THE SYNTHESIS AND REACTIONS OF DEOXYVASICINONE AND ANALOGOUS COMPOUNDS

A THESIS SUBMITTED BY

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D E C L A R A T I O N

I hereby declare that the work presented in this thesis was carried out by me at Dundee College of Technology, Dundee, except where due acknowledgement is made, and has not been submitted by me for any other Degree.

Signed .[redacted]

Date ..12th March 1986....

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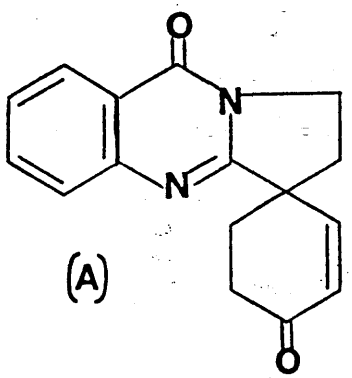
The Synthesis and Reactions of Deoxyvasicinone and Analogous Compounds.

Kenneth I. Kinnear, B.Sc.(Hons).

Abstract

The synthesis of deoxyvasicinone and a number of its C-ring substituted pyrrolo[2,1-b]quinazolin-9(1H)-one analogues was achieved. Modified 2-pyrrolidinones, the precursor molecules in many of the aforementioned syntheses, were prepared using standard techniques or via the reduction of nitrocarboxylic acid esters with reduced iron in acetic acid. The ability of deoxyvasicinone analogues to react at C-3 with electrophiles was demonstrated, the reactions yielding a range of modified pyrrolo[2,1-b]quinazolones. Mechanistic pathways to account for the products formed are included. A deuterium labelling experiment indicated that these reactions probably progress through the intermediacy of a pseudo-enamine. Deprotonation at the C-3 methylene group of 2,3-dihydro-pyrrolo[2,1-b] quinazolin-9(1H)-one and 2,3-dihydro-1,1-dimethylpyrrolo [2,1-b]quinazolin-9(1H)-one was achieved using lithium diisopropylamide and the lithiated species were used in situ for further synthetic transformations.

Attempts to prepare novel tetracyclic systems utilising the sp^2 nitrogen atom of the quinazolinone ring were unsuccessful. However, the tetracyclic spiroenone (A) was produced from deoxyvasicinone via an intermediate hydroxymethylene derivative.



(A)

FOREWORD

Bracketed arabic numerals in the text refer to the diagrams of the formulae and the arabic superscripts indicate references.

The following abbreviations have been used in the text.

m.p.	-	melting point
m.m.p.	-	mixed melting point
g.l.c.	-	gas liquid chromatography
p.l.c.	-	preparative layer chromatography
t.l.c.	-	thin layer chromatography
i.r.	-	infra red
u.v.	-	ultra violet
n.m.r.	-	nuclear magnetic resonance
p.m.r.	-	proton magnetic resonance
m.s.	-	mass spectrum
Ac	-	acyl
Ar	-	aryl
Et	-	ethyl
Me	-	methyl
Ph	-	phenyl
DMAD	-	dimethyl acetylenedicarboxylate
DMF	-	dimethyl formamide
DMS	-	dimethyl sulphate
DMSO	-	dimethyl sulphoxide

EDTA	-	ethylenediaminetetraacetic acid
LDA	-	lithium diisopropylamide
NBS	-	N-bromosuccinimide
PTSA	-	para toluenesulphonic acid
THF	-	tetrahydrofuran
R_f	-	retention index for thin layer chromatography
R_t	-	retention time
J	-	coupling constant
Hz	-	hertz
δ	-	p.p.m.
ξ	-	molar extinction coefficient

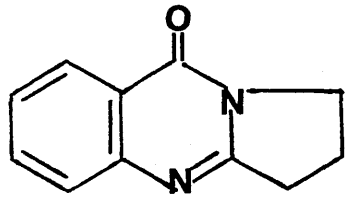
INTRODUCTION

Introduction

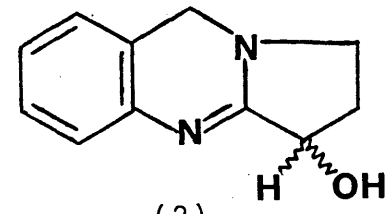
The leaves of **Adhatoda Vasica Nees**, a highly reputed Ayurvedic medicinal plant, have been used in Indian medicine for more than 2,000 years. During the latter half of the nineteenth century medical scholars and authors began to investigate the use of **Adhatoda Vasica Nees** and other plants containing quinazoline derived alkaloids in the treatment of respiratory ailments, particularly cough, bronchitis, asthma and tuberculosis. The 'active' components from the medicines derived from these leaves were subsequently extracted, characterised and unambiguously synthesised. The history of the alkaloid deoxyvasicinone (1) is therefore linked inexorably with the histories of the numerous similar 'active' alkaloids present in these crude medicines.

Hooper[1] in 1888 undertook the chemical investigation of the plant **Adhatoda Vasica** and separated the volatile and non volatile fractions by steam distillation. The non volatile fraction showed positive tests for alkaloids and also behaved as an organic acid and was therefore named Adhatodic acid. Further work on the chemistry of the plant remained at a standstill for approximately four decades when Sen and Ghosh[2] started investigations again and isolated a solid they named as vasicine (2). It was whilst establishing the structure of (2) that

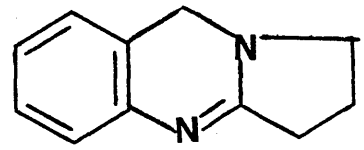
Morris, Hanford and Adams[3] obtained the compound(1) via hydrogen peroxide oxidation of deoxyvasicine(3).



(1)



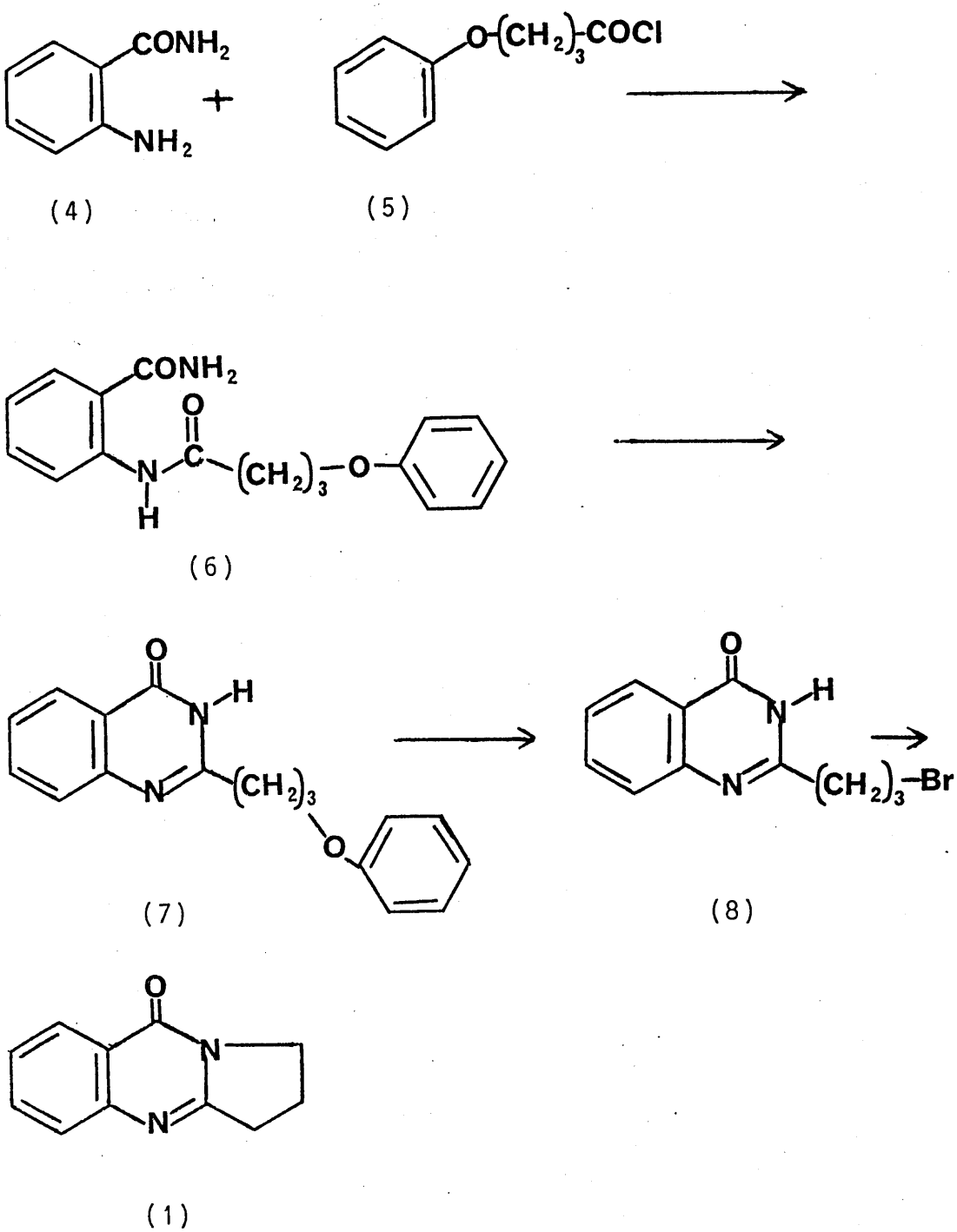
(2)



(3)

Deoxyvasicinone was assigned structure (1) by an unambiguous synthesis involving anthranilamide (4) and 4-phenoxybutyryl chloride (5). (Scheme 1).

Thermal cyclisation of the intermediate 2-(3-phenoxybutyrylamino)benzamide (6) gave 2-(3-phenoxypropyl)quinazolin-4-one (7) which could be brominated at the 3-position in the alkyl side chain with concommitant removal of the phenoxy ether grouping. Cyclisation of this bromo compound 2-(3-bromopropyl)-quinazolin-4-one (8) in alkaline media gave (1).


CONH2
NH2
O-(CH2)3-COCl
(4)
(5)
CONH2
O
C
N
H
(CH2)3-O
(6)
O
N
H
(CH2)3
O
(7)
O
N
H
N
(CH2)3-Br
(8)
O
N
N
(1)

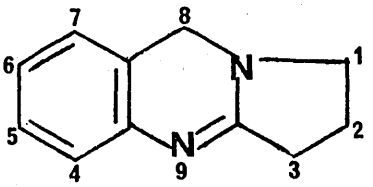
Scheme 1

Deoxyvasicinone (1) was shown to be identical with the product 9-pegen-8-one synthesised several months earlier by Späth and Platzer[4]. Spath's synthesis involved heating 2-pyrrolidinone (9) with one equivalent of isatoic anhydride (10) at 120^{0} - 130^{0}. Loss of carbon dioxide gave the intermediate 1-(2-aminobenzoyl) pyrrolidin-2-one (11) which by elimination of water yielded a compound mp $110\text{-}111^{0}$ named 9-Pegen-8-one after **Peganum Harmala** the original floral source of alkaloids used by Späth. (Scheme 2, Pg.10).

Chatterjee and Ganguly[5], Koretskaya[6,7], Liljegren[8] and Plekhanova[9] have all since recovered deoxyvasicinone (1) from this same species. Deoxyvasicinone (1) has also been isolated from **Mackinlaya Macrosciadia**[10], **Peganum Nigellastrum**[11] and **Linaria Transiliensis**[12].

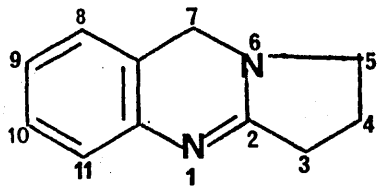
Nomenclature

The different names given to (1) by Späth and Adams highlight the problems encountered when reviewing the literature for these alkaloids. Indeed the numbering system for vasicine type alkaloids which involve fused pyrroloquinazoline or pyrrolo benz-1:3-diazine systems have developed quite strangely[13] e.g. the earlier numbering system was as shown in (3A).



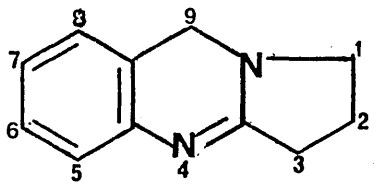
3A

which was later changed to (3B)[14].



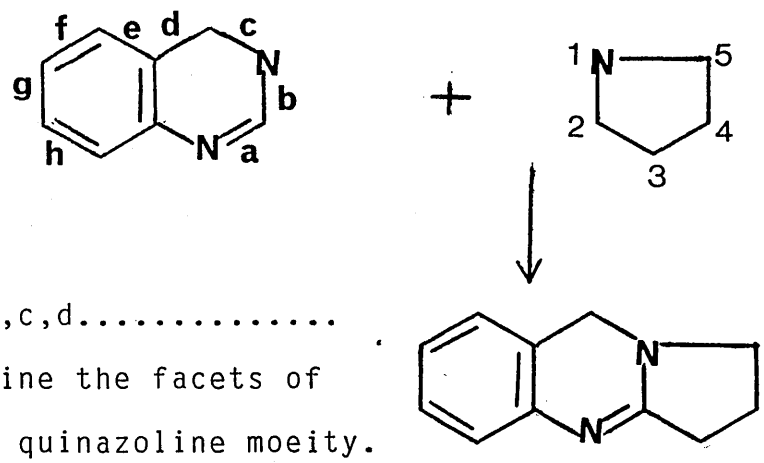
3B

However, the numbering system[15] normally encountered in the literature in the present day for vasicine type alkaloids involves the pyrroloquinazoline condensed ring system with numbering shown as in (3C).



3C

The N of the pyrrolo ring (saturated) and 3N of the quinazoline being common N to both pyrrolo and quinazoline systems, i.e.

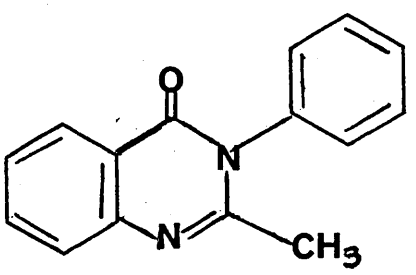


a,b,c,d..... define the facets of the quinazoline moeity.

Thus according to the above numbering system deoxyvasicinone (1) will be 1,2,3,9-tetrahydropyrrolo-[2,1-b]quinazolin-9-one. However, it should be noted that chemical abstracts use 2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one as the preferred name for deoxyvasicinone and it will be called as such during this discussion.

Pharmacological Activity

The pharmacological activity associated with the quinazolone moeity is well documented[16-22] and two excellent review articles by Johne[23,24] are available which describe quinazolines as central nervous system depressants, e.g. methaqualone (12),



(12)

anti-inflammatories, diuretics, antihypertensives and antiallergics or with anti-infectious, antimalarial coccoidiostatic or anthelmentic properties.

Other groups have reported the use of quinazolones as fungicides[23,24], acaricides[25] and herbicides[26].

Despite the numerous studies undertaken in an effort to establish structure activity relationships in the 2,3-substituted quinazoline alkaloids extracted from Adhatoda Vasica, no definitive rules have been established, indeed conflicting reports have tended to confuse the issue, Devi et al[29]. However, a comprehensive investigation by Sharma et al[30] has shown that bronchodilatory activity may be enhanced with the inclusion of an oxygen at C-3 or C-9 in the 6,6,5 pyrroloquinazoline molecule. An N-N-O triangle can be visualised (Fig 1). These triangles have identical bond lengths whether the molecule is deoxyvasicinone (1) or vasicine (2).

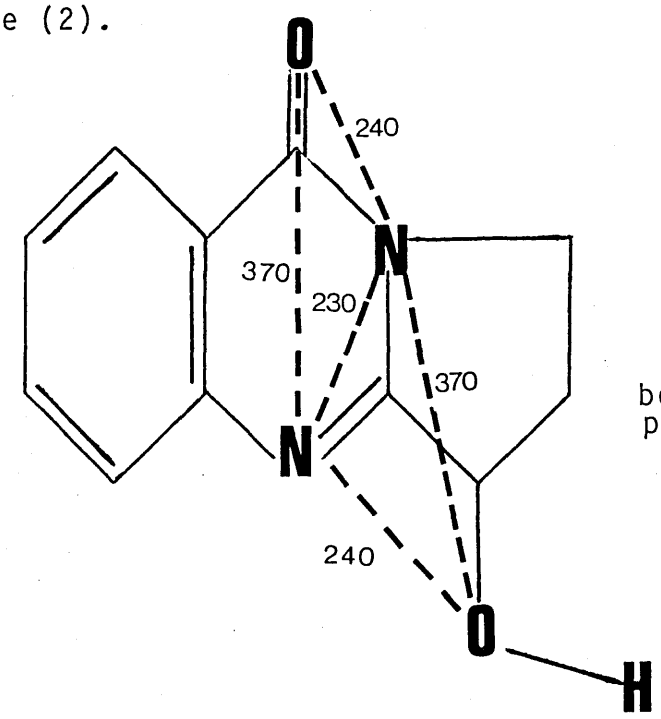


Fig. 1

bond lengths in picometres

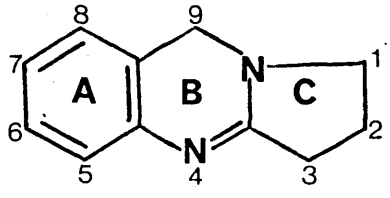


Fig. 2

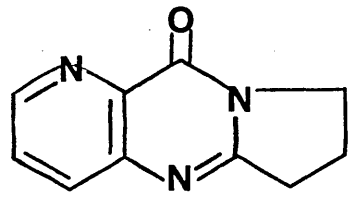
If either the carbonyl group in deoxyvasicinone (1) type derivatives or the hydroxyl group in vasicine (2) type analogues is absent then a subsequent reduction in activity is recorded.

An investigation into the roles of the A and C rings (Fig 2) by Sharma[30] discovered that not only must the C ring be present for bronchodilatory activity (i.e. 2,3-dialkylquinazolones are not as active as their cyclic counterparts) but that the ring should be large (i.e. a 7 membered ring has enhanced bronchodilatory activity when compared to a cyclic 5 membered ring.) Pharmacological screening of vasicine derivatives following substitution in the A ring revealed no enhancement of activity. Presumably deoxyvasicinone type compounds were excluded from this study due to their aforementioned correlation in activity with vasicine analogues. Earlier negative results reported by Devi, Kapil and Popli[29], who introduced hydroxy, alkoxy, acetoxy and chloro substituents into the A ring may also have influenced this decision.

Numerous other groups have also generated substituted A-ring pyrroloquinazolones. Hydroxy[31], halo[32,33], carboxyl, nitro and amino groups[23,32,33,34,35], benzamido[35], alkyl[31], and acetamido[23,32,33,34] groups have all replaced hydrogen in the A ring. Johne[35] illustrated that the benzo ring in position A may be

replaced by similar aromatic heterocycles with the preparation of 8-azadeoxyvasicinone (13).

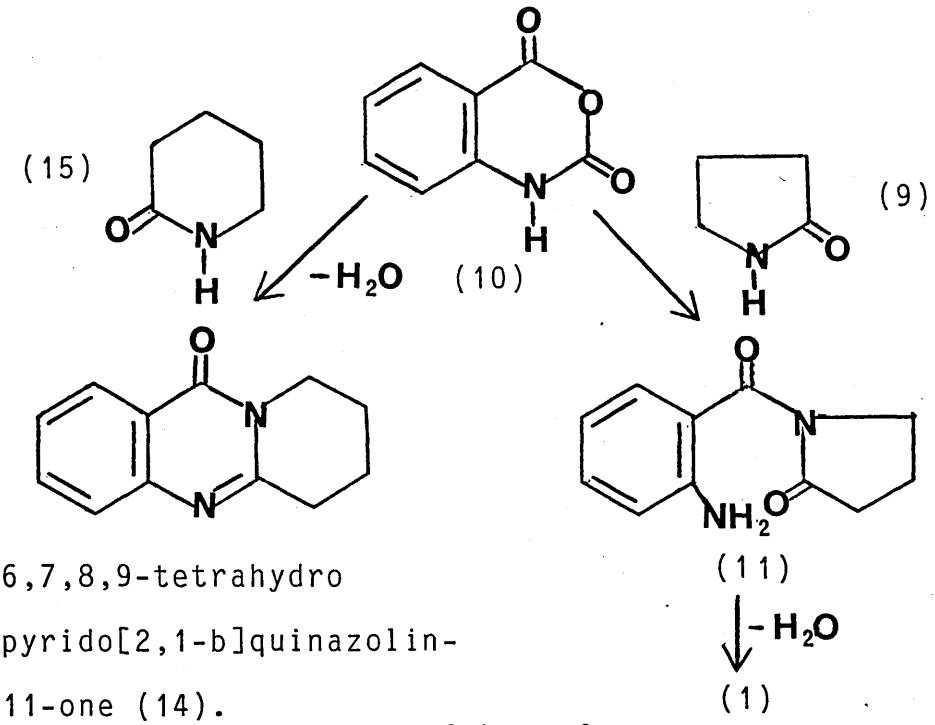
Unfortunately, much of the work has provided little biological data and that obtained[22] lends support to the ineffectiveness of this type of substitution. Despite this, interest in A ring substitution continues and an Italian pharmaceutical company[36] have recently published a patent application for the preparation of numerous substituted pyrrolo[2,1-b]quinazolones and pyrido[2,1-b]quinazolones.



(13)

Synthesis of pyrrolo[2,1-b]quinazolones

As previously noted, the alkaloid deoxyvasicinone (1) was first synthesised in vitro by Späth and Platzer[4]. The pyrido analogue (14) of (1) was also prepared by this group from 2-piperidone (15). (Scheme 2).



6,7,8,9-tetrahydro pyrido[2,1-b]quinazolin-11-one (14).

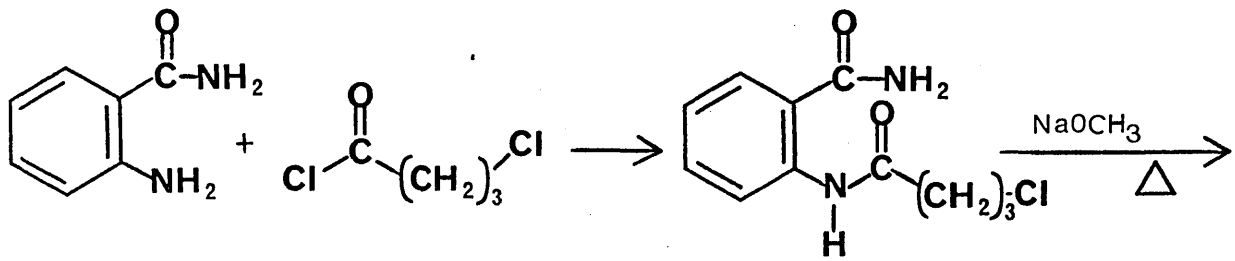
(11)

(1)

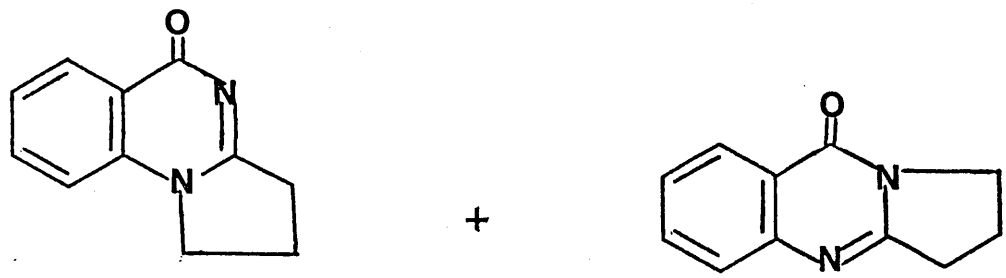
Scheme 2

Since then interest in pyrroloquinazolones has grown and consequently so has the number of synthetic routes to them. This interest, generated mainly by the latent biological activity of these molecules has been heightened by the use of pyrroloquinazolones as intermediates in natural product synthesis[37,38] and as models for larger compounds such as steroids[39].

A method developed by Landii Vittory and Gatta[40] for the preparation of (1) and its [1,2-a] analogue (16) involves the base catalysed thermal cyclisation of 2-(4-chlorobutyrylamino)benzamide (17) previously prepared from anthranilamide (4) and 4-chlorobutyryl chloride (18). This reaction, although similar to that reported by Morris et al[3] allows the nitrogen atom of the secondary amide to act as a nucleophile with the subsequent formation of (16) (Scheme 3). No such attack is possible using the method of Morris as this route to cyclisation is blocked by the presence of the tertiary amino group in the preformed quinazolone ring.



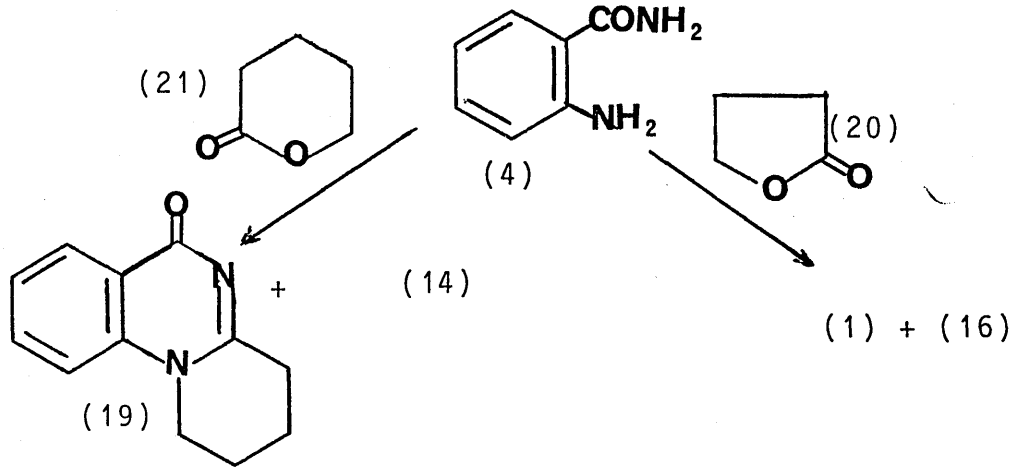
(4) (18) (17)



1,2,3,5-tetrahydropyrrolo[1,2-a] quinazolin-5(1H)-one.(16). (1)

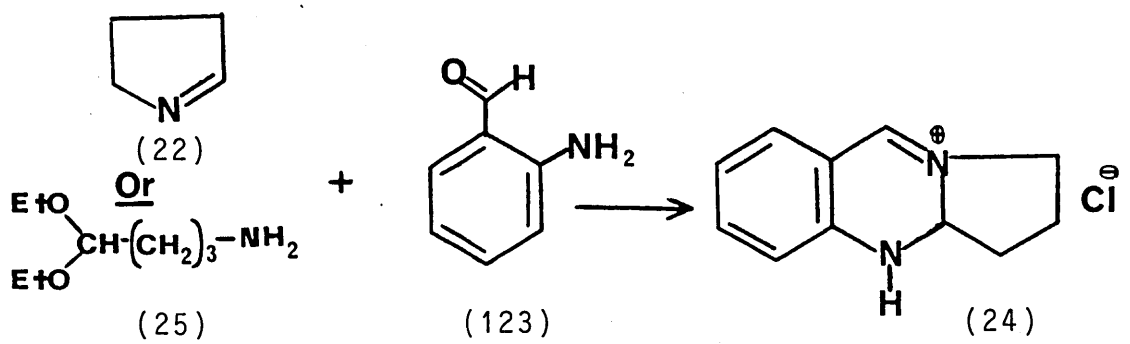
Scheme 3

Similarly Mohrle and Siedel[41] describe the synthesis of these isomeric [1,2-a] and [2,1-b] pyrroloquinazolones or their pyridoquinazolone counterparts (14) and (19) from the reaction of (4) with either γ-butyrolactone (20) or δ-valerolactone (21) at high temperature and pressure (sealed tube). The reported yields are good (64% for the pyrroloquinazolones) but unlike the Vittory Landii synthesis shown earlier the product ratio lies in favour of the [1,2-a] analogues (Scheme 4). Although the reactions of Mohrle and Landii Vittory are not identical the alteration in product ratio may indicate that the [2,1-b] analogue is the kinetic product in this type of cyclisation reaction although this is by no means certain.



Scheme 4

In 1936 Schöpf[42] synthesised deoxyvasicine (3) under the so called "physiological conditions" in vitro from Δ^1-pyrroline (22) and 2-aminobenzaldehyde (23).



(22) (25) (123) (24)

The condensation product of these two compounds the dihydroquinazolinium derivative (24), undergoes a rearrangement to give (3) in the presence of a platinum catalyst. However it was not until 1947 when Schöpf[37] revised this synthesis that (24) was used to prepare deoxyvasicinone(1). In this revised scheme Schöpf employed (23) and 4-aminobutanal-diethylacetal (25) to obtain (24) which was then oxidised at constant pH with potassium ferricyanide. The deoxyvasicinone (1) thus obtained was characterised via its picrate.

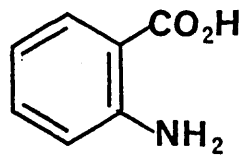
Sakamoto[43] has since modified the Schöpf synthesis and isolated (24) as its hydroxide from Δ^1-pyrroline (22) and 2-aminobenzaldehyde (23). This hydroxide was almost quantitatively converted to (1) by chromic acid oxidation in dilute sulphuric acid.

Δ^1-pyrroline (22) has been identified[44] as the product of enzymatic oxidation of putrescine (1,4-diaminobutane) (26) and this may explain the choice of reactants by Chatterjee and Ganguly[5] in their synthesis of deoxyvasicinone (1). In this synthesis anthranilic acid (27) and 4-aminobutanoic acid (28) were heated at reflux

in xylene with one equivalent of P_2O_5 as dehydrating reagent. Purification of the reaction mixture by chromatography gave (1) as the major product. Johne et al[35] and Jain et al[22] have subsequently used this preparatory method to good effect in their respective investigations into nitrated A ring analogues of deoxyvasicinone. Such derivatives were subsequently reduced to benzamido and amino derivatives using standard reductive techniques.

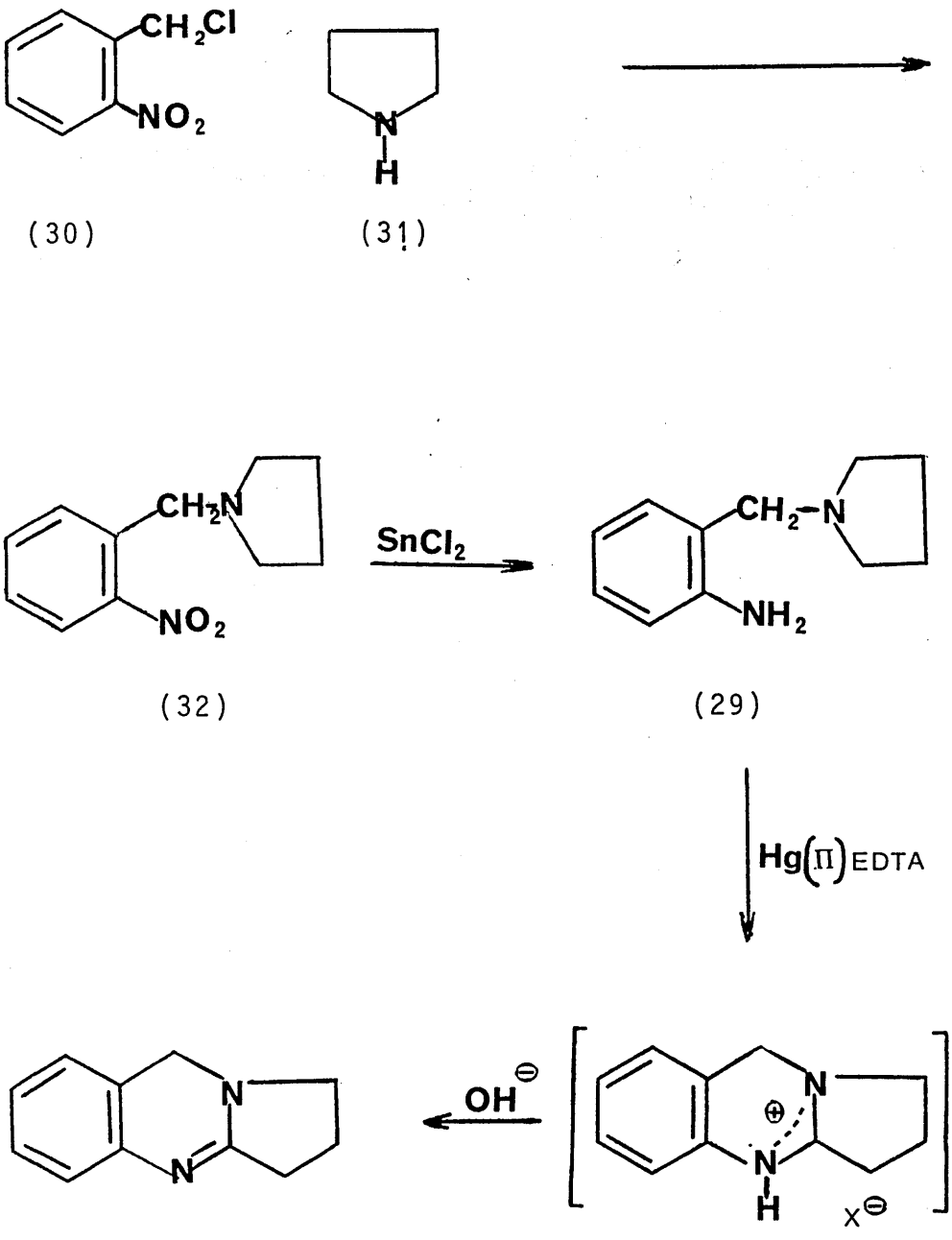
$NH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}NH_2$ (26)

$NH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}COOH$ (28)



(27)

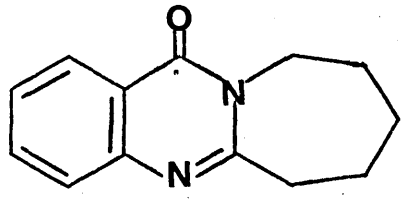
Mohrle and Gundlach[45] discovered that the mercuric EDTA dehydrogenation of cyclic amines with neighbouring aromatic amino groups yielded in every case a cyclic amidine identical to Schöpf's[42] (Scheme 5). Thus, deoxyvasicine (3) was obtained from 1-(2-aminobenzyl) pyrrolidine (29) derived from 2-nitrobenzyl chloride (30) and pyrrolidine (31), via reduction of the intermediate 1-(2-nitrobenzyl)pyrrolidine (32) with stannous chloride.



(30) (31) (32) (29) (3)

Scheme 5

Meth Cohn, Suschitzky and Sutton[46] previously postulated an intermediate dihydroquinazolone in their preparation of quinazolones via the dehydrogenation/oxidation of 2-aminobenzylamines with manganese dioxide. Mohrle and Gundlach employed this oxidation technique and prepared (1), (14) and 1,2,3,4,5,11-hexahydroazepino[2,1-b]-quinazolin-11-one (33) in good yields.

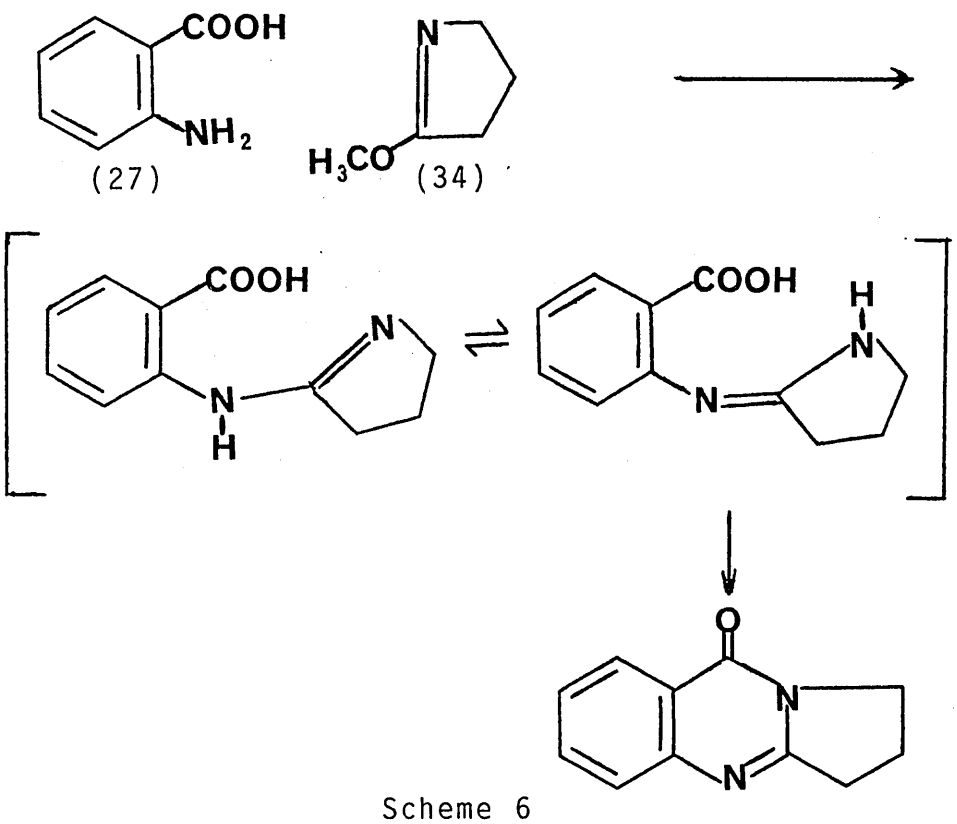


(33)

Although the synthetic pathways illustrated are effective and allow the preparation of pyrrolo[2,1-b]quinazolones in reasonable yields, the facts that isomeric pairs are often formed and that the syntheses are circuitous or time consuming is unsatisfactory. In order to overcome these problems a number of new preparatory routes which utilise the condensation reaction between anthranilic acids and cyclic amides or their O-alkyl ethers have been developed.

The predominant type of pathway involving O-alkyl ethers was instigated by Peterson and Tietze[47], who achieved the formation of pyrrolo, pyrido and azepino[2,1-b] quinazolones in high yields using mild conditions, via the reaction of a cyclic 2-aminocarboxylic acid having an unsubstituted amino group with a cyclic lactim ether.

Generally the reaction proceeded by mixing the acid and the required unsubstituted imidate together in a suitable solvent (or neat in some cases). Ring closure occurred following simple stirring or was promoted by the occasional heating of the reaction mixture. The reaction itself is thought to be a two stage process which goes to completion through an intermediate cyclic amidine, the tautomeric form of which loses one mole of water to yield the required product, e.g. the reaction of 2-methoxy-1-pyrroline (34) with (27) yielded (1). (Scheme 6).



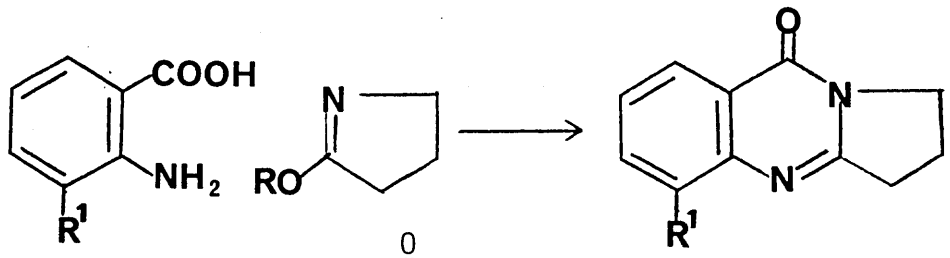
Scheme 6

(1)

Nucleophilic displacement of the methoxy ether grouping by the amino group of the O-amino carboxylic acid leads to the formation of the amidine intermediate which spontaneously rearranges to its tautomer, the existence of which is not unreasonable as enamine-imine tautomerism is well known[48] . Condensation/cyclisation, presumably the driving force for the intermediate rearrangement, then takes place via reaction of the sp^3 hybridised nitrogen of the pyrrolidine ring with the carboxyl grouping.

Shkrob et al[49] and Devi et al[29] have achieved similar results, the latter using benzene as solvent to prepare A and C ring substituted analogues of deoxyvasicinone.

Onaka[31] sought to correlate the in vitro synthesis of (1) and 5-hydroxy-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (35) with similar processes in vivo. He thus postulated intermediates (37) and (38) as the biological equivalents of the cyclic lactim ethers, and proposed that these Vilsmeier type amide phosphates or pyrophospates could play an important part as active precursors in alkaloid biosynthesis.

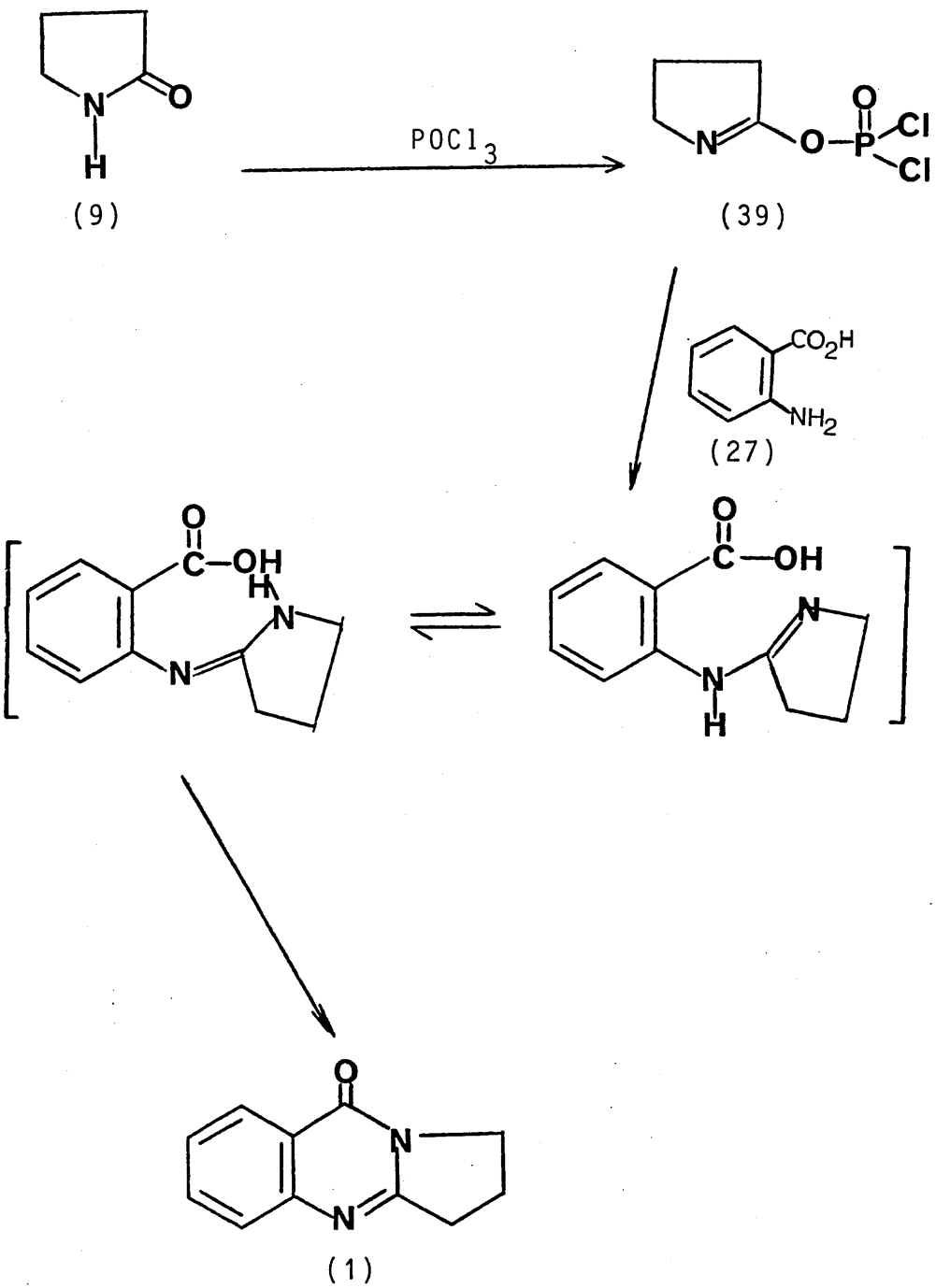


(27) R^1=H (37) R= $-P(=O)(O^{\ominus})-O^{\ominus}$ (1) R^1=H

(36) R^1=OH (38) R= $-P(=O)(O^{\ominus})-O-P(=O)(O^{\ominus})-O^{\ominus}$ (35) R^1=OH

It may have been this observation which prompted Shakhidoyatov et al[50] to initiate their major study into polymethylenequinazolone formation. Pyrrolo, pyrido and azepino[2,1-b]quinazolones were isolated following the reaction of a lactam with an anthranilic acid in the presence of a dehydrating reagent such as phosphorus oxychloride, thionyl chloride or phosphorus trichloride /phosphorus pentachloride.

The first step in the reaction is assumed to be the formation of a cyclic imine (39) similar to that postulated by Onaka[31]. This was substantiated following the treatment of 2-pyrrolidinone (9) with $POCl_3$ at room temperature. An exothermic reaction is observed with vigorous evolution of hydrogen chloride. The reaction between this Vilsmeier type imine (39) and an anthranilic acid gave cyclic amidines, which cyclised following rearrangement to yield the desired pyrrolo[2,1-b]quinazolinones. (Scheme 7).

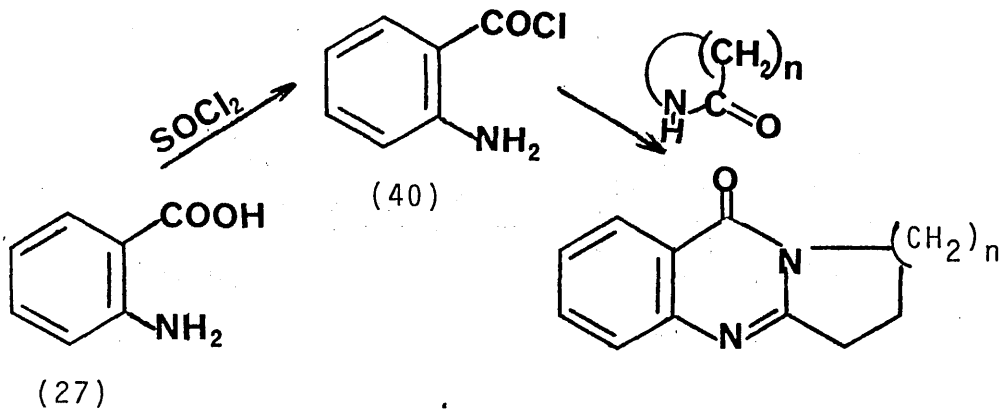


Scheme 7

This revised synthetic route has been used by Shakhidoyatov to prepare numerous substituted and unsubstituted pyrrolo, pyrido and azepino[2,1-b]quinazolones. The effects of introducing substituents into the A and C rings via substituted anthranilic acids and substituted lactams respectively were investigated. Although the introduction of nitro, amino and halo substituents into the aromatic nucleus had little effect on the subsequent yield of the product, the reactivity of various lactams was shown to decrease with increasing ring size and with the introduction of substituents (chloride and phenyl). Following this investigation two other groups developed synthetic routes to pyrrolo[2,1-b]quinazolones using dehydrating conditions.

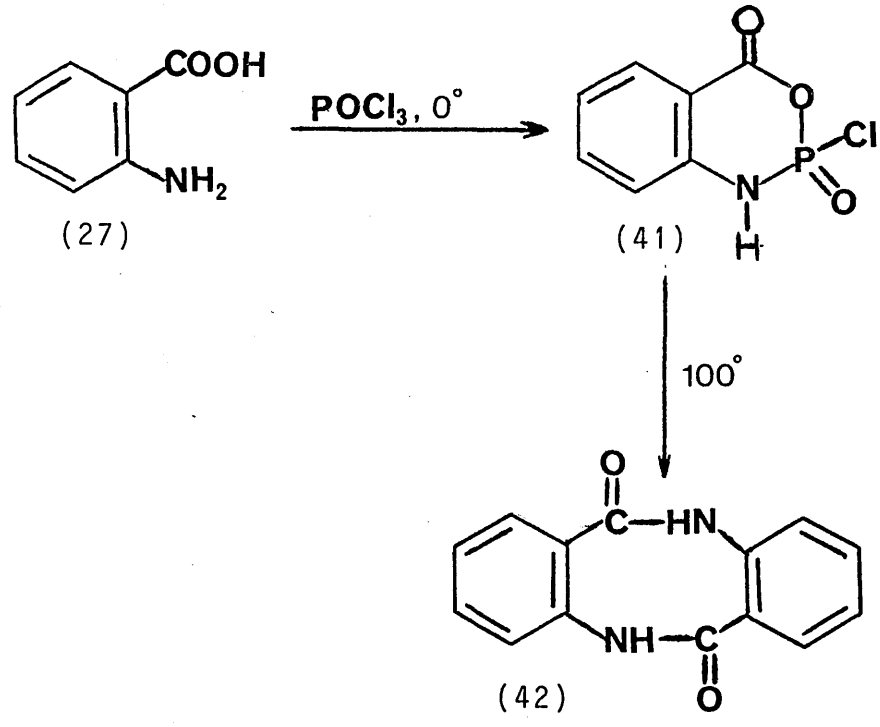
Koizumi et al[51] prepared numerous A-ring substituted pyrrolo and azepino[2,1-b]quinazolones from the reaction of anthranilic acids with lactams and thionyl halides in a variety of non polar solvents.

Koizumi has since postulated an intermediate anthranoyl chloride (40) unlike the intermediate (39) proposed by Shakhidoyatov. (Scheme 8).



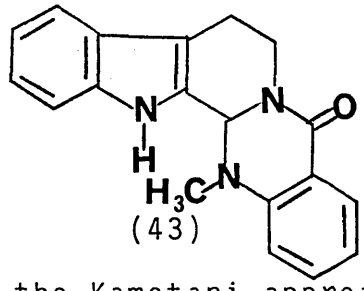
Scheme 8

While solvent effects cannot be disregarded in this context, the Koizumi intermediate (40) has already been postulated and repudiated by the Shakhidoyatov group[50], who cite as evidence the formation of an anthranilic acid lactam, presumably of structure (41) following reaction of anthranilic acid with $POCl_3$ at 0^o . This lactam (41) when heated to 100^o with or without $POCl_3$ gave the dianthranilate (42). (Scheme 9)

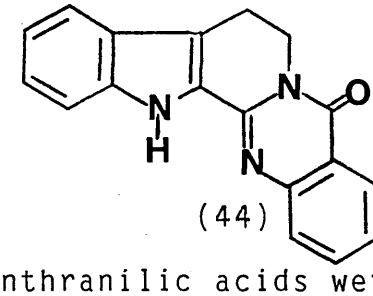


Scheme 9

A similar intermediate would be expected to be formed in the reaction of anthranilic acids with the other dehydrating reagents (PCl_3/PCl_5, $SOCl_2$) consequently leading to the formation of dianthranilate (42). The dianthranilate was in fact isolated as the major product from the reactions of anthranilic acids with lactams in the presence of these dehydrating reagents and because it is known that anthranilic acid chlorides react with lactams to given anthranilamide derivatives which then cyclise to give (1) or its analogues as the major product[50] it seems unlikely that (40) is an intermediate in the syntheses. Further substantiation of Shakhidoyatov's claims is provided by examining the results of Kametani and co-workers[38] obtained during their investigations into the synthesis of evodiamine (43) and ruteacarpine (44).



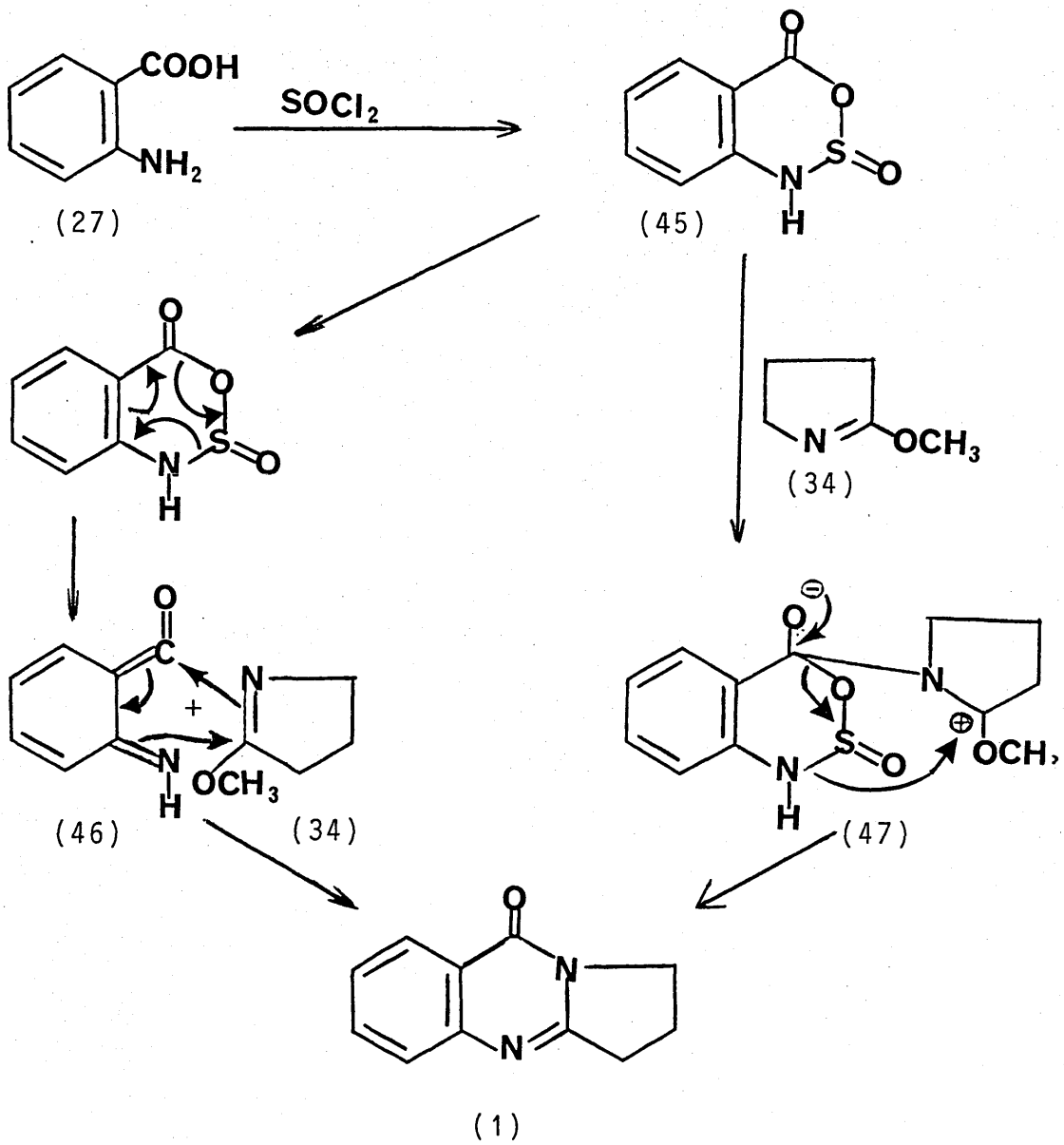
(43)



(44)

In the Kametani approach anthranilic acids were treated with thionyl chloride in a non polar solvent (benzene) prior to the addition of cyclic lactams or their derviatives. Unlike Koizumi[51] no intermediate anthranoyl chloride (40) was proposed because of the isolation of an intermediate anthranilic acid lactam similar to that produced by Shakhidoyatov[50]. This

sulphur analogue (45) was isolated as a pale yellow syrup and identified as the sulfinamide anhydride after comparing mass spectral and infrared data[52]. The reaction of (9)[38e] or (34)[38d] with this precursor (45) in dry benzene afforded (1) in 93% and 64.5% yields respectively. The authors have proposed two mechanistic pathways for the latter of these syntheses (Scheme 10).



Scheme 10

In the first pathway the anhydride (45) may have spontaneously rearranged to the iminoketene (46) with loss of SO_2. Regiospecific addition of (46) to (34) via a concerted (4 + 2)π cycloaddition reaction would give the required product. However, since (45) is prepared at 80° without such a decomposition to the iminoketene (46) taking place, a step wise mechanism via the intermediate (47) is more likely. A number of errors exist in these papers. The most obvious and blatant of these being the inclusion of the melting point of deoxyvasicinone (1) as 196°- 198°, an error of almost 90° and consistent with the melting point of the hydrochloride of (1). This error is compounded by the fact that Kametani refers to Onaka's spectral data in support of his own proposed structure[38d]. Unfortunately, Onaka's data is itself erroneous showing the C-2 methylene group of (1) at δ 3.17 and not at the normally recognised δ 2.30. Also no mention is made to a melting point for (1) by Onaka except by means of reference.

The methods derived from the techniques of Shakhidoyatov[50] and Peterson and Tietze[47] have obvious advantages over the other synthetic routes outlined above. They both yield monoisomeric product and are relatively simple reactions (one and two step from the required 2-pyrrolidinone respectively). This compares favourably with the circuitous routes illustrated.

Nitroalkanoic Acid Esters

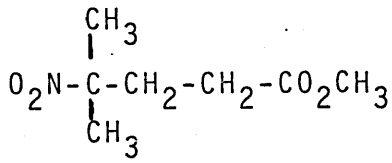
The addition of nitromethane as the sodio derivative, to esters of benzalmalonic, cinnamalmalonic and benzoylacrylic acids has been described by Kohler et al[53,54].

Kloetzel[55] attempted such Michael condensations using feebly basic condensing agents such as piperidine but was unable to obtain analytically pure compounds.

It was Bruson[56] who eventually succeeded in using amines as catalysts in the condensation of acrylic acid esters and mononitroalkanes having a reactive hydrogen atom contiguous to the nitro group. This was achieved using benzyltrimethylammonium hydroxide (Triton B) as catalyst in inert solvents, such as benzene, ether or dioxan. Compounds such as methyl 4-methyl-4-nitropentanoate (48) and dimers such as dimethyl 4-nitropimelate (49) were isolated in high yields from the appropriate nitroalkane and methyl acrylate. (Page 27).

Kloetzel[55] eventually effected such condensations with triethylamine as catalyst and succeeded in isolating similar compounds to those of Bruson. Moffett[58] used a refinement of the Bruson technique in the preparation of (48) for organic syntheses and this remains a most detailed account of this type of reaction.

Nelson J. Leonard and Gradus L. Shoemaker[59] prepared mono and di-esters such as methyl 2-methyl-4-nitrobutanoate (50) and dimethyl 2,6-dimethyl-4-nitropimelate (51),



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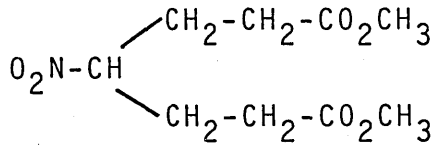

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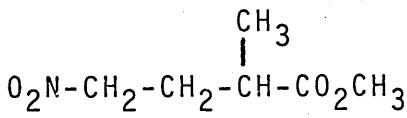
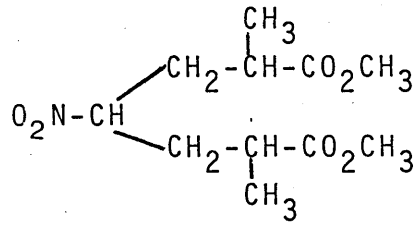


(50)



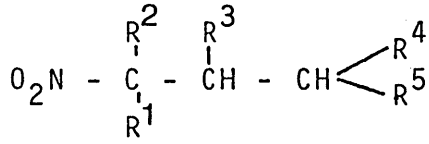
(51)

which they found useful as precursors in their subsequent synthesis of substituted pyrrolizidines. They seemed oblivious to Bruson's work and identified diethylamine as the most effective catalyst for promoting the formation of (50) and similar compounds. Interestingly the group did employ quaternary ammonium salts as catalysts in the subsequent reaction of (50) or its analogues with acrylic esters to prepare (51) or its analogues in improved yields.

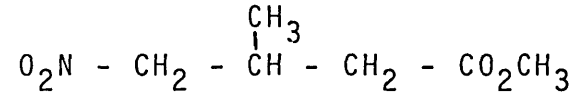
A comprehensive investigation was conducted by Cologne and Pouchol[60] into the use of sodium alkoxides, Triton B and secondary and tertiary amines as promoters of

Michael type condensations between nitroalkanes and esters of acrylic acids or between esters having an active methylene group and nitroalkenes[61]. The methods of Bruson[56,57] and Bahner[61] being routinely employed to prepare a wide range of esters of substituted nitroalkanoic acids.

An interesting choice of catalyst was made by Kambe and Yasude[62]. This group had previously reported the additions of reactive methylene compounds to α,β - unsaturated compounds using potassium fluoride as catalyst and found that compounds of general formula



could be prepared in a similar fashion from nitroalkanes and a range of Michael acceptors, e.g. methyl 3-methyl-4-nitrobutanoate (52).



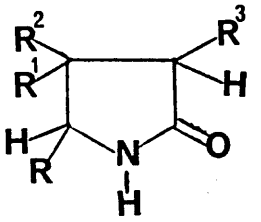
(52)

The yields of all the compounds mentioned by Kambe and Yasude were found to increase with increased KF concentrations and increased solvating power of the solvent employed.

2-Pyrrolidinones

Numerous preparatory routes to 2-pyrrolidinone (9) have been developed since the early work of Gabriel[63] and Tafel[64]. These routes were devised due to the increased usage of 2-pyrrolidinones as solvents for polymers, insecticides, in petroleum processing and separation or as plasticisers for acrylic polymers and copolymers or as decolourising agents in kerosene or other hydrocarbons[65]. As a consequence both 2-pyrrolidinone (9) and its analogue 5-methyl-2-pyrrolidinone (53) are now established commercial reagents. Other 2-pyrrolidinones have as yet no commercial importance but recent interest in these γ-amino acid derivatives as precursors of different biologically active substances[66,67] or in the area of heterocyclic polymers[68-71] has resulted in a number of pathways for their synthesis being developed e.g. catalytic hydrogenation or chemical reduction.

Cologne and Pouchol[72] developed a simple method of preparing numerous 2-pyrrolidinones via the catalytic hydrogenation of the esters of nitro-alkanoic acids over Raney nickel. 3-Carbalkoxy-2-pyrrolidinones were also prepared from the esters of γ-nitrodiacids. These pyrrolidonyl esters were saponified and then decarboxylated at high temperature to give the required 2-pyrrolidinone.



(9) $R=R^1=R^2=R^3=H$

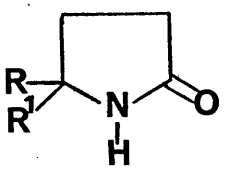
(53) $R=CH_3, R^1=R^2=R^3=H$

(54) $R^1=CH_3, R^1=R^2=R^3=H$

(55) $R^1=R^2=CH_3, R=R^3=H$

(56) $R^3=CH_3, R=R^1=R^2=H$

Smirnova[66] et al have used similar techniques to prepare (9), (54) and 5-carbethoxy-2-pyrrolidinone (57), whilst Moffett[73] has written a detailed account of the synthesis of 5,5-dimethyl-2-pyrrolidinone (58) also using a similar method.



(57) $R=H, R^1=CO_2C_2H_5$

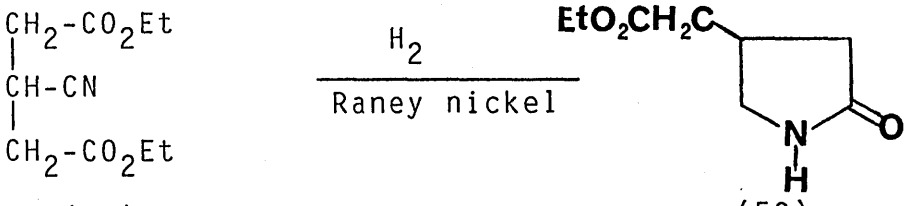
(58) $R=R^1=CH_3$

The pyrrolidinone (58) has been prepared by the hydrogenation of 5-amino-2,2-dimethylpyrroline-1-oxide over Raney nickel[74] and also via the hydrolysis of 5-imino-2,2-dimethylpyrrolidine in the presence of Raney nickel[75].

A minor deviation from the technique of Cologne and Pouchol was devised by Larkin and Kreuz[65] who isolated 2-pyrrolidinones by the catalytic hydrogenation of nitrocarboxylic acids (previously prepared from the oxidation of dinitroalkanols).

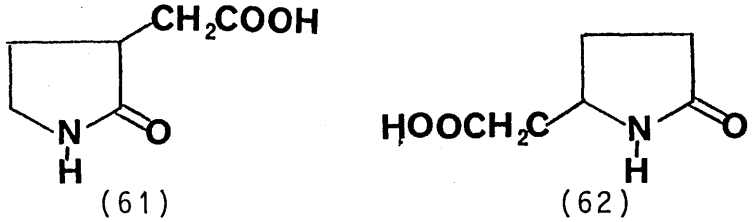
Although the hydrogenation of gaseous 2-cyanopropionic acid alkyl esters over a variety of catalysts is

efficient, producing 2-pyrrolidinones in yields exceeding 90%[76], the equipment required prohibits its general application. However, Henecka et al[77] demonstrated that the reductive process could be achieved by 'normal' catalytic hydrogenation over Raney nickel and isolated 4-ethoxycarbonylmethyl-2-pyrrolidinone (59) in excellent yield from diethyl 3-cyanoglutarate (60).



(60) (59)

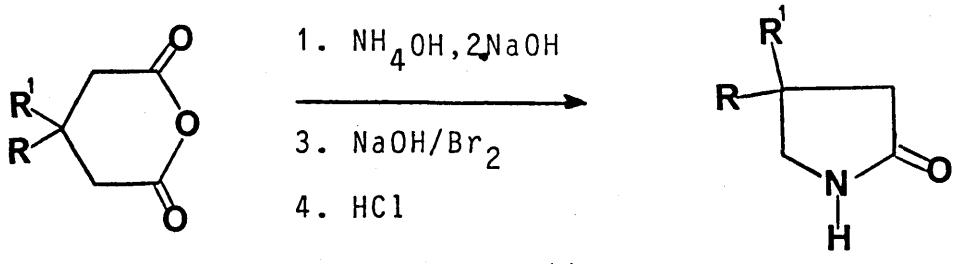
Similar compounds to (59) are known. Yakhontov[78] has reported the acid (61), whilst Evans[79] and Kato et al[80] have recorded the preparation of the acid (62) and a number of its esters.



(61) (62)

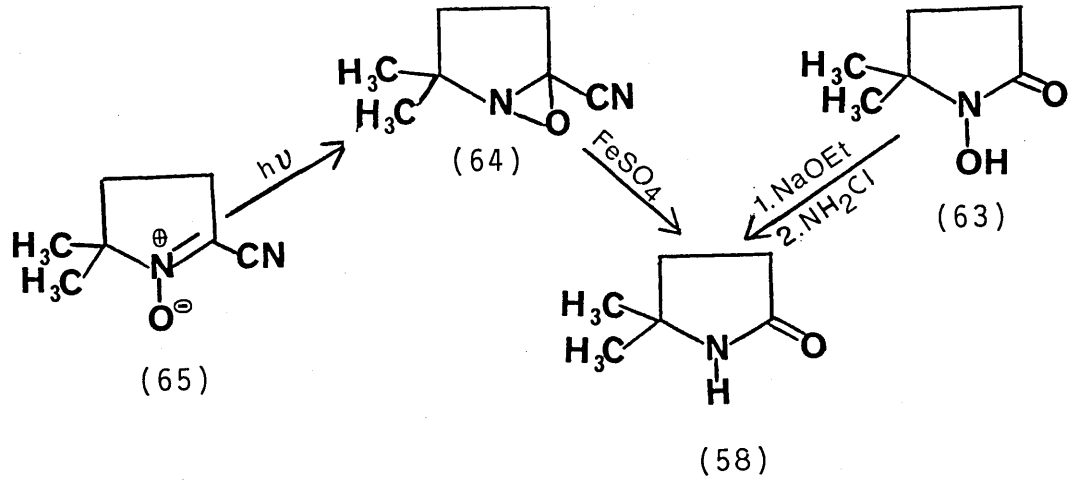
The hydrogenation techniques illustrated are generally more efficient than other chemical routes to 2-pyrrolidinones. However, a number of interesting pathways to these 2-pyrrolidinones do exist and some of these are illustrated in the following section.

Sircar[81] obtained (9), (54) and (55) from the Hoffman degradation of the appropriate sodium glutaramate (prepared from the corresponding glutaric anhydride). (Scheme 11).



Scheme 11

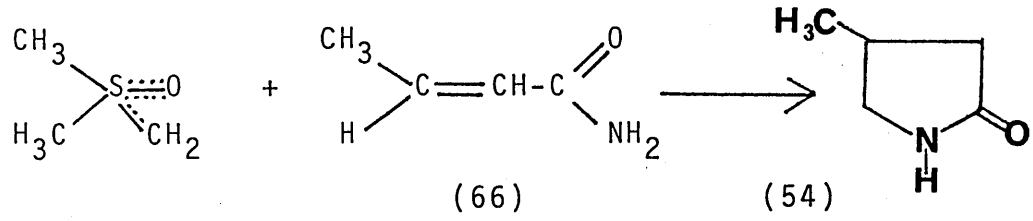
Other relevant preparations of disubstituted 2-pyrrolidinones include the method of Bellasio and co-workers[82], who isolated 5,5-dimethyl-2-pyrrolidinone (58) as its hydrochloride following treatment of the sodium salt of 1-hydroxy-5,5-dimethyl-2-pyrrolidinone (63) with chloramine. The hydroxy compound (63) was prepared from (48) followed by reduction in the presence of zinc dust and ammonium chloride. Black et al[83] prepared (58) via iron II sulphate treatment of the cyanooxaziridine (64) derived from the photorearrangement of 2-cyano-5,5-dimethyl-1-pyrroline-1-oxide (65).



A one step synthesis of 2-pyrrolidinones, involving the amido ethylation of simple esters with N-acylaziridines was developed by Stamm, Woderer and Wiesert . Thus triphenylmethyl sodium (trityl sodium) was used to generate the enolate salt of ethyl 2-methylpropanoate the reaction of which with N-benzoylaziridine afforded 3,3-dimethyl-2-pyrrolidinone.

Monosubstituted analogues of 2-pyrrolidinone have been isolated by several groups.

Metzger and Seelert[85] discovered that 2-pyrrolidinones could be prepared from amides of α,β-acrylic acids following a methylene insertion reaction using the Corey reagent dimethylsulphoxonium methylid. For example reaction of crotonamide (66) with this oxosulphonium ylid gave (54) in 61% yield. (Scheme 12).



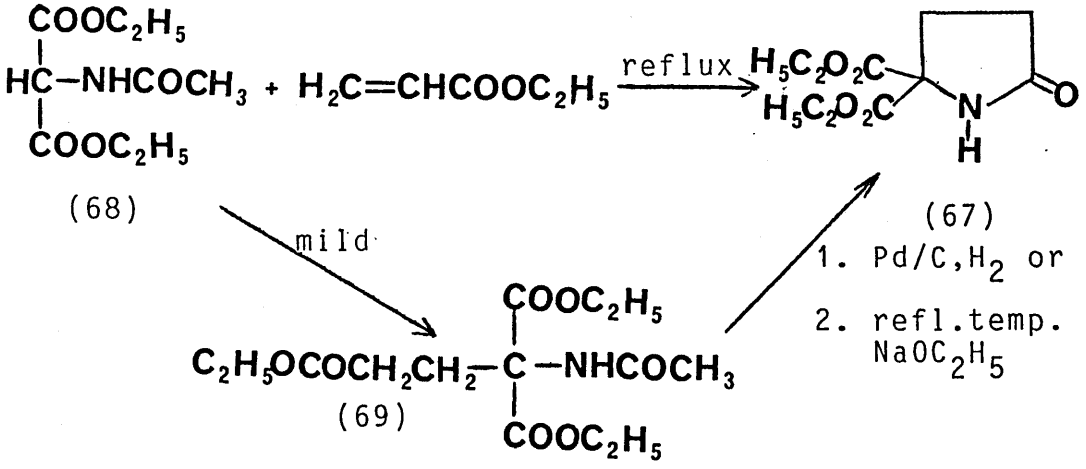
(66) (54)

Scheme 12

3-Methyl-2-pyrrolidinone (56) has been prepared by Fles et al[86] from free 4-amino-2-methylbutanoic acid generated in situ from 2-methyl-4-phthalimidobutanoic acid following treatment with hydrazine hydrate. Cyclisation of this free acid was effected by

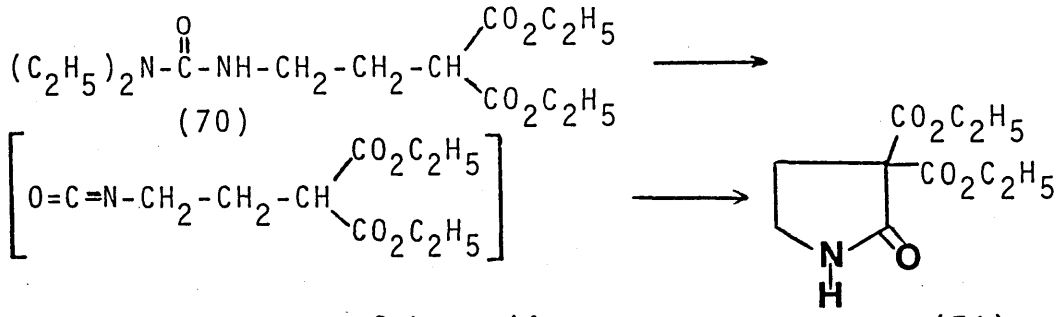
esterification and ammonolysis.

Many syntheses of esters of 2-pyrrolidinones exist in addition to those outlined in the preceeding text. Blicke and Jung Lu[87] successfully converted diethyl glutamate to 5-carbethoxy-2-pyrrolidinone (57) by refluxing the former in xylene, whilst its disubstituted analogue (67) was isolated as one of the products from the addition of diethyl acetamidomalonate (68) to ethyl acrylate by Cocolas and Hartnung[88]. The compound (67) was formed at reflux temperatures whereas mild conditions favoured the normal Michael adduct (69). (Scheme 13). The elevated temperatures which promote cyclisation are also condusive to bimolecular hydrolysis thereby aiding cleavage of the amide bond and hence formation of the desired 2-pyrrolidinone. This type of cyclisation was not entirely unexpected having previously been reported by Connor and McClellan[89].



Scheme 13

Stamm and Budny[90] similarly used heat to induce the cyclisation of the substituted urea (70) to give 3,3-dicarbethoxy-2-pyrrolidinone (71) (Scheme 14).

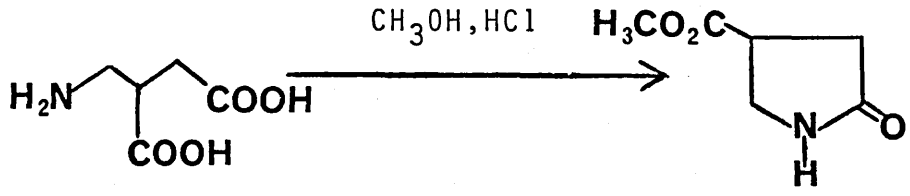


Scheme 14

(70)

(71)

whilst thermal cyclisation of aminomethylsuccinic acid (72), by refluxing in a hydrogen chloride saturated solution of methanol for three hours afforded 4-carbomethoxy-2-pyrrolidinone (73).



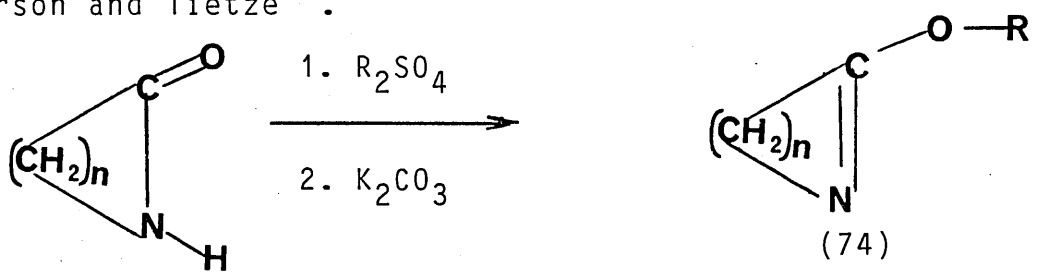
(72)

(73)

O-alkylpyrrolines.

The application of lactams to the synthesis of heterocyclic systems depends on the activation of their amide function. Thus the conversion of 2-pyrrolidinones into their O-alkylpyrroline derivatives offers great scope for the use of these lactams in organic chemistry[91].

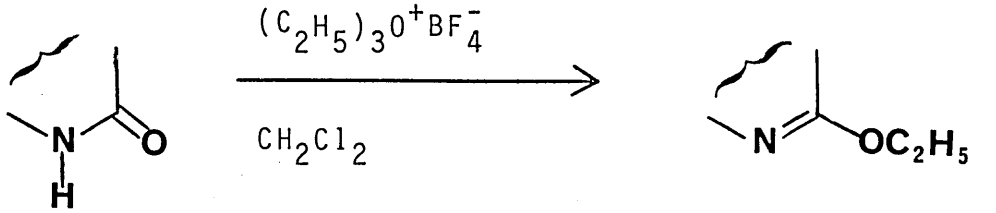
Two main alkylation techniques are available for the formation of such O-alkylimino ethers. The first, using the direct action of dialkyl sulphates on solutions of the corresponding lactam has been demonstrated by Schlack[92] and Benson and Cairns[93]. Schlack proposed the use of hydroxyl free solvents which aided the preparation of numerous O-alkyllactim ether salts by preventing ring cleavage. The free ethers (74) were obtained from these salts by carefully discharging them into potassium carbonate solutions (Scheme 15) and purifying them by distillation. These techniques have been used to good effect by Etienne and Correia[48] and Peterson and Tietze[94].



(74)

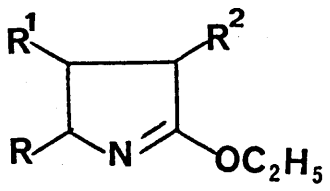
Scheme 15

In cases where alkylation cannot be effected by dimethyl sulphate, triethyloxonium tetrafluoroborate[95] may be used. O-alkylation of secondary amides using triethyloxonium tetrafluoroborate is usually carried out in dichloromethane or similar solvent. (Scheme 16).



Scheme 16 $+Et_2O$

Isolation of the free ethers was accomplished using the method previously described. Glushkov et al[91] illustrated the effectiveness of triethyloxonium tetrafluoroborate when attempting to alkylate 3-carbethoxy-2-piperidone (75). DMS proved ineffectual yet (75) was readilly ethylated with triethyloxonium tetrafluoroborate. Other Russian scientists used triethyloxonium tetrafluoroborate to prepare numerous cyclic lactim ethers even though DMS or similar alkylating reagents may have been as effective.



(76)[91,96] $R=R^1=R^2=H$

(77)[96] $R=CH_3, R^1=R^2=H$

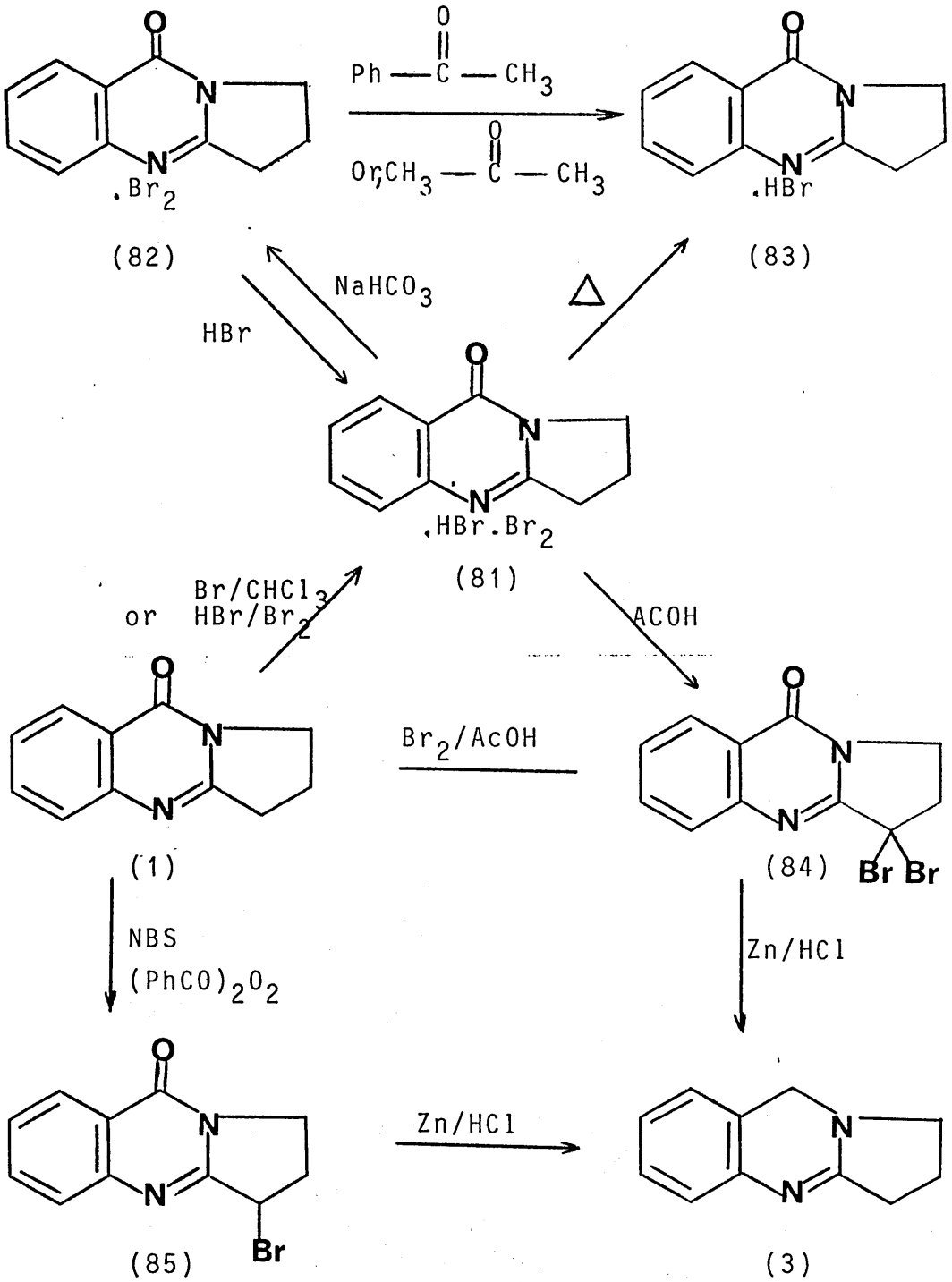
(78)[96] $R=R^2=H, R^1=CH_3$

(79)[97] $R=R^1=H, R^2=CH_3$

Reactions of deoxyvasicinone (1)

Tne reaction of deoxyvasicinone (1) and a number of its analogues with electrophilic reagents have been reported as following three main pathways. Reaction takes place either at the active methylene group (C-3 in the pyrrolo ring) or via co-ordination of the sp^2 hybridised nitrogen atom of the quinazolone fragment or by 'normal' electrophilic aromatic substitution.

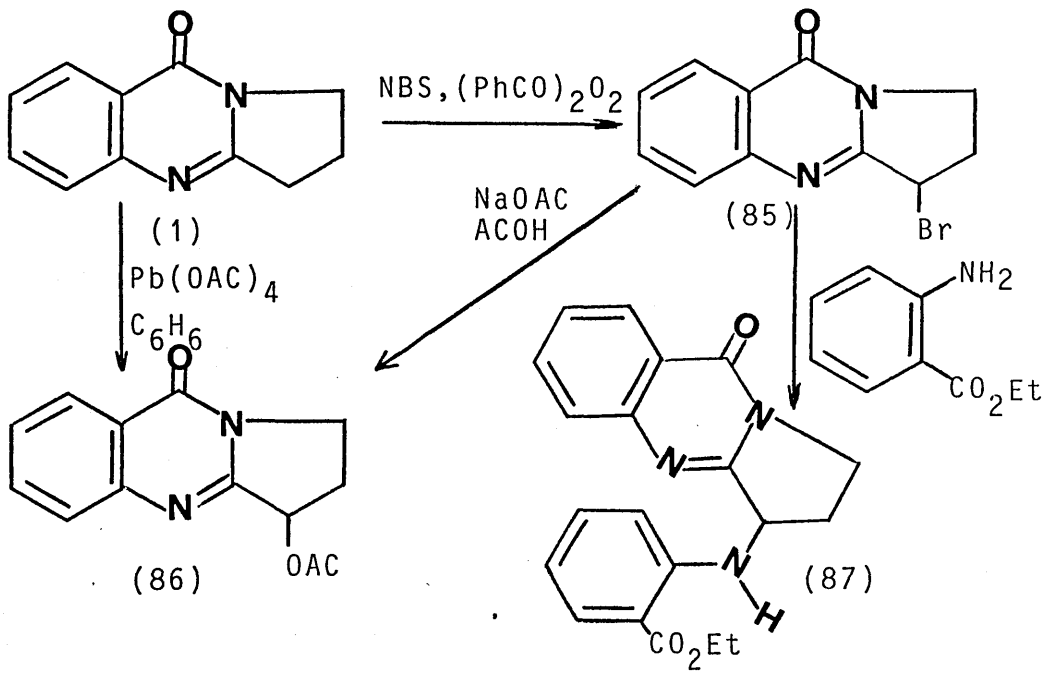
Oripov et al[34,99] investigated the bromination in pyrrolo, 7-nitropyrrolo-, pyrido-, azepino- quinazolones and discovered that the product was dependant upon the brominating reagent and the solvent system employed (Scheme 17). The perbromide (81) was isolated from the bromination of (1) conducted in various solvent systems (chloroform, glacial acetic acid, concentrated sulphuric acid and 80% methanol) in the cold with catalysts present (iron filings, iron filings and iodine or aluminium chloride) or in the absence of catalysts. Interestingly no aromatic bromination occurred despite the use of ferric chloride or the other catalysts illustrated even when the reaction was carried out in the presence of pyridine.


Ph — C — CH3
O
Or CH3 — C — CH3
O
.Br2
.HBr
(82)
(83)
NaHCO3
HBr
Δ
.HBr.Br2
(81)
Br/CHCl3
or HBr/Br2
ACOH
Br2/AcOH
(1)
(84)
Br Br
NBS
(PhCO)2O2
Zn/HCl
Zn/HCl
Br
(85)
(3)

Scheme 17

The perbromide (81) was also obtained from the reaction of (1) with hydrogen bromide and bromine as well as from the reaction of the molecular complex (82) with hydrobromic acid. This latter reaction may be reversed by the addition of a 5% aqueous solution of sodium bicarbonate. On heating or prolonged standing (81) loses a molecule of bromine to give the hydrobromide (83) which can be isolated from the reaction mixture following preparation of the perbromide (81) or by treatment of the molecular complex (82) with either acetone or acetophenone. The bromination of (1) effected by heating in 75% acetic acid gave only the 3,3-dibromo-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (84). Oripov suggested that the sp^2 hybridised nitrogen atom of the quinazolone ring imparts lability to the hydrogen atoms of the methylene group in the α position to the carbon-nitrogen double bond of (1). Subsequent abstraction of a hydrogen atom followed by attack by a bromine cation leads to the intermediate (85). The methine proton of (85) is as a consequence made more acidic and therefore rapid conversion to (84) takes place. The more selective N-bromosuccinimide was employed with benzoyl peroxide as initiator in carbon tetrachloride to prepare the monobromo derivative (85). Onaka[31] has used this latter technique to prepare (85) in 57% yield. Treatment of (85) with a mixture of acetic acid and sodium acetate gave acetylvasicinone (86) identical to that obtained via free radical

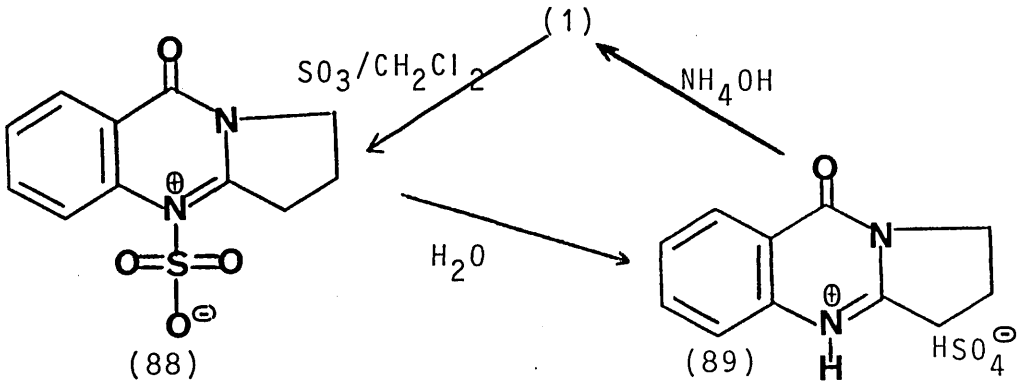
oxidation of (1) with lead tetraacetate in benzene[3],



whilst nucleophilic displacement of the bromine atom with a suitable amine realised a number of anisotes alkaloids such as anisessine (87).

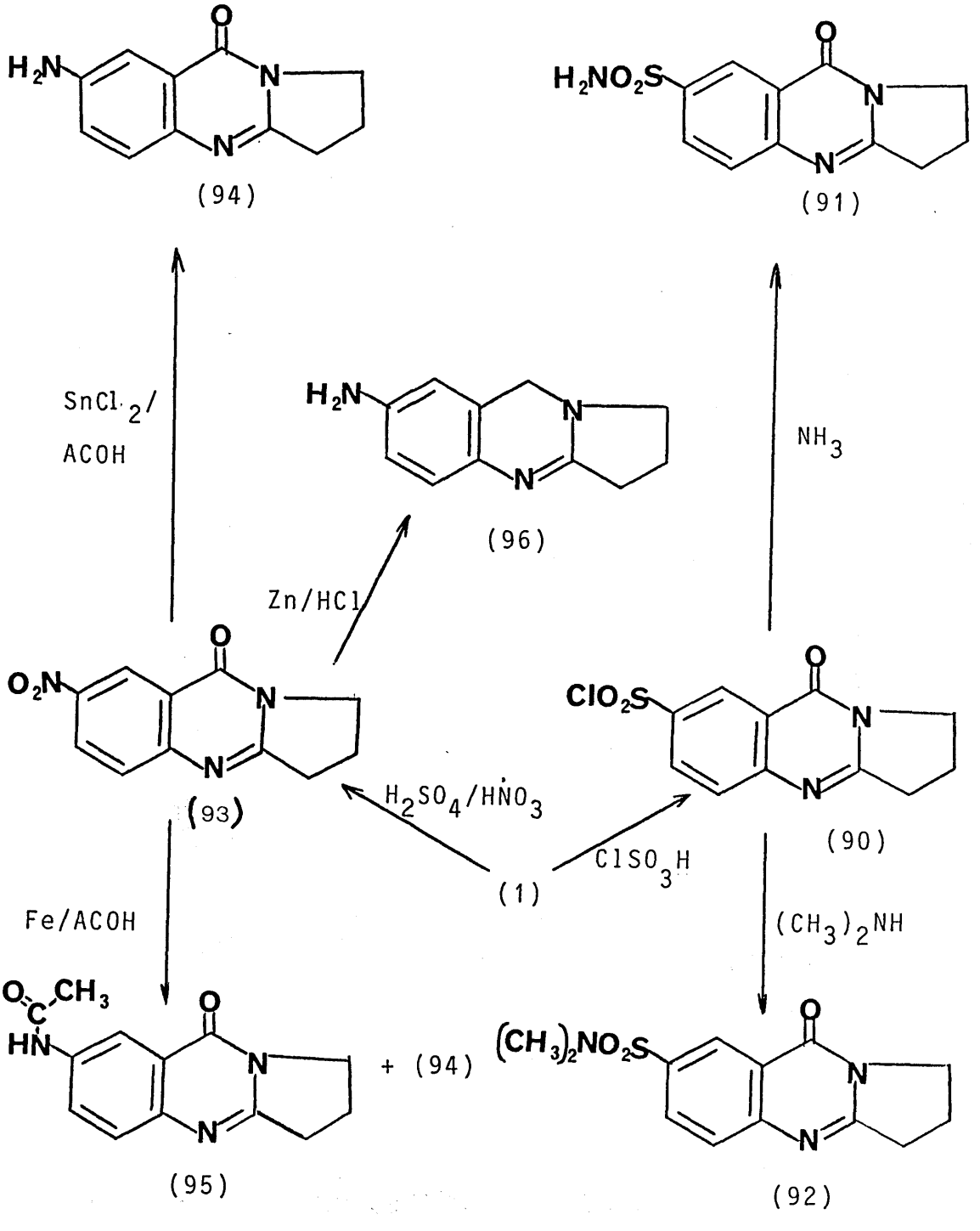
Reduction of (85) and (84) using zinc and hydrochloric acid resulted in the splitting out of bromine to give (3)[99].

The sulphonation of (1) was effected using sulphur trioxide in dichloromethane[99]. Attack takes place at the 4-position resulting in the formation of a complex (88) which is easily destroyed by water to give the hydrogen sulphate salt (89).

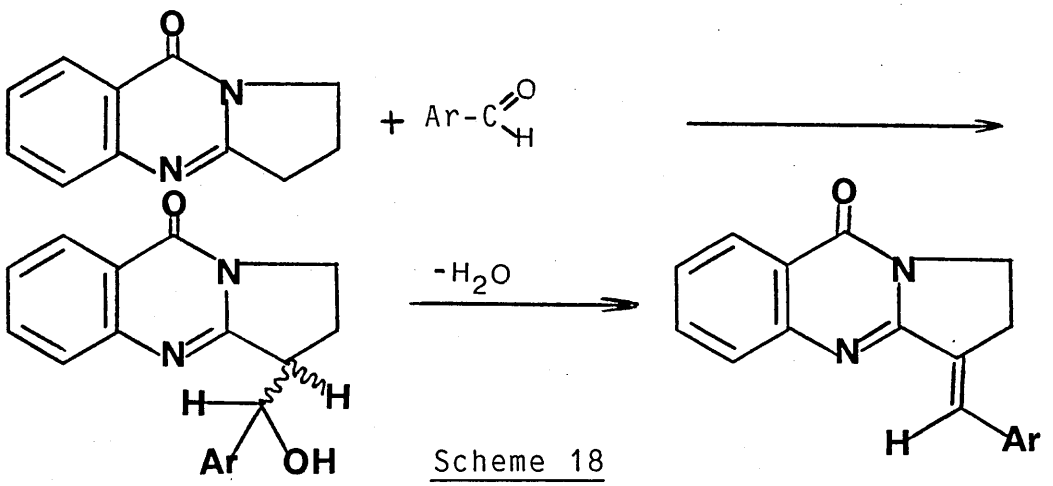


In contrast to bromination and sulphonation the chlorosulphonation of (1) yielded a product of electrophilic aromatic substitution[99]. The 7-chlorosulphonyl derivative (90) thus obtained was shown to react with ammonia or dimethylamine to yield 7-sulphonamido- and 7-(N,N-dimethylsulphonamido)-derivatives (91) and (92).

Treatment of (1) with a nitrating mixture of H_2SO_4/HNO_3 yielded 2,3-dihydro-7-nitropyrrolo[2,1-b]quinazolin-9-(1H)-one (93) indicating that nitration followed a similar course to chlorosulphonation[34,99]. Reduction of the nitro group in (93) with iron in glacial acetic acid gave a mixture of 7-amino and 7-acetylamino deoxyvasicinones (94) and (95) with a total yield of 56%, whilst reduction in the presence of stannous chloride afforded only (94) in 90% yield. The 7-benzamido deoxyvasicinone has been isolated in a similar fashion by Jain et al[23]. More drastic reduction of (93) using zinc and HCl afforded 7-aminodeoxyvasicine (96) in excellent yield.

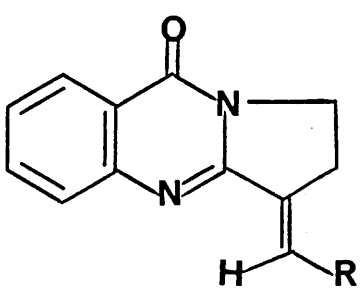

(94)
(91)
SnCl2/
ACOH
(96)
NH3
Zn/HCl
(93)
H2SO4/HNO3
(90)
(1)
ClSO3H
Fe/ACOH
(CH3)2NH
+ (94)
(95)
(92)

Condensation between aromatic aldehydes and deoxyvasicinone analogues has been investigated by several authors[3,22,36,100,101,102], the usual product being a 3-arylidene derivative. However when the substrate is a 3- or 4-nitrobenzaldehyde the intermediate alkanol may be isolated. (Scheme 18).



Scheme 18

Heterocyclic aldehydes, such as furfural (furan-2-aldehyde) undergo reaction also, yet aliphatic and unsaturated aldehydes were shown to be unreactive at atmospheric pressure[100]. Jain and Sharma[101] have recently claimed to have obtained seven derivatives from the reaction of (1) with these aliphatic and unsaturated aldehydes at elevated pressures. However, no spectral evidence was provided in support of these claims.



(97) R=CH=CH-Ph

(98) R=CH_3

(99) R=CH_2CH_3

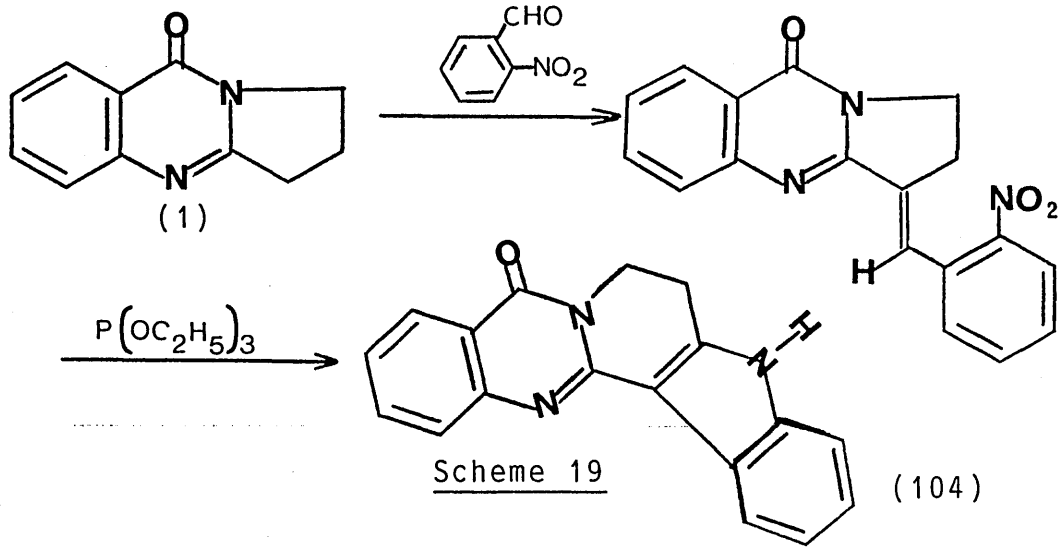
(100) R=$(CH_2)_2CH_3$

(101) R=$(CH_2)_3CH_3$

(102) R=$CH_2CH(CH_3)_2$

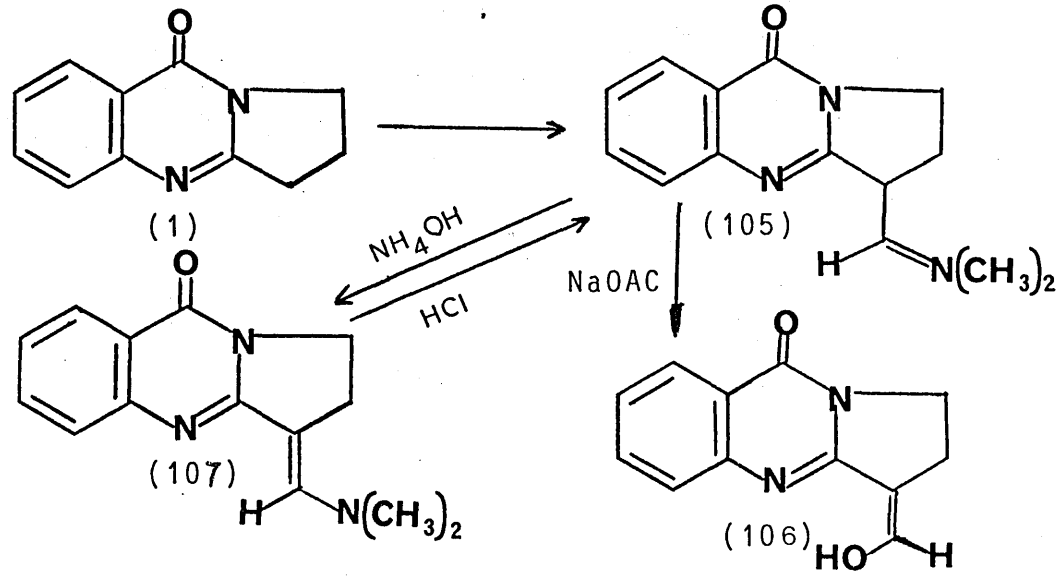
(103) R=CH=CH-CH_3

Kametani[102] has attempted to apply the condensation of 2-nitrobenzaldehyde and deoxyvasicinone (1) to the preparation of rutaecarpine (44). However the product isolated was identified as the isomeric pseudorutaecarpine (104) as shown in Scheme 19.

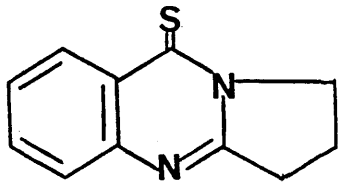


Scheme 19 (104)

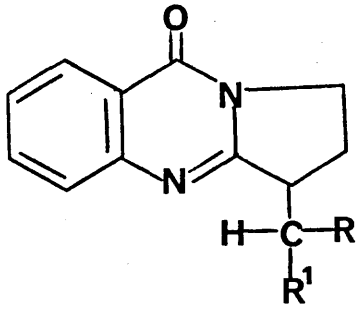
Vilsmeier-Haack formylation of (1) yielded the intermediate (105)[103,104] which was then converted to 2,3-dihydro-3-hydroxymethylenepyrrolo[2,1-b]quinazolin-9(1H)-one (106) or 2,3-dihydro-3-(N,N-dimethylamino) methylenepyrrolo[2,1-b]quinazolin-9(1H)-one (107) following treatment with aqueous solutions of either sodium acetate or ammonia.



Oripov[104] showed that the reaction of (107) with acetone cyanohydrin afforded the N,N-disubstituted amino acid (108), whilst (106) realised the cyanohydrin (109) under similar conditions.



(110)

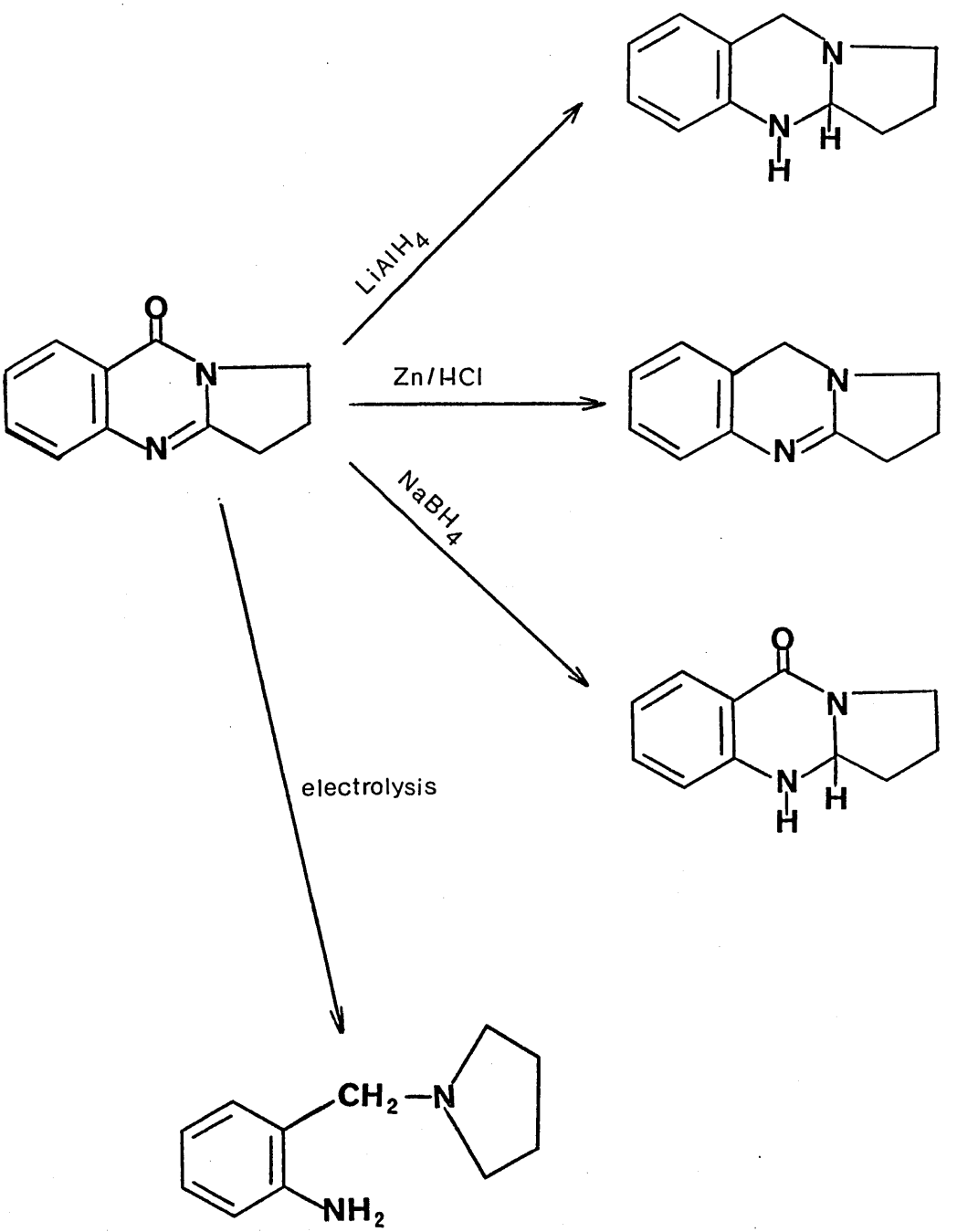


(108) R=N(CH$_3$)$_2$
R^1=COOH

(109) R=OH
R^1=CN

Both (106) and (107) were shown to be capable of acylation, amination and bromination and a detailed account of the products isolated from these reactions is given in the original literature[104]. Treatment of deoxyvasicinone (1) with phosphorus pentasulphide yields its 9-thio analogue (110) which may be selectively reduced to deoxyvasicine (3) in the presence of zinc and HCl[105].

A number of techniques have been employed to reduce deoxyvasicinone (1). Reduction of the carbonyl group is effected using dissolving metal reduction[33,106], whilst selective reduction of the carbon-nitrogen double bond has been achieved using sodium borohydride[40,107]. Both these functional groups may be reduced using lithium aluminium hydride[76,40], whereas electrolytic reduction yields only the N-(2-aminobenzyl)-2-pyrrolidinone following rupture of the quinazolone ring. (Scheme 20).



Scheme 20

Enamines

The term 'enamine' was first introduced in 1927 by Wittig and Blumenthal[108] to emphasise the structural similarity between the α,β-unsaturated amine system and the α,β-unsaturated alcohol moeity present in enols. Isolated reports concerning the reaction of enamines date back to the early nineteen hundreds; indeed in 1916 Robinson[109] correctly interpreted the course of the reaction between an alkyl halide and ethyl β- aminocrotonate. However, it was not until 1954, when Stork and his associates[110] described alkylation and acylation reactions and demonstrated the ease of preparation of a number of enamines that interest was aroused.

Tautomerism

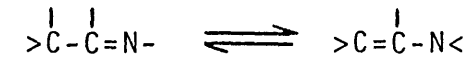
Enamines may be formed via the condensation between an aldehyde or ketone and a secondary amine

$$>\overset{|}{C}-\overset{|}{C}=O + H-N< \rightleftharpoons >C=\overset{|}{C}-N< + H_2O$$

Primary amines also react with carbonyl compounds to form imines

$$>\overset{|}{C}-\overset{|}{C}=O + H_2N- \rightleftharpoons >\overset{|}{C}-\overset{|}{C}=N- + H_2O$$

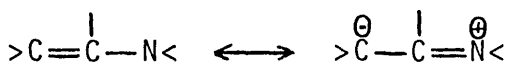
and whereas tautomerism is possible with the formation of the enamine:



the equilibrium usually lies in favour of the imine structure.

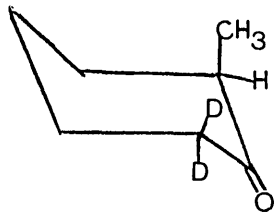
Protonation and basicity.

The structure of the enamine system may be regarded as a resonance hybrid to which the canonical forms (111) and (112) are the important contributors. Hence electrophilic reagents,



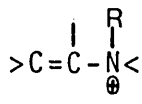
(111) (112)

including protons, may attack the system at either the nitrogen atom, to give the ammonium salt or, more importantly, at the carbon atom β to the nitrogen to yield an iminium salt. A direct application of this is the preparation of deuterated ketones (112), e.g. (113) is formed when the pyrrolidine enamine of 2-methylcyclohexanone is treated with deuteroacetic acid in deuterium oxide (CH_3CO_2D/D_2O).

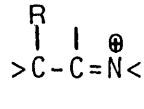


(113)

In principle, an alkyl halide may attack an enamine at nitrogen to give the salt (114) or at the β-carbon to yield the ion (115).



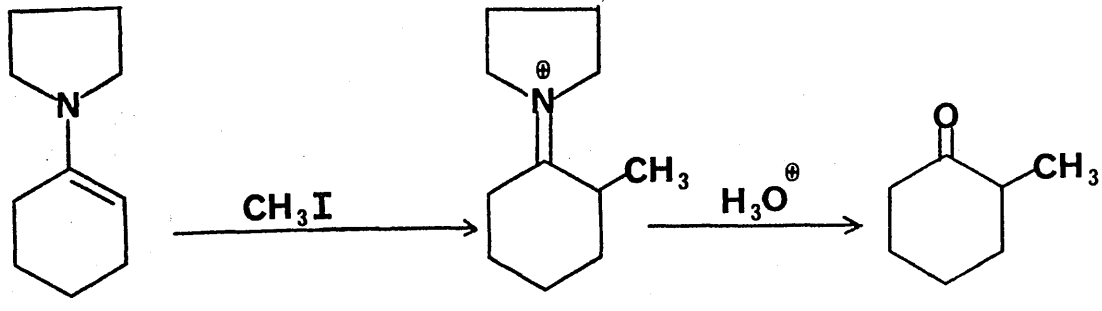
(114)



(115)

However, it is the latter reaction that has synthetic usefulness.

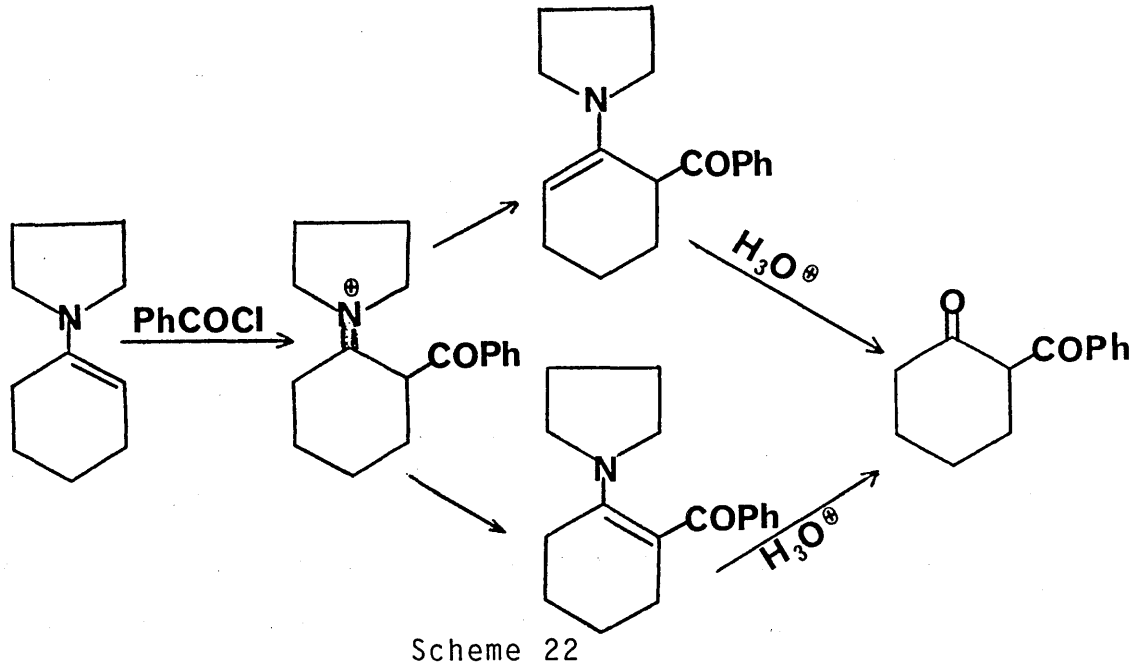
In 1954 Stork et al[110] reported that the alkylation of the pyrrolidine enamine of cyclohexanone (116) with methyl iodide followed by acid hydrolysis led to the monoalkylated ketone. (Scheme 21).



(116)

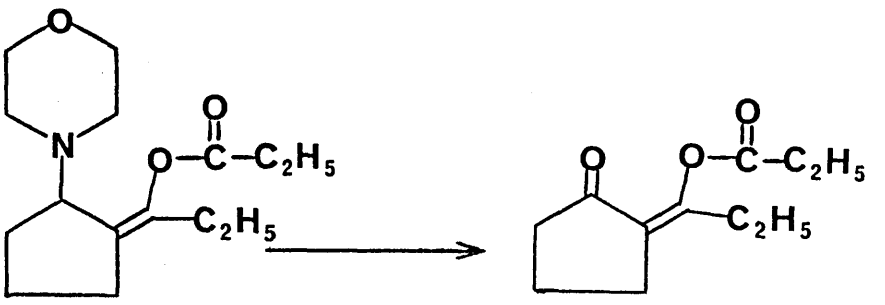
Scheme 21

In this original definitive paper Stork et al described the acylation reactions of enamines. Reaction can in theory, as with alkylation, occur either at the nitrogen atom or the carbon atom β to the nitrogen. Since the N-acylated products are unstable and are themselves good C-acylating agents, satisfactory yields of the required C-acylated enamines are usually obtained. Stork was thus able to prepare the monobenzoyl cyclohexanone following treatment of the pyrrolidine enamine of cyclohexanone with benzoyl chloride. (Scheme 22).



Scheme 22

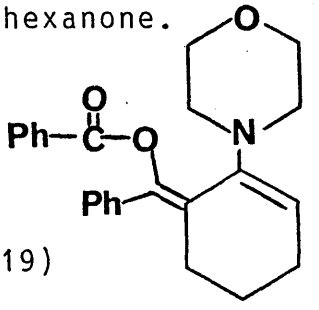
However, Hunig and Lendle[113] found that the treatment of the morpholine enamine of cyclopentanone with 2 moles of propionyl chloride followed by acid hydrolysis gave the enol ester (117) via the intermediate (118) following O-acylation of the original enamine product.



(118) (117)

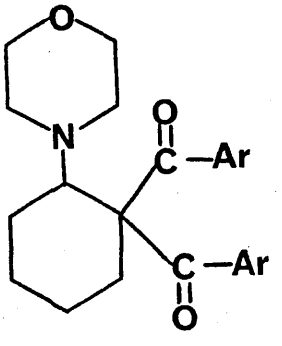
A similar enol ester (119) was reported by Helmers[114] as being formed via the benzoylation of the morpholine enamine of 2-benzoylcyclohexanone.

Cis/Trans isomers

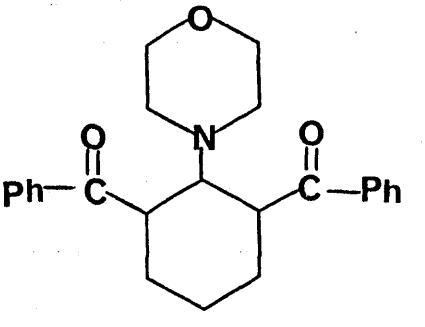


(119)

whilst other more complex products such as (120) and (121) have also been isolated in small amounts from acylation reactions[115,116].



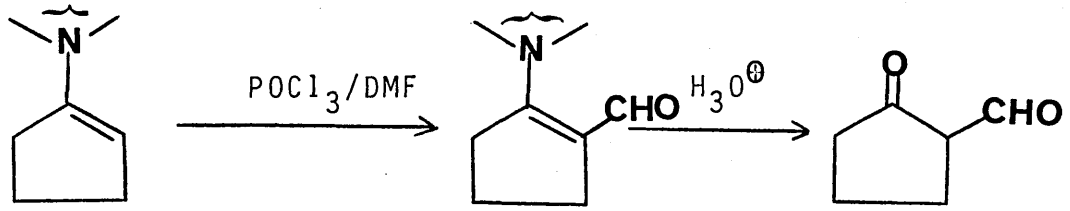
(120)



(121)

It would thus appear that O-acylation is the normal course of the acylation of enaminoketones.

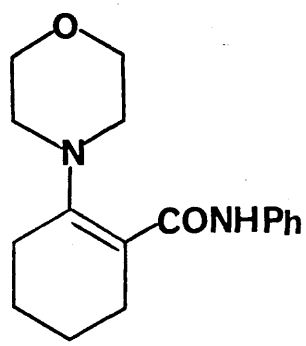
Enamine acylations have been extended to include the Vilsmeier reaction providing a method for the generation of formyl ketones without the use of strong base. Ketoaldehydes have thus been obtained in high yields[117]. (Scheme 23).



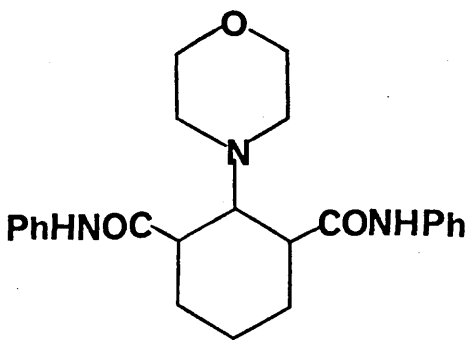
Scheme 23

Miscellaneous Reactions.

The reaction of the morpholine enamine of cyclohexanone (122)* with one mole of phenyl isocyanate has been reported[118,119] to give the monoadduct (123) whilst its reaction with 2 moles of phenyl isocyanate gives the bis adduct (124).



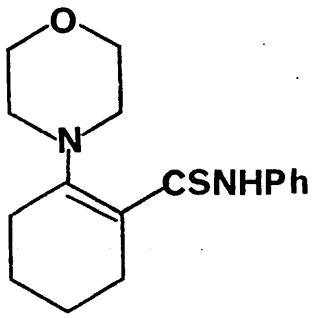
(123)



(124)

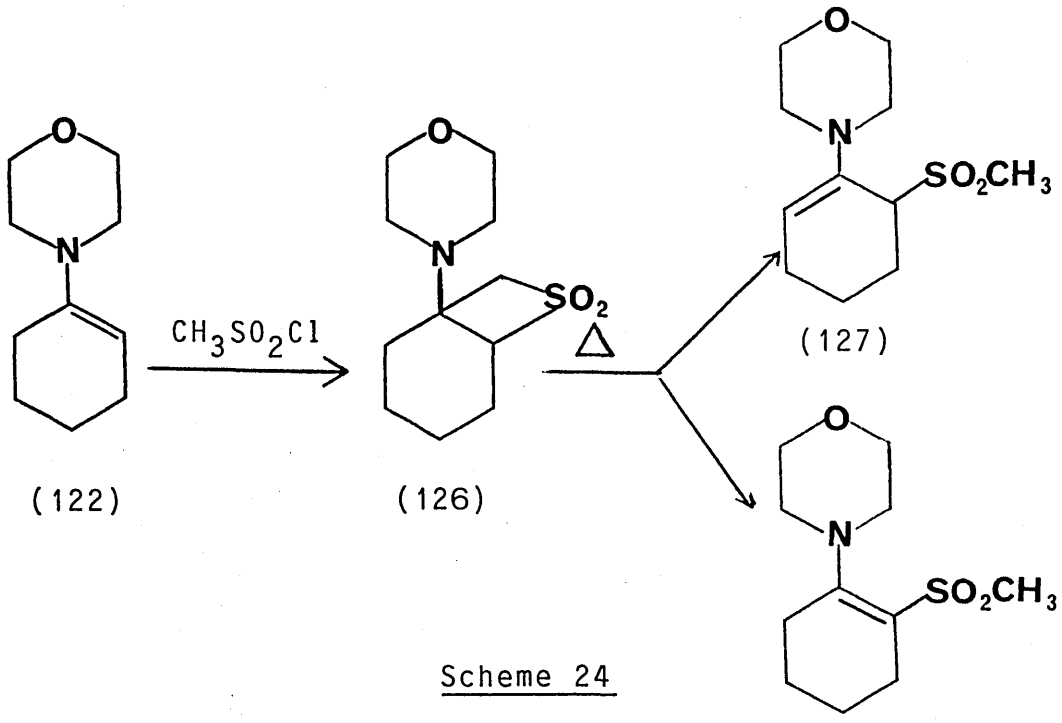
*See Page 55.

However, the reaction of (122) with phenyl isothiocyanate led only to the tetrasubstituted isomer of the monoadduct (125) which failed to yield the thio analogue of (124) despite the addition of more phenyl isothiocyanate. The formation of only the tetrasubstituted isomer has been attributed by Hunig et al[119] to the stronger conjugation of the C=S group with the enamine double bond than that of the C=O group in the enamine (123).



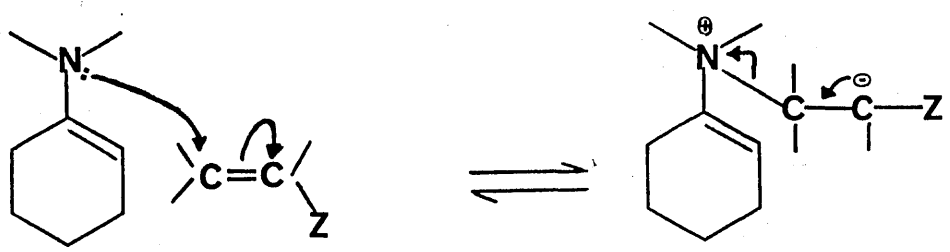
(125)

Borowitz[120] has demonstrated that aliphatic sulphonyl halides which possess an α hydrogen yield cyclic sulphones when reacted with enamines. The reaction of the morpholine enamine of cyclohexanone (122) with methanesulphonyl chloride in the presence of a proton abstractor gave the cyclic aminosulphone (126) which rearranged on heating to give a 2:1 mixture of isomers (127) and (128), (Scheme 24).



Scheme 24

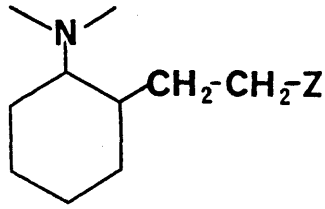
Since enamines are nucleophilic reagents they can react with electrophilic olefines (i.e. olefines in which an unsaturated electron withdrawing group is directly attached to the double bond, at the β carbon atom. The undesired N-alkylation is normally reversible so that, usually, high yields of carbon-alkylation products may be obtained[121]. (Scheme 25).



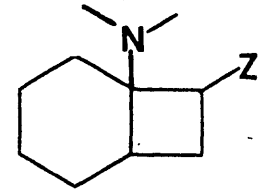
Z = electron withdrawing group.

Scheme 25

Simple alkylation products (129)[122-125] or cyclobutanes (130)[126-128] may be obtained from the reaction of enamines with these electrophilic olefines.



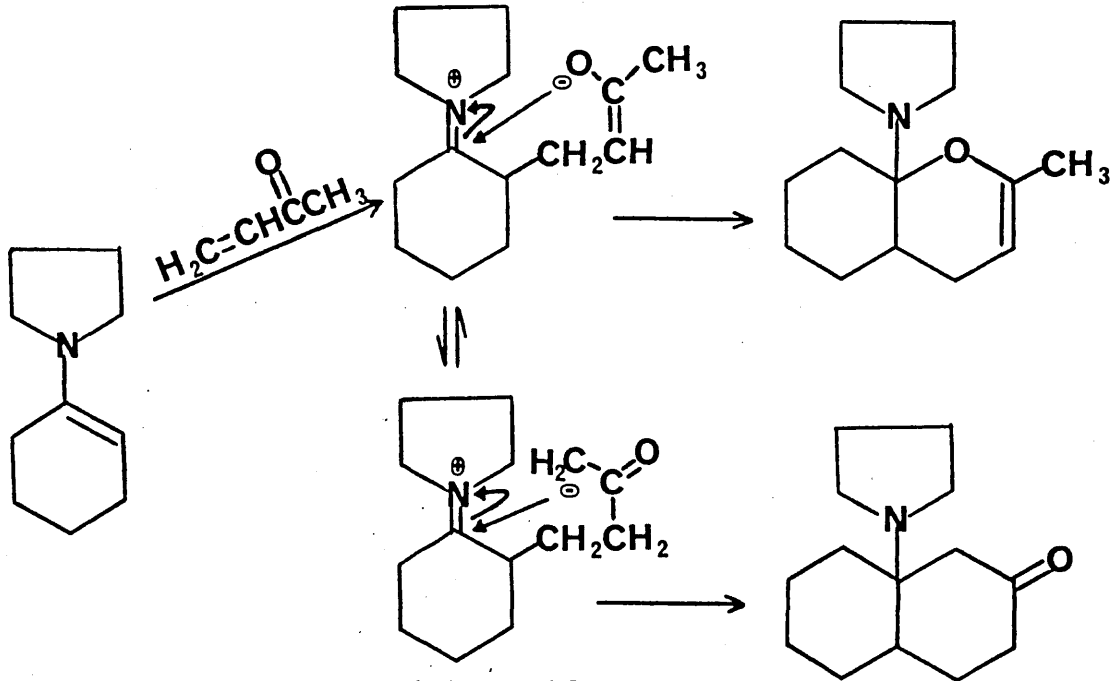
(129)



(130)

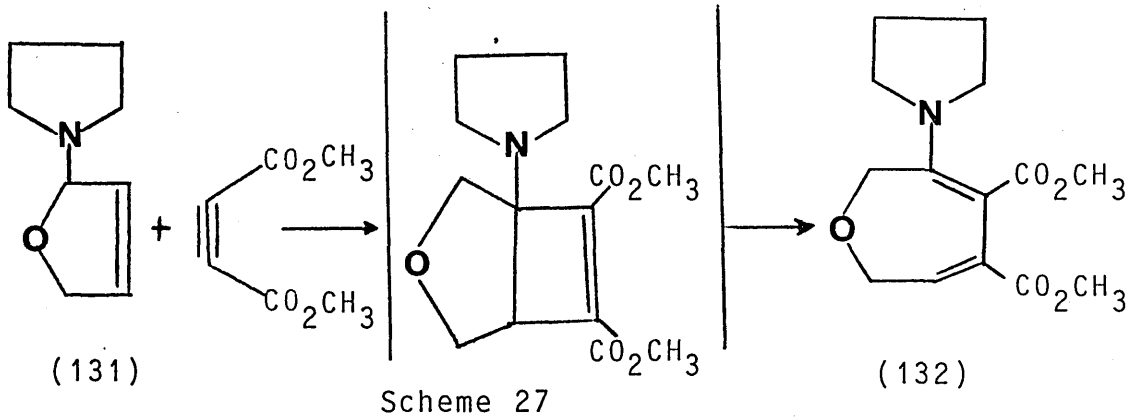
It has been proposed that the cyclobutane derivatives of type (130) are intermediates which thermally rearrange to give the simple alkylated product (129)[122].

As well as leading to simple alkylated products or cyclobutane derivatives, alternative pathways of reaction are available to enamines undergoing reaction with α,β-unsaturated ketones. Dihydropyrans[128,129,130] or octalones[111] being common products. (Scheme 26).



Scheme 26

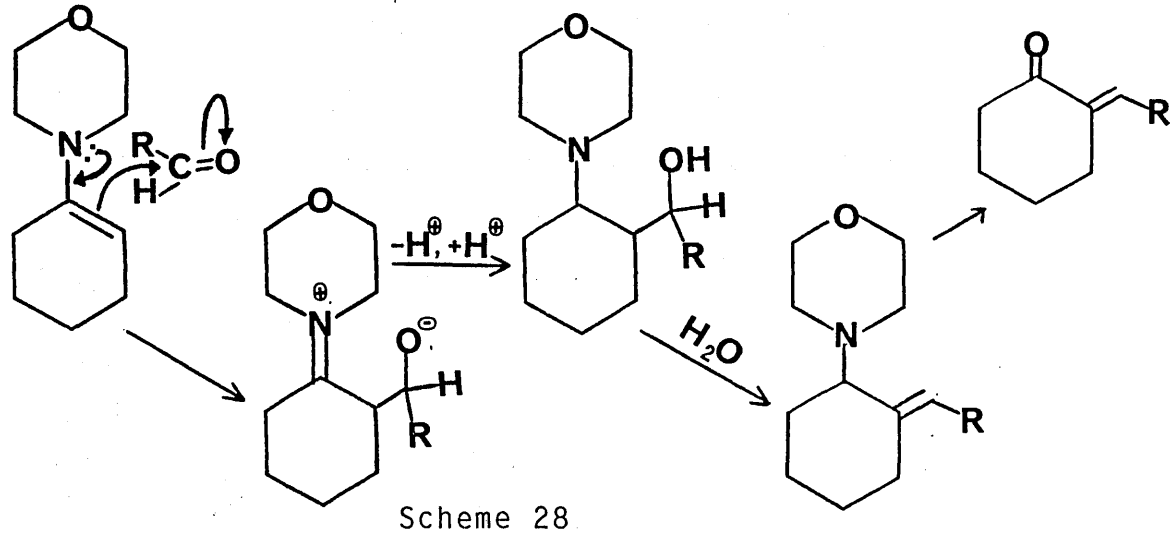
A more conventional cycloaddition occurs during the reaction of enamines with activated acetylenes. However the intermediate cyclobutene adducts undergo rearrangement leading to the insertion of two carbon atoms into the enamine ring or chain[123,131,132,133]. Thus the enamine (131) reacts with dimethyl acetylenedicarboxylate at room temperature in ether to give dimethyl 2,7-dihydro-3-pyrrolidienyl-4,5-oxepindicarboxylate (132). (Scheme 27).



(131) (132)

Scheme 27

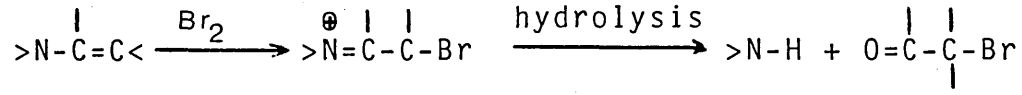
Good yields of 2-alkylidene ketones are easily achieved by reaction of an enamine with an aldehyde, especially an aromatic aldehyde[134]. (Scheme 28).



Scheme 28

Reaction with Halogens.

Chlorination and bromination reactions of enamines have been described[135,136] yielding the β -haloiminium salt which is readily hydrolysed. (Scheme 29). Stable β-haloenamines have been isolated when N-halosuccinimides were used as halogenating agents.

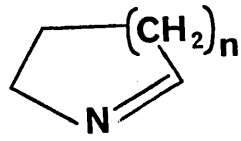


Scheme 29

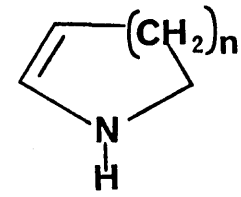
Heterocyclic Enamines.

The term heterocyclic enamine is used to describe those compounds that posses the >C=C-N< group as part of the ring system. Typical behaviour of enamines has been mainly observed for compounds possessing a tertiary nitrogen atom[137]. In this group are included various susbstitued dehydroderivatives of pyrrolidine (pyrrolines), piperidine (piperideines), the derivatives of dehydro-1-azacycloalkanes with more than six membered rings, and finally compounds containing some of the basic skeletons : enamines of quinolizidine, indolizidine, pyrrolizidine and their benzoderivatives which occur in a large number of alkaloids. Analogous compounds with a secondary amine group (α , β-unsaturated

secondary amines) can, in principle, exist in either the form of imines (133) or the tautomeric form of enamines (134).

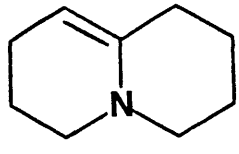


(133)

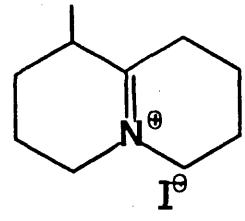


(134)

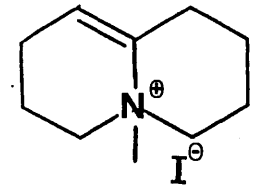
All enamines do not react in the same way. Both reactive sites are available for electrophilic alkylation. Whether this alkylation occurs on the nitrogen or the carbon atom depends on the reactivity of the alkylation reagent, the structure of the enamine, and finally the polarity of the solvent. Alkylating reagents exhibit a greater tendency to react with the nitrogen atom to form quaternary ammonium salts. The more reactive alkyl halides such as allyl halides, α-halogenoketones and α-halogenoesters would by contrast react mainly with the β-carbon atom of the enamine grouping. Thus treatment of $\Delta^{1,10}$ dehydroquinolizidine (135) with methyl iodide[138,139] gives a mixture of three products, (136), (137) and (138) containing 83% of the quaternary ammonium salt (137)



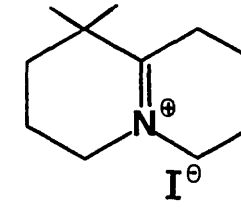
(135)



(136)



(137)



(138)

whilst treatment of the same compound (135) with ethyl chloroformate furnished only 1-carbethoxy-$\Delta^{1,10}$ dehydroquinolizidine after basification.

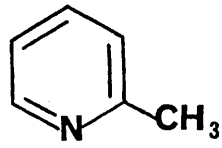
This chapter is by no means a detailed account of the chemistry of enamines but intended only as an illustrative guide to the nature of enamines and to the types of reaction they undergo.

DISCUSSION

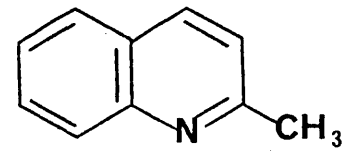
Discussion

Introduction

The alkaloid deoxyvasicinone (1) undergoes a number of interesting chemical transformations in the A, B and C rings. As illustrated in the introductory section these transformations include several which occur at the C-3 methylene group of the pyrrolidine ring. The protons in this position bear a strong resemblance to the protons of the methyl group in 2-picoline (139)[140] and quinaldine (140)[141].



(139)



(140)

However, the fact that (1) condenses with aromatic and aliphatic aldehydes with no catalysis indicates that they are much more reactive (see Introduction). Despite this reactivity and the fact that a similar reactive methylene group has been observed by Taylor and Shvo[39] in the fused quinazolone (16) little use has been made of these or similar reactions to prepare compounds which could function as intermediates in the synthesis of novel alkaloids[81,102]. This thesis presents an account of the synthesis and reactivity at C-3 of deoxyvasicinone and a number of its substituted C-ring analogues. The reaction of these compounds with a

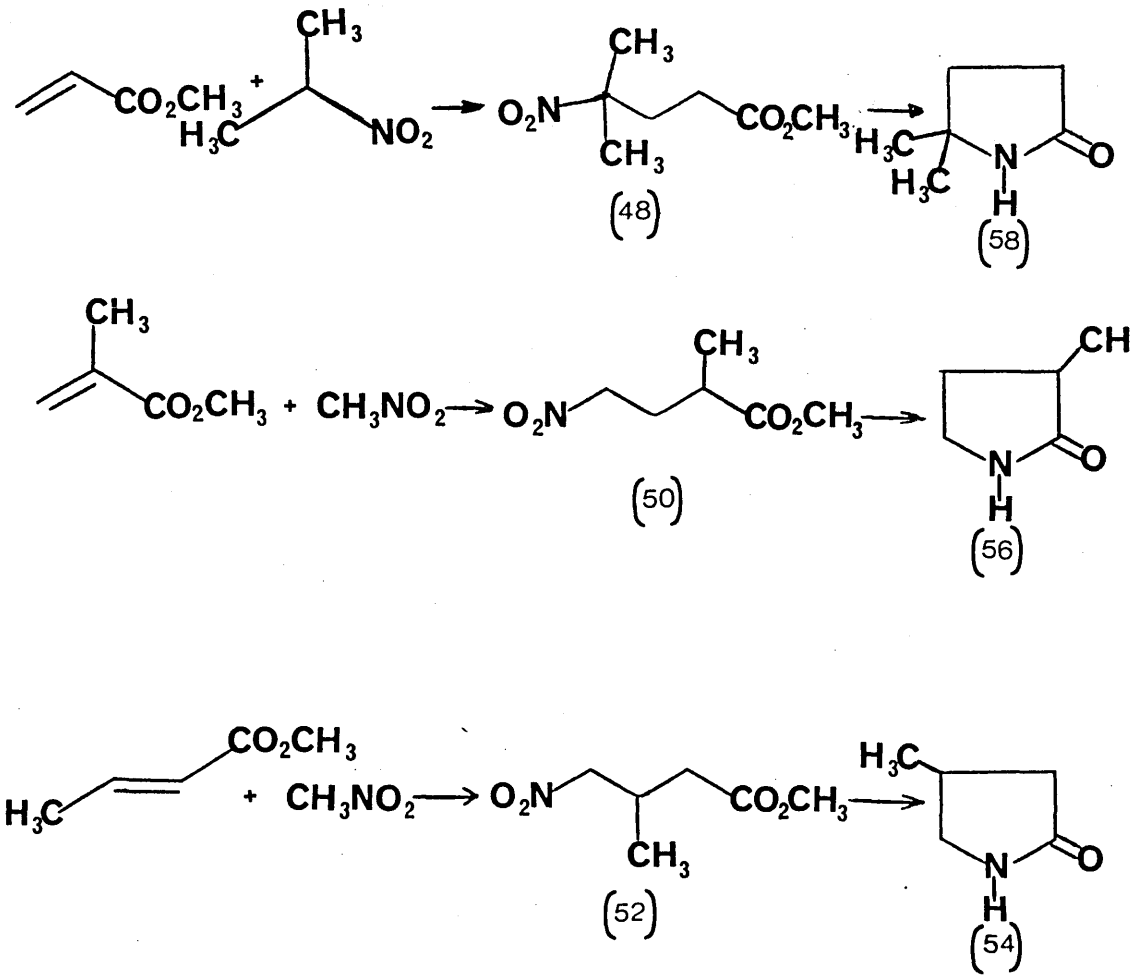
variety of reagents resulted in the formation of many new pyrrolo[2,1-b]quinazolinones. The thesis also describes the utilisation of several of these products in further synthetic transformations especially with respect to the preparation of novel tetracyclic systems.

Three main techniques were employed to synthesise deoxyvasicinone (1) and analogous compounds. Deoxyvasicinone (1) was initially prepared by the method of Landii Vittory and Gatta[40] (Scheme 3). Unfortunately this method though efficient was time consuming and was abandoned in favour of variations of less laborious techniques such as those demonstrated by Shakhidoyatov[50] and Devi[29]. Thus (1) and analogous compounds where the pyrrolo ring carries a substituent were prepared via the condensation of anthranilic acid and either the appropriate 2-pyrrolidinone or its imidate (Schemes 6, 7 and 8).

Only 2-pyrrolidinone (9) and 5-methyl-2-pyrrolidinone (53) were commercially available and the other alkylated pyrrolidinones (54), (56) and (58) were obtained by a method devised from the preparation of cyclic amides[142]. The starting materials were the nitroesters (52), (50) and (48) prepared by the condensation of the appropriate nitroalkane and α, β-unsaturated ester[56-62]. The other 2-pyrrolidinones required, (57) and (59) were prepared using established techniques[87,77].

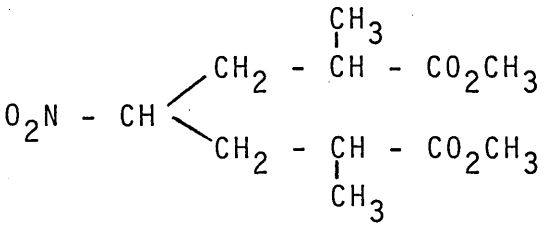
Preparation of nitrocarboxylic acid esters.

The technique of Moffett[58] (see Introduction) was used to prepare methyl 4-methyl-4-nitropentanoate (48) in 71% yield following the reaction of 2-nitropropane with methyl acrylate in dioxan. Adapting the Moffett method gave methyl 3-methyl-4-nitrobutanoate (52) and methyl 2-methyl-4-nitrobutanoate (50) in (50%) and (16%) yields respectively, following reaction of nitromethane with methyl crotonate or methyl methacrylate. (Scheme 30).



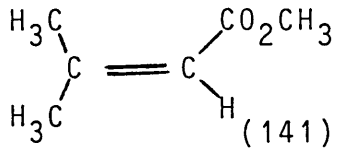
Scheme 30

The course of all these reactions was similar involving the generation of a carbanion following treatment of the original nitroalkane with the base triton B in the solvent 1,4-dioxan. Condensation of the desired carbanion with the appropriate acrylate derivative yielded the expected Michael adduct which had spectroscopic data consistent with the proposed structure. The low yield of (50) and the fact that the dimer (51)



(51)

is formed as a minor product is indicative of the formation of a second carbanion generated from the primary product (50). Attack by this second carbanion on another molecule of methyl methacrylate leads to the formation of the dimer (51). The formation of this compound previously reported by Leonard and Shoemaker[59] may be minimised by replacing triton B with diethylamine as catalyst but this was unnecessary as enough of the monoester was obtained to continue the study[59]. An attempted condensation between nitromethane and methyl senecioate (141) using the Moffett technique failed to realise the desired product methyl 3,3-dimethyl-4-nitrobutanoate. The β-carbon atom of (141) carries two methyl groups and it is this steric effect which presumably renders (141) unreactive to normal Michael addition reactions.



(141)

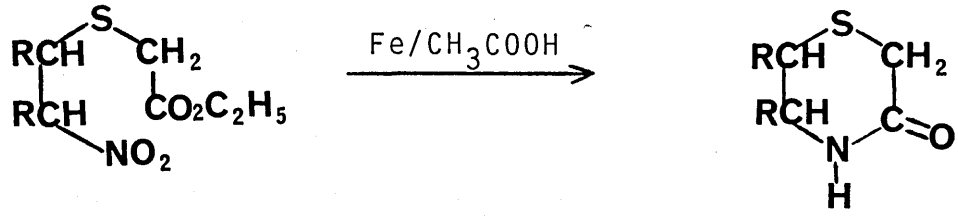
A comparable hindering effect resulting from substitution on the β-carbon of the acceptor has been observed in other Michael condensations[55,59].

Preparation of 2-pyrrolidinones

An extensive review of the techniques available for the preparation of 2-pyrrolidinones has been included in the introductory section. This review illustrates that many effective and simple techniques leading to the formation of alkylated 2-pyrrolidinones incorporate high pressure hydrogenation to effect cyclisation of a nitroalkanoic acid or ester precursor. Unfortunately no hydrogenation facilities were initially available and consequently a comprehensive literature search and experimental programme was initiated to produce an alternative to hydrogenation for the production of alkylated 2-pyrrolidinones.

Lehr, Karlan and Goldberg[142] reported the synthesis of a number of substituted 3-thiomorpholinones using three different methods. The last step of one of these routes involved the reductive ring closure of various nitroalkyl mercaptoacetates (142) to 3-thiomorpholinones

(143) using a refluxing mixture of iron filings, water and acetic acid. (Scheme 31).



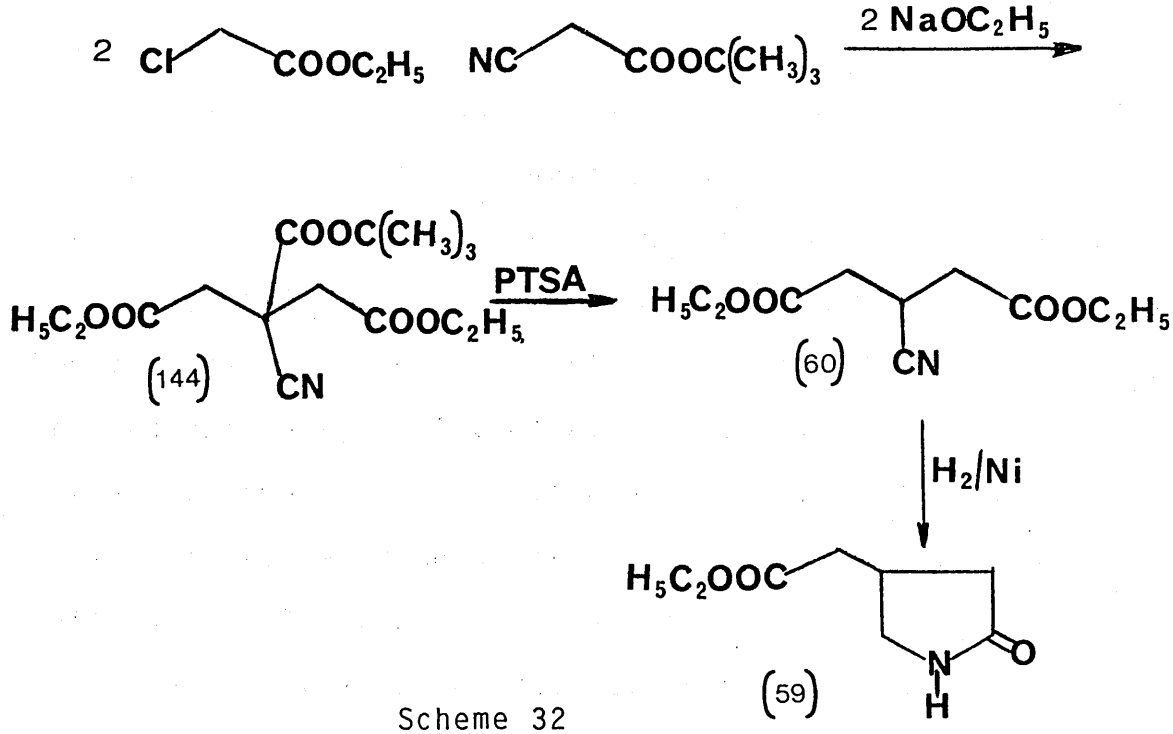
(142) (143)

Scheme 31

The technique of Lehr et al[142] was subsequently adapted and used to prepare the pyrrolidinones (54), (56) and (58) from the corresponding nitroesters (Scheme 30). Thus the desired nitroester was reductively cyclised during heating at 90^{0} with a mixture of acetic acid, reduced iron powder and water. Subsequent purification by distillation gave the required pyrrolidinone. All the pyrrolidinones synthesised in this manner crystallised as colourless solids on standing and had spectral data in accord with the proposed structures. The yields of approximately 50% were satisfactory but substantially lower than those reported for the same compounds using high pressure hydrogenation techniques.

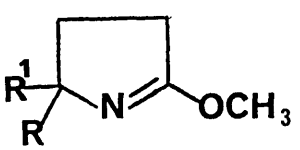
5-Carbethoxy-2-pyrrolidinone (57) was obtained in 64% yield via the thermal cyclisation of diethyl glutamate in toluene [87].

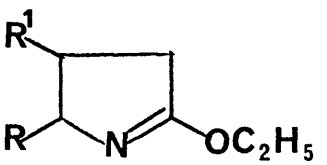
The method of Henecka et al[77] was used to prepare the required pyrrolidinone 4-ethoxycarbonylmethyl-2-pyrrolidinone (59) (Scheme 32). The base catalysed condensation reaction between t-butyl cyanoacetate and two mole equivalents of ethyl chloroacetate yielded the crude diethyl 3-t-butoxycarbonyl-3-cyanoglutarate (144) as a thick red syrup. Selective acidic hydrolysis and subsequent decarboxylation was effected using a catalytic amount of para toluenesulphonic acid and gave the pale yellow product diethyl 3-cyanoglutarate (60) in 75% yield. Intramolecular cyclisation of this diester (60) was achieved using high pressure hydrogenation and gave the crude (59) as a syrup. Purification by distillation under reduced pressure afforded the product (59) as described by Henecka et al.[77]



Scheme 32

Imidates of a number of these pyrrolidinones were prepared using standard techniques and yields were generally in excess of 60%. The compounds (9), (53) and (58) were converted into their imidates (34), (145) and (146) by the reaction of the former with dimethyl sulphate followed by conversion of the intermediate salts with potassium carbonate. The ethylation of compounds (54), (57) and (59) with triethyloxonium tetrafluoroborate followed by similar basification gave the imidates (78), (147) and (148).





(34) $R=R^1=H$

(145) $R=H, R^1=CH_3$

(146) $R=R^1=CH_3$

(78) $R=H, R^1=CH_3$

(147) $R=CO_2C_2H_5, R^1=H$

(148) $R=H, R^1=CH_2CO_2C_2H_5$

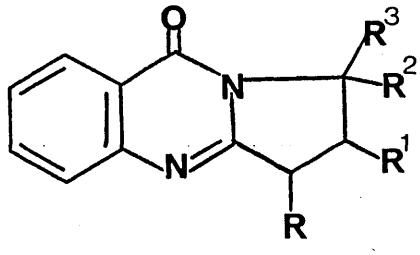
Pyrroloquinazolinones

Deoxyvasicinone (1) was initially prepared by a modification of the method of Landii Vittory and Gatta[40] (Scheme 3).

Acylation of anthranilamide with 4-chlorobutyryl chloride in acetic acid/saturated sodium acetate at room temperature gave the diamide (17) in 62% yield. Cyclisation of (17) with sodium methoxide in methanol gave a mixture of two isomeric fused quinazolinones (1) and (16). Separation was elegantly achieved by continuous soxhlet extraction with ether in which (1) is soluble and (16) almost completely insoluble, thus eliminating the need for chromatography as reported in the original literature. This method though efficient was time consuming and was abandoned in favour of less laborious techniques.

The techniques which proved effective for the synthesis of (1) and analogous compounds where the pyrrolo ring carries a substituent were variations of the techniques of Shakhidoyatov[50], Devi[29], Onaka[31] and Shkrob[49]. As indicated earlier these methods involve the condensation of either the appropriate 2-pyrrolidinone or its imidate (Schemes 6, 7 and 8) with anthranilic acid. When compounds (9), (53) and (56) were heated with anthranilic acid in phosphorus oxychloride solution the compounds (1),

(149), (150) were obtained whilst condensation of (78), (34), (145), (146), (147) or (148) with anthranilic acid in hot toluene gave (151), (1), (149), (152), (153) and (154) respectively. Hydrolysis of the ester (154) was achieved following treatment with sodium ethoxide and yielded the acid (155) in 61% yield.



(1) $R\text{-}R^3 = H$

(149) $R\text{-}R^2 = H, R^3 = CH_3$

(150) $R = CH_3, R^1\text{-}R^3 = H$

(151) $R = R^2 = R^3 = H, R^1 = CH_3$

(152) $R = R^1 = H, R^2 = R^3 = CH_3$

(153) $R\text{-}R^2 = H, R^3 = CO_2C_2H_5$

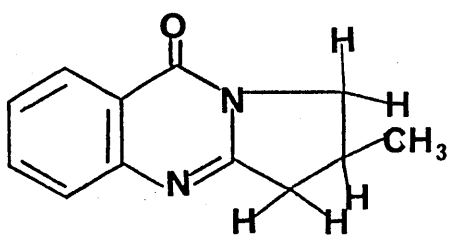
(154) $R = R^2 = R^3 = H, R^1 = CH_2CO_2C_2H_5$

(155) $R = R^2 = R^3 = H, R^1 = CH_2CO_2H$

The method involving condensation with $POCl_3$ was abandoned in favour of the imidate/anthranilic acid technique for several reasons. The vigorous conditions required to prepare the substituted pyrrolo[2,1-b]quinazolinones using the method of Shakhidoyatov[50] resulted in some decomposition necessitating extensive purification processes and the reaction conditions and neturalisation step were clearly unsatisfactory for the preparation of esters due to the acid/base sensitivity of such groups.

The pyrroloquinazolinones prepared using the aforementioned techniques had spectroscopic data which was consistent with their proposed structures, however the presence of monosubstituents (methyl or ester) in the pyrrolo ring in compounds (149), (150), (151), (153) and (154) made their p.m.r. spectra extremely complex. This complexity was due to the extensive vicinal and geminal coupling throughout the spectrum as a result of the non equivalence of the protons in the five membered ring.

Examination of the p.m.r. spectrum of 2,3-dihydro-2-methylpyrrolo[2,1-b]quinazolin-9(1H)-one (151), which appeared less complex than those of similar compounds allowed the coupling constants to be examined in greater detail.

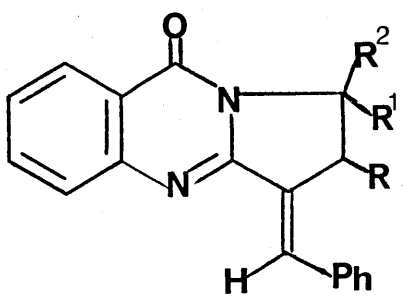


(151)

Although the signals corresponding to the methylene protons at C-3 and the methine proton at C-2 overlapped and were not easily interpretable, the signals corresponding to the non equivalent methylene protons at C-1 were clearly visible as two double doublets each of which had an integral of 1 proton at δ 3.64 and δ 4.28 respectively. The complexity of the total spectrum made

definite assignment of the couplings difficult but it is thought that each of the methylene protons is geminally coupled to the other (12Hz) and vicinally to the methine proton at C-2 (7Hz). Shielding or deshielding may account for the non equivalence demonstrated by these methylene protons.

Benzylidene derivatives (156) to (161) were obtained from (151) to (154) and (1) and (149) respectively, when the latter compounds were heated with benzaldehyde, however no condensation occured when (150) was heated with benzaldehyde.



(156) $R=CH_3, R^1=R^2=H$

(157) $R=H, R^1=R^2=CH_3$

(158) $R=R^1=H, R^2=CO_2C_2H_5$

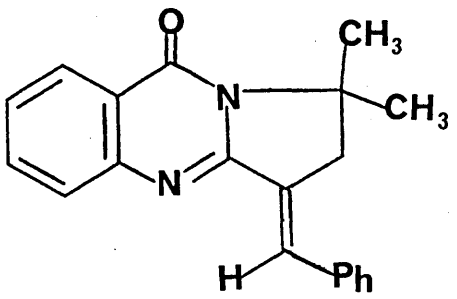
(159) $R=CH_2CO_2C_2H_5, R^1=R^2=H$

(160) $R-R^2=H$

(161) $R=R^1=H, R^2=CH_3$

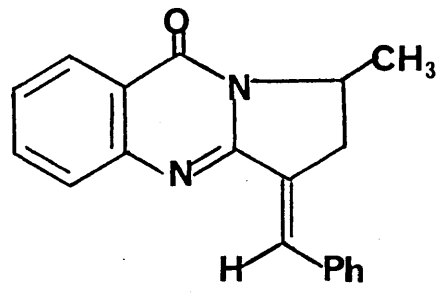
The geminal coupling outlined previously for the original pyrrolo[2,1-b]quinazolin-9(1H)-ones was in evidence in a number of these benzylidene derivatives. However, the p.m.r. spectra of these compounds was further complicated by the long range allylic coupling and the extensive vicinal coupling resulting from the shielding and deshielding effects of the various substituent groups (methyl, ester or phenylmethylene).

The allylic coupling is normally small (0 - 3Hz) and often observed where two or more of the intervening atoms are π-bonded. This coupling was illustrated in 2,3-dihydro-1,1-dimethyl-3-phenylmethylenepyrrolo[2,1-b]quinazolin-9(1H)-one (157) whose p.m.r. spectrum shows the C-2 methylene group centered on δ 3.08 as a two proton doublet. Although the complexity of the remainder of the spectrum made assignment difficult it is thought that this methylene group is coupled to the alkenyl proton of the benzylidene moeity with the coupling protons possibly being held in a W-type configuration. The coupling constant of 2.4Hz is consistent with this type of long range coupling.

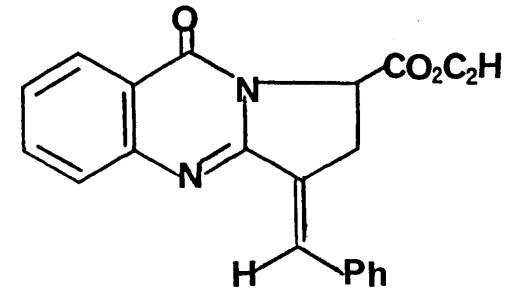


(157)

The p.m.r. spectra of the benzylidene derivatives 2,3-dihydro-1-methyl-3-phenylmethylenepyrrolo[2,1-b]quinazolin-9(1H)-one (161) and 1-carbethoxy-2,3-dihydro-3-phenylmethylenepyrrolo[2,1-b]quinazolin-9(1H)-one (158) superbly illustrate the geminal, the allylic and vicinal couplings previously mentioned.



(161)



(158)

In (161) the methylene protons of C-2 in the pyrrolo ring appear as a doublet of triplets (integral 1) at δ 2.88 and a doublet of double doublets (integral 1) at δ 3.53. Once again the complexity of the complete spectrum makes absolute assignment difficult but analysis of the coupling constants indicates that not only do these two protons couple with one another (17.7Hz) but that their respective coupling with the methine proton at C-1 is dependent on the dihedral angle each makes with that methine proton.

The influence which the dihedral angle ($\emptyset$) between two vicinal C-H bonds makes on the vicinal coupling is easily predicted and the values predicted using the Karplus equations are frequently in agreement with the observed figures.

Karplus equations.

$$J_{VIC} = 8.5 \cos^2 \emptyset - 0.28 \qquad 0^o < \emptyset^o < 90^o$$

$$J_{VIC} = 9.5 \cos^2 \emptyset - 0.28 \qquad 90^o < \emptyset^o < 180^o$$

It is more convenient to express this roughly using a graph as many variables other than the dihedral angle are important in deciding the magnitude of J_{VIC} (vicinal coupling constant).[143]

In compound (161) the larger vicinal coupling (8.7Hz) is consistent with predicted figures for an approximate 0^{o} orientation of the atoms (H_A- H_B) (Fig. 3) whilst the smaller coupling 2.7Hz is consistent with the values normally associated with protons separated by a dihedral angle of 120^{o} (H_A- H_C).

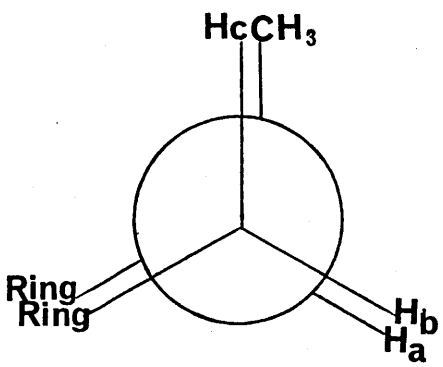


Fig. 3.

The signals for protons H_B and H_C are subsequently seen as a doublet of double doublets and a doublet of triplets respectively as a consequence of the small allylic coupling each of the protons H_B and H_C also makes with the alkenyl proton of the benzylidene group. This coupling being much smaller (3.3Hz) than either the vicinal coupling between proton H_A and H_B (8.7Hz) or the

normal geminal coupling (17.7Hz) consequently splits the signal corresponding to proton H_B a third time and the signal for H_B is manifested as eight lines on the spectrum. However, the signal corresponding to H_C is seen only as six lines on the spectrum because of the identical magnitudes of the vicinal and the allylic couplings (2.7Hz). The coupling in the ester (158) is similarly explained using the Newman projection shown below. (Fig. 4).

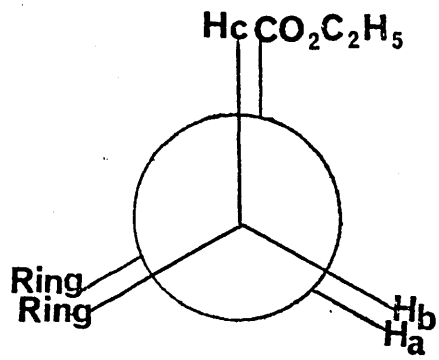
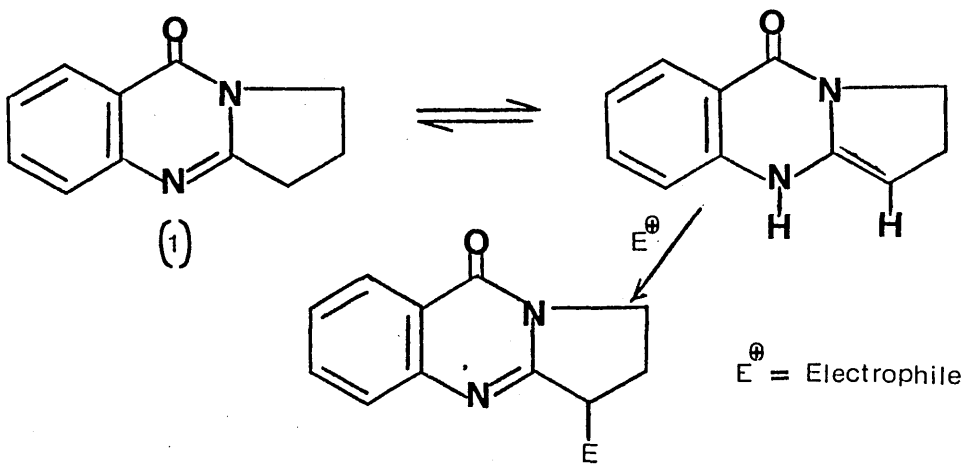


Fig. 4

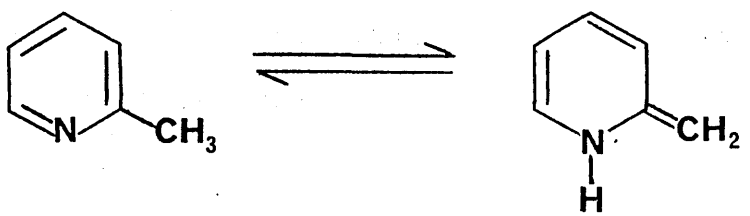
Reaction of Pyrrolo[2,1-b]quinazolin-9(1H)-ones at C-3

It has been shown by a number of authors that fused quinazolinones, e.g. (1) react with electrophiles at the carbon atom β to the sp^2 hybridised nitrogen atom of the quinazolinone ring (see Introduction). Two possible mechanisms to account for such reactivity may be postulated. The first involves the protopic enamine tautomer of the original fused quinazolinone, the formation of which would lead to classical enamine reactions. (Scheme 33).



Scheme 33

This is similar to the mechanism proposed by Tschitschibabin[144] to account for the reactivity in 2-picoline (139) (Scheme 34).

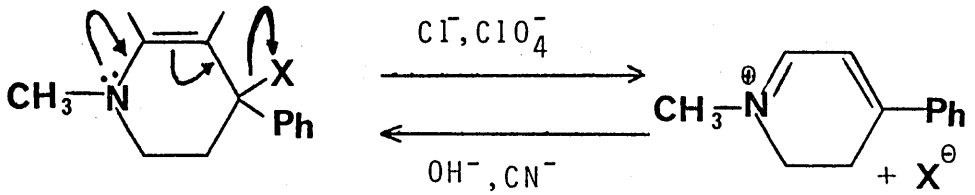


Scheme 34

The second proposal is that the apparent reactivity of the carbon atom β to the sp^2 hybridised nitrogen atom of the quinazolinone ring may be due to the formation of a pseudo-base.

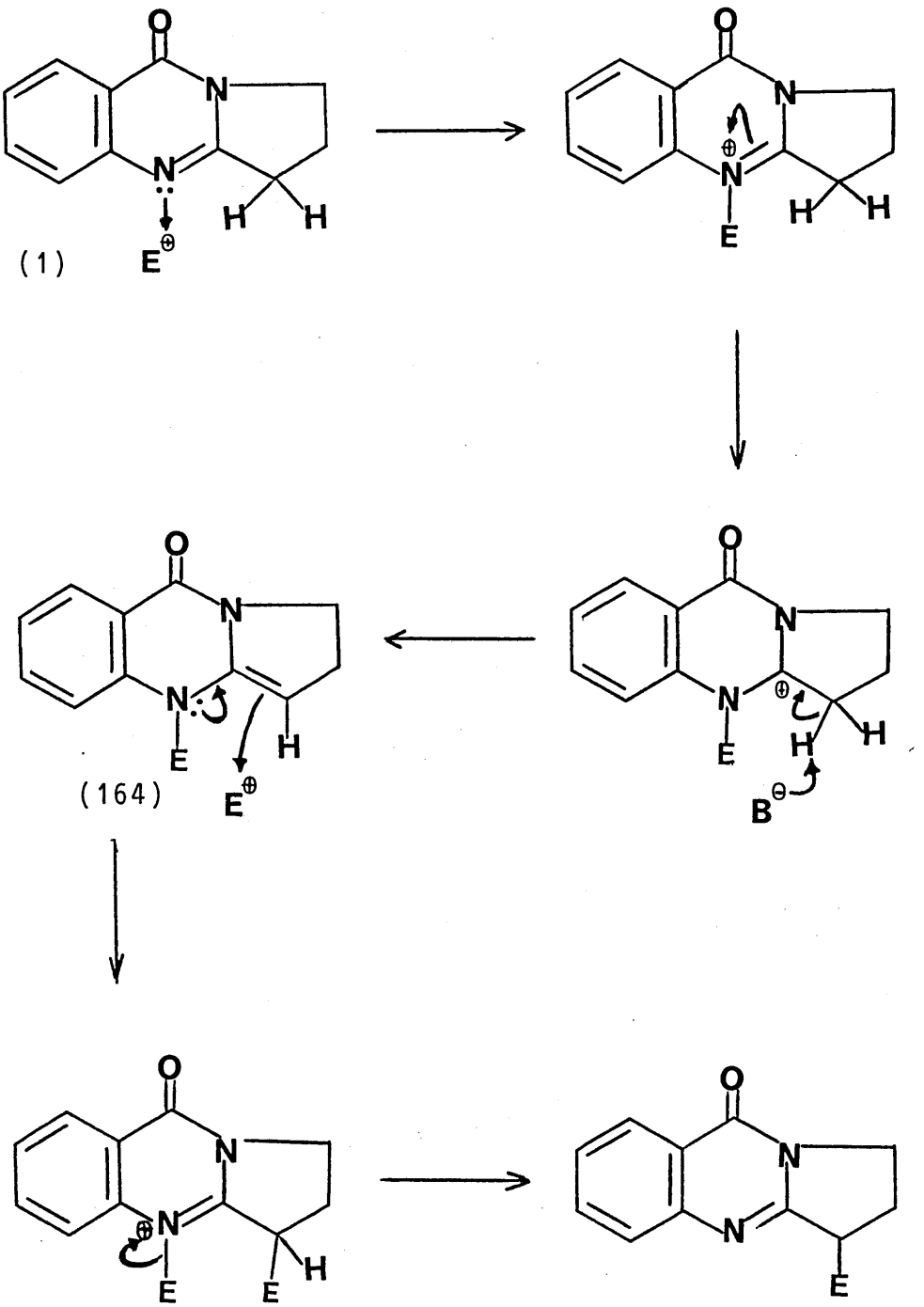
Pseudo-basicity

Hantsch[145,146] was the first to recognise a form of tautomeric change in the reversible conversion between ionised quaternary ammonium hydroxides having double bonded nitrogen and the isomeric non-ionic carbinols. The latter he termed pseudobases. The salts with strong acids such as hydrochloric acid are typical quaternary salts (162). However on treatment with a sufficiently nucleophilic anion such as hydroxide the covalent molecule (163) is predominantly produced.



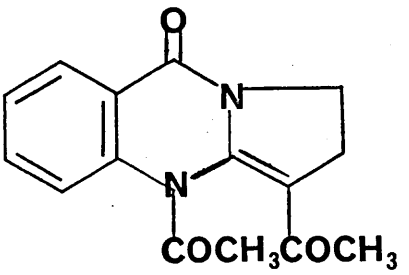
(163) (162)

The formation and subsequent reaction of such a pseudobase of deoxyvasicinone (1) may be reasoned as follows. Nucleophilic attack by the lone pair of the sp^2 nitrogen atom to give the initial quaternary ammonium salt. Electronic migration and attack by a basic anion would eventually lead to the formation of the C-alkylated product via the pseudobase (164). (Scheme 35).



Scheme 35

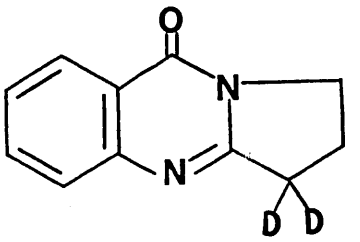
The 'latent enamine' type reaction is thought to be the more feasible mechanism. No carbamate derivatives such as (165) have been isolated and although the possibility of hydrolytic cleavage at the C-N bond should not be discounted, the absence of any N-acylated/alkylated product would seem to indicate that the pseudobase mechanism is unlikely to take place.



(165)

Enamine Formation

The enamine mechanism was investigated using a high temperature deuterium exchange study. When (1) was treated at 150°- 156° for 15 hours with excess deuterium oxide (D_2O) complete exchange of the C-3 hydrogen atoms occurred and the 3,3-dideutero analogue of (1) (166) was recovered in 80% yield.



(166)

Although this dideutero compound (166) was identical (t.l.c., m.p.) to (1) the incorporation of deuterium into (1) can be easily demonstrated from a comparison of the spectra (i.r., m.s. and p.m.r.) of (1) and (166).

The infrared spectrum of (166) showed only slight changes to that of (1) particularly around the region 1450 - 1000 cm^{-1} . The mass spectrum indicates a molecular ion two mass units higher than that of (1) at m/e 188. The p.m.r. spectrum indicated beyond any doubt that

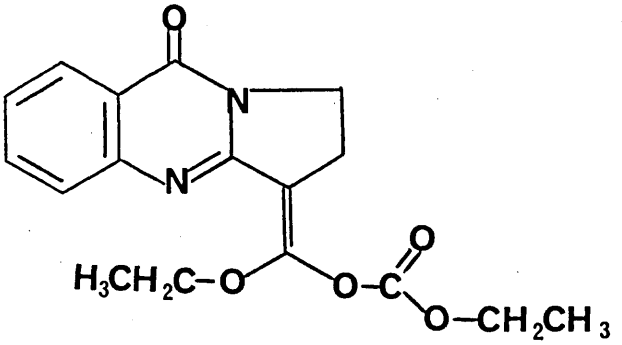
a) deuteration had occurred.
b) the 3 position of deoxyvasicinone (1) is the site of deuteration.

Comparison of the p.m.r. spectra of (1) and (166) showed that the low field triplet (integral 2) at δ 3.2 vanished in the spectrum of the deuterated compound and the signal due to the C-2 hydrogen atoms was considerably simplified and replaced by a triplet (integral 2). Other workers have used similar exchange methods in preparing the deuterated derivatives of more simple nitrogen containing heterocycles. Brown et al[147] succeeded in deuterating the methyl protons of various substituted pyrimidines following dissolution of their salts in deuterium oxide. The deuteration of methyl protons in α-picoline (139) was shown to occur in

deuterium oxide or deuterium oxide-hydrochloric acid at 164.6° by Zoltewicz and Kandetzki[148].

Previously the reaction of deoxyvasicinone (1) with electrophiles has been studied (see Introduction) and it was decided to extend our knowledge of such reactions by examining the reaction of deoxyvasicinone (1) and a number of its analogues with electrophiles.

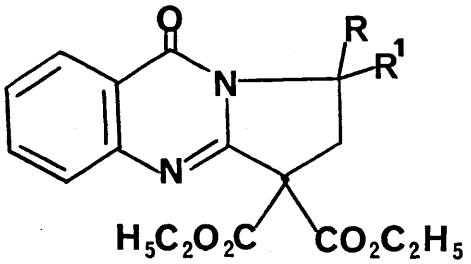
Deoxyvasicinone was originally shown not to react with chloroformic esters in a variety of solvent/base mixtures. However, in neat ethyl chloroformate using (1) as both reactant and base reaction did occur. The product was dependent upon the reaction times and temperature. Short reaction times (8 - 10 hours) at low temperatures (110°- 120°) favoured the formation of 3-(ethoxyethoxycarbonyloxymethylene)-2,3-dihydropyrrolo [2,1-b]quinazolin-9(1H)-one (167).



(167)

Longer reaction times at these temperatures gave 3,3-dicarbethoxy-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-

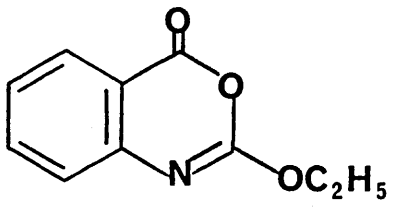
one (168) and 2-ethoxy-(4H)-3,1-benzoxazin-4-one (169). Conversion of (167) into (168) was easily accomplished by heating the former with ethyl chloroformate and the hydrochloride of (1).



(168) $R=R^1=H$

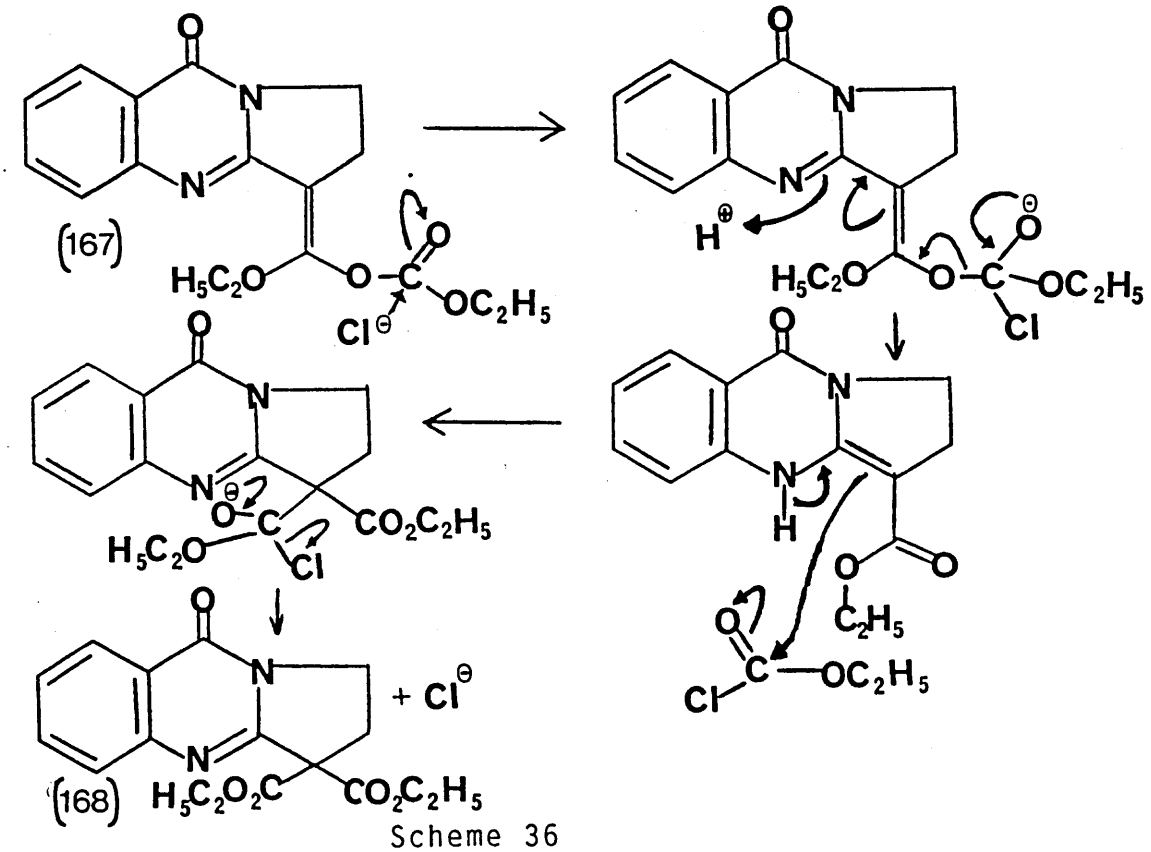
(173) $R=CH_3, R^1=H$

(174) $R=R^1=CH_3$



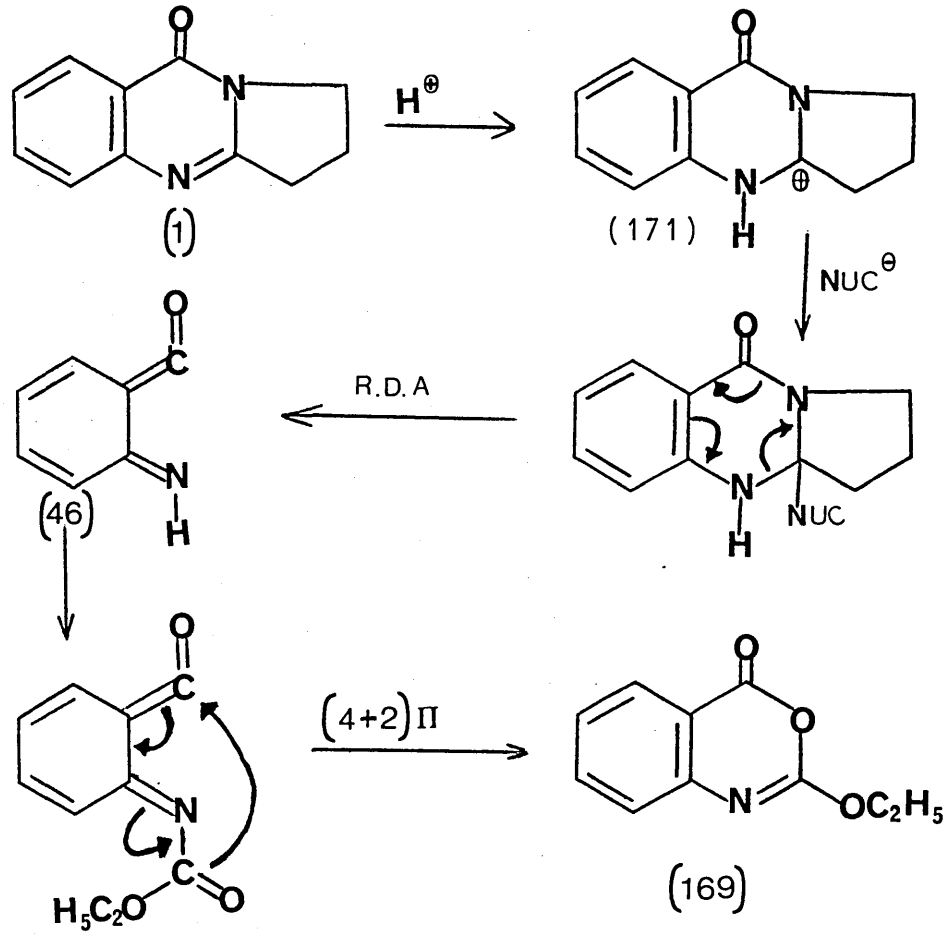
(169)

The alteration in product ratio is consistent with a kinetic thermodynamic reaction mechanism. The formation of the thermodynamic product (168) may proceed via the intermediacy of the enamine of the monoester (170) (Scheme 36).



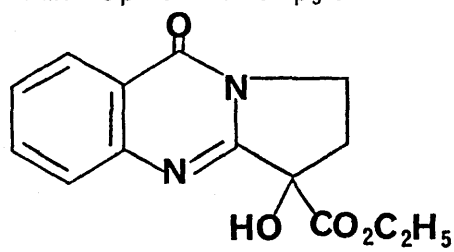
Scheme 36

A possible mechanism to account for the formation of the benzoxazinone (169) is shown below (Scheme 37). Protonation of deoxyvasicinone (1) yields the positively charged species (171). Attack by a nucleophile (possibly ethanol) followed by a retro Diels-Alder reaction yields the ketene imine (46) of a type previously recorded. Acylation at the imine nitrogen followed by a (4 + 2)Π cycloaddition reaction regenerates the aromatic ring to give (169) which had physical and spectral properties consistent with its structure[149].

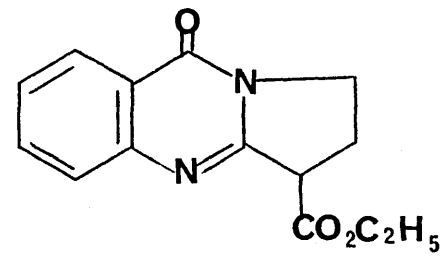


Scheme 37

The reaction of deoxyvasicinone (1) with ethyl chloroformate at higher temperatures (>160^{o}) still gave (168) as the major product but surprisingly the alcohol 3-carbethoxy-2,3-dihydro-3-hydroxy pyrrolo[2,1-b] quinazolin-9(1H)-one (172) was also recovered in good yield. No mechanism to account for the formation of (172) has as yet been postulated. The esters (168) and (172) and the enol carbonate (167) were identified using ^{13}C nmr spectroscopy.



(172)



(170)

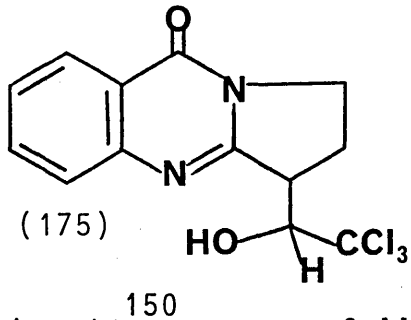
Treatment of the diester (168) with a variety of bases (ethanolic ammonia, hydrazine, sodium methoxide and N-methylpiperazine) yielded only the monoester 3-ethoxycarbonyl-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (170). Attempted reduction of (168) using the technique of Zharakeev[107] produced one polar product (t.l.c.). Isolation and purification by preparative t.l.c. yielded colourless crystals which decomposed prior to positive identification.

Although early experiments had shown that deprotonation of (1) in a variety of solvent/base mixtures failed it was later found that (1) could be lithiated smoothly at -20^{o} using lithium diisopropylamide (LDA) generated *in situ* from n-butyl lithium and anhydrous diisopropylamine. Reaction of the intermediate organo metallic species with excess ethyl chloroformate gave the diester (168) in 28% yield. However, the treatment of lithiated (1) with other electrophiles (acetyl chloride, ethyl bromopyruvate) produced complex mixtures (t.l.c.) the components of which could not be isolated. The formation of the diester (168) in low yield is thought to be as a result of the lithiation of the intermediate monoester (170) by a mole equivalent of the original lithiated (1). Such an exchange reaction should not be unexpected as the remaining proton at C-3 in the monoester (170) would be rendered more acidic due to electron withdrawal effect of the attached ester grouping.

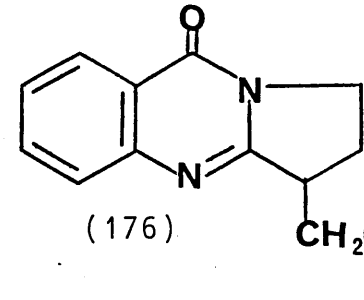
Analogues of (1) demonstrated similar reactivities towards electrophiles, e.g. treatment of the monomethyl analogue (149) with excess ethyl chloroformate over 47 hours at 140^{o} produced 3,3-dicarbethoxy-2,3-dihydro-1-methylpyrrolo[2,1-b]quinazolin-9(1H)-one (173). Metallation, using a slight excess of LDA, of the dimethyl analogue (152) followed by reaction of the organolithium derivative with ethyl chloroformate

produced a 58% yield of 3,3-dicarbethoxy-2,3-dihydro-1,1-dimethylpyrrolo [2,1-b]quinazolin-9(1H)-one (174).

The condensation reaction between 2-picoline (139) and chloral hydrate has been known for almost one hundred years[150]. More recently Taylor and Shvo[39] have shown that pyrrolo[1,2-a]quinazolinones also undergo condensation with chloral to yield adducts. When deoxyvasicinone (1) was heated gently with excess chloral hydrate a thick dark red paste was isolated from which was formed the colourless adduct 3-(2,2,2-trichloro-1-hydroxyethyl)-2,3-dihydropyrrolo[2,1-b] quinazolin-9(1H)-one (175) in 41% yield.



(175)

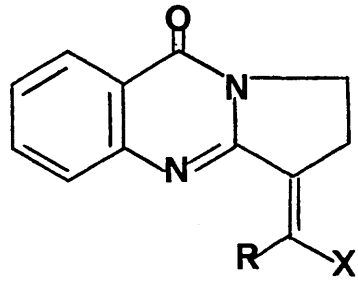


(176)

Liebrecht[150] successfully prepared 3-(2-pyridyl)acrylic acid from 1,1,1-trichloro-3-(2-pyridyl)propan-2-ol by treating the former with ethanolic potassium hydroxide. However, similar treatment of the chloral derivative of (1) (175) yielded only a purple black solid from which only unreacted (175) was recovered.

The preparation of (175) prompted an investigation into the reaction of (1) with other reagents possessing

halogen atoms α to a carbonyl group. The reaction of (1) with the halogenated esters ethyl chloroacetate or ethyl bromoacetate afforded the expected product, 3-ethoxycarbonylmethyl-2,3-dihydropyrrolo[2,1-b] quinazolin-9(1H)-one (176) in low yields. When (1) was heated with excess chloroacetyl chloride, dichloroacetyl chloride or trichloroacetyl chloride the products obtained were the chloroethylidene derivatives (177) and (178) and the enol (179) respectively. A reaction also took place when (1) was heated with 3-chloropropionoyl chloride but the golden flakes (m.p. 130°) recovered have not been identified.

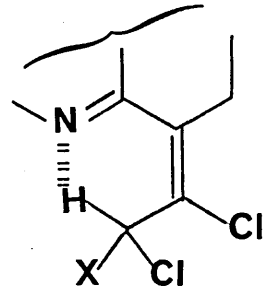


(177) R=CH_2Cl, X=Cl

(178) R=$CHCl_2$, X=Cl

(179) R=OH, X=CCl_3

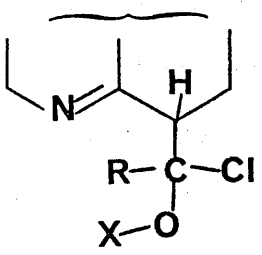
It is probable that the chloroethylidene (177) and (178) exist in the E configuration and that there is a weak hydrogen bond between the acidic chloromethyl (or dichloromethyl) protons and the sp^2 nitrogen atom (Fig. 5).



X = H or Cl

Fig. 5

The hypothesis is supported by the low δ value for these protons (see experimental). It is also likely that an unfavourable dipole-dipole interaction between this nitrogen atom and chlorine in a Z configuration may be a contributing factor for the exclusive stereochemical course of these reactions. In all these reactions an intermediate of the type shown in Fig. 6 is almost certainly involved.



X=H, or $COCH_nCl_{(3-n)}$

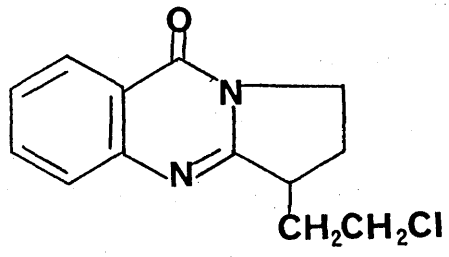
R=$CH_nCl_{(3-n)}$

Fig. 6

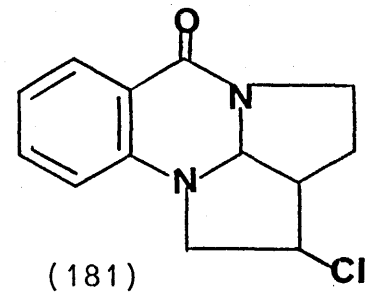
In the case of the trichloroacetyl chloride steric factors will compel the trichloromethyl group to adopt a trans position and since a Z chlorine atom is probably undesirable, elimination of hydrogen chloride is the preferred route in the decomposition of the intermediate. It is unclear whether the initial product from the reaction of (1) and trichloroacetyl chloride is the enol (179) or a labile enol trichloroacetate.

A nucleophilic displacement reaction using benzylamine was conducted on the chloroethylidene derivative (177) but proved unsuccessful, however reduction of (177) was effected using sodium borohydride. Two products were isolated following purification by p.l.c. The more polar compound was

identified using spectroscopic techniques as the (E) 3-ethylidene-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (98). The less polar component was shown by elemental analysis and mass spectrometry to have the formula $C_{13}H_{13}ClN_2O$ but its actual structure has not been ascertained although two possible structures (180) and (181) are proposed.

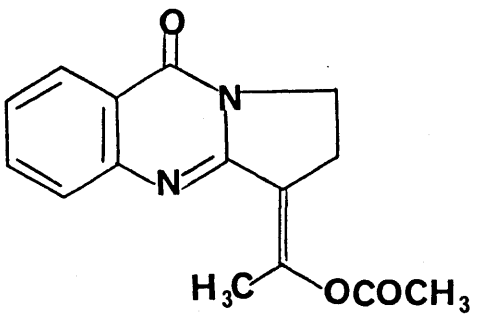


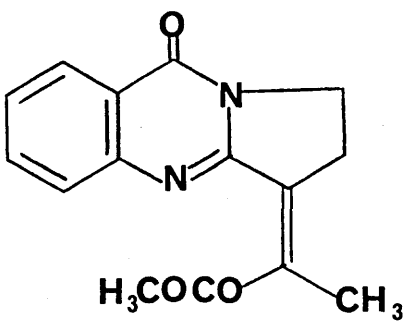
(180)



(181)

Acylation of (1) with acetyl chloride using free radical initiation, base catalysis or lithiation techniques proved unsuccessful. Taylor and Shvo's[39] investigation into active methylene groups resulted in C and N acylation of pyrrolo[1,2-a]quinazolinones being effected by refluxing in acetic anhydride and pyridine. This technique proved ineffectual when applied to deoxyvasicinone (1). However, when (1) (or its hydrochloride) were refluxed with excess acetic anhydride for prolonged periods two products were produced which, after purification by chromatography, were shown to be the isomeric enol acetates (E) 3-acetoxyethylidene-2,3-dihydropyrrolo [2,1-b]quinazolin-9(1H)-one (182) and (Z) 3-acetoxyethylidene-2,3-dihydropyrrolo[2,1-b]quinazolin- 9(1H)-one (183).

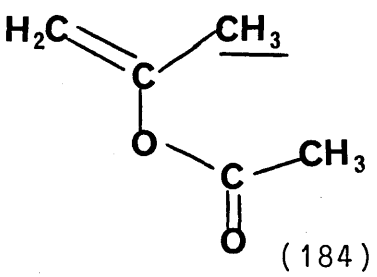




(182) (183)

The less polar isomer (182), which was the main product, was assigned the E-configuration from its p.m.r. spectrum. In the p.m.r. spectrum of (182) the acetate methyl group appears at δ 2.18 and the alkene methyl group at δ 2.60 whilst in the p.m.r. spectrum of (183) the relative positions are δ 2.38 and δ 2.06 respectively.

Jackman [151] has reported the value of a methyl group attached to a C=C bond in an enol acetate (184) at δ 1.91.

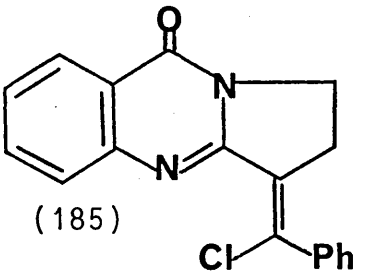


(184)

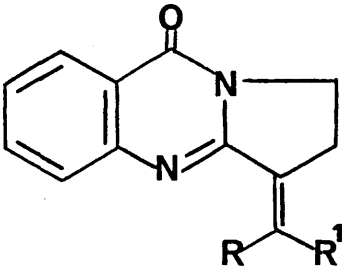
In the isomeric enol acetates (182) and (183) the magnetic environment of the acetate methyl group should not vary too much between the two isomers whereas the methyl group (attached to the C=C) in the (E)-isomer should be more downfield shifted due to the facial geometry of the compound and the proximity of the ring

sp^2 nitrogen atom. In the p.m.r. spectrum of both (182) and (183) the alkene methyl group is complex due to the homoallylic coupling to the protons of C-2 in the pyrrolo ring. No diacetyl compounds of the type reported by Taylor and Shvo[39] were isolated from this reaction or when the acetic anhydride was replaced with acetyl chloride. When (1) was heated with acetyl chloride at reflux for 89 hours the enol acetates (182) and (183) were recovered in low yield following a chromatographical separation of the concentrated reaction mixture. A third more polar component which was also isolated has not as yet been identified.

Interestingly the condensation reaction which occurred when (1) or its hydrochloride was heated with benzoyl chloride yielded the α-chlorobenzylidene derivative (185) as the major reaction product.



(185)



(98) $R=H, R^1=CH_3$
(186) $R=CH_3, R^1=H$

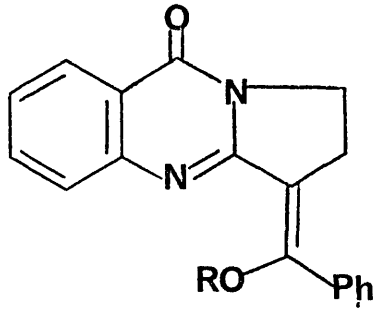
The (E) enol acetate (182) was shown not to undergo nucleophilic attack when heated with benzylamine but was reduced successfully using the Zharakeev[107] technique to afford the (Z)3-ethylidene-2,3-dihydropyrrolo[2,1-b] quinazolin-9(1H)-one (186). The (Z) enol acetate (183)

was similarly reduced to (E) 3-ethylidene-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (98). Both (186) and (98) were obtained from the condensation of (1) with vinyl acetate and triethylamine in a sealed tube. The isomers were separated by chromatography and assigned the relative configurations by examination of their p.m.r. spectra. In the p.m.r. spectrum of the major isomer (98) the alkene methyl group appears at δ 1.80 and the olefin proton at δ 6.5 - 7.1 which is consistent with an E-configuration. In the p.m.r. spectrum of the minor isomer (186) the alkene methyl group appears at δ 2.38 and the alkene proton at δ 6.1 which is compatible with a Z configuration. In both these compounds the alkene hydrogen and the methyl group are allylically and homoallylically coupled to the protons of C-2 of the pyrrolo ring. Spin-spin decoupling experiments confirmed these observations. The ethylidene derivative (98) has been reported as a syrup by Jain et al[101] but both (98) and (186) were isolated in this study as colourless needles.

When (1) was heated with acrylonitrile in a sealed tube a substance derived from the polymerisation of acrylonitrile was recovered. The unreacted deoxyvasicinone was isolated in 96% yield.

The reaction between (1) and benzoic anhydride was investigated following the formation of both the (E) and

(Z) enol acetates from the reaction between (1) and acetic anhydride. When (1) was treated with an excess of benzoic anhydride no significant reaction below 200° was observed. However, condensation was rapid at 230° and two compounds of almost identical R_f value were obtained from the reaction mixture. Separation was achieved by repeated fractional crystallisation. The major product was shown by spectroscopic methods to be the enol benzoate (187) and the Z stereochemistry is assumed for steric reasons. The minor product was shown by elemental analysis and mass spectrometry to have the formula $C_{18}H_{14}N_2O_2$, however it was not possible to unambiguously deduce its structure from spectroscopic data alone. The structure of this minor product was elucidated by X-ray crystallographic techniques and shown to be the (Z) α-hydroxybenzylidene derivative (188) (see X-ray Section Pg. 105) which was stabilised due to intramolecular hydrogen bonding between the sp^2 nitrogen atom and the hydroxyl hydrogen atom.

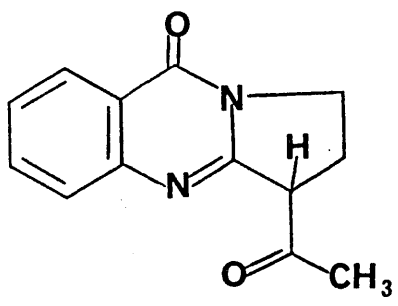


(187) R = COPh

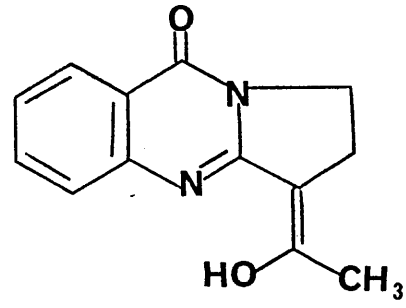
(188) R = H

The stabilising influence of the sp^2 hybridised nitrogen atom of the quinazoline ring in (188) may lend support to the earlier hypothesis that compounds such as (177), (178) and (179) are similarly stabilised by hydrogen bonding.

Further evidence to substantiate this theory was obtained following preparation of the 3-hydroxymethylene derivative (106) which was obtained in 83% yield. Spectroscopy confirmed the enol structure and it is probably favoured due to the intramolecular hydrogen bonding between the sp^2 nitrogen atom and the hydroxyl hydrogen atom. The 3-acetyl derivative (189) was carefully prepared by the treatment of the (E) enol acetate (182) with sodium methoxide. The crystalline material obtained analysed as a monoacetyl derivative. The infra-red spectrum of this compound contained an OH stretch and no band corresponding to a ketone C=O was evident. The p.m.r. spectrum indicated that in solution both tautomeric forms (189a) and (189b) were present.

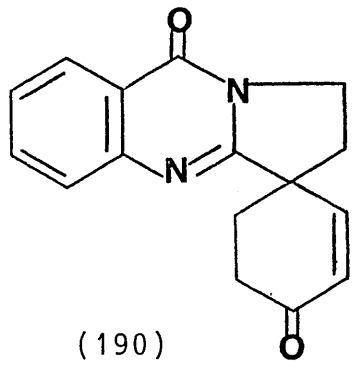


(189a)

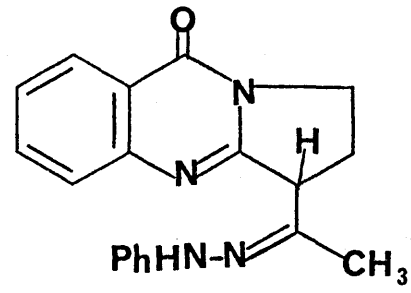


(189b)

The proton on C-3 appeared as an exchangeable doublet of doublets integrating for approximately half a proton and there appears to be two methyl singlets at δ 2.43 and δ 2.02 in a ratio of approximately 2:1. No signals appeared below δ 10 but the signal for the hydroxyl proton may be broad and hence not be easily observed. Therefore the probable structure of the 3-acetyl derivative in solid state is (189b). Both (189) and the hydroxymethylene compound (106) reacted as carbonyl compounds. The hydroxymethylene compound (106) underwent a Robinson type anellation with methyl vinyl ketone to yield the spiroenone (190) whilst (189) formed a phenylhydrazone (191).



(190)

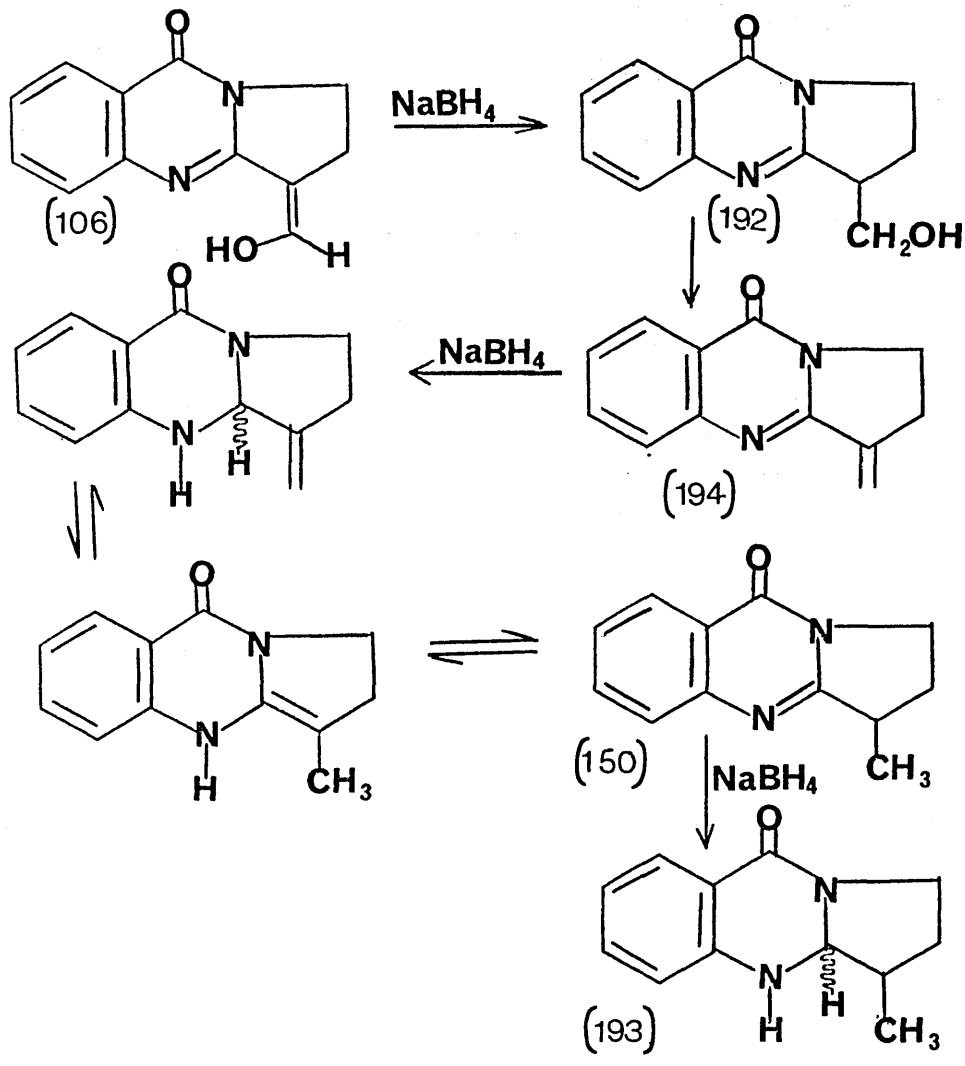


(191)

Prolonged hydrolysis of the (E) enol acetate (182) or its (Z) benzoate counterpart (187) yielded deoxyvasicinone (1) in 85% and 67% yields respectively.

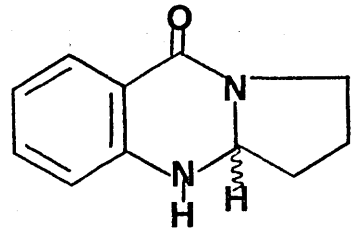
The reaction of (106) with excess sodium borohydride did not yield any 3-hydroxymethyl derivative (192). Instead the two compounds which were isolated from the reaction mixture were identified as the methyl compound (150) and

the more polar component as the secondary amine (193) which is present as a mixture of diastereoisomers. One possible mechanism to account for the formation of these compounds is shown in Scheme 38. The expected compound (192) is produced during the reaction but suffers dehydration to yield the 3-methylene derivative (194). Reduction of the C=N bond in (194) followed by tautomerism yields (150) which is further reduced to (193).



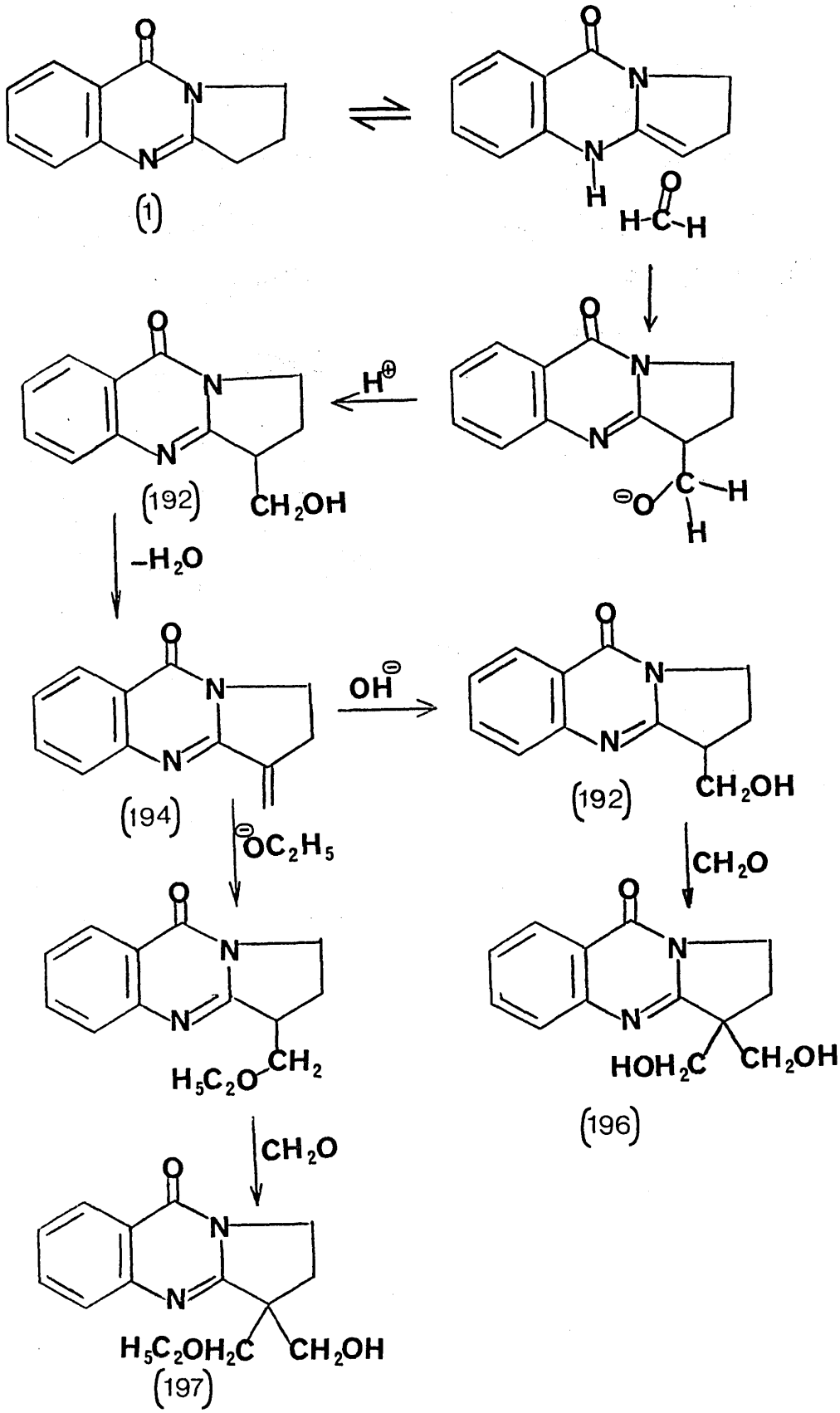
Scheme 38

This mechanism is supported by the results of several experiments. Deoxyvasicinone (1) is known to undergo reduction at the C=N bond and when the reduction was undertaken by Zharakeev the reduced analogue (195) was isolated. The analogue of (1) 3-methyl-2,3-dihydro pyrrolo[2,1-b]quinazolin-9(1H)-one (150) was shown to be similarly reduced to (193).



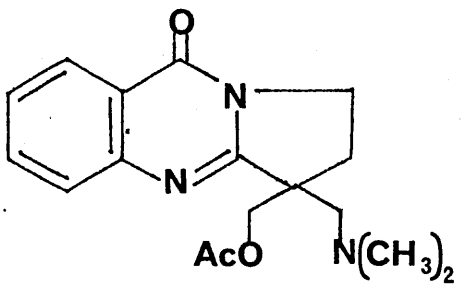
(195)

Further supporting evidence was obtained by the result of an attempted direct hydroxymethylation of (1) with a large excess of formaldehyde and potassium hydroxide in ethanol. In addition to unreacted (1) a three component mixture was obtained. The mixture crystallised to yield the diol (196) whilst chromatography of the residue gave (194) and (197). The mechanism is thought to proceed as shown in Scheme 39. Any (192) which is formed is immediately dehydrated to yield (194). Attack by hydroxide or ethoxide on (194) followed by reaction with formaldehyde leads to both (196) and (197).


(1)
(192)
CH2OH
-H2O
(194)
OC2H5
H5C2O
CH2
CH2O
H5C2OH2C
CH2OH
(197)
OH
(192)
CH2OH
CH2O
HOH2C
CH2OH
(196)

Scheme 39

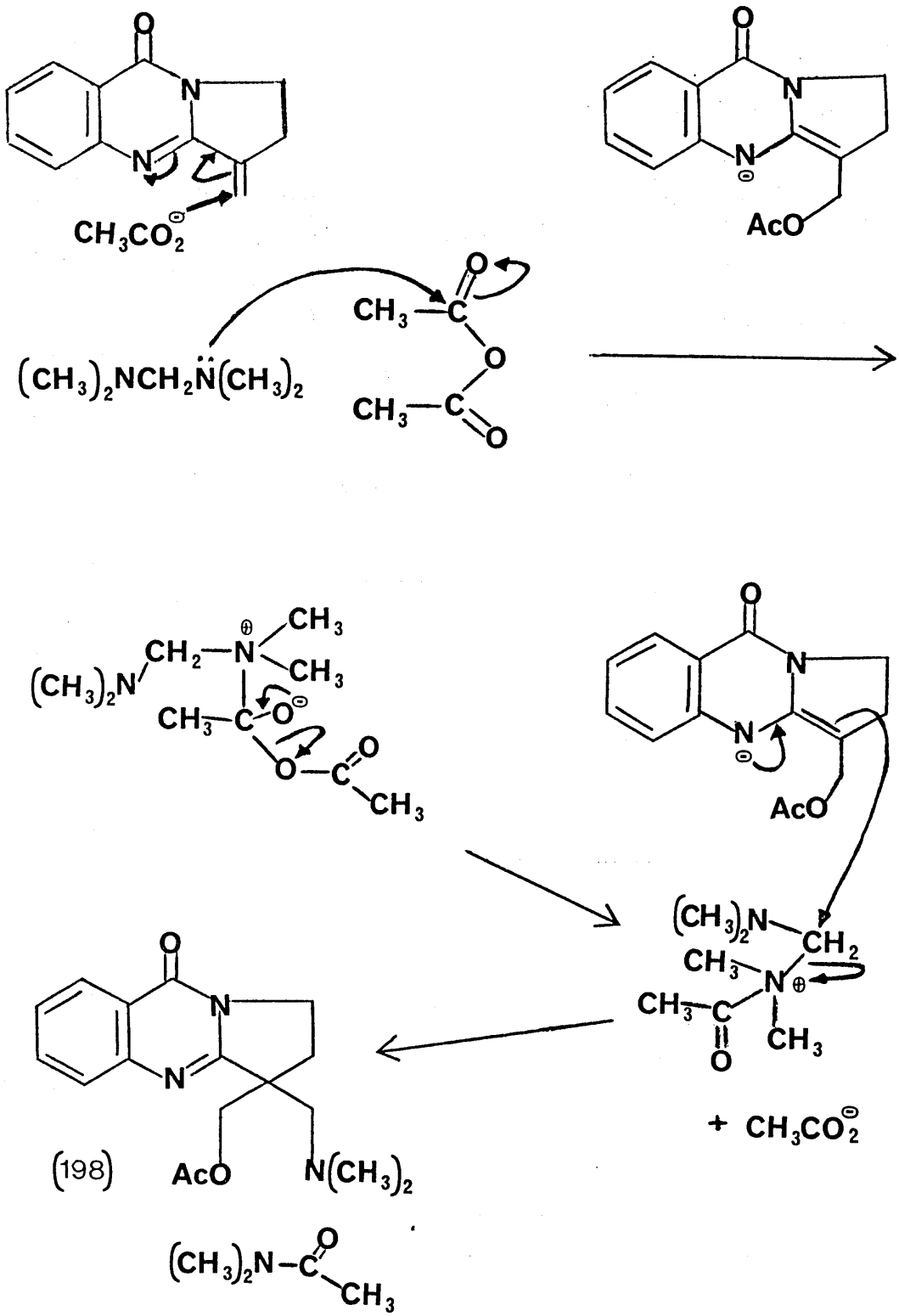
Taylor[39] has reported that the [1,2-a] analogue of (1) undergoes condensation with bis(dimethylamino)methane to yield an exocyclic methylene derivative similar to (194). When a solution of (1) in acetic anhydride was treated with bis(dimethylamino)methane the expected 3-exomethylene derivative (194) was isolated as the major product by column chromatography. A second more polar product was recovered from the column and shown by microanalysis and spectroscopy to have the structure (198).



(198)

The formation of the 3-acetoxymethyl-2,3-dihydro-3-dimethylaminomethylpyrrolo[2,1-b]quinazolin-9(1H)-one (198) can be rationalised on the basis of the reaction of the original exomethylene product (194) with an acetate anion followed by reaction with a further mole equivalent of amine. (Scheme 40).

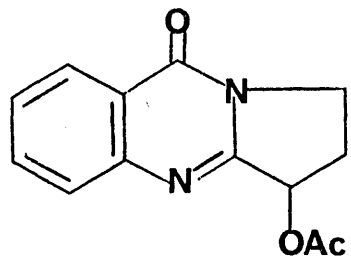
The reaction of a number of active methylene compounds with the Mannich reagent tris(dimethylamino)methane has been reported by Weingarten and Edelmann[152]. The reaction of deoxyvasicinone (1) with this reagent yielded a complex mixture from which no new products could be isolated.


O
N
N
CH3CO2⊖
AcO
(CH3)2NCH2N(CH3)2
CH3
C
O
CH3
C
O
(CH3)2N
CH2
N⊕
CH3
CH3
C
O
O
C
CH3
CH3
C
O
+ CH3CO2⊖
(198)
AcO
N(CH3)2
(CH3)2N
C
O
CH3

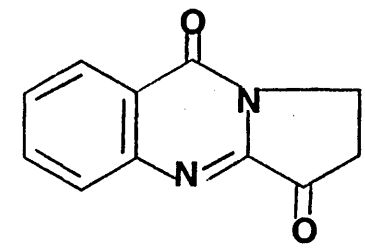
Scheme 40

The exomethylene compound (194) was shown to react extensively with the Diels-Alder reagent dimethyl acetylenedicarboxylate but isolation of pure components from the complex reaction mixture did not prove possible.

Although the formation of acetylvasicinone (86) has been reported[3,31] the oxidation of deoxyvasicinone at the 3-position to give the 3-oxo derivative (199) has never been achieved.



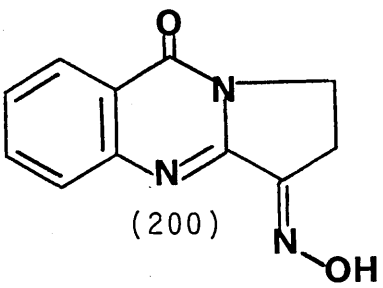
(86)



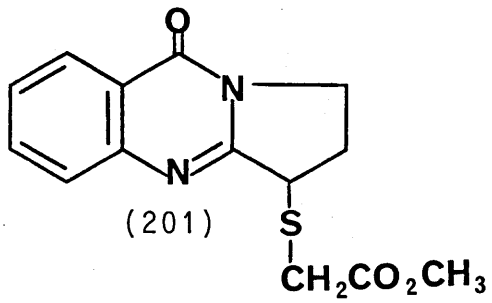
(199)

Unfortunately experiments conducted during this study which attempted to effect the isolation of such a 3-oxo derivative were unsuccessful. Thus treatment of (1) or its benzylidene derivative (160) with the oxidising mixture of sodium chromate/acetic anhydride/acetic acid yielded only unreacted starting material whereas the reaction of (1) with selenium dioxide resulted in extensive decomposition yielding a purple black mixture which could not be resolved.

Taylor[39] has reported that the [1,2-a] analogue of (1) undergoes condensation with amyl nitrite in the presence of sodium ethoxide to yield an oxime. It was hoped that the hydrolysis of such an oxime of (1) would result in the formation of the desired 3-oxoderivative (199). When (1) was treated with amyl nitrite under basic conditions the oxime (200) was isolated in 71% yield.



(200)



(201)

It was not possible to record the p.m.r. spectrum of this compound because of its highly insoluble nature. This insolubility made the compound extremely difficult to hydrolyse. A reaction was induced when the oxime (200) was stirred for fourteen days with lead tetraacetate in glacial acetic acid, however the brown solid obtained from the reaction mixture decomposed prior to isolation of any pure component (t.l.c.).

Onaka[31] has shown that 3,3-dibromo-2,3-dihydropyrrolo [2,1-b]quinazolin-9(1H)-one (84) and 3-bromo-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (85) may be obtained from the free radical initiated bromination of (1) with N-bromosuccinimide. This reaction was repeated but the low yield of the dibromo product (84) obtained

prevented it being used to prepare the 3-oxo derivative via a hydrolysis reaction. However, the monobromo derivative (85) was characterised following a nucleophilic displacement reaction with the anion of methyl thioglycolate. The product from this latter reaction, the 3-carbomethoxymethylthio-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (201) was identified as a thio ester using i.r. and p.m.r. spectroscopy. The p.m.r. spectrum of (201) was unusual in that the methylene protons attached to the sulphur atom appeared as a doublet at δ 3.754. The coupling constant appears to be smaller than normal geminal coupling yet larger than might have been expected for long range coupling.

Other nucleophilic displacement reactions on either (85) or similar compounds have been reported by Onaka[31] or Kökösi et al[153].

Deoxyvasicinone or its analogues have been treated with a number of other electrophilic reagents (ethyl bromopyruvate, ethyl oxalyl chloride, methanesulphonyl chloride, phenacyl bromide, phenyl isocyanate, p-toluenesulphonyl azide, ethoxycarbonyl isothiocyanate) but to date no other products have been isolated (see Experimental).

X-Ray Crystallography

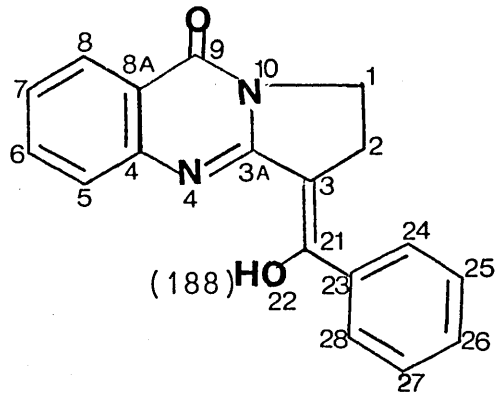
X-rays have wavelengths comparable to the distances between atoms in a crystal. An X-ray beam is therefore diffracted by a crystal and it is possible to obtain a detailed picture of the contents of the crystal at the atomic level by analysing the diffraction pattern produced. Once this information is available and the positions of the individual atoms are known precisely, the interatomic distances, bond angles and other features of the molecular geometry can be calculated.

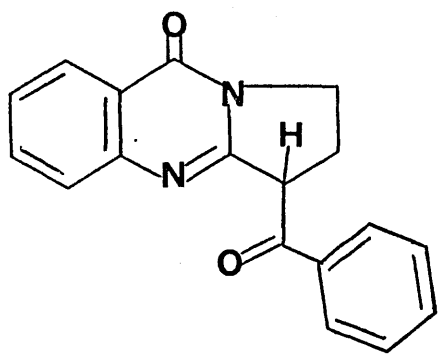
A crystal can be regarded as being built up by the continuing three dimensional translational repetition of a basic structural pattern. Each repeating unit cell may be represented by a point and the arrangement of these points reproduces the size, orientation and shape of the unit cell. The array formed is a lattice and the points are lattice points. A crystal lattice is a regular three dimensional arrangement of points such that the view in a given direction from each point in the lattice is identical with the view in the same direction from any other lattice point.

When an X-ray beam strikes a crystal the diffraction pattern obtained is of a crystal arranged on a lattice that is reciprocal to the real lattice. A picture of this reciprocal lattice may be obtained using a number

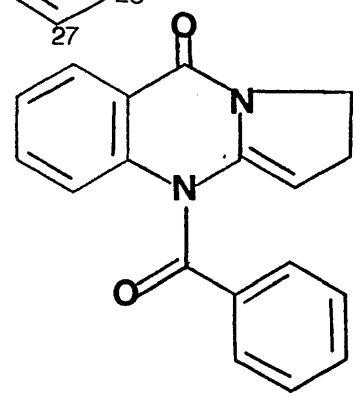
of techniques and the reciprocal lattice may then be used to work out the unit cell and eventually the crystal structure.

The reaction between deoxyvasicinone (1) with benzoic anhydride at 230^{o} gave the expected enol benzoate (186) and a second compound of spectral mass 290.3288 which could not be identified confidently from the spectroscopic data. Three possibilities for the structure were proposed (188), (202) and (203) and the X-ray analysis conducted has shown the product to be (Z) 2,3-dihydro-3-hydroxyphenylmethylenepyrrolo[2,1-b] quinazolin-9(1H)-one (188).





(202)



(203)

The study was conducted using the following methods. Small yellow prisms of (188) were obtained following recrystallisation from dimethylformamide or ethanol. Two crystals (0.3 x 0.4 x 0.3 mm), free from any obvious defects and small enough to be bathed in the X-ray beam were selected under a microscope and mounted with shellac (which does not diffract X-rays) onto a glass fibre attached to a goniometer head. Each of the crystals was in turn set optically on a two circle goniometer to align a principle zone of faces with the goniometer axis. Initial data was then collected on a Weissenberg camera. Firstly a single oscillation photograph was taken, the crystal to be examined was mounted on the camera and the mounting shaft oscillated by $\pm 10^{o}$ while the X-ray beam (40kV, 20mA, Ni filtered CuKα radiation) was directed through a collimator onto the crystal.

A double oscillation photograph was then taken. This photograph has two images of the layers on the same film produced by the crystal rotating by 180^{o} between exposures. As well as checking the crystal setting these oscillation techniques gave information about lattice type and the unit cell dimensions. When the crystal was perfectly aligned a Weissenberg photograph of the zero layer was taken and from this and the oscillation photographs the complete set of unit cell dimensions and symmetry information was obtained. The

compound (188) was shown to crystallise in space group $P2_1/C$, the unit cell is monoclinic with dimensions a=113.0pm, b=1167.2pm and c=964.7pm, $\beta = 110.23^{o}$. The next step in the data collection, i.e. the measurement of the upper layers in the crystal involved the use of a stoe STADI 2 diffractometer to collect intensities $i_{(hkl)}$ which were later processed to give a list of observed structure factor amplitudes $f_{(hkl)}$. The diffractometer is a quantum counting device which directly measures the number of photons from the diffracted X-ray beam. This diffractometer has two moving circles.

a) ω- rotates the crystal shaft and is used to bring any chosen reflexion of an orientated crystal into the diffracting position.

b) 2θ - moves the detector so that it rotates about a vertical axis, i.e. in a horizontal plane, ensuring that the plane containing the incident and diffracted beam is always horizontal.

Intensities were collected over the range $0 < 2\theta < 55^{o}$ for crystals mounted on the a(h=0 to 2) and b(k=0 to 8) axes. The ω-scan technique was employed and 2552 unique reflexions were measured.

Direct methods of structure solution were then employed to solve the structure from the collected data. Two assumptions are made whenever direct methods are used ;

a) The electron density map can never be negative in the cell.

b) Atoms are atom shaped, i.e. electron density around an atomic centre is approximately spherically symmetrical.

Direct methods attempt to assign the phases of a limited number of the most intense reflexions by statistical relationships. A Fourier map (or E-map) is then calculated for these phased reflexions and is examined to see if the peaks correspond to a model which is recognisable as at least a part of the expected structure. If the peaks do correspond with the model they are called atoms and are then used to phase the whole data set.

The routine Tang (on SHELX 76)[154] using 1115 of the most intense of the original 2552 reflexions, was employed to produce the best E-map which revealed all the non H-atoms. Once the approximate positions of the non H-atoms were known refinement of the structure took place. The atomic parameters (co-ordinates of atoms in cell) which were obtained from the E-map were used to

calculate structure factors (fc) for all the hkl values. The data set and that of the observed structure factor amplitudes $(fo)_{(hkl)}$ were refined via a process of systematic variation in order to give the best possible agreement between the two data sets. Since this problem involved many parameters succesive refinement cycles were needed before the structure converged to the stage at which shifts in the atomic parameters from cycle to cycle were negligible with respect to experimental error. The co-ordinates were then refined using a least squares procedure with isotropic thermal parameters for each atom to give improved values of (fc). The least squares method of refinement works on the basis that the best values for the principles of a linear function are those which minimise the sums of the squares of differences between (fc) and (fo) values for all the observed hkl's, the process being repeated until a reasonable match of fc and fo is obtained. At this point R=0.11 (R being a measure of how well the calculated model fits the observed data and it should be 0.1 for most structures). Once the match of (fc) and (fo) was obtained the atoms were made anisotropic (i.e. instead of having a spherical model for the thermal vibration of each atom, the parameters are altered to produce an ellipsoidal distribution of electron density, which is more like the movement of a real atom). The structure was now complete except for the position of

the hydrogen atoms. The H atoms were included as riding atoms at calculated positions with grouped isotropic temperature parameters except for the hydroxyl proton which is involved in hydrogen bonding. This atom was located on a difference Fourier map and refined with an isotropic temperature parameter. Further refinement of the structure by least squares gave a final R value of 0.0689 for 1115 observed reflexions although the hydroxyl proton did not refine completely satisfactorily giving a final temperature parameter of $0.16A^{o2}$. The atomic co-ordinates are given in Table 1*(estimated standard deviations in parenthesis). Table 2*gives the bond lengths and angles within the compound whilst figures 7, 8 and 9 show the molecule from a number of angles. The X-ray analysis has proved the molecule to be the Z isomer of (188) stabilised by a hydrogen bond between O(22) and N(4) (257.1(6)pm) as previously mentioned. The respective bond lengths were O(22) - H(221)103.1pm(10) and N(4).....H(221)169.8(10)pm. The phenyl group C(23).....C(28) is close to coplanar with the pyrroloquinazolinone fragment giving the maximum extended Π - bonding. The torsion angle C(3)-C(21)-C(23)-C(24) is $171.27(7)^{o}$ and the angle between the normals to the mean planes of the two benzene rings is $7.55^{o}(8)$. All calculations were performed on the Dundee University DEC 10 computer using the SHELX 76[154], XANADU[155] and PLUTO[156] program packages. A list of structure factors, anisotropic thermal parameters and H-atom co-

(* See Appendix at end of Section).

ordinates have been deposited in the British Library, Lending Division.

Screening Results

A number of the compounds prepared during the course of this study were screened for possible fungicidal, insecticidal and herbicidal activity. Generally the benzylidene derivatives (156), (157), (159), (160) and (161) were demonstrated to have little activity over the range of screening tests however (156) was reported to be slightly active as a fungicide. Slight fungicidal activity was also recorded for the methyl analogues of (1) being (150) and (152) and the ester (154). No herbicidal, insecticidal or fungicidal activity was recorded for the other compounds (151), (167), (168), (174), (177), (179) and (182) tested. No data was available on the herbicidal activity of (154), (156), (177) and (182) or the fungicidal activity of (177) and (182). The above information is the result of a screening program performed by Shell Research Ltd., Sitttingbourne, Kent, England. The action of the (E) enol acetate (182) and the chloroethylidene derivative (177) as anti tumour agents was also investigated.

However the observation that these compounds exhibited high toxicities at increased dosage meant that studies into their activity were terminated.

These data are the results of screening performed under the auspices of the Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland.

Fig. 7 View XO

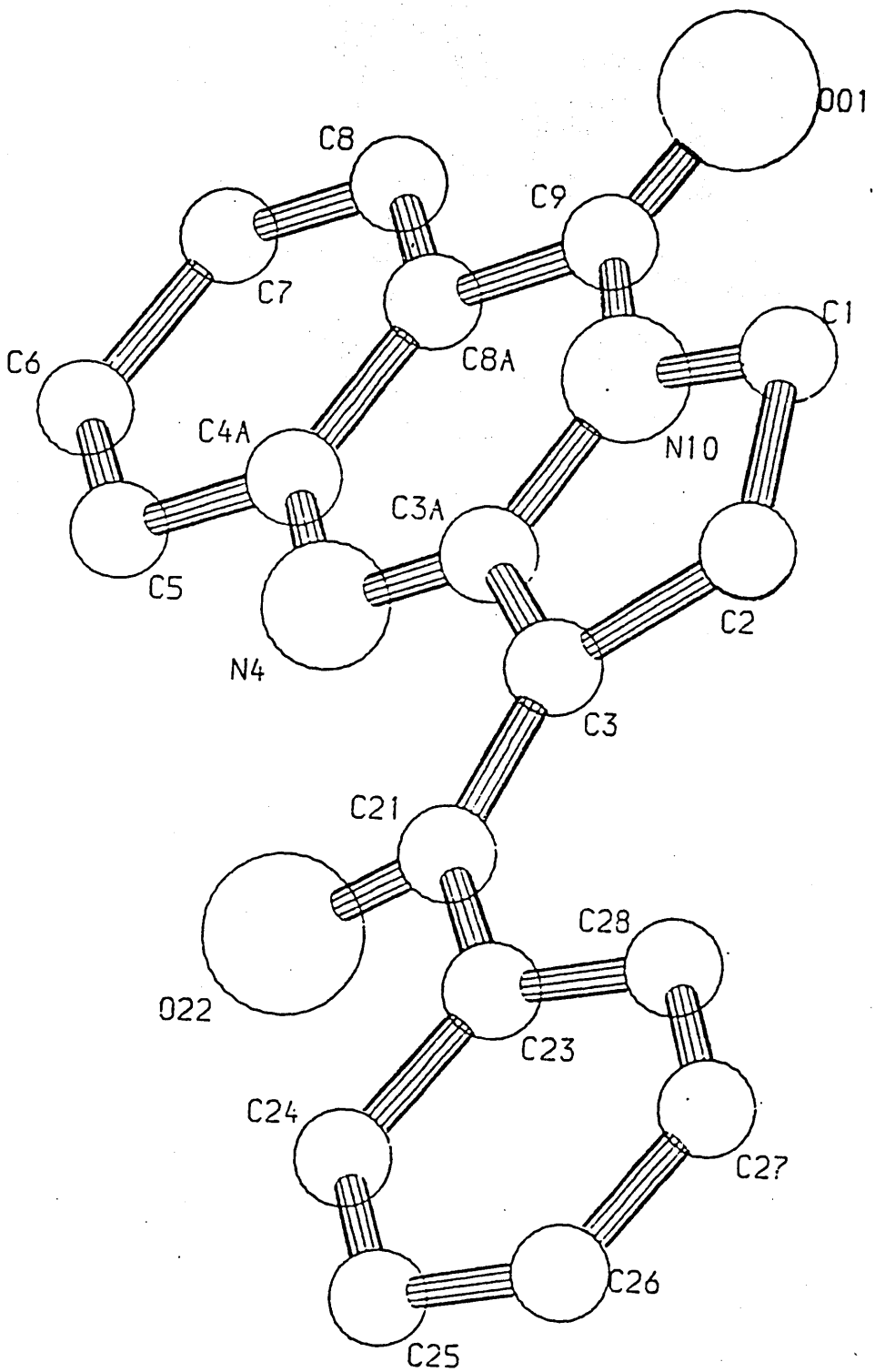

O01
C8
C9
C7
C1
C6
C8A
C4A
N10
C3A
C5
C2
N4
C3
C21
C28
O22
C23
C24
C27
C26
C25

Fig. 8 View YO

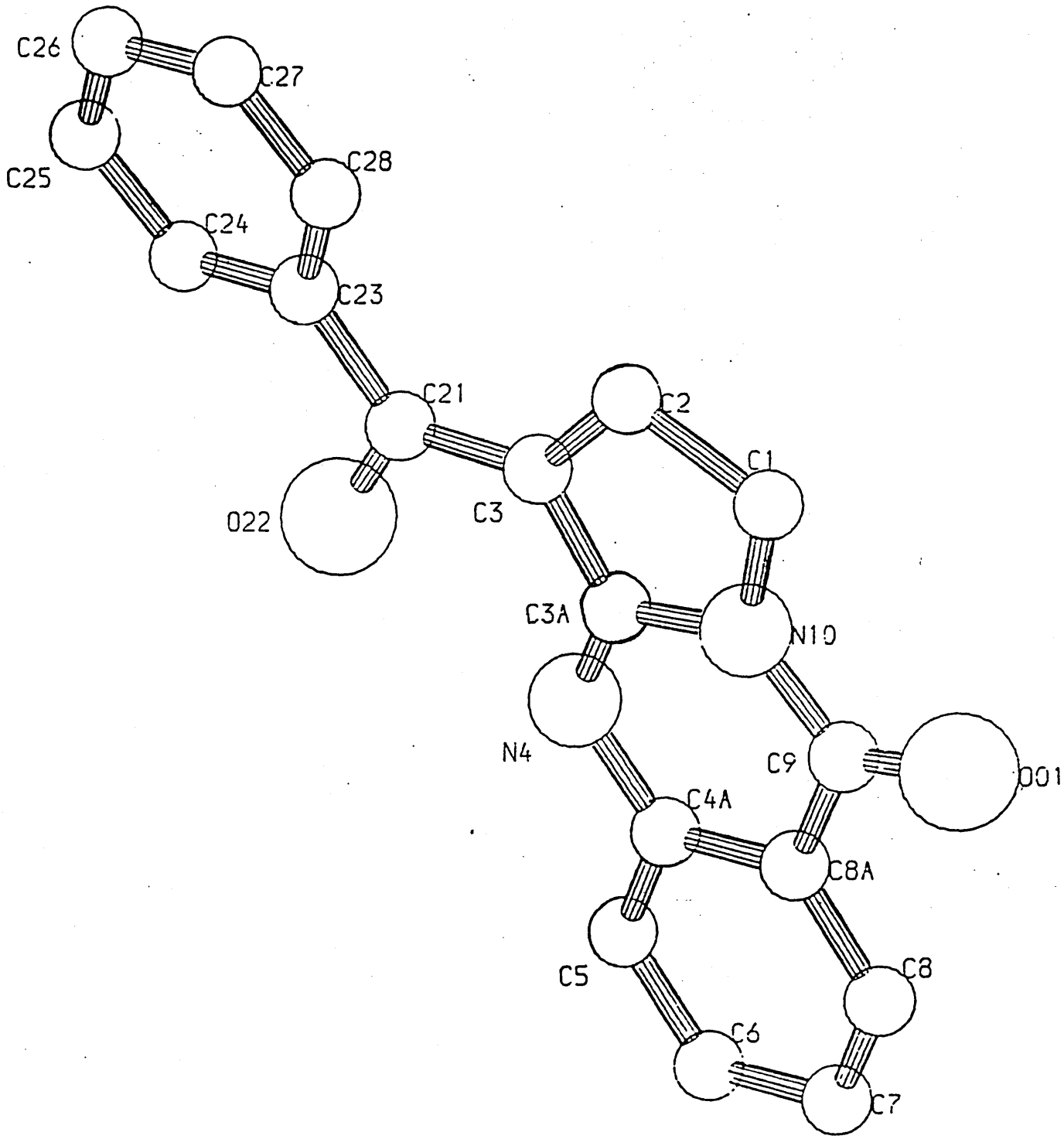

C26
C27
C25
C28
C24
C23
C21
C2
C1
O22
C3
C3A
N10
N4
C9
O01
C4A
C8A
C5
C8
C6
C7

Fig. 9 View Z0

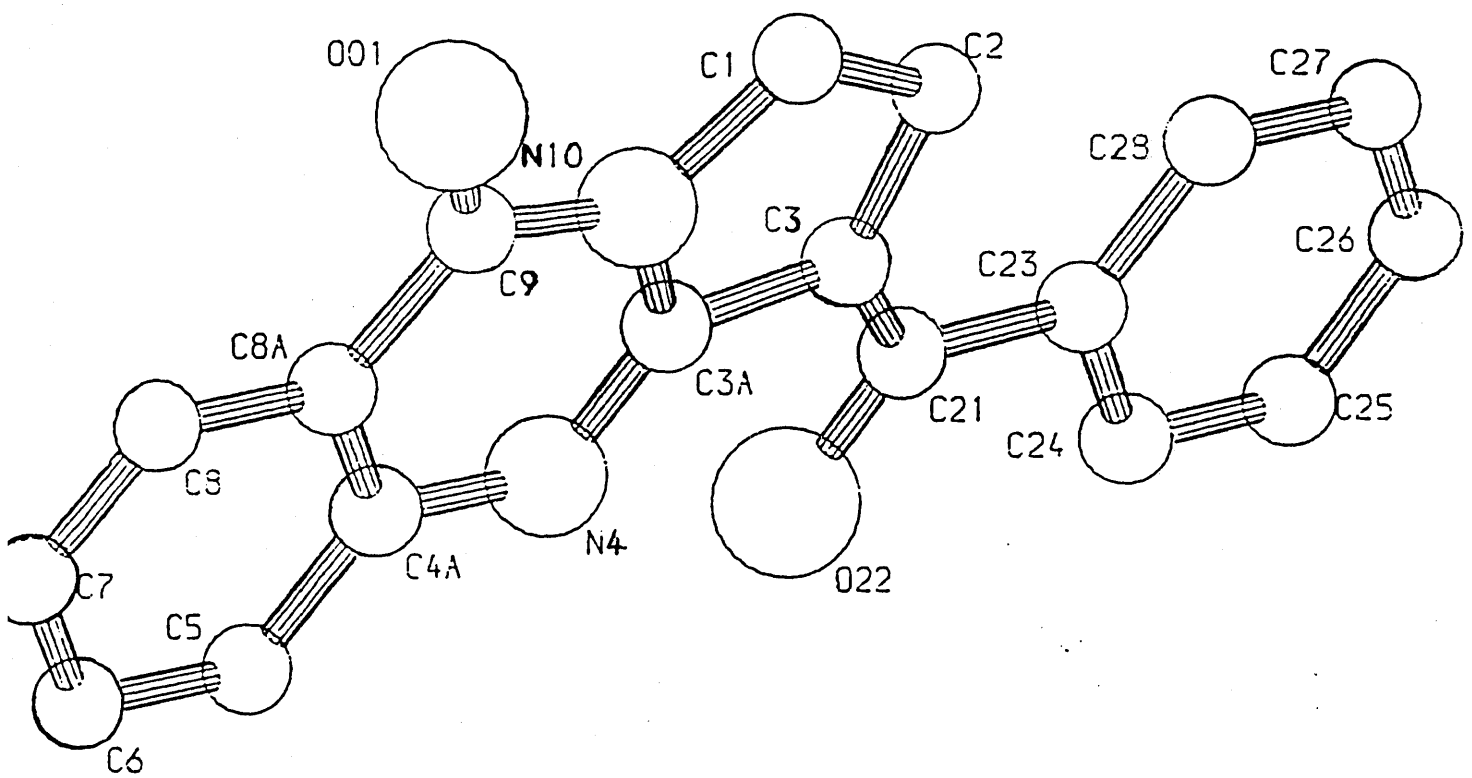

001
C1
C2
C27
N10
C28
C3
C26
C9
C23
C8A
C3A
C21
C25
C8
C24
N4
C4A
C7
O22
C5
C6

Table 1. Fractional coordinates (x 10^4) and equivalent isotropic thermal parameters ($Å^2$ x 10^3).

$$U_{eq} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j^* a_i . a_j .$$

	x	y	z	U_{eq} or U
C(1)	4700 (4)	5088 (4)	8188 (4)	53 (1)
C(2)	5570 (4)	4911 (4)	7437 (4)	49 (1)
C(3)	5001 (4)	3871 (3)	6593 (4)	38 (1)
C(3a)	3887 (4)	3493 (3)	6797 (3)	36 (1)
C(4a)	2085 (4)	2414 (4)	6557 (4)	41 (1)
C(5)	1285 (5)	1472 (4)	5983 (4)	50 (1)
C(6)	206 (5)	1259 (5)	6256 (4)	60 (2)
C(7)	-82 (5)	2001 (5)	7095 (5)	60 (2)
C(8)	709 (5)	2916 (5)	7668 (4)	55 (2)
C(8a)	1810 (5)	3132 (4)	7420 (4)	43 (1)
C(9)	2675 (5)	4078 (4)	8063 (4)	48 (2)
C(21)	5360 (5)	3337 (4)	5709 (4)	39 (1)
C(23)	6470 (5)	3610 (4)	5375 (4)	43 (1)
C(24)	6743 (5)	2839 (5)	4559 (5)	64 (2)
C(25)	7728 (6)	3063 (6)	4160 (5)	77 (2)
C(26)	8482 (5)	4048 (6)	4580 (5)	68 (2)
C(27)	8232 (5)	4817 (5)	5389 (5)	64 (2)
C(28)	7238 (5)	4599 (4)	5790 (4)	55 (2)
N(4)	3146 (3)	2617 (3)	6249 (3)	41 (1)
N(10)	3696 (4)	4196 (3)	7687 (3)	41 (1)
O(01)	2548 (3)	4748 (3)	8847 (3)	68 (1)
O(22)	4634 (3)	2457 (3)	5016 (3)	48 (1)

Table 2. Interatomic distances (Å) and angles (°).

C(2)-C(1)	1.540(8)	N(4)-C(3a)-C(3)	126.6(4)
N(10)-C(1)	1.468(5)	N(10)-C(3a)-C(3)	109.7(3)
C(3)-C(2)	1.511(6)	N(10)-C(3a)-N(4)	123.7(5)
C(3a)-C(3)	1.424(7)	C(8a)-C(4a)-C(5)	120.3(5)
C(21)-C(3)	1.368(7)	N(4)-C(4a)-C(5)	118.3(4)
N(4)-C(3a)	1.300(5)	N(4)-C(4a)-C(8a)	121.4(4)
N(10)-C(3a)	1.376(6)	C(6)-C(5)-C(4a)	119.7(5)
C(5)-C(4a)	1.395(6)	C(7)-C(6)-C(5)	119.8(5)
C(8a)-C(4a)	1.402(7)	C(8)-C(7)-C(6)	120.5(6)
N(4)-C(4a)	1.385(7)	C(8a)-C(8)-C(7)	120.5(5)
C(6)-C(5)	1.383(9)	C(8)-C(8a)-C(4a)	119.2(4)
C(7)-C(6)	1.403(8)	C(9)-C(8a)-C(4a)	120.3(5)
C(8)-C(7)	1.367(7)	C(9)-C(8a)-C(8)	120.5(5)
C(8a)-C(8)	1.392(8)	N(10)-C(9)-C(8a)	113.2(4)
C(9)-C(8a)	1.456(6)	O(01)-C(9)-C(8a)	126.3(5)
N(10)-C(9)	1.375(8)	O(01)-C(9)-N(10)	120.5(4)
O(01)-C(9)	1.226(6)	C(23)-C(21)-C(3)	127.9(4)
C(23)-C(21)	1.469(8)	O(22)-C(21)-C(3)	119.2(5)
O(22)-C(21)	1.352(5)	O(22)-C(21)-C(23)	112.9(4)
C(24)-C(23)	1.393(8)	C(24)-C(23)-C(21)	117.8(4)
C(28)-C(23)	1.382(7)	C(28)-C(23)-C(21)	124.2(5)
C(25)-C(24)	1.372(10)	C(28)-C(23)-C(24)	118.0(5)
C(26)-C(25)	1.370(8)	C(25)-C(24)-C(23)	121.2(5)
C(27)-C(26)	1.374(9)	C(26)-C(25)-C(24)	120.1(6)
C(28)-C(27)	1.380(9)	C(27)-C(26)-C(25)	119.6(6)
		C(28)-C(27)-C(26)	120.6(5)
N(10)-C(1)-C(2)	104.2(3)	C(27)-C(28)-C(23)	120.5(5)
C(3)-C(2)-C(1)	104.9(4)	C(4a)-N(4)-C(3a)	117.6(4)
C(3a)-C(3)-C(2)	108.6(4)	C(3a)-N(10)-C(1)	112.5(4)
C(21)-C(3)-C(2)	130.8(5)	C(9)-N(10)-C(1)	123.8(4)
C(21)-C(3)-C(3a)	120.6(4)	C(9)-N(10)-C(3a)	123.7(4)

Appendix II

EXPERIMENTAL

Experimental

Infra-red spectra were recorded for potassium bromide discs and for films in sodium chloride plates using Perkin-Elmer 197 and Pye Unicam SP3-200 spectrophotometers. Ultra violet spectra were measured on a Perkin-Elmer 402 ultraviolet-visible spectrophotometer. The proton magnetic resonance spectra were recorded either neat or in the appropriate solvent using tetramethylsilane as internal standard on Jeol JMN PMX 60 si and Jeol FX90Q machines at 60 MHz and 90 MHz respectively. ^{13}C n.m.r. spectra were recorded on a Bruker WP80DS spectrometer and mass spectra with an AEI MS9 spectrometer at 70 eV. X-ray diffraction analysis was conducted using a Stoe STADI-2 diffractometer.

The melting points are uncorrected and were determined on an Electrothermal melting point apparatus.

Hydrogenation over Raney Nickel was carried out by the Boots Co. Ltd.

Chromatographical Techniques

A Perkin-Elmer 8310 gas chromatograph containing an OV-17 column was utilised for gas chromatography. Absorption chromatography was carried out using silica gel (Merck, 70-230 mesh). Separations using pressurised short path columns were achieved with Kieselgel 60H as absorbent. Thin layer chromatography was conducted exclusively on pre-coated aluminium backed plates (Merck D.C. Alufolein Kieselgel $60F_{254}$). The following systems were used as eluents in chromatography.

System 1 - Ethylacetate : Triethylamine (9:1)
System 2 - Ether
System 3 - Ether : Light Petroleum (1:1)
System 4 - Ether : Light Petroleum (7:3)
System 5 - Ether : Light Petroleum (2:3)
System 6 - Ether : Light Petroleum (1:3)
System 7 - Ethyl Acetate : Light Petroleum (1:4)
System 8 - Ethyl Acetate : Light Petroleum (3:7)
System 9 - Ethyl Acetate : Light Petroleum (1:1)
System 10 - Ethyl Acetate : Light Petroleum (2:1)
System 11 - Ethyl Acetate : Light Petroleum (7:3)
System 12 - Ethyl Acetate : Light Petroleum (4:1)
System 13 - Ethyl Acetate : Light Petroleum (9:1)
System 14 - Ethyl Acetate : Dichloromethane (3:1)

System 15 - Ether : Ethyl Acetate : Light Petroleum (2:2:6)

System 16 - Propan-1-ol : Water (3:1)

System 17 - Ethanol : Chloroform (1:19)

System 18 - Ethanol : Chloroform (1:99)

Preparative layer chromatography was achieved on glass plates (20 x 20cm) coated with silica gel (Kieselgel 60H), thickness 2mm or the equivalent precoated glass plates (Merck P.S.C. Kieselgel $60F_{254}$).

Developing Reagents for Thin Layer Chromatography

The following detection methods were used:

(a) Ultraviolet irradiation of t.l.c. plates impregnated with a fluorescent indicator was routinely employed.

(b) Iodine vapour was a general but indiscriminating reagent.

(c) Development using 0.5% aqueous potassium permanganate solution with warming if necessary was used as a general method.

(d) Development using 5% ethanolic solution of anisaldehyde with a trace of concentrated sulphuric acid and heating was often used.

This reagent was found to be particularly useful since each reaction component developed at a different rate to afford a different colour. Hence coincidental components, or components with similar R_f values could be readily distinguished.

Solvents

All solvents are reagent grade unless otherwise stated. Light petroleum refers to petroleum ether boiling range 60 - 80°. Ether refers to diethyl ether. Tetrahydrofuran and diethyl ether were dried by distillation from lithium aluminium hydride. Diisopropylamine was dried over KOH pellets for 48 hours prior to use. When necessary chlorinated hydrocarbons were dried over calcium chloride prior to storage over molecular sieve. Aromatic solvents were dried over sodium wire or sodium/lead alloy prior to use.

Anhydrous magnesium sulphate was used as a standard drying agent for all organic solutions. Charcoal was employed routinely as the decolourising agent.

Reagents

Bis(dimethylamino)methane was prepared using aqueous solutions of dimethylamine and formaldehyde according to the method of Lindsay and Hauser[157].

Benzoic anhydride was prepared from benzoic acid and acetic anhydride using the procedure of Clarke and Rahrs[158].

Lithium diisopropylamide was prepared in situ using a standard technique from n-butyllithium and diisopropylamine as demonstrated by Jahngen, Phillips, Kobelski and Demko[159].

Triethyloxonium tetrafluoroborate was produced in situ according to the method of Meerwein[95] from boron fluoride etherate, ether and epichlorohydrin.

General Preparatory and Isolatory Techniques

Procedure (a)

The mixture was heated at 80-90^{o} for 4 hours and cooled to room temperature. After cooling the contents of the flask were acidified (dilute hydrochloric acid) and extracted with ether. The ether layer was washed twice with water, then with approximately 50ml of 0.1% sodium bicarbonate, 20ml of brine and finally again with water. After drying the ethereal solution was concentrated by distillation and the products obtained by distillation through a 30cm Vigreux column at reduced pressure.

Procedure (b)

An equivalent quantity of water was added portionwise to the flask throughout the reaction and after a further 30 minutes the mixture was cooled and the colloidal iron removed by filtration through sand and cotton cloth. Concentration of the filtrates afforded a brown mass which was extracted with acetone and filtered. The solid was washed with acetone and the mother liquors and washings were combined. Concentration ***in vacuo*** of these combined extracts yielded a thick brown syrup which was distilled under reduced pressure to give the product.

Procedure (c)

As much benzene as possible was decanted from the reaction mixture and the mixture was stirred with a 50% aqueous solution of potassium carbonate (4ml/g pyrrolidinone) for 30 min. This heterogeneous liquid was extracted with ether (2 x 100 ml) and the combined ethereal extracts dried over magnesium sulphate in a stoppered flask for 30 min. This dried solution was quickly filtered into a second flask and the ether removed by distillation through a 30cm Vigreux column.

The remaining benzene was removed by distillation under reduced pressure (water pump) and continued distillation yielded the required imidate.

Procedure (d)

The thick suspension which formed was quickly filtered and washed with dichloromethane. The filtrate was separated and the organic phase dried over magnesium sulphate in a sealed flask. Rapid filtration followed by distillation through a 30cm Vigreux column removed the solvents. The concentrated solution was distilled under reduced pressure (water pump) to give the product.

Procedure (e)

The mixture was cooled, diluted with ice/water and made alkaline with concentrated ammonium hydroxide. The aqueous solution was extracted with chloroform (3 x

150 ml) and the combined extracts dried, decolourised and concentrated in vacuo to give the crude pyrroloquinazolone as a syrup.

Procedure (f)

The mixture was cooled and concentrated **in vacuo**. The concentrated reaction mixture was partitioned between dichloromethane (100ml) and a saturated solution of sodium bicarbonate (10ml) followed by water (5ml). The organic phase was dried, decolourised and concentrated in vacuo to give the crude pyrroloquinazolone as an orange syrup.

Procedure (g)

The flask was cooled to 0^{o} and treated with ether. Agitation induced crystallisation of the crude benzylidene which was recrystallised from ethanol.

Procedure (h)

The mixture was cooled and excess reagent destroyed with glacial acetic acid. Neutralisation was effected using a saturated solution of sodium bicarbonate. The mixture was concentrated **in vacuo** and evaporated with methanol (3 x 20ml) to remove borate. The residue was partitioned between dichloromethane (150ml) and water (5ml). The organic layer was dried and concentrated **in vacuo**.

Procedure (i)

A solution of (1) in dry tetrahydrofuran (10ml/g(1)) was added dropwise over 30 min. to a solution of lithium diisopropylamide prepared according to the method of Jahngen et al[159] from the addition of n-butyllithium (2.7 l of a 1.6M solution in hexane/mol. of (1)) to anhydrous diisopropylamine (408g/mol.(1)) in dry tetrahydrofuran (10ml/g diisopropylamine) at -20° in a dry nitrogen atmosphere. The mixture (a deep burgundy red) was stirred for 1 hour prior to the addition of electrophiles.

2-(4-Chlorobutyryl)aminobenzamide (17)

Acetic acid (400 ml) followed by a saturated solution of sodium acetate (200 ml) was added to anthranilamide (54.4g). The mixture was stirred to give a golden yellow solution. 4-chlorobutyryl chloride (84.4g, 1.5 mol.equiv.) was added dropwise to the solution with constant stirring at room temperature. After 1 hour the solution was diluted to 1600 ml with water to produce a white slurry. Filtration, drying and subsequent recrystallisation from ethanol gave the white crystalline product (17)(59.7g, 62%) m.p. 114° (reported m.p. 120° (Landii Vittory and Gatta[40])) t.l.c. (system 2) R_f 0.425.

2,3-Dihydropyrrolo[2,1-b]quinazolin-9(1H)-one(deoxy-vasicinone) (1) and 2,3-dihydropyrrolo[1,2-a]-quinazolin-5(1H)-one (16)

The chloro compound (17)(59.7g) was added portionwise to a solution of sodium methoxide (prepared from sodium metal (6.07g, 0.26g/atom) in methanol (500 ml) and the mixture refluxed on a water bath for 4 hours. On cooling the methanolic solution was decanted into a large round bottomed flask. The residue in the reaction vessel was washed with methanol and dichloromethane and these washings were also added to the round bottomed flask.

Concentration of the organic solution afforded a pink solid, t.l.c. (system 1) R_f 0.03, 0.482. The solid was extracted portionwise with hot ether (soxhlet). t.l.c. (system 1) indicated R_f 0.482 in ethereal solution, R_f 0.03 in the crystalline residue. The crystalline residue was dried and gave white crystals of (16)(9.82g, 21%), m.p. 222° (reported m.p. 222° Landii Vittory and Gatta[40]).

The ethereal solution was cooled and the ether reduced in volume on the evaporator. The addition of light petroleum promoted crystallisation of (1) (22.07g, 47%), m.p. 109°- 110° (reported m.p. 110°, Landii Vittory and Gatta[40]), t.l.c. (system 1) R_f 0.482; νmax(KBr):3050 - 2875, 1675 (C=O), 1620 (C=N), 1460, 1380, 1030, 780, 690cm^{-1}; λmax ($CHCl_3$): 245 (ξ 7000), 267 (ξ 3800), 304 (ξ 1750), 311nm (ξ 1500); δ (60MHz, $CDCl_3$): 2.30 (2H, quintet, J_{AB}7Hz, >N-CH_2-$\underline{CH_2}$-CH_2-), 3.20 (2H,t,J_{AB}7Hz, >N-CH_2CH_2-$\underline{CH_2}$-), 4.30 (2H,t,J_{AB}7Hz, >N-$\underline{CH_2}$-CH_2-CH_2-), 7.40-8.05 (3H,m,3 aromatic protons), 8.43 (1H,d,J 8Hz, C-8-H).

2,3-Dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (1)

Phosphorous oxychloride (50ml) was added to a mixture of anthranilic acid (21g) and 2-pyrrolidinone (9) (19g, 1.5 mol.equiv.) and the mixture heated for 1 hour on a water bath. The product was isolated as in procedure (e). The crude product was recrystallised from cyclohexane to give deoxyvasicinone as a white powder (14.96g, 52%) identical in all respects (m.p., m.m.p., t.l.c. and i.r.) to an authentic sample.

2,3-Dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (1)

Anthranilic acid (20g) and 1-aza-2-methoxycyclopent-1-ene (34) (17.2g, 1.2 mol.equiv.) in toluene (300ml) were heated at reflux for 1.5 hours and the crude product isolated using procedure (f). The syrup crystallised from ether/light petroleum to give colourless prisms of (1) (15.6g, 58%) identical in all respects (m.p., m.m.p., t.l.c., i.r.) to an authentic sample.

Nitroesters

These were obtained using the method of Moffet[58] which was a refinement on the techniques of many authors[53-61].

Methyl 4-methyl-4-nitropentanoate (48)

Methyl acrylate (86g) was added over 15 minutes to a stirring solution of 2-nitropropane (89g, 1 mol. equiv.) dioxane (50ml) and Triton B (10ml) heated to 70°. A slight exotherm was recorded and isolation by procedure (a) gave (48)(155g, 89%) as a nearly colourless oil, b.p. 68°/0.7mm Hg (reported bp 79°/1mm Hg, Moffet[58]); GLC(155°, Gas Pressures N_2 60lb/in^2, air 20.5lb/in^2, $H_2$23lb/in^2 R_t = 3.88 minutes. Area (100%); νmax(NaCl, film): 3000 - 2875, 1738 (C=O), 1540(NO_2), 1350(NO_2), 1200 (C-O)cm^{-1} ; δ (60MHz): 1.58(6H,s,>C(CH_3)$_2$), 2.28(4H,s,-CH_2-CH_2-), 3.62(3H,s,-OCO-CH_3).

Methyl 2-Methyl-4-nitrobutanoate (50) and dimethyl 2,6-dimethyl-4-nitropimelate (51).

Methyl methacrylate (100g) was added over 15 minutes to a stirring solution of nitromethane (91.5g, 1.5 mol. equiv.), dioxane (50ml) and Triton B (10ml) heated to 70 A slight exotherm was recorded. Isolation using procedure (a) gave the monoester (50)(25.59g, 16%) as a faint yellow oil, b.p. 64°- 66°/0.8mm Hg (reported b.p.

82°- 83°/3mm Hg, Leonard and Shoemaker[59]; νmax(NaCl, film): 2975, 2950, 1735(C=O), 1550(NO_2), 1380(NO_2), 1200(C-O)cm^{-1}; δ (60 MHz): 1.14(3H,d,J_{AB}7Hz, >CH-$\underline{CH_3}$), 1.80 - 2.70(3H,m,-CH_2-CH<), 3.54(3H,s,-OCO-CH_3) 4.28 (2H,t,J_{AB}7Hz,-CH_2-$\underline{CH_2}$-NO_2).

Continued distillation gave the diester (51)(20.38g, 8%) as a yellow oil, b.p. 117.5°- 119.5°/0.7mm Hg (reported 134-136°/3mm Hg, Leonard and Shoemaker[59]); νmax(NaCl,film): 2975, 2950, 1730(C=O), 1550(NO_2), 1380(NO_2), 1200(C-O)cm^{-1}; δ (60 MHz): 0.94 (6H,dd,J_{AB}7HzJ_{AM}1Hz,2 x >CH-$\underline{CH_3}$), 1.32 - 2.48(6H,m,2 x -CH_2-CH<), 3.20(6H,s,2x-OCO-CH_3), 4.32(1H,quintet,J_{AB}7Hz, $-CH_2$ $-CH_2$>$\underline{CH}$-NO_2).

Methyl 3-methyl-4-nitrobutanoate (52)

Methyl crotonate (100g) was added over 15 minutes to a stirring solution of nitromethane (91.5g, 1.5mol.equiv.) dioxane (50ml) and Triton B (10ml). A slight exotherm was recorded. Isolation using procedure (a) afforded the monoester (52)(80.37g, 50%) as a faint yellow oil, b.p. 84°/2mm Hg (reported b.p. 77 - 79°/1mm Hg, Kambe and Yasude[62]); νmax(NaCl,film): 3100, 2900, 1740 (C=O), 1555(NO_2), 1385(NO_2), 1180(C-O)cm^{-1}; δ (60 MHz): 1.03(3H,d,J_{AB}7Hz, >CH-$\underline{CH_3}$), 2.20-3.00(3H,m, $-CH_2$>$\underline{CH}$-$\underline{CH_2}$ -CO_2CH_3), 3.56(3H,s,-OCO-CH_3), 4.00-4.64(2H,m, $-CH_2$>CH-$\underline{CH_2}$-NO_2).

Attempted Preparation of Methyl 3,3-dimethyl-4-nitrobutanoate.

Several attempts were made to obtain the expected condensation product from methyl senecioate and nitromethane using similar reaction conditions to those shown previously. However, distillation of the liquid obtained using procedure (a) realised only starting materials (i.r., p.m.r. analysis) and these condensations were terminated prior to obtaining the desired product (methyl 3,3-dimethyl-4-nitrobutanoate) (see discussion).

Preparation of Pyrrolidinones

5,5-Dimethyl-2-pyrrolidinone (58)

Methyl 4-methyl-4-nitropentanoate (48)(155g, 1.08 mol.) was added to a stirring solution of glacial acetic acid (1200ml) and water (300ml) at 90°. Reduced iron powder (500g, 8.95g/atom) was added portionwise over 2 hours. Procedure (b) was used to isolate 5,5-dimethyl-2-pyrrolidinone (45g, 37%) as a clear oil which solidified on standing as colourless needles, b.p. 89°/0.4 mm Hg; m.p. 40°- 41° (reported b.p. 126.5 - 128.5°/12mm Hg; m.p. 42°- 43°, Moffet[75]. g.l.c. (120°, gas pressures N_2

- 60lb/in^2, air - 20.5lb/in^2, H_2-23lb/in^2 Rt = 2.52 min. (area 100%); νmax(NaCl,film): 3700 - 3000 (N-H), 2970 - 2875, 1690(C=O), 1420, 1385, 1365, 1240, 1220cm^{-1}; δ(60MHz, $CDCl_3$): 1.26(6H,s,>C(CH_3)$_2$), 1.68 - 2.60(4H,m,-CH_2-CH_2-), 7.81(1H,s,D_2O exchangeable, >N-H).

3-Methyl-2-Pyrrolidinone(56)

Methyl 2-methyl-4-nitrobutanoate (50)(34.42g, 0.21 mol) was added to a stirring solution of glacial acetic acid (250 ml) and water (60 ml) at 90°. Reduced iron powder (100g, 1.79g/atom) was added portionwise over a 2 hour period. Isolation using procedure (b) afforded 3-methyl-2-pyrrolidinone (9.72g, 47%) as a clear oil which solidified as colourless needles on standing. b.p. 76°/0.4mm Hg; m.p. 59-60° (reported b.p. 96-97/4mm Hg, Cologne and Pouchol[72], m.p. 58-59.5°, Adams and Fles[86]) νmax(NaCl,film): 3600-3000(N-H), 3000-2850, 1700 (C=O), 1490, 1460, 1430, 1380, 1295, 1260cm^{-1}; δ(60MHz, $CDCl_3$): 1.18(3H,d,J_{AB}7Hz, >CH-CH_3), 1.24-3.96 (5H,m, >CH-CH_2-CH_2-), 7.78(1H,s,D_2O exchangeable, >N-H).

4-Methyl-2-pyrrolidinone (54)

Methyl 3-methyl-4-nitrobutanoate (52)(107g, 0.66 mol) was added to a stirring solution of glacial acetic acid (750

ml) and water (180 ml) at 90°. Reduced iron powder (160g, 2.86g/atom) was added portionwise over 4 hours. Isolation using procedure (b) gave 4-methyl-2-pyrrolidinone (37g, 57%) as a clear oil which solidified as colourless needles on standing. b.p. 98°/1.5mm Hg; m.p. 42-45° (reported b.p. 89-92°/1mm Hg, m.p. 42.4°, Crook[67]; νmax(NaCl,film), 3600-3000(N-H), 3000 - 2850, 1695 (C=O), 1490, 1460, 1420, 1380, 1345, 1290, 1270, 1060cm^{-1}; δ (60MHz, $CDCl_3$): 1.18(3H,d,J_{AB}7Hz, >CH-$\underline{CH_3}$, 1.64-3.80(5H,m, -CH_2-$\underset{|}{C}$H-CH_2), 7.38(1H,s, D_2O exchangeable, >N-H).

5-Carbethoxy-2-pyrrolidinone (57)

Crystalline sodium bicarbonate (35g, 0.99 mol.equiv.) was added portionwise with stirring to a suspension of diethyl glutamate hydrochloride (100g) in water (100 ml). After 30 minutes the suspension was concentrated in vacuo and the concentrated mass extracted with dicholoromethane (2 x 100 ml). The organic extracts were dried and concentrated in vacuo to yield an orange syrup (68.8g). This was heated under reflux with toluene (300 ml) for 2h. The solvents were removed in vacuo to produce a second syrup (57.8g) which was distilled under reduced pressure to give the crude pyrrolidinone (48.72g, 74%). Recrystallisation afforded

pure (57)(42.15g, 64%) as colourless needles. m.p. 54 - 55° ; ν_{max}(NaCl,film): 3500-3100(N-H), 3050-2950, 1745(C=O, ester), 1705(C=O, ring), 1470-1420, 1390, 1200cm^{-1}; δ (60MHz, $CDCl_3$): 1.27(3H,t,J_{AB}7Hz,-OCO-CH_2-$\underline{CH_3}$), 1.88-2.48(4H,m,-CH_2-CH_2-), 3.92-4.38(3H, m,-CH_2>$\underline{CH}$-CO_2-$\underline{CH_2}$-CH_3), 7.30(1H,D_2O exchangeable, >N-H); m/e 157 [$M^{+\cdot}$] (2%), 84 [M-73]$^+$(100%). (Found: C, 53.0; H, 7.0; N, 8.9. $C_7H_{11}NO_3$ requires C, 53.5; H, 7.0; N, 8.9%).

Diethyl 3-cyanoglutarate (60)

A solution of ethanolic sodium ethoxide (2 mol.equiv.) (prepared from sodium (23g) in ethanol (500 ml)) was added portionwise to a mixture of t-butyl cyanoacetate (70.5g) and ethyl chloroacetate (122.5g, 2 mol.equiv.) over a period of 5 hours so that the temperature remained below 40°. The mixture was heated at 35 - 40° for 2 hours and then cooled to room temperature. Concentrating the mixture **in vacuo** afforded a white slurry which was partitioned between water (100 ml) and ether (3 x 150 ml). The ethereal extracts were combined and washed with a 1% aqueous acetic acid solution (50 ml) and then water (15 ml) prior to drying over magnesium sulphate. The dried organic extracts were concentrated **in vacuo** to give the crude red (diethyl 3-t-butoxycarbonyl-3-cyanoglutarate) (144)(149.73g). This

liquid was heated at 140 ^{o} - 160 ^{o} with PTSA (125 mg) for 3 hours until elimination of carbon dioxide had ceased. Fractional distillation under reduced pressure yielded the pale yellow diethyl 3-cyanoglutarate (60)(79.69g, 75%) b.p. 120^{o}/0.5 mm Hg (reported b.p. 141-144^{o}/2 mm Hg Henecka[77]); νmax(NaCl,film): 3000-2890, 2250(C=N), 1730 (C=O); 1470, 1445, 1200cm^{-1}; δ (60MHz, $CDCl_3$) 1.26(6H,t,J_{AB}7Hz, 2 x-OCO-CH_2-CH_3), 2.54-3.64(5H,m,-CH_2-CH(CN)-CH_2-), 4.14(4H,q,J_{AB}7Hz, 2 x-OCO-CH_2-CH_3).

4-Ethoxycarbonylmethyl-2-pyrrolidinone (59)

Diethyl 3-cyanoglutarate (60) was reductively cyclised with hydrogen over Raney Nickel to give the crude pyrrolidinone (59). A portion (20g) of the crude material was purified by distillation under reduced pressure to give the pure ester (59)(11.80g), b.p. 165^{o}-169^{o}/2mm Hg (reported b.p. 180-185^{o}/4mm Hg (Henecka[77]); νmax(NaCl,film): 3700-3050(N-H), 3000-2080, 1740(C=O, ester), 1700(C=O, ring) 1460, 1390, 1190(C-O)cm^{-1}.

Preparation of Imidates

1-Aza-2-methoxycyclopent-1-ene (34)

Dimethyl sulphate (92.60g, 1 mol.equiv.) in dry benzene (100 ml) was added dropwise with stirring to a refluxing solution of 2-pyrrolidinone (9)(62.5g) in dry benzene (367 ml) over 4 hours. The reaction mixture was left to cool and purified as shown in procedure (c) to give (34) as a colourless oil (45.86g, 63%), b.p. 35^{o}- 40^{o}/30mm Hg (reported b.p. 118-120^{o}, Peterson and Tietze[94]); ν_{max}(NaCl,film): 2950, 2850, 1695(C=N), 1440, 1345, 1238, 1040cm^{-1}.

1-Aza-2-methoxy-5-methylcyclopent-1-ene (145)

Dimethyl sulphate (25.45g, 1mol.equiv.) in dry benzene (150 ml) was added dropwise with stirring to a refluxing solution of 5-methyl-2-pyrrolidinone (53)(20g) in dry benzene (100 ml) over 2.5 hours. The mixture was stirred at reflux for 4 hours and allowed to cool. Isolation using procedure (c) yielded (145) (13.31g, 59%) as a clear colourless liquid, b.p. 55^{o}/15mm Hg; ν_{max}(NaCl,film): 2975, 2875, 1650(C=N), 1462, 1460, 1445, 1440, 1298, 1258, 1208, 1020, 990, 950cm^{-1}; δ (60MHz): 1.21 (3H,d,J_{AB}7Hz, >CH-$\underline{CH_3}$), 1.84-2.64(4H,m,-CH_2-CH_2-), 3.34(1H,q,J_{AB}7Hz, >$\underline{CH}$-CH_3), 3.68(3H,s,-OCH_3).

1-Aza-2-methoxy-5,5-dimethylcyclopent-1-ene (146)

Dimethyl sulphate (22.30g, 1 mol.equiv.) in dry benzene (50 ml) was added dropwise with stirring to a refluxing solution of 5,5-dimethyl-2-pyrrolidinone (58)(20g) in dry benzene (100 ml) over 2.5 hours. The mixture was stirred at reflux for 6.5 hours and allowed to cool. Isolation following procedure (c) gave (146) (13.84g, 62%) as a clear colourless liquid, νmax(NaCl,film): 2950, 2875, 1640(C=N), 1440, 1345(gem methyl), 1238, 1205, 1015, 975cm^{-1}; δ(60MHz): 1.20(6H,s, >C(CH_3)$_2$), 1.74(2H,t, J_{AB}7Hz,-$\underline{CH_2}$-CH_2-(OCH_3)C=N-), 2.47(2H,t,J_{AB}7Hz, -$CH_2\underline{CH_2}$-(OCH_3)C=N-, 4.68(3H,s,-OCH_3).

1-Aza-2-ethoxy-4-methylcyclopent-1-ene(78)

70.11g (1.3 mol.equiv.) of triethyloxonium tetrafluoroborate were generated **in situ** from dry ether (123 ml), boron fluoride etherate (69.86g) and epichlorohydrin (34.44g) according to the method of Meerwein[95]. The white etherate was washed thrice with dry ether (50 ml) and dissolved in dry dichloromethane (50ml). To this solution was added dropwise with stirring the 4-methyl-2-pyrrolidinone (54)(28.90g) in dry dichloromethane (50 ml). The solution was stirred for 16 hours under dry nitrogen then treated with a cold 50% aqueous solution of potassium carbonate (150 ml).

Procedure (d) was employed to isolate the imidate (78) (30.07g, 81%) as a colourless oil, b.p. 80°- 82°/30mm Hg; ν_{max}(NaCl,film): 3000-2850, 1645(C=N), 1370, 1335, 1225, 1030cm^{-1}; δ (60MHz): 1.12-1.72(6H,m,-O-CH_2-CH_3,>CH-CH_3), 2.92-4.12(5H,m,-CH_2-(CH_3)CH-CH_2-), 4.30(2H,q,J_{AB} 7Hz, -O-CH_2-CH_3).

1-Aza-5-carbethoxy-2-ethoxycyclopent-1-ene (147)

Triethyloxonium tetrafluoroborate (35.05g, 1.3 mol.equiv.) were generated in situ from dry ether (61.5ml), boron fluoride etherate (34.93g) and epicholorohydrin (17.22g) according to the method of Meerwein[95] . The white etherate was washed with dry ether (3 x 50 ml) and dissolved in dry dichloromethane (20 ml). To this solution was added dropwise with stirring 5-carbethoxy-2-pyrrolidinone (57)(22.57g) in dry dichloromethane (50ml). The solution was stirred for 12 hours under dry nitrogen whereupon a cold solution of 50% aqueous potassium carbonate (100 ml) was added. Isolation using procedure (d) yielded the imidate (147) (17.15g, 65%) as a colourless liquid, b.p. 78°/0.5mm Hg; ν_{max}(NaCl,film): 3000-2890, 1740(C=O), 1635(C=N), 1480-1420, 1405, 1380, 1340, 1270, 1030cm^{-1}; δ (60MHz): 1.24(3H,t,J_{AB}7Hz,-CH_2-CH_3), 1.28(3H,t,J_{AB}7Hz,-CH_2-CH_3), 2.0-2.72(4H,m,-CH_2-CH_2-), 3.32-3.62(1H,m,>CH-CO_2CH_2-CH_3 3.88-4.60(4H,m,-O-CH_2-CH_3,-OCO-CH_2CH_3).

1-Aza-4-carbethoxymethyl-2-ethoxycyclopent-1-ene (148)

Triethyloxonium tetrafluoroborate (16.18g, 1.3 mol.equiv.) were generated *in situ* from dry ether (29.5 ml), boron fluoride etherate (16.74g) and epichlorohydrin (8.25g) according to the method of Meerwein[95]. The white etherate was purified by washing with dry ether (3 x 50 ml) and dissolved in dry dichloromethane (10 ml). To this solution was added dropwise with stirring 4-carbethoxymethyl-2-pyrrolidinone (59)(11.80g) in dry dichloromethane (25 ml). The solution was stirred for 12 hours under dry nitrogen. A cold solution of 50% aqueous potassium carbonate solution (75 ml) was added and isolation using procedure (d) afforded the pure imidate (148) (8.7g, 63%) as a colourless liquid. b.p. 140^{o}- 142^{o}/3.5mm Hg, νmax(NaCl,film): 3000-2850, 1740(C=O), 1630(C=N), 1390, 1340, 1270, 1180(C-O)cm^{-1}.

Preparation of substituted 2,3-dihydropyrrolo[2,1-b] quinazolin-9(1H)-ones.

2,3-Dihydro-1-methylpyrrolo[2,1-b]quinazolin-9(1H)-one (149)

$POCl_3$ (20 ml) was added portionwise to a mixture of anthranilic acid (8.4g) and 5-methyl-2-pyrrolidinone (53) (7.6g, 1.3 mol.equiv.) and the mixture heated on a steam bath for 1 hour. Procedure (e). A short path bulb to bulb distillation (Kugelrohr) at 150°/0.8 mm Hg of this orange syrup yielded the pure compound (149) as a clear syrup which crystallised from ether/light petroleum as colourless prisms (6.6g, 55%), (149), m.p. 70°- 71°; t.l.c. (system 1), R_f 0.529; νmax(KBr): 3075, 2975-2800, 1670(C=O), 1610(C=N), 1560, 1465, 1440, 1423, 1380, 1370, 1330, 1260, 1180, 1140, 1108, 1030, 870, 790, 702 cm^{-1}; δ(60 MHz, $CDCl_3$): 1.29(3H,d,J_{AB}7Hz, >CH-$\underline{CH_3}$, 1.6-2.6(2H,m,-CH_2-$\underline{CH_2}$-CH<), 2.72-3.32(2H,m,-$\underline{CH_2}$-CH_2-CH<), 4.62(1H,m,-CH_2-$\underline{CH}$-CH_3), 6.98-7.72(3H,m, aromatic protons), 8.00(1H,d,J 7Hz, C-8-H); m/e 200 [$M^{+\cdot}$]; (Found: C, 71.6; H, 6.1; N, 13.9. $C_{12}H_{12}N_2O$ requires C, 72.0; H, 6.0; N, 14.0%).

2,3-dihydro-1-methylpyrrolo[2,1-b]quinazolin-9(1H)-one (149)

Anthranilic acid (6.58g) and 1-aza-2-methoxy-5-methylcyclopent-1-ene (145) (5.96g, 1.1 mol.equiv.) in toluene (150 ml) were heated at reflux with stirring for 2 hours. The orange syrup obtained following isolation using procedure (f) was crystallised from ethyl acetate/light petroleum to give (149), as a colourless solid (7.04g), 73%). An analytical sample was obtained as colourless prisms following a short path bulb to bulb distillation (Kugelrohr) at 150°/0.4mm Hg and was found to be identical to an authentic sample (m.p., m.m.p., i.r.).

2,3-Dihydro-1,1-dimethylpyrrolo[2,1-b]quinazolin-9(1H)-one (152)

Anthranilic acid (9.67g), 1-aza-2-methoxy-5,5-dimethylcyclopent-1-ene (146) (10.76g, 1.2 mol.equiv.) in toluene (200 ml) were mixed and heated at reflux for 1h, and the crude product isolated using procedure (f). The syrup crystallised on agitation and recrystallisation from ether/light petroleum afforded colourless prisms of (152) (10.16g, 67%). An analytical sample was prepared via a short path bulb to bulb distillation (Kugelrohr) at 150°/0.8 mm Hg (152); m.p.

105 - 106°; t.l.c. (system 1) R_f 0.665; νmax(KBr): 3075, 3010 - 2900, 1670(C=O), 1620(C=N), 1470, 1455 (doublet, gem methyls), 1350, 1330, 785, 705, 695cm^{-1}; δ (60 MHz, $CDCl_3$): 1.68(6H,s, >C(CH_3)$_2$), 2.02(2H,t,J_{AB}7Hz,-CH_2-CH_2 -C(CH_3)$_2$-), 3.00(2H,t,J_{AB}7Hz, -CH_2-CH_2-C(CH_3)$_2$-), 7.00-7.64(3H,m,aromatic protons), 8.06(1H,d,J 7Hz, C-8-H); m/e 214 [$M^{+\cdot}$] (58%), 199 [M-15]$^+$ (100%); (Found: C, 72.4; H, 6.8; N, 12.7. $C_{13}H_{14}N_2O$ requires C, 72.8; H, 6.6; N, 13.1%).

2,3-Dihydro-2-methylpyrrolo[2,1-b]quinazolin-9(1H)-one (151)

Anthranilic acid (5.48g) and 1-aza-2-ethoxy-4-methylcyclopent-1-ene (78) (6.30g, 1.1 mol.equiv.) in toluene (150 ml) were heated at reflux with stirring for 2 hours. Isolation of the crude product was achieved using procedure (f). The orange syrup (7.5g) was purified via a short path bulb to bulb distillation (Kugelrohr) at 130°/1 mm Hg to give (151) as a colourless solid (3.32g, 42%). An analytical sample was obtained as colourless needles after chromatography on silica gel (25g) using ethyl acetate as eluant. (151), m.p. 154.5-155.5°; t.l.c. (system 2) R_f 0.26; νmax(KBr): 3100-3000, 3000-2875, 1670(C=O), 1625(C=N), 1465, 1435, 1335, 790, 775, 700cm^{-1}. δ (60 MHz, $CDCl_3$): 1.24(3H,d,J 7Hz, >CH-CH_3), 2.98-3.42(3H,m,CH_2-CH-CH_3),

3.64(1H,dd,J_{GEM}12Hz, J_{AB}7Hz, -CON-$\underline{CH}$-CH(CH_3)-), 4.28(1H,dd,J_{GEM}12Hz, J_{AB}7Hz, -CON-$\underline{CH}$-CH(CH_3)-), 7.05-7.78(3H,m,aromatic protons), 8.10(1H,m,C-8-H); m/e 200 [M^+] (66%), 185 $[M-15]^+$(100%); (Found: C, 71.9; H, 6.0; N, 13.75. $C_{12}H_{12}N_2O$ requires C, 72.0; H, 6.0; N, 14.0%).

2,3-Dihydro-3-methylpyrrolo[2,1-b]quinazolin-9(1H)-one (150)

Phosphorous oxychloride (30 ml) was added portionwise to a mixture of anthranilic acid (12.0g) and 3-methyl-2-pyrrolidinone (56) (13g, 1.5 mol.equiv.) and the mixture heated on a water bath for 1 hour. The black syrup (15.2g) isolated using procedure (e) was chromatographed on silica gel (150g) and elution with system 9 yielded a yellow syrup which crystallised from ether. Recrystallisation from ether gave colourless needles of (150) (4.50g, 26%). An analytical sample was prepared via a short path bulb to bulb distillation (Kugelrohr) at 155°/0.3 mm Hg (150), m.p. 135-135.5°; t.l.c. (system 1) R_f 0.627; νmax(KBr): 3100-2850, 1665(C=O), 1620(C=N), 1470, 1385, 1345, 1335, 788, 740, 700cm^{-1}; λ max($CHCl_3$) 246(ξ 6000), 267(ξ 8000), 305(ξ 4000), 317nm(ξ 3600); δ (60MHz, $CDCl_3$): 1.24(3H,d,J_{AB} 7Hz,>CH-$\underline{CH_3}$), 1.58-4.24 (5H,m,-CH_2-CH_2-CH<), 7.10-7.70(3H,m,aromatic protons), 8.08(1H,d,J 7Hz, C-8-H); m/e 200 [$M^{+\cdot}$] (82.4%), 185 [M-

15]$^{+}$, (25.25%); (Found: C, 71.7; H, 6.0; N, 13.9. $C_{12}H_{12}N_2O$ requires C, 72.0; H, 6.0; N, 14.0%).

1-Carbethoxy-2, 3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (153)

Anthranilic acid (2.74g) and 1-aza-5-carbethoxy-3-ethoxycyclopent-1-ene (147) (4.01g, 1.1 mol.equiv.) in dry toluene (100 ml) were heated at reflux for 2 hours. The syrup obtained using procedure (f) crystallised from ether/light petroleum as colourless needles of (153) (2.25g, 44%), m.p. 118.5-120°; t.l.c. (system 2) R_f 0.269; ν_{max}(KBr): 3075, 3000-2890, 1740(C=O, ester), 1690(C=O, ring), 1625(C=N), 1470, 1390, 1380, 1330, 1320, 1220(C-O), 1040, 770, 700cm^{-1}; δ (60MHz, $CDCl_3$): 1.24(3H,t,J_{AB}7Hz,-OCO-CH_2-$\underline{CH_3}$), 2.00-3.68(4H,m,-CH_2-CH_2-4.16(2H,q,J_{AB}7Hz,-OCO-$\underline{CH_2}$-CH_3), 4.98(1H,dd,J_{AB} 2.4Hz, J_{AB}6.0Hz), 7.00-7.80(3H,m,aromatic protons), 8.08(1H,d,J 7.0Hz, C-8-H); (Found: C, 65.0; H, 5.4; N, 10.65. $C_{14}H_{14}N_2O_3$ requires C, 65.1; H, 5.4; N, 10.85%).

2-Carbethoxymethyl-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (154)

Anthranilic acid (4.35g) and 1-aza-4-carbethoxymethyl-2-ethoxycyclopent-1-ene (148)(7.30g, 1.1 mol.equiv.) were heated for 2.5 hours in toluene (200 ml). The syrup (7.59g) obtained using procedure (f) was chromatographed on silica gel (200g) and elution with system 7 yielded a second orange syrup (6.14g) which crystallised on cooling at 0^{o}. Recrystallisation of the solid from ethyl acetate/light petroleum afforded the product (5.20g, 58%) as colourless needles,(154) m.p. 90-91^{o}; t.l.c. (system 1) R_f 0.65; νmax(KBr): 3000-2900, 1730 (C=O, ester), 1680(C=O, ring), 1620(C=N), 1480, 1430, 1390, 1340, 1180(C-O), 788, 705cm^{-1}; δ(60MHz, $CDCl_3$): 1.26(3H,t,J_{AB}7.0Hz,-OCO-CH_2-CH_3), 2.24-4.64(9H,m, -CH_2 -CH_2 >CH-CH_2-OCO-CH_2-CH_3), 7.08-7.60(3H,m,aromatic protons), 8.10(1H,m,C-8-H). (Found: C, 65.80; H, 5.80; N, 10.25. $C_{15}H_{16}N_2O_3$ requires C, 66.20; H, 5.90; N, 10.30%).

2-Carboxymethyl-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (155)

The ester (154)(690 mg) was added to a previously prepared solution of sodium ethoxide (sodium 280 mg, 0.12g/atom) and ethanol (18 ml). The flask was sealed

and stirred for 16 hours at room temperature and the colourless precipitate was removed by filtration. The precipitate (500 mg) was dissolved in water (20 ml) and the resulting solution made slightly acidic (pH 6) with dilute sulphuric acid. Cooling produced a crystalline deposit which was filtered from the flask. Drying gave (155)(380mg, 61%) as colourless needles, m.p. 247-249°; t.l.c. (system 9) R_f 0.55; νmax(KBr): 3700-2200(H-bonded OH), 1730(C=O, acid), 1680(C=O, ring), 1630(C=N), 1480, 1420, 1400, 1205(C-O), 780, 710cm^{-1}; (Found: C, 63.6; H, 5.0; N, 11.35. $C_{13}H_{12}N_2O_3$ requires C, 63.9; H, 4.9; N, 11.37%).

Preparation of Benzylidene Derivatives

2,3-Dihydro-3-phenylmethylenepyrrolo[2,1-b]quinazolin-9(1H)-one (160)

The compound (1)(5.65g) and benzaldehyde (20 ml) were heated together at 150°- 160° for 1 hour. The product was isolated following procedure (g) as feathery yellow needles (7.00g, 85%), m.p. 136°- 138° (reported m.p. 137° - 139°, Shakhidoyatov[100]).

2,3-Dihydro-1-methyl-3-phenylmethylenepyrrolo[2,1-b]quinazolin-9(1H)-one (161)

The compound (149) (1.32 g) and benzaldehyde (5 ml) were heated at 150 - 160° for 1 hour. Isolation of the product using procedure (g) gave (161) (1.02g, 54%) as feathery white needles, m.p. 168.5 - 169.5°; t.l.c. (system 1) R_f 0.667; νmax(KBr): 3050, 2975-2925, 1665(C=O, ring), 1590(C=N), 1558, 1460, 1445, 1435, 1382, 1370, 1330, 770, 760, 695, 685cm^{-1}; δ(90MHz,d_6 DMSO): 1.45(3H,d,J_{AB} 7Hz, >CH-CH_3, 2.88(1H,dt,J_{AB}=J_{AX} 2.7Hz, J_{GEM} 17.7Hz, ^{CH_3}>CH-$\underline{^{H}CH}$>C=C<$^{Ph}_{H}$), 3.53(1H,ddd,J_{AB} 8.7Hz, J_{AX},3.3Hz, J_{GEM}17.7Hz, ^{CH_3}>CH-$\underline{^{H}CH}$>C=C<$^{Ph}_{H}$)4.74-4.95(1H,m,>$\underline{CH}$-CH_3), 7.36-7.90(9H,m,>C=C<$\frac{Ph}{\underline{H}}$, 3 aromatic protons), 8.15(1H,d,J 7Hz, C-8-H); m/e 288 [$M^{+\cdot}$] (40%), 287 [M-1]$^+$ (100%); (Found: C, 7.87; H, 5.5; N, 9.75. $C_{19}H_{16}N_2O$ requires C, 79.2; H, 5.6; N, 9.7%).

2,3-Dihydro-1,1-dimethyl-3-phenylmethylenepyrrolo[2,1-b]quinazolin-9(1H)-one (157)

The compound (152), (1.70g) and benzaldehyde (5ml) were heated together at 150 - 180° for 1 hour. Isolation using procedure (g) gave the product (157) (1.62g, 66%) as yellow prisms, m.p. 172.5-173°; t.l.c. (system 3) R_f 0.49; νmax(KBr): 3075-2900, 1665(C=O), 1590(C=N), 1560, 1470, 1378, 1355, 1330, 765, 698, 690cm^{-1}; δ(60MHz, $CDCl_3$

1.78(6H,s,>C(CH_3)$_2$), 3.08(2H,d,J_{AX} 2.4Hz, $\overset{-CH_2}{\longrightarrow}$>C=C<$\overset{Ph}{H}$ 7.16-7.96(9H,m,>C=C<$\underline{\overset{Ph}{H}}$, 3 aromatic protons), 8.24(1H,d,J 7.0Hz, C-8-H); m/e 302[M^+] (58%), 301[M-1]$^+$ (100%); (Found: C, 79.5; H, 5.96; N, 9.3. $C_{20}H_{18}N_2O$ requires C, 78.9; H, 6.25; N, 9.4%).

2,3-Dihydro-2-methyl-3-phenylmethylenepyrrolo[2,1-b] quinazolin-9(1H)-one (156)

The compound (151), (800 mg) and benzaldehyde (5 ml) were heated together at 150°- 160° for 1 hour. Procedure (g) realised the product (156) (580 mg, 50%) as colourless needles, m.p. 154.5-155.5°; t.l.c. (system 4) R_f 0.445; νmax(KBr): 3500-3000, 3000-2875, 1670(C=O), 1590(C=N), 1495, 1465, 1450, 1390, 1380, 770, 760, 690cm^{-1} δ(90MHz,d_6DMSO): 1.252(3H,d,J_{AB}7Hz, >CH-$\underline{CH_3}$), 3.798-4.360(3H,m,N-$\underline{CH_2}$-$\underline{CH}$-CH_3), 7.377-7.817(9H,m,>C=C<$\underline{\overset{Ph}{H}}$, 3 aromatic protons), 8.149(1H,d,J 7.0Hz, C-8-H); m/e 288 [$M^{+\cdot}$] (36%), 287 [M-1]$^+$ (100%); (Found: C, 79.15; H, 5.65; N, 9.60. $C_{19}H_{16}N_2O$ requires C, 79.2; H, 5.56; N, 9.72%).

Treatment of 2,3-dihydro-3-methylpyrrolo[2,1-b]quinazolin-9(1H)-one (150) with benzaldehyde.

The compound (150), (500 mg) was heated with benzaldehyde (5ml) at 150 - 180° for 3 hours. No reaction appeared to take place. Treatment of the cooled reaction mixture with ether afforded the crude starting material (430 mg) identical in all respects m.p., m.m.p. and i.r. to an authentic sample.

1-Carbethoxy-2,3-dihydro-3-phenylmethylenepyrrolo[2,1-b]quinazolin-9(1H)-one(158)

The compound (153), (500 mg) and benzaldehyde (5 ml) were heated together at 150 - 160° for 1 hour. Isolation using procedure (g) furnished (158) (480 mg, 76%) as colourless needles, m.p. 204-205°; t.l.c. (system 4) R_f 0.50; νmax (KBr) 3100-2900, 1735(C=O, ester), 1680(C=O, ring), 1590(C=N), 1465, 1450, 1400, 1380, 1330, 1215(C-O), 780, 700cm^{-1}; δ (90 MHz,d_6DMSO) : 1.206(3H, t,J_{AB}7Hz, -OCO-CH_2-CH_3), 3.234(1H,dt,J_{AX}= J_{AB},3.0Hz, J_{GEM} 18Hz, Ph(H)C=C(H)-C<H CH<), 3.760(1H,ddd,J_{AX}3.06Hz,J_{AB}9.4Hz,J_{GEM} 18Hz, Ph(H)C=C(H)-C<H CH<), 4.184(2H,q,J_{AB}7Hz,-OCO-CH_2-CH_3), 5.237(1H,dd,J_{AB}3.50Hz,J_{AB}9.80Hz,-CH<CO_2Et CH_2-), 7.416 - 7.939(9H,m,>C=C(H)-Ph , 3 aromatic protons), 8.090-8.197(1H,complex doublet,C-8-H); m/e 346 [$M^{+\cdot}$] (25%), 345 [M-1]$^+$ (15%), 273 [M-$CO_2C_2H_5$]$^+$ (100%); (Found: C, 72.7;

H, 5.3; N, 8.0. $C_{21}H_{18}N_2O_3$ requires C, 72.8; H, 5.2; N, 8.1%).

2-Carbethoxymethyl-2,3-dihydro-3-phenylmethylenepyrrolo [2,1-b]quinazolin-9(1H)-one (159)

The compound (154), (1.57g) and benzaldehyde (10 ml) were heated at 150°- 180° for 1 hour. The isolation technique (g) was used to obtain the product (159) (1.30g, 65%) as colourless needles, m.p. 156°; t.l.c. (system 1) R_f 0.63; ν_{max}(KBr): 3100-2800, 1730(C=O, ester), 1680(C=O, ring), 1590, 1470, 1400, 1385, 1190(C-O), 1030, 780, 770, 700cm-1; δ (90MHz, $CDCl_3$): 1.245(3H,t,J 7Hz, $-CH_2-CH_3$), 2.377-2.905(2H,m,$-CH_2-CO_2C_2H_5$), 4.047-4.389(5H,m, $>N-CH_2-CH-CH_2-CO_2-CH_2-CH_3$), 7.265-7.875(9H,m, $>C=C<^{Ph}_{H}$,3 aromatic protons), 8.305(1H,d,J 7.87Hz,C-8-H); (Found : C, 73.2; H, 5.7; N, 7.8. $C_{22}H_{20}N_2O_3$ requires C, 73.34; H, 5.56; N, 7.78%).

3,3-Dideutero-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (166)

Deoxyvasicinone (1) (200 mg) and deuterium oxide (D_2O) (5ml) were heated together in a sealed tube for 15 hours at 150°- 156°. The tube was cooled to room temperature and the solvents removed in vacuo. The residue was

dissolved in dichloromethane and the resulting solution decolourised. The mixture was filtered and concentrated under reduced pressure. .Recrystallisation of the residue from ether yielded the white crystalline (166) (160mg, 79%), m.p. 109.5-110°; t.l.c (system 1) R_f 0.482; ν_{max}(KBr): 3050-2875, 1675(C=O), 1620(C=N), 1460, 1380, 1330, 775, 700cm^{-1}; δ(60MHz, $CDCl_3$): 2.30(2H,t,J_{AB}7Hz, >N-CH_2-CH_2-), 4.30(2H,t,J_{AB}7Hz, >N-CH_2-CH_2-), 7.04-8.05(3H,m,aromatic protons), 8.43(1H,d,J 8Hz, C-8-H); m/e 188 [M^+]; (Found : C, 69.7; H, 6.5; N, 14.75. $C_{11}H_8D_2N_2O$ requires C, 69.5; H, 6.4; N, 14.75%).

Reactions of (1) and its analogues.

Reaction of (1) with ethyl chloroformate

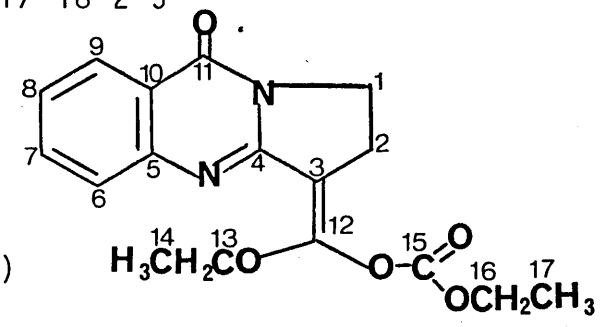
Method A

3-(Ethoxyethoxycarbonyloxymethylene)-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (167)

Ethyl chloroformate (25 ml) and (1) (21.5 g) were heated under reflux until a thick paste was produced (ca 1 hour). Further quantitites of ethyl chloroformate (4 x 10 ml) were added at 30 minute intervals and the paste heated at 110 - 120° for a further 5 hours. The mixture was diluted with ethyl acetate (100 ml) and filtered to

remove the hydrochloride of (1) (14.1g). After decolourisation and concentration the syrupy residue was crystallised from ether to yield (167) (4.35 g). Recrystallisation from ethyl acetate/ether gave pure (167) (4.06 g, 11%), m.p. 100-101°; νmax(KBr): 2990, 2940, 2800, 1750(C=O,ester), 1690(C=O,ring), 1625(C=N)cm^{-1} δ(60 MHz,$CDCl_3$), 1.20(6H,t,J_{AB}7Hz, 2 x O-CH_2-CH_3), 2.83(2H,m,>N-CH_2-CH_2-), 4.10(6H,m, 2 x O-CH_2-CH_3,>N-CH_2-CH_2-), 6.95-8.20(4H,m,aromatic protons); ^{13}C ppm 13.92(C-14), 14.41(C-17), 25.79(C-2), 43.34(C-1), 60.03(C-13), 64.03(C-16), 98.81(C-3), 119.73(C-12), 120.00(C-10), 125.09(C-6), 127.31(C-9), 133.70(C-8), 138.74(C-7), 143.29(C-5), 152.07(C-4), 159.07(C-11), 164.42(C-15); m/e 330(23%)[$M^{+\cdot}$](Found: C, 62.1; H, 5.5; N, 8.3. $C_{17}H_{18}N_2O_5$ requires C, 61.8; H, 5.45; N, 8.5%).

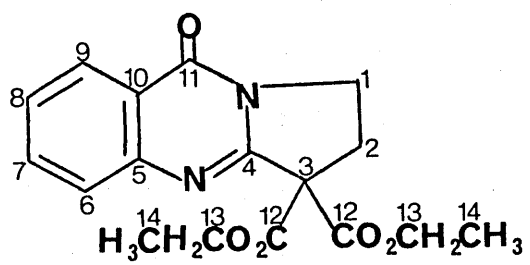
(167)



Method B

Ethyl chloroformate (50 ml) and deoxyvasicinone (22.80 g) were heated under reflux until a thick paste was formed. The paste was maintained at 100°- 120° for 1 hour. Ethyl chloroformate (50 ml) was added to the paste and the mixture heated until the paste was again produced. The paste was again heated at 100°- 120°

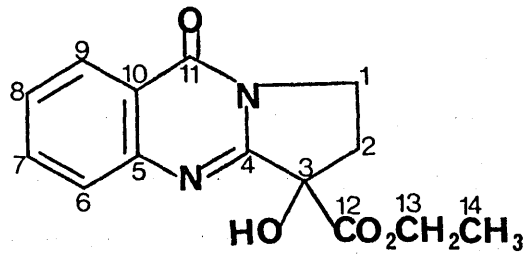
prior to cooling and dilution with ethyl acetate. The hydrochloride of (1) was removed by filtration and reconverted to (1) with dilute sodium hydroxide solution. The regenerated starting material was combined with the organic filtrates, the solution concentrated **in vacuo** and the above cycle repeated another 4 times. Finally the mixture was heated to 155° for 1 hour and cooled. Ethyl acetate (100 ml) aided the removal of the hydrochloride of (1) (5.29 g). The organic filtrates were washed with dilute sodium hydroxide solution and water prior to being dried and decolourised. On concentration a colourless syrup was obtained which rapidly crystallised from ether as colourless prisms of the diester, 3,3-dicarbethoxy-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (168). (3.16g, 10%). m.p. 119-120°; t.l.c (system 2)R_f 0.531; ν_{max}(KBr): 2990, 2970, 2800, 1730(C=O, ester), 1680(C=O, ring), 1625, 1610(C=N), 1465, 1380, 1275(C-O, ester), 780, 700cm^{-1}; δ(60MHz, $CDCl_3$): 1.38(6H,t,J_{AB}7Hz, 2x-OCO-CH_2-$\underline{CH_3}$), 3.00(2H,t,J_{AB}7Hz, >N-CH_2-$\underline{CH_2}$-), 4.1-4.5(6H,m, 2 x OCO-$\underline{CH_2}$-CH_3, >N-$\underline{CH_2}$-CH_2-), 7.40-8.05(3H,m, aromatic protons), 8.42(1H,d,J 8Hz,C-8-H); ^{13}C ppm (Downfield from TMS): 14.0(C-14), 30.07(C-2), 43.87(C-1), 62.88(C-13), 64.95(C-3), 121.03(C-10), 126.09(C-8), 127.08(C-9), 128.06(C-6), 134.10(C-7), 149.00(C-5), 153.73(C-4), 160.53(C-11), 166.91(C-12); m/e 330 [$M^{+\cdot}$] (19%); (Found: C, 61.7; H, 5.6; N, 8.4. $C_{17}H_{18}N_2O_5$ requires C, 61.8; H, 5.45; N, 8.5%).



(168)

The mother liquors from the crystallisation were concentrated and chromatographed on silica gel. Elution with system 5 gave crude 2-ethoxy-(4H)-3,1-benzoxazin-4-one (169)(2.64g) as a pink solid. Recrystallisation from ether/light petroleum gave pure (169) as colourless leaflets (2.15g, 12%) m.p. 92°, t.l.c. (system 9) R_f 0.650; νmax(KBr): 3050-2875, 1760(C=O), 1635, 1610 cm^{-1}; δ (60MHz, $CDCl_3$): 1.48(3H,t,J_{AB} 7Hz,-OCO-CH_2-$\underline{CH_3}$), 4.59(2H,q,J_{AB} 7Hz,-OCO-$\underline{CH_2}$-CH_3), 7.20-8.00 (3H,m, aromatic protons), 8.25(1H,d,J 8Hz, C-8-H); m/e 191 [$M^{+\cdot}$] (60%); (Found: C, 63.1; H, 4.6; N, 7.0. $C_{10}H_9NO_3$ requires C, 62.8; H, 4.7; N, 7.3). Further elution with system 10 afforded the 3-carbethoxy-2,3-dihydro-3-hydroxypyrrolo[2,1-b]quinazolin-9(1H)-one (172)(1.8g, 7%) as colourless needles, m.p. 126.5-127.5°; t.l.c. (system 1) R_f 0.608; νmax(KBr): 3240(O-H), 2970, 2900, 1750(C=O, ester), 1690(C=O, ring) 1625 (C=N), 1480, 1405, 1280, 1200(C-O), 780-700cm^{-1}; δ (60MHz, $CDCl_3$): 1.23(3H,t,J_{AB}7Hz, -OCO-CH_2-$\underline{CH_3}$), 2.72(2H,t,J_{AB}7Hz, >N-CH_2-$\underline{CH_2}$-), 4.00-4.50(4H,m, >N-$\underline{CH_2}$-CH_2-,OCO-$\underline{CH_2}$-CH_3), 5.63(1H,s,D_2O exchangeable, -O-H), 7.10-7.86(3H,m, aromatic protons), 8.21(1H,d,J 8Hz, C-8-H), ^{13}C ppm (off resonance, downfield from TMS): 13.9821(q, C-14), 32.7811(t, C-2), 43.6501(t, C-1), 63.2911(t, C-13),

80.4259(s, C-3), 121.1709(s, C-10), 126.4661(d, C-6), 127.1035(d, C-9), 127.7524(d, C-8), 134.2798(d, C-7), 149.0217(s, C-5), 157.2661(s, C-4), 160.7184(s, C-11), 171.1521(s, C-12); m/e 274 [$M^{+}\cdot$]; (Found: C, 61.2; H, 5.15; N, 10.1. $C_{14}H_{14}N_2O_4$ requires C, 61.3; H, 5.10; N, 10.2%).



(172)

Method C

Ethyl chloroformate (50 ml) and (1) (10.71g) were heated as shown in Method B omitting heating to 155°. The hydrochloride of (1) was removed as previously shown and concentration of the filtration residues gave a colourless syrup which rapidly crystallised in ether. Recrystallisation of the product from ether/ dichloromethane gave colourless prisms of (168) (6.18g, 33%) identical in all respects to an authentic sample.

The mother liquors from the crystallisation were concentrated and purified by p.l.c. Desorption with hot ethyl acetate yielded (169) (0.55g, 5%) identical in all respects to an authentic sample.

Conversion of (167) into (168)

Ethyl chloroformate (10 ml), the hydrochloride of (1) (0.25g) and (167) (0.67g) were heated under reflux until a thick paste was produced. The paste was maintained at 120 for 8 hours, cooled and ethyl acetate (20 ml) added. The mixture was filtered and the filtrate concentrated to yield a solid. Recrystallisation from ether/ dichloromethane gave (168) (0.45 g), m.p. 118-119°, identical in all respects to an authentic sample.

3-Ethoxycarbonyl-2,3-dihydropyrrolo[2,1-b]quinazolin-9-(1H)-one (170)

A solution of (168) (0.47g) in ethanol (25 ml) presaturated with dry ammonia gas was allowed to stand overnight. The solvents were removed in vacuo and the residue crystallised from ether. Recrystallisation from ether gave the pure monoester (170) (0.21g, 62%), m.p. 91-92°; νmax(KBr): 2975, 2900, 1735 (C=O, ester), 1685 (C=O, ring), 1620 cm^{-1}, δ(60MHz, $CDCl_3$) 1.29(3H,t,J_{AB} 7Hz,-OCO-CH_2-CH_3), 2.60(2H,t,J_{AB}7Hz,-OCO-CH_2-CH_3), 4.23(5H,m,>N-CH_2-CH_2-CH-), 7.30-7.90(3H,m, aromatic protons), 8.30(1H,d,J 8Hz,C-8-H); m/e 258 [M] (23%). (Found : C, 64.8; H, 5.4; N, 10.6%. $C_{14}H_{14}N_2O_3$ requires C, 65.1; H, 5.4; N, 10.85%).

Reaction Between (168) and Sodium Borohydride

The diester (168) (500 mg) and sodium borohydride (60 mg, 1 mol.equiv.) in ethanol (20 ml) were stirred at room temperature for 48 hours. The original pink solution became vibrant yellow and analysis by t.l.c. (system 1) showed one polar spot (R_f 0.177). The yellow syrup (430 mg) obtained using procedure (h) was purified via p.l.c. (2 plates) using system 1 as eluant. Desorption with ethyl acetate and concentration in vacuo afforded a colourless syrup which crystallised as prisms (120 mg) the identity of which has not been ascertained. m.p. 134-136°(dec), t.l.c.(system 1) R_f0.177. νmax(KBr): 3600-3000, 3000-2900, 1660, 1618, 1560, 1468, 1388, 1338, 1300, 1275, 1050, 780, 700cm^{-1}; δ (60 MHz, $CDCl_3$): 2.22(2H,t,J 7Hz), 3.26-3.58(1H,t,J 7Hz), 3.60-4.40(4H,m), 7.0-7.64(3H,m), 7.96(1H,d,J 7Hz).

3,3-Dicarbethoxy-2,3-dihydro-1-methylpyrrolo[2,1-b]quinazolin-9(1H)-one (173)

The compound (149) (1.5g) and ethyl chloroformate (7ml) were heated at reflux for 2 hours. A further 30 ml of ethyl chloroformate were added portionwise to this refluxing mass over the period of 45 hours. Cooling and treatment with ethyl acetate (25 ml) afforded the pink hydrochloride of (173). This was removed by filtration

and reconverted to starting material (0.72g) with dilute sodium hydroxide. The organic filtrates were concentrated **in vacuo** to realise an orange syrup (0.80g). Purification by chromatography on silica gel (20g) gave the white crystalline solid (173)(510 mg, 38%), m.p. 90.5-91°, t.l.c. (system 1) R_f 0.78; ν_{max}(KBr): 3000-2860, 1740, 1730(C=O, ester), 1680(C=O, ring), 1625, 1610(C=N), 1470, 1450, 1390, 1380, 1335, 1285, 1260, 1220, 1185, 1120, 1035, 1025, 785, 720cm^{-1}; δ (60MHz, $CDCl_3$): 1.30(6H,t,J_{AB}7Hz, 2 x -OCO-CH_2-CH_3), 1.52(3H,d,J_{AB}6Hz, >CH-CH_3), 2.56(1H,dd,J_{GEM} 13.2Hz,J_{AB} 2.4Hz,>CH-CH-H), 3.16(1H,dd,J_{GEM}13.2Hz,J_{AB}8.4Hz,>CH-CH-H), 4.06-4.58(4H,q,J_{AB}7Hz, 2 x -OCO-CH_2-CH_3), 4.60-4.92(1H,m,CH_3-CH-CH_2), 7.16-7.82(3H,m, aromatic protons), 8.18(1H,d,J 7Hz, C-8-H).

3-Carbethoxymethyl-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (176)

Method 1

Ethyl chloroacetate (10 ml) and (1) (1g) were heated under reflux for 7 hours, cooled and excess ethyl chloroacetate removed **in vacuo**. The residue was chromatographed on silica gel (30 g). Elution with

ether gave an orange syrup which rapidly crystallised. Decolourisation and recrystallisation gave the pure ester (176) (170 mg, 11%), m.p. 92°; t.l.c. (system 1) R_f 0.75; ν_{max}(KBr): 3050, 2975-2900, 1730(C=O, ester), 1670(C=O, ring), 1620, 1610(C=N), 1470, 1450, 1390, 1378, 1285, 1275, 1180(C-O), 770, 695cm^{-1}; δ(60 MHz, $CDCl_3$): 0.98(3H,t,J_{AB} 7Hz, -OCO-CH_2-CH_3), 1.26-4.16(9H,m, >N-CH_2-CH_2-CH-CH_2-$CO_2CH_2CH_3$), 6.8-7.4(3H,m, aromatic protons) 7.82(1H,d,J 7Hz, C-8-H); m/e 272 [$M^{+\cdot}$]; (Found: C, 66.2; H, 5.8; N, 10.3. $C_{15}H_{16}N_2O_3$ requires C, 66.2; H, 5.9; H, 10.3%).

Method 2

(1) (1g) and ethyl bromoacetatewere heated under reflux for 1.5 hours. Isolation using the method shown above gave the mono ester (176)(300 mg, 20%) identical in all respects to an authentic sample.

Preparation of (E) and (Z) 3-acetoxyethylidene-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-ones (182) and (183)

Method 1 - Condensation with acetic anhydride

A mixture of (1) (2g) and acetic anhydride (5ml) was heated under reflux for 12 hours. The mixture was cooled,

solvents removed in vacuo and the residue chromatographed on silica gel (70 g). Elution with system 4 gave the E-enol acetate (182) which was recrystallised from ether/ethyl acetate to yield pure (182) as colourless needles (550 mg, 19%), m.p. 177°; t.l.c. (system 1) R_f 0.84; νmax(KBr): 2900, 1750(C=O, acetate), 1670(C=O, ring), 1600(C=N) 1470, 1380, 1180, 780, 700cm^{-1}; δ(60MHz, $CDCl_3$): 2.18(3H,s, $-O_2C-\underline{CH_3}$), 2.60(3H,d,J_{AX}, 1.60Hz, >N-CH_2-CH_2-C=C$\langle^{CH_3}_{OAC}$), 2.76(dt,J_{AB} 7Hz, J_{AX}1.60Hz, >N-CH_2-$\underline{CH_2}$-C=C$\langle^{CH_3}_{OAC}$), 4.02(2H,t,J_{AB}7.2Hz, >N-$\underline{CH_2}$-CH_2-), 7.10-7.80(3H,m,aromatic protons), 8.16(1H,d,J 8Hz,C-8-H); m/e 270 [M$^+$]; (Found: C, 66.8; H, 5.3; N, 10.3. $C_{15}H_{14}N_2O_3$ requires C, 66.7; H, 5.2; N, 10.4%). Further elution gave the isomer (183) as a syrup which rapidly crystallised. Recrystallisation gave pure (183) as fine colourless needles (100 mg, 4%), m.p. 184.5-185.5°; t.l.c. (system 1) R_f 0.74; νmax(KBr): 2900, 1760(C=O, acetate), 1680(C=O, ring), 1600(C=N), 1470, 1380, 1330, 1190, 775, 700cm^{-1}; δ(60 MHz, $CDCl_3$): 2.06(3H,d,J_{AX}1.60Hz, $^{-CH_2}$>C=C$\langle^{CH_3}_{OAC}$), 2.38(3H,s, $-O_2C-\underline{CH_3}$), 2.90(2H,dt,J_{AB}7Hz,J_{AX} 2.4Hz, ^{OAC}-CH_2-CH_2>C=C$\langle^{CH_3}_{OAC}$), 4.11(2H,t,J_{AB}7Hz, >N-$\underline{CH_2}$-CH_2-), 7.08-7.76(3H,m, aromatic protons), 8.16(1H,d,J 8Hz, C-8-H); m/e 270 [M$^+$]; (Found: C, 66.4; H, 5.3; N, 10.3. $C_{15}H_4N_2O_3$requires C, 66.7; H, 5.2; N, 10.4%).

Method 2 - Condensation between deoxyvasicinone hydrochloride and acetic anhydride.

A mixture of the hydrochloride of (1) (6.1g) and acetic anhydride (15ml) was heated under reflux for 72 hours. The solvents were removed in vacuo and the residue extracted with ethyl acetate. The concentrated extracts were purified by preparative t.l.c. (12 plates) using system 1 as eluant and gave the pure(E) enol acetate (182) (1.21g, 17%) and the pure(Z) enol acetate (183) (550 mg, 8%). Both products were identical in all respects to the compounds described above.

Method 3 - Condensation of deoxyvasicinone (1) with acetyl chloride.

A mixture of (1) (5g) and acetyl chloride (30 ml) was heated at reflux for 89 hours. The reaction mixture was cooled, diluted with ethyl acetate and the hydrochloride of (1) (5.21g) was filtered from the mixture. The mother liquors were concentrated in vacuo then partitioned between ethyl acetate (100 ml) and a saturated solution of sodium bicarbonate (5 ml). The organic phase was separated, dried and reduced in volume on the evaporator. Addition of ether promoted crystallisation of the(E) enol acetate (182) (110 mg, 4%). The crystallisation residues were concentrated in vacuo and

chromatographed on silica gel (20g). Elution with system 4 gave the (Z) enol acetate (183) (50 mg, 2%) and finally a third unidentified component (40 mg), m.p. 141-143°; t.l.c. (system 1) R_f 0.698; νmax(KBr): 3070, 3000-2925, 1730, 1690, 1665, 1600, 1463, 1380, 1370, 1263, 1190, 1180, 1080, 1060, 1020, 890, 780, 705, 700cm^{-1}.

(Yields are based on 3g of (1) being isolated from its hydrochloride).

Methods 1 and 3 were repeated using pyridine as a solvent. t.l.c. analysis of these reaction mixtures showed the component ratios to be similar to those shown above.

Treatment of (182) with sodium methoxide (Method A)

2,3-Dihydro-3-(2-hydroxyethylidene)pyrrolo[2,1-b]quinazolin-9(1H)-one (189).

The enol acetate (182) (660mg) in methanol (100 ml) was added to a solution of methanolic sodium methoxide (prepared from sodium (5mg) in methanol (10 ml)). On gentle warming the reaction darkened through yellow to brown/black. The reaction was quenched with acetic acid (2 drops) and the solvent removed in vacuo. The residue

was partitioned between dichloromethane (100 ml) and water (5 ml). The organic phase was dried, decolourised and concentrated in vacuo to give a yellow syrup. Crystallisation from ether afforded the product (189) as lustrous yellow needles (320mg, 64%), m.p. 221 - 223°; t.l.c. (system 1) R_f0.58; νmax(KBr): 3325 (O-H, enol), 3080-2890, 1670(C=O, ring), 1640(C=N), 1545, 1495, 1494, 1360, 755, 710cm^{-1}; δ(90MHz, $CDCl_3$): 2.02(~1H,s), 2.27-2.48(3H,m,+s), 2.85(1H,t), 4.05(2H,t), 4.39(~½H,dd, exchangeable), 7.29-8.16(4H,m,aromatic protons). m/e 228 [$M^{+\cdot}$]; (Found: C, 68.1; H, 5.25; N, 12.1. $C_{13}H_{12}N_2O$ requires C, 68.4; H, 5.3; N, 12.3%).

Proof of structure (189)

A solution of (189) (100mg), phenylhydrazine (40mg, 1 mol.equiv.) and glacial acetic acid (3 drops) in ethanol (15ml) was heated carefully on a water bath for 20 minutes. The mixture was allowed to cool at 0° and the white crystalline deposit (110mg) which formed was removed by filtration. The solid was dissolved in hot ethanol and the solution decolourised and reduced in volume on the evaporator. A crystalline solid was filtered off from the cooled ethanolic solution and after drying was identified as (191) (80mg, 57%), m.p. 185° - 186°; t.l.c. (system 11) R_f 0.69; νmax(KBr): 3340 (N-H), 3100-2900, 1670(C=O), 1620(C=N), 1610(C=N), 1470,

1380, 1345, 1320, 1155, 775, 695cm^{-1}; m/e 318 [$M^{+\cdot}$] (56%); (Found: C, 71.9; H, 5.70; N, 17.7. $C_{19}H_{18}N_4O$ requires C, 71.8; H, 5.67; N, 17.6%).

Treatment of (182) with sodium methoxide (Method B)

Sodium methoxide generated from sodium metal (60mg) and methanol (10ml) was added to (182) (326mg). The mixture was refluxed for 40 minutes. The mixture was cooled, neutralised (dilute acetic acid) and concentrated **in vacuo**. Column chromatography of the residue on silica gel (10g) using ether as eluant gave deoxyvasicinone (1) (190 mg, 85%) identical in all respects (m.p., t.l.c., i.r.) to an authentic sample.

Reduction of (182) with $NaBH_4$.

To a stirring solution of the enol acetate (182) (500mg) in ethanol (100 ml) was added sodium borohydride (140mg, 2 mol.equiv.). After heating at reflux for 1 hour, t.l.c. (system 1) of the reaction mixture indicated no starting material and a major spot at R_f 0.80. The brown syrup obtained using procedure (h) was chromatographed on 4 plates using system 1 as eluant. Desorption, filtration and subsequent concentration of the band gave colourless needles of the (Z) ethylidene derivative (186) (240mg, 61%) identical in all respects

to an authentic sample. (See page 187).

Reduction of (183) with $NaBH_4$

To a stirring solution of the (Z) enol acetate (103) (410mg) in ethanol was added sodium borohydride (90mg, 1.5 mol.equiv.). The mixture was heated at reflux for 2 hours t.l.c. (system 1) showed one major spot R 0.70. An orange syrup was obtained following isolation using procedure (h). The syrup was purified following chromatography on a short column (silica gel 20g). Elution with system 9 afforded the pure (E) ethylidene derivative (98) (110mg, 34%) as colourless needles identical to an authentic sample (m.p., i.r., t.l.c.). (See page 186).

Attempted reaction of (182) with benzylamine.

The enol acetate (182) (100mg) and benzylamine (41mg, 1 mol.equiv.) in dry THF (5ml) were heated at reflux for 8 hours. t.l.c. (system 1) indicated no reaction had taken place and the reacion was abandoned.

Attempted acylation of (1)

Benzoyl peroxide (5mg) was added to a stirring solution of (1) (100 mg) in dry carbon tetrachloride (10 ml).

After 10 minutes acetyl chloride (84 mg, 1.95 mol.equiv.) was added and the mixture refluxed for 10 hours. On cooling, the mixture was dissolved in CCl_4 and washed with water (2 x 5ml). The organic phase was dried. Filtration followed by concentration under reduced pressure gave (1) (50mg) identical in all respects to an authentic sample.

Attempted acylation of (1)

Deoxyvasicinone (1) (667mg) was added to a solution of sodium amide (140mg, 1 mol.equiv.) in dry xylene (50 ml) to give a yellow/orange solution. Acetyl chloride (280mg, 1 mol.equiv.) was added and the mixture stirred at room temperature for 1 hour. t.l.c. (system 1) showed one component R_f 0.482. Heating the reaction for 4 hours and reanalysis by t.l.c. showed the reaction to be similar to that between (1) and acetyl chloride in pyridine. No isolation of this reaction was attempted.

Reaction of (1) with benzoic anhydride

Liquified benzoic anhydride (13ml) and (1) (5g) were heated at 230° for 2 hours. The cooled mixture was diluted with ethanol to yield a brown solid. The crude solid was dissolved in warm chloroform, decolourised and concentrated in vacuo to yield colourless needles of pure 3-(benzoyloxyphenylmethylene)-2,3-dihydropyrrolo

[2,1-b]quinazolin-9(1H)-one (187) (1.39g, 13%), m.p. 186-187°; t.l.c. (system 18) R_f 0.323; νmax(KBr): 3050, 1738(C=O, benzoate), 1680(C=O, ring), 1595(C=N), 1558, 1495, 1470, 1385, 1250(C-O), 1190, 1180, 1025, 780, 710, 700cm^{-1}; δ(60MHz, $CDCl_3$): 3.22(2H,t,J_{AB}7Hz, >N-CH_2-CH_2-), 4.12(2H,t,J_{AB}7Hz, >N-CH_2-CH_2-), 6.58(1H,dd,J 7Hz,J 1Hz, C-5-H), 7.04-7.96(10H,m, 2 x Ph), 8.08(3H,m, aromatic protons); m/e 394 [M^+] (23%). (Found: C, 75.8; H, 4.6; N, 7.1. $C_{18}H_{14}N_2O_2$ requires C, 74.15; H, 4.8; N, 9.7%). Concentration of the mother liquors from the crystallisation gave a solid which was repeatedly recrystallised from dimethylformamide to yield (188) (400 mg, 4%) as pale yellow prisms, m.p. 164-165°; t.l.c. (system 18) R_f 0.242; νmax(KBr): 3600-3000(OH-H bonded), 3100-2800, 1675(C=O), 1630, 1580(C=N), 1475, 1390, 1330, 1290, 1275, 765, 760, 690, 680; P.M.R(due to the insolubility of this material a satisfactory spectrum was not obtained; m/e 290 [M^+] (14%); (Found: C, 74.1; H, 4.8; N, 9.9. $C_{18}H_{14}N_2O_2$ requires C, 74.15; H, 4.8; N, 9.7%).

Hydrolysis of (187) with sodium methoxide

The enol benzoate (187) (500 mg) was added to a previously prepared solution of methanolic sodium methoxide (prepared from Na (10mg) in methanol (100 ml)). The mixture was stirred for 48 hours at room temperature

decolourised and concentrated in vacuo. Ether induced crystallisation of the salt of (1) and the crude free base was obtained following acidification with dilute acetic acid. The crude mixture was partitioned between chloroform (100 ml) and a saturated solution of sodium bicarbonate (5 ml). The organic phase was dried, concentrated and the solid obtained recrystallised from ether/light petroleum as colourless needles of (1) (160 mg, 67%) identical to an authentic sample (m.p., m.m.p., t.l.c., i.r.).

3-(Chlorophenylmethylene)-2,3-dihydropyrrolo[2,1-b]quinazolin-9(-1H)-one (185)

Method 1). Benzoyl chloride (12 ml) and (1) (1.4g) were heated under reflux for 1.5 hours. The mixture was cooled, flooded with light petroleum and the insoluble material crystallised from ether to yield a cream solid (1.12g). Recrystallisation from ethyl acetate gave the pure α-chlorobenzylidene derivative (185) (1.01g, 43%), m.p. 162-163°; νmax(KBr) 3050-2875, 1675(C=O), 1610(C=N), 1590, 1470, 1380, 780, 700cm^{-1}; δ(60MHz, $CDCl_3$) : 3.10 (2H,t,J_{AB}7Hz, >N-CH_2-CH_2-), 4.17(2H,t,J_{AB}7Hz, >N-CH_2-CH_2-), 7.07-7.90(8H,m,3 aromatic protons,Ph), 8.19(1H,dd,J 2Hz,J 8Hz,C-8-H); m/e 310 [M^{+}] (25%) 308 [$M^{+\cdot}$] (75%); (Found: C, 70.00; H, 4.0; Cl, 11.3; N, 9.0. $C_{18}H_{13}ClN_2O$ requires C, 70.00; H, 4.2; Cl, 11.5; N, 9.1%).

Method 2). Benzoyl chloride (5ml) and the hydrochloride of (1) (510mg) were heated under reflux for 5 hours. The mixture was treated as above to yield pure (185) (210 mg, 29%). m.p. 162-163°.

3-(2,2,2-Trichloro-1-hydroxyethyl)-2,3-dihydropyrrolo [2,1-b]quinazolin-9(1H)-one (175)

Chloral hydrate (5.34g) and (1) (5g) were intimately mixed and heated gently until the resulting clear homogeneous solution darkened. The mixture was cooled and the thick red paste treated with chloroform/ether to yield a white crystalline solid. Recrystallisation from ether gave white needles of the chloral derivative (175) (3.7g, 41%), m.p. >300° (dec); t.l.c. (system 1) R_f 0.70; ν_{max}(KBr): 3700-3100(OH, broad), 3050, 3000-2900, 1660(C=O), 1620(C=N), 1465, 1390, 1340, 1278, 805, 780, 700cm^{-1}; δ (60MHz,d_6DMSO): 2.10-2.90(2H,m, >N-CH_2-CH_2-), 3.60-4.40(3H,m,CH_2-CH-CH(OH)CCl_3), 4.90(1H,d,J 7Hz, >CH-CH(OH)CCl_3), 7.14(1H,d,J 7Hz, D_2O exchangeable, O-H), 7.30-7.80(3H,m, aromatic protons), 8.06(1H,d,J 7Hz, C-8-H); m/e 334, 332 both [M^+]; (Found: C, 46.5; H, 3.4; Cl, 31.9; N, 8.1. $C_{13}H_{11}Cl_3N_2O_2$ requires C, 46.8; H, 3.3; Cl, 31.9; N, 8.1%).

Reaction between (175) and a solution of ethanolic KOH.

A solution of ethanolic KOH (prepared from KOH (3.2g) in ethanol (10 ml) was delivered portionwise to a solution of the chloral derivative (175) (1.7g) in ethanol (20ml). The mixture was heated for 3 hours and stirred at room temperature for 48 hrs. to give a purple/black solution. The solution was cooled, neutralised (glacial acetic acid) and then concentrated in vacuo. The black solid was partially dissolved in chloroform and the insoluble material filtered off to give 220 mg of starting material (175). The mother liquors and washings from filtration were combined, washed (H_2O, 2 x 5ml) and dried. Decolourisation of this organic solution was unsuccessful and isolation of the desired acid was not achieved.

Condensation of (1) with chlorinated acid chlorides.

a) Chloroacetyl chloride. Preparation of 3-(1,2-dichloroethylidene)-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (177)

A mixture of (1) (1g) and chloroacetyl chloride (10ml) was heated under reflux for 3.5 hours. The mixture darkened considerably during the reaction and on cooling the excess chloroacetyl chloride was removed **in vacuo**. The

residue crystallised from ethyl acetate and the crude product was decolourised and recrystallised from ethyl acetate to yield pure (177) (820 mg, 57%), m.p. 211.5-212.5°; t.l.c. (system 1) R_f 0.88; νmax(KBr): 3025, 2975, 1670(C=O), 1590(C=N), 1485, 1465, 1430, 1380, 1330, 1290, 1270, 780, 700cm-1; δ(90MHz,d_6DMSO): 3.05 (2H,quintet,J_{AX}1Hz,J_{AB}7Hz, >N-CH_2-CH_2-C=C<$^{Cl}_{CH_2}$), 4.08(2H, t,J 7Hz, >N-CH_2-CH_2-), 5.49(2H,t,J_{AX}1Hz, >N-CH_2-CH_2-C=C<$^{Cl}_{CH_2Cl}$) 7.4-7.9(3H,m, aromatic protons), 8.14(1H,m,C-8-H); m/e 284, 282, 280 all [M^+]; (Found: C, 55.7; H, 3.6; N, 9.95. $C_{13}H_{16}Cl_2N_2O$ requires C, 55.5; H, 3.6; N, 10.00%).

Attempted reaction of (177) with benzylamine.

Benzylamine (20 mg, 1 mol. equiv.) and the chloroethylidene compound (177) (50 mg) in dry THF (5 ml) were heated together for 63 hours. t.l.c. (system 1) indicated no reaction had taken place and the reaction was abandoned.

Reduction of (177) with sodium borohydride.

The chloroethylidene (177) (800 mg) was dispersed in ethanol (100 ml) and to this stirring solution was added sodium borohydride (200 mg, 1.8 mol.equiv.). After

heating at reflux for 1 hour, t.l.c. (system 1) of the translucent green mixture showed no starting material. The brown syrup which was obtained following isolation using procedure (h) was chromatographed on 4 plates using system 5 as eluant. Desorption, filtration and subsequent concentration of the least polar band gave colourless needles of (180) or (181) (220 mg, 31%) from ether. m.p. 79-80°. t.l.c. (system 1) R_f 0.79; ν_{max}(KBr): 3080, 3020-2950; 1680(C=O), 1630(C=N), 1470, 1400, 1340, 1320, 795, 710cm^{-1}; δ(60MHz, $CDCl_3$): 1.40-2.90(4H,m), 3.04-4.60(5H,m), 7.00-7.80(3H,m, aromatic protons), 8.06(1H,d,J 7Hz, C-8-H). m/e 248 [M^+]. (Found: C, 62.4; H, 5.1; Cl, 14.4; N, 11.1. $C_{13}H_{13}ClN_2O$ requires C, 62.8; H, 5.25; Cl, 14.3; N, 11.25%).

The polar band was treated similarly and afforded the (E)3-ethylidene derivative of (1), (98) (250 mg, 41%) as colourless prisms from ether. Identical in all respects (m.p., m.m.p., t.l.c., i.r., p.m.r.) to an authentic sample.

b) Dichloroacetyl chloride. 3-(1,2,2-trichloroethylidene)-2,3-dihydropyrrolo[2,1-b] quinazolin-9(1H)-one (178)

A mixture of (1) (1g) and dichloroacetyl chloride (10 ml) was heated gently under reflux for 1.5 hours. the mixture

was cooled, excess acid chloride removed in vacuo and the residue chromatographed on silica gel (24g). Elution with system 3 gave an orange oil which crystallised from ether. Recrystallisation and decolourisation gave (178) (200 mg, 12%), m.p. 189-190.5°; t.l.c. (system 1) R_f 0.88; ν_{max}(KBr): 2990, 1685(C=O), 1600(C=N), 1485, 1465, 1430, 1390, 1340, 780, 700cm^{-1}; δ (90MHz,d_6DMSO): 3.09(2H,t,J_{AB}8Hz, >N-CH_2-CH_2-), 4.10(2H,t,J_{AB}8Hz, >N-CH_2-CH_2-), 7.40-8.00(3H,m,aromatic protons), 8.20(1H,dd,J 1Hz,8Hz,C-8-H), 9.27(1H,s,>C=C<$\underset{Cl}{CH}Cl_2$) m/e 318, 316, 314, all [$M^{+\cdot}$] ; (Found: C, 49.4; H, 2.8; N, 9.0. $C_{13}H_9Cl_3N_2O$ requires C, 49.4; H, 2.8; N, 8.9%).

c) Tricholoroacetyl chloride.

3-(Hydroxytrichloromethylmethylene)-2,3-dihydro pyrrolo[2,1-b]quinazolin-9(1H)-one (179).

A mixture of (1) (2.02g) and tricholoroacetyl chloride (10ml) was heated under reflux for 1.5 hours. The mixture was cooled, excess tricholoroacetyl chloride removed in vacuo and the residue chromatographed on silica gel (60g). Elution with system 14 gave a brown semi-solid mass. Decolourisation and recrystallisation gave pale yellow needles of (179) (310 mg, 9%), m.p. > 235°(dec); t.l.c. (system 18) R_f 0.55; ν_{max}(KBr): 3600-3100(OH, broad), 3100-2850, 1690(C=O), 1640(C=N), 1542, 1480, 1420, 1340, 1320, 1300, 1280,

1202, 770, 700cm^{-1}; δ(90MHz,d_6DMSO), 3.19(2H,t,J_{AB}8Hz, >N-CH_2-CH_2-), 4.16(2H,t,J_{AB}8Hz, >N-CH_2-CH_2-), 7.20-8.10(4H,m, aromatic protons), 11.84(1H,s,D_2O exchangeable, O-H); m/e 334, 332, 330 all [M^+]; (Found: C, 47.1; H, 2.4; Cl, 32.5; N, 8.5. $C_{13}H_9Cl_3N_2O_3$ requires C, 47.1; H, 2.7; Cl, 32.1; N, 8.5%).

d) 3-Chloropropionyl Chloride

A homogeneous solution of deoxyvasicinone (1) (2g) and 3-chloropropionyl chloride (10 ml) was heated at reflux for 5 hours, t.l.c. (system 1) indicated no starting material and the excess 3-chloropropionyl chloride was removed under reduced pressure after cooling. Flooding the flask with ether promoted precipitation of a powdery brown solid. This was recrystallised from ether/ethanol as golden flakes (120 mg) the identity of which is unknown. m.p. 130^0 (dec); νmax(KBr): 3700-3200, 2950, 1720, 1650, 1580-1540, 1400, 1380, 1290, 1190, 1020, 760, 680cm^{-1}; (Found: C, 57.1; H, 5.4; Cl, 8.5; N, 5.2%).

Reaction between (1) and tris(dimethylamino)methane

To an ice cold suspension of deoxyvasicinone (1) (1g) and tris(dimethylamino)methane (1.6 ml, 1 mol.equiv.) under dry nitrogen was injected acetic anhydride (10 ml). An immediate red hue was observed in the original colourless solution. t.l.c. (system 1) indicated a complex mixture of products were present and the experiment was abandoned.

2,3-Dihydro-3-methylenepyrrolo[2,1-b]quinazolin-9(1H)-one (194) and 3-Acetoxymethyl-2,3-dihydro-3-dimethyl aminomethylpyrrolo[2,1-b]quinazolin-9(1H)one (198)

Acetic anhydride (60 ml) was added slowly to an ice cold suspension of (1) (3.3g) in freshly distilled bis(dimethylamino)methane (60 ml). The mixture was stirred at room temperature for 1 hour and the excess reagents removed **in vacuo**. The residue was treated with ice/water, neutralised with solid sodium bicarbonate and then extracted with dichloromethane. The dried, concentrated organic extracts were chromatographed on a column of silica gel (100g). Elution with system 9 gave crude (194) as a syrup. Preparative t.l.c. (5 plates) using system 6 as eluant was employed to further purify this syrup. Pure (194) was thus obtained as a colourless crystalline solid (660mg, 19%). m.p. 140-144^{o}, t.l.c.

(system 6) R_f 0.66; νmax(KBr): 3100, 2900, 1670(C=O), 1598(C=N), 1435, 1410, 1395, 1385, 1340, 1310, 800, 800, 700cm^{-1}, λmax($CHCl_3$), 249(ξ 18000), 308nm(ξ 105000), δ (60MHz, $CDCl_3$), 3.24(2H,m, >N-CH_2-CH_2-), 4.14(2H,t, J_{AB}7.2Hz, >N-CH_2-CH_2-), 5.48(1H,t,J 2.4Hz, -CH_2>C=C<$\frac{H}{H}$), 6.36(1H,t,J 2.4Hz, $_{CH_2}$>C=C<$\frac{H}{H}$), 7.26-7.80(3H,m, aromatic protons), 8.18(1H,d,J 7Hz, C-8-H); m/e 198 [$M^{+\cdot}$] (89%); 197 $[M-1]^+$ (100%) (Found: C, 73.2; H, 5.5; N, 13.9. $C_{12}H_{10}N_2O$ requires C, 72.8; H, 5.8; N, 14.1%).

Further elution of the column with system 12 gave pure (198) as a syrup which crystallised rapidly from toluene as colourless prisms (840 mg, 17%), m.p. 110.5-111°; t.l.c. (system 1) R_f 0.67; νmax(KBr): 2940, 2770, 1740(C=O, acetate), 1675(C=O, ring), 1470, 1340, 1240(C-O, acetate), 785, 700cm^{-1}; δ(60MHz, $CDCl_3$): 1.96(3H,s, -CH_2-OCO-CH_3), 2.20-2.80(10H,m,>N-CH_2-CH_2-C-CH_2-N(CH_3)$_2$) 4.14(2H,t,J_{AB}7Hz, >N-CH_2-CH_2-), 4.30(2H,s, -CH_2-OCO-CH_3), 7.20-7.70(3H,m, aromatic protons), 8.20(1H,d,J 7Hz, C-8-H); m/e 314 $[M-1]^+$ (3%); (Found: C, 64.8; H, 6.7; N, 13.3. $C_{17}H_{21}N_3O_3$ requires C, 64.8; H, 6.7; N, 13.3%).

Reaction of (194) with dimethyl acetylenedicarboxylate

(194) (140 mg) and DMAD (100mg, 1 mol. equiv.) were carefully heated on a steam bath for 3 hours. t.l.c. (system 1) indicated no reaction and a mantle was used to heat the mass for 1 hour. The dark brown mass produced was cooled, dissolved in ethyl acetate, decolourised and concentrated **in vacuo** to give a thick syrup. Analysis by t.l.c. (system 1) of the syrup showed a complex mixture of products. No attempt was made to isolate the numerous components from the syrup.

2,3-Dihydropyrrolo[2,1-b]quinazolin-3,9(1H)-dione-3-oxime (200)

A solution of (1) (4.23 g) in ethanolic sodium ethoxide (prepared from sodium (2.3g) and absolute ethanol (150 ml)) was stirred at room temperature and amyl nitrite (5.6g) added. The mixture was warmed to 60^{o} and stirred at this temperature for 40 minutes. The resulting orange solution was stirred at room temperature overnight and the solvent removed **in vacuo**. A pale green solid which became pink on addition of aqueous acetic acid was obtained. The mixture was treated with saturated sodium bicarbonate solution until neutral and the mixture extracted with chloroform (2 x 150 ml).

From the dried chloroform extracts unreacted (1) (2.5g) was recovered whilst filtration of the aqueous phase gave a pink solid. Recrystallisation of the solid from a large volume of ethanol gave the pure oxime (200) as lustrous needles (1.50g, 71%, based on recovered starting material), m.p. >300^{o} (dec); νmax(KBr), 3160(=N-OH, oxime), 3050, 2850, 1680(C=O), 1600(C=N), 1480, 1460, 1400, 1320, 1300, 780, 690cm^{-1}; m/e 215 [$M^{+\cdot}$] (100%); (Found: C, 61.7; H, 4.2; N, 19.4. $C_{11}H_9N_3O_2$ requires C, 61.4; H, 4.2; N, 19.5%).

Due to the insolubility of this compound p.m.r. and R_f measurements were impossible.

Attempted hydrolysis of (200)

A suspension of the oxime (200) (1g) in a (1:1) solution of acetone/HCl (200 ml) was stirred for 48 hours room temperature. The solid was filtered from the mixture and the filtrate neutralised with a solution of saturated sodium bicarbonate and extracted with chloroform (3 x 150 ml). t.l.c. (system 1) of the extracts and the original solid indicated no new products and the reaction was discontinued.

Reaction between (200) and lead tetraacetate.

The oxime (200) (2g) was added to a stirring mixture of lead tetraacetate (4.25g, 1.03 mol.equiv.) in glacial acetic acid (100 ml). The suspension was stirred at room temperature in a sealed flask and after 95 hours a dark brown mixture was apparent. After 336 hours the brown precipitate of lead salts was removed by filtration. Neutralisation of the filtrates with aqueous concentrated ammonia solution followed by further filtration afforded a second brown liquid. This liquid was extracted with ethyl acetate (6 x 100 ml), dried and concentrated in vacuo to give a brown solid (t.l.c. (system 1), R_f 0.42) which rapidly decomposed on standing. t.l.c. (system 1) R_f 0.42, 0.62, 0.82).

Reaction between (1) and selenium dioxide

Selenium dioxide (3g, 1 mol.equiv.) was added to a solution of deoxyvasicinone (1) (5g) in dioxan (100 ml) and allowed to stir at room temperature for 16 hours. t.l.c. (system 1) indicated no reaction had taken place. After a further 48 hours t.l.c. evidence showed no reaction and the mixture was carefully heated to reflux. Heating promoted a rapid darkening of the mixture through purple to black. After 30 minutes the mixture was cooled to room temperature. t.l.c. (system 1) evidence exposed extensive decomposition and the reaction was abandoned.

Attempted oxidation of (1) with sodium chromate in acetic acid/anhydride.

Sodium chromate (210 mg, 0.4 mol.equiv.) was added portionwise to a stirring solution of deoxyvasicinone (1) (615mg) in 12.5 ml of a 3:2 mixture of acetic acid/ acetic anhydride at 0^{o}. The mixture was allowed to rise to room temperature and after 72 hours a bright green colour was visible in the flask. t.l.c. (system 1) R_f 0.50. The reaction mixture was slowly added with stirring to a saturated solution of sodium bicarbonate. After 3 hours the aqueous solution was extracted with chloroform (2 x 150 ml). The organic extracts were combined, dried, decolourised and concentrated **in vacuo** to afford a yellow syrup (700 mg) which crystallised from ether/light petroleum. Subsequent recrystallisation from the same solvent system gave (1) (500 mg) identical in all aspects (m.p., m.m.p. , t.l.c. and i.r.) to an authentic sample.

Attempted oxidation of (160) with sodium chromate in acetic acid/anhydride.

To an ice cold stirring solution of the benzylidene derivative (160) (1g) in 50 ml of a 1:1 mixture of acetic acid/acetic anhydride was added portionwise

chromium VI oxide (380 mg, 1.05 mol.equiv.). The orange brown mixture was allowed to rise to room temperature and stirred for 18 hours. The now dark green solution was partitioned between water (30 ml) and dichloromethane (2 x 150 ml). Analysis of the organic extracts (t.l.c. (system 3)) R_f major 0.195, 0.00, R_f minor 0.707, 0.780. The combined organic extracts were washed with a saturated solution of sodium bicarbonate (40 ml) and then with water (40 ml). Drying, decolourisation and concentration **in vacuo** of the extracts gave a white solid (780 mg) shown to be identical in all respects (m.p., m.m.p. , t.l.c., i.r., p.m.r.) to a sample of (160).

Reaction of (1) with ethyl bromopyruvate

Deoxyvasicinone (1) (500 mg) and ethyl bromopyruvate (520 mg, 1 mol.equiv.) were heated gently together for 5 min. The black mass was cooled and t.l.c. (system 1) showed extensive decomposition had occured. No attempt was made to isolate compounds from the mass.

Reaction of (1) with ethyl oxalyl chloride

Deoxyvasicinone (1)(1g) and ethyl chloroglyoxalate (5 ml) were heated together under reflux for 1 hour. t.l.c. (system 1) indicated one major component R_f 0.89 and that no deoxyvasicinone remained. The now black tar was cooled and excess reagent removed on the rotary evaporator. The concentrated tar was dissolved in toluene yet despite repeated chromatography followed by decolourisation the expected product could not be isolated due to its rapid decomposition (t.l.c. evidence).

Attempted condensation of (1) with methanesulphonyl chloride).

Deoxyvasicinone (1) (1g) and methanesulphonyl chloride (680 mg, 1 mol.equiv.) were gently heated on a mantle at 100^{o} for 1 hour. The cooled black solid obtained was treated with water (1ml) and allowed to stand for 2 hours. The mixture was extracted with chloroform (100 ml) and the organic extract separated, washed with a saturated solution of sodium bicarbonate (2ml) and finally dried. Concentration **in vacuo** of this dried solution gave deoxyvasicinone (1) as a yellow powder with identical physical properties (m.p., i.r., t.l.c.) to those described previously.

Reaction between (1) and phenacyl bromide.

Deoxyvasicinone (1) (2.15g) and 2-bromoacetophenone (2.3g, 1 mol.equiv.) were heated for 1 hour at 120°. t.l.c. (system 1) $R_f$major 0.73, 0.69, 0.58, 0.48 (on prolonged heating extensive decomposition ensued). Separation of the individual components from the reaction via column chromatography proved to be impossible.

Reaction between (1) and phenacyl bromide in pyridine

Deoxyvasicinone (1) (1g), phenacyl bromide (1.06g, 1 mol.equiv.) and pyridine (15 ml) were heated gently under reflux for 20 minutes. A colourless solid precipitated from the refluxing solution. Ethyl acetate (20 ml) was added to the cooled solution and the solid collected by filtration. The solid (800 mg) m.p. 275-277° gave a positive sodium fusion test for bromine and is thought to be an addition product formed between pyridine and phenacyl bromide.

Reaction between (1) and phenyl isocyanate

Deoxyvasicinone (1) (290 mg) and phenyl isocyanate (1ml) were heated gently under reflux for 30 minutes. The red brown liquid was analysed by t.l.c. (system 1). This showed extensive decomposition had occurred during the reaction. No attempt was made to resolve the mixture.

Reaction between (152) and phenyl isocyanate.

The compound (152) (1.0g) and phenyl isocyanate (620 mg, 1.05 mol.equiv.) were heated gently together under dry nitrogen for 24 hours. On cooling toluene was added to the flask and a crystalline deposit filtered off at the pump. The crude solid was washed with ether and dried to give N, N-diphenylurea m.p. 239-241° (reported m.p. 238-239°, Dictionary of Organic Compounds[160]. t.l.c. (system 1) R_f 0.83, Vmax(KBr): 3030, 1645(C=O), 1595, 1550, 1495, 1455, 755, 700. δ (60MHz, $CDCl_3/d_6$DMSO): 6.8 - 7.6(10H,m, 2 x Ph), 8.12(2H,s, 2 x N-H) t.l.c. analysis of the filtrates indicated (152) and diphenylurea.

Reaction between (1) and para-toluenesulphonyl azide and piperidine.

Deoxyvasicinone (1) (186mg) and para-toluene sulphonyl azide (196mg, 1 mol.equiv.) and piperidine (85mg, 1 mol.equiv.) were stirred at room temperature for 8 hours and heated at reflux for 68 hours. Analysis of the brown/black mixture by t.l.c. (system 1) showed the major component of the mixture to be starting material R_f 0.48; three minor components were also seen R_f 0.50, 0.66, 0.84 but no attempt was made to isolate the minor quantities of these products from the reaction mixture.

Attempted condensation of (1) with ethoxycarbonyl isothiocyanate.

Deoxyvasicinone (1) (186 mg) and ethoxycarbonyl isothiocyanate (130 mg, ·1 mol.equiv.) were heated together under reflux in dry toluene (5ml) for 80 hours, t.l.c. (system 1) indicated no reaction and (1) (105mg) was extracted from the mixture.

(E)3-ethylidene-2,3,-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (98) and (Z)3-ethylidene-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (186).

A mixture of (1) (5g), triethylamine (0.5ml) and vinyl acetate (12ml) was heated at 150° for 18 hours in a sealed tube during which time the mixture darkened considerably. The cooled tube was opened, volatiles removed in vacuo and the residue chromatographed on silica gel (150g). Elution with system 9 gave (98) as a white solid. Recrystallisation from ethyl acetate/light petroleum gave pure (98) as fine white needles (350mg, 6%), m.p. 148-150° (dec); t.l.c. (system 1) R_f 0.80; νmax (KBr): 3050, 2960, 1675(C=O), 1600(C=N), 1470, 1390, 1380, 780, 700, 670cm^{-1}; λmax ($CHCl_3$): 250 (ξ 27000), 307nm(ξ 13000); δ(60 MHz, $CDCl_3$): 2.38(3H,dt,J_{AM} 7.2Hz, J_{AX}2Hz,-CH_2>C=<$^{H}_{\underline{CH_3}}$), 2.86(2H,m,>N-CH_2-$\underline{CH_2}$>C=<$^{H}_{CH_3}$), 4.05(2H,t,J_{AB}7.2Hz, >N-$\underline{CH_2}$-CH_2-), 6.10(1H,m,$^{-CH_2}$>C=C<$^{H}_{CH_3}$), 7.10-7.70(3H,m, aromatic protons), 8.08(1H, d,J 7.2Hz, C-8-H), double irradiation at δ 6.10 causes the signal at δ 2.38 to reduce to a triplet and the signal at δ 2.86 to simplify; m/e 212 [$M^{+\cdot}$]; (Found: C, 73.3; H, 5.65; N, 13.0. $C_{13}H_{12}N_2O$ requires C, 73.6; H, 5.7; N, 13.2%).

Further elution with the same solvent gave (186) as fine needles. Recrystallisation from ethyl acetate/light petroleum gave pure (186) (570 mg, 10%), m.p. 169-170°; t.l.c. (system 1) R_f 0.75; νmax(KBr): 3050, 2900, 1665

(C=O), 1600(C=N), 1470, 1390, 1340, 785, 700, 690cm^{-1}; λmax($CHCl_3$), 246(ξ16000), 307nm(ξ12000), δ(60MHz, $CDCl_3$) 1.80(3H,dt,J_{AM}7.2Hz, J_{AX}2Hz, $-CH_2>C=C<\frac{CH_3}{H}$), 2.70(2H, m, $>N-CH_2-\underline{CH_2}>C=C<\frac{CH_3}{H}$), 4.04(2H,t,J_{AB}7.2Hz, $>N-\underline{CH_2}-CH_2-$), 6.50-7.10(1H,m,$-CH_2>C=C<\frac{CH_3}{\underline{H}}$), 7.10-7.80(3H,m, aromatic protons), 8.10(1H,d,J 7.2Hz, C-8-H), double irradiation of the signal at δ1.80 causes the signal at δ2.70 to simplify and the signal at δ6.50 - 7.10 to collapse to a singlet with a slight shoulder at δ6.82; m/e 212[$M^{+\cdot}$]; (Found: C, 73.6; H, 5.7; N, 13.2. $C_{13}H_{12}N_2O$ requires C, 73.6; H, 5.7; N, 13.2%).

Attempted condensation of (1) with acrylonitrile.

Deoxyvasicinone (1) (5g) and acrylonitrile (5 ml) were heated at 150^{o} - 156^{o} for 18 hours in a sealed tube. Treatment of the contents of the cooled tube with acetone, followed by filtration gave a crystalline polymeric substance derived from acrylonitrile (spectroscopic evidence), νmax(KBr): 2250(C=N)cm^{-1}; δ (60MHz, $CDCl_3$): large unresolved peaks at δ1.40-3.20.

The filtrate and washings were combined and on concentration afforded crude deoxyvasicinone (4.8g) identical in all respects (m.p., m.m.p., i.r.) to an authentic sample.

3-Bromo-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (85) and 3,3-dibromo-2,3-dihydropyrrolo[2,1-b] quinazolin-9(1H)-one (84).

Deoxyvasicinone (1)(4.1g) and N-bromosuccinimide (3.92g, 1 mol.equiv.) in carbon tetrachloride (25ml) were heated at reflux for 41 hours. The mixture was cooled and concentrated **in vacuo** to give a dark brown mass which was chromatographed on silica gel (100g). Elution with (system 6) gave the dibromo derivative (84) as colourless prisms (310mg, 4%). m.p. 189° (dec). (reported m.p., 189-191°, Oripov[34,99] t.l.c. (system 1) R_f 0.84; νmax(KBr): 3100-2900, 1685(C=O), 1625(C=N), 1470, 1380, 1335, 1325, 1280, 780, 700cm^{-1}; δ (60MHz, $CDCl_3$): 3.26 (2H,t, J_{AB} 6Hz, >N-CH_2-CH_2-), 4.17(2H,t,J_{AB} 6Hz, >N-CH_2-CH_2-), 7.14-7.94(3H,m, aromatic protons), 8.20(1H,d,J 7Hz, C-8-H); m/e 185 (56%), 184 (100%), 183 (32%), all $[M-160]^{+\cdot}$; (Found: C, 38.85; H, 2.2; N, 8.0. $C_{11}H_8Br_2N_2O$ requires C, 38.4; H, 2.3; N, 8.1%).

Further elution using system 9 gave the monobromo derivative (85) (2.09g, 39%) also as colourless prisms m.p. 146° - 147°; (reported m.p. 144° - 146°, Oripov[34,99] t.l.c. (system 1) R_f 0.70; νmax(KBr): 3050-2900, 1685(C=O), 1625, 1610(C=O, doublet), 1470, 1390, 1330, 1290, 1280, 750, 740, 695, 690cm^{-1}; δ (60MHz, $CDCl_3$): 2.24-3.00 (2H,m, >N-CH_2-CH_2-CHBr-), 3.84-4.44(2H,m, >N-CH_2-CH_2-CHBr-), 5.18(1H,dd,J_{AB} 2Hz, J_{AB} 5Hz,N-CH_2-CH_2-CHBr), 7.16-

7.84(3H,m, aromatic protons), 8.14(1H,d,J 8Hz, C-8-H); m/e 185 (100%)$[M-80]^{+\cdot}$; (Found: C, 50.5; H, 3.4; N, 10.4. $C_{11}H_9BrN_2O$ requires C, 49.8; H, 3.4; N, 10.6%).

3-Carbomethoxymethylthio-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (201).

The bromo compound (85) (300 mg) was added to a previously prepared solution of the methyl thiogylcolate anion (prepared in situ from methanolic sodium methoxide (Na (50mg) in methanol (20 ml)) and methyl thioglycolate (20 ml). A slight exotherm was recorded and the mixture was stirred at ambient temperature for 48 hours. The mixture was concentrated **in vacuo** and flooded with dichloromethane. The precipitated sodium bromide was removed by filtration and concentration of the organic filtrates under reduced pressure afforded a yellow syrup. The syrup crystallised from ethyl acelate/light petroleum to give colourless prisms of the thio ester, 3-carbomethoxymethylthio-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (85) (190mg, 58%), m.p. 92-93°; t.l.c. (system 1) R_f 0.84; νmax(KBr): 2990-2900, 1745 (C=O, ester), 1665(C=O, ring), 1625(C=N), 1470, 1380, 1330, 1320, 1120(C-O, ester), 775, 695cm^{-1}; δ(90MHz, d_6 DMSO): 1.987-2.260(1H,m, >N-CH_2-C<$\frac{H}{H}$-CH-S-), 2.485 (1H,m, >N-CH_2-C<$\frac{H}{H}$-CH-S-), 3.564(3H,S,-OCO-CH_3), 3.754(2H,d,J 7.9Hz, >CH-S-CH_2-CO_2CH_3), 4.081(2H,m,>N-CH_2-CH_2-),

4.530(1H,dd,J 7.5Hz,J 4.5Hz,-CH_2-CH-S-CH_2-), 7.446-7.870(3H,m, aromatic protons), 8.085-8.188(1H,m, C-8-H); (Found: C, 57.9; H, 4.8; N, 9.8; S, 11.1. $C_{14}H_{14}N_2O_3S$ requires C, 57.9; H, 4.8; N, 9.65; S, 11.0%).

3-Hydroxymethylene-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (106).

$POCl_3$ (13.6g, 2.2 mol.equiv.) was added with vigorous stirring and cooling to ice cold DMF (6.96g, 2.4 mol. equiv.). A further 10ml of DMF was added prior to the portionwise delivery of (1) (7.44g) to the flask. The reaction mixture was stirred for 12 hours, heated for 2 hours on a water bath and allowed to cool. The mixture was diluted with ice/water and neutralised with a saturated solution of sodium acetate. The cream precipitate was removed by filtration and redissolved in dichloromethane. Decolourisation and concentration in vacuo gave the crude α-hydroxyformylidene compound (106) (7.1g, 83%). An analytical sample was isolated as yellow needles following chromatography on silica gel. The crude product was used in all subsequent reactions without further purification. (106) m.p. 200 - 203^{o} (reported m.p. 205 - 206^{o}, Shakhidoyatov[103,104], t.l.c. (system 1) R_f 0.55; νmax (KBr): 3700-3200(OH, broad), 3100-3050, 3000-2800, 1650(C=O), 1585(C=N), 1485, 1440, 1390, 1380, 1300, 770, 700cm^{-1}.

Reduction of (106) with sodium borohydride.

The hydroxyformylidene derivative (106) (1.5g) in ethanol (150 ml) was heated for 48 hours in the presence of $NaBH_4$ (3.25g). The syrup (1.2g) obtained following isolation using procedure (h) was analysed by t.l.c. (system 1) and showed 2 components R_f 0.63, 0.54. The syrup was purified by preparative thin layer chromatography (4 plates) eluant system 17. Desorption of the least polar band using ethyl acetate afforded (150) (400 mg, 28%), identical in all respects (m.p., m.m.p., t.l.c., i.r., p.m.r.) to an authentic sample.

The polar band was desorbed in a similar fashion to yield (193) as a mixture of diastereoisomers (250 mg, 18%) as lustrous silver flakes, m.p. 181°- 186°; t.l.c. (system 1) R_f 0.54 (fluorescent); νmax(KBr): 3260(N-H), 3020, 3000-2870, 1630(C=O), 1480, 1450, 1435, 1305, 790, 695, 650cm^{-1}; δ(90MHz,d_6DMSO): 1.02(1H,J_{AB}7Hz, >CH-CH_3), 1.147(2H,d,J 6Hz,>CH-CH_3), 1.30-2.56(3H,m,-CH_2>CH-CH_3), 3.408-3.574(2H,m,>N-CH_2-CH_2-) 4.462($\frac{2}{3}$H,d,J 7.4Hz, >N-CH-CH(CH_3),(Trans)), 4.980($\frac{1}{3}$H, d,J 4.8Hz, >N-CH-CH(CH_3),(Cis)), 6.698-6.816(4H,m,C-5-H,C-6-H,C-7-H,N-H), 7.599(1H,m,C-8-H). m/e 202 [$M^{+\cdot}$] (76%); (Found: C, 71.3; H, 7.1; N, 13.6. $C_{12}H_{14}N_2O$ requires C, 71.3; H, 6.95; N, 13.85%.)

Reduction of (150) with sodium borohydride.

(150) (820 mg) in ethanol (100 ml) was heated at reflux with $NaBH_4$ (500 mg, 3.2 mol.equiv.) for 8 hours t.l.c. (system 1) indicated a fluorescent component R_f 0.54. A white solid (780 mg) was obtained using procedure (h). This was purified by preparative t.l.c. (3 plates) eluant system 17. Desorption with ethyl acetate of this fluorescent band gave silver needles of (193) (110 mg, 13%) which had identical R_f and i.r. characteristics to an authentic sample.

Reaction of (1) with potassium hydroxide and formaldehyde.

Potassium hydroxide (33 g, 27 mol.equiv.) and paraformaldehyde (78g, 113 mol.equiv.) were added portionwise over 8 hours to a solution of (1) (4g) in ethanol (180 ml). On cooling the suspension was neutralised with sodium bicarbonate and the ethanol removed on the rotary evaporator. The aqueous suspension was extracted with dichloromethane (3 x 150 ml), and the organic extracts dried. Concentration of these extracts under reduced pressure yielded an ochre syrup (4.5g). The original aqueous suspension was reduced in volume and extracted with dichloromethane (2 x 100 ml). Drying and concentration of these extracts

yielded a colourless crystalline material (700 mg) which was recrystallised from ethanol to give colourless needles of the diol, 2,3-dihydro-3,3-dihyroxymethyl pyrrolo[2,1-b]quinazolin-9(1H)-one (196) (500 mg, 11%) m.p. 207.5-209° (dec), t.l.c. (system 1) R_f 0.17; νmax(KBr): 3700-3200(OH, peaks at 3470 and 3290), 1670(C=O), 1620(C=N), 1470, 1395, 1345, 1040, 780, 700cm^{-1} ; λmax($CHCl_3$): 245(ξ 8500), 270(ξ 6200), 304(ξ 3600), 316 nm(ξ 3100); δ(90MHz,d_6DMSO): 2.319(2H,t,J_{AB}7.4Hz,>N-CH_2-CH_2-), 3.624(2H,d,J 5.5Hz, -CH_2OH, 3.683(2H,d,J 5.5Hz,-CH_2OH), 3.993(2H,t,J_{AB}7.7Hz, >N-CH_2-CH_2-), 4.946(2H,t,J 5.5Hz, D_2O exchangeable, 2 x OH), 7.426-7.9(3H,m, aromatic portons), 8.134(1H,m,C-8-H). On deuteration the hydroxyl protons signal δ 4.946 disappeared as expected and the signals at δ 3.624 and δ 3.683 were simplified to 2 singlets; m/e 246 [$M^{+\cdot}$] (19%); (Found: C, 63.1; H, 5.8; N, 11.2. $C_{13}H_{14}N_2O_3$ requires C, 63.4; H, 5.7; N, 11.4%).

The ochre syrup was chromatographed on silica gel (100g) and elution with system 11 gave (1) (400 mg) identical in all respects to an authentic sample (m.p., m.m.p., i.r.). The earlier fractions from the column were combined and concentrated **in vacuo**. The colourless syrup (1.8g) was separated into its pure components via preparative t.l.c. (6 plates) using system 15 as eluant. Desorption of the least polar band with ethyl acetate

gave on concentration 2,3-dihydro-3-methylenepyrrolo [2,1-b]quinazolin-9(1H)-one (194) (670 mg, 17%) as colourless needles identical in all respects (i.r., R_f, p.m.r.) to an authentic sample but with a sharper m.p. 144 - 145°. Similar treatment of the second band gave a thick orange syrup (800 mg) which crystallised from ether as colourless needles of 3-ethoxymethyl-2,3-dihydro-3-hydroxymethylpyrrolo[2,1-b]quinazolin-9(1H)-one (197) (700 mg, 13%), m.p. 82-84°; t.l.c. (system 11) R_f 0.57; νmax (KBr): 3580, 3510(OH, doublet), 3000 - 2850, 1675(C=O), 1615(C=N), 1560, 1470, 1390, 1380, 1100(C-O), 1060(C-O), 770, 695cm^{-1}; λmax($CHCl_3$): 245(ξ 6400), 270(ξ 6200), 304(ξ 3300), 311nm(ξ 2900); δ (60MHz, d_6DMSO): 1.06(3H,t,J_{AB}7Hz, -O-CH_2-CH_3), 2.38(2H,t,J 7.2Hz,>N-CH_2-CH_2-), 3.10-5.80(9H,m, >N-CH_2-CH_2-C<$\frac{CH_2\text{-}OH}{CH_2\text{-}O\text{-}CH_2\text{-}CH_3}$), 7.10-7.70(3H,m, aromatic protons), 8.10(1H,d, J 7.2Hz, C-8-H); m/e 274 [$M^{+\cdot}$] (8%), 199 (100%); (Found: C, 63.3; H, 6.7; N, 9.8. $C_{15}H_{18}N_2O_3$ 0.5H_2O requires C, 63.6; H, 6.36; N, 9.9%).

2,3-Dihydropyrrolo[2,1-b]quinazolin-9(1H)-one-3-spiro-1^1-cyclohex-2^1-en-4^1-one (190).

The 3-hydroxymethylene compound (106) (1g), triethylamine (0.5 ml) and methyl vinyl ketone (500mg, 1.5 mol.equiv.) were heated on a steam bath for 18 hours. The thick black syrup produced was chromatographed on silica gel (20g)

using system 13 as eluant. The crude pink orange syrup (600 mg) thus obtained was further purified by separation on 3 preparative t.l.c. plates. Desorption with ethyl acetate and concentration under reduced pressure produced an orange syrup which crystallised from ethyl acetate/cyclohexane as colourless prisms of (190) (350 mg, 28%). m.p. 169°- 170° t.l.c. (system 1) R_f 0.73. νmax(KBr): 3150-2850, 1680, 1690, 1685, 1670 (multiple bands 2 x C=0), 1620, 1615, 1610(multiple bands C=C and C=N), 1470, 1390, 1340, 1320, 1285, 790, 705cm^{-1}; δ(90MHz,d_6DMSO): 2.158-2.709(6H,m,>N-CH_2-CH_2><C=C CH_2-CH_2>=0), 3.925-4.311(2H,m, >N-CH_2-CH_2-), 6.057(1H,d,J 10.07Hz ><H-C=C-H> = 0), 7.062(1H,d,J 10.06Hz, ><H-C=C-H> = 0 7.416-7.909(3H,m, aromatic protons), 8.110-8.320(1H,m, C-8-H); (Found: C, 70.9; H, 5.4; N, 10.0. $C_{16}H_{14}N_2O_2$ 0.25 H_2O requires C, 70.98; H, 5.4; N, 10.35%).

Organometallic Reactions of Deoxyvasicinone Analogues.

3,3-Dicarbethoxy-2,3-dihydropyrrolo[2,1-b] quinazolin-9(1H)-one (168).

A solution of (1) (930mg) in dry tetrahydrofuran (20 ml) was added dropwise over 30 minutes to a solution of lithium diisopropylamide (prepared by the addition of n-butyllithium solution (6.75 ml, 1.6 mol. in hexane) to anhydrous diisopropylamine (1.02g) in dry

tetrahydrofuran (10 ml) at -20°. Ethyl chloroformate (4.4g, 8 mol.equiv.) in dry tetrahydrofuran (10ml) was added slowly. The burgundy colour was rapidly discharged and the mixture became pale yellow and finally bottle green. The mixture was stirred at room temperature for 1 hour, solvents removed **in vacuo** and the residue partitioned between water (100 ml) and dichloromethane (3 x 100ml). The combined, dried organic extracts were concentrated **in vacuo** to yield a colourless syrup (168). The syrup was chromatographed on silica gel (20g). Elution with system 7 gave (168) as colourless plates, (460 mg, 28%), identical in all respects (m.p., m.m.p., i.r.) to an authentic sample.

3,3-Dicarbethoxy-2,3-dihydro-1,1-dimethylpyrrolo[2,1-b]quinazolin-9(1H)-one (174).

(152) (4.28g) was metallated according to procedure (i) (replacing (1) for (152)). Ethyl chloroformate (8.68g, 4 mol.equiv.) in dry tetrahydrofuran (20 ml) was slowly added to the red solution. The mixture was stirred at room temperature for 1.5 hours, water (5ml) was added and after 1 hour the yellow solution was concentrated **in vacuo** to afford an orange syrup. t.l.c. analysis (system 2) indicated 2 major componenets, R_f 0.65, 0.72. The syrup was chromatographed on silica gel (120g) and elution with system 6 gave an orange syrup which was

crystallised using ether/light petroleum. Recrystallisation of this solid using the same solvents afforded (174) as colourless prisms (3.00g, 58%), m.p. 91°, t.l.c. (system 2) R_f 0.72; νmax(KBr): 3080-2950; 1755, 1730, 1720(C=O, ester, multiple bands), 1680(C=O, ring), 1620, 1610(C=N), 1470, 1390, 1370, 1355, 1330, 1305, 1290, 1280, 1260, 1240(C-O, ester, multiple bands), 1020, 780, 700cm^{-1}; δ(60MHz, $CDCl_3$): 1.30(6H,t,J_{AB} 7Hz, 2 x -OCO-CH_2-CH_3), 1.72(6H,s, >C(CH_3)$_2$), 2.80(2H,s,>N-C(CH_3)$_2$-CH_2-C<), 4.30(4H,q,J_{AB}7Hz, 2 x -OCO-CH_2-CH_3), 7.07-7.78(3H,m aromatic protons), 8.13(1H,d,J 7.2Hz, C-8-H); m/e 358 [$M^{+\cdot}$] (51%); (Found: C, 63.7; H, 6.2; N, 7.7. $C_{19}H_{22}N_2O_5$ requires C, 63.7; H, 6.1; N, 7.8%).

Further elution with ethanol gave unreacted starting material (152) (1.21g), identical in all respects (m.p., m.m.p., i.r.) to an authentic sample. The yield of (174) is based on the recovery of this starting material.

Reaction of lithiated (1) with ethylbromopyruvate.

A solution of lithiated (1) was prepared from (1) (1.86g) using method (i). To the cold stirring solution was slowly added ethyl bromopyruvate (2.92g, 1.5 mol.equiv.) in dry tetrahydrofuran (20 ml). After 1 hour the solution was allowed to rise to room

temperature. t.l.c. (system 1) of the resulting brown solution indicated extensive decomposition had taken place in the mixture and the experiment was abandoned.

Reaction of lithiated (1) with acetyl chloride.

A solution of lithiated (1) was prepared from (1) (1.86g) using method (i). Acetyl chloride (2g, 2.5 mol.equiv.) in dry tetrahydrofuran (10ml) was added dropwise to the cold stirring solution. The resultant orange solution was allowed to stir at room temperature for 1 hour t.l.c. (system 1) indicated a complex mixture the individual components of which could not be isolated.

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