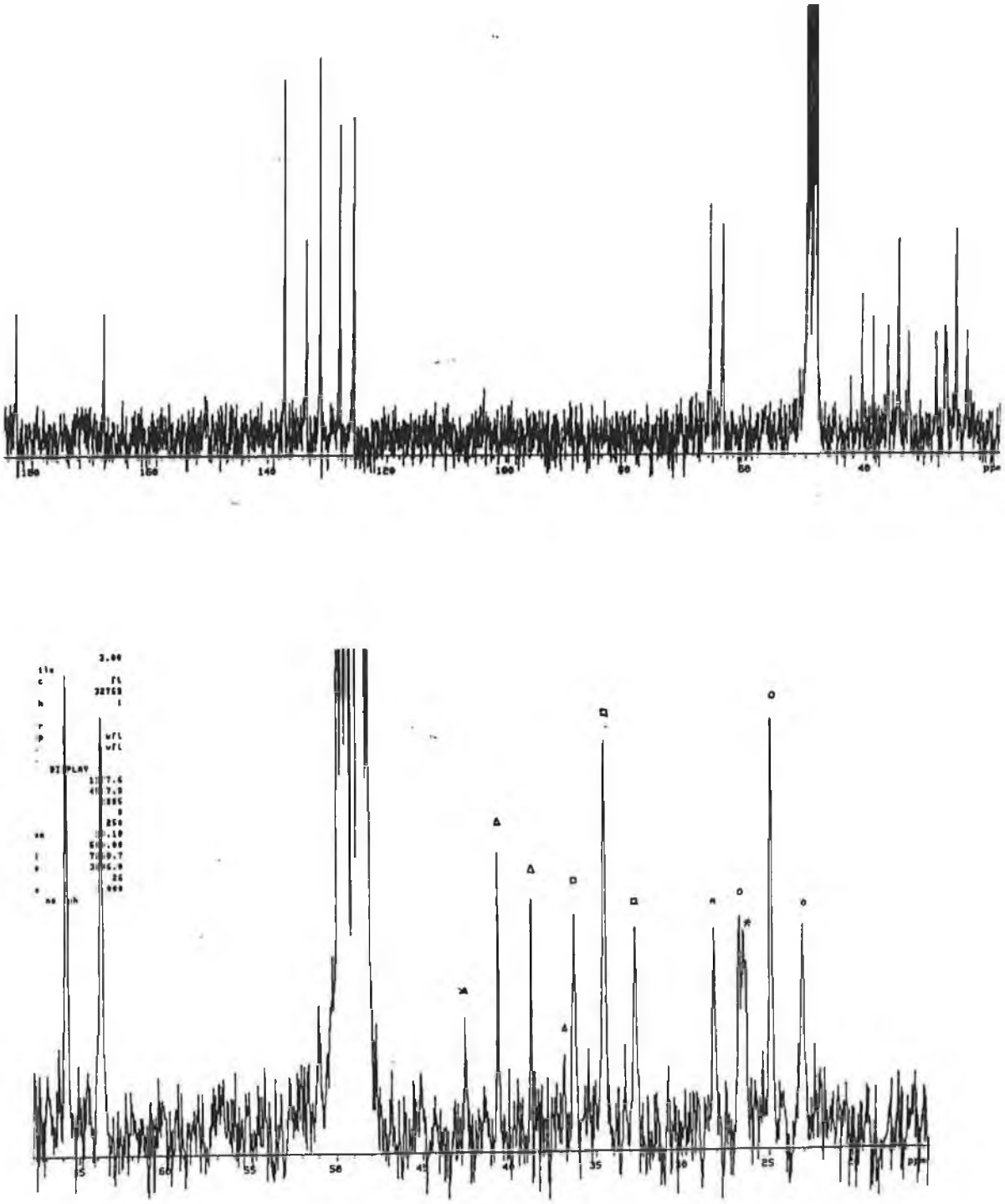
Spectrum 14 ^{13}C - ^{1}H coupled NMR spectrum of 2'-(3,5-dimethoxyphenyl)-8-methyl-8-azabicyclo[3.2.1]-octane-3-spiro-4'(5)-imidazoline (**Ic**, CD_3OD, 75.4 MHz)



Spectrum 15 ^{13}C NMR of 2'-Phenyl-1-azabicyclo[2.2.2]octane-3-spiro-4'(5')-imidazoline (**IIa**, CD_3OD, 75.4 MHz)



Spectrum 16 ^{13}C NMR of exo-5´-(8-Methyl-8-Azabicyclo-[3.2.1]-octan-3-yl)-3'-(3,5-dichlorophenyl)-1,2,4-oxadiazole hydrochloride (**IIId**, CD_3OD, 75.4 MHz)

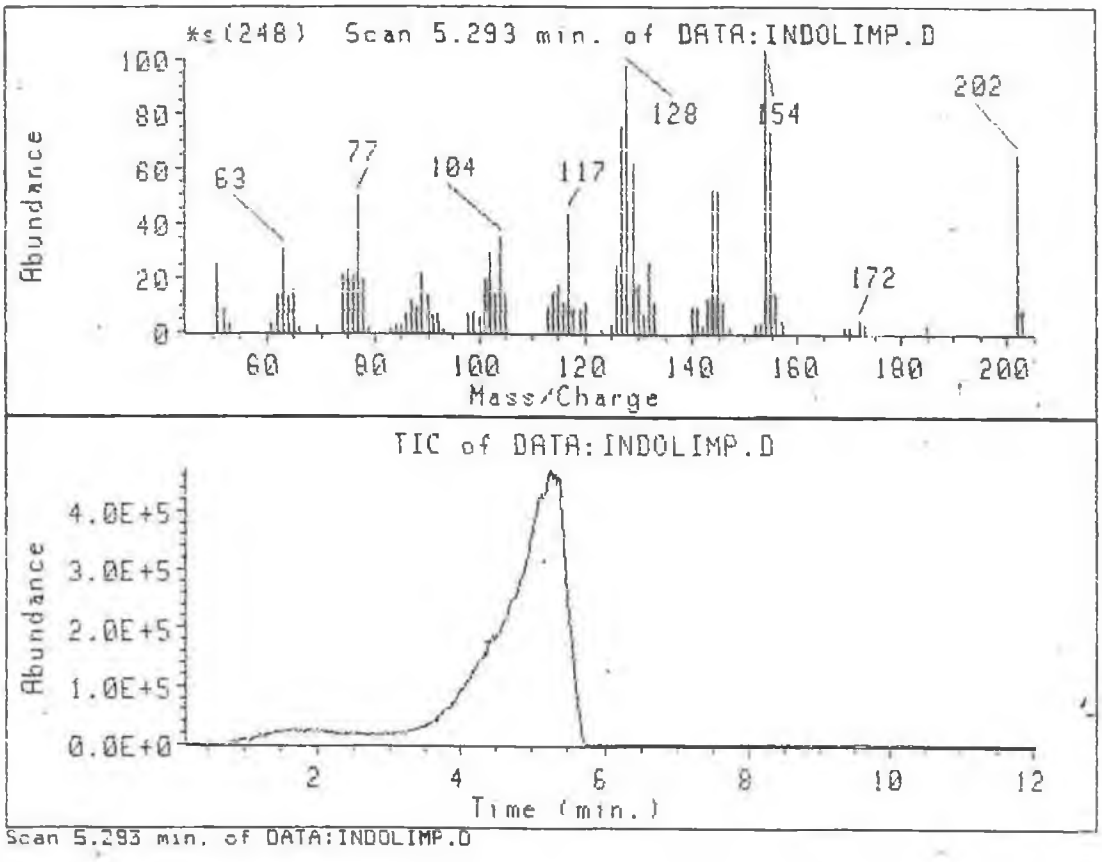


Spectrum 17 ^{13}C - ^{1}H coupled NMR spectrum of exo-5´-(8-methyl-8-azabicyclo-3.2.1]-octan-3-yl)-3'-(3,5-dichlorophenyl)-1,2,4-oxadiazole hydrochloride (**IIId**, CD_3OD, 75.4 MHz)

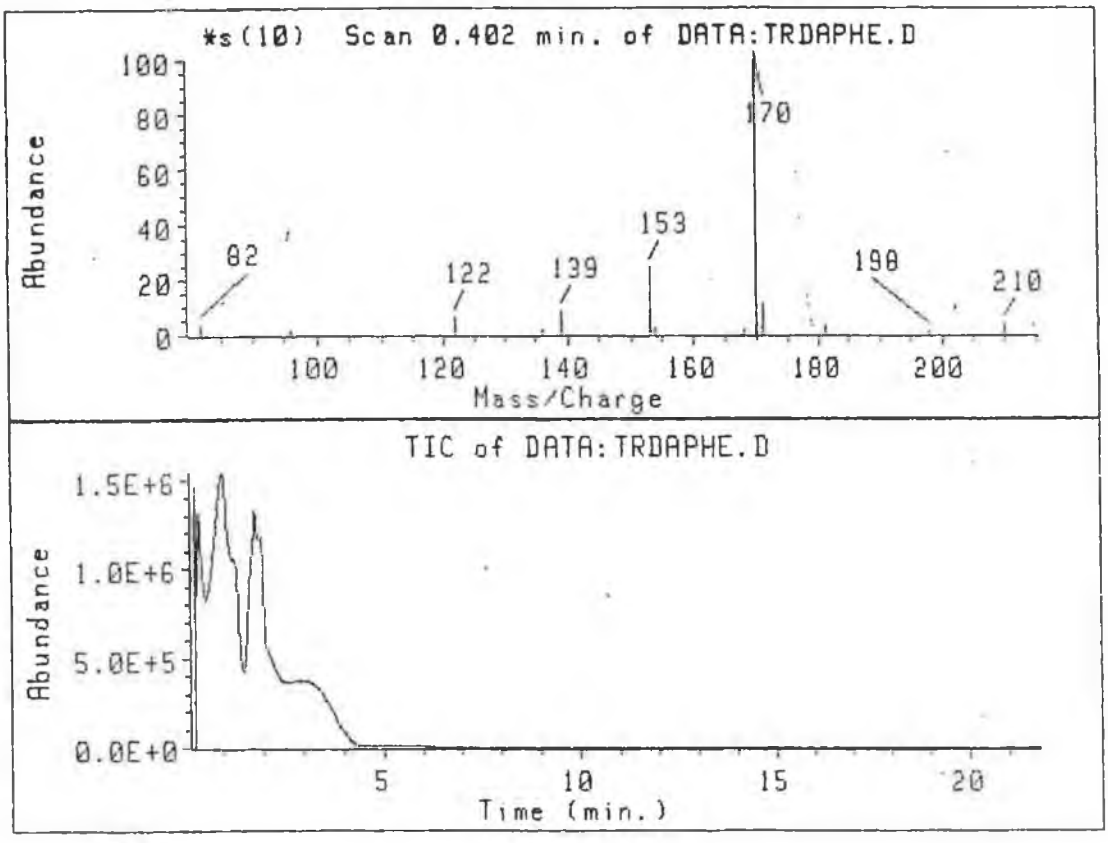
Appendix V

Mass Spectra*

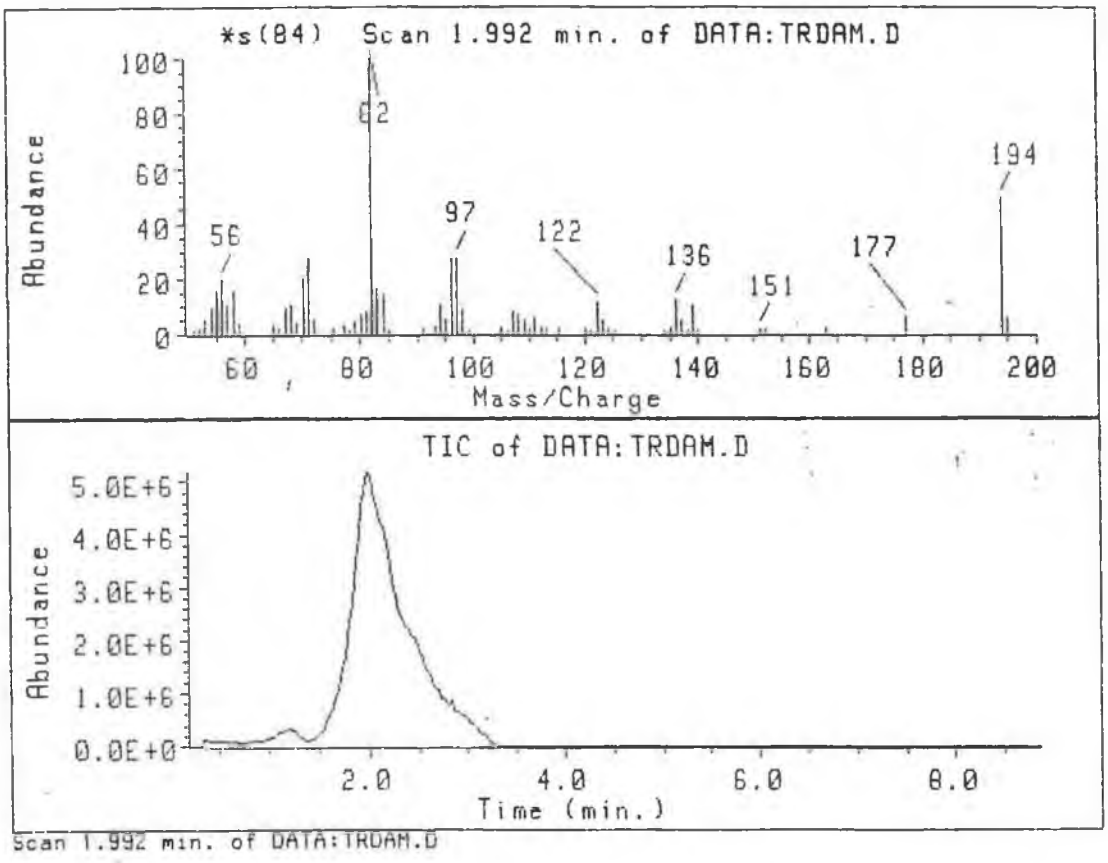
* EI = Electron Impact; CI = Chemical Ionisation



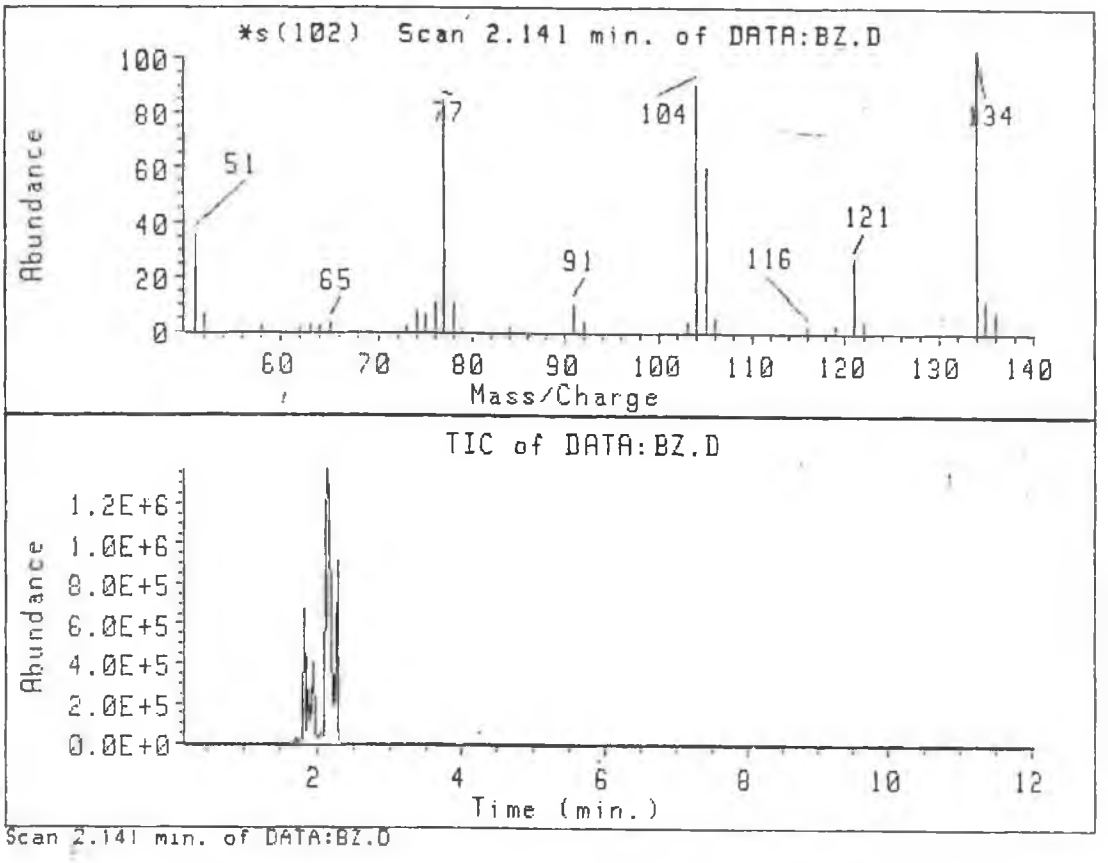
Spectrum 18 Mass spectrum (EI) of the indole-2-nitropropene impurity **126a** (M^+ = 202).



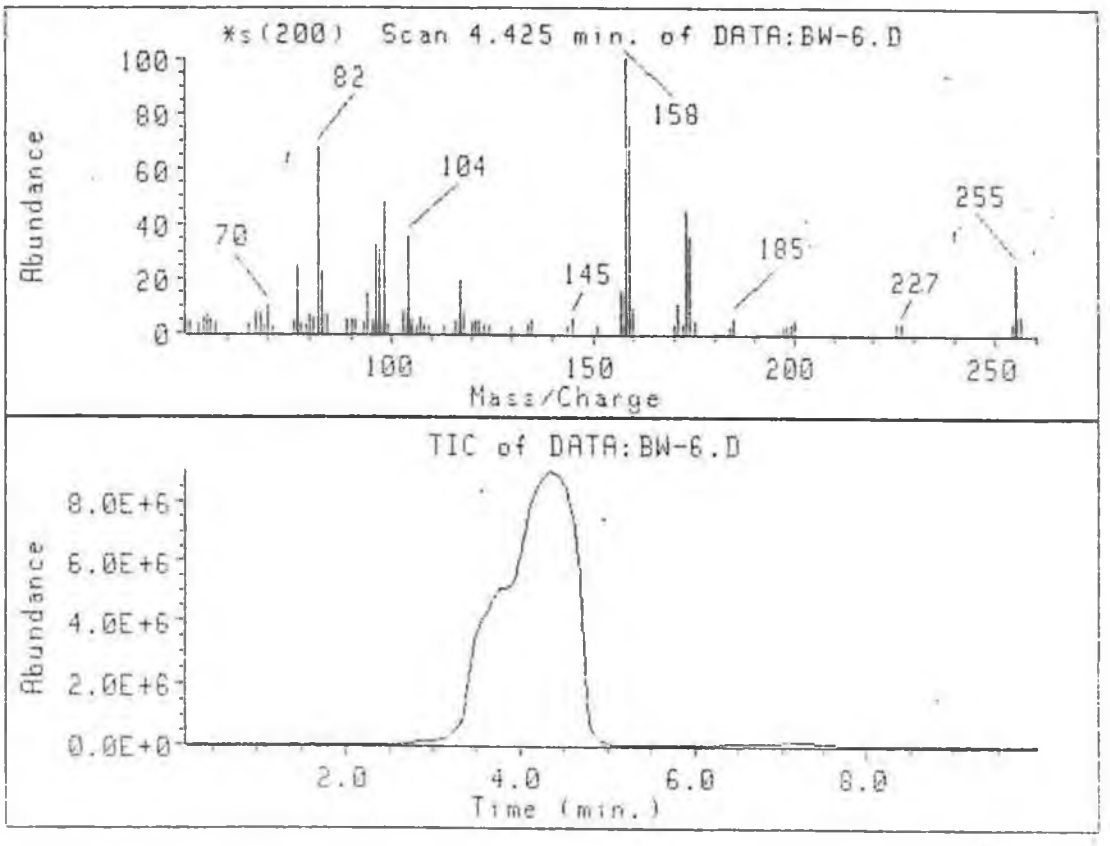
Spectrum 19 Mass spectrum (CI) of 3α-aminomethyl-8-methyl-8-azabicyclo[3.2.1]-octane-3β-amine **122** (M^++1 = 170).



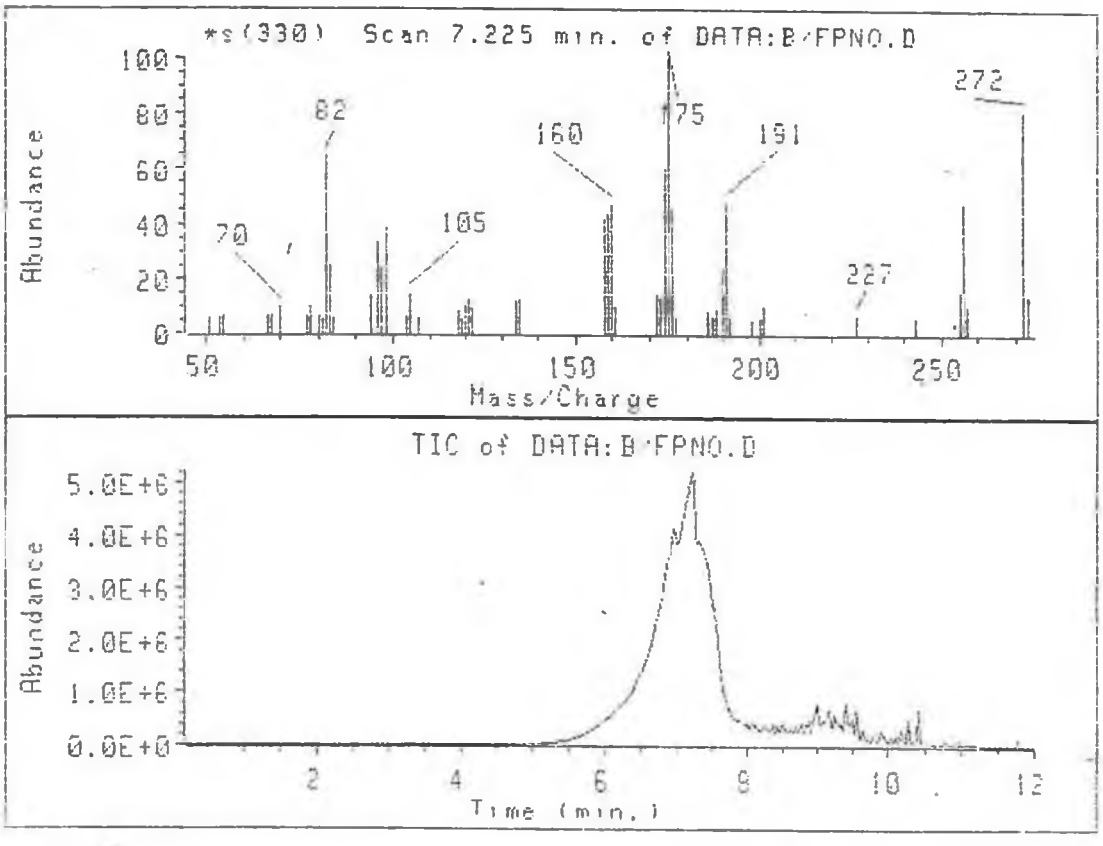
Spectrum 20 Mass spectrum (EI) of the aluminium complex of 3α-aminomethyl-8-methyl-8-azabicyclo[3.2.1]octane-3β-amine (**154**, M^+ = 195).



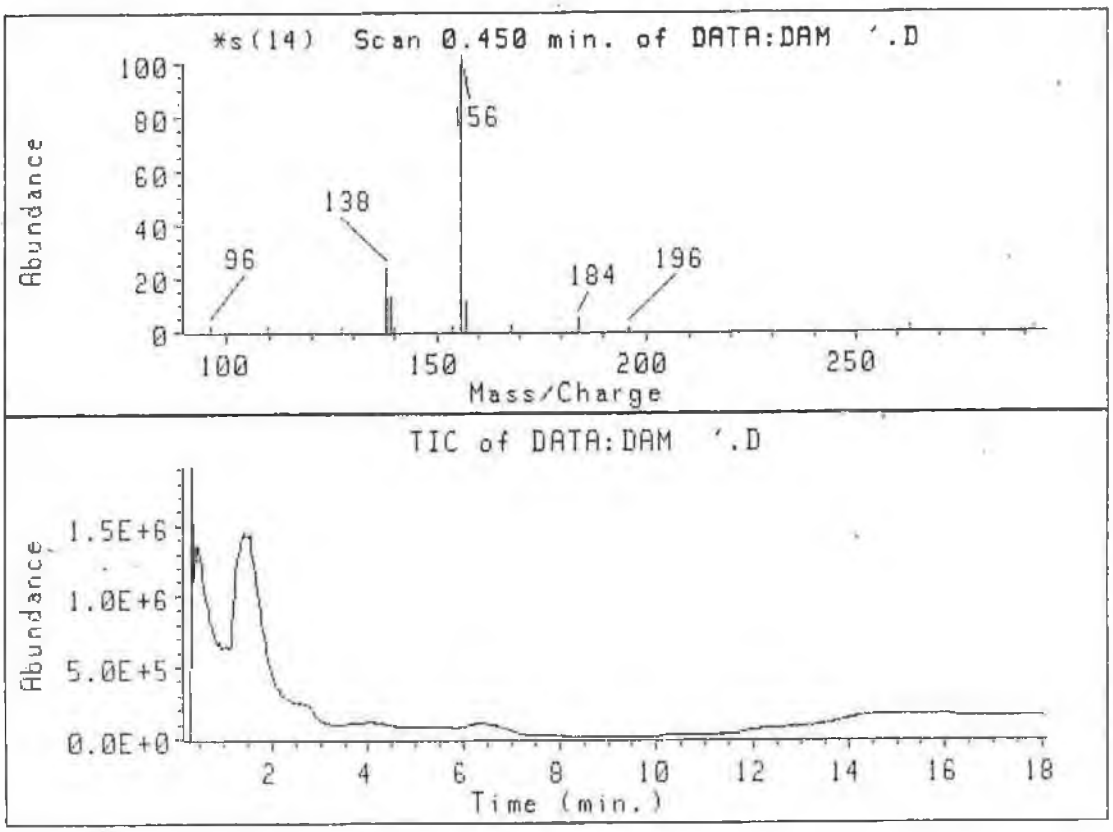
Spectrum 21 Mass spectrum (EI) of the phenyl carboximidate **129a** ($M^+ = 135$).



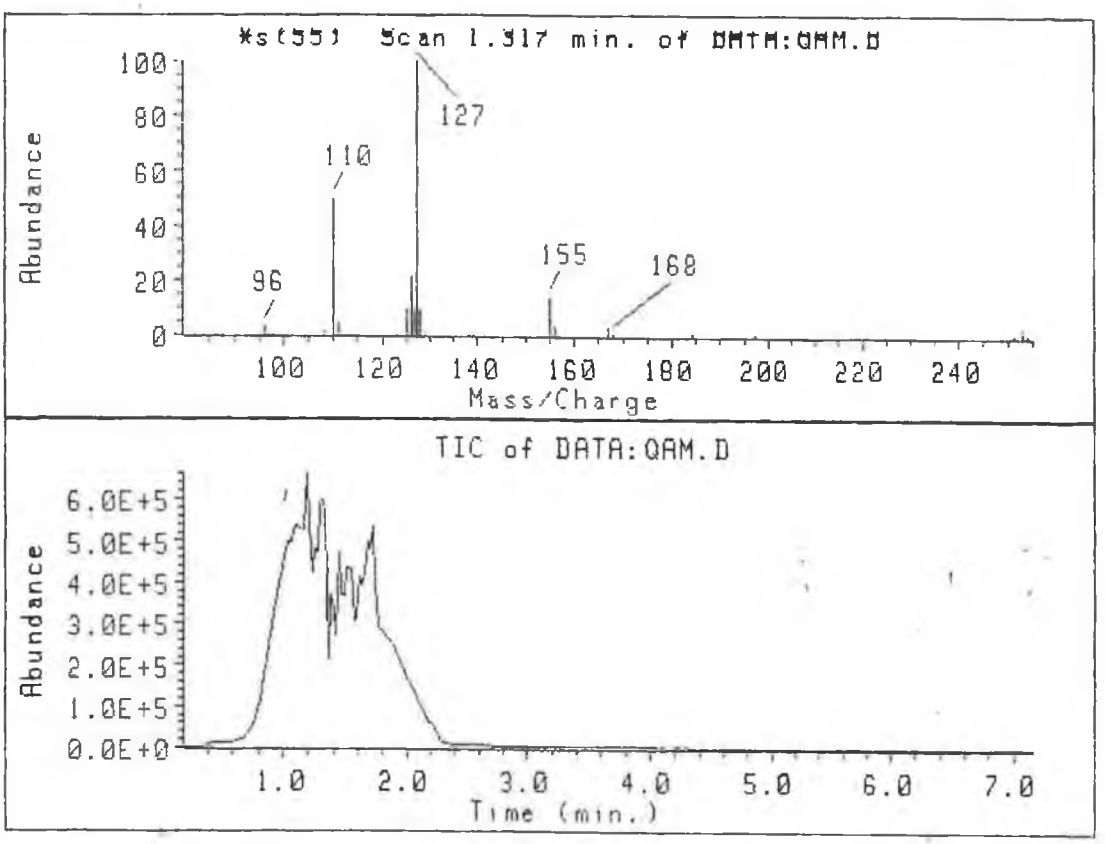
Spectrum 22 Mass spectrum (EI) of 2'-Phenyl-8-methyl-8-azabicyclo[3.2.1]-octane-3-spiro-4'(5)-imidazoline **Ia** ($M^+ = 255$).



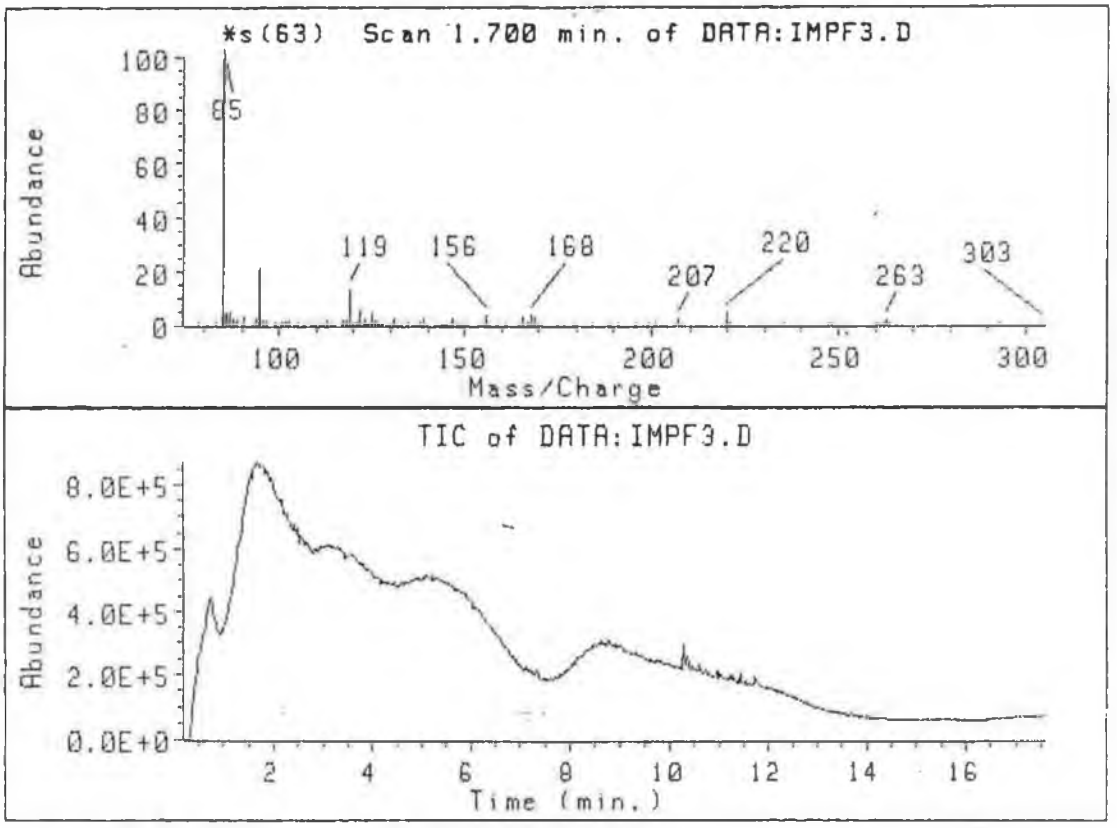
Spectrum 23 Mass spectrum (EI) of the 2'-(*N*-oxido-4-pyridyl)-8-methyl-8-azabicyclo[3.2.1]octane-3-spiro-4'(5)-imidazoline dihydrochloride (**Ig**, $M^+ = 272$).



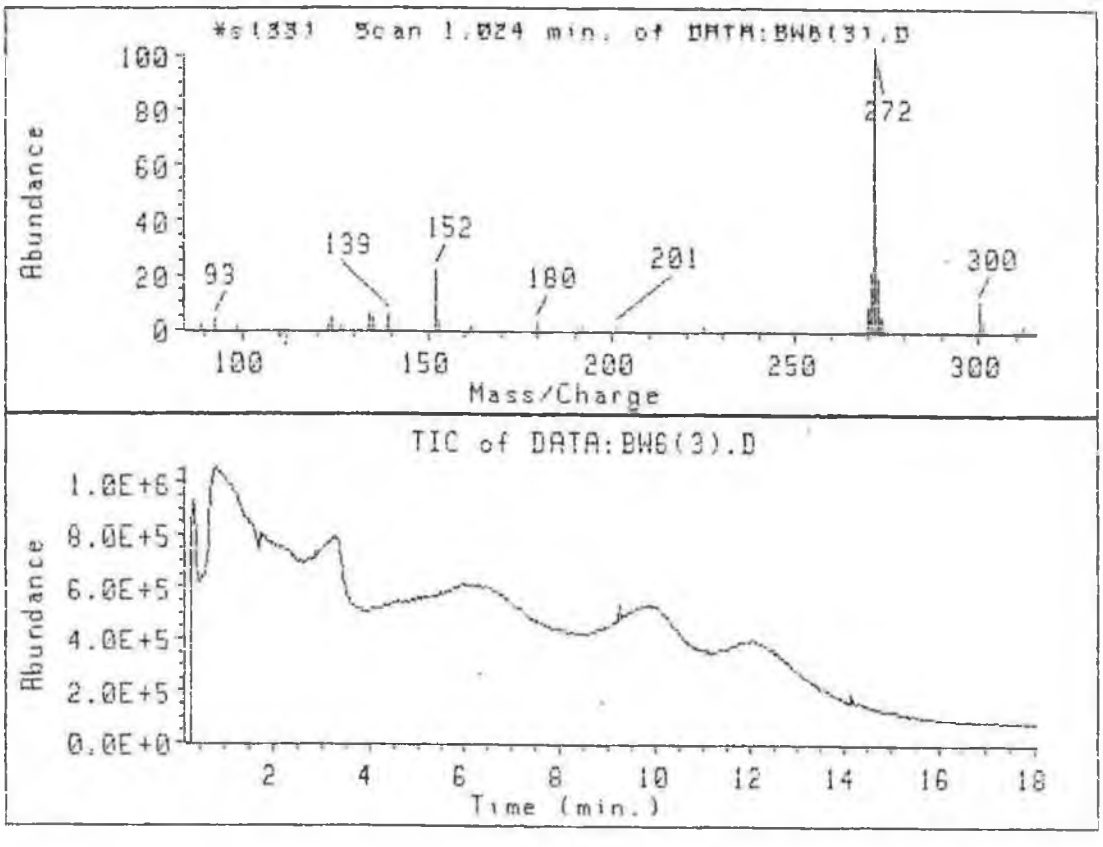
Spectrum 24 Mass spectrum (CI) of 3-aminomethyl-1-azabicyclo[2.2.2]octyl-3-amine (**159**, M^++1 = 156)



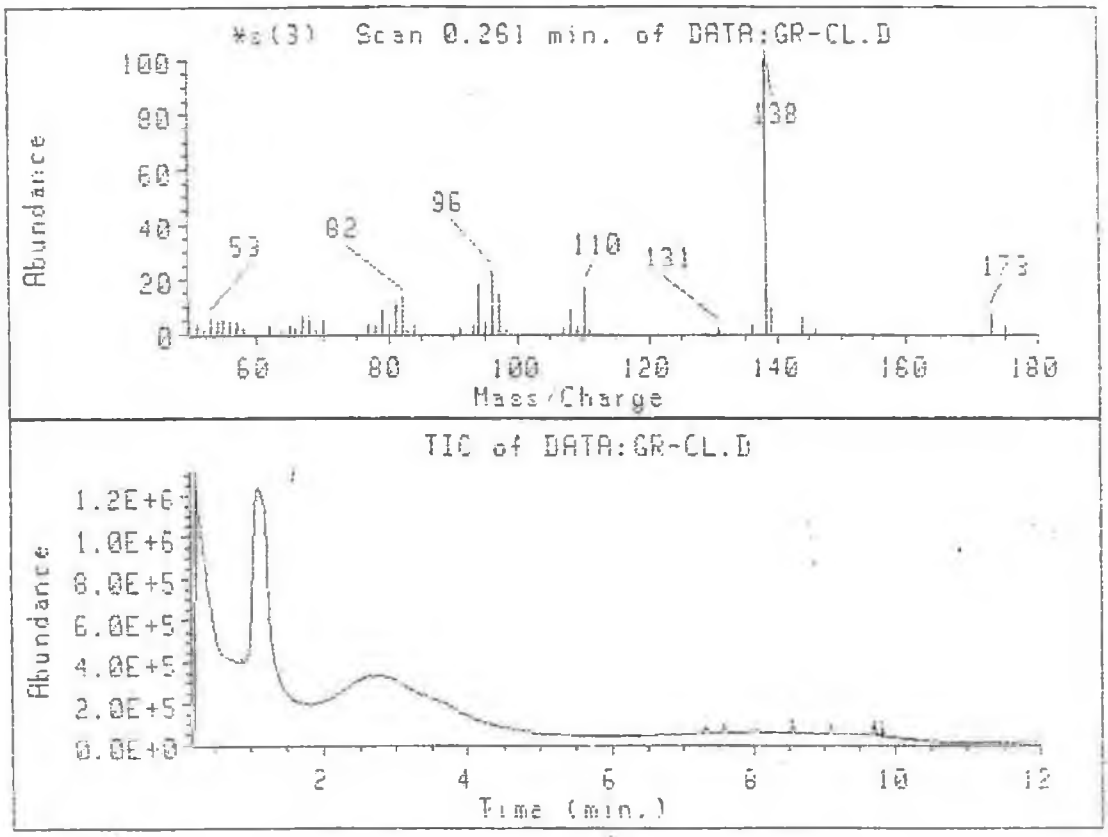
Spectrum 25 Mass spectrum (CI) of the hydrogenolysis impurity **(160)** from the $LiAlH_4$ reduction of quinuclidine aminonitrile (M^++1 = 127)



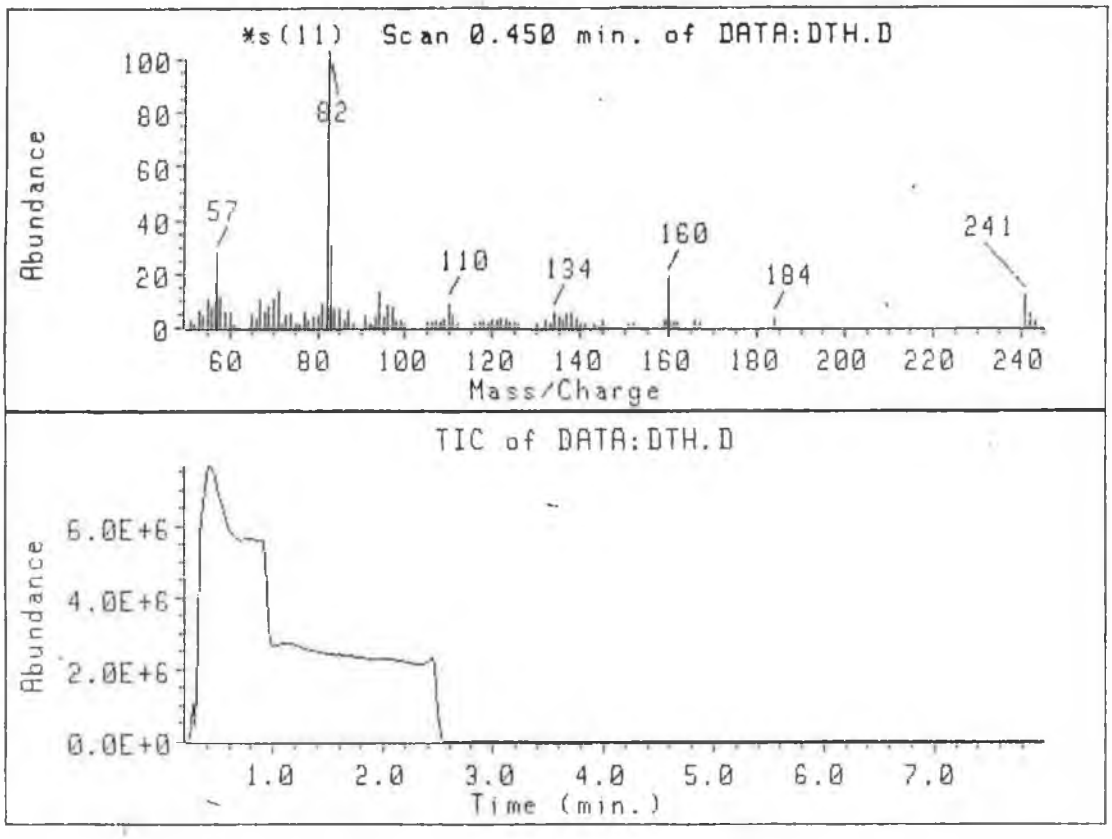
Spectrum 26 Mass spectrum (CI) of the dimerisation impurity **(161)** from the $LiAlH_4$ reduction of quinuclidine aminonitrile (M^++1 = 303)



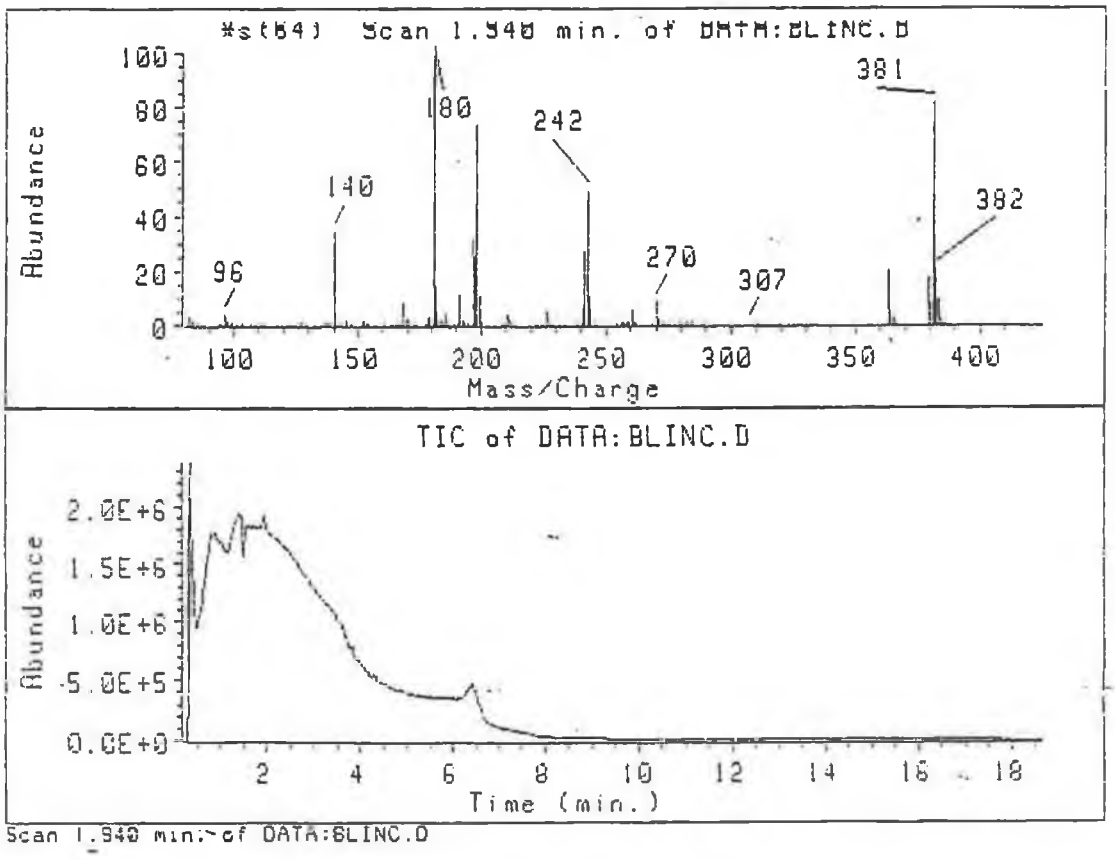
Spectrum 27 Mass spectrum (CI) of 2'(2-methoxyphenyl)-1-azabicyclo[2.2.2]octane-3-spiro-4'(5')-imidazoline (**IIb**, M^++1 = 272)



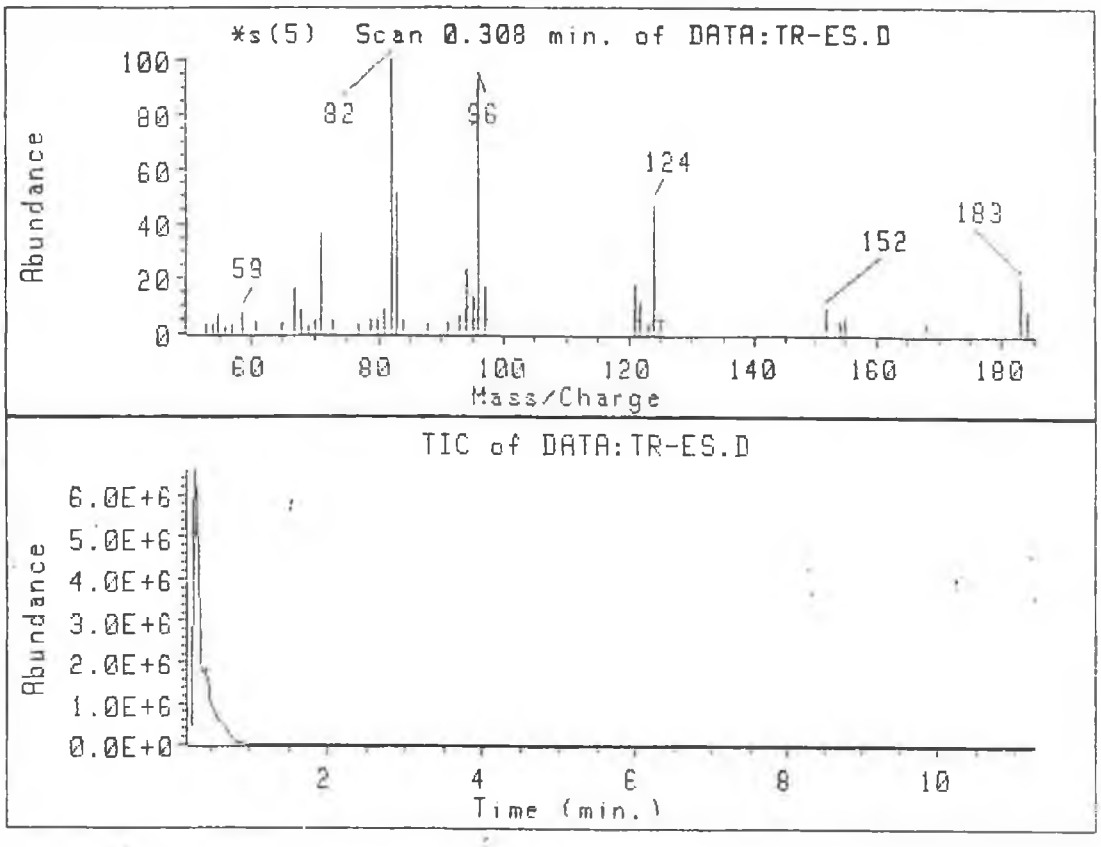
Spectrum 28 Mass spectrum (EI) of 3α-chlorotropane (**166**, M^+ = 173)



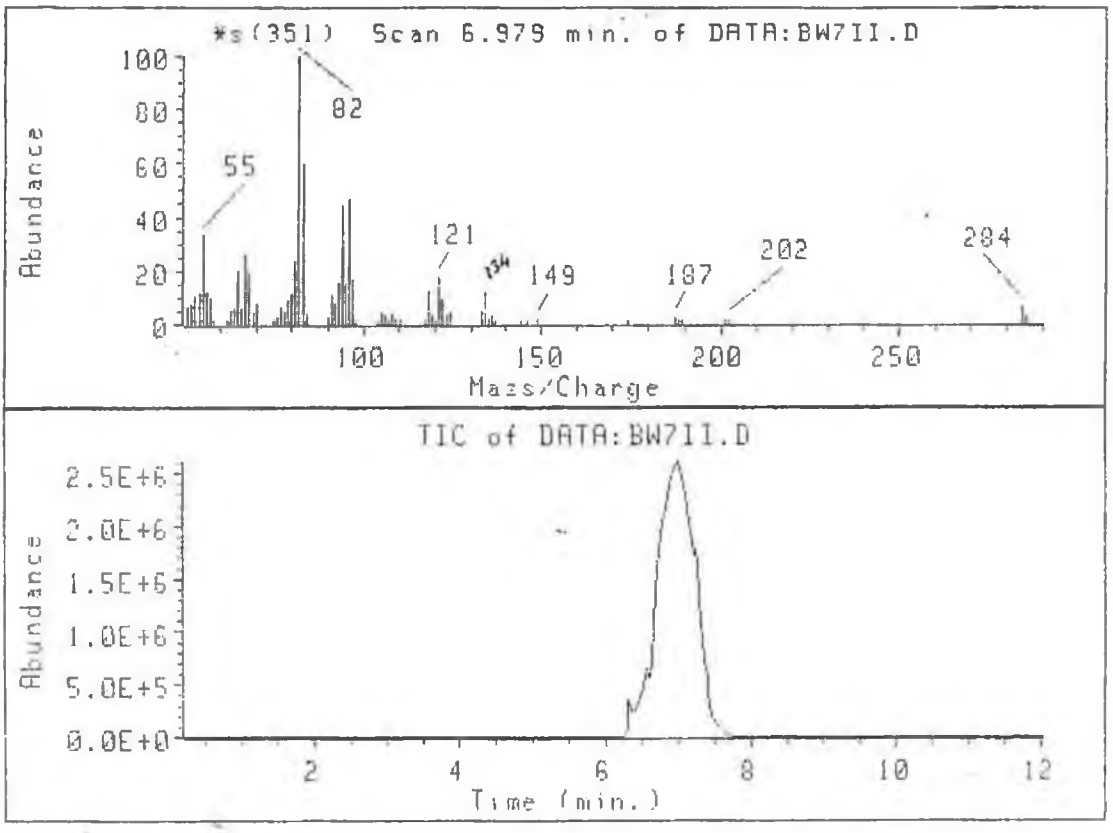
Spectrum 29 Mass spectrum (EI) of 3-(1,3-dithiane-2-ylidene)-8-methyl-8-aza-bicyclo[3.2.1]octane (**170**, $M^+ = 241$).



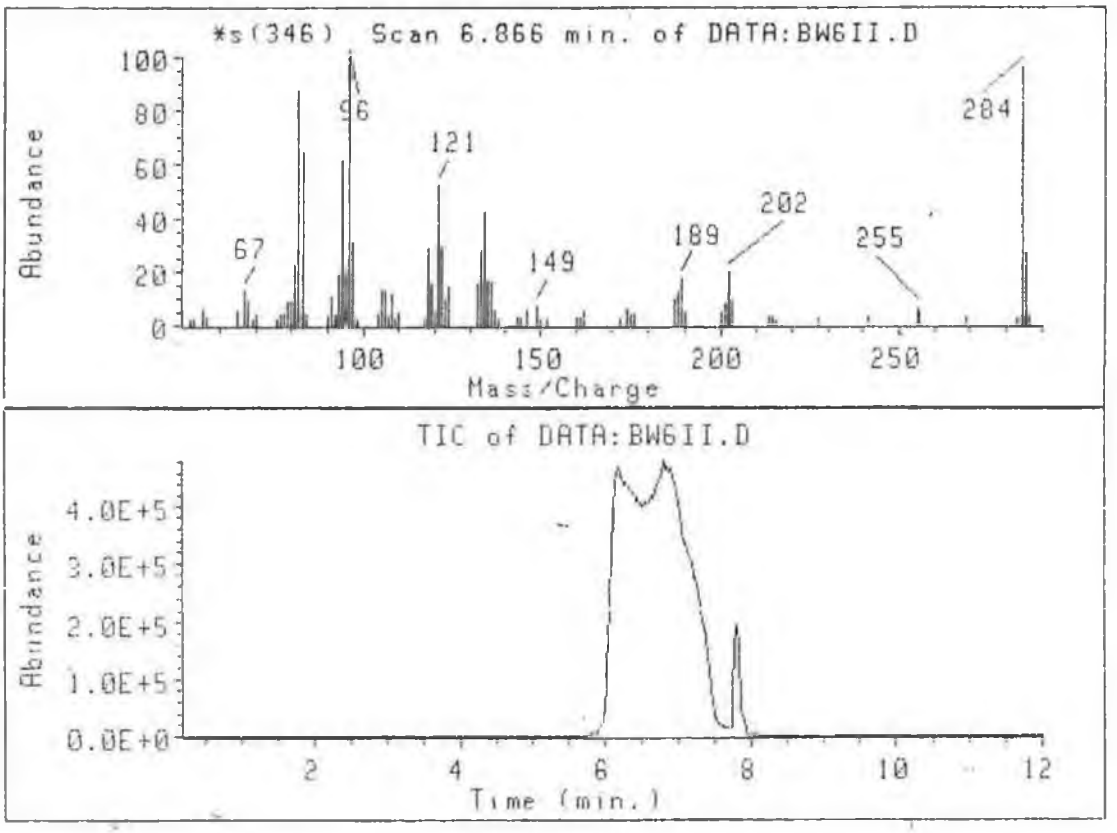
Spectrum 30 Mass spectrum (EI) of the dimeric impurity **171** isolated from the synthesis of 3-(1,3-dithiane-2-ylidene)-8-methyl-8-azabicyclo[3.2.1]-octane **170** (M^+ = 382)



Spectrum 31 Mass spectrum (EI) of exo-3-carbomethoxy-8-methyl-8-azabicyclo-[3.2.1]octane (**163**, M^+ = 183)



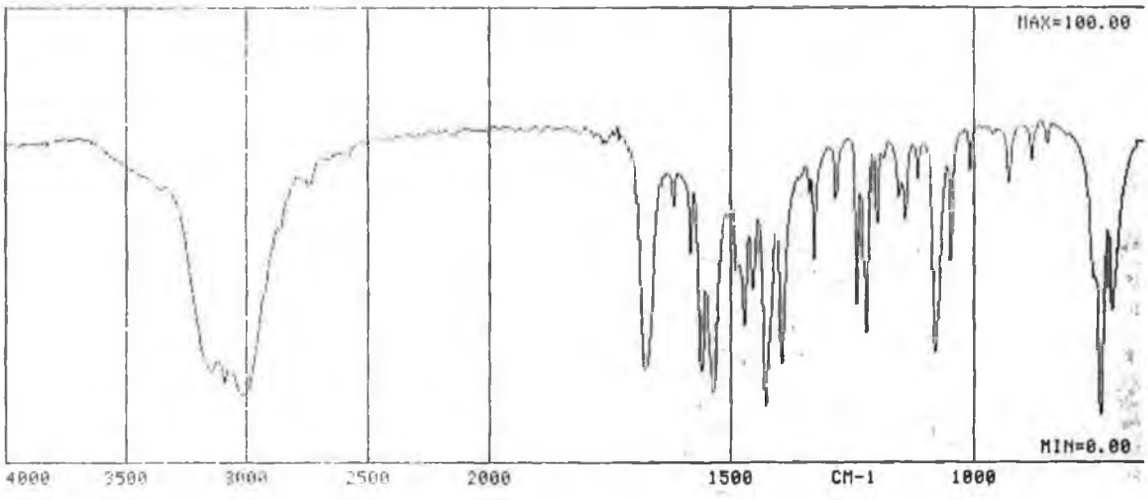
Spectrum 32 Mass spectrum (EI) of exo-5'-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-3'-(3-aminophenyl)-1,2,4-oxadiazole dihydrochloride (**IIIe**, M^+ = 284)



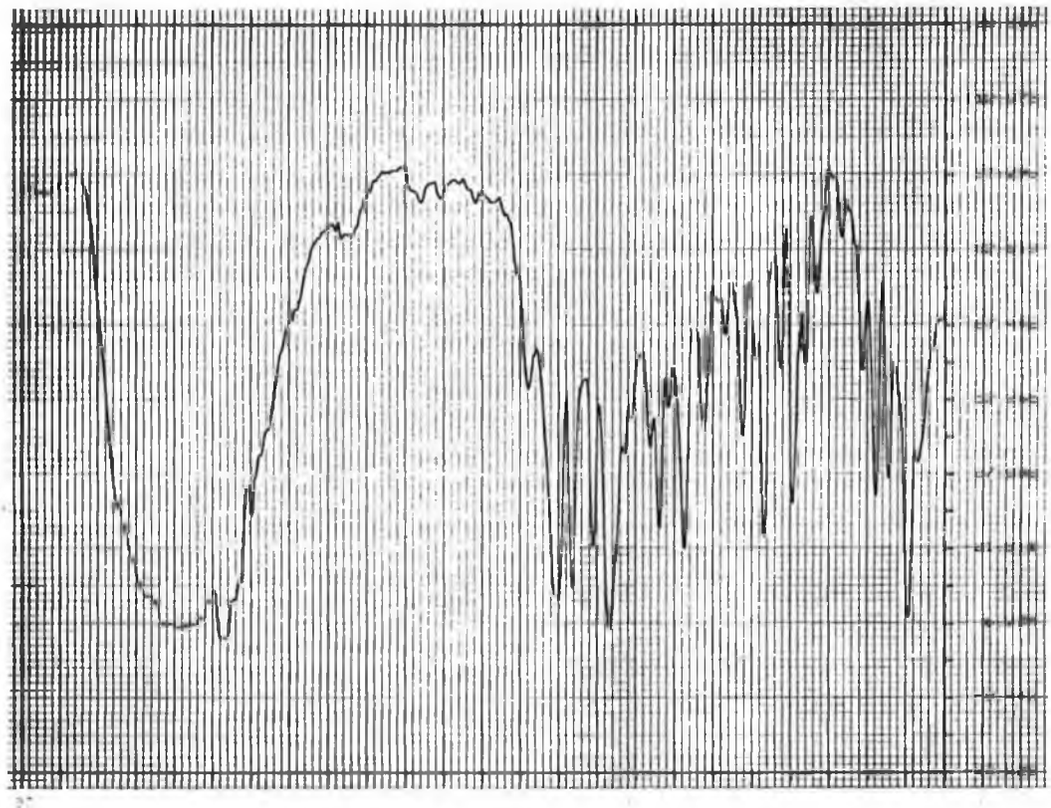
Spectrum 33 Mass spectrum (EI) of exo-5'-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-3'-(4-aminophenyl)-1,2,4-oxadiazole dihydrochloride (**IIIg**, M^+ = 284)

Appendix VI

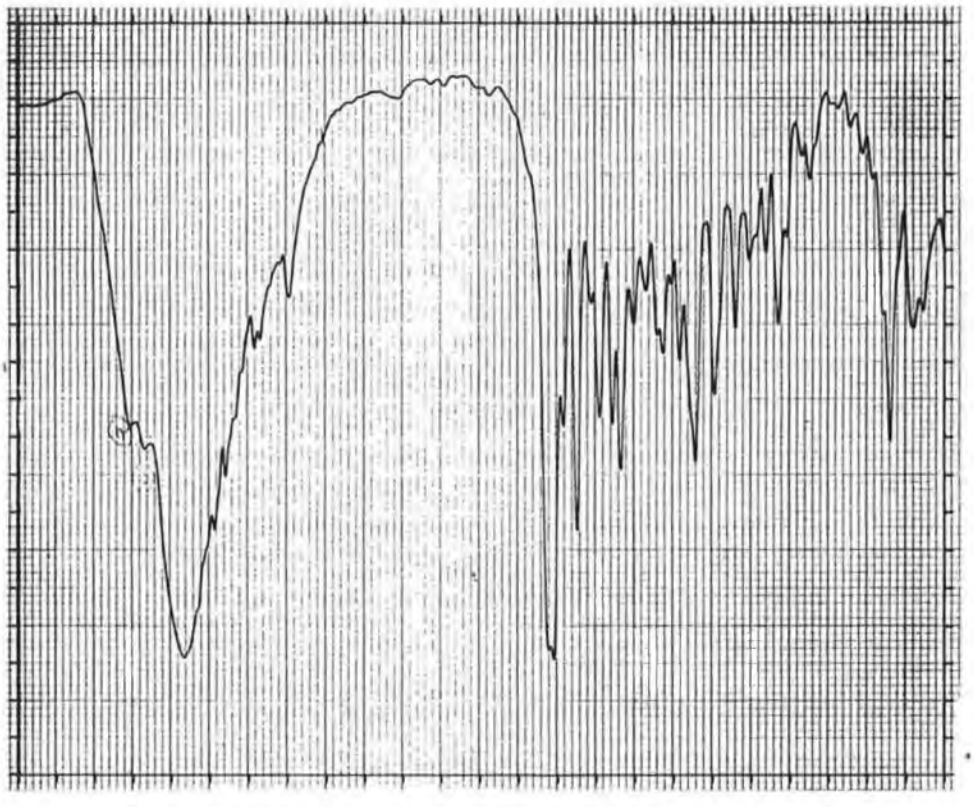
Infrared spectra.



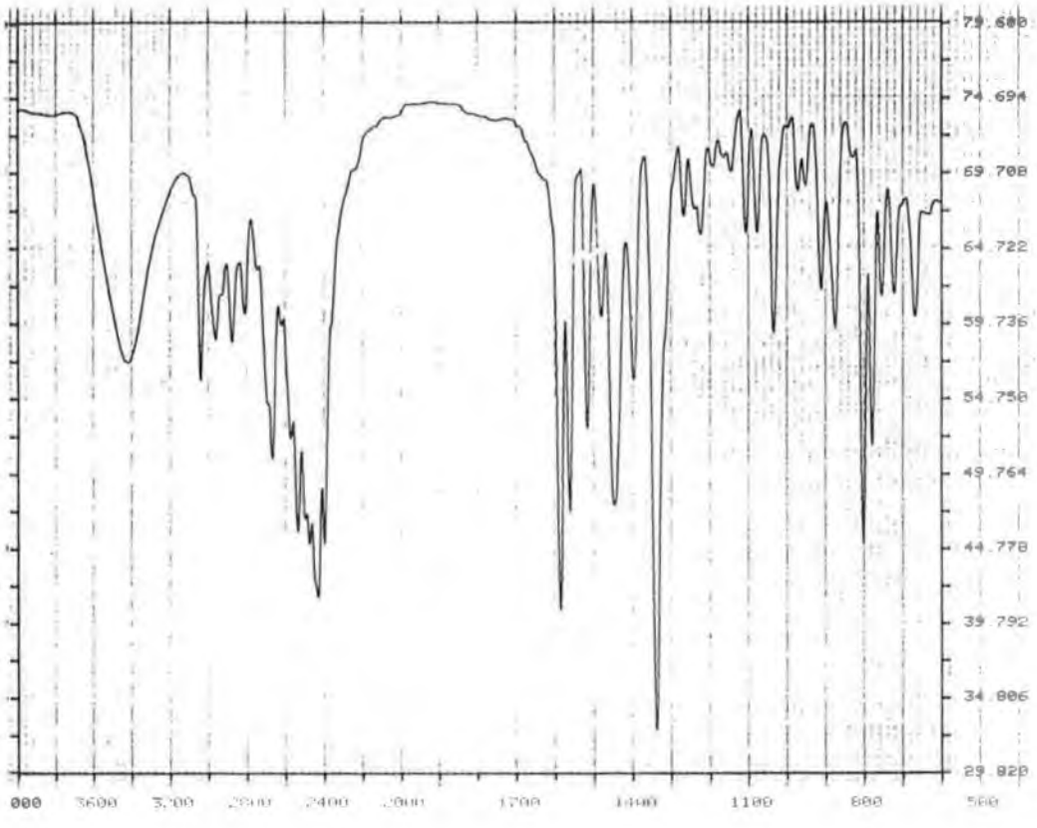
Spectrum 34 IR spectrum of 1*H*-indole-3-carboximidate hydrochloride **129h** (KBr)



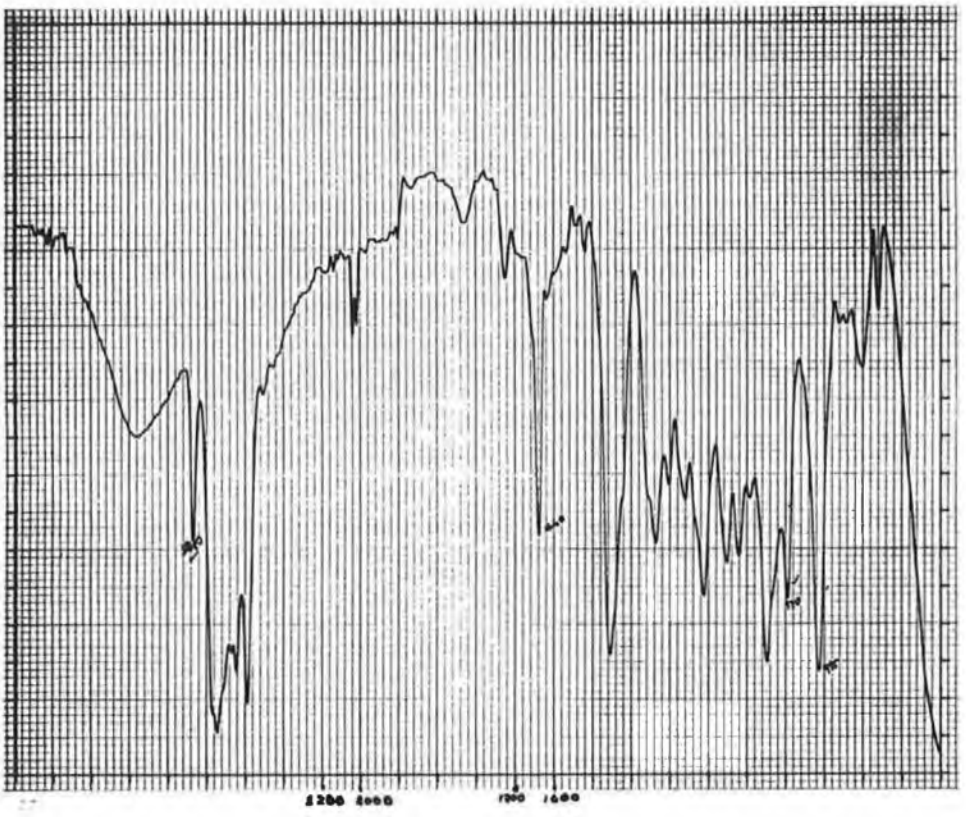
Spectrum 35 IR spectrum of 2'-Phenyl-8-methyl-8-azabicyclo[3.2.1]octane-3-spiro-4'(5')-imidazoline **Ia** (KBr)



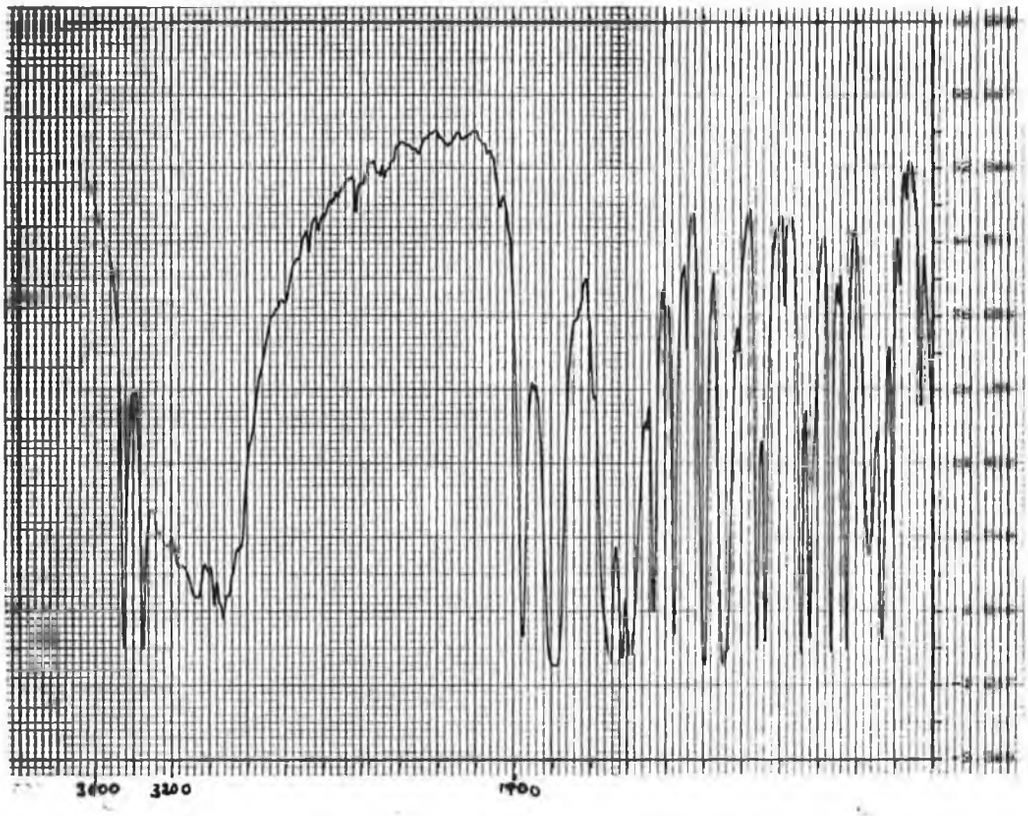
Spectrum 36 IR spectrum of 2'-(1*H*-indol-3-yl)-8-methyl-8-azabicyclo[3.2.1]octane-3-spiro-4'(5')-imidazoline dihydrochloride **Ig** (KBr)



Spectrum 37 IR spectrum of 2'-(3,5-Dichlorophenyl)-8-methyl-8-azabicyclo-[3.2.1]octane-3-spiro-4'(5')-imidazoline **Id** (KBr)

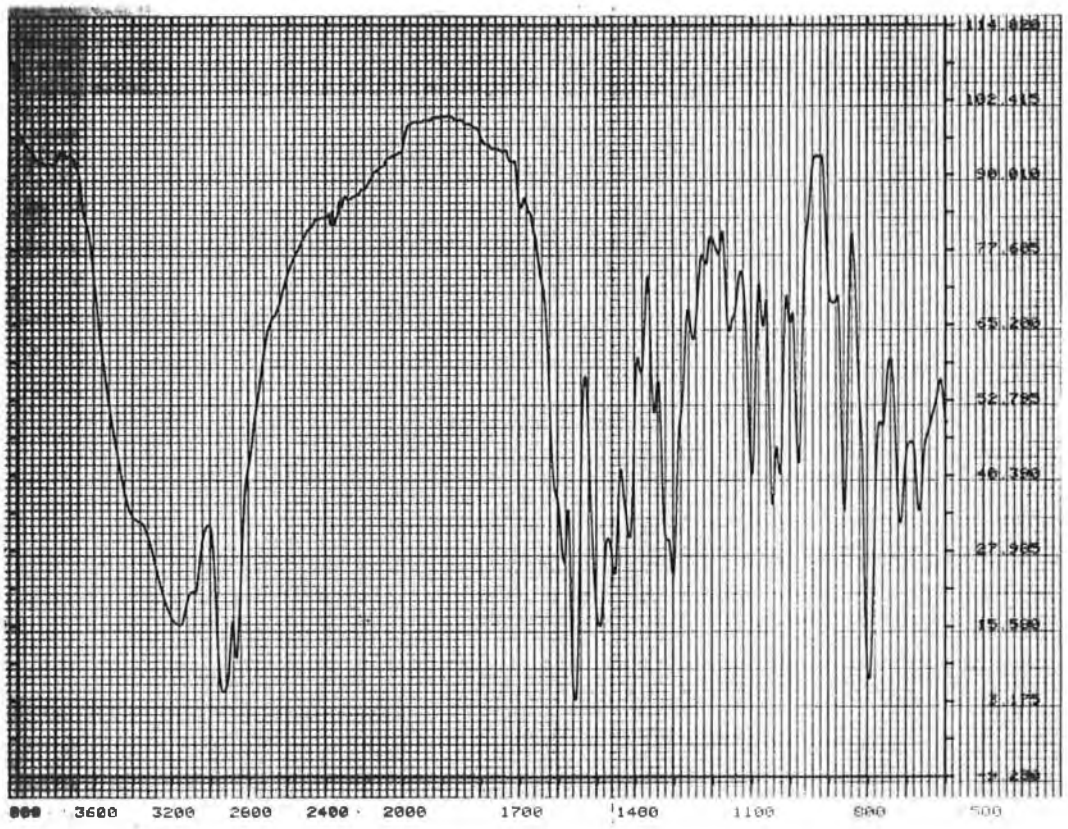


Spectrum 38 IR spectrum of the mixture of 2-allyl-4-cyano-1-methylpyrrolidines (**Fig.4.1**) from the ring opening of 3β-chlorotropane with CN^-.



Spectrum 39 IR spectrum of 3,5-dimethoxyphenyl-carboxamide oxime (**164c**).

(KBr)



Spectrum 40 IR spectrum of exo-5'-(8-methyl-8-azabicyclo[3.2.1]octane-3-yl)-3'-(3,5-dichlorophenyl)-1,2,4-oxadiazole hydrochloride **IIId** (KBr).