APPROACHES TO THE SYNTHESIS OF TELEOCIDINS A AND B

A thesis presented by

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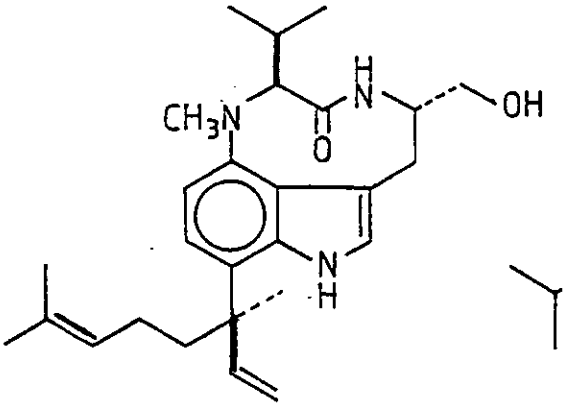
Approaches to the Synthesis of Teleocidins A and B

ABSTRACT

The isolation, biosynthesis, chemistry and synthesis of naturally occurring 3-alkyl-4-heterodisubstituted indoles is reviewed. The isolation and biology of Teleocidins A (1) and B (2) is also discussed.



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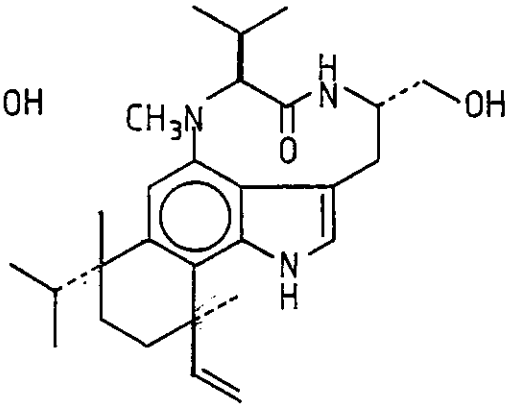

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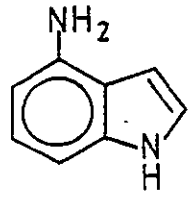
In studies directed towards the synthesis of Teleocidin A (1) a number of new reactions have been discovered. Investigation of alternative routes to 4-aminoindole (3) resulted in three new syntheses of this key intermediate. Selective mono-4-N-alkylation of (3) gave a series of compounds (4) that underwent a facile and novel rearrangement to 1-alkyl-4-aminoindoles (5). Dialkylation of 4-aminoindole to give N,N-dialkylamino acids necessitated the use of a novel procedure to reduce dehydroamino acids.



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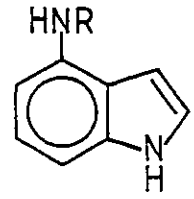

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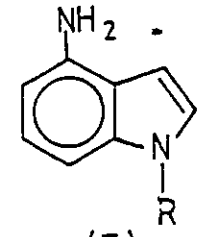
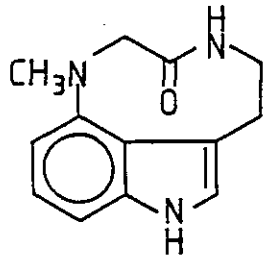


(5)

Treatment of 4-aminoindoles with electrophiles proceeded with poor and unusual regioselectivity under standard conditions. A new methodology was therefore developed to permit the regiospecific preparation of 3,4 or 4,7-disubstituted indoles.

The pyrrolo-1,4-benzodiazonin-3-one skeleton (6) of Teleocidin A was prepared by a standard peptide coupling procedure from the appropriate 3,4-disubstituted indole. The ring system (7) has also been prepared with the ring functionality of the natural product. X-Ray crystallographic analysis confirmed the structure of the cis isomer of (7). Also a de-azamethyl analogue (8) of (6) was prepared efficiently.



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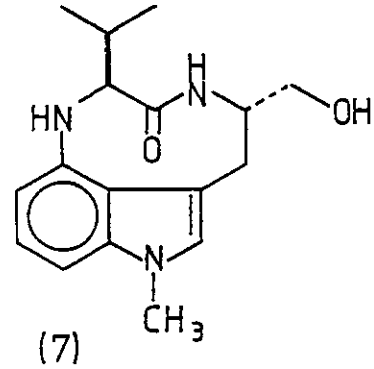

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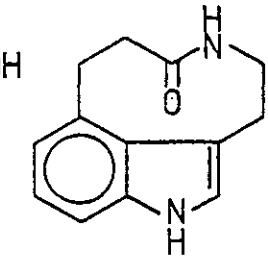

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An alternative route to the tricyclic skeleton of Teleocidin A through carbon-carbon bond formation at the

indole C-3 position of a 4-aminoindole proved unsuccessful.

Introduction of the linalyl moiety of Teleocidin A by either an aza-Claisen rearrangement of 1-geranyl-4-N,N-dialkylamino indoles or by more direct means also proved unsuccessful. It was found, however, that the geranyl group was introduced directly to the indole C-7 position in a modest yield.

Attempts to synthesise a crystalline derivative of Teleocidin A for X-ray analysis failed and a possible explanation for this failure discussed. Further characterisation of the natural product was undertaken by a nuclear Overhauser effect study and by a series of variable temperature high field ^{1}H n.m.r. experiments.

TO MY PARENTS

"All the business of war, and indeed all the business of life, is to endeavour to find out what you don't know by what you do; that's what I called 'guessing what was at the other side of the hill'."

Attributed to the Duke of Wellington,
The Croker Papers 1885, vol iii, p. 276

ACKNOWLEDGEMENTS

I wish to thank Dr. Steven V. Ley for the opportunity of working with him and for his friendship and advice. I would similarly like to thank Dr. John Ruddock of Pfizer Central Research, my industrial supervisor.

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Finally I wish to thank the Science and Engineering Research Council and Pfizer Central Research, Sandwich, Kent for the provision of a C.A.S.E. grant.

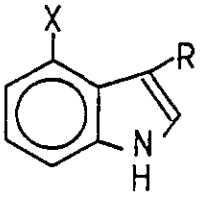
CONTENTS

NATURALLY OCCURRING 3-ALKYL-4-HETERODISUBSTITUTED INDOLES

1. Introduction

3,4-Dialkylsubstituted indoles, epitomised by the extensive range of ergot alkaloids, have been known for many years and their chemistry has been studied extensively. Two recent reviews[1,2] and several total syntheses[3-6] demonstrate the great interest still shown in this important group of compounds.

3-Alkyl-4-heterodisubstituted indoles (1) by contrast however, occur only rarely in nature, being represented by three small structurally quite simple groups of compounds:- (a) 4-chloroindole-3-acetic acid and related compounds, (b) psilocybin and other 4-hydroxytryptamines and finally (c) the most recently isolated group of compounds based on chuangxinmycin, which have been shown to contain a 4-thio substituent.

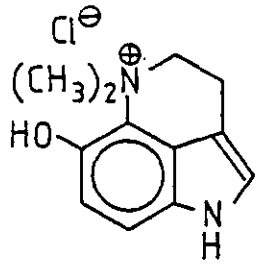


X = O, S, Cl
R = Alkyl

(1)

A number of more highly substituted 4-heteroindoles have also been isolated from a variety of sources but will not be discussed in this review. These include the interesting tricyclic compound dehydrobufotenine[7] (2) from Bufo marinus, a South American toad, the structure of which has been confirmed by total synthesis[8] and

amarorine (3) and amaroridine (4) from the bark of Amaroria soulameoides Gray[9].



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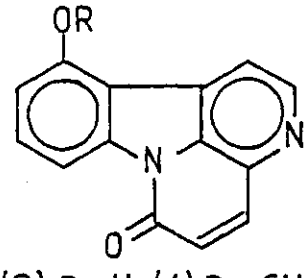
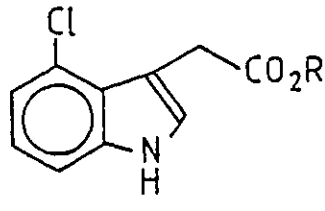


(3) R=H (4) R=CH_3

2. 4-Chloroindole-Acetic Acid (5) and Related Compounds

(i) Isolation and Occurrence

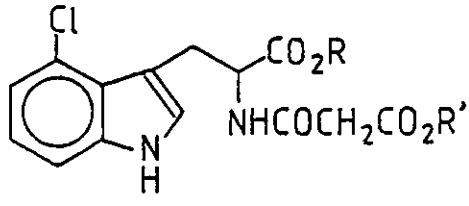
During the latter half of the 1960's two groups[10-12] reported the isolation of the new indole auxins (5) and (6) from the immature seeds of Pisum sativum (pea). These compounds were identified by spectral methods and, somewhat unusually in natural product chemistry, by comparison of the physical properties with previously synthesised authentic samples (vide infra).

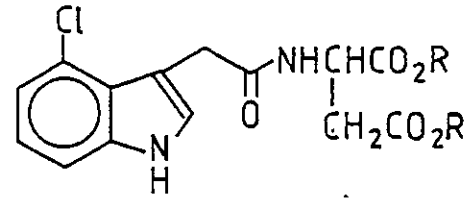


(5) R=H (6) R=CH_3

From the natural source these compounds are isolated in only very small amounts. For example only 3.8 mg of acid (5)[11] and 25 mg of the ester (6)[12] were obtained from 276 Kg of immature seeds of Pisum sativum. That the ester was not an artefact of the isolation procedure was shown by the similarity in auxin activity of neutral and acidic fractions when different solvents were used for their extraction[11].

Shortly after these reports Hattori's group also reported the presence of three other components (7-9) possessing auxin-like activity from the acidic fraction of the methanol extract of immature seeds of Pisum sativum[13,14]. These compounds were isolated as their methyl esters (10 - 12) and were identified as before by comparison with synthetic material (vide infra).





(7) R = H; R' = CH_2CH_3

(8) R = H; R' = CH_3

(9) R = H; R' = CH_3 or R = CH_3; R' = H

(10) R = CH_3; R' = CH_2CH_3

(11) R = R' = CH_3

(12) R = R' = CH_3

Optical rotatory dispersion studies on the ester (10) showed the presence of the unusual D-tryptophan. It was shown in a similar manner that aspartic acid, obtained by acid hydrolysis of (9) was of the natural L-absolute configuration. Counter current distribution experiments with an ethyl acetate/ tartrate buffer pH 4.1 suggested the presence of a monocarboxylic acid in (9). It was not, however, possible to determine which of the two carboxyl groups was methylated.

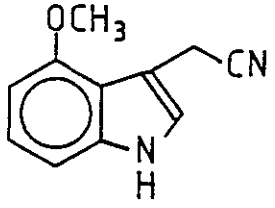
The biological activities of the compounds (7 - 9) are of some interest. For example a mixture of (7) and (8) induced hypocotyl swelling of Phaseolus mungo after some 60 h. Compound (9) however induced the same effect after only some 24 h, which is similar to 4-chloroindoleacetic acid (5). This observation suggests that (7) and (8) are the biosynthetic precursors of (5).

Since these early reports, improvements in chromatographic methods[15] have enabled resolution of the five chloro substituted-3-indole acetic acids, to give a rapid unequivocal method for determining the substitution pattern of the indole moiety. Perhaps of greater significance has been the development of gas chromatography-mass spectroscopy techniques to identify (1)[16,17]. These advances resulted in the discovery that (5) was widely distributed in the plant kingdom. It has been found to be present in Vicia faba[18,19] (Vetch), Lathyrus latifolius[18]

(Everlasting Pea) and amongst a number of higher indole-3-carboxylic acids in Pinus sylvestris[20] (Scots Pine).

An alternative assay method using autoradiography to determine (5) using a ^{36}Cl label proved less reliable[21].

Finally in this section, Nomoto and Tamura[22] have reported the interesting methoxy compound (13). This was isolated from the neutral fraction obtained from the extraction of club roots of Brassica pekinensis (Chinese Cabbage) infected with the fungus Plasmodiophora brassicae. However assay of (13) in the Avena coleoptile straight growth test showed no auxin-like activity.



(13)

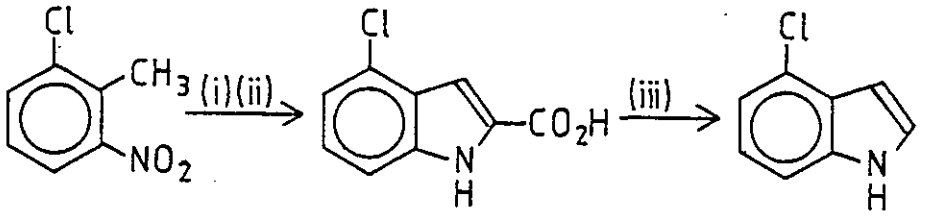
(ii) Synthesis

As has already been mentioned, (5) has the unusual distinction of being one of the few natural products to be isolated after its total synthesis and biological activity had been reported in the literature.

Indole-3-acetic acid has been known as a growth hormone for many years and a number of syntheses have been described[23] which will not be discussed here. During investigations of this auxin-like activity a number of substituted indole-3-acetic acids have been prepared, including (5).

4-Chloroindole (14), the intermediate most frequently used for the synthesis of (5), has been prepared regiospecifically by a variety of methods. Uhlés Reissert synthesis of (14) reported in 1949[24] (Scheme 1), which has been subsequently modified by Rydon and Tweedle[25], has been widely used. Although only moderate yields are obtained, reactions are facile and product isolation easy.

SCHEME 1

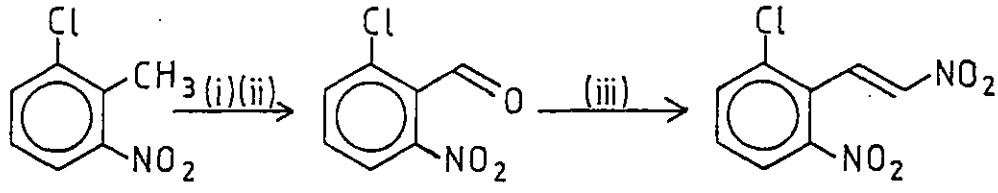


(15) (16) (14)

(i) Diethyloxalate,Na (or K), EtOH. (ii) $Na_2S_2O_4$ or, $FeSO_4/NH_4OH$. (iii) CuCl, quinoline. reflux.

A Russian group prepared the substituted benzaldehyde (17) from (15) in two stages, which gave the

intermediate nitrostyrene (18) with nitromethane and base. Reduction gave the product (14) in an acceptable yield[26] (Scheme 2).



(15) (17) (18)

(iv)

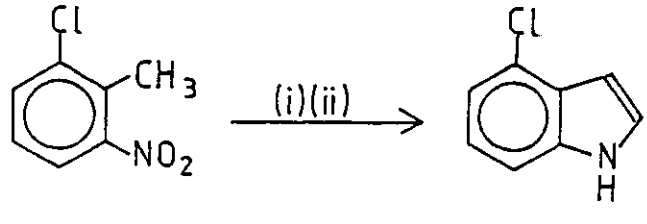
(14)

SCHEME 2

(i) N.B.S. (ii) Pyridine, $(CH_3)_2NC_6H_4NO$, 68% overall (iii) CH_3NO_2, base, 60%. (iv) Fe/AcOH/EtOH, 85%.

More recently Leimgruber and Batcho[27] reported the sythesis of (14) in only two stages (Scheme 3). This process is clearly an important development in 4-substituted indole synthesis.

SCHEME 3

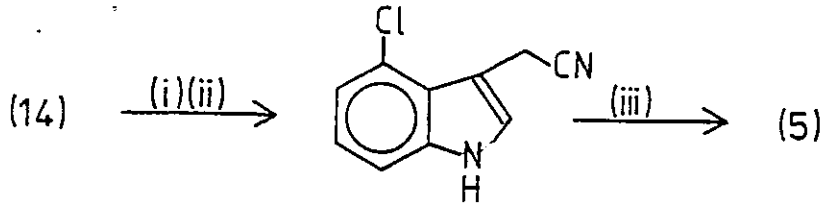


(15) (14)

(i) $(CH_3)_2NCH(OCH_3)_2$ (ii) [H]

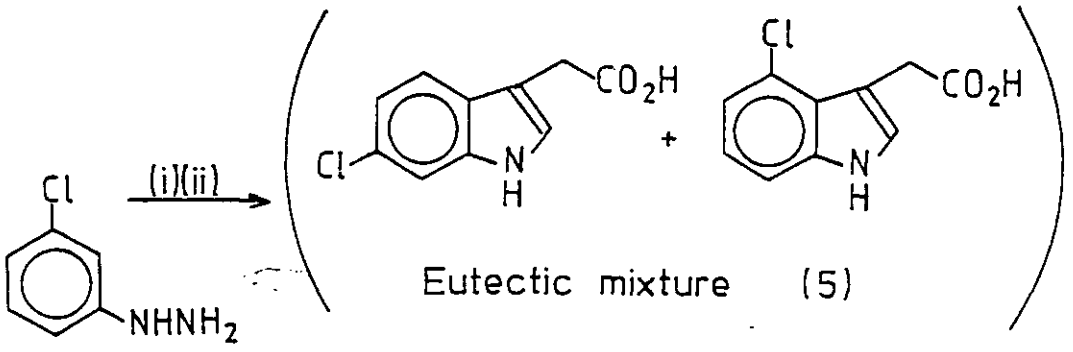
Preparation of (5) from 4-chloroindole (14) has been reported by two groups. Fox and Bullock reported that the magnesium salt of 4-chloroindole (14) on treatment with chloroacetonitrile followed by hydrolysis gave (5) in only 19% yield [28] (Scheme 4). This same group were unsuccessful in attempts at preparing (5) by a classical Fischer indole synthesis from succinaldehydic acid phenylhydrazone (Scheme 5). Hansch's group obtained (5), again in poor yield, by conventional reaction of the gramine (19) with potassium cyanide, followed by hydrolysis[29] (Scheme 6).

SCHEME 4



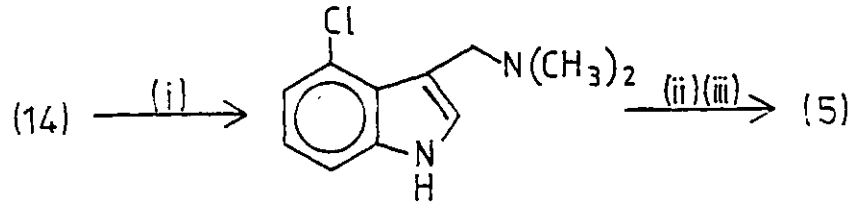
(i) CH_3MgI, Et_2O. (ii) $ClCH_2CN$. (iii) HO^- 19% overall.

SCHEME 5



(i) $(CH_3O)_2CHCH_2CH_2CO_2CH_2CH_3$, H_2SO_4. (ii) KOH.

SCHEME 6

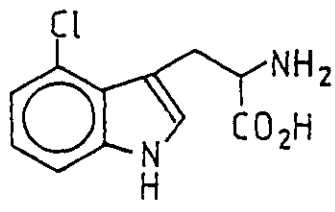


(19)

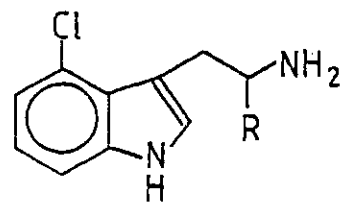
(i) HCHO, $(CH_3)_2NH$, AcOH 91%. (ii) KCN, H_2O, EtOH. (iii) KOH 19% overall.

These poor yields may be accounted for by the steric bulk of the chloro-substituent. It has been reported that oxalyl chloride, which reacts smoothly and rapidly with indole and 6-chloroindole, reacts only slowly and incompletely with 4-chloroindole and not at all with 4-bromoindole[30].

4-Chlorotryptophan (20) has been prepared by two groups [25,31] and is also reported to be a plant growth hormone. 4-Chlorotryptamines (21) have also been synthesised. These compounds are claimed to possess stimulant and anticonvulsant activities in rodents and to induce behavioural changes in cats[32].



(20)

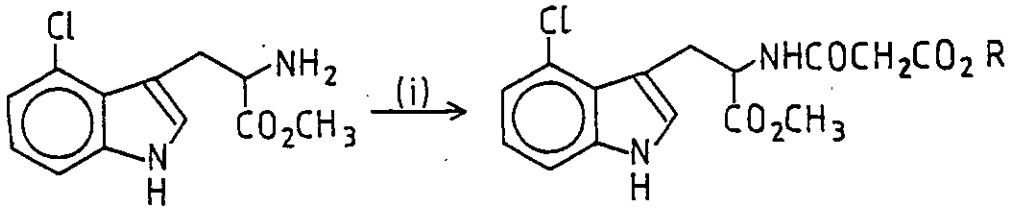


(21) R = CH_3, CH_2CH_3

The ester (6) is readily prepared by treatment of (5) with diazomethane[12].

The methyl esters (10) and (11) were synthesised from 4-chlorotryptophan methyl ester (22) by treatment with malonyl chloride and triethylamine in ethanol and methanol respectively[13] (Scheme 7).

SCHEME 7



(22) (10) R = CH_2CH_3

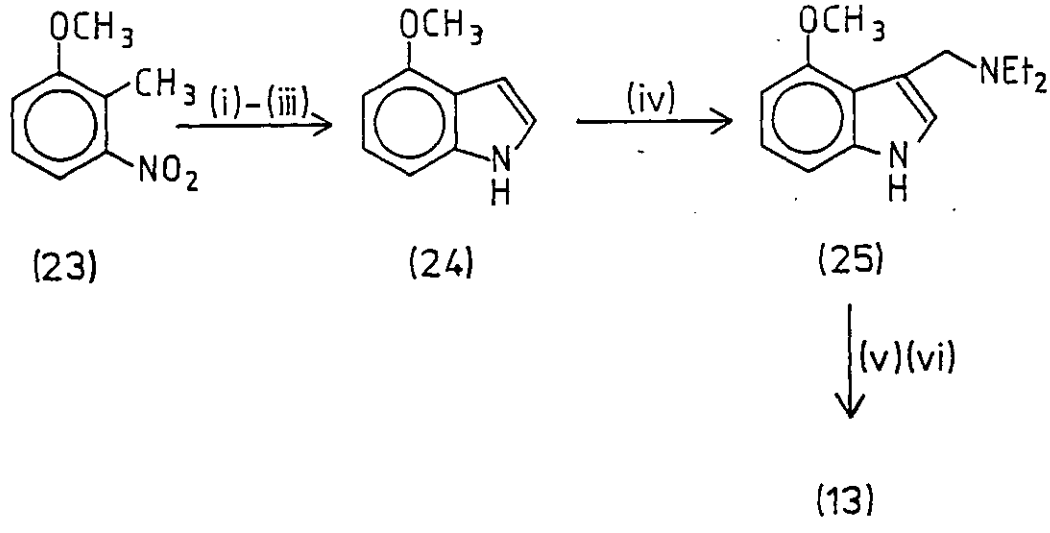
(11) R = CH_3

(i) $ClCOCH_2COCl$, Et_3N, ROH.

Condensation of the mixed anhydride from (5) and ethyl chlorocarbonate with L-aspartic acid dimethyl ester gave (12)[14].

The 4-methoxyindole (13) has been prepared as an intermediate in the synthesis of 5- and 8-methoxyyobyrines[33]. The methoxy-2-nitrotoluene (23) was converted to 4-methoxyindole (24) in three stages with a 23% overall yield. Preparation of the gramine (25) followed by treatment with dimethyl-sulphate and sodium cyanide gave (13) in 53% yield (Scheme 8).

SCHEME 8



(23) (24) (25)

(13)

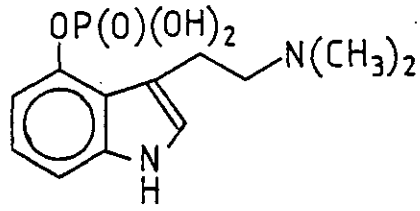
(i) Diethyl oxalate, K, EtOH. (ii) [H]. (iii) Δ 23% overall. (iv) Et_2NH, AcOH, HCHO. (v) $(CH_3)_2SO_4$, THF, AcOH. (vi) NaCN, H_2O, dioxan, 53% overall.

3. Psilocybin (26) and Psilocin (27)

(i) Isolation

The Mexican Indians are known to have used mushrooms possessing hallucinogenic properties in religious ceremonies for many hundreds of years[34-37]. It was only in 1957 however that these basidiomycetes were identified as agarics belonging to the species Psilocybe[38]. In 1958 and 1959 Hofmann and his co-workers reported the isolation of the hallucinogenic constituents of these mushrooms classified as Psilocybe mexicana Heim[39]. The major component psilocybin (26) was characterised as the phosphate ester of the other component psilocin (27),

a 4-hydroxytryptamine[40-42]. This was the first report of the isolation of 4-hydroxyindoles and in addition, the first report of a phosphorylated hydroxyindole from natural sources.



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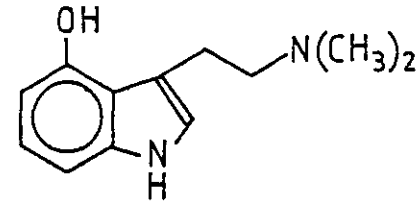


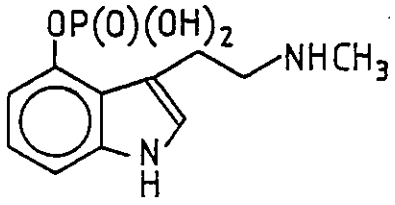
(27)

The structures of these two alkaloids were confirmed by unambiguous chemical synthesis[40,42] and later by X-ray crystallographic studies[43,44].

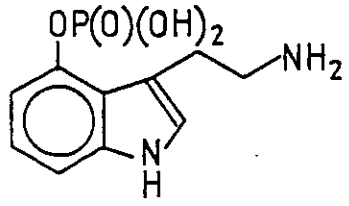
Following this first report of the isolation of (26) and (27) they have since been shown to have a worldwide distribution in Psilocybe species[45-47]. For example, Psilocybe semilanceata found in Europe and the U.K. contains both (26) and (27)[48,49]. Other groups of basidiomycetes such as Panaeolus[50] and Conocybe[51,52] have also been reported to produce (26) and (27). The precise taxonomy of some of these species however appears to be uncertain and so early reports of the presence of (26) and (27) in apparently different species need to be treated with some caution[53].

With the improvement in chromatographic techniques in recent years a further two hydroxy-indoles related to (26) have been isolated from

P. semilanceata[54], P. baeocystis[55-57] Conocybe, Panaeolus and Copelandia species[53,57,58]. These have been designated baeocystin (28) and norbaeocystin (29). These compounds always occur in the presence of psilocybin (26) and psilocin (27) and are thought to be biosynthetic precursors of (26) and (27). Although these desmethyl compounds have only been characterised quite recently, unidentified minor indole constituents of Psilocybe extracts had been reported previously[52].



(28)



(29)

Psilocybe cubensis (Earl) Singer has been grown under controlled culture conditions and the level of (26) and (27) measured from successive harvests of the carpophores[59]. Interestingly it was shown that while the levels of (26) remained essentially constant with successive harvests, the levels of (27) rose from none from the first harvest to a maximum after the fourth.

Submerged cultures of P. cubensis achieve maximum production of (26) after seven days at pH 4.Ø - 4.6 after which time the levels of (26) slowly decline. Extraction of mycelia grown in a glucose free medium produced no psilocybin (26)[6Ø].

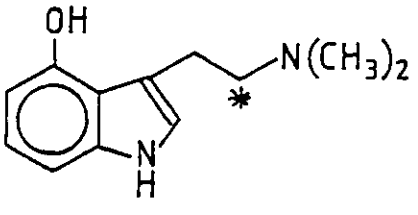
A considerable effort has been devoted to developing quantitative techniques for measuring (26) and (27) from carpophores of various Psilocybe species[61-64]. This is partly due to the concern of regulatory authorities over the illicit use of hallucinogenic mushrooms. Reports on the levels of (26) and (27) in different mushrooms must however be treated with care since it has been shown that differences in the method of drying sporophores has very significant effects on the levels of (26) and (27). Freeze drying of the sample is now thought to be the best way of preserving (26) and (27).

(ii) Biology of Psilocybin (26) and Psilocin (27)

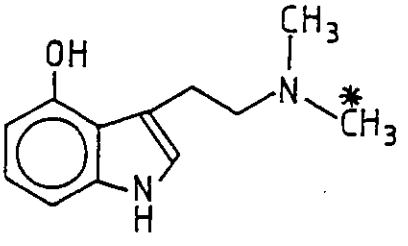
The pharmacological actions of (26) and (27) are qualitatively and quantitatively so similar[65] that it is thought that (26) is dephosphorylated in the mammalian body to (27) by a non-specific monophosphoesterase. Indeed it has been shown that incubation of (26) with purified calf intestinal alkaline phosphatase produced (27) and inorganic phosphate[66]. In addition, the intact mouse[67] and rat kidney homogenates[68] caused rapid dephosphorylation of (26) to give (27).

The metabolic fate of psilocin (27) is uncertain. One report based on the metabolism of radiolabelled psilocin species (30) and (31) suggests that some 25% of psilocin (27) administered to rats is recovered in the urine. Small quantities of material which had undergone oxidative demethylation of the side chain

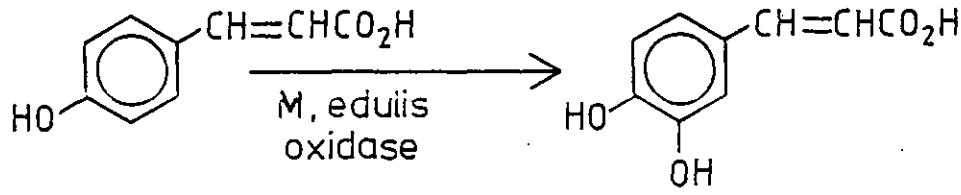
(4%) and unidentified "highly hydrophilic substances" were also isolated[69]. Horita and Weber[68], however, report that rat kidney homogenates cause psilocin (27) to undergo oxidation to a deep blue substance which they postulate to be an o-quinone. This oxidase action was shown to be fastest in the heart of all species studied. The oxidase action of this enzyme is that of a phenolase, since it is inhibited by cyanide but not by standard monoamine oxidase inhibitors such as β-phenyl isopropylhydrazine and its optimal activity was at pH 9.0. Caeruloplasmin from pig plasma[70] and a purified enzyme from Mytilus edulis (edible mussels)[71] also oxidised (27). In the latter case it was demonstrated that oxygen was consumed and hydrogen peroxide produced. Another substrate of this mussel oxidase enzyme was shown to be 4-coumaric acid (32) which was converted to the 1,2-dihydroxy compound (33).



(30)



(31)

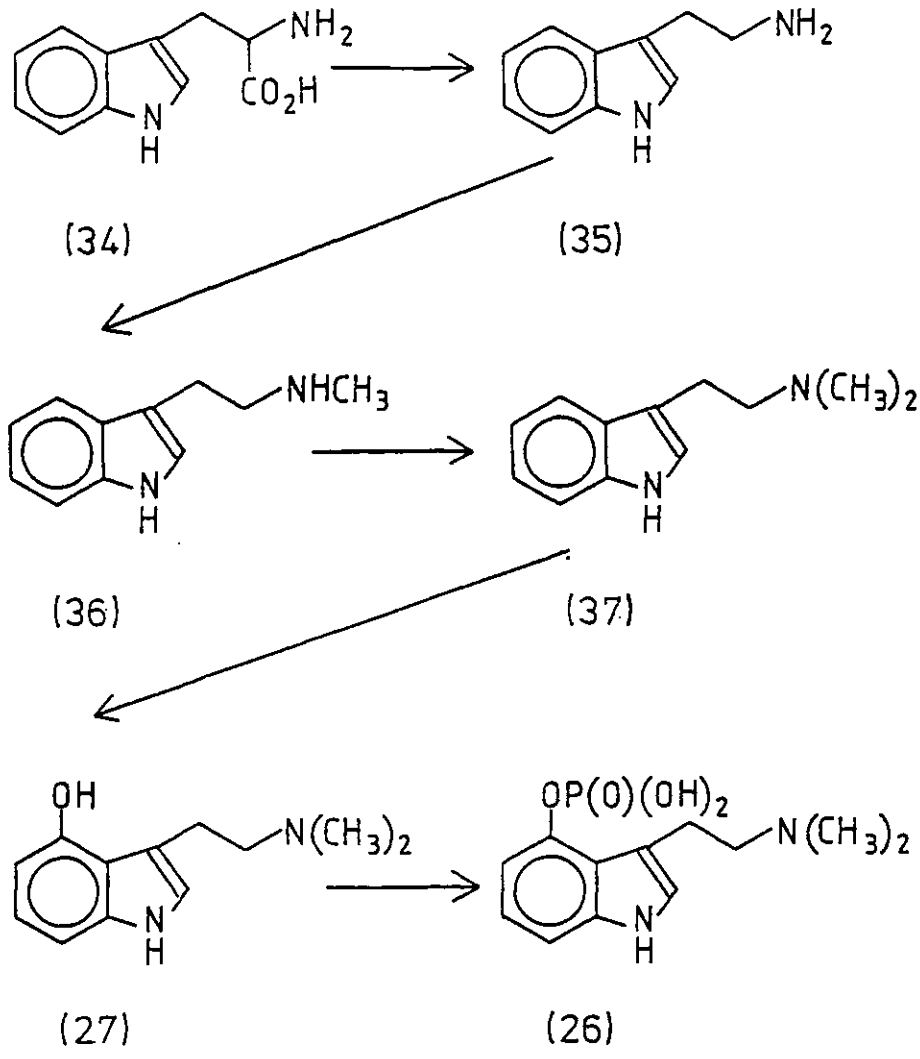


(32) (33)

It has been observed that the stipe and pileus of psilocybin (26) and psilocin (27) containing mushrooms frequently exhibit a blue green staining[52,72]. It has also consistently been found that psilocybin (26) is present in greater quantities than psilocin (27) and that the latter is sometimes completely absent from mushrooms containing the former. Enzymatic oxidation of psilocin (27) in carpophores would account for both these observations[73], psilocybin (26) being resistant to phenoloxidase action through its phosphate ester.

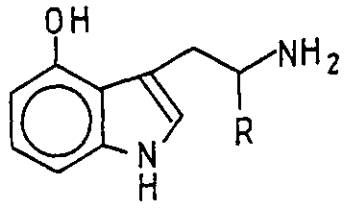
No definitive biosynthetic pathway to psilocin (27) has been proposed. Brack's group[74] observed that psilocybin (26) was biosynthesised from tryptophan in still cultures of P. semperviva. Agurell and Nilsson in a more detailed study[75,76] prepared a series of radiolabelled indoles which they considered to be potential biosynthetic precursors of psilocin (27). From feeding experiments with these compounds in submerged cultures of P. cubensis a biosynthetic pathway (Scheme 9) was proposed. This

pathway does not however explain the occurrence of desmethyl compounds such as baeocystin (28) and norbaeocystin (29).



SCHEME 9

Further feeding experiments by the same group showed that 4-hydroxytryptamine (38) was also converted to psilocybin (26) but that 4-hydroxytryptophan (39) was not.



(38) R = H (39) R = CO_2H

In conclusion, biosynthesis of (26) and (27) has been shown to proceed from tryptophan (34) to tryptamine (35). From tryptamine (35) several alternative routes, of which only one has been positively identified, are available for the conversion of (35) to psilocin (27) and psilocybin (26).

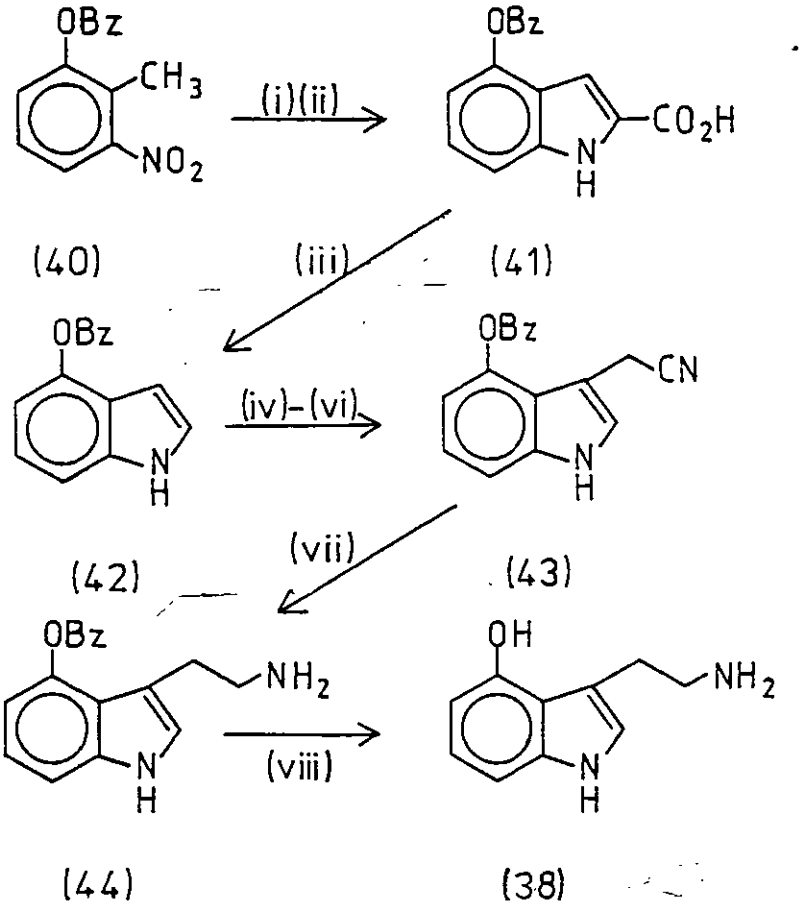
The pharmacology of psilocybin (26) and psilocin (27) has been studied extensively[77]. They have a low toxicity being some 2.5 times less toxic than mescaline. Lysergic acid diethylamide (L.S.D.) and psilocin (27) show cross tolerance suggesting that their behavioural effects may be mediated at a similar site in the central nervous system. Psilocybin (26), like L.S.D., has been used as an aid in psychotherapy and because of its minimal adverse reactions and shorter duration of action, (26) is being increasingly substituted for L.S.D.

(iii) Synthesis

As early as 1955, that is before the isolation and characterisation of (26) and (27), Hofmann's group had reported the synthesis of 4-hydroxy-tryptamine (38)[78]. This compound prepared by the

route outlined in Scheme 10 was one of a series of hydroxy-substituted indoles synthesised to compare with 5-hydroxytryptamine (serotonin). Synthesis of 4-benzyloxyindole (42) was accomplished according to the Reissert procedure[79,80]. Introduction of the 2-aminoethyl substituent proceeded smoothly via the gramine and nitrile to give the tryptamine (38).

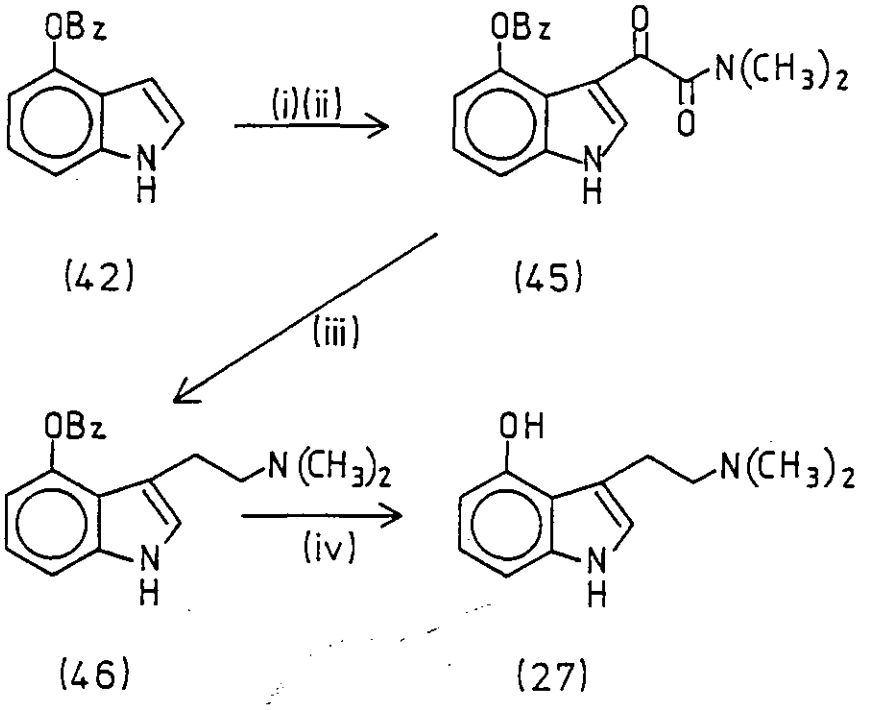
SCHEME 10



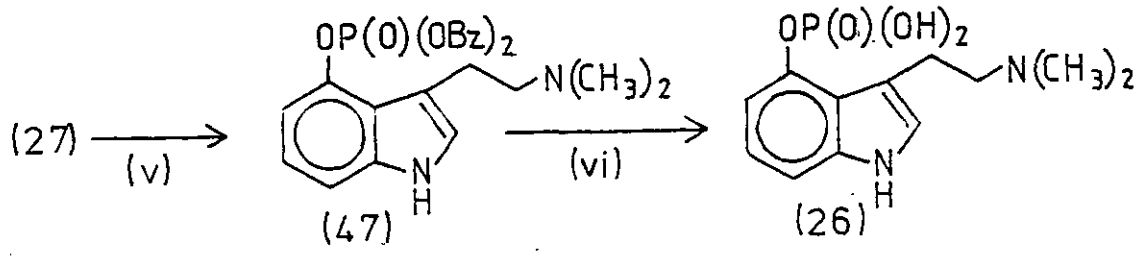
(i) Diethyl oxalate, KOEt. (ii) $Na_2S_2O_4$, 64% overall. (iii) Cu powder, quinaldine 62%. (iv) HCHO, Me_2NH, 89%. (v) CH_3I. (vii) NaCN, 60% overall. (vii) $LiAlH_4$ 81%. (viii) H_2/Pd/C, No yield

Psilocin (27) and psilocybin (26) were synthesised by the same group[42] using the more versatile oxalyl chloride procedure for introducing the 3-substituent, (Scheme 11). Phosphorylation proceeded in only a moderate yield with an overall yield for the conversion of (27) to (26) of 38%. A Japanese group however, who more recently attempted to repeat this conversion of psilocin (27) to psilocybin (26) using an identical procedure, only obtained 7.8% overall yield for the two stage synthesis[81].

SCHEME 11



SCHEME 11 (cont)

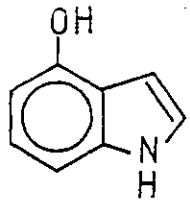


(i) Oxalyl chloride. (ii) $(CH_3)_2NH$, 73% overall. (iii) $LiAlH_4$ 85%. (iv) H_2/5%Pd/Al_2O_3, 81%. (v) (1) NaOH, H_2O, (2) $ClP(O)(OBz)_2$, 46%. (vi) H_2/5% Pd/C, 82%.

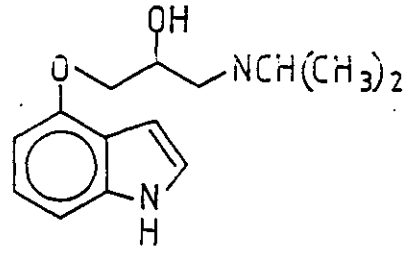
An interesting alternative approach to psilocin (27) reported by Julia and his co-workers involves the free radical hydroxylation of N,N-dimethyl tryptamine (37)[82-84]. Conversion of (37) to hydroxylated indoles results in a regioisomeric mixture of 4-, 5-, 6- and 7-hydroxy-N,N-dimethyl-tryptamines. Julia demonstrated, however, that by a careful choice of reaction conditions the desired 4-hydroxyindole (27) became the major product. In addition it was found that (27) was readily separated from the other regioisomers formed by chromatography, presumably due to intramolecular hydrogen bonding in (27). At pH 9 with a modified Fenton's reagent, in which iron (II) was replaced by copper (II) sulphate and ascorbic acid, exclusive 4-hydroxylation of (37) was observed. Unfortunately conversion to products (1.8%) and yield of psilocin (27) (9%) were too low to be of any synthetic value. Improved conversion to

products was observed at lower pH's where the quantity of oxygenated water had been reduced and the reaction performed under nitrogen with additional ethylene diamine tetra-acetic acid added to the Fenton reagent. Up to 20% conversion of (37) to products was observed under these conditions, of which some 70% consisted of hydroxyindoles. It was however found that the regiospecificity of the reaction had declined, the desired 4-substituted product (27) representing less than 50% of the hydroxylated material.

As has been shown (vide supra), synthesis of 4-hydroxyindole (48) in principal constitutes a total synthesis of psilocybin (26) and psilocin (27). Although the Reissert synthesis of indoles is generally efficient it has several stages and can give variable yields. In particular, decarboxylation of for example (41) is by no means easy and frequently requires drastic conditions. Recently further interest in 4-hydroxyindole (43) has arisen from the synthesis of pindolol (49), a potent and specific β-adrenoceptor blocking agent. Synthesis of this compound and a number of analogues employs 4-hydroxyindole (48) as an intermediate[85-88]. As a consequence several alternative routes to the hydroxyindole (48) have been developed, a number of which will be considered here.



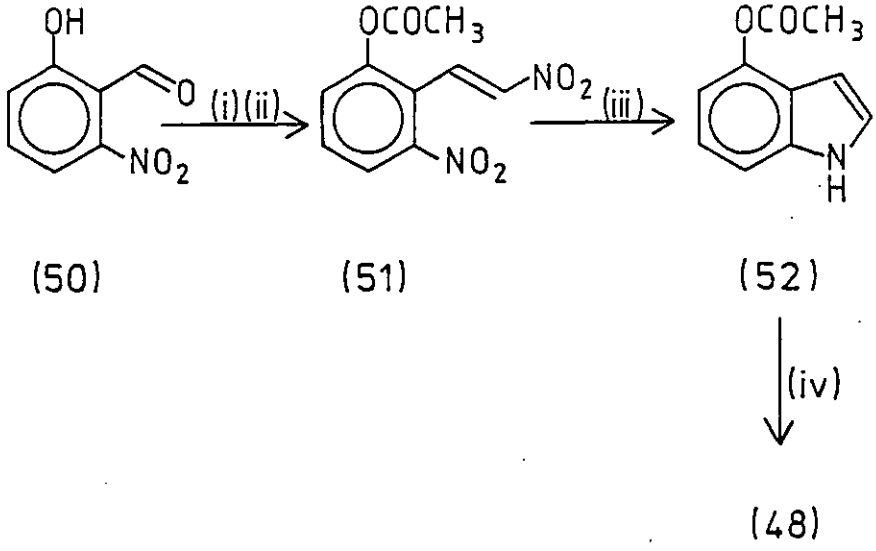
(48)



(49)

An early synthesis of (48) proceeded through the β-nitrostyrene (51) (Scheme 12), which on reduction with iron, acetic acid and ethanol and subsequent deprotection gave (48)[89]. It was observed that prolonged reduction times gave decreased yields of product (52). A common feature of the chemistry of 4-hydroxyindoles is their lability towards acids and oxidising conditions, so that yields are frequently only modest. Repke has exploited the indole (52) for the synthesis of a number of psilocin analogues[90].

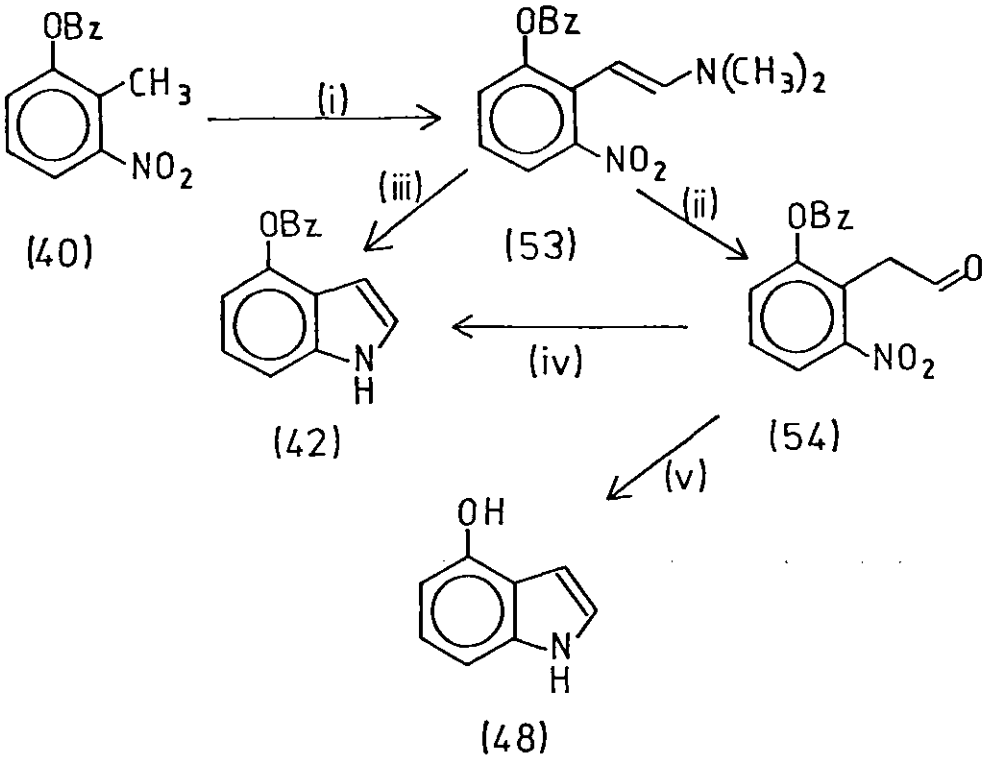
SCHEME 12



(i) CH_3NO_2, KOH. (ii) NaOAc, Ac_2O, 89% overall. (iii) Fe, AcOH, EtOH 32%. (iv) CH_3OH, NH_4OH 75%.

More recently both Somei and Kruse have exploited Leimgruber and Batcho's methodology for indole synthesis[27]. Somei's group reduced the enamine (53) or, the aldehyde (54) derived from it, by acid hydrolysis, with titanium (III) chloride or by catalytic hydrogenation (Scheme 13) to give respectively (42) and (48)[91].

SCHEME 13

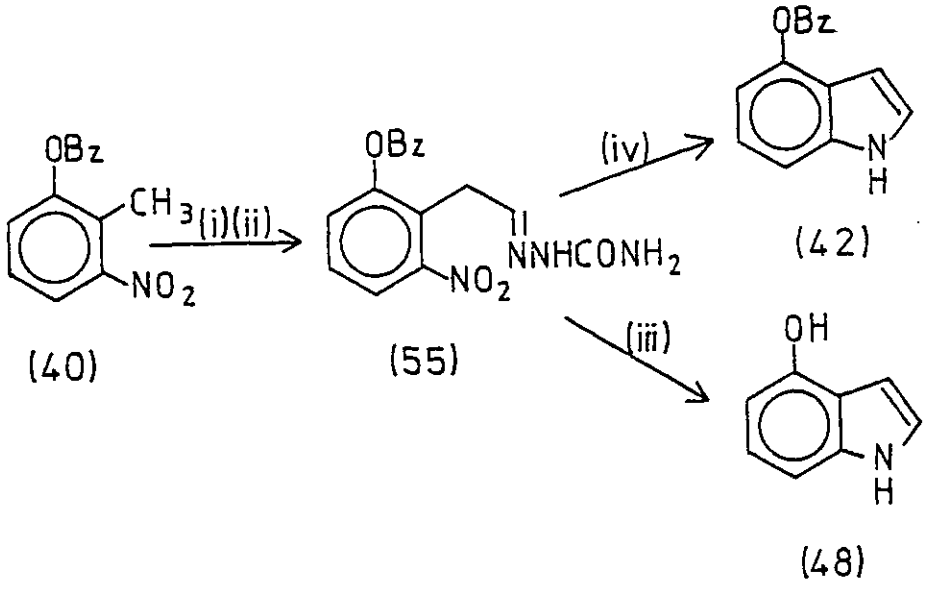


(i) $(CH_3)_2NCH(OCH_3)_2$, 100%. (ii) SiO_2, CH_2Cl_2, H_2O, 84%. (iii) $TiCl_3$, H_2O, MeOH, 51%. (iv) $TiCl_3$, NH_4OAc, H_2O, MeOH, 75%. (v) H_2, Pd/C, PtO_2, MeOH, 68%.

Kruse has introduced two modifications to Leimgruber and Batcho's original procedure. The more reactive tris(dimethylamino)methane gave much more rapid homologation of the deactivated nitrotoluene (40). Catalytic hydrogenation of the enamine (53) is complicated by competing intermolecular reactions as opposed to the desired intramolecular reaction. One procedure that reduces this problem is to use a high catalyst to substrate ratio. Kruse has elegantly

circumvented this expensive procedure by hydrolysing the enamine (53) to the aldehyde (54) and generating the insoluble semicarbazone (55) <u>in-situ</u>. Catalytic reduction of the semicarbazone (55), gave a reasonable yield of 4-hydroxyindole (48), while reduction with ammoniacal iron (II) sulphate gave good yields of the protected indole (42) (Scheme 14)[92].

SCHEME 14

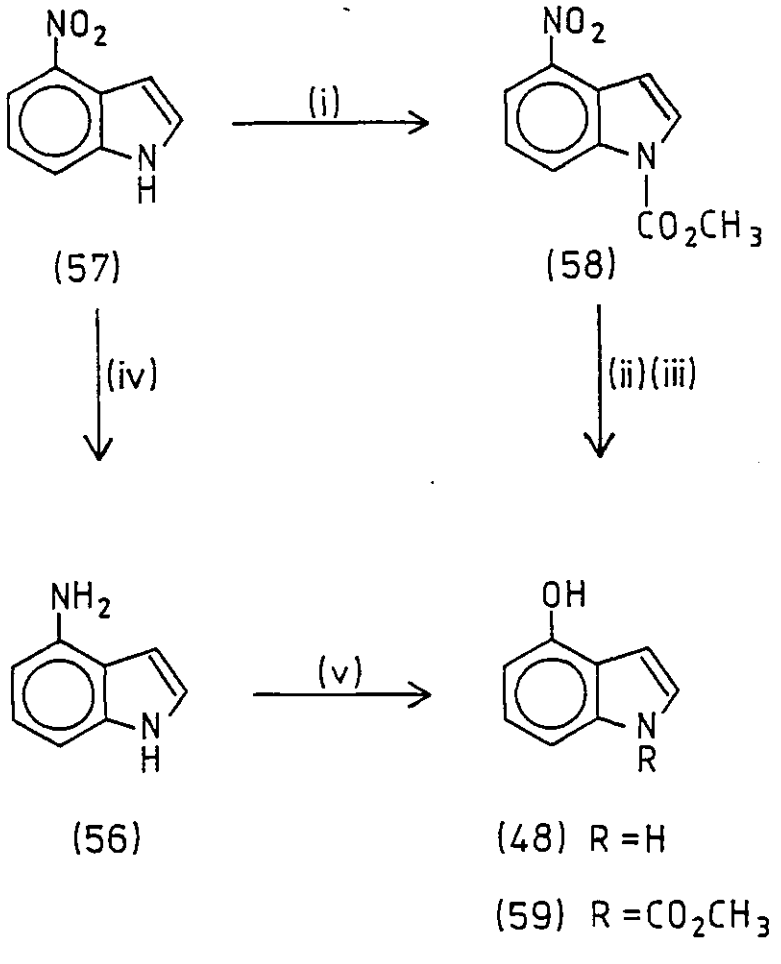


(i) $((CH_3)_2N)_3CH$. (ii) HCl, $NH_2NHCONH_2$ 84%.
(iii) H_2, Pd/C MeOH 55%. (iv) $FeSO_4$, NH_4OH 71%

A classical approach to phenols is of course the pyrolysis of diazonium salts generated from the corresponding amine. Until recently this has not been a useful approach to the synthesis of (48), due to the inaccessibility of 4-aminoindole (56). Somei's group have however recently described a

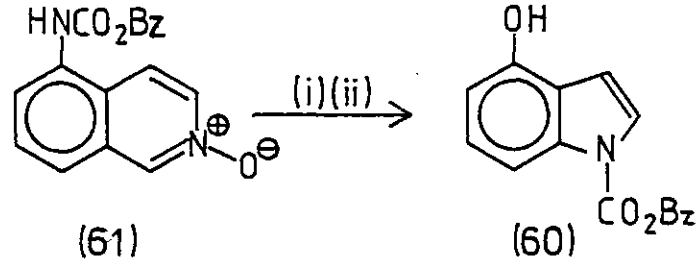
synthesis of 4-nitroindole (57) in a 66% yield, from which a number of 1-protected derivatives such as (58) have been prepared[93]. Reduction, diazotisation and pyrolysis of the diazonium salt so formed gave variable yields of the corresponding hydroxyindoles e.g. (59). In addition, pyrolysis of the diazonium salt of (56) gave a low yield of 4-hydroxyindole (48). (Scheme 15).

SCHEME 15



(i) NaH, DMF, $ClCO_2CH_3$, 95% (ii) $TiCl_3$, 93%.
(iii) $NaNO_2$, HCl, heat, 94%. (iv) $TiCl_3$, 89%.
(v) $NaNO_2$, HCl, heat, 39%.

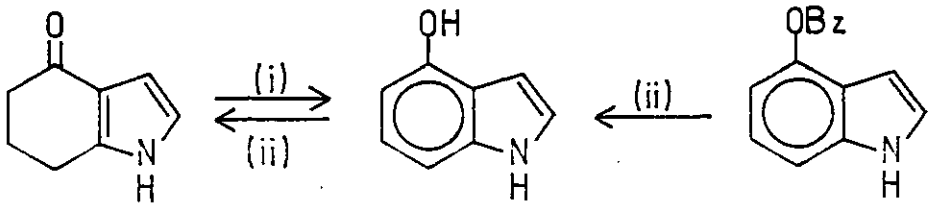
Finally from Somei's group comes an interesting, albeit inefficient, synthesis of the stable protected hydroxyindole (60)[94]. Photolysis of the isoquinoline-2-oxide (61) followed by acid treatment gave (60) in a 21 - 26% yield.



(61) (60)

(i) hν, acetone. (ii) CH_3OH, H_2SO_4 reflux, 21 - 26% overall.

An approach to 4-hydroxyindole that has been investigated by a number of groups is that involving 4-oxo-4,5,6,7-tetrahydroindole (62) as a key intermediate. This compound is readily oxidised to 4-hydroxyindole (48) by treatment with Pd/C at elevated temperatures. Interestingly it has been shown that the reverse reaction also takes place surprisingly easily. Reduction of (42) with Pd/C was shown to give in addition to the expected indole (48) small quantities of (62)[95].

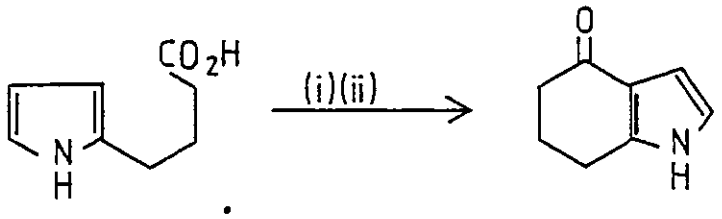


(62) (48) (42)

(i) Pd/C, mesitylene ,75%. (ii) Pd/C, H_2.

Two general approaches to the tetrahydroindole (62) have been reported. Julia based his work (Scheme 16) on the construction of the benzene ring from the readily available pyrrole (63)[96].

SCHEME 16

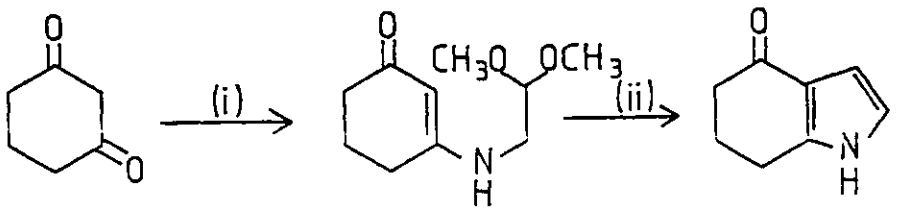


(63) (62)

(i) EtOCOCl, Et_3N. (ii) $SnCl_4$.

The second approach requires the construction of the pyrrole ring. Bobbitt prepared the enamine (64) from 1,3-cyclohexanedione and aminoacetaldehyde dimethyl acetal in an unspecified yield, which cyclised on treatment with dilute hydrochloric acid to the desired tetrahydroindole (62) (Scheme 17)[97].

SCHEME 17

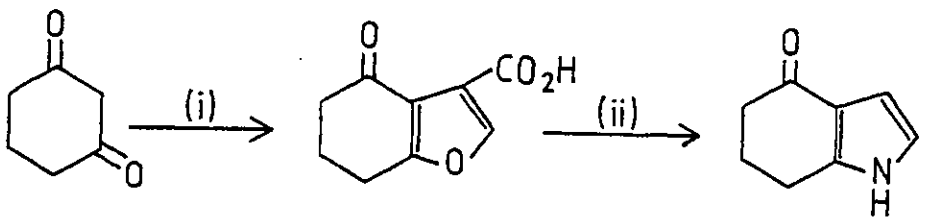


(64) (62)

(i) $H_2NCH_2CH(OCH_3)_2$, H^+, C_6H_6. (ii) 3N HCl, 50%.

Perhaps the most versatile synthesis of (62) is due to Stetter and Lauterback[98]. In this method (Scheme 18) 1,3-cyclohexanedione was alkylated with ethyl bromopyruvate and the resulting tetrahydrobenzofuran (65) treated with ammonia to give tetrahydroindole (62). A number of alkylamines have also been used, yielding N-alkylated tetrahydroindoles.

SCHEME 18



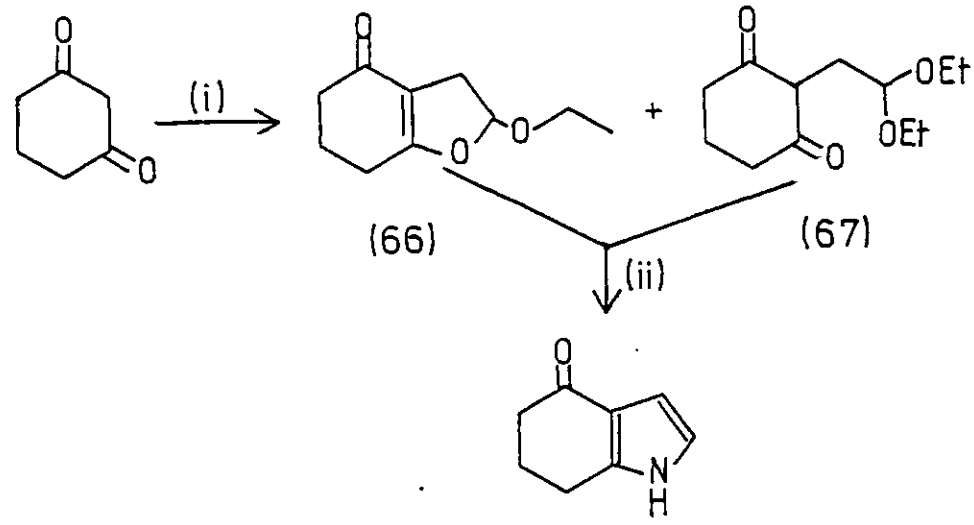
(65) (62)

(i) $BrCH_2COCO_2Et$. (ii) NH_3, 150° C, 92%.

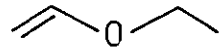
Finally Torii's group reported a novel synthesis of (62) by electrooxidative coupling of 1,3-cyclohexanedione and ethylvinyl ether, followed by ammonolysis of the two intermediates (66) and (67)[99], (Scheme 19).

Remers[100,101], Plieninger[102] and Repke[103] have all exploited the interesting chemistry of (62) for the synthesis of a number of indole species. Of particular relevance to this review is Repke's use of (62) as a source of 4-hydroxyindole (48), from which a number of psilocin analogues were synthesised.

SCHEME 19



(62)



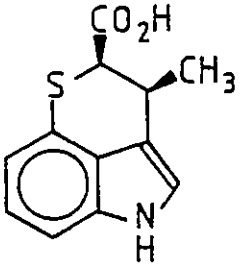
(i) NaOEt, EtOH, e^-, Pt foil, 65%. (ii) $(NH_4)_2CO_3$, MeOH, 150°C, 80%.

Of the large number of reports of analogue chemistry in the psilocin (27) area, only one perhaps warrants special mention. Troxler, Seemann and Hofmann shortly after their publication of the total synthesis of (26) and (27) reported the synthesis of a large number of closely related compounds. These compounds covered all the major groups of analogue compounds that have been reported since, both by them and by other workers[104].

4. Chuangxinmycin

(i) Introduction

In 1976 Chinese workers reported the isolation of a new antibiotic to which they gave the name chuangxinmycin. This was obtained from Actinoplanes tsinanensis a novel microorganism found in a soil sample from Tsinan, Shantung Province, China[105]. From its spectral data[106] and an X-ray diffraction study[107] chuangxinmycin was shown to have the unique heterocyclic structure (68).



(68)

Since the original isolation of chuangxinmycin, two new compounds, chuangxinmycin B and chuangximycin

C have been discovered in the fermentation broth of mutants NT-II and B-I of A. tsinanensis. Although spectral data have been reported for these two new compounds no structures have been proposed[108].

Fermentation of Actinoplanes species in a medium containing ^{35}S sodium sulphate or ^{35}S L-cystine revealed incorporation of radioactivity into the produced Chuangxinmycin (68). From these experiments the authors concluded that the sulphur present in chuangxinmycin (68) was derived from L-cysteine[109].

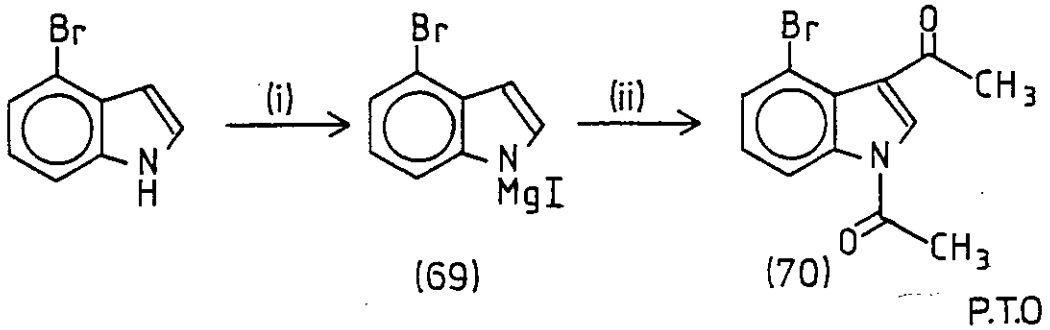
Interest in chuangxinmycin (68) is by no means confined to its unique structure. It has been shown to inhibit the growth of Escherichia coli and hence is considered to be a bacteriostatic agent. The same study showed that mesosome-like substances usually observed in normal E. coli cells disappeared after treatment with chuangxinmycin (68)[110]. It is also reported that chuangxinmycin (68) is active in vitro against a number of gram-positive and gram-negative organisms, while in mice activity against E. coli and Shigella dysenteriae has been demonstrated. Chuangxinmycin (68) has a low toxicity in mice with an LD_{50} of 600mg/Kg (i.v.) and 1770mg/Kg (oral). Preliminary clinical results have shown that chuangxinmycin (68) is effective in the treatment of septicaemia, urinary and biliary infections caused by E. coli. Chuangxinmycins B and C also possess antibacterial activity in vitro against a number of organisms[108].

(ii) Synthesis of Chuangxinmycin (68)

Two total syntheses of chuangxinmycin (68) have been reported. The first in 1976 was non-stereospecific[111], while the second by Kozikowski was stereospecific[112].

The Chinese group's approach to chuangxinmycin (68) (Scheme 20) made use of 4-bromoindolyl magnesium iodide (69) as a starting material which gave 1,3-diacetyl-4-bromoindole (70) upon treatement with excess acetyl choride in ether. Displacement of bromide and *in-situ* condensation with loss of water was achieved with the copper salt from ethyl mercaptoacetate in quinoline/pyridine at 170 - 180° C to give dehydrochuangxinmycin ethyl ester (71). Reduction and hydrolysis of the ester functionality of (71) gave racemic chuangxinmycin (68). No yields at any stage of this synthesis were given[111].

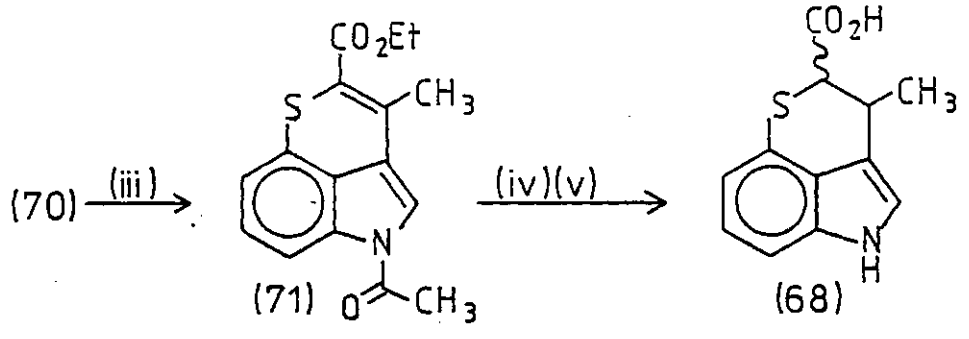
SCHEME 20



(69) (70)

P.T.O

SCHEME 20 (cont)

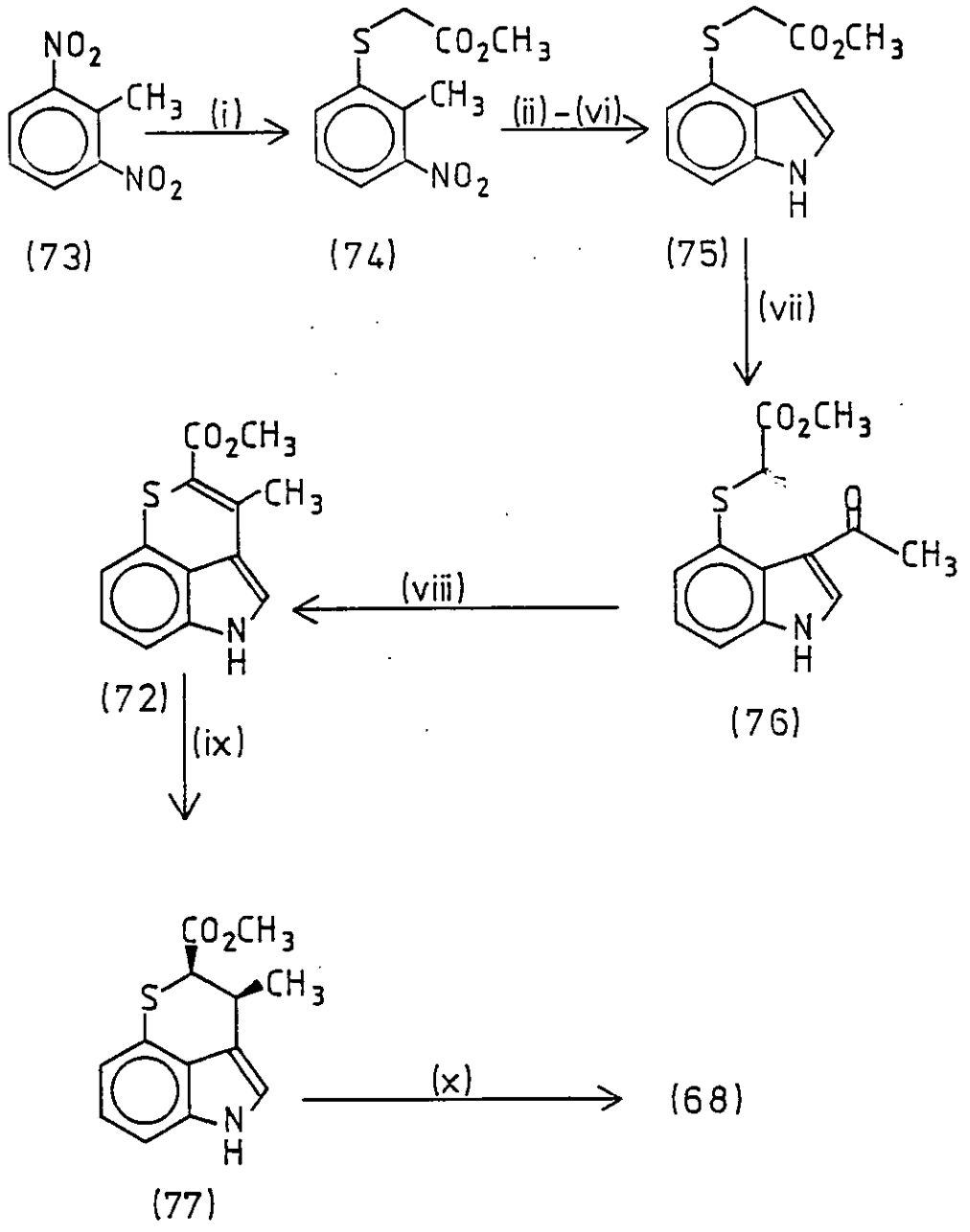


(i) RMgI. (ii) excess CH_3COCl, Et_2O.
(iii) $CuSCH_2CO_2Et$, quinoline/pyridine 170 - 180°C.
(iv) $SnCl_2$, HCl/AcOH. (v) NaOH, EtOH.

Kozikowski's approach to chuangxinmycin (68) (Scheme 21) proceeded through a dehydro intermediate (72) similar to that described above. The synthetic strategy to this compound however relies on the initial synthesis of an appropriately substituted 4-thioindole. Commercially available 2,6-dinitrotoluene (73) underwent nucleophilic substitution with methyl thioglycollate and lithium hydroxide in H.M.P.A. to give the substituted 2-nitrotoluene (74). Saponification followed by application of a modified Leimgruber-Batcho reaction sequence gave the required indole (75) in a 30% overall yield from 2,6-dinitrotoluene.

Friedel-Crafts acetylation and Knoevenagel condensation of the resultant ketone (76) proceeded smoothly in quantitative yield to give dehydrochuangxinmycin methyl ester (72).

SCHEME 21



(i) $HSCH_2CO_2CH_3$, LiOH, H.M.P.A. (ii) KOH, MeOH. (iii) $(CH_3)_2NCH(OCH_3)_2$, D.M.F., reflux. (iv) cold HCl. (v) $FeSO_4$, NH_4OH. (vi) CH_2N_2, Et_2O, 30% overall. (vii) CH_3COCl, $SnCl_4$, 100%. (viii) NH_4OAc, HOAc, C_6H_6, reflux, 100%. (ix) H_2/Pd/S, 70 p.s.i. 70%. (x) $(CH_3)_2CHSLi$, H.M.P.A.

Hydrogenation using a poisoned palladium catalyst gave a stereochemically homogeneous product (77) identical to Chuangxinmycin methyl ester prepared from the natural product. This established the relative stereo chemistry of the natural product as cis. The ester was dealkylated to Chuangxinmycin (68) with lithium thioisopropoxide in H.M.P.A.. Some epimerisation was shown to take place during this reaction.

Further investigation of the chemistry of chuangxinmycin (68) and the preparation of related compounds is to be expected owing to its unusual structure and to the interesting biological properties of this molecule.

5. Conclusion

The 4-heterosubstituted indoles represent an intriguing group of compounds. Although of simple structure the three groups of compounds discussed in this review have been shown to demonstrate auxin activity, effective bacteriostatic properties and hallucinogenic behaviour. It must therefore be anticipated that the development of new procedures for the preparation of 4-substituted indoles will lead to further investigation of this interesting class of compounds.

6. Review References

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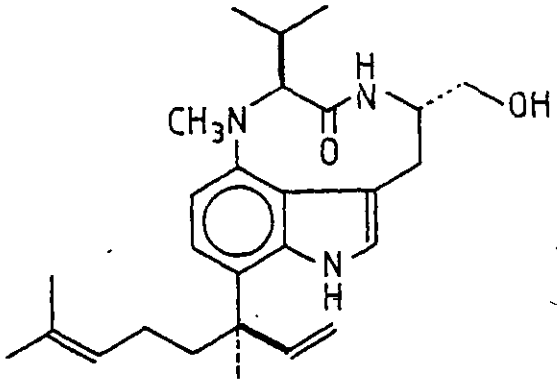
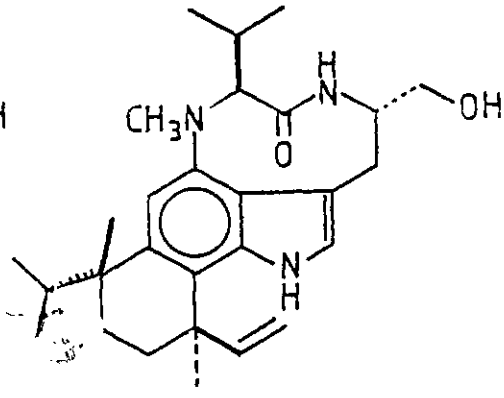
RESULTS AND DISCUSSION

The Targets



Teleocidin A

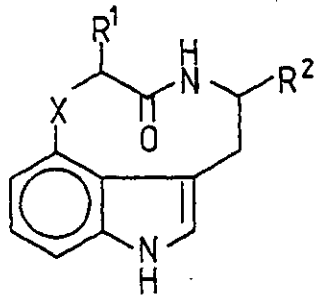


Teleocidin B

Teleocidin A (Lyngbyatoxin A):- 3H-Pyrrolo[4,3,2-g,h]-1,2,4,5,6,8-hexahydro-9-(1-ethenyl-1,5-dimethyl-4-hexenyl)-5-(hydroxymethyl)-1-methyl-2-(1-methylethyl)-1,4-benzodiazonin-3-one.

Teleocidin B:- [4S-(4R*,7R*,10R*,13R*)]-6H-Benzo[g]-13-ethenyl-1,3,4,5,7,8,10,11,12,13-decahydro-4-(hydroxymethyl)[1,4]-diazonino[7,6,5-c,d]indol-6-one.

Model Compounds



X = NCH_3, CH_2, O, S

R^1 = H, $(CH_3)_2CH$

R^2 = H, CH_2OH

1. Thesis Plan

The project was designed to achieve a number of objectives. The prime target was undoubtedly the total synthesis of the Teleocidins. In addition however it was proposed to prepare a number of related model compounds. These were designed to not only more fully explore this unusual and suprisingly neglected area of chemistry, but also to probe the functional groups responsible for the biological activity of the Teleocidins. Although the first of these targets has not been achieved, several closely related pyrrolo-1,4-benzodiazonin-3-ones have been successfully synthesised. In addition a considerable effort has been devoted to the investigation of the chemistry of 4-aminoindoles such that a potential synthetic strategy to the parent system has now emerged.

In order to avoid fragmentation and duplication, the thesis is organised progressively such that all the chemistry of the individual steps towards the Teleocidins and related analogues are each fully discussed. The steps do not necessarily follow a chronological order.

2. The Teleocidins and Lyngbyatoxin A

(i) Introduction

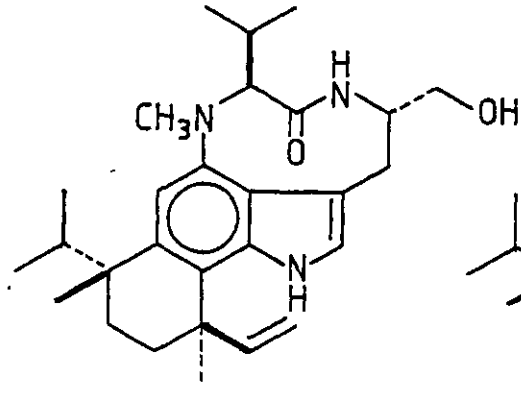
In 1960 Takashima and Sakai reported the isolation of a new toxic substance from the fermentation of a Streptomyces mediocidus species[1]. This compound, named Teleocidin, demonstrated a

specific and potent toxic action against mice and Japanese killifish but failed to show any antibacterial, antifungal or antiprotozoal activity. Further investigation of the biological properties of this compound[2] revealed toxicity towards a number of other higher organisms. For example Daphnia magna, the larvae of Bugula neritina a bryozoa, Ascaris suilla and Turbatrix aceti a nematode, were all killed by this substance. In addition it was observed during the isolation work that Teleocidin demonstrated a potent vesicant action in man.

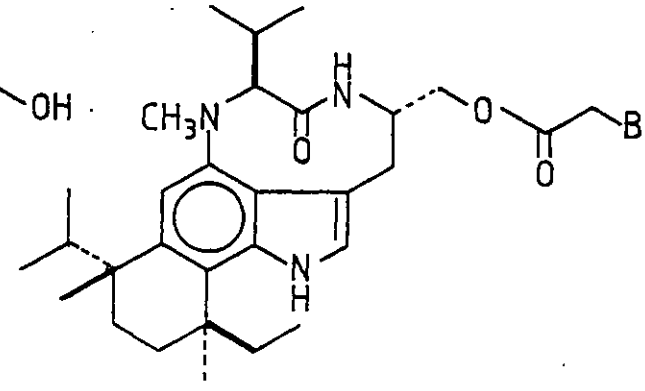
Unfortunately chemical characterisation of this compound isolated as a foam was by no means complete. U.v. and i.r. spectral data revealed the probable presence of a substituted indole ring, a hydroxy group and an amide. Catalytic hydrogenation with Adam's catalyst resulted in the absorption of two equivalents of hydrogen. No further characterisation of this compound has however been reported.

In 1962 the same group isolated a second metabolite from fermentation of streptomyces organisms which was assigned the name Teleocidin B, the first compound being renamed Teleocidin A[3]. The new metabolite revealed similar biological properties to those of Teleocidin A. In addition the u.v. and i.r. spectral data of the two compounds were shown to be very similar. Hydrogenation however resulted in the absorption of only one equivalent of hydrogen.

From chemical degradation studies and a 40MHz ^{1}H n.m.r. study[1] the structure (1) was proposed for Teleocidin B[4-6]. This was later confirmed by X-ray crystallographic analysis of the bromoacetyl ester of dihydroteleocidin B, (2) obtained by catalytic hydrogenation of Teleocidin B (1) followed by treatment with bromoacetyl bromide[7,8].



(1)

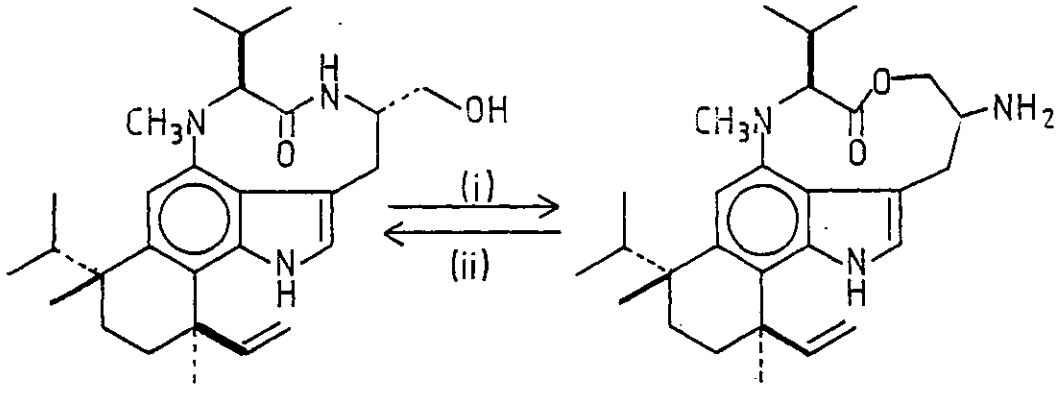


(2)

The structure of the dihydro compound (2) reconstructed from the published X-ray crystallographic data is depicted in Appendix 1.

Although Teleocidin A was reported to be unstable to acid[2], Teleocidin B (1) was shown to undergo a ring opening and subsequent ring closure reaction to give the less toxic lactone (3) (Scheme 1), which displayed a carbonyl absorption at 1715cm^{-1} compared to 1655cm^{-1} in the parent compound (1). Its reversion to (1) upon treatment with base provided further evidence for the structure of lactone (3)[3].

SCHEME 1



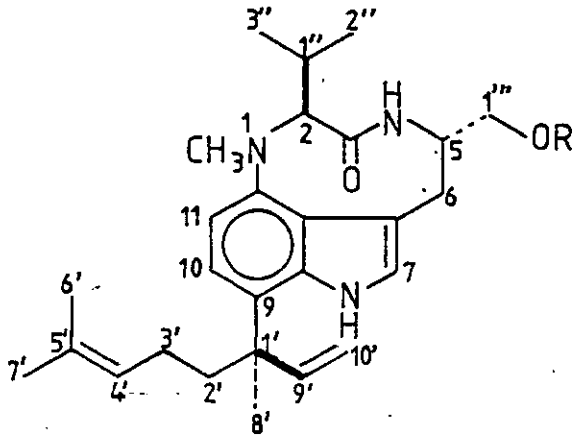
(1) (3)

(i) 6N HCl, EtOH 76%. (ii) base.

Until 1978 there were no further developments in this area. Ruddock working at Pfizer Central Research, Sandwich, Kent then reported the isolation of an ascaricidal compound from the culture of FM 1545 an unidentified microorganism, possessing vesicant properties in man. From a comparison of the u.v. and i.r. data, the uptake of two equivalents of hydrogen on treatment with Adam's catalyst in ethanol, and similar biological properties it was concluded that Teleocidin A and the compound isolated by Ruddock were identical[9].

In addition Cardellina, Marner and Moore reported the isolation of a highly inflammatory and vesicatory substance from the lipid extract of an Hawaiian shallow water variety of Lyngbya majuscula Gomont[10]. The gross structure (4) of this compound was determined by the inspection of u.v., i.r., mass

spectral, ^{1}H n.m.r. and ^{13}C n.m.r. data. It was concluded from comparison of circular dichroism measurements for this compound called Lyngbyatoxin A and Teleocidin B that the two compounds had the same relative and absolute configuration. Lyngbyatoxin A is reported to be the first basic indole alkaloid to be isolated from marine sources.



(4) R = H (5) R = 4-$NO_2C_6H_4CO$

The structure (4) assigned to Lynbyatoxin A is the same as that assigned by Ruddock to Teleocidin A from a study of a similar range of spectral data. Comparison of the ^{13}C n.m.r. data for these two compounds revealed a difference of 2 p.p.m. for one methyl group, all other signals were however found to be within ±Ø.5 p.p.m. of each other. A fuller discussion of the comparison of spectral data for these two compounds will not be undertaken here since such a comparison has already been published[9].

(ii) ^{1}H n.m.r. and Semisynthetic Studies on Teleocidin A

Neither Teleocidin A (4) (Lyngbyatoxin A) or the monoacetate of Lyngbyatoxin A were isolated as crystalline solids suitable for X-ray crystallographic analysis. A possible reason for this will be discussed later (vide infra). It was therefore evident that further high field ^{1}H n.m.r. studies of Teleocidin A[11] (4) and additional attempts to prepare a crystalline derivative of (4) would be beneficial.

The ^{1}H n.m.r. spectrum of Teleocidin A (4) at 250MHz in deuteriochloroform was found to be identical with that previously obtained by Ruddock[4] at 100 MHz (Table 1).

A difference decoupling experiment (Appendix 2) performed by irradiation of the two proton pseudo doublet at δ 4.34 produced a singlet at δ 7.82 due to the resonance of the lactam NH and two doublets at δ 3.74, 3.58, J_{gem}-11.5Hz, for the hydroxymethyl methylene. Two doublets at δ 3.14, 3.05 J_{gem}-17.5Hz were assigned to resonances of the two non-equivalent 6-H protons and a septet J 6.3Hz at δ 2.59 to the 1-methylethyl methine proton (1^{11}-H). The two protons at δ 4.34 from these results are clearly due to the 2-H and 5-H protons.

In $(CD_3)_2SO$ at 250MHz a number of chemical shift changes were observed relative to those observed in deuteriochloroform (see Table 1). Of particular note are the downfield shift of 7-H from δ 6.83 to 6.91

TABLE 1:- Comparison of ^{1}H n.m.r. Data for Lyngbyatoxin A and Teleocidin A ($CDCl_3$ and $(CD_3)_2SO$)

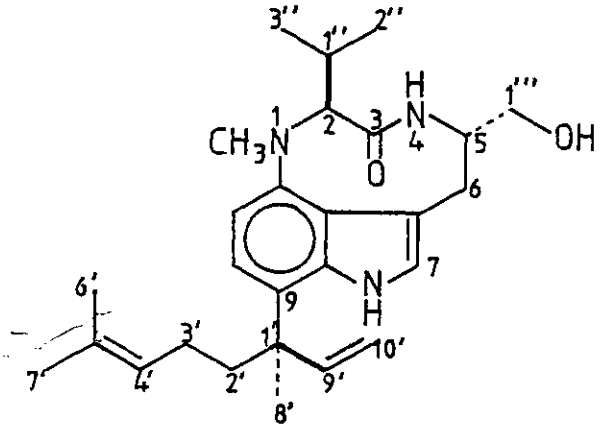
Proton	Lyngbyatoxin A[a] 360MHz $CDCl_3$[10] δ	Teleocidin A[a] 100MHz $CDCl_3$[9] δ	Teleocidin A[a] 250MHz $CDCl_3$ δ	Teleocidin A[b] 250MHz $(CD_3)_2SO$ δ
1-CH_3	2.87	2.92	2.93	2.77
2-H	4.33	4.39	4.36	4.27
4-H			7.37	6.80
5-H	4.32	4.39	4.36	4.00
6-H	3.08	3.10	3.10	2.99
7-H	6.81	6.80	6.83	6.91
8-H			8.54	9.66
10-H	6.96	6.95	6.97	6.81
11-H	6.44	6.46	6.48	6.35
2^{1}-H	1.90	1.80-2.00	1.75-2.00	1.60-2.10
3^{1}-H	1.80	1.80-2.00	1.75-2.00	1.60-2.10
4^{1}-H	5.06	5.10	5.08	5.05
6^{1}-H	1.63	1.47	1.46	1.40
7^{1}-H	1.47	1.63	1.63	1.55
8^{1}-H	1.44	1.42	1.40	1.29
9^{1}-H	6.15	6.25	6.22	6.12
10^{1}-H	5.30	5.30	5.29	5.05
1^{11}-H	2.55	2.50	2.58	2.45
2^{11}-H	0.89	0.90	0.92	0.80
3^{11}-H	0.62	0.60	0.62	0.51
1^{111}-H	3.60	3.60	3.65	3.38
-O-H				4.84

(a) Relative to $(CH_3)_4Si$ at δ 0

(b) Relative to $(CD_3)_2SO$ at δ 2.49

and the separation of 2-H and 5-H, the former now occurring as a sharp doublet J 9.2Hz at δ 4.26 and the latter at δ 4.00 as a multiplet. The hydroxyl proton resonates at δ 4.83 as an undefined triplet. As can be seen with the exception of the indole NH at δ 9.66 every other proton has undergone a shift upfield to varying degrees.

A study of through space proton nuclear Overhauser effects (n.O.e) was undertaken to investigate the solution conformation of Teleocidin A (4). It was also found possible to assign the individual protons in the lactam ring and the indole nucleus with the exception of the geminal protons of the hydroxymethyl group, from these results. The spectra resulting from this study are depicted in Appendix 3 while Table 2 summarises the results.



(4)

TABLE 2:- Summary of Nuclear Overhauser Effects for Teleocidin A (4) in $CDCl_3$ at 250MHz

Entry	Irradiated Proton (δ)	Enhancements Observed (δ)[a]
1	3^{11}-H(0.61)	2^{11}-H(0.89)S, 1^{11}-H(2.55)S, 1-N-CH_3(2.81)M, 2-H(4.34)S, 11-H(6.46)S
2	2^{11}-H(0.89)	3^{11}-H(0.61)M, 1^{11}-H(2.55)S, 2-H(4.34)S
3	1^{11}-H(2.55)	3^{11}-H(0.61)M, 2^{11}-H(0.89)S, 1-N-CH_3(2.81)M, 2-H(4.34)W
4	1-N-CH_3(2.81)	3^{11}-H(0.61)M, 1^{11}-H(2.55)S,5-H(4.34)W, 11-H(6.46)V.S.
5	6-H(3.04)	2-H+5-H(4.34)W, 7-H(6.80)W
6	6-H(3.15)	2-H(4.34)S, 7-H(6.80)M
7	6-H(3.19)	2-H(4.34)S
8	2-H+5-H(4.34)	3^{11}-H(0.61)M, 2^{11}-H(0.89)M, 1^{11}-H(2.55)S,1-N-CH_3(2.81)W, 6-H(3.08-3.14)S, 1^{111}-H(4.58-4.75)S, 3-H(7.80)W
9	7-H(6.80)	6-H(3.03-3.14)M, 8-H(8.55)S

(a) S refers to strong enhancement, M to medium and W to weak. V as a prefix indicates very.

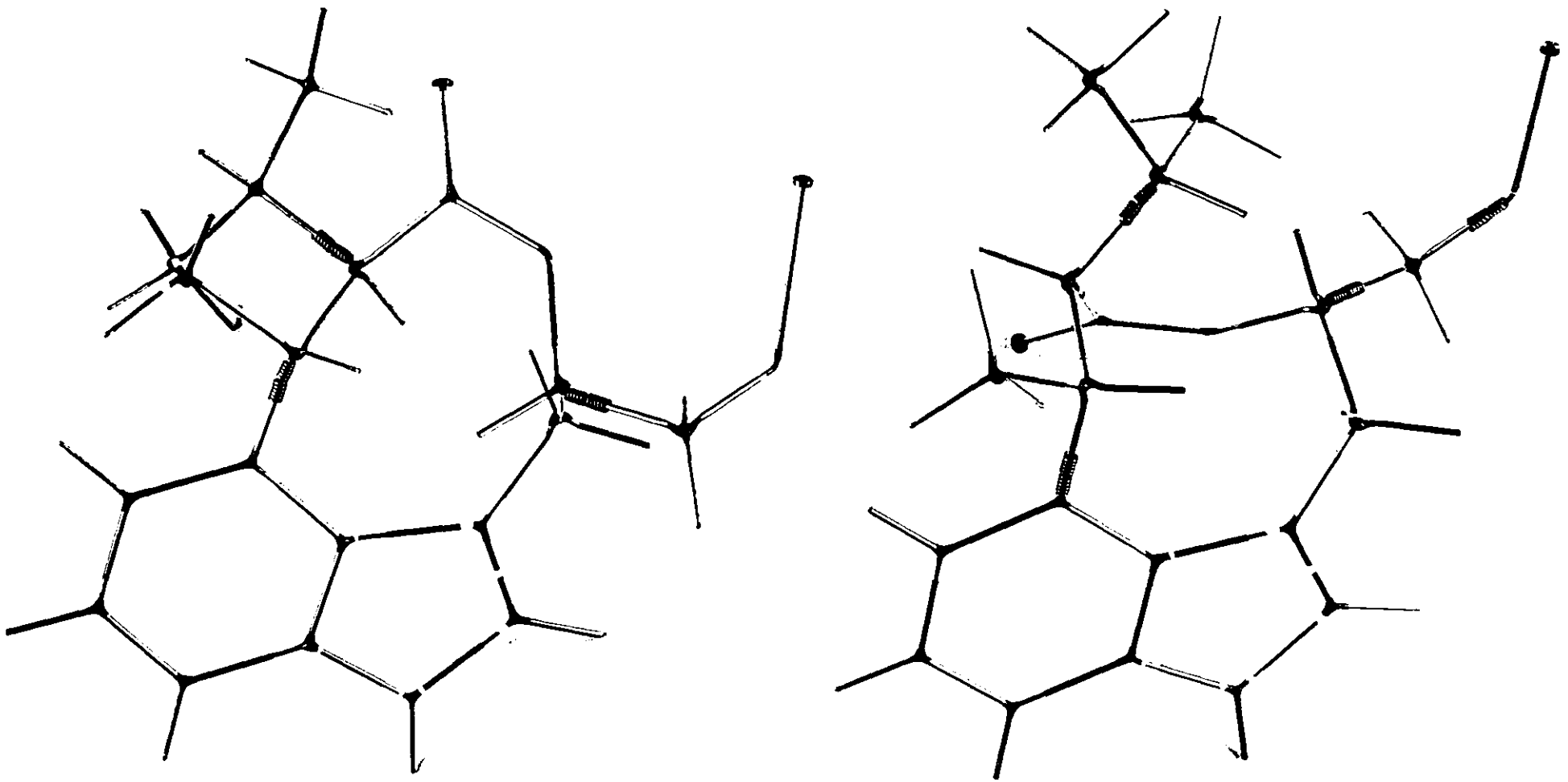
It is evident that there are striking differences in the environment of the two methyl groups 2^{11} and 3^{11}. One at the highest field exhibits a strong n.O.e. with 11-H while the other does not (Table 2 entry 1). Clearly therefore the methyl group at highest field must be situated in the aromatic ring current causing its shift upfield and bringing it into proximity with 11-H. It is thought that the reduced n.O.e.effect of the methine 1^{11}-H with the highest field methyl group (3^{11}) compared to that with 2^{11}-H is due to the additional relaxation of 3^{11}-H with the aromatic ring (Table 2, entry 3). In addition, the weak effect observed with the vicinal 2-H proton suggests a large dihedral angle between 2-H and 1^{11}-H. This is supported by the large coupling constant (10Hz) between these two protons indicating from the Karplus equation a dihedral angle of 180^{o}. Of particular note in entry 4 is the n.O.e. effect, albeit weak, observed between 1-N-CH_3 and 5-H despite the large distance between protons. Entries 5-7 illustrate the drawbacks involved in attempting a n.O.e. study involving an unresolved multiplet. As can be seen however, irradiation at three separate points in the multiplet reveal that the downfield proton in the multiplet is directed into the nine membered lactam ring and has no effect on 5-H or on 7-H. The upfield proton however (entry 5) has no interaction into the ring but weak effects on the above mentioned 5-H and 7-H protons. These results

are perhaps more clearly illustrated in entries 8 and 9 (Table 2).

A similar study on the hydroxymethyl methylene protons 1^{111}-H did not reveal any further information. The results of these experiments are neither included in Appendix 3 nor Table 2.

Study of Dreiding molecular models showed that the most reasonable solution conformation of Teleocidin A (4) (Fig. 1 Major) to agree with the experimental data, is the same as that observed in the solid state for the Teleocidin B derivative (2) illustrated in Appendix 1. Key to this deduction is the cross ring n.O.e. interaction between 2-H and 6-H. Furthermore the experimental data shows that the relative stereochemistry about C-2 and C-5 must be <u>trans</u>. No conformation of a <u>cis</u> arrangement agrees satisfactorily with the observed n.O.e. data. This provides further support to Ruddock's contention[9] that the stereochemistry of Teleocidin A is that shown in (4)[9,10].

Both Cardellina[10] and Ruddock[12] observed some minor peaks in the ^{1}H n.m.r. and ^{13}C n.m.r. spectra. These minor peaks constitute, from comparison of integrals for the 1-N-CH_3 singlet at δ2.90 (major peak) and the singlet at δ2.75, some 12-15% of the material at room temperature in deuteriochloroform. These peaks may be due to one of a number of possibilities. Firstly the compound may be impure, however it is difficult to explain why material from



Major

Minor

Fig 1:- Proposed Solution Conformations of Teleocidin A (4).

widely different sources (sea algae and the fermentation of microorganisms) and purified by different chromatographic protocols should be contaminated to the same extent by what appears to be the same material. Cardellina and Moore[10] report signals with the following chemical shifts for the smaller signals, sharp doublets (J=8Hz) at δ7.07 and 6.99, a broad singlet at δ8.75, a doublet of doublets J 18, 10Hz at δ6.20 and a singlet at δ2.70. These correspond well with the signals observed in Ruddock's sample of material. Additional resonances were also observed in this material and are summarised in Table 3. A second possibility is that the minor resonances are due to a regioisomer of Teleocidin A (4) in which the linalyl group is at C-11 rather than C-9. This alternative is less readily rejected by inspection of a ^{1}H n.m.r. spectrum performed at room temperature in deuteriochloroform. The third possibility and that which appears most probable is that Teleocidin A (4) exists in two distinct conformers at room temperature.

The 4-nitrobenzoyl ester (5) of Teleocidin A (4) was prepared in a 66% yield on treatment of (4) with 4-nitrobenzoyl chloride and 4-N,N-dimethylamino-pyridine. This compound revealed the expected downfield shift[10] of the 1^{111}-H protons from δ3.50 - 3.80 to δ4.30 - 4.50 and the downfield shift from δ4.34 to δ4.75 for 5-H. Additionally it was found that the proportion of the minor resonances in the ^{1}H

TABLE 3:- ^{1}H n.m.r. Data for Teleocidin A (4) and its 4-Nitrobenzoyl Ester (5)

Proton	4[a]		5[a]	
	Major Component δ	Minor Component δ	Major Component δ	Minor Component δ
1-N-CH_3	2.93	2.75	2.93	2.76
2-H	4.36	4.71	4.36	4.74
4-H	7.37	-	-	6.17
5-H	4.36	-	4.75	-
6-H	3.10	-	3.24	-
7-H	6.83	-	6.87	6.93
8-H	8.54	8.75	8.59	8.78
10-H	6.97	7.10	7.00	7.12
11-H	6.48	7.01	6.53	7.02
2^1-H	1.75-2.00		1.75-2.00	-
3^1-H	1.75-2.00	-	1.75-2.00	-
4^1-H	5.08	-	5.08	-
6^1-H	1.46	1.49	1.46	1.49
7^1-H	1.63	1.64	1.63	1.67
8^1-H	1.40	-	1.40	-
9^1-H	6.22	-	6.18	-
10^1-H	5.29	5.29	5.31	5.31
1^{11}-H	2.58	2.39	2.61	2.30
2^{11}-H	0.92	0.95	0.92	0.94
3^{11}-H	0.62	1.25	0.63	1.25
1^{111}-H	3.65	3.44	4.40	4.15
$NO_2C_6H_4$			8.24	8.24

(a) Relative to $(CH_3)_4Si$ at δ 0, $CDCl_3$ solvent.

n.m.r. had increased from some 12% in (4) to 41% in (5) (Table 3). These results suggest that the second possible explanation of the occurrence of these minor resonances, that is the presence of two regioisomers of Teleocidin A, is unlikely since no significant change in resonance intensity would be expected upon esterification.

To finally attempt to demonstrate the existence of two different conformations of Teleocidin A (4) at room temperature a series of ^{1}H n.m.r. variable temperature experiments were performed. In deuteriochloroform at 293K the minor resonances contributed some 12% to peak intensities while at 323K the distribution had changed such that the minor resonances contributed to the extent of 29%. Furthermore on cooling the sample to 313K it was shown that the minor resonances only contributed some 22%. These ratios were obtained from the integrals of the 1-N-CH_3 singlets at δ2.90 and δ2.75 and must of course be considered as approximations only. It was also observed that most resonances associated with the lactam ring protons had started to broaden although no such effect was noticed with protons associated with the linalyl side chain.

The operating temperature range for deuteriochloroform is limited, in the above experiment only a 30^{o} C temperature range being achieved. In an attempt to reach the coalescence temperature of the two conformers, therefore, $^{2}H_6$-dimethylsulphoxide was

substituted for deuteriochloroform. It was disappointing to discover that in a temperature range of 313K to 435K no significant change in the ratio of major to minor resonance intensities of about 9% was observed although a number of other interesting observations were made. In general it was found that resonances of protons occurring in the nine membered ring and the indole ring gradually broadened as the temperature was raised to 390K and then slowly started to resolve again as the temperature was further increased. The rate at which the resonances broadened and sharpened varied somewhat. For example, the 6-H protons exhibited a sharp double doublet at 435K although the hydroxymethyl methylene protons were still unresolved. As expected the lactam-NH and the hydroxyl protons underwent a gradual shift upfield and a rapid broadening of their resonances as the temperature was raised.

The most intriguing and unexpected properties were however demonstrated by the 3^{11}-H and 11-H protons. It was found that as the temperature was increased the doublets corresponding to these two protons broadened at a similar rate such that they were both occurring as unresolved envelopes at 390 and 415K. At 435K however these two resonances were again sufficiently resolved to reveal doublets. Additionally both resonances were gradually shifted downfield although the rates of change of chemical shift were not directly proportional to the rate of

change in temperature. These results are summarised in Table 4. Surprisingly it was found that the second methyl group of the 1-methylethyl moiety underwent only minor changes in chemical shift (< 0.05 p.p.m.). Nor did it suffer any significant broadening effects as the temperature was raised. Equally the remaining aromatic proton (7-H and 10-H) resonances, although as mentioned underwent broadening to a limited extent, demonstrated only minor changes in chemical shift.

TABLE 4:- ^{1}H n.m.r. Chemical Shifts at Different Temperatures of Selected Protons in $(CD_3)_2SO$

		Proton			
$T^{o}K$	ΔT	3^{11}-H	$\Delta\delta$	11-H	$\Delta\delta$
313	-	0.520	-	6.350	-
340	27	0.542	0.022	6.366	0.016
365	25	0.566	0.024	6.405	0.039
390	25	0.608	0.042	6.462	0.112
415	25	0.750	0.142	6.533	0.071
435	20	0.775	0.025	6.558	0.025

The similarity in the behaviour of the 3^{11}-H and 11-H protons resonances and their known spacial proximity from n.O.e. experiments (vide supra) suggests some kind of cooperative relaxation effects between them.

It was also found somewhat suprisingly that on cooling Teleocidin A (4) from 435K to 315K and

reexamination of the ^{1}H n.m.r. spectrum no decay of the material was observed. That no change in the ratio of minor to major resonance peaks was observed in $^{2}H_{6}$ dimethylsuphoxide may be due to the increased viscosity and polarity of the solvent relative to deuteriochloroform.

One additional piece of evidence suggesting the presence of two different conformers giving rise to major and minor ^{1}H n.m.r. resonances, rather than these being due to two different regioisomers, came from the previously discussed n.O.e. experiments. Saturation of the highest field methyl group (3^{11}-H) gave rise also to saturation of the minor resonance at δ1.25. This result suggests that the resonances occurring at δ1.25 and Ø.62 are due to the same group in two different conformations. Evidently if the major and minor resonances were due to two regioisomers then of course no saturation of one signal (for example a minor) by irradiation of a major signal could result.

Having established the probable presence of two different conformers in solutions of Teleocidin A (4) and having determined the conformation of the major conformer by n.O.e. experiments it is interesting to speculate on the possible conformation of the second. Attempts to construct a model containing a (Z)-amide linkage proved impossible suggesting that two different amide rotamers are not the reason for two sets of proton resonances. Inspection of the ^{1}H

n.m.r. data (see Table 3) for the major and minor resonances of (4) and the nitrobenzoyl ester (5) revealed considerable similarities between resonances with however four signficant exceptions. The resonance due to the minor component 11-H has moved downfield by Ø.5 p.p.m. suggesting a decrease in the contribution of the 1-nitrogen lone pair to the aromatic ring system. The resonance at δ4.7 due to the minor component of 2-H has undergone a downfield shift. Bringing this proton into the plane of the lactam group would produce this effect due to the well known anisotropic effect of the carbonyl group. The 1-N-methyl group has moved upfield due to an increased shielding effect of the aromatic ring system. Finally the minor resonance of 3^{11}-H, assigned from n.O.e. experiments (<u>vide supra</u>) at δ1.25 has suffered a downfield shift of no less than Ø.63 p.p.m. Inspection of the conformation of (2) (see Appendix 1) reveals that 3^{11}-H is situated in the ring current of the indole ring causing the unusually high chemical shift of 3^{11}-H in the major conformer. To account for the large downfield shift of 3^{11}-H in the minor conformer it is evident that the indole ring current can no longer effect the group. Additionally it is possible that the minor conformer presents a more sterically crowded environment than does the major conformer, shifting the resonance further downfield. One further observation needs to be accounted for in considering

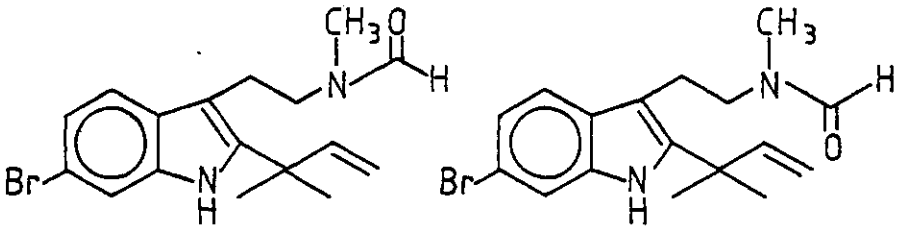
alternative conformers for Teleocidin A (4). The 4-nitrobenzoyl ester (5) as has already been discussed reveals a significantly higher proportion of the minor conformer. It is well known that aromatic systems will adopt a "stacked" mode by interaction of π molecular orbitals as in, for example, the formation of picrates. This suggests that in the minor conformer the 4-nitrobenzoyl group can "stack" with the indole ring. The major conformer cannot undergo this interaction due to the buttressing of the 5-H proton.

Study of Dreiding molecular models and considering the above observations, the most probable minor conformer of the molecule would appear to be that illustrated in Fig. 1 Minor. Relative to the major conformation, the 1-N-methyl group has been twisted towards the aromatic ring and the nitrogen lone pair has been shifted further out of the plane of the indole ring. The 2-H proton is situated in the plane of the lactam carbonyl and 3^{11}-H has been moved away from the aromatic ring current. Significantly 2^{11}-H has undergone only minor changes in its environment reflected in its unchanged chemical shift. The hydroxymethyl group is also suitably situated to place an aromatic ester in the molecular orbital system of the indole ring. Interconversion of the two conformers is brought about by a rotation of approximately 120° of the 6-6A

carbon-carbon bond and is hindered by the interaction of 5-H with the 1-N lone pair.

It had been expected that the 4-nitrobenzoyl ester (5) would be crystalline and suitable for an X-ray diffraction study. Evidently the existence of two conformers stable at room temperature prevents crystallisation of the compound.

Finally Christopherson's group have recently reported the isolation of a marine alkaloid Flustrabromine (6) which is thought to occur as two rotamers about the amide as evidenced by ^{1}H n.m.r.[13]. This compound was isolated as an amorphous solid.



(E)(6a) (Z)(6b)

Although it has been shown that Teleocidin B (1) undergoes a ring opening followed by ring closure reaction to the lactone (3) similar attempts to prepare the corresponding lactone from Teleocidin A (4) were unsuccessful. Warming Teleocidin A (4) in conc. HCl resulted in a number of products. Treatment of (4) with cold conc. HCl however formed a compound in 50% yield after chromatography which revealed M^{+} 455 in the mass spectrum corresponding to

a hydrated Teleocidin A derivative. A number of other acids were found to induce either extensive decomposition or else have no effect on (4).

(iii) The Biology of the Teleocidins

From the early biological data (vide supra) on the Teleocidins and Lyngbyatoxin A it was apparent that these compounds possessed potential applications as veterinary drugs. More recently however these compounds have demonstrated some less useful although interesting biological properties, which will now be discussed.

Human lymphoblastoid cells enriched in human leukocyte antigens by transformation with Epstein-Barr virus were aggregated to a quantifiable degree by nanogram quantities of dihydroTeleocidin B[14]. It has also been observed that Teleocidin aggregated T-enriched lymphocyte preferentially and had a mitogenic effect on both T- and B- enriched lymphocytes although immunoglobulin synthesis was unaffected[15]. A platelet metabolism dependent irreversible aggregation of human platelets by Teleocidin has been reported[16]. Divalent cations and fibrinogen are required for aggregation to take place. No significant shape change was observed in the aggregated platelets. ^{14}C-Serotonin and A.T.P. release were observed after the onset of irreversible aggregation had occurred. Finally in this section adhesion of human promyelocytic leukaemia cells to the surface of culture vessels was induced by small

quantities of dihydroteleocidin B added to the culture medium[17].

Teleocidin B also inhibits the mitogenic effect of epidermal growth factor (E.G.F.) to rat A.H.66 hepatoma cells by reducing cell membrane E.G.F. receptor affinity[18,19]. It was found however that prolonged treatment of A.H.66 cells with Teleocidin B reversed this antagonistic effect. By contrast Collins and Rozengurt have found that Teleocidin is a potent mitogen for murine fibroblasts and synergistically stimulates D.N.A. synthesis with a wide range of purified growth factors (including E.G.F.)[20]. There was however no synergism of Teleocidin with vasopressin suggesting that they could both operate by the same mitogenic pathway.

Lyngbyatoxin A and dihydrotelecidin B induced a rapid increase in the release of prostaglandins and in the turnover of choline in He La cells[21]. An earlier report from the same group showed a rapid release of arachidonic acid when C3H 10T1/2 cells were incubated in a medium containing Teleocidin B or dihydroteleocidin B. Additionally it was noted that 2-deoxyglucose uptake was greatly enhanced[22].

Stimulation of superoxide anion radical production in polymorphonuclear leukocytes treated with Teleocidin B was also noted. This particular stimulation was shown to be inhibited by the addition of <u>trans</u> retinol, retinyl acetate or retinoic acid to the culture medium[23].

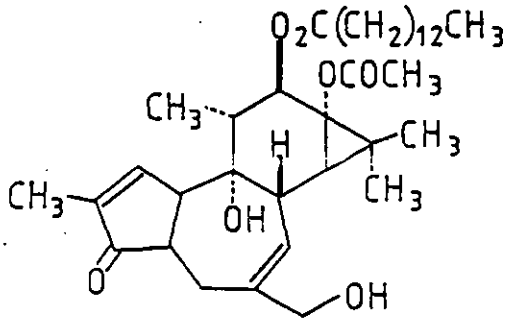
Inhibition of terminal differentiation of Friend erythroleukaemia cells induced by dimethyl sulphoxide has also been illustrated[17]. Induction of ornithine decarboxylase occurred on painting dihydroteleocidin B, Teleocidin or Lyngbyatoxin A on mouse skin. It was again found that retinoic acid inhibited the observed inductive effect[17,24]. Ornithine decarboxylase is involved in the decarboxylation of ornithine to putrescine which is a biosynthetic intermediate to spermidine and spermine. These two polyamines are important compounds in the stabilisation of membrane structures in bacteria as well as in the structures of ribosomes, some viruses, and the D.N.A. of many organisms.

It should be noted that in the above discussion reference has been made in some cases to Teleocidin rather than more specifically to Teleocidin B. In a recent report Fujiki has stated that Teleocidin consists of two compounds Teleocidin A and Teleocidin B[25]. This observation was reported previously during the original isolation of the Teleocidins! It is probable therefore that recent references to Teleocidin in the biological literature refer to a mixture of both Teleocidins A and B.

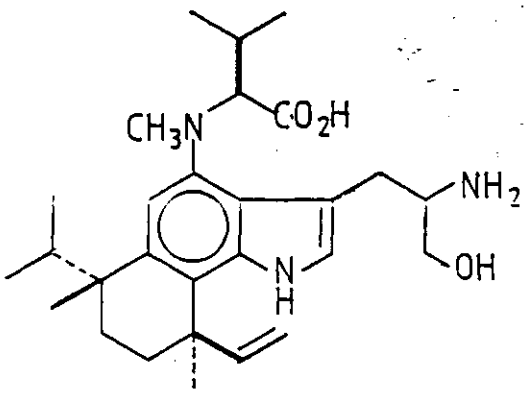
It is evident from this discussion that Teleocidin and Lyngbyatoxin A have a significant effect on the intact cell membrane. Similar effects were observed in parallel experiments in which the known tumour promoting vesicant 12-O-tetradecanoyl-

phorbol-13-acetate (T.P.A.) was substituted for Teleocidin. Additionally in competition experiments for cell membrane binding sites T.P.A. and Teleocidin were shown to act antagonistically towards each other. Such similarity in biological behaviour at very similar concentrations suggested that Teleocidin should also be a tumour promoter. Indeed it has been recently shown that this is the case[24,26]. On painting a solution of the known carcinogen 7,12-dimethylbenz[a]anthracene onto the skin of mice and subsequent treatment in the same way with Teleocidin resulted in the appearance of skin tumours on 90% of test animals within nineteen weeks. Control animals which had only been treated with 7,12-dimethylbenz[a]anthracene only, showed no signs of tumour growth after the same time.

Finally it was found that dihydroteleocidin B after treatment with hydrochloric acid in the presence of thioglycollic acid produced a compound inert in a number of the above experiments[14,24]. It is thought that this compound is the seco amino acid (7) since a moleular ion at 471 a.m.u. has been observed equivalent to the addition of the elements of water to dihydroteleocidin B (m/e 453)[24].



T.P.A

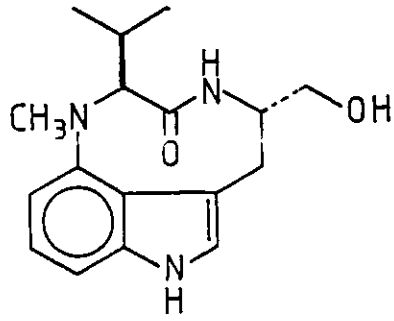


(7)

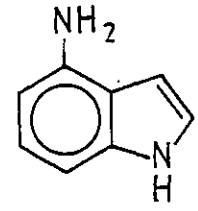
3. Retrosynthesis

(i) Introduction

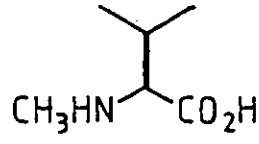
The Teleocidins present a number of challenging features to the organic chemist. The tricyclic "northern zone" lactam skeleton (8) can be regarded as being made up from a 4-aminoindole nucleus (9) which would necessitate a strategy of both differential 4-N,N-dialkylation and specific C-3 substitution. Alternatively the molecule may be viewed as a cyclic dipeptide constructed from N-methylvaline (10) and tryptophanol (11) formed by the reduction of tryptophan.



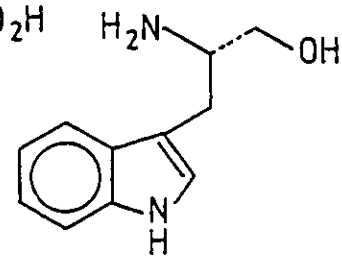
(8)



(9)



(10)

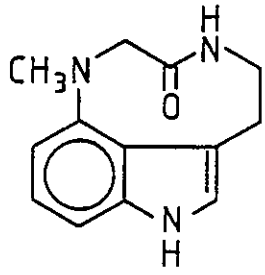


(11)

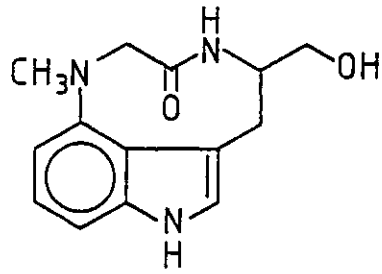
The 4-aminoindole skeleton which is also present in dehydrobufotenine (see review) has previously received little attention from the synthetic organic chemist. The construction of the 9-membered lactam ring is also likely to propose a difficult task due to unfavourable entropic and thermodynamic factors[27] and the need to be able to stereoselectively prepare just one isomer (<u>trans</u>) common to the natural product. Finally the stereo and regiospecific introduction of the linalyl group of Teleocidin A

provides an awkward twist in the tail of any proposed synthesis.

Owing to these many potential problems it was felt that it would be necessary to use a number of model compounds in order to be able to establish a total synthetic strategy. To this end it was decided that such species should initially permit:- (a) the investigation of the influence of the hydroxymethyl functionality and (b) the correct strategy for the synthesis of the lactam ring. Consequently the two model compounds (12) and (13) were proposed as targets to study these problems. Furthermore it was proposed to synthesise the lactam (8) to provide a "nothern zone" containing all the lactam ring features of the natural product but lacking the lipophilic "southern zone".



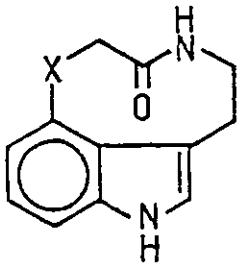
(12)



(13)

It is thought that the biological properties of the Teleocidins are largely due to the novel lactam ring (see 2 (iii) Biology of the Teleocidins). These model compounds should also therefore act as useful probes for biological activity.

Finally the compounds (14)-(16) were also considered as appropriate target compounds. Although only indirectly related to the Teleocidins their synthesis is of both theoretical and biological interest. Variation of bond length between (14, X=S) and (12, X-NCH_3) is a significant Ø.39Å for the indole C4-X bond and Ø.34Å for the X-CH_2 bond. It was expected that such differences in bond length could lead to some interesting changes in the facility of lactam formation and to some changes in conformational effects around the ring reflected in the ^1H n.m.r. In addition, these compounds (14)-(16) serve to further explore the biology of the Teleocidins.



(12) X = NCH_3

(14) X = S

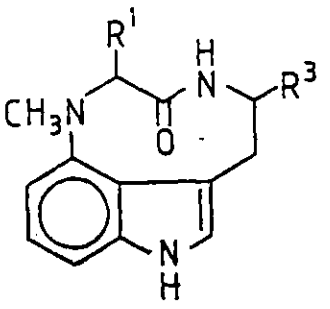
(15) X = CH_2

(16) X = O

(ii) Retrosynthesis

In order to fulfill the dual biological and chemical targets of the project a versatile synthetic scheme was obviously required. The general synthetic strategy adopted for the preparation of (8), (12) and (13) is outlined in Scheme 2.

SCHEME 2

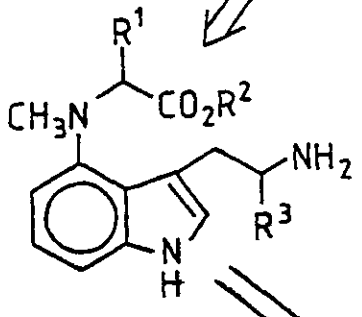


(8) $R^1 = (CH_3)_2CH$; $R^3 = CH_2OH$ (12) $R^1 = R^3 = H$

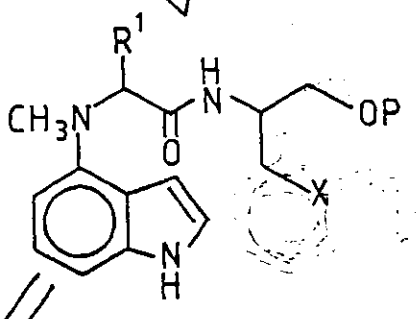
(13) $R^1 = H$; $R^3 = CH_2OH$

a

b



(19)



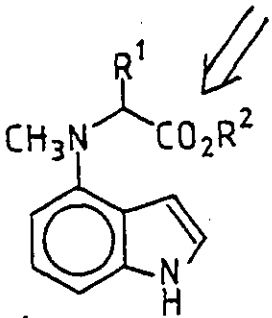
(20) X = leaving group

$R^1 = (CH_3)_2CH$; H

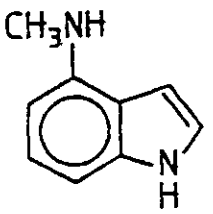
$R^2 = CH_3$; CH_2CH_3

$R^3 = H$; CH_2OP

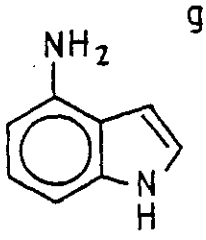
P = H; protecting group



(18)



(17)



(9)

The initial starting material in this sequence is 4-aminoindole (9) which although it is a known compound[28] has never been investigated in detail previously. Selective 4-N-monomethylation of a 4-aminosubstituted indole *via* a two stage formylation and reduction procedure has been reported[29]. Application of these reaction conditions to indole (9) followed by alkylation of the so formed N-methylaminoindole (17) with an appropriate α-bromo-carboxylic acid ester should lead to the key intermediate (18). As can be seen, two alternative routes (a) and (b) (Scheme 2) now arise. To synthesise the tricyclic models and analogues (8), (12) and (13) introduction of a suitable tryptamine or tryptophanol 3-substituent was anticipated to present few problems (path a, Scheme 2). Evidently a versatile procedure was required to permit the preparation of different 3,4-disubstituted compounds (19, R^3=H,CH_2OH,CH_2OP). It was expected that protection of the hydroxymethyl group of (19, R^3=CH_2OH) would be required to prevent cyclisation of the hydroxy group to form a 10-membered lactone ring competing with the required cyclisation to the 9-membered lactam.

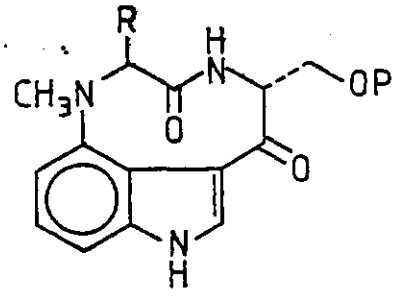
In order to complete the synthesis of the tricyclic models (8), (12) and (13) cyclisation of the *seco* amino acid ester (19) is required. Although a number of macrocyclic lactone forming procedures have been reported[30] few are readily applicable to

lactam formation. However there are now many and varied methods of forming amide (peptide) bonds[31]. It would seem eminently reasonable therefore to apply such methodology to the preparation of the cyclic dipeptide lactams (8), (12) and (13).

Up to this point no mention has been made of stereochemical considerations. Synthesis of the seco amino acid ester (19, $R^1=(CH_3)_2CH$, $R^2=CH_2OP$) in a non-stereoselective manner provides four enantiomers (two diastereomers). Consideration of the diastereomer of (19, $R^1=(CH_3)_2CH$, $R^2=CH_2OP$) which results in the formation of a cyclic product (8) with a trans relative stereochemistry should proceed more rapidly than cyclisation of the other diastereomer. It is well known that epimerisation at the α position of an amino acid readily takes place. Indeed this can be a serious problem in peptide synthesis. In our case however epimerisation of the unreacted diastereomer (12, $R^1=(CH_3)_2CH$, $R^3=CH_2OP$) followed by resubmission to cyclisation could well lead to an additional yield of the trans racemic lactam (8). It should also be noted that a synthesis of both diastereomers of (8) would in any case be of interest.

An attractive alternative route to the tricyclic models (8), (12) and (13) proceeds through the dipeptide (20) (path b, Scheme 2) which could be readily prepared by conventional means from the key intermediate (18). Intramolecular reaction of (20)

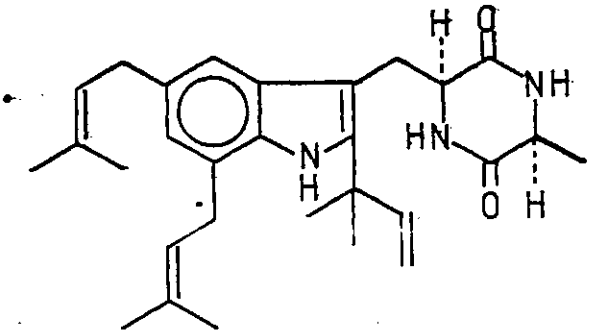
between the indole 3-position and a suitable leaving group X leads to the desired tricyclic products. A bonus to this route is that a chiral amino acid such as serine may be condensed with (18) permitting the stereospecific introduction of the hydroxymethyl substituent. Use of serine in this procedure gives for example (20, X=COCl), which, after intramolecular Friedel Crafts reaction would result in the vinylogous amide (21). Selective reduction of such species to the corresponding indole in the presence of an ester has been reported[32].



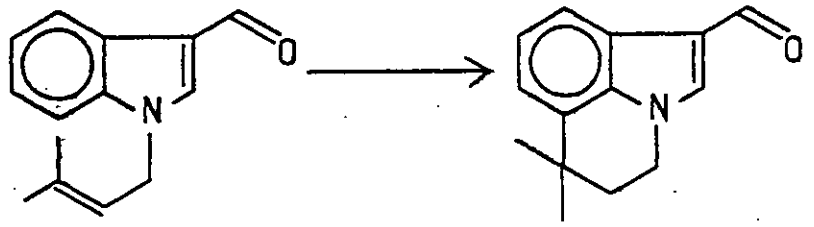
P = protecting group
R = $(CH_3)_2CH$

(21)

Finally, in order to complete a total synthesis of Teleocidin A introduction of the "southern zone" linalyl group is required. It has been postulated that inverted isoprenoid units present in some indole alkaloids such as echinulin (22) may be introduced by rearrangement of a 1-isoprenyl substituent[33]. In addition 1-allyl-3-formylindole (23) has been shown to undergo rearrangement to the 1,3,7-trisubstituted system (24) via an intramolecular Friedel-Crafts reaction[34,35].



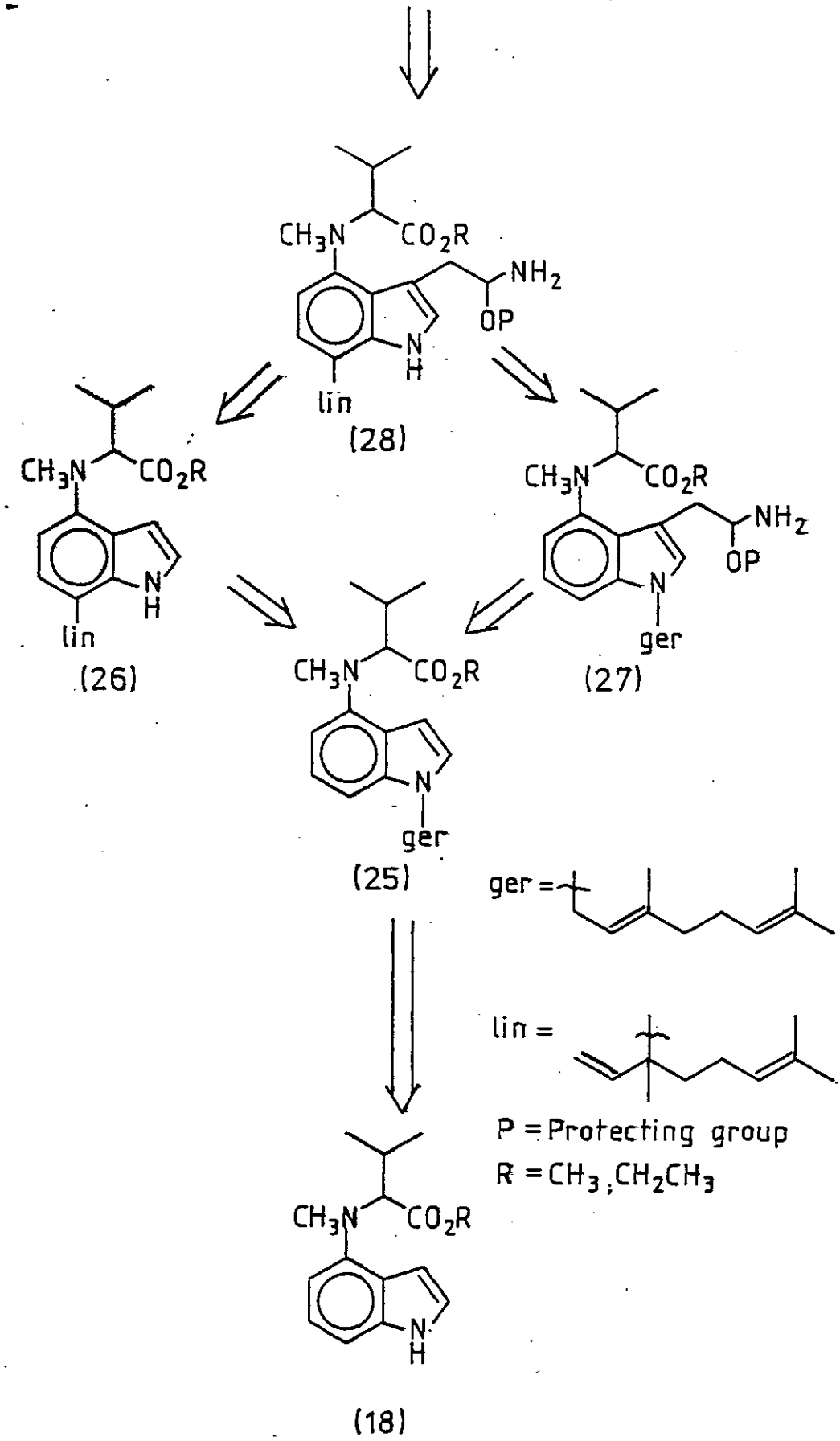
(22)



(23) (24)

In principle therefore a concise approach to the introduction of the linalyl group presents itself (Scheme 3). By choice of the appropriate conditions it should be possible to rearrange a 1-geranyl adduct such as (25, Scheme 3) or more probably a 1,3,4-trisubstituted compound (27) to the desired 7-linalyl substituent. Conditions that might be considered for this transposition would include acid catalysis or conditions favouring an aza-Claisen [3,3] sigmatropic rearrangement. Further manipulation of the rearranged product (26) or (28) could lead to Teleocidin A.

SCHEME 3

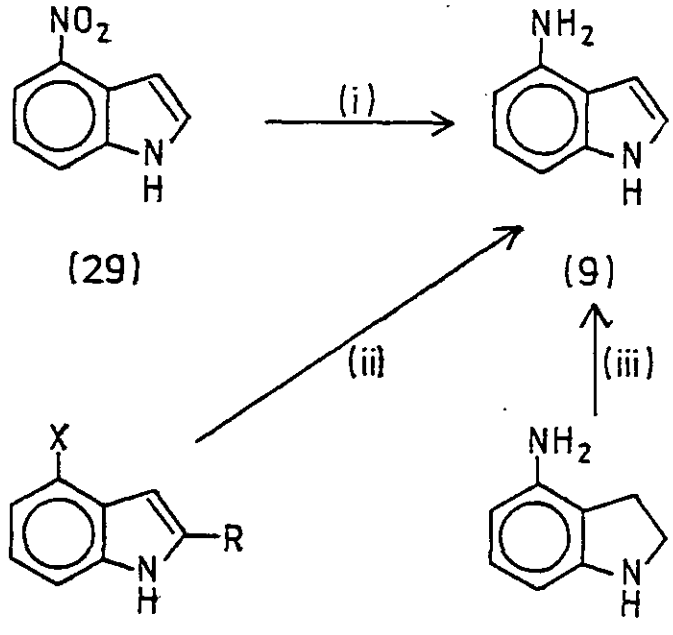

Teleocidin A
CH3N
CO2R
NH2
OP
N
H
lin
(28)
(26)
(27)
ger
(25)
(18)
ger =
lin =
P = Protecting group
R = CH3, CH2CH3

4. Preparation of 4-Substituted Indoles

(i) Introduction

It is evident from the previous section that a successful synthesis of Teleocidin A relies on an efficient route to 4-aminoindole (9). Surprisingly when this project was initiated there were few routes to this relatively simple compound. Essentially three approaches have been adopted in the past which are summarised in Scheme 4:- (a) the reduction of 4-nitroindole[36,37] (29) itself formed in poor yield (<10%) by Fischer indole synthesis[38], (b) by nucleophilic substitution of 4-haloindoles[28,39] (30)

SCHEME 4



(i) [H]. (ii) CuX, NH_4OH. (iii) Pd/C

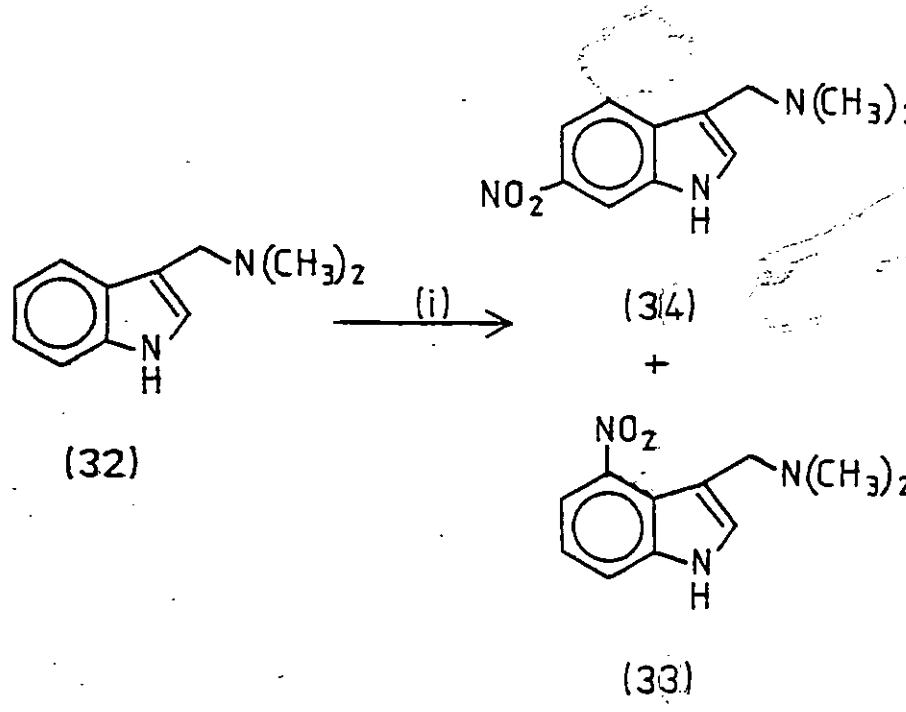
and (c) by Bakke's multi-stage procedure in which commercially available 2,6-dinitrotoluene is

converted in three stages to 4-aminoindoline (31) from which (9) is reported to be formed in poor yield[40].

The second alternative seemed most promising since the starting indole (30, X=Cl, R=CO_2H) is readily available[41] and the procedure conducive to large scale opertions.

Two further reports of 4-aminoindole chemistry were also considered. Gramine (32) is reported to give a mixture of 4- and 6-nitrogramine (33) and (34) when treated with nitric acid in acetic acid (Scheme 5)[27, 42]. Yields are however poor and would involve a regioisomer separation and also additional functional group manipulation at a later stage of a projected synthesis[43].

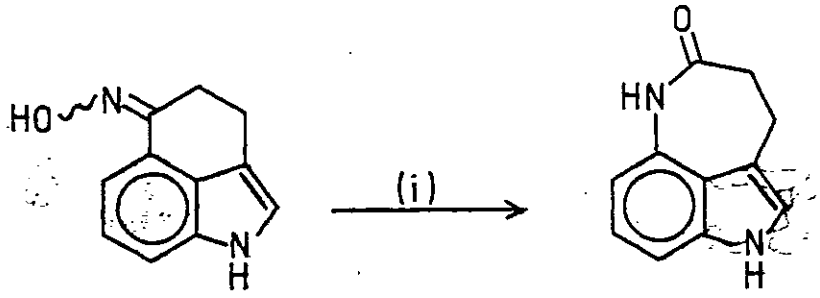
SCHEME 5



(i) HNO_3, AcOH.

Beckmann rearrangement of the oxime (35) of Uhle's ketone is reported to give the seven membered lactam (36), (Scheme 6). Yields are again poor however and Uhle's ketone is not readily available[44].

SCHEME 6



(35) (36)

(i) Polyphosphoric acid.

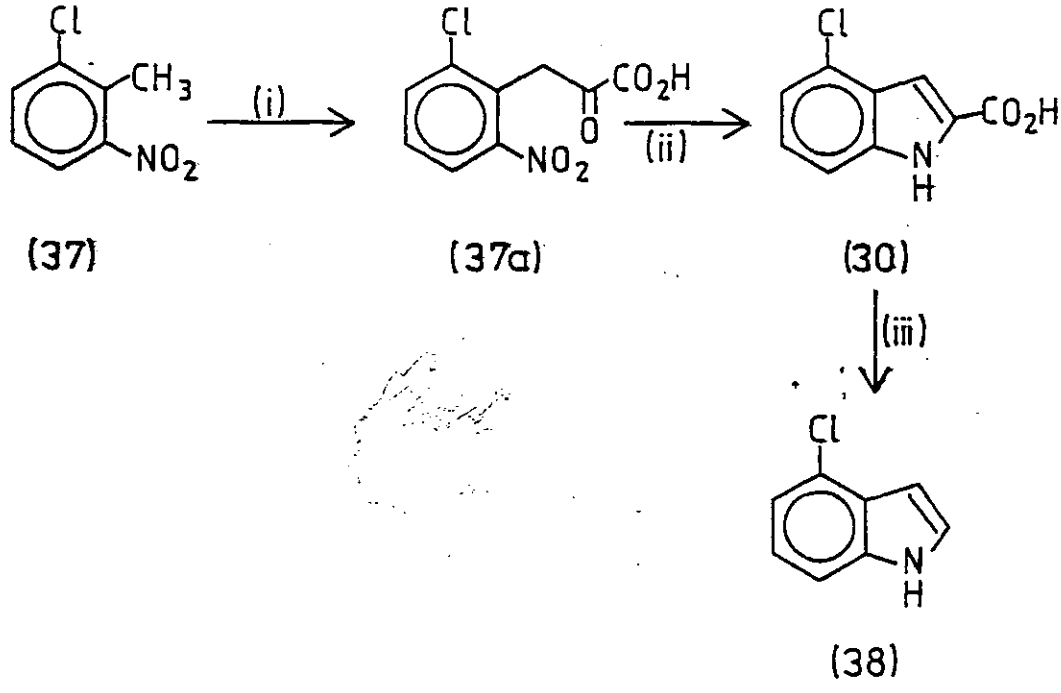
More recently a further two syntheses of the key indole (9) have been reported and will be discussed in the appropriate section[45-47].

(ii) Attempted Amination of 4-Haloindoles (30)

It has been reported by Walton, Holly and Jenkins[28] that the known indole-2-carboxylic acid (30, X=Cl, R=CO_2H) is converted into 4-aminoindole (9) in a 60% yield on treatment with conc. ammonium hydroxide and cuprous chloride. In an attempt to repeat this work the acid (30, X=Cl, R=CO_2H) was synthesised from the commercially available 2-chloro-6-nitrotoluene (37) in two stages according to the literature procedure in a 43% overall yield (Scheme 7)[41a]. Reaction of the indole (30, X=Cl, R=CO_2H) with ammonium hydroxide and cuprous chloride

under a variety of conditions, however, resulted in the isolation of 4-chloroindole (38) only, in modest yields.

SCHEME 7



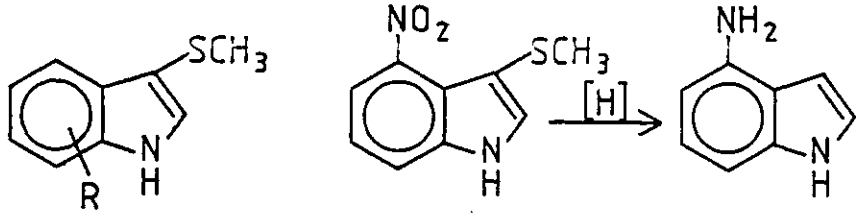
(i) NaOEt, NaOH, EtO_2CCO_2Et. (ii) $FeSO_4$, NH_4OH, or $Na_2S_2O_4$, NaOH, 43% overall. (iii) NH_4OH, CuCl, 260°C, 37%.

It was evident from these results that an alternative approach to 4-aminoindole (9) was required.

(iii) The Gassman Indole Synthesis

Recently Gassman and his coworkers reported a new indole synthesis leading to readily desulphurised 3-methylthioindoles (39)[48,49]. Amongst the indoles synthesised by this new methodology was the

nitroindole (40), formed regiospecifically from 3-nitroaniline which on reduction should lead to the required indole (9).

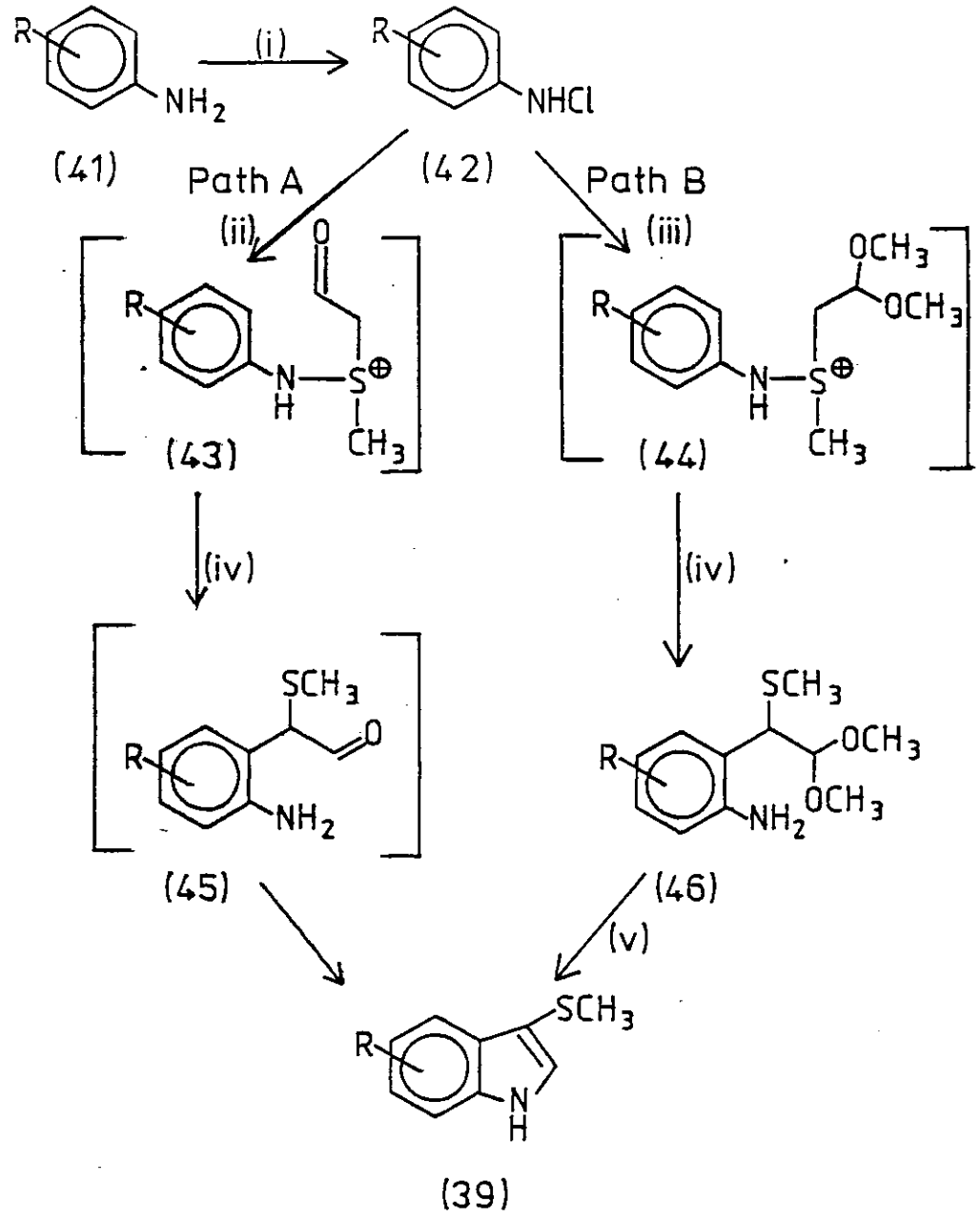


(39) (40) (9)

The mechanism believed to be involved in this one pot multi-stage synthesis is outlined in Scheme 8. N-Chlorination of an appropriately substituted aniline (41) with tert-butylhypochlorite leads to (42). Nucleophilic displacement of chloride with either the aldehyde (47) (Path A) or the acetal (48) (Path B) leads respectively to the azasulphonium salts (43) and (44). Treatment of either salt (43) or (44) with mild base generates a ylid which undergoes Sommelet-Hauser rearrangement to give either the 2-substituted aniline (45, Path A) or (46, Path B). The aldehyde (45) undergoes *in situ* dehydration to the indole (39) while the isolable acetal (46) forms the indole (39) on treatment with dilute mineral acid.

Methylthioacetaldehyde dimethylacetal (48) was readily prepared by reaction of the corresponding bromide[50] (49) with sodium thiomethoxide[51] (Scheme 9). Hydrolysis of the acetal (48) to the aldehyde (47) was however less satisfactory. Treatment of

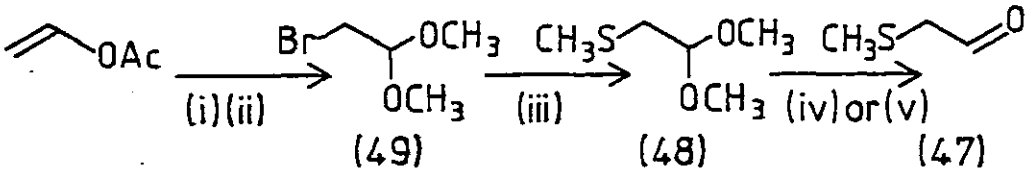
SCHEME 8



(i) $(CH_3)_3COCl$. (ii) CH_3SCH_2CHO (47). (iii) $CH_3SCH_2CH(OCH_3)_2$ (48). (iv) Et_3N. (v) HCl.

(48) with dilute mineral acid at reflux followed by distillation gave only a 19% yield of pure-aldehyde[49,51] (47). Reaction of acetal (48) with silica gel and sulphuric acid according to Conia's procedure[52] gave only incomplete conversion to the product (47). It was found however, that although hydrolysis was inefficient, few side products were formed and so the crude hydrolysis product was used for indole synthesis without any apparently detrimental effects on yields obtained. Alternative hydrolysis procedures investigated were found to be uniformly unsatisfactory.

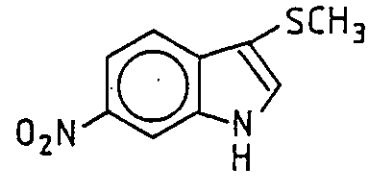
SCHEME 9



(i) Br_2, CCl_4. (ii) CH_3OH, 63%. (iii) $NaSCH_3$, EtOH, THF, 69%. (iv) Ø.1N HCl reflux. (v) SiO_2, H_2SO_4.

Chlorination of 3-nitroaniline followed by treatment with the acetal (48) (Scheme 8, Path B) gave the azasulphonium salt (44, R=3-NO_2). Reaction of this salt however with a number of bases followed by acetal hydrolysis with mineral acid gave only modest yields (<19%) of the deep red nitroindole (4Ø). In addition, the regioisomeric lemon yellow

indole (50) was also formed in variable amounts, in some cases forming half the indolic material isolated.



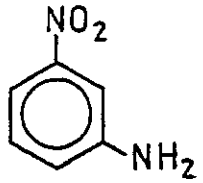
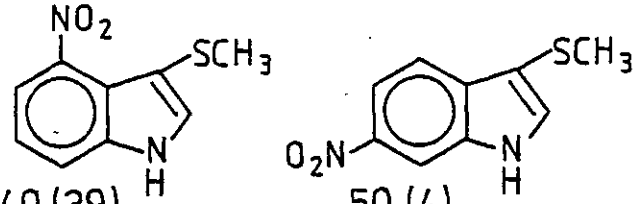
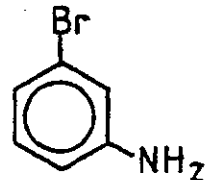
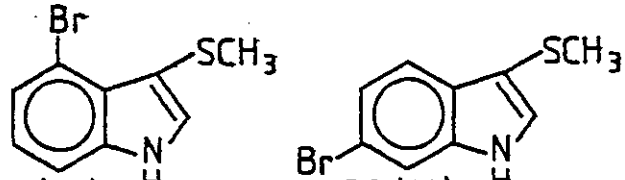
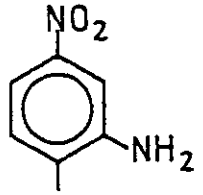
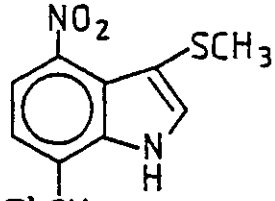
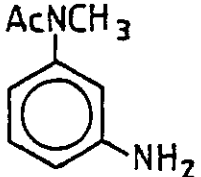
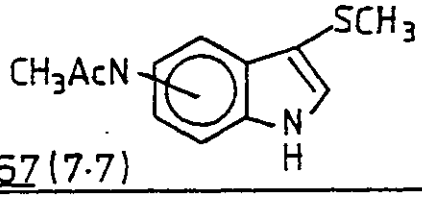
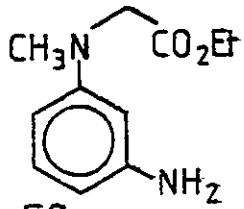
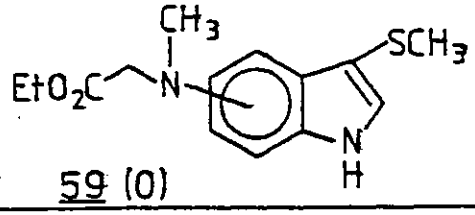
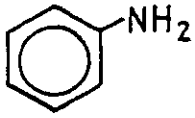
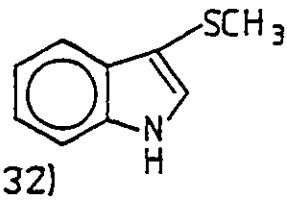
(50)

In view of these poor yields use of the aldehyde (47) (Scheme 8, Path A) was investigated. Treatment of the N-chloroaniline (42, R=3-NO_2) with crude aldehyde (47) (vide supra) and base according to Gassman's procedure[49] gave a 36% yield of the indole (40) and in addition the regioisomeric indole (50) in a 4% yield. The yield of (40) compares favourably with that previously reported[49], however formation of (50) had not been observed previously.

A number of other indoles were prepared by the same procedure (Table 5). 3-Bromoaniline (51) gave in a low yield the two regioisomers (52) and (53) (entry 2). The poor regioselectivity of this reaction is thought to be due to the steric bulk of the bromo substituent. This bulk disfavours rearrangement of ylid (61) by Path a (Scheme 10) compared with rearrangement by Path b.

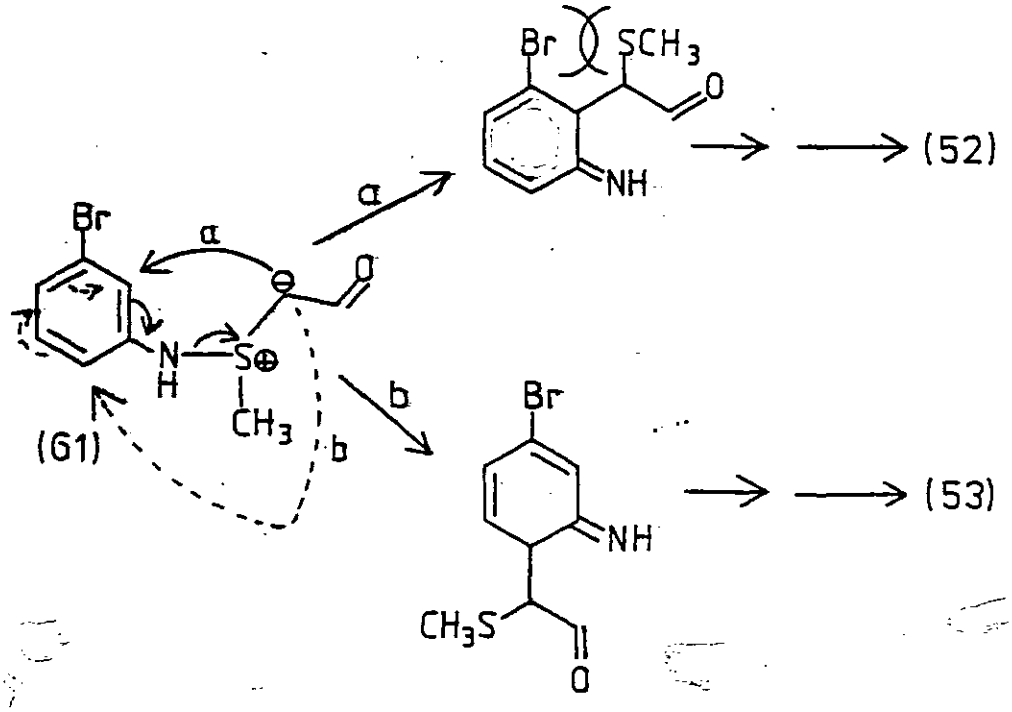
It is evident that the aniline (54) can only form the trisubstituted indole (55). This interesting compound was prepared to provide unambiguous ^1H

TABLE 5:- Synthesis of Indoles from Methylthioacetaldehyde and Substituted anilines

Entry	Aniline	Products (yield%)
1		 40 (39) 50 (4)
2	 51	 52 (13) 53 (14)
3	 54	 55 (35)
4	 56	 57 (7·7)
5	 58	 59 (0)
6		 60 (32)

n.m.r. spectral data for 4,7-disubstituted indoles (vide infra) and as a potential precursor to the Teleocidins.

SCHEME 10

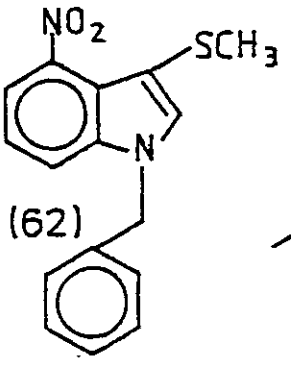


It was unfortunate that the more highly functionalised diamines, (56) and (58) prepared by standard methods proved to be such poor substrates for the Gassman reaction, (entries 4 and 5). It is thought that the failure of these reactions is due to the enhanced electron density of the aromatic ring inhibiting the Sommelet-Hauser rearrangement compared with anilines such as (51) and (54). In addition tert-butylhypochlorite might be expected to chlorinate diamine (58) in the aromatic ring rather than, as required, on nitrogen.

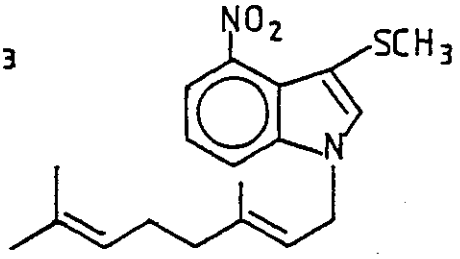
(iv) General Chemistry of 3-Methylthio-4-nitroindole (40)

With the indole (40) available in reasonable quantities a brief study of its chemistry was undertaken with a particular view to utilising the 3-methylthio group to further functionalise the molecule.

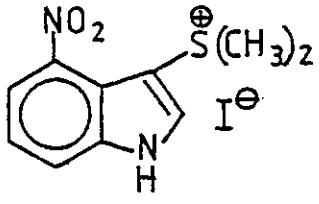
The benzylated indole (62) and a potential aza-Claisen precursor (63) were prepared in excellent yields according to Ley and Heaney's procedure[53] from the corresponding chloride and indole (40). Treatment of indole (40) with methyl iodide in ether gave the pale yellow sulphonium iodide (64) in a 57% yield.



(62)



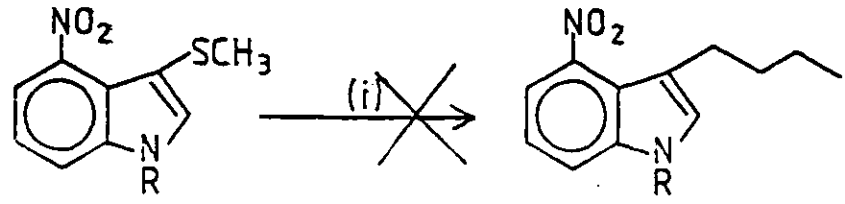
(63)



(64)

It has been reported that vinylic sulphides produce, on treatment with an alkyl Grignard reagent and a nickel (II) catalyst, an alkylated olefin[54]. Neither (40) or (62) however, gave any identifiable product on treatment with $NiCl_2(PPh_3)_2$ and n-butyl magnesium bromide (Scheme 11) under a variety of conditions.

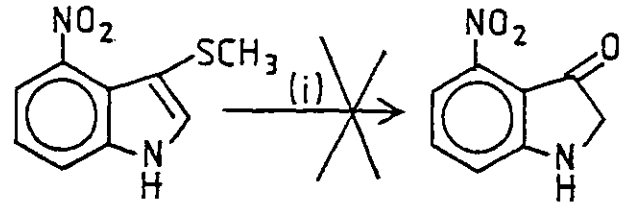
SCHEME 11



(40) R = H (62) R = Bz

(i) $CH_3(CH_2)_3MgBr$, $NiCl_2(PPh_3)_2$

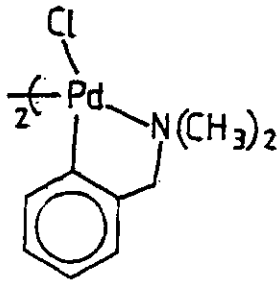
The hydrolysis of vinyl sulphides to carbonyl compounds is well known but (40) gave none of the indoxyl (65) on treatment with for example mercuric acetate and acid[55].



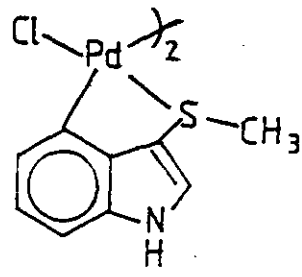
(40) (65)

(i) $Hg(OAc)_2$, H^+

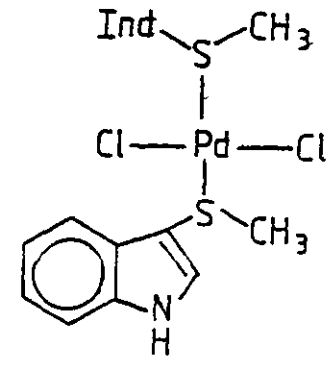
The nucleophilic substitution of species such as (66) has been known for some years[56,57]. In an effort to prepare an analogous species (67) 3-methylthioindole (60) was treated with Li_2PdCl_4. Microanalysis of the resultant orange product however suggested a complex of structure (68) due to the thiophilicity of palladium.



(66)



(67)



(68)
Ind = Indole

In conclusion these studies demonstrated that the indole (40) required reductive desulphurisation as a prelude to further functionalisation of the molecule.

(v) Reduction and Desulphurisation of 3-Methylthio-4-Nitroindole (40)

Gassman has reported that the 3-methylthioindoles (39) are readily desulphurised by Raney nickel[49]. It was found however that neither the nitroindole (40) nor its alkylated derivatives (62) and (63) reduced readily by the same procedure. In particular it was found that amongst the reduction products isolated were 4-N-alkyl adducts formed by reductive alkylation of the amine with the hydroxylic solvent[58]. Also, although the nitro group reduced rapidly, desulphurisation occurred much more slowly (see Table 6). However, the simple indole (60) was readily reduced by the same Raney nickel[59].

TABLE 6:- Reduction of 3-Methylthio-4-nitroindoles

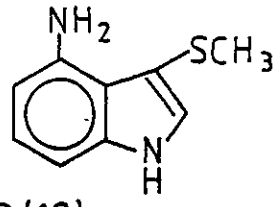
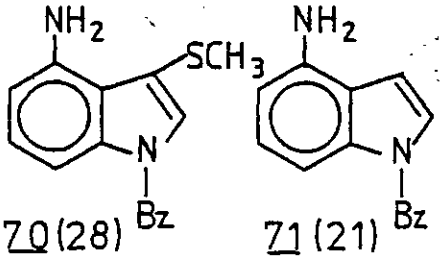
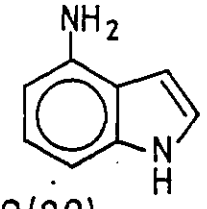
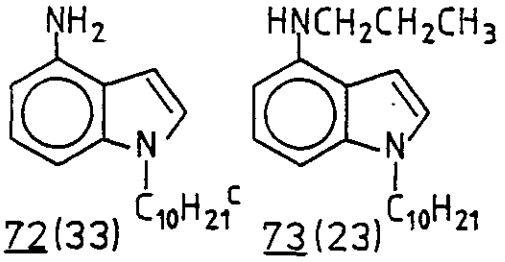
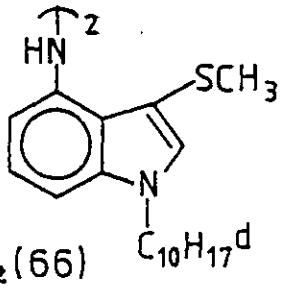
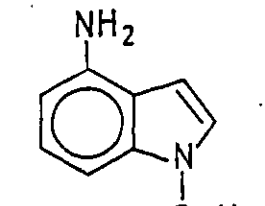
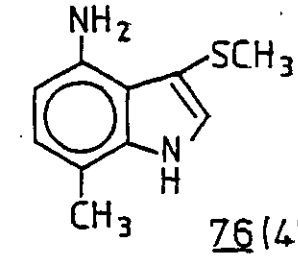
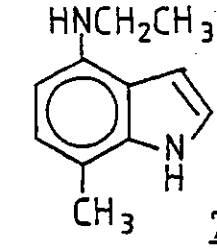
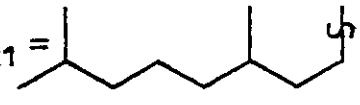
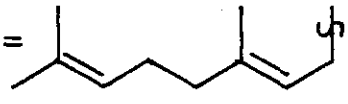
Entry	Substrate	Conditions[a]	Product(s) (yield%)[b]
1	40	RaNi, EtOH	 69 (10)
2	62	RaNi, EtOH	 70 (28) 71 (21)
3	40	RaNi, nPrOH	 9 (80)
4	63	RaNi, nPrOH	 72 (33) 73 (23)
5	63	$LiAlH_4$, THF	 74 (66)
6	40	$NiCl_2$, $NaBH_4$	9 (76)

TABLE 6 (cont)

Entry	Substrate	Conditions[a]	Product(s) (yield%)[b]
7	62	$NiCl_2$.$NaBH_4$	71(72)
8	63	,,,, ,,,,	 75(71)
9	55	,,,, ,,,,	 76(47)
10	76	RaNi.EtOH	 77(14)

[c] $C_{10}H_{21}$ = 

[d] $C_{10}H_{17}$ = 

a. Reflux in the indicated solvent until reaction complete.

b. Yield of chromatographically homogeneous material.

Reduction of (63) with lithium aluminium hydride led, as expected, to the highly crystalline hydrazo compound (74) (Table 6, entry 5). Finally it was found that treatment of a refluxing ethanolic solution of the indole (40, 62 or 63) with nickel boride[60] generated in-situ from excess nickel (II)

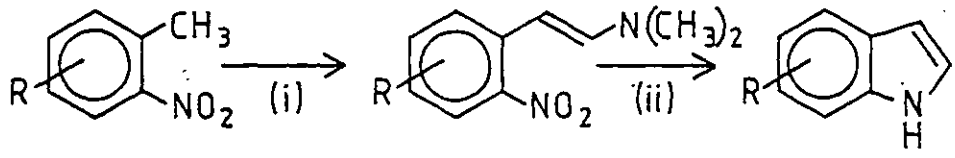
chloride and sodium borohydride gave satisfactory yields of the required 4-aminoindoles (Table 6). A further advantage of this procedure was that no reduction of the olefinic bonds present in (63) took place (compare entries 4 and 8, Table 6). As with Raney nickel, 3-methylthio-4-aminoindoles such as (69) and (70) were formed as intermediates during the reduction, which then underwent smooth desulphurisation.

Although yields of the aminoindoles (9) and (71) were satisfactory, isolation of the products from the large excess of inorganic material produced was laborious and reaction conditions did not lend themselves to large scale work. With the additional drawback of having to separate the two regioisomers (40) and (50) it was decided to develop a more practical synthesis of 4-aminoindole (9).

(vi) The Leimgruber-Batcho Indole Synthesis

In 1977 Leimgruber and Batcho patented an elegant two stage procedure for synthesising indoles from 2-nitrotoluenes (78), (Scheme 12)[61]. Condensation of dimethylformamide dimethylacetal (DMFDMA) with 2-nitrotoluenes (78), first reported by Meerwein[62] results in the efficient formation of the enamine (79). Facile reduction yields the indole (80) in what is probably the most rapid and highest yielding, of general indole syntheses. In addition this route is regiospecific and so is especially suitable for the synthesis of 4-substituted indoles.

SCHEME 12

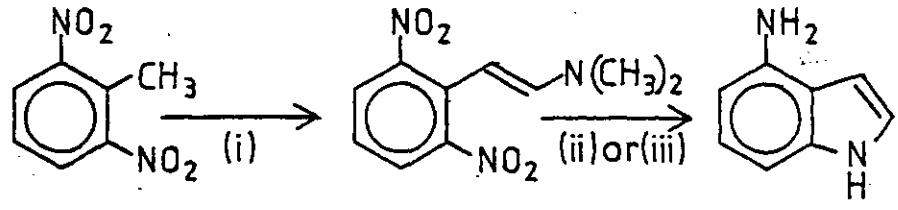


(78) (79) (80)

(i) $(CH_3)_2NCH(OCH_3)_2$, D.M.F. (ii) H_2, catalyst or Fe/AcOH/EtOH.

Until recently no reports on the synthesis of 4-aminoindole (9) by this method had been made. It was found that the doubly activated commercially available 2,6-dinitrotoluene (81) reacted smoothly and rapidly with DMFDMA to give the deep purple enamine (82) in yields routinely greater than 90%. The <u>trans</u> geometry of (82) was assigned from the 14Hz coupling constant for the two vinylic protons resonating at δ5.28 and 6.41.

SCHEME 13



(81) (82) (9)

(i) $(CH_3)_2NCH(OCH_3)_2$,D.M.F., >90%. (ii) 10% Pd/C, H_2, 60p.s.i., T.H.F. 89%. (iii) EtOH, AcOH, Fe, 69%.

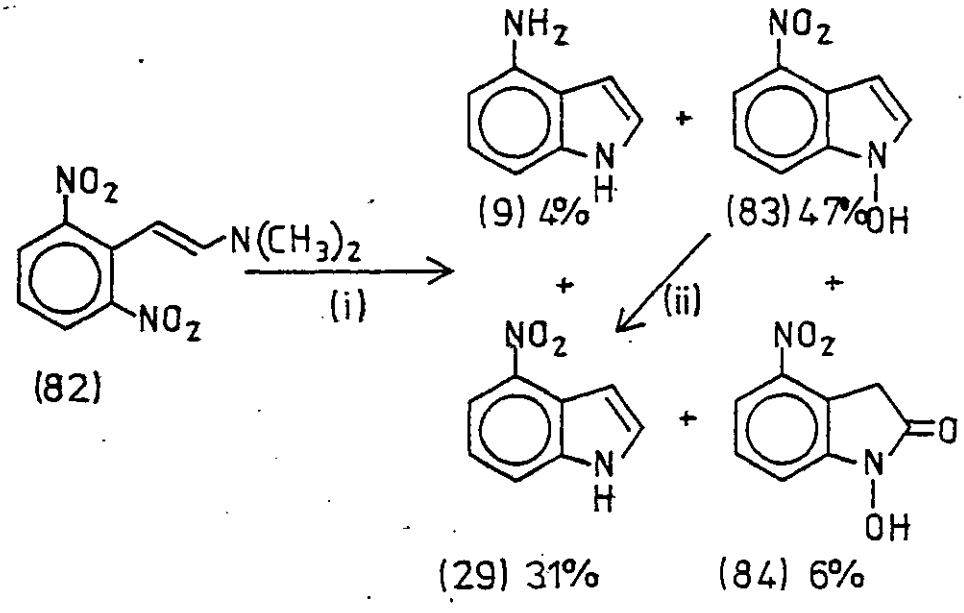
Reduction of the crude enamine (82) to (9) was accomplished with either iron/acetic acid/ethanol or, more efficiently, in an 89% yield by catalyic reduction in T.H.F. The product was isolated as a slightly oily solid which was however sufficiently pure for further tranformation (Scheme 13). Recently Kruse reported the reduction of enamine (82) to (9) by catalytic reduction in benzene[47], however attempts to repeat this result were unsuccessful. The enamine (82) is particularly susceptible to intermolecular reactions generating dimeric and trimeric products. To overcome this problem rapid reduction is necessary, that is a relatively high catalyst to substrate ratio. In benzene, however, as the reaction proceeds water is generated which being immiscible with the solvent causes the catalyst to conglomerate and effectively reduce the catalyst to substrate ratio. In THF no such problem can arise due to the miscibility of the solvent and water.

It was found that the reduction of enamine (82) with iron and acetic acid in ethanol gave inconsistent results. Yields of the desired amine (9) as high as 69% were recorded in some instances. Other experiments resulted however, in the formation of only very low yields of (9) and, in addition, up to 10% of the partially reduced 4-nitroindole (29). A number of conditions designed to selectively produce 4-nitroindole (29) from the enamine (82) were however unsuccessful. Somei's group[45,46] have shown

that the enamine (82) on treatment with 4 mole equivalents of titanium (III) chloride, that is insufficient to reduce the enamine (82) completely to (9) gave a number of products (Scheme 14). It was found that 1-hydroxy-4-nitroindole (83) was converted to (29) on treatment with ethyl bromoacetate to give a 67% overall yield of (29).

The utility of the Leimgruber-Batcho synthesis has been further extended by the report of the preparation of racemic tryptophans[63]. This involves the functionalisation of enamines such as (79) prior to cyclisation. Attempts to exploit this methodology for the synthesis of 3,4-disubstituted indoles however, proved disappointing. The substituted acrolein (85) and the enamino aldehyde (86) were

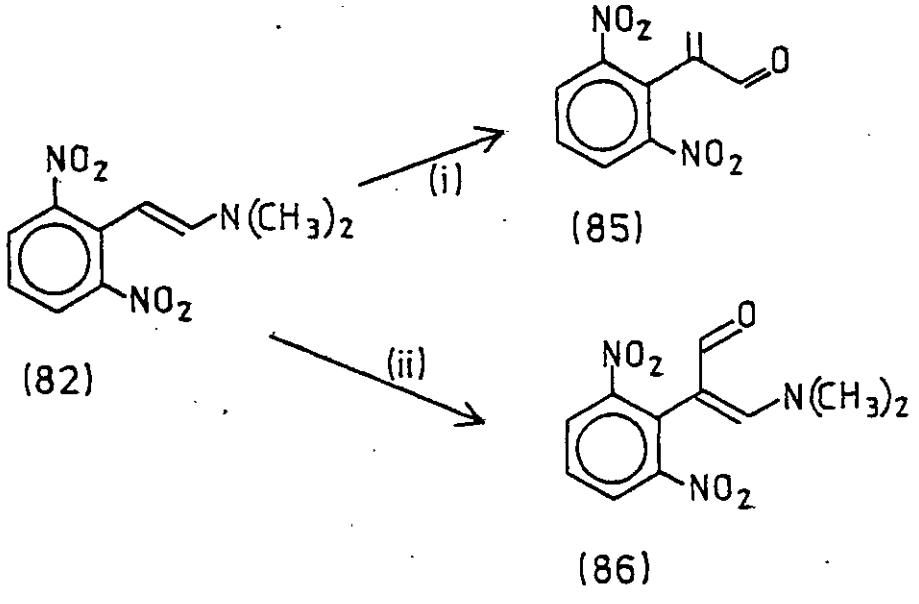
SCHEME 14



(i) $TiCl_3$, MeOH. (ii) (1) $BrCH_2CO_2Et$, Et_3N.
(2) $NaHCO_3$, MeOH, 87%

obtained in excellent yields from the enamine (82) by literature procedures (Scheme 15)[63]. Unfortunately neither (85) or (86) would undergo further functionalisation and this potentially useful route to 3,4-disubstituted indoles was therefore abandoned. Reasons for the failure of this route are by no means obvious, but are probably due to steric factors. It would appear that the electron withdrawing properties of the aromatic ring would favour the Michael addition and condensation reactions that were investigated. Both (85) and (86), however, have an exocylic olefinic system in conjugation with the aromatic ring. The exocyclic system would therefore

SCHEME 15

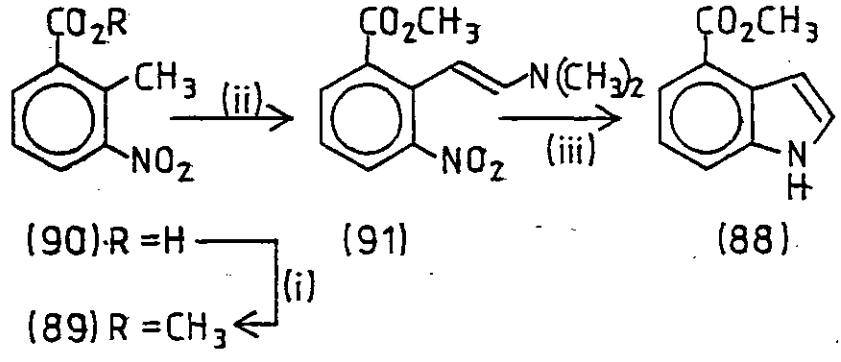


(i) $(CH_3)_2NH$, HCHO, AcOH, 92%. (ii) $POCl_3$, D.M.F., 82%

be expected to adopt a conformation that is coplaner with the aromatic ring. This effect would bring the sites designed to undergo reaction into close proximity with the two large ortho nitro substitutents.

An intriguing alternative route to 4-aminoindole (9) that has not been previously explored is the Curtius rearrangement of indole-4-carboxylic acid (87). Methyl indole-4-carboxylate (88) is a well known intermediate in ergot alkaloid synthesis. Older reports of the synthesis of this compound have generally been multistage with poor overall yields[64]. Recently however two groups[65,66] have reported the synthesis of the ester (89) using the Leimgruber-Batcho methodology (Scheme 16). This route was successfully reproduced to give a 65% overall yield of (88) from the starting benzoate ester (89) which was in turn prepared from the commercially available acid (90).

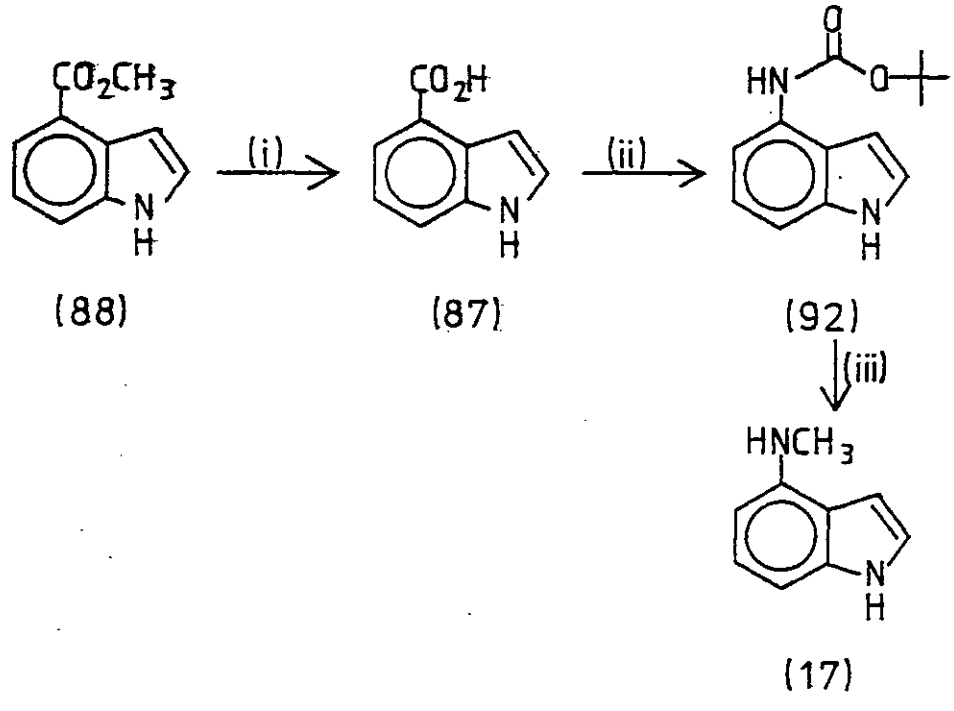
SCHEME 16



(i) CH_3OH, HCl 88%. (ii) D.M.F.D.M.A. 93%.
(iii) H_2/Pd/C, 70%

Hydrolysis of the ester proceeded smoothly to give a 73% yield of the desired acid (87). Curtius rearrangement of carboxylic acids has classically required quite drastic conditions, making it unsuitable for use with indoles. Yamada in 1972, however, reported the use of diphenyl phosphoryl azide for carrying out this transformation under mildly basic conditions[67]. On treatment with this reagent in refluxing tert-butanol and triethylamine, the acid (87) underwent a smooth rearrangement to the urethane (92) (Scheme 17). Interestingly the urethane (92) was reduced to 4-N-methylaminoindole (17) with lithium aluminium hydride in a low but unoptimised yield.

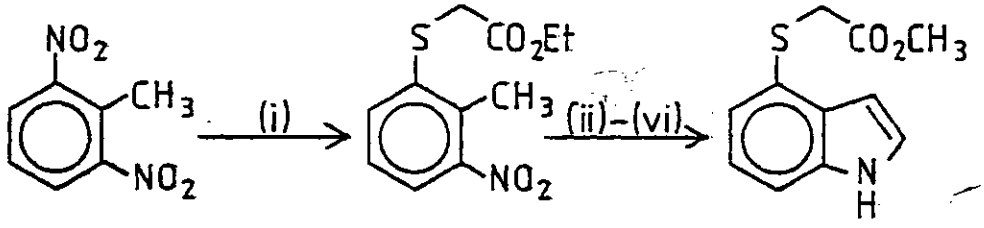
SCHEME 17



(i) NaOH, EtOH, 73%. (ii) $(PhO)_2P(O)N_3$, Et_3N, t-BuOH, 61%. (iii) $LiAlH_4$, T.H.F, 37%.

2,6-Dinitrotoluene (81) is a particularly versatile intermediate for the synthesis of 4-substituted indoles. Kozikowski synthesised the indole (93)[68] by a multistage modification of the Leimgruber-Batcho method from the nitrotoluene (94). This was prepared in turn from (81) by treatment with ethyl mercaptoacetate in H.M.P.A. in an excellent yield (Scheme 18). The indole (93) was of some interest as a precursor of a thio-analogue (14) of the teleocidin skeleton. It was found however that although (94) was readily prepared, only low yields of the indole (93) were isolated.

SCHEME 18

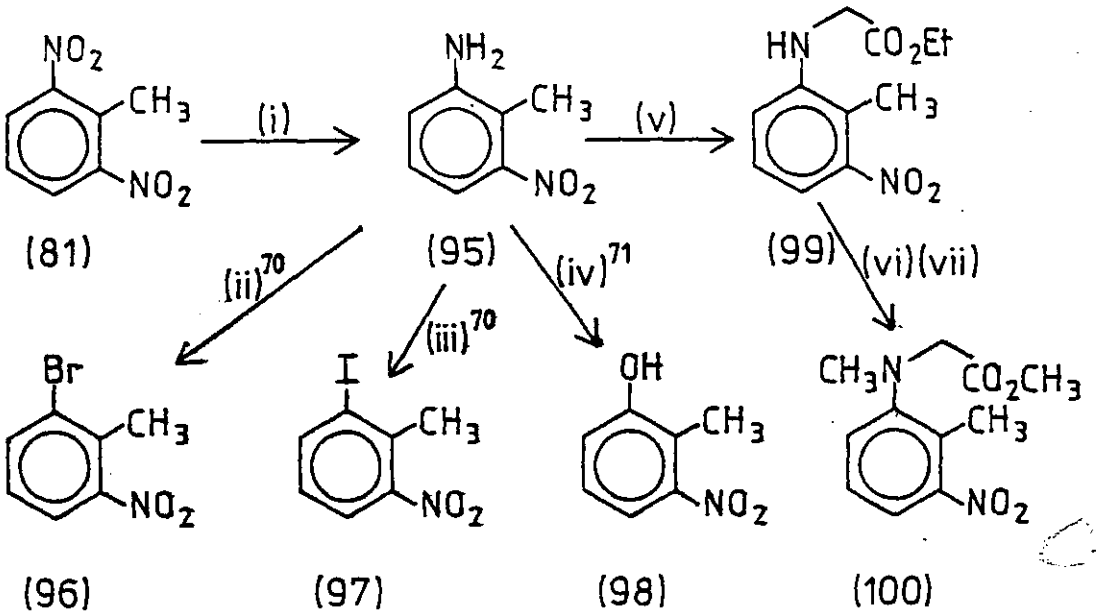


(81) (94) (93)

(i) $HSCH_2CO_2Et$, LiOH, H.M.P.A. (ii) KOH, CH_3OH, 78%. (iii) D.M.F.D.M.A. (iv) HCl (v) $FeSO_4$, NH_4OH. (vi) CH_2N_2, Et_2O, <20% overall.

Partial reduction of (81) according to Heck's procedure[69] gave the useful nitroaniline (95) from which a number of potential indole precursors were readily prepared according to literature procedures (Scheme 19).

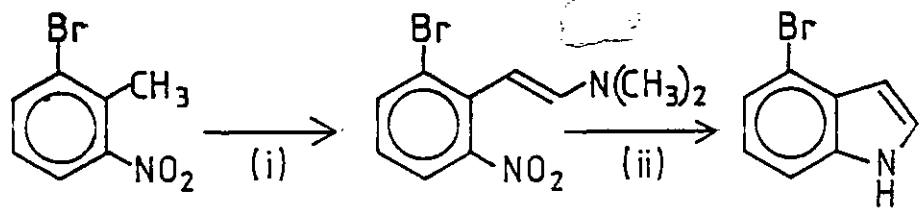
SCHEME 19



(i) Et_3N, HCO_2H, Pd/C, 66%. (ii) $NaNO_2$, CuBr. (iii) $NaNO_2$, I_2. (iv) $NaNO_2$, heat. (v) $KHCO_3$, KI, $BrCH_2CO_2Et$, D.M.F. (vi) NaOH, EtOH. (vii) CH_3I, K_2CO_3, D.M.F.

The bromocompound (96) was converted in two stages into 4-bromoindole (101) (Scheme 20). Reduction of the enamine (102) proceeded rapidly at atmospheric pressure in the presence of Raney nickel[59], to give a 59% overall yield of (101) from (96).

SCHEME 20



(96) (102) (101)

(i) D.M.F.D.M.A. 85%. (ii) RaNi, H_2, 1 atmosphere 69%.

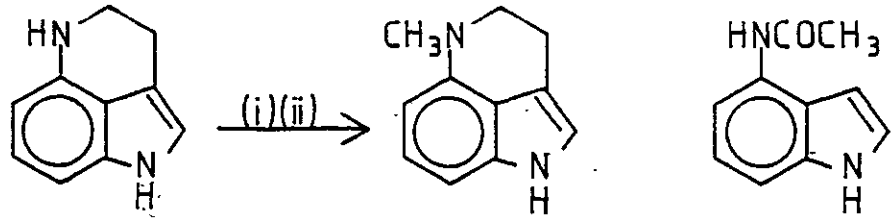
(vii) Conclusion

Three new procedures have been developed for the synthesis of 4-aminoindole (9) of which one is suitable for the large scale preparation of this key intermediate. In addition, a number of other 4-substituted indoles have been efficiently synthesised by similar procedures.

5. Preparation of 4-N-Mono, and 4-N,N-Dialkylamino-indoles

(i) As 4-aminoindole (9) was now readily available its selective N-alkylation was undertaken. In principle 4-aminoindole may be considered to be an ambident substrate for alkylation, since both the 4-amino group and the indole 1-position are potential reactive sites. Hester has however previously prepared the methylated tetrahydropyrrolo-[4,3,2-d,e] quinoline (103) by a two stage formylation/reduction sequence from (104)[29]. In addition, Walton and

Holly[28] have also reported the acetylation of (9) to give 4-acetamidoindole (105).

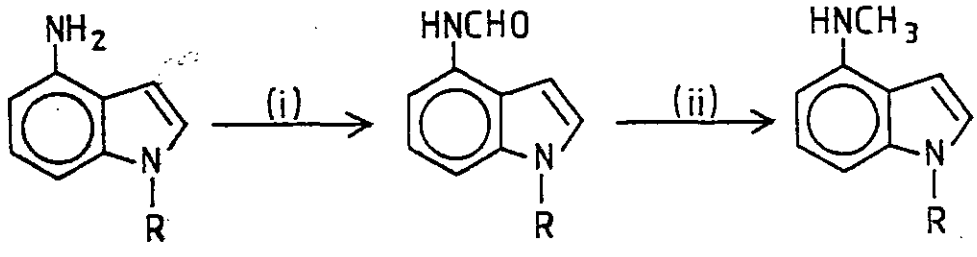


(104) (103) (105)

(i) $CH_3COOCHO$, Et_2O. (ii) $LiAlH_4$, T.H.F.

Treatment of the amine (9) with formic acetic anhydride[72] gave the air stable crystalline 4-formamidoindole (106) as the only product in an excellent yield. 4-Aminoindole was found to rapidly darken in air and was routinely converted to the more stable formamide (106) to assist storage. Reduction

SCHEME 21



(9) R = H (106) R = H (17) R = H

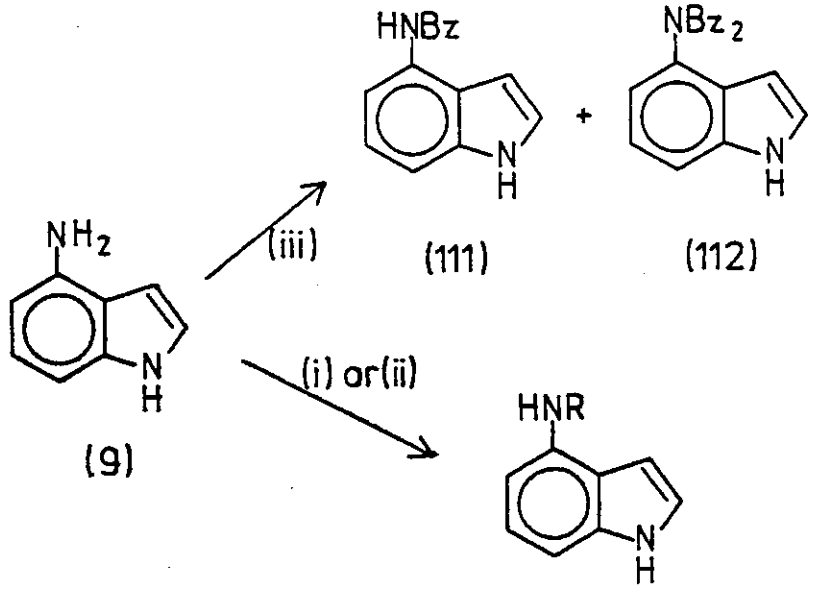
(71) R = Bz (107) R = Bz (108) R = Bz

(i) $CH_3COOCHO$, T.H.F. (9) -> (106) 82%, (71) -> (107) 77%. (ii) $LiAlH_4$, T.H.F. (106) -> (17) 78%, (107) -> (108) 41%.

of the formamide (106) gave, in good yield, the methylamine (17) (see also Section 4 (iii)) (Scheme 21)[73]. The methylated indole (17) was less stable to air than (9) although the crystalline 1-benzylindole (108) was quite stable.

The N-alkylamino acid esters (109), (110) (Scheme 22) were prepared by treating (9) with the corresponding 2-bromoester and silver oxide. Yields in this sequence were poor, due to the oxidation of (9) by silver oxide to a number of uncharacterised highly coloured products. However treatment of (9) with ethyl bromoacetate in the presence of potassium carbonate and potassium iodide gave an excellent yield of (109). There was no evidence in this reaction of dialkylated products. By contrast, however, treatment of indole (9) with benzyl bromide under the same conditions gave a 23% yield of 4-N,N-dibenzylaminoindole (112) in addition to the desired (111). Under a variety of reaction conditions it was found that methyl-2-bromo isovalerate did not react with 4-aminoindole. This result will be discussed further later in this section.

SCHEME 22



(109) $R = CH_2CO_2Et$

(110) $R = CH(CH_3)CO_2Et$

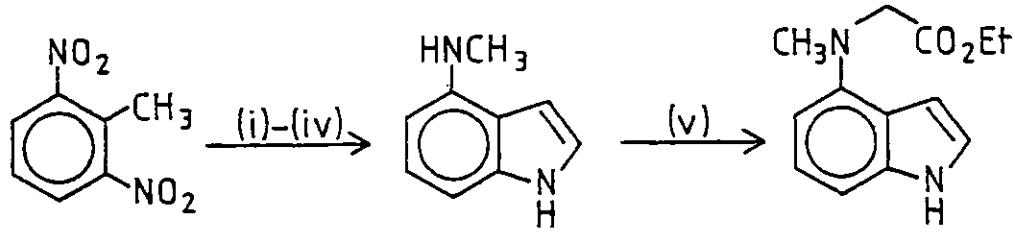
(i) Ag_2O, RBr, D.M.F. (ii) K_2CO_3, KI, $BrCH_2CO_2Et$ (109) 84%. (iii) K_2CO_3, KI, BzBr, (111) 47% and (112) 23%

(ii) <u>4-N,N-Dialkylaminoindoles</u>

Monoalkylation of 4-aminoindole (9) had proceeded readily. However, attempts to prepare 4,N,N-dialkylaminoindoles were with one exception not at all easy. Treatment of 4-N-methylaminoindole (17) with ethyl bromoacetate, potassium carbonate and potassium iodide in DMF gave excellent yields of the stable crystalline N,N-dialkyl glycine (113). This compound which was required for the synthesis of the model

lactams (12) and (13) (see Retrosynthesis, Scheme 2), became a key intermediate in the investigation of the chemistry of the 4-aminoindole system due to its stability and ready availability. As summarised in Scheme 23, this important compound was prepared in five stages from the commercially available 2,6-dinitrotoluene (82). Overall yields of up to 36% were obtained which represent yields of greater than 80% for each stage. Also, purification was only necessary at the final stage.

SCHEME 23



(82) (17) (113)

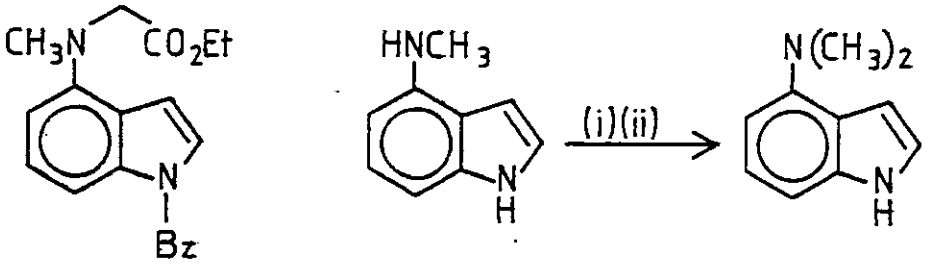
(i) D.M.F.D.M.A., D.M.F. (ii) H_2/Pd/C, T.H.F. (iii) $CH_3COOCHO$. (iv) $LiAlH_4$. (v) $BrCH_2CO_2Et$, K_2CO_3 KI, D.M.F, 30% overall.

Somewhat less successful was the attempted preparation of (113) from the glycine derivative (109) by reaction with methyl iodide. Not only was the recovery of material inefficient but conversion to the desired (113) was incomplete and product and starting material were only poorly separated by a

variety of t.l.c. solvent systems. The failure of this reaction is probably due to the low nucleophilicity of the alkylated amino acid ester (109).

The 1-benzyl dialkylglycine derivative (114) was prepared in a low yield from the benzyl derivative (108) by treatment with silver oxide and ethyl bromoacetate. An alternative and more efficient route to this potentially useful protected indole will be discussed in Section 6.

The 4-N,N-dimethylaminoindole (115) was prepared by iterative formylation/reduction of the monomethyl adduct (17). This compound was synthesised as a model to study the chemistry of the 4-aminoindole system.

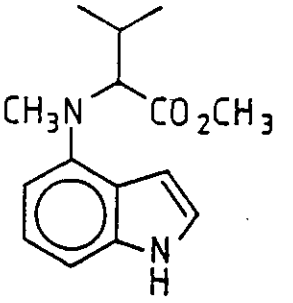


(114) (17) (115)

(i) $CH_3COOCHO$, 84%. (ii) $LiAlH_4$, 95%.

Numerous attempts to synthesise the dialkylated valine (116) by the reaction of (17) with methyl-2-bromo<u>iso</u>valerate[74] under a wide variety of reaction conditions proved uniformly unsuccessful. It was thought that this failure was due to both the steric

bulk of the 1-methylethyl group and to the ability of the bromo ester to undergo elimination of HBr with base.

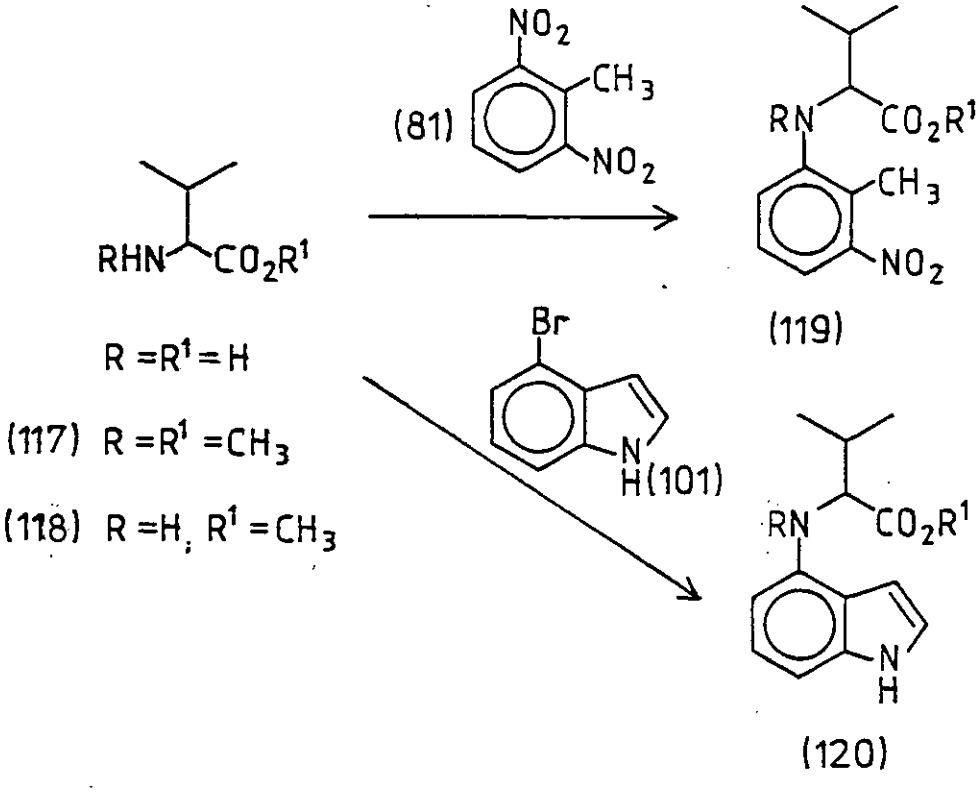


(116)

Evidently from these results a different approach to the key intermediate (116) was required. An attractive route to such an aminoindole would appear to be *via* the nucleophilic displacement of an aromatic substrate by valine, N-methylvaline methyl ester (117) or by valine methyl ester (118). The N-methylamino acid ester (117) was prepared by a four stage literature procedure, involving esterification[75], carbobenzoxylation[76], methylation with methyl iodide and silver oxide[77] and finally decarbobenzoxylation with H_2/Pd/C. A number of experiments of the general form outlined in Scheme 24, however, demonstrated the futility of this approach. Amongst the evident drawbacks of this methodology are the low nucleophilicity of the amino acid amine and the possibility of polymerisation of valine leading to polyvalyl peptides. It was anticipated that toluene (119) formed by these nucleophilic displacements and

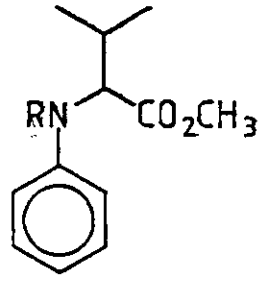
the simpler model compound (100) would undergo the Kruse modification[47] of the Leimgruber Batcho synthesis. In this modification the more reactive tris(dimethylamino)methane is substituted for DMFDMA to facilitate the reaction of deactivated nitrotoluenes. 4-Bromoindole (101) would, of course, give the required indole (116) with N-methylvaline methyl ester (117). With the failure of this potentially very useful procedure a futher alternative route to compound (116) was required.

SCHEME 24



Both aniline and N-methylaniline which were used as models for (9) and (17) respectively, were shown to undergo reductive alkylation with methyl-2-keto-

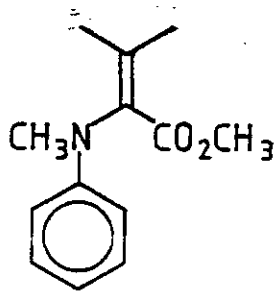
isovalerate[78] and sodium cyanoborohydride[79], to give (121) and (122). Unfortunately application of this procedure, which is performed under weakly acid conditions, to 4-aminoindole (9) resulted in the formation of complex reaction mixtures. It is well known that indoles are reduced to indolines with sodium borohydride under acidic conditions[80]. Also, it was found that the mild acid conditions employed also resulted in considerable amounts of polar polymeric material.



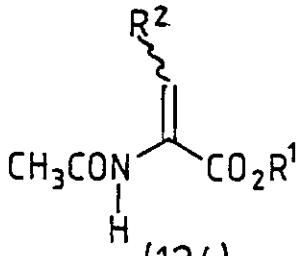
(121) R = H

(122) R = CH_3

To further investigate this reductive alkylation procedure the dehydrovaline derivative (123) was prepared from N-methylaniline and methyl-2-ketoisovalerate by boiling in toluene containing 4-toluenesulphonic acid in an 80% yield. The compound was isolated as a stable pale yellow oil.



(123)

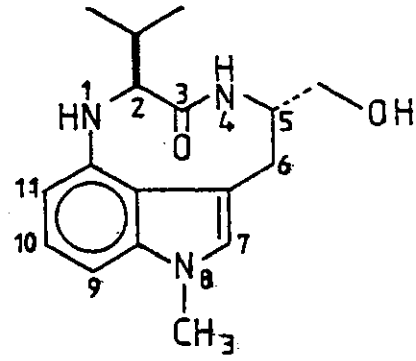


(124)

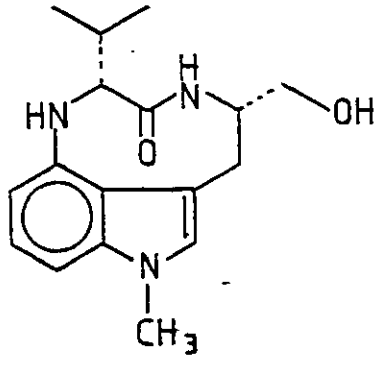
A number of procedures are known for the reduction of enamines and N-acylated dehydroamino acids (124)[81]. Application of several of these procedures to the enamino ester (123) failed completely! Particularly disappointing was the failure of rhodium catalysed hydrogenation methods successfully employed for the chiral reduction of N-acyldehydroamino acids (124)[81e] to acylamino acids. Reduction of the dehydrovaline species (123) present a number of difficulties particularly as the double bond is tetrasubstituted disfavouring conjugate reduction and classical hydrogenation procedures.

It was eventually found that (123) was cleanly and efficiently reduced by ten mole equivalents of magnesium in methanol to give the valine derivative (122) in isolated yields of greater than 80%. This simple and effective procedure has previously been applied to the reduction of acrylamides[82] and is thought to proceed by a series of one electron transfers. More important however was the discovery that indole itself could be recovered intact when treated with the MeOH/Mg system.

From these results it appeared therefore that a facile sythesis of the N-methyl indolyl valine (116) was now at hand. Treatment of 4-N-methyl aminoindole (17) with methyl-2-ketoisovalerate and 4-toluene-sulphonic acid followed by reduction of the crude dehydroamino acid ester resulted in the isolation of a 61% yield (82% based on recovered starting material) of material initially identified as the desired product (116). However subsequent 3-substitution and cyclisation of the 3,4-disubstituted product gave a separable diastereomeric mixture of the two tricylic products, (125a) and (125b). X-ray analysis of the more polar cis isomer (125b) revealed a remarkable and unexpected shift of the N-methyl group from the 1-position to the 8-position (see (125a) for numbering system). The synthesis of these two tricylic lactams will be fully discussed in subsequent sections.



(125a)

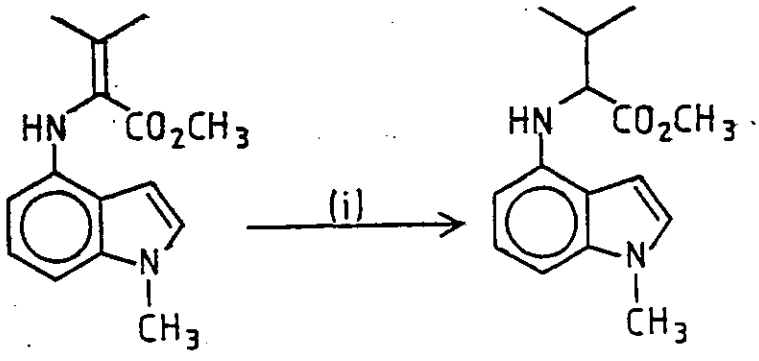


(125b)

Re-examination of the material previously identified as the N-methylvaline derivative (116) showed that the N-methyl group had rearranged during

the reaction of 4-N-methylaminoindole (17) with 4-toluenesulphonic acid and methyl-2-ketoisovalerate. The dehydroamino acid ester so formed was identified as (126) which on reduction gave the 1-methylindole (127) (Scheme 25). This novel rearrangement reaction will be discussed in detail in the next section.

SCHEME 25

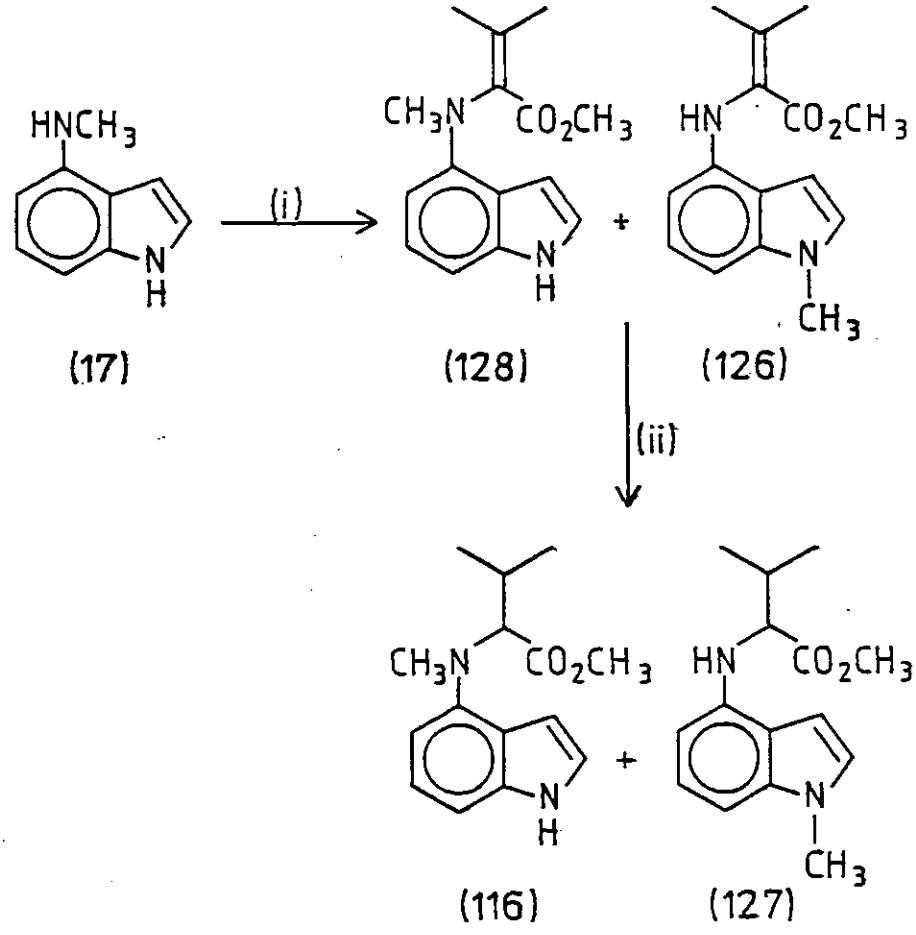


(126) (127)

(i) Mg, MeOH, 61%

The important "northern zone" intermediate (116) (see Retrosynthesis, Scheme 2) was eventually produced, albeit in poor yields, by treating (17) with methyl-2-ketoisovalerate and camphor sulphonic acid with continuous entrainment of water. Reduction of the crude mixture containing the unrearranged dehydroamino acid ester (128) with magnesium in methanol and subsequent column chromatography gave the desired product (116) in a 20% overall yield (Scheme 26). Some (19%) of the rearranged product (127) was also produced in this reaction.

SCHEME 26

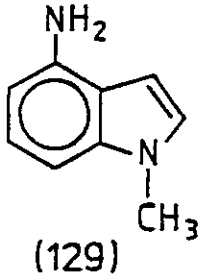


(i) Methyl-2-keto<u>iso</u>valerate, C.S.A. (ii) Mg, MeOH

(iii) <u>Rearrangement of 4-N-Alkylaminoindoles</u>

As already mentioned 4-N-methylaminoindole (17) is particularly air sensitive and rapidly turns dark green on exposure to the air. Additionally it was observed that on standing for a prolonged period of time (approximately 4 months) and subsequent chromatography a new colourless compound was isolated which was quite different but isomeric with the starting indole. ^{1}H n.m.r. at 60MHz of this compound

revealed a downfield shift of the N-methyl singlet resonance form δ 2.90 for (17) to δ 3.63 more characteristic of 1-methylindoles[83]. Also the disappearance of the indole NH proton, and a relative increase in the integral of the amine NH were noted. Careful inspection of ^{1}H n.m.r. spectra obtained at 250MHz for the aromatic region revealed other differences. In the indole (17) the C-2 proton resonance assigned at δ 7.05 occurs as a pseudo triplet due to coupling with the C-3 proton and the N-1 proton. Irradiation of the N-1 proton caused this signal to collapse to a doublet J 3.4Hz while the multiplet due to C-3 at δ 6.43 collapsed to a double doublet J 3.4, 0.83Hz. This double doublet is due to coupling with C-2 and to long range coupling to the C-7 proton[84]. The newly formed compound possessed a doublet J 3.1Hz at δ 6.87 due to C-2. Unfortunately the C-3 and C-5 protons were coincident at δ 6.32. Consideration of this data clearly indicated the structure (129) for this new compound.

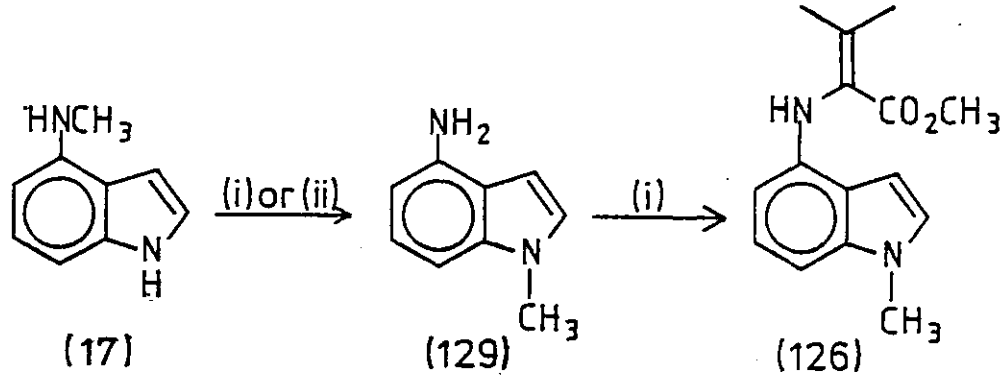


(129)

To further investigate this unexpected rearrangement (also observed previously during the synthesis of the dehydrovaline (126)) 4-N-methyl-

aminoindole (17) was treated with 4-toluenesulphonic acid at reflux temperature in toluene for 21h. Here it was found that (17) was completely converted to (129). Evidently, therefore, the rearranged dehydroamino acid ester, (126) was being formed from (17) *via* the rearranged compound (129) as outlined in (Scheme 27). This was confirmed by the isolation of a good yield of the same dehydro compound (126) on treatment of 1-methyl-4-aminoindole (129) with methyl-2-ketoisovalerate and 4-toluenesulphonic acid.

SCHEME 27



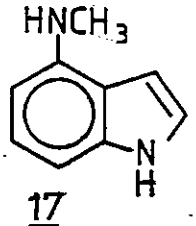
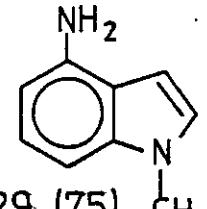
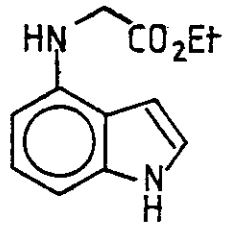
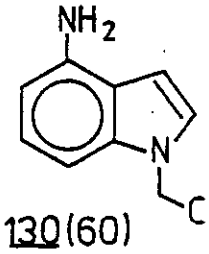
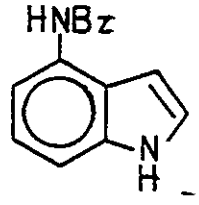
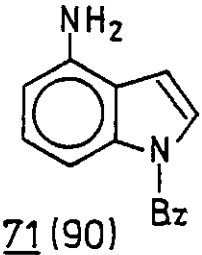
(17) (129) (126)

(i) Methyl-2-ketoisovalerate, TsOH. (ii) TsOH

Futher examples of this novel rearrangment are summarised in Table 7. It can be seen that under aqueous (i.e. no acid) or strictly anhydrous acid conditions (entries 2 and 3) no rearrangement products were observed. However treatment of the two 4-N-alkylaminoindoles (109) and (111) with 4-toluene-sulphonic acid gave the corresponding rearranged products (71) and (130). Noteable is the partial rearrangement only of the amino acid ester (109)

after 24h, while rearrangement was still incomplete after 48h.

TABLE 7:- Rearrangement of 4-N-Alkylaminoindoles

Entry	Substrate	Conditions[a]	Product(s)(Yield%)[b]
1	 17	p.T.S.A 21h	 129 (75)
2	17	H_2O 21h	17
3	17	C.S.A 21h	17
4	 109	p.T.S.A 21h	 130(60) + 109(40)[c]
5	109	p.T.S.A 48h	130 (77) + 109 (13)
6	 111	p.T.S.A 22h	 71 (90)

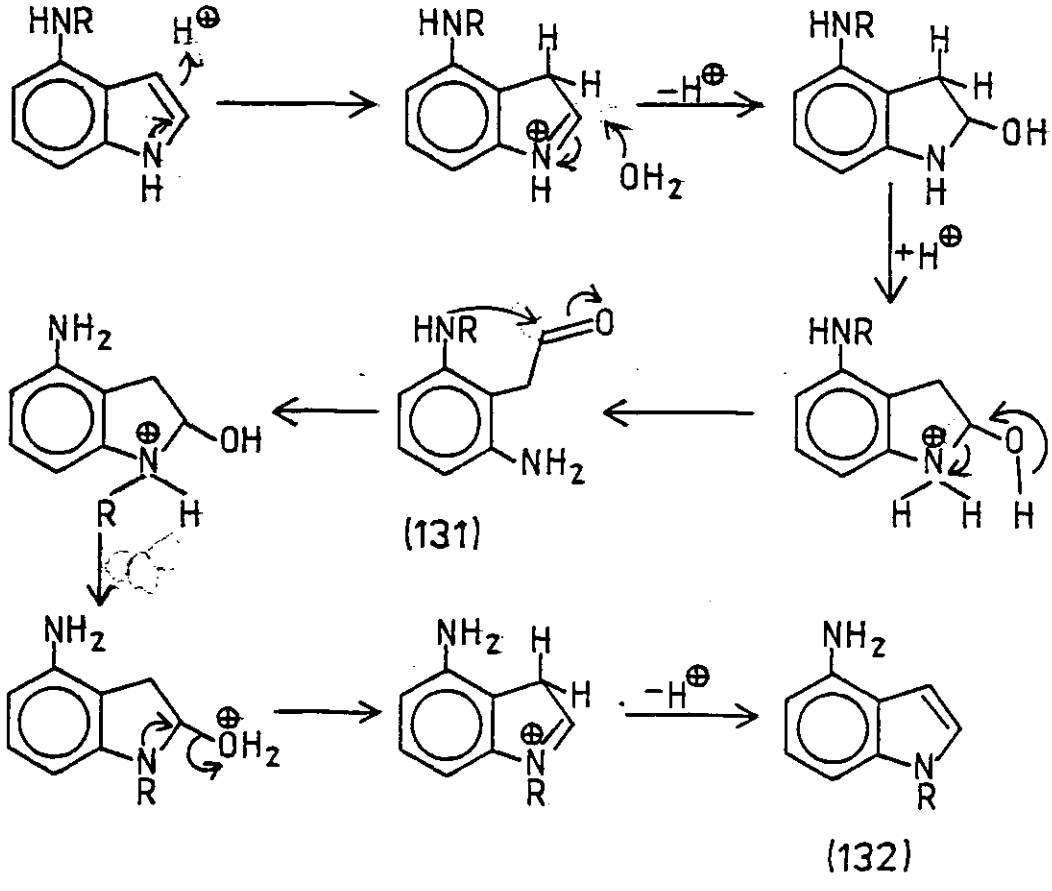
(a) Reaction conditions: reflux in toluene (10ml/mm) for the specified time, P.T.S.A. = 4-toluenesulphonic acid, C.S.A. = camphor sulphonic acid.

(b) Yield after chromatography.

(c) Yield from integration of ^1H n.m.r. signals.

A possible mechanism for this novel rearrangement is proposed in Scheme 28 and involves the hydrolysis and ring opening of the indole "enamine" system to the aldehyde (131) followed by recyclisation to the thermodynamically more stable product (132). The sluggish reaction of the indole (109) is accounted for by the reduced nucleophilicity of the amino group of amino acids caused by the inductive electron withdrawing properties of the carboxylic acid. Evidently both water and acid are required for this rearrangement to take place (Table 7, entries 2 and 3).

SCHEME 28

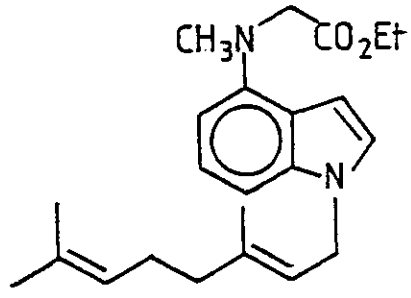


(iv) Conclusion

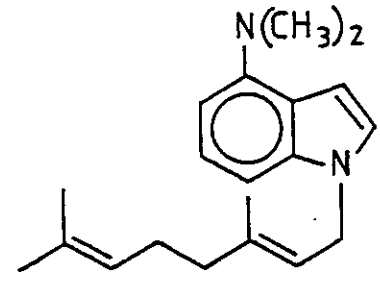
The model compound (113) was efficiently synthesised under basic conditions. Attempts to use the same methodology for the synthesis of the real "northern zone" intermediate (116) proved unsuccessful. Subsequent investigation of an acid mediated two stage procedure for the introduction of the five carbon iso-valerate unit led to the synthesis of (127) and revealed a novel rearrangement of 4-N-alkylaminoindoles to 1-alkyl-4-aminoindoles. Careful control of reaction conditions however eventually permitted the synthesis of (116) in poor yield. It is felt however that this reaction could be optimised to give respectable yields.

6. 1-Substituted-4-N,N-Dialkylaminoindoles

To investigate the proposed aza-Claisen rearrangement of 1-geranyl substituted indoles it was necessary to synthesis, among others, compounds such as (133) and (134).



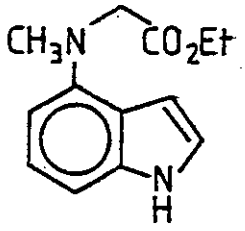
(133)



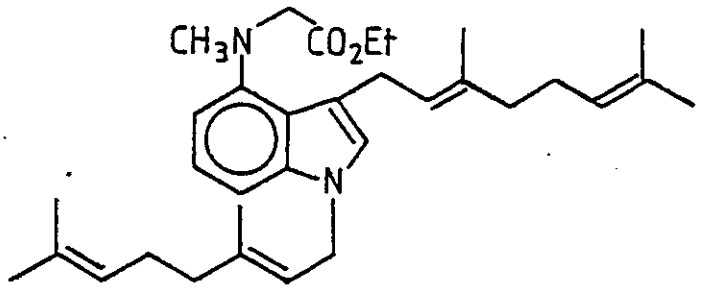
(134)

Although many procedures have been reported for the preparation of 1-alkyl substituted indoles[53,85] it was found that the alkylated indole (133) could

only be prepared when (113) and geranyl chloride[86] were added simultaneously to an ice cooled suspension of sodium hydride in D.M.F. Yields of (133) by this procedure were satisfactory being consistently greater than 70%. In addition, the dialkylated product (135) was also isolated in lower and more variable yields.

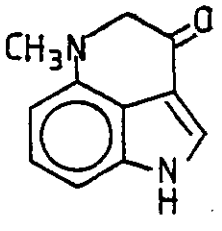


(113)

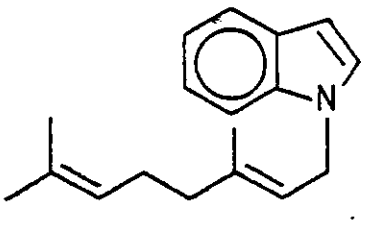


(135)

Attempts to preform the anion of (113) followed by alkylation with geranyl chloride proved unsuccessful as a number of products were isolated, including a low yield of (133). It might be thought that the anion of indole (113) could undergo intramolecular condensation to give (136) or alternatively undergo intermolecular polymerisation through its ester. However in a blank experiment, in which the indole (113) and sodium hydride were stirred together, only the starting indole (113) was recovered.



(136)

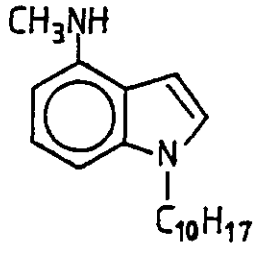


(137)

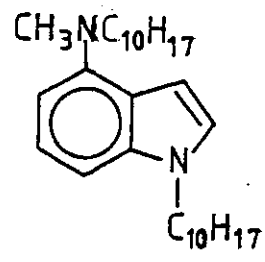
The indole (134) was readily prepared by Heaney and Ley's method[53] although yields here were poor, only some 45% of (134) being isolated. This method is not, of course, applicable to the preparation of (133) due to the rapid ester hydrolysis that occurs under the strongly basic reaction conditions. The indole (137) was efficiently prepared by the same method as an additional model for the aza-Claisen rearrangement.

The 1-benzylindole (114) reported in the previous section was synthesised in an improved yield by the simultaneous addition of (113) and benzyl chloride to sodium hydride.

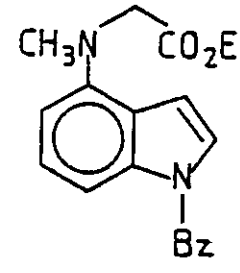
The indoles (138) and (139) were prepared in equal quantities on treatment of 4-N-methylamino-indole (17) with geranyl chloride, and potassium hydroxide in dimethylsulphoxide[53]. Evidently this procedure provides no selectivity in N-alkylations.



(138)



(139)

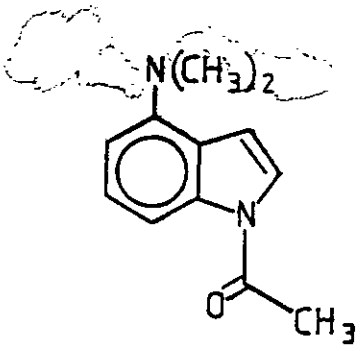


(114)

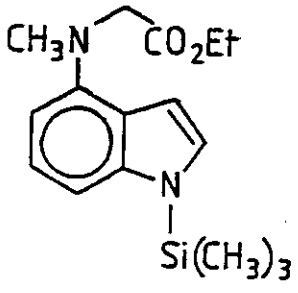
$C_{10}H_{17}$ = geranyl

Finally the introduction of some labile 1-substituents was investigated. Acylation of the indole (115) with acetic anhydride, triethylamine and

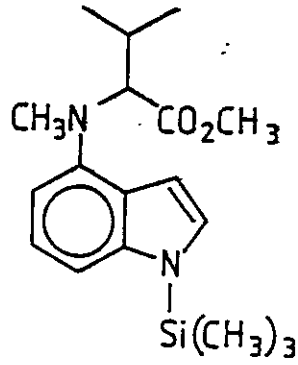
4-N,N-dimethylaminopyridine[87] proceeded smoothly and efficiently to give (140). The indolylamino acid esters (113) and (116) were smoothly silylated under similar conditions using chlorotrimethylsilane. The indoles (141) and (142) were isolated as stable oils in yields of greater than 80%. The novel chemistry of these interesting silylated compounds will be discussed in the next section.



(140)



(141)



(142)

Stannylation of (113) with either tributyltin oxide or tributyltin chloride was attempted without success[88,89].

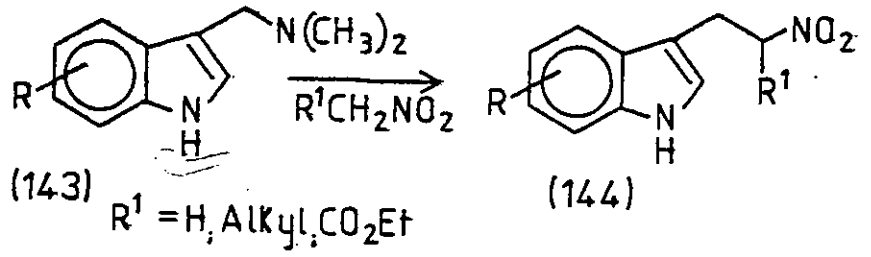
7. The Regiospecific Electrophilic Substitution of 4-Aminoindoles

(i) Introduction

It is well known that indoles with an unsubstituted 3-position usually react at that position with electrophilic species. In order to be able to prepare both Teleocidins A and B and a number of analogous compounds a versatile 3-substitution procedure was necessary. Of the many methods that

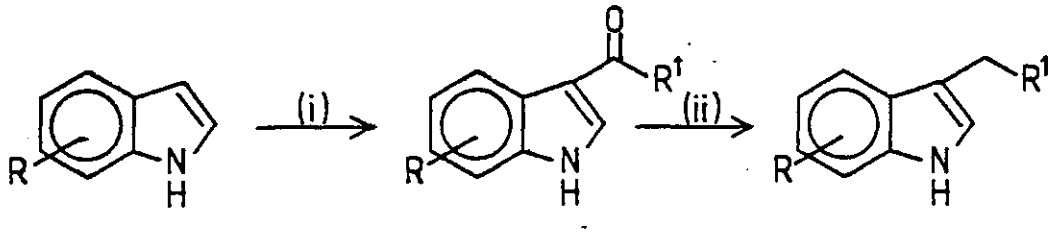
have been developed for the electrophilic substitution of indoles[90] several appeared to be applicable to our route. For example, gramines (143) which are readily available from the Mannich reaction, undergo nucleophilic displacement with the anions derived from nitroalkanes[91] or ethyl nitroacetate[92] (Scheme 29). Michael acceptor's are also known to undergo reaction at the indole-3-position in both acid[93] and neutral conditions[91b,94]. Finally C-3 acylation of indoles can be achieved under Friedel-Crafts conditions with a number of activated esters[95-97]. The vinylogous amides (146) produced by this procedure are reported to be readily reduced by sodium borohydride[95] or diborane[32] (scheme 30).

SCHEME 29



(143) R^1 = H, Alkyl, CO_2Et (144)

SCHEME 30



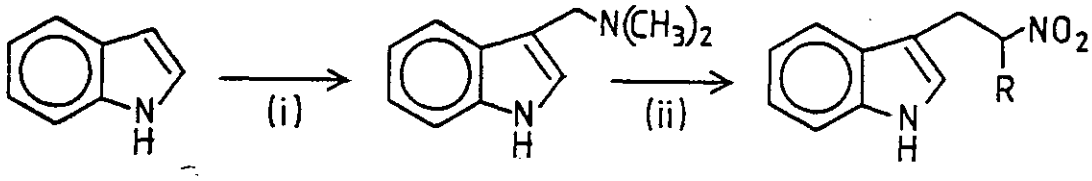
(145) (146) (147)

(i) R^1COCl, Lewis Acid. (ii) $NaBH_4$ or B_2H_6.

(ii) Gramines

In order to investigate the introduction of the tryptophanol side chain into the teleocidin precursors, gramine (148) was prepared by Kozikowski's modification of the Mannich reaction. This involves reaction of the readily available preformed Mannich salt N,N-dimethylmethyleneammonium chloride[99] with the indole. In our work it was found that upon treatment with methyl iodide, nitromethane and base, gramine (148) gave the 3(2-nitroethyl) adduct (149). Under similar conditions 2-(2-nitroethoxy)tetrahydropyran[100] gave in an unoptimised yield of 36% the tryptophanol intermediate (150) (Scheme 31). From these preliminary studies it appeared therefore that gramines were suitably versatile intermediates for the introduction of more complex C-3 substituents.

SCHEME 31



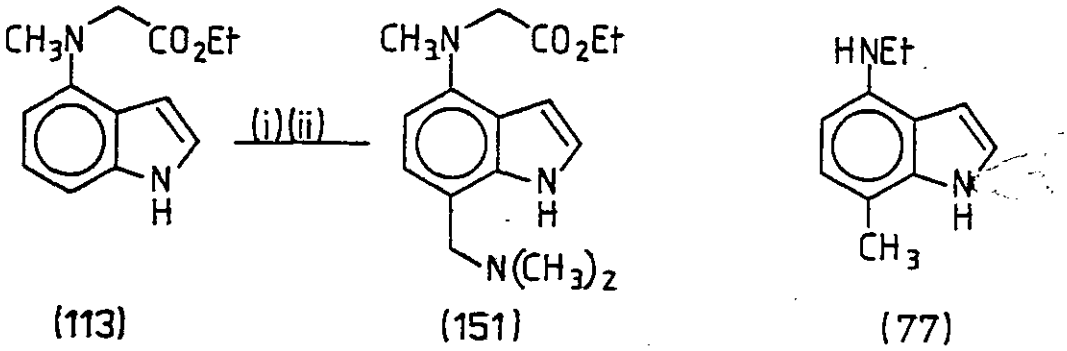
(148) (149) R = H

(150) R = CH_2OTHP

(i) (a) $(CH_3)_2N^+=CH_2$ Cl^-, (b) NaOH, 88%. (ii) CH_3I, base, RCH_2NO_2.

Encouraged by these model studies the aminoindole (113) was similarly treated with N,N-dimethyl-methyleneammonium chloride. The product of this reaction isolated in up to 96% yield, was shown to be the monosubstituted product (151). No C-3 substitution was observed (Scheme 32). The corresponding iodide (Eschenmosser's salt) was found to react similarly. This compound was inert to both nitromethane and 2-(2-nitroethoxy)tetrahydropyran under a variety of reaction conditions. Inspection of the aromatic region of the ^1H n.m.r. spectrum at 250MHz revealed two doublets at δ 6.42 and 6.83 J 7Hz and two multiplets at δ 6.53 and 7.10, confirming the substitution pattern in compound (151). Also, inspection of the ^1H n.m.r. spectrum at 250MHz of the 4,7 disubstituted indole (77) revealed a similar resonance pattern in the aromatic region.

SCHEME 32



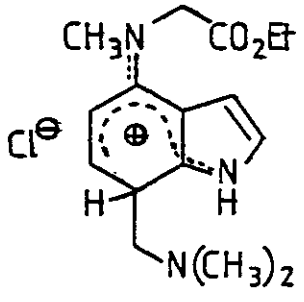
(113) (151) (77)

(i) $(CH_3)_2N^+ = CH_2\ Cl^-$. (ii) NaOH.

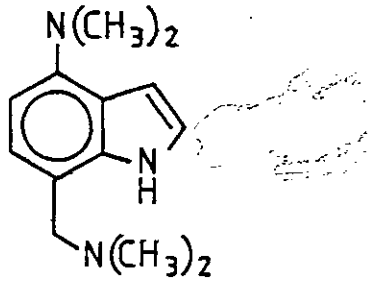
Evidently the 4-amino substituent significantly alters the electron density of the benzo ring. This

result was somewhat unexpected since formation of (151) must involve an intermediate such as (152) in which the resonance stabilisation of the aromatic ring has been disrupted. By contrast 3-substitution does not involve such a loss of resonance energy. It was therefore thought possible that the glycyl substituent of (113) is preventing reaction at the 3-position by steric hinderance. Treatment of the less sterically demanding 4-N,N-dimethylaminoindole (115) with N,N-dimethylmethyleneammonium chloride, however, also resulted in the regiospecific formation of the 4,7-disubstituted adduct (153). In addition the formamide (106), in which the electron donation of the 4-amino group to the aromatic ring is substantially reduced, gave a mixture of at least three unidentified products under the same reaction conditions.

Application of the classic Mannich reaction conditions of dialkylamine, formalin and acetic acid to the indole (113) gave a mixture of uncharacterised products.



(152)



(153)

These unusual results although disappointing in the context of a synthesis of the tricyclic lactam skeleton of the Teleocidins are encouraging with respect to the proposed later introduction of the linalyl side chain.

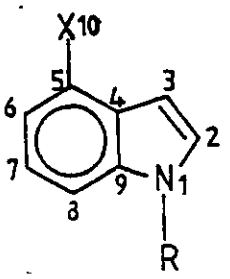
(iii) Approximate Superdelocalizability Towards Electrophiles of the 4-Aminoindole System

Calculation of the relative reactivity towards electrophiles of different positions in an aromatic system expressed as, the approximate superdelocalizability towards electrophiles, is now well established in the armoury of the synthetic organic chemist. A number of such calculations for 4-substituted indoles have been performed on the MOLECORB program SUSIE at Pfizer Central Research, Sandwich, Kent[101]. The results of this study are illustrated in Table 8. The more negative the number in the table the more probable it is that electrophiles will react at that position. It is important to realise that approximate superdelocalizability towards electrophiles is a relative term, applying solely to the particular molecule under discussion. That is, for example, an absolute comparison of the approximate superdelocalizabilities of entries 1 and 2 (Table 8) is not valid. Entry 1 however, shows that by comparison of the approximate superdelocalizability towards electrophiles for each position of the molecule in this case indole itself, position 3 has the most negative coefficient. This

indicates that position 3 will react preferentially with an electrophile, a well known fact in conventional indole chemistry.

Entries 3 and 5 are of particular interest with reference to the previous section. Entry 3 reveals that position 8 of 4-N,N-dimethylaminoindole (115) (position 7 in conventional indole nomenclature) should be the most reactive towards electrophiles. This is confirmed by the experimental evidence previously discussed. For 4-acetamidoindole (105) (entry 5) values for the 3-position of 0.801 and for the 8-position of 0.891 are not sufficiently different to give selective reaction at either position. Again this predicted finding is confirmed by the experimental results obtained with the closely related compound 4-N-formamidoindole (106). Introduction of a second acetyl group into the molecule (entry 6) has only a minor effect on the relative magnitudes of the approximate superdelocalizability towards electrophiles of positions 3 and 8. 4-(4-Nitrobenzamido)indole (entry 7) shows similar relative magnitudes of coefficients at positions 3 and 8 as in 4-acetamidoindole (105) (entry 5). 4-Hydroxyindole (entry 8) shows a considerably greater magnitude of the approximate superdelocalizability towards electrophiles at position 3 relative to that at position 8. This is confirmed by the facile synthesis of 3-substituted-4-hydroxyindoles by

TABLE 8: Approximate Superdelocalizability Towards Electrophiles of 4-Substituted Indoles



ENTRY	X	R	1	2	3	4	5	6	7	8	9	10
1	H	H	.544[a]	.466	1.061	.017	.634	.086	.409	.402	.092	-
2	H	Ac	.431	.532	.988	.033	.607	.061	.414	.360	.099	-
3	NMe_2	H	.501	.537	.781	.190	.669	.677	.296	1.007	.045	1.202
4	NMe_2	Ac	.396	.582	.692	.224	.643	.625	.280	.947	.038	1.202
5	NAc	H	.499	.505	.801	.148	.676	.555	.305	.891	.045	.854
6	NAc_2	H	.501	.487	.821	.121	.680	.473	.314	.815	.047	.639
7	NPNB[b]	.H	.499	.505	.798	.150	.676	.558	.305	.895	.045	.863
8	OH	H	.544	.497	.930	.987	.729	.369	.357	.738	.056	.360

(a) All results x -1

(b) PNB=4-nitrobenzoyl

N.B. The numbering system of the indole has been modified to facilitate the construction of the matrix required to perform the calculations.

the action of electrophiles on 4-hydroxyindole (see review for examples).

The results of Table 8 (entries 3-7) have been determined on the assumption that the aromatic ring is receiving the full contribution of the heterosubstituents nitrogen lone pair. That is, the molecular orbital of the nitrogen occupied by the lone pair is fully aligned with the π molecular orbitals of the aromatic ring system. Such an assumption is reasonable when 4-aminoindole is alkylated with small non-sterically demanding groups. If however a larger group is involved then some rotation of the indole C-4-nitrogen bond (diagram 1) is probable in order to reduce steric congestion. Twisting of this bond will result in a poorer alignment of the molecular orbital of the 4-nitrogen lone pair with the π molecular orbitals of the aromatic ring system. The net result of this would be a reduction of the magnitude of the approximate superdelocalizability towards electrophiles of the 8-position relative to that of the 3-position. Such a variation in the angle θ (diagram 1) is readily calculated by the same MOLECORB program. The contribution of the nitrogen lone pair to an aromatic system is calculated using the coefficient β (the resonance integral). When the angle θ is 0° then overlap of molecular orbitals is assumed to be complete. This is represented by a resonance integral β of 0.9. An angle θ of 90° that is when

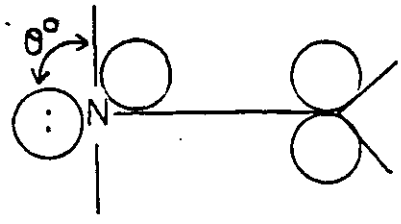
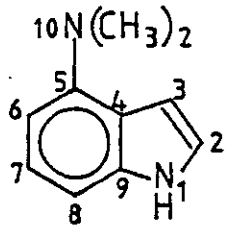


Diagram 1

TABLE 9:



Entry	β	Post. θ	1	2	3	4	5	6	7	8	9	10
1	0.9	0	.50	.54	<u>.78</u>	.19	.66	.68	.30	<u>1.01</u>	.05	1.2
2	0.6	45	.498	.454	<u>.854</u>	.078	.667	.332	.327	<u>.670</u>	.051	.715
3	0.1	90	.542	.464	<u>1.052</u>	.018	.637	.093	.406	<u>.410</u>	.090	.028

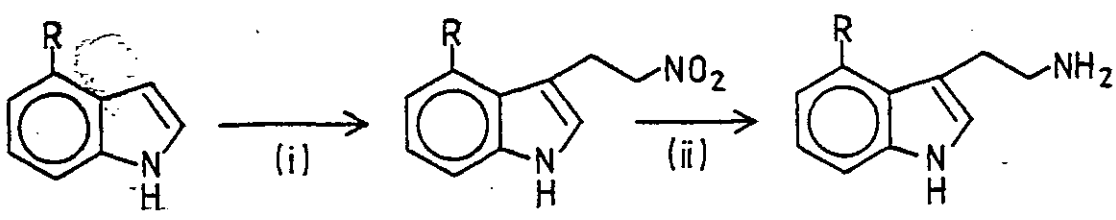
the nitrogen lone pair is making no contribution to the aromatic ring system is represented by a value of Ø.1 for β. A number of such calculations have been performed and are shown in Table 9.

It can be readily seen that a rotation of the C-4-nitrogen bond of 4-aminoindoles of somewhat less than 45° renders the 3-position more susceptible to electrophilic attack than the 7-position.

(iv) Addition of Nitroethylene to 4-Aminoindoles

The efficient Michael addition of nitroethylene to indole reported by Ranganathan[94b] and recently used by both Kozikowski's[94a] and Oppolzer's[91b] groups in the synthesis of ergot alkaloids is a useful method for introducing the 2-aminoethyl group into an indole (Scheme 33). In addition the known versatility of the nitro group in for example undergoing the nitroaldol reaction[102] renders the 3(2-nitroethyl)indoles such as (154) particularly appropriate for elaboration to the tryptophanol substituent of the Teleocidins.

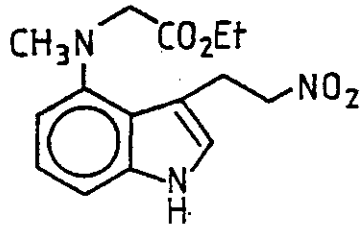
SCHEME 33



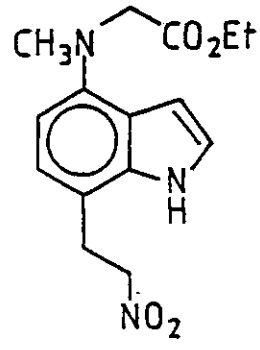
R=H; Alkyl (154)

(i) $CH_2:CHNO_2$. (ii) [H]

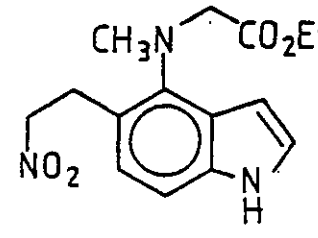
Treatment of the 4-aminoindole (113) with nitroethylene (prepared in a 60% yield by dehydration of nitroethanol according to Ranganathan's procedure[94b]) at room temperature for two days gave a 1:1 inseparable mixture of regioisomers. At 0°C the regioisomer ratio changed to 4:1. It was anticipated from inspection of Table 8 entry 3 that the regioisomers formed would be the 3,4- (155) and 4,7-disubstituted (156) products.



(155)



(156)

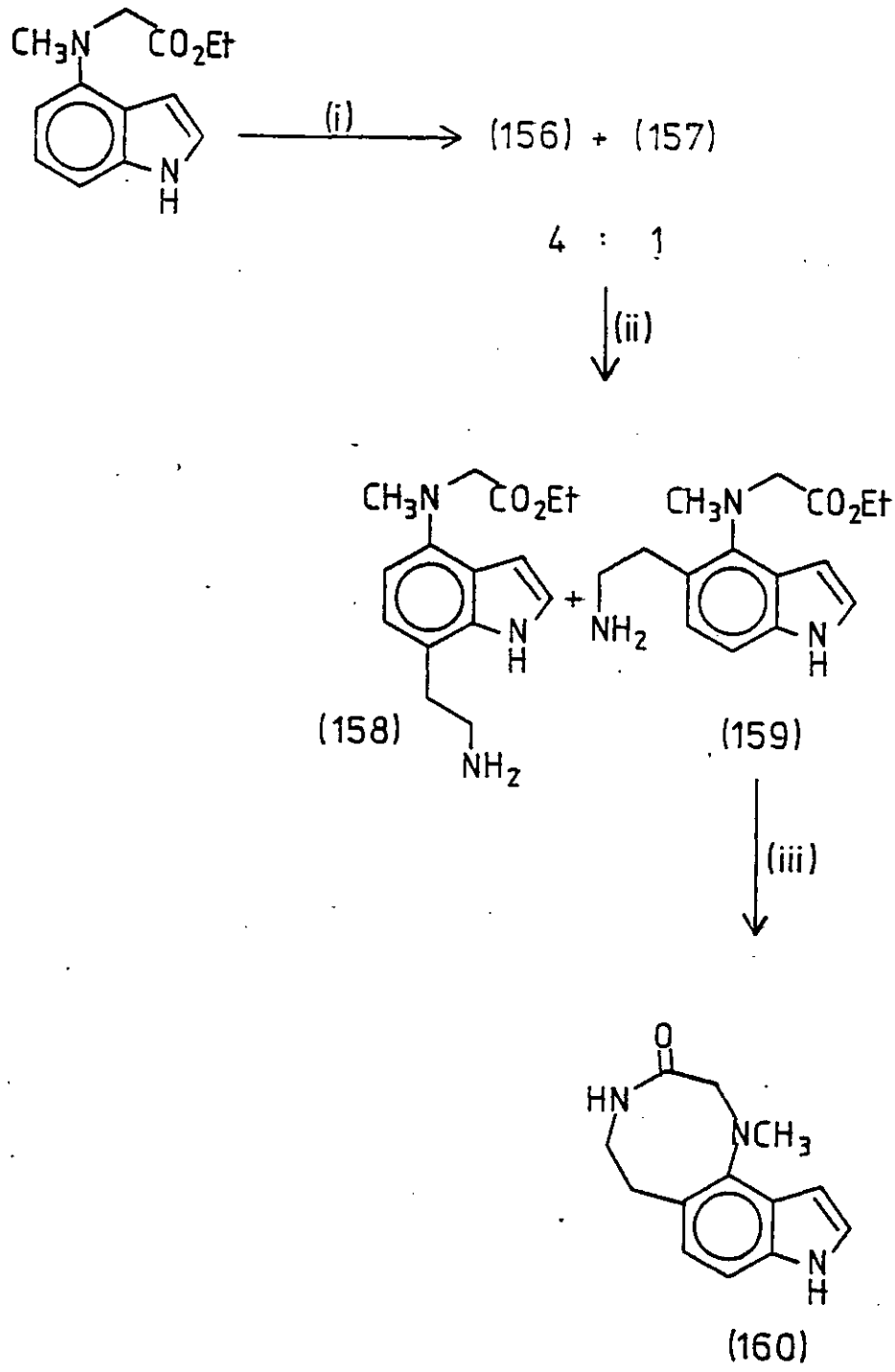


(157)

Inspection of the aromatic region of the ^{1}H n.m.r. spectrum at 250MHz of the mixture however, proved largely uninformative. To establish the structures of the two regioisomers therefore the nitroethyl group was reduced with nickel (II) chloride and sodium borohydride in hot ethanol. Thermolysis of the crude mixture of amines (158) and (159) in boiling degassed xylene gave a 12% yield of a compound (160) (Scheme 34) containing a carbonyl stretch at 1655cm^{-1} in the i.r., characteristic of an amide or lactam. Mass spectral analysis revealed a molecular ion at 229.1217 corresponding to an

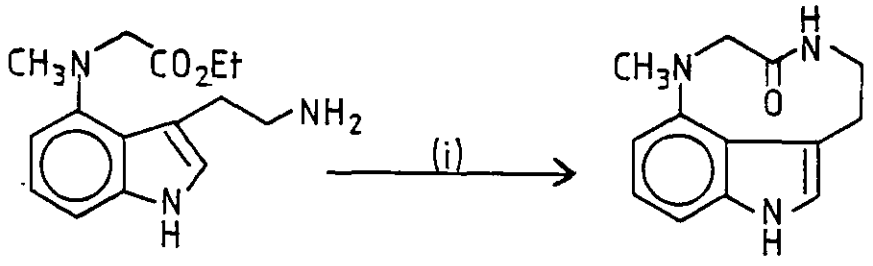
empirical formula of $C_{13}H_{15}N_3O$ suggesting an intramolecular cyclisation to a lactam. Two doublets at δ 6.89 and 7.08 J 7Hz and two multiplets at δ 6.63 and 6.15 in the 250MHz ^1H n.m.r. were assigned to indole proton resonances at C-6, C-7, C-2 and C-3 respectively. One of the regioisomers formed by the reaction of nitroethylene and (113) was therefore assigned the unexpected 4,5-disubstituted structure (157). It has been shown (vide infra) that the 3-(2-aminoethyl) indole (161) under thermal reaction conditions also undergoes intramolecular cyclization. The tricyclic product (12) (Scheme 35) so obtained has significant differences in its ^1H n.m.r. spectrum compared with that of the tricyclic compound (160). Therefore the second regioisomer from the reaction of nitroethylene with (113) has been assigned the structure (156). The amine (158) derived from this compound evidently cannot undergo intramolecular cyclization due to the constraints of the planer aromatic ring.

SCHEME 34



(i) CH_2:$CHNO_2$, 0°C, 50%. (ii) $NiCl_2$, $NaBH_4$, 78%. (iii) xylene, reflux, 12%.

SCHEME 35



(161) (12)

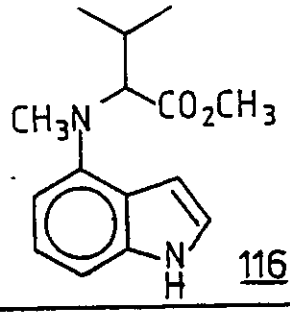
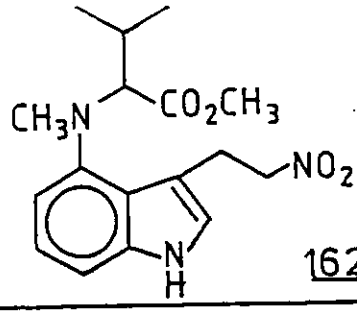
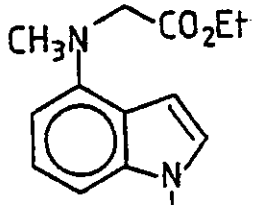
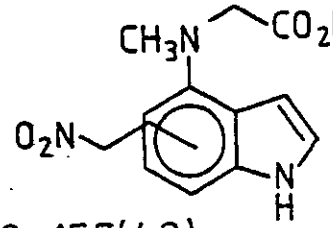
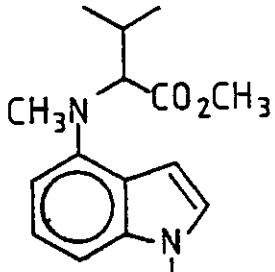
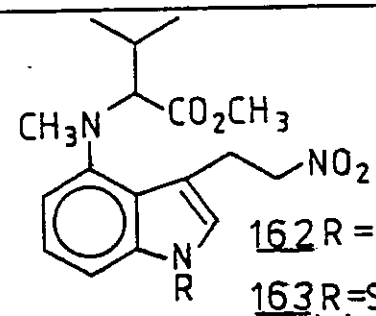
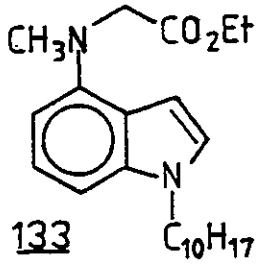
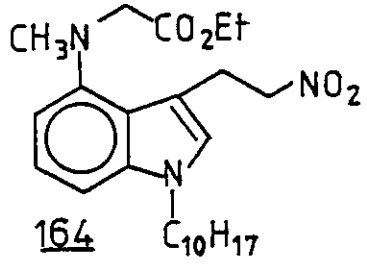
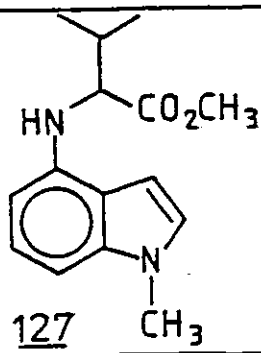
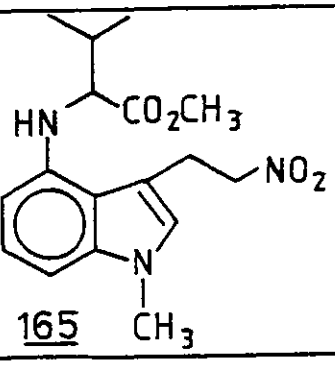
(i) DMF, 140°C, 42%.

It is thought that the minor isomer generated is the 4,5-disubstituted compound (157). The resonance due to the N-methyl group of the minor regioisomer occurs at δ 2.85, upfield from that of the regioisomer at δ 2.98 suggesting an increased shielding of the N-methyl group by the aromatic ring current. Increased shielding would be brought about by a slight rotation of the indole C-4-N bond to relieve steric congestion from an adjacent substituent.

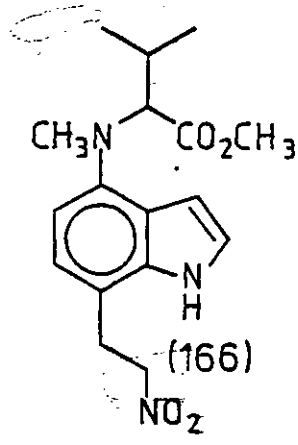
A number of other 4-amino indoles have been subjected to reaction with nitroethylene (Table 10) and have demonstrated a number of interesting features.

Perhaps most interesting is entry 1 of Table 10. Examination of C.P.K. space filling molecular models suggests that the lowest energy conformation of the indolylvaline (116) is that in which the lone pair of the nitrogen 4-substituent has been twisted out of conjugation with the indole ring. It has already

TABLE 10: Michael Addition of Nitroethylene to Substituted 4-Aminoindoles

Entry	Substrate	Product (yield%)
1	 116	 162(47)
2	 141	 156 + 157(42)
3	 142	 162 R = H (49) 163 R = $Si(CH_3)_3$ (4)
4	 133	 164
5	 127	 165

been shown that such a loss of conjugation favours electrophilic substitution at the indole C-3 position (see Table 9). Small quantities of another regioisomer were formed during the reaction, constituting up to some 15% of the product. It is thought that this is the 4,7-disubstituted adduct (166). The glycylsilane (141) gave a mixture of two uncharacterised inseparable regioisomers. By contrast the silylated valine derivative (142) gave results comparable to those obtained with (116).

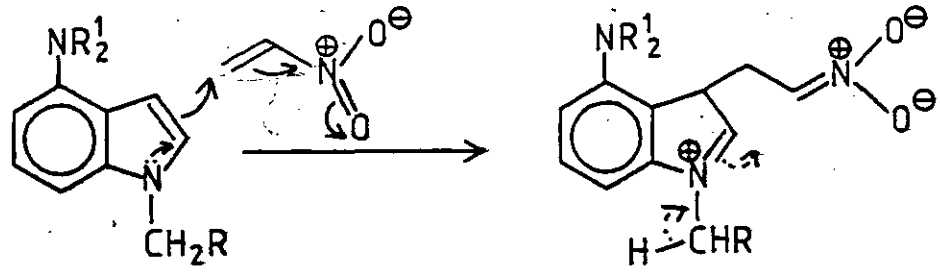


(166)

The 1-alkylindoles (127) and (133) underwent regiospecific 3-substitution. Once again from inspection of C.P.K. space filling molecular models it would appear improbable that this selectivity is due to steric crowding of the 7-position by the 1-alkyl substituent. Nor can the selectivity be ascribed in both cases to the enforced rotation of the C-4-N bond since the glycyl indoles (113) and (141) have already been shown to provide regio-isomeric mixtures of products. It is thought that an intermediate (167) (Scheme 36) must be involved in

this reaction. Stabilisation of the iminium species (167) by hyperconjunction of the alkyl group would help to maximise Michael addition at the indole 3 position.

SCHEME 36

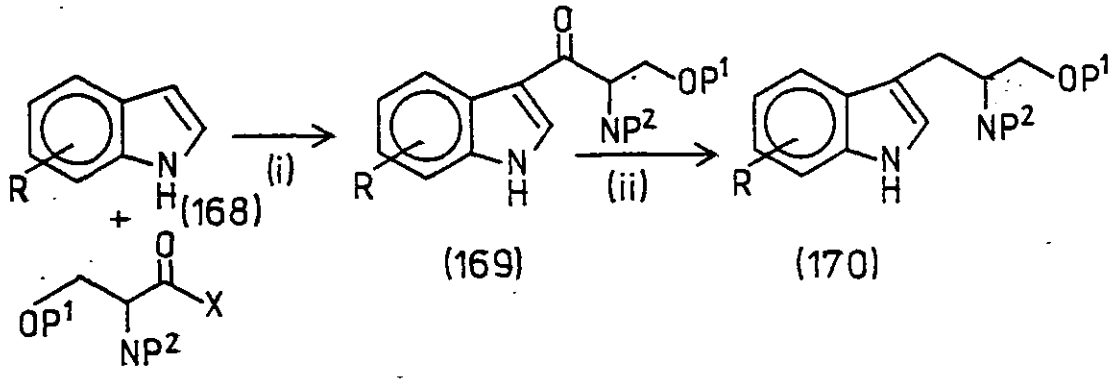


(167)

(v) Friedel-Crafts Acylation of 4-Aminoindoles

An attractive approach to substituted tryptophanols (170) or other substituted tryptamines is via acylation of an indole (168) with an amino acid and subsequent reduction of the vinylogous amide (169) so formed (Scheme 37).

SCHEME 37

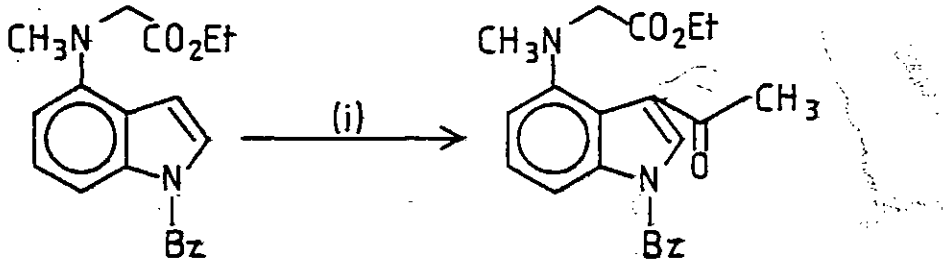


X = leaving group P^1, P^2 = protecting group

(i) Friedel-Crafts reaction. (ii) [H].

A number of attempts at acylating indole under various reaction conditions with different protected amino acids proved unsuccessful. Furthermore the amino indole (113) proved intractable to acylation with acetyl chloride or acetic anhydride and Lewis acids such as aluminium trichloride, tin (IV) chloride or boron trifluoride diethyl etherate. The 1-benzyl indole (114) however, underwent a facile and efficient acylation with acetyl chloride and tin (IV) chloride to give regiospecifically the indole (171) (Scheme 38). Less effective was the reaction of (114) with acetic anhydride and boron trifluoride diethyl etherate.

SCHEME 38



(114) (171)

(i) CH_3COCl, $SnCl_4$, CH_2Cl_2, -78°C, 83%.

(vi) Regiospecific Electrophilic Substitution of N-Methyl-N-(4-indolyl)glycine Ethyl Ester (113)

Although the indolyl valine (116) has been satisfactorily substituted in a regioselective fashion at the indole 3-position no successful procedure was available for the synthesis of

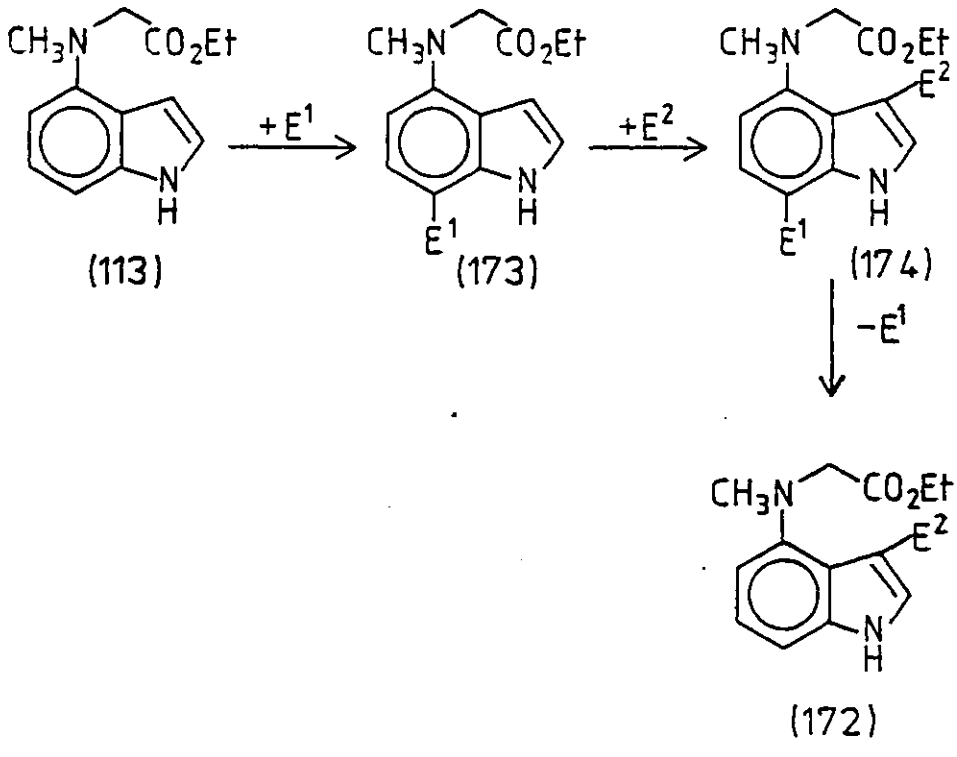
3,4-disubstituted indolyl glycines (172). The two indolyl glycines (164) and (165) in which a 3-substituent has been introduced regiospecifically each have a 1-substituent which would be difficult if not impossible to remove in the presence of the other functionality in the molecule. It was evidently necessary, therefore, to develop a new procedure for the introduction of a 3-substituent to the indole (113). Two approaches to the solution of this problem were investigated.

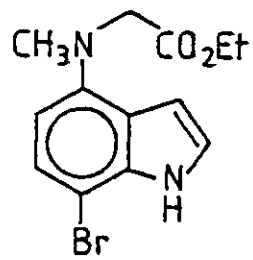
It is evident from the previous discussion that electrophiles react preferentially at the indole 7-position in the indolylglycine (113). Electrophilic substitution of this position with a readily removed electron withdrawing group would therefore favour reaction with a second electrophile at the indole 3-position, after which removal of the first substituent would lead to the desired 3,4-disubstituted indole (172) (Scheme 39).

Aryl bromides and iodides which are readily prepared from a source of positive halogen and the corresponding aromatic compound are cleaved easily by hydrogenolysis. Treatment of the indolylglycine (113) with iodine or bromine however gave a complex mixture of highly coloured compounds. On the other hand N-bromosuccinimide in DMF[103] gave a 41% yield of an unstable blue oil identified by ^{1}H n.m.r. as the 4,7-disubstituted product (175). Due, however, to its low yield of formation and its instability, no

further investigation of the chemistry of bromoindole (175) was undertaken.

SCHEME 39





(175)

It is well known that allylsilanes undergo substitution with concomitant double bond migration and loss of silicon on treatment with an electrophile and a Lewis acid[104] or a source of fluoride ion[105]. Inspection of the indole silane (141) reveals an analogous system in which nitrogen has replaced one carbon of the allylic system. It was anticipated

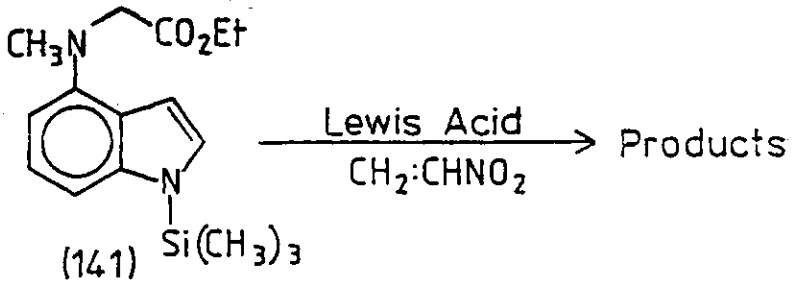
therefore that treatment of the silylated indole (141) with a Lewis acid and an electrophile could give regiospecifically a 3,4-disubstituted indole (172) with simultaneous loss of the silicon residue.

To test this idea, reaction of the silylated indole (141) with nitroethylene and a number of Lewis acids was investigated. Some of the results of this study are illustrated in Table 11.

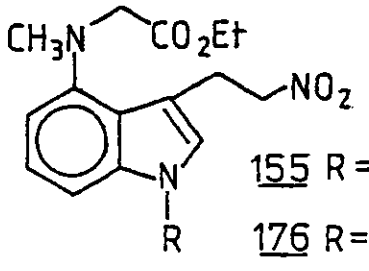
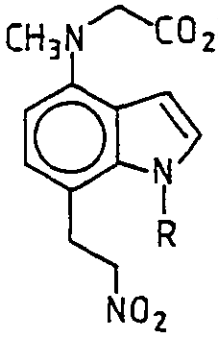
Lewis acids such as zinc chloride aluminium trichloride, trimethylsilyltrifluoromethane-sulphonate, boron trifluoride diethyl etherate and powdered glass proved ineffective. These Lewis acids gave either low regioselectivity or no reaction at all. Additionally yields of products were poorer than those illustrated in Table 11. Reactions were rapid being complete within a few hours at -78°C with tin (IV) chloride and titanium (IV) chloride. By contrast reaction of the indolyl glycine (113) with nitroethylene proceeded to completion after two days at room temperature while the silyl indole (142) under the same conditions took 24 hours to achieve complete reaction. It is evident that the Lewis acids accelerate the reaction to a significant degree.

Three features of the results in Table 11 are of particular note. Firstly it can be seen that quite unexpectedly the silicon moiety has been largely preserved in the product. It is thought that partial desilylation has been caused by the presence of trace

TABLE 11:- Reaction of (141) with Nitroethylene and Different Lewis Acids



(141)

Entry	Lewis Acid	Temp°C	Products (yield%)
1	$SnCl_4$	-78	 155 R=H (20) 176 R=Si(CH3)3 (43)
2	ZnI_2	-20	 156 R=H[a] 177 R=Si(CH3)3 (27)
3	$TiCl_4$	-78	176 : 177, 4 : 1[b] (30)[c]

a. Yield not recorded

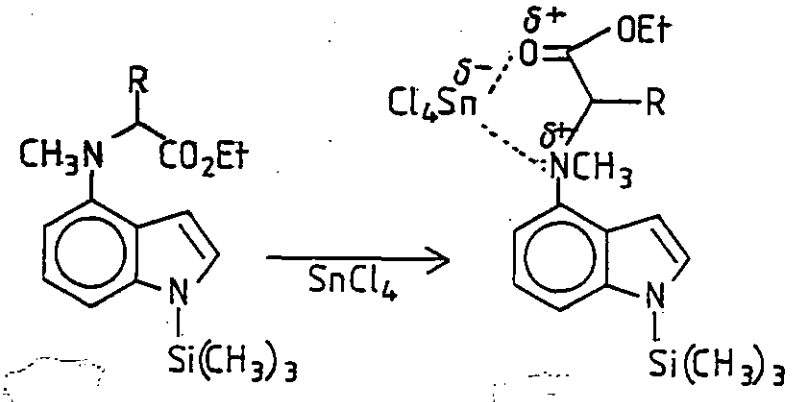
b. Not seperable by column chromatography

c. Also isolated 12% of (155) and (156)

amounts of acid impurity in the Lewis acid. Secondly tin (IV) chloride and zinc iodide both demonstrate excellent regioselectivity in the reaction giving products with a greater than 95% regiochemical purity. No other Lewis acid investigated showed such regioselectivity. A useful qualitative difference in the behaviour of the two regioisomers (176) and (177) has been observed. The 3,4-disubstituted indole (176) was shown to char when a silica gel analytical t.l.c. of it was developed with conc. sulphuric acid followed by warming. The 4,7-disubstitued indole (177) however turned red-purple in colour followed by charring when treated in the same manner.

Finally and most interestingly is the difference in the regioselectivity of the reaction with a change of Lewis acid from tin (IV) chloride to zinc (II) iodide. Most probably tin (IV) chloride is forming a complex (178) with the glycyl moiety of the indole (141). The observation that the reaction mixture rapidly darkened after the addition of 0.5 equivalents of tin (IV) chloride possibly supports this contention. It was also shown that the bulkier valine species (142) gave a 1:1 mixture of two regioisomers under the same reaction conditions. A complex such as (179) has a very hindered 3-position partially preventing reaction at that site. The donation to the aromatic ring of the nitrogen lone pair in complex (178) is considerably reduced such that the 3-position becomes the most favoured site

for electrophilic substitution. Acceleration of the reaction is brought about by activation of nitroethylene to Michael addition by the Lewis acid. By contrast it is thought that zinc iodide serves only to activate nitroethylene towards Michael addition and has no effect on the electronic configuration of the aromatic nucleus hence leading to a 4,7-disubstituted product.



(141) R =H

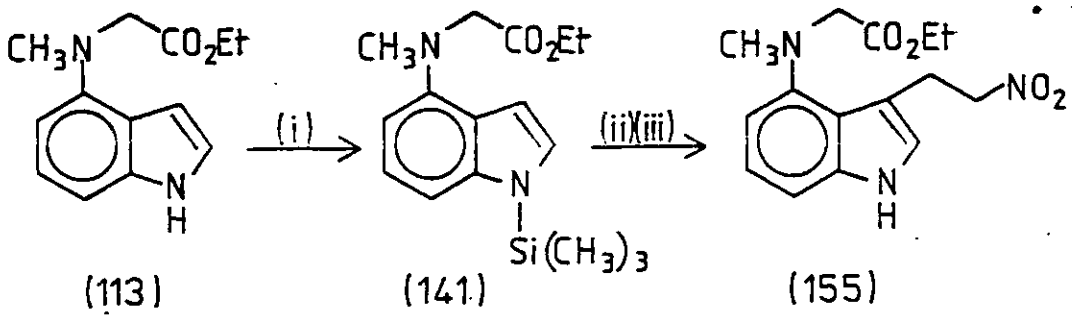
(142) R =$(CH_3)_2CH$

(178) R =H

(179) R =$(CH_3)_2CH$

The silylated indole (176) was quantitatively desilylated with tetrabutylammonium fluoride, thus providing an efficient synthesis of the desired 3,4-disubstituted indole (155). Overall yields of up to 50% were obtained for the three stage conversion of (113) to (155) and the steps involved are summarised in Scheme 40.

SCHEME 40



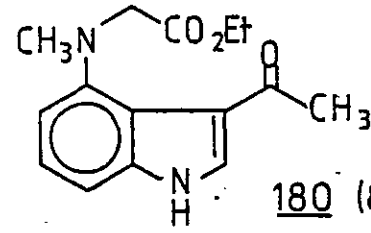
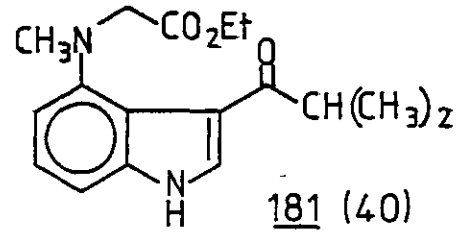
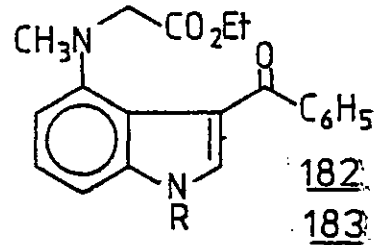
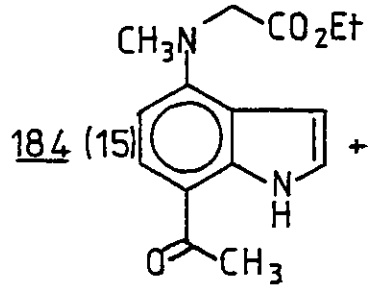
(113) (141) (155)

(i) $(CH_3)_3SiCl$, Et_3N, DMAP. (ii) $CH_2{:}CHNO_2$, $SnCl_4$. (iii) Bu_4NF, 50% overall yield.

To further explore the versatility of the silylated species (141) reaction with a number of other electrophiles was investigated. Disappointingly it was discovered that no reaction took place with ethyl acrylate, propylene oxide, methyl chloroformate bromoacetaldehyde dimethyl-acetal, trimethyl orthoformate or γ-butyrolactone. Friedel-Crafts acylation however occurred with acid chlorides or anhydrides and these results are summarised in Table 12.

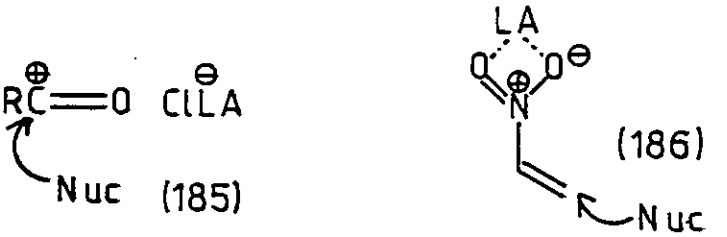
With tin (IV) chloride as Lewis acid reactions proceeded efficiently in a regiospecific manner. Zinc iodide however gave only a 15% yield of the expected 4,7-disubstituted product (184) together with 48% yield of the 3,4-disubstituted indole (180). This loss of selectivity is probably due to the increased bulk of the acylium ion (185) involved compared with the activated species (186) generated from nitroethylene. In the acylium ion (185) the

Table 12:- Friedel-Crafts acylation of N-Methyl-N-[4-(1-trimethylsilyl)indolyl]glycine Ethyl Ester (141)

Entry	Lewis Acid[a]	Electrophile	Product(s)(yield%)
1	$SnCl_4$	CH_3COCl	 180 (88)
2	$SnCl_4$	$(CH_3CO)_2O$	180 (78)
3	$SnCl_4$	iPrCOCl	 181 (40)
4	$SnCl_4$	C_6H_5COCl	 182 R = H (34)+ 183 R = C_6H_5CO (45)
5	ZnI_2	CH_3COCl	 184 (15) + 180 (48)
6	ZnI_2	$(CH_3CO)_2O$	No reaction

a. Reaction conditions, (141) one equivalent, Lewis acid 2 equivalents, electrophile 3 equivalents, stirred 4 hours at -78^oC ($SnCl_4$) or -20^oC (ZnI_2).

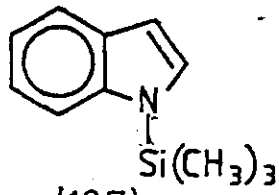
sterically demanding Lewis acid must come into close proximity with the large silicon group attached to the indole (141) for 7-substitution to take place. In the activated species (186) however the bulky Lewis acid is relatively remote from the silylindole.



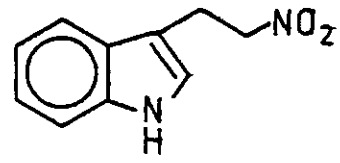
Nuc = Nucleophile LA = Lewis Acid

Simultaneous treatment of the silylated indole (141) with nitroethylene and tetrabutylammonium fluoride[105] resulted only in the isolation of the desilylated starting indole (113). Other sources of fluoride proved equally ineffective.

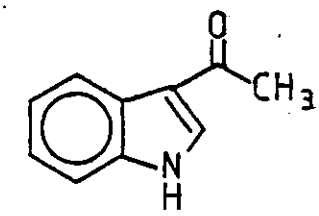
Finally to further explore the generality of this reaction 1-trimethylsilylindole (187) was prepared from indole, chlorotrimethylsilane, triethylamine and 4-N,N-dimethylaminopyridine. Reaction with nitroethylene and tin (IV) chloride gave a 10% yield of the substituted indole (149). This contrasts poorly with Ranganathan's[94b] synthesis of (149) in an 80% yield by simply treating indole with nitroethylene. Additionally Friedel-Crafts acylation of (187) with acetyl chloride and tin (IV) chloride yielded 47% of the known 3-acetyl derivative (188).



(187)



(149)



(188)

(vii) Conclusion

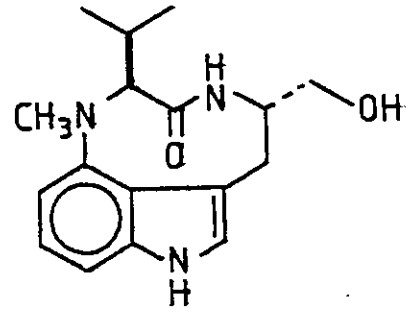
In this section the electrophilic substitution of 4-aminoindoles has been discussed. It was shown that substitution proceeded most readily at the indole C-7 position. Computer calculations from Simple Huckel Molecular Orbital Theory revealed the unusual electron density round the aromatic nucleus of 4-aminoindoles. Also it was shown how this was altered by rotation of the nitrogen lone pair out of conjugation with the aromatic ring. These calculations have been used to explain some of the unusual characteristics of electrophilic substitution in 4-aminoindoles discovered experimentally. Furthermore a new and regiospecific substitution procedure has been developed such that the 3,4-disubstituted indoles (155) and (162) which are necessary for our teleocidin work could now be synthesised.

8. Synthesis of the Seco Amino Acid Esters

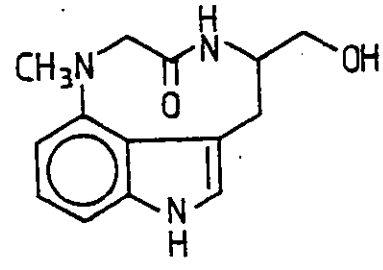
(i) Hydroxymethylation

Continuing the synthesis towards substituted pyrrolo-1,4-benzodiazonin-3-one models (8) and (13)

of the Teleocidins, further functionalisation of the 3-substituted-4-aminoindoles (described in the last section) is required. Following ample literature precedence hydroxymethylation α to the activating nitro substituent is an obvious choice[103,106].



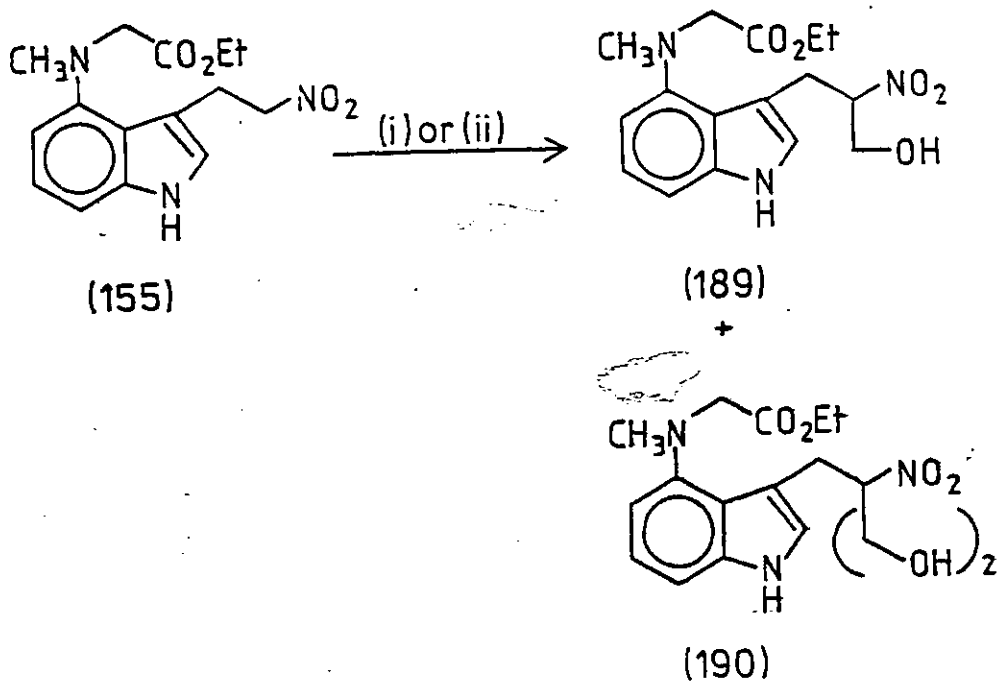
(8)



(13)

Initial studies of the hydroxymethylation of the 3-(2-nitroethyl)indole (155) using potassium bicarbonate and formalin gave disappointing results. Yields of the desired nitroalcohol (189) (Scheme 41) were generally poor, not reproducible and gave considerable quantities of the unwanted bis-(hydroxymethyl) adduct (190). The low yields were attributed to extensive hydrolysis of the ethyl ester under these reaction conditions.

SCHEME 41



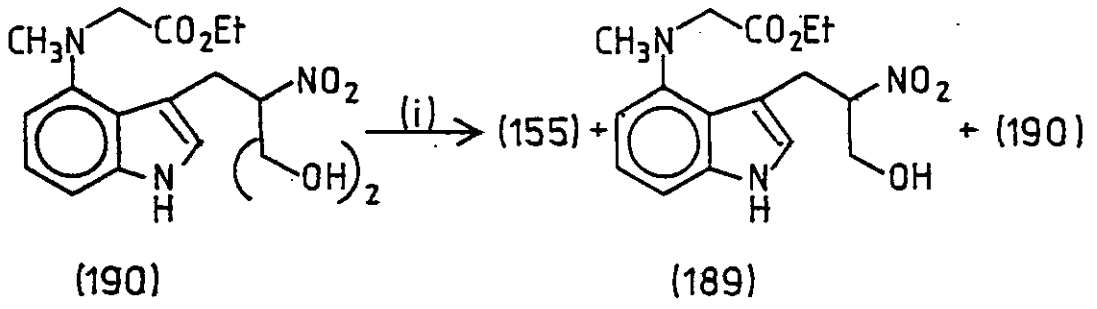
(155) (189) + (190)

(i) $KHCO_3$, formalin, H_2O, EtOH. (ii) $NaOCH_3$ (cat), paraformaldehyde, D.M.F., 60°C.

Further investigation of the reaction revealed that treatment of (155) with one equivalent of paraformaldehyde in D.M.F. in the presence of a catalytic quantitiy of sodium methoxide afforded reproducible yields of 60 - 70% of the mono (hydroxymethylated) compound (189) (Scheme 41). Bis-(hydroxymethylation) to give (190) still occurred to some extent but it was shown that retreatment of (190) with sodium methoxide in warm D.M.F. gave an equilibrium mixture of (190) the required mono (hydroxymethyl) compound (189) and (155) which were

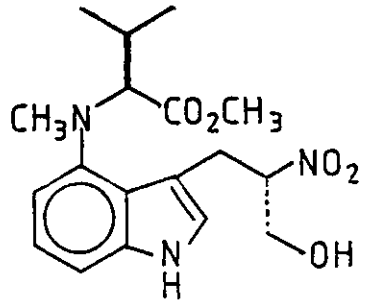
easily separated by chromatography (Scheme 42). This re-equilibration procedure increased yields of the β-nitroalcohol (189) to an acceptable 75%.

SCHEME 42

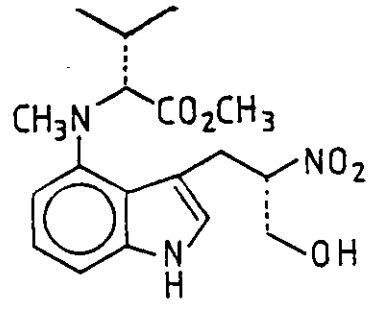


(i) $NaOCH_3$, D.M.F. 60°C.

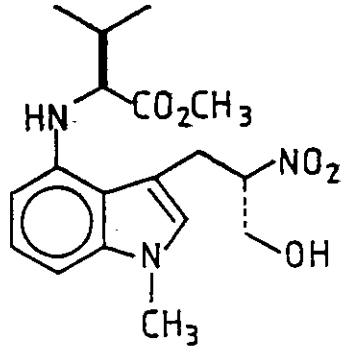
The more highly substituted 3-(2-nitroethyl)-indole (162) and the 'rearranged' indole (165) were successfully hydroxymethylated in a similar manner to give (191a,b) and (192a,b) respectively, each occurring as a 1:1 diastereomeric mixture. The two diastereomers, (192a) and (192b), were readily separated by careful column chromatography. The relative stereochemistries of the less polar (192a) and the more polar (192b) compounds were assigned by later examination of the tricyclic lactams derived from them.



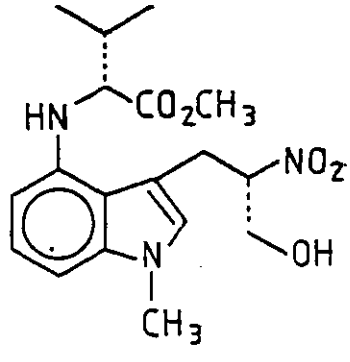
(191a)



(191b)



(192a)

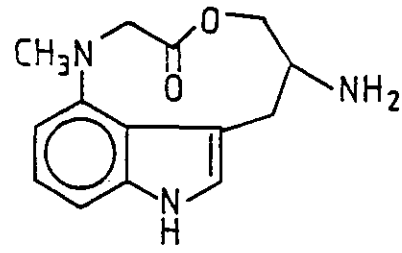


(192b)

(ii) Hydroxyl Protection

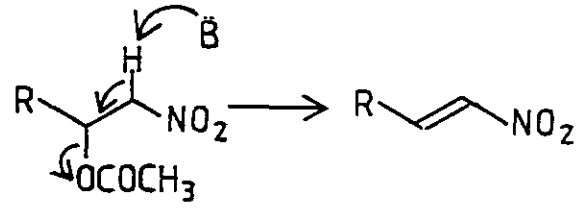
At this stage of the synthesis we were uncertain as to the necessity of protecting the newly introduced hydroxylic functionality. Peptide synthesis involving serine normally proceeds effectively without prior hydroxyl protection[107]. In our case however there is a possible competition between formation of a sterically constrained 9-membered lactam and formation of a less sterically constrained 10-membered lactone ring (193), in which the less reactive hydroxyl moiety has undergone preferential reaction. With this potential but real

problem in mind, it was decided to study the protection of the β-nitroalcohols described above.



(193)

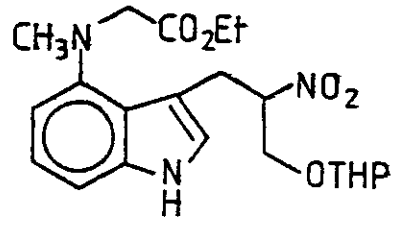
Choice of a suitable protecting group was limited by the known properties of β-hydroxysubstituted nitroalkanes. We have already shown that the bis-(hydroxymethylated) compounds such as (190) undergo a facile reverse reaction in which either one or both hydroxymethyl groups may be eliminated under mildly basic conditions. Additionally β-nitroacetates (194) have been shown to be unstable and decompose readily under mildly basic conditions to the corresponding nitroolefin (195)[108].



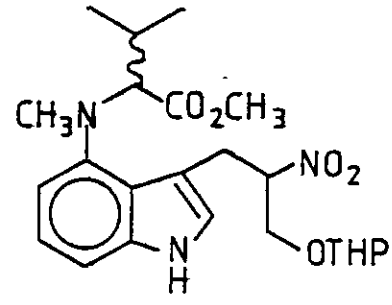
(194) (195)

It is evident from the above observations that introduction of any protecting group should preferably proceed under mildly acidic conditions. Of the hydroxyl protecting groups that are introduced

under these conditions perhaps the acetals are best known. Of these the 'classical' tetrahydropyranyl group still offers several advantages. It is cheap, readily available and is introduced and removed efficiently under mild conditions. Perhaps one particular drawback to this protecting group should be noted. That is, the introduction of an additional asymmetric centre to the molecule. It was found however that on treatment of the appropriate nitroalcohol (189), (191a,b), (192a,b) or diastereomerically pure (192a) with excess dihydropyran and pyridinium 4-toluenesulphonate[100] the tetrahydropyranyloxy ethers (196), (197a,b), (198a,b) and (198a) were formed in yields of 82 - 97%.

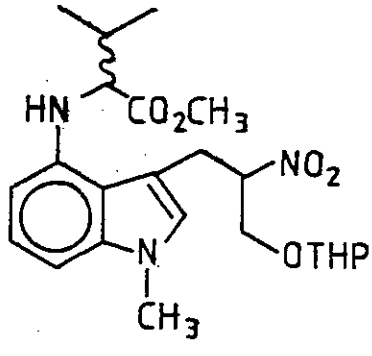


(196)

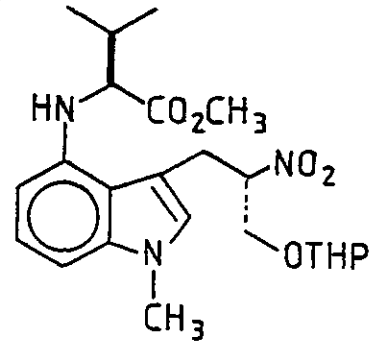


(197a and b)

THP=



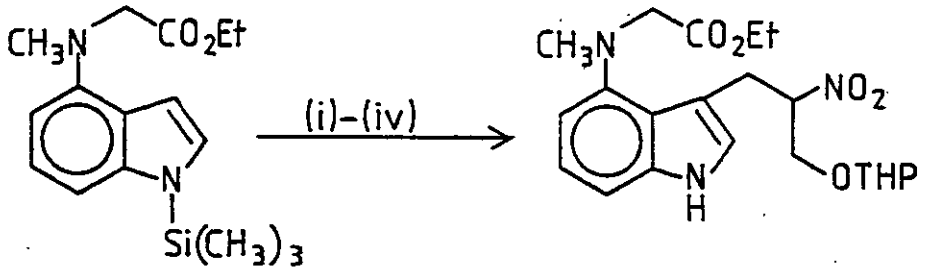
(198a and b)



(198a)

Synthesis of, for example, the protected 3,4-disubstituted indole (196) from the silylated indole (141) therefore involves a four stage sequence of reactions summarised in Scheme 43.

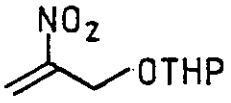
SCHEME 43



(141) (196)

(i) CH_2=$CHNO_2$, $SnCl_4$. (ii) Bu_4NF. (iii) HCHO, $NaOCH_3$. (iv) dihydropyran, pyridinium 4-toluenesulphonate.

An attractive alternative to this multi-stage procedure was the replacement of nitroethylene by the functionalised nitroolefin (199) which could avoid the necessity of separate hydroxymethylation and protection stages.

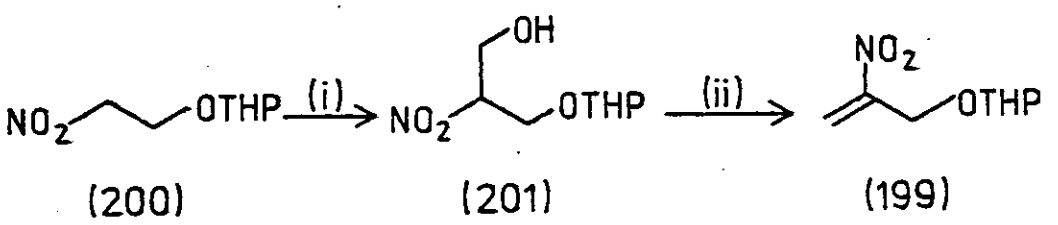


(199)

Attempts to prepare this compound by, for example, treatment of (200) with formalin in basic solution and subsequent elimination of the

methanesulphonate generated *in situ*[100] (Scheme 44) or by Corey's nitromercuation elimination procedure[109] as applied to the tetrahydropyranyloxy ether of allyl alcohol failed. We therefore had to abandon this attractive approach.

SCHEME 44

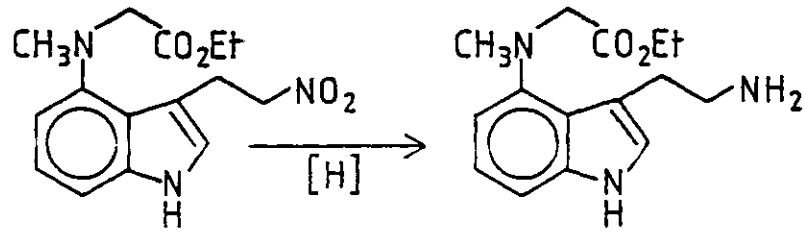


(200) (201) (199)

(i) HCHO, base. (ii) CH_3SO_2Cl, Et_3N.

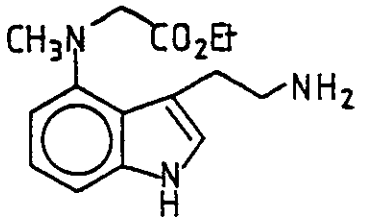
(iii) Reduction to Tryptamines

Finally in this section an efficient general methodology for the reduction of 3-(2-nitroethyl) indoles to the corresponding amines was required. Of the literature procedures[110] for this type of transformation, catalytic hydrogenation appeared to be the simplest option. However treatment of the unfunctionalised model compound 3-(2-nitroethyl)-indole (155) at four atmospheres pressure of hydrogen in a variety of solvents in the presence of 10% palladium on charcoal gave a mixture of unstable products.

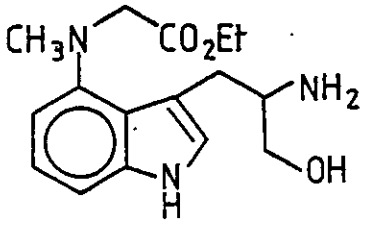


(155) (202) same as (161)

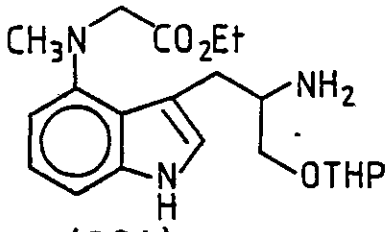
After an extensive exploration of this apparently simple transformation it was found that a combination of nickel (II) chloride and sodium borohydride in hot ethanol[111] was a most effective method. An experimentally simpler process that was eventually applied generally to the reduction of our nitro-alkanes was the use of a cobalt (II) chloride/sodium borohydride reagent combination[112]. This system proved efficient and rapid at (or below) room temperature. The tryptamines (202), (203), (204), (205a,b), (206a,b) and (206a) were all thus obtained from the corresponding nitro compounds in yields of 71 - 89%. The unprotected β-amino alcohol (203) was prepared to explore the previously discussed competition between the amine and hydroxyl group in the proposed cyclisation reaction.



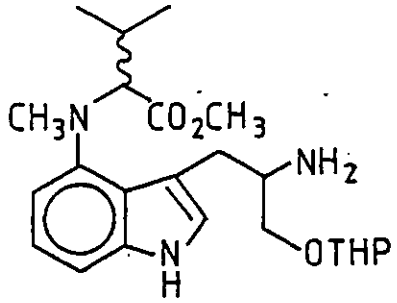
(202)



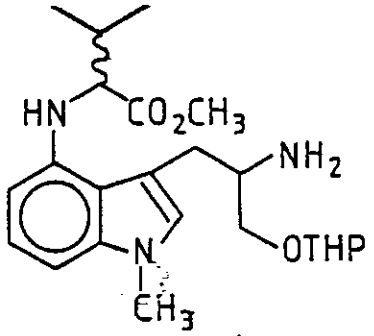
(203)



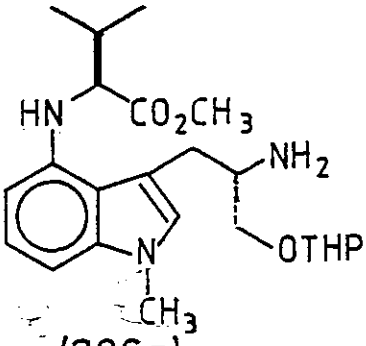
(204)



(205a and b)



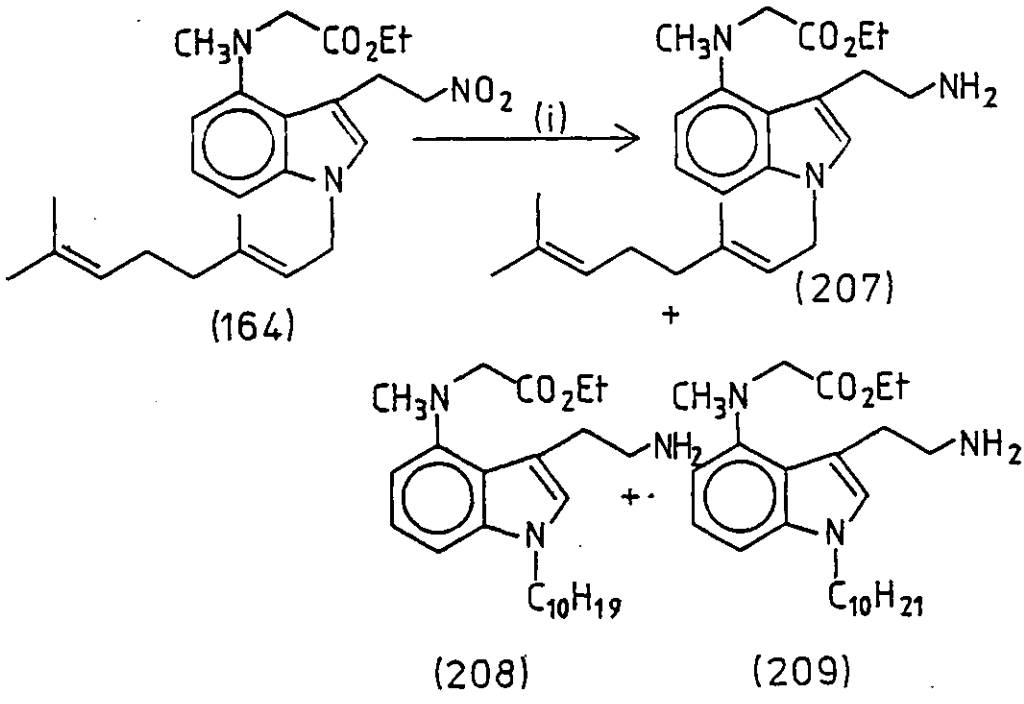
(206a and b)



(206a)

Although cleanly and efficiently reducing 3-(2-nitroethyl)indoles, it was found that the $CoCl_2/NaBH_4$ reagent also reduced the trisubstituted olefinic bonds[113] of an indole geranyl substituent. Reduction of the 1,3,4-trisubstituted indole (164) with $CoCl_2/NaBH_4$ according to the general procedure resulted in a mixture of three products (207), (208) and (209) (Scheme 45). The previously discussed $NiCl_2/NaBH_4$ system has however already been shown to leave a geranyl substituent intact (Section 4 (v)).

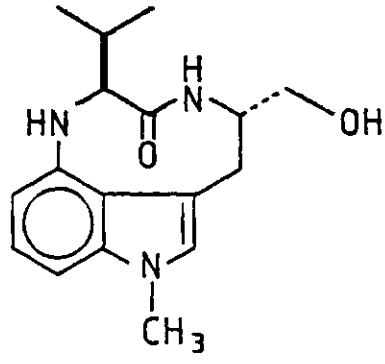
SCHEME 45



(208) (209)

(i) $CoCl_4/NaBH_4$, MeOH.

Thus we were able to synthesise a number of important <u>seco</u> amino acid esters necessary for further work towards the target tricyclic lactams (8), (12) and (13). Also synthesis of the additional targets (125a,b) and (125a) from cyclisation of the readily available 'rearranged' indoles (206a,b) or the diastereomerically pure (206a) respectively.



(125a)

N.B. Where diastereomers have been formed they have been described by the same number but a different lower case letter. Where diastereomeric mixtures are under discussion both letters are included, where a single diastereomer is being discussed only one lower case letter is included. For example, structure (206a,b) describes a diastereomeric mixture while (206a) describes a single diastereomer.

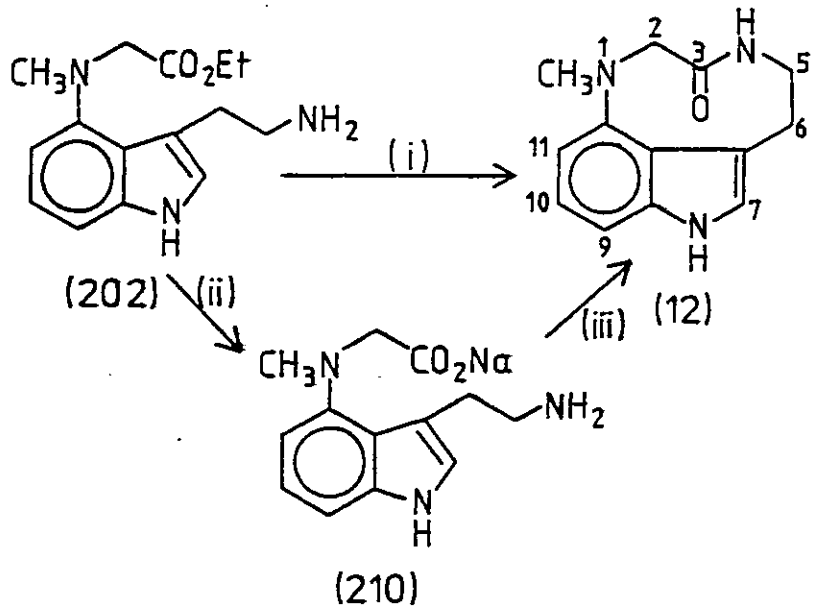
9. Synthesis of the Tricyclic Lactams

(i) Synthesis

Having overcome a number of synthetic problems en route to the target molecules (8), (12) and (13) we finally reached the crucial macrolactam cyclisation step. This was originally anticipated to be one of the more difficult stages in the synthesis of these unusual tricyclic ring systems. With some relief therefore it was observed that the simple 4-substituted tryptamine (202) gave the tricyclic lactam (12) in a 40% yield on simply warming in D.M.F. at 140°C at a concentration of 1mg/ml≡ 3.6 x

10^{-3}M (Scheme 46). However a two stage procedure proved to be more effective than this classical thermolysis method. Thus hydrolysis of the ester (202) with one equivalent of aqueous sodium hydroxide followed by careful drying gave the sodium salt (210). Treatment of the salt (210) with diphenylphosphoryl azide[67] and triethylamine in D.M.F. resulted in yields of up to 57% of the tricycle (12) (Scheme 46).

SCHEME 46



(i) D.M.F., heat, 40%. (ii) NaOH, H_2O, EtOH.
(iii) $(PhO)_2P(O)N_3$, D.M.F., 57% overall.

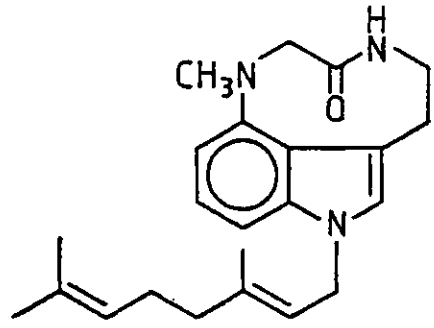
Dicyclohexylcarbodiimide (DCC) a classical peptide coupling reagent, proved to be less effective and purification more troublesome than the diphenylphosphoryl azide route. Attempts to improve the yields of the cyclisation reaction by for example

slow addition of a solution of the sodium salt (210) in D.M.F. to diphenylphosphoryl azide over a period of 8h or by variation of the initial concentration of the reaction mixture proved to be ineffective. Generally reactions were performed at a concentration of the sodium salt (210) of 1-3mg/ml $\equiv 3.6 \times 10^{-3} - 10^{-2}$M.

Inspection of the ^{1}H n.m.r. spectrum of (12) obtained at 250MHz revealed very extensive broadening of resonances due to the ring methylene protons. Warming the deuteriochloroform solution of (12) to 50°C however resulted in the resolution of a triplet J 6Hz at δ 3.24 assigned to the ring methylene C-6 protons. Also the previously broad resonance centred at δ3.90 assigned to the ring C-2 and C-5 protons sharpened significantly. The possibility of the existence of two distinct conformers of Teleocidin A at room temperature has already been extensively discusssed (Section 2). It is thought that the lactam (12) also exists in two different conformations which at room temperature equilibrate much faster than the conformers of Teleocidin A and happen to produce coalescence in the ^{1}H n.m.r. spectrum. This is due to the greater flexibility of the unsubstituted macrocyclic ring of (12) compared to the 'locked' nature of the substituted lactam ring of Teleocidin A.

The 8-geranyl compound (211) was successfully prepared by the simultaneous addition of (12) and

geranyl chloride to sodium hydride. No evidence of alkylation of the lactam nitrogen was observed. It was thought that this compound should display interesting biological properties since not only does it possess the important 9-membered lactam but also contains a lipophilic terpenoid side chain.

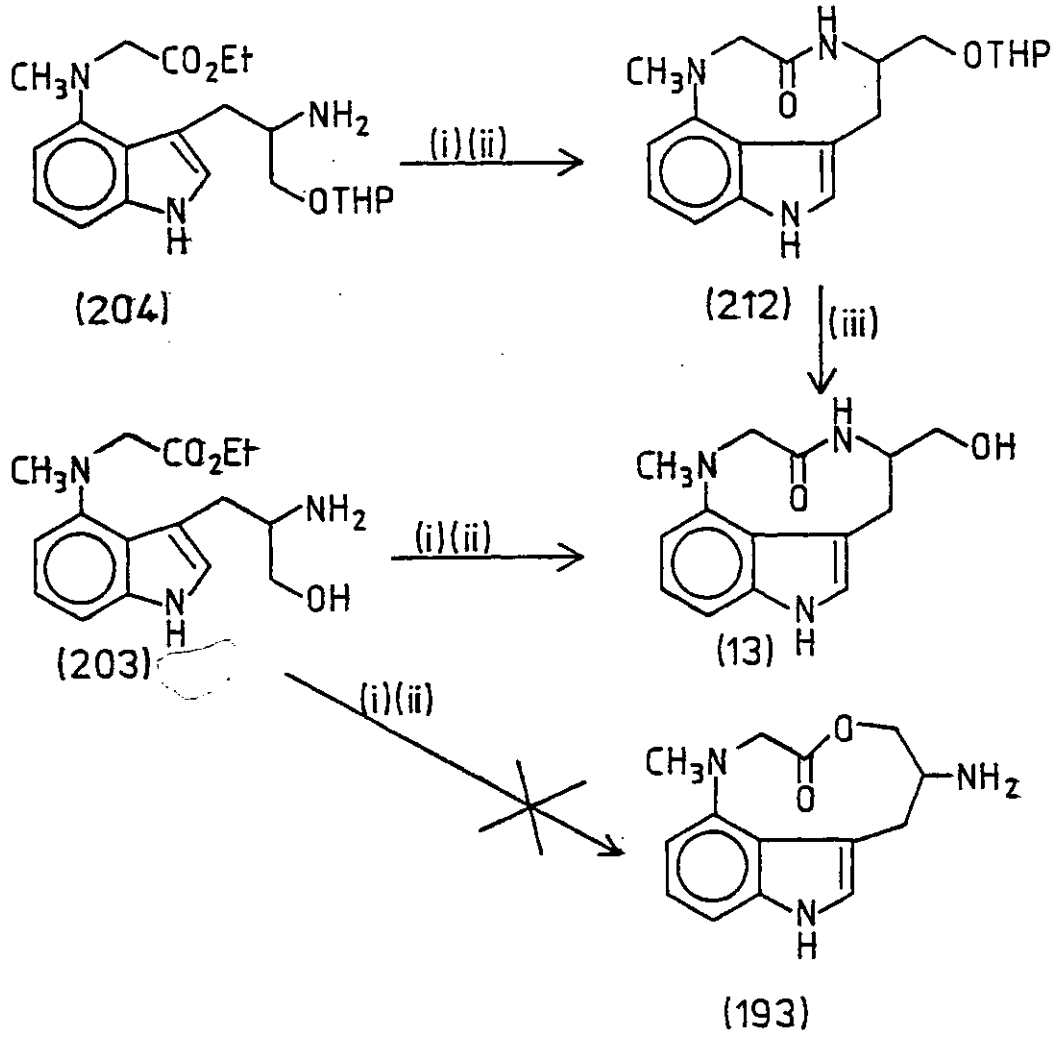


(211)

The protected precursor to (13), (212) was prepared by a similar two stage hydrolysis/ cyclisation procedure from the protected amino alcohol (204) (Scheme 47). Interestingly the unprotected amino alchohol (203) gave (13) directly by the same protocol (Scheme 47), no sign of the corresponding lactone (193) being observed from inspection of the i.r. of the crude reaction product. The isolated yield in this reaction was however poor due to the low solubility of (13) in typical organic solvents. Thus protection of the hydroxylic functionality of (13) proved to be unnecessary from the chemical reactivity of the system. However in practice protection proved to be of value in solubilising this tricyclic product. Deprotection of (212) was accomplished with dilute hydrochloric acid

at room temperature (Scheme 47). Acetic acid in THF[113a] or Amberlyst resin[113b] failed in this case.

SCHEME 47

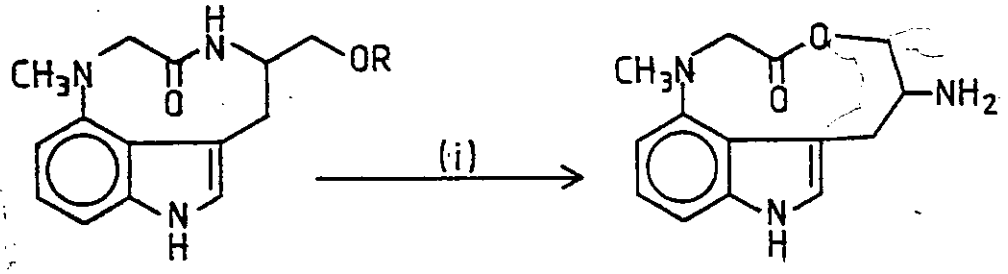


(i) NaOH, EtOH, H_2O. (ii) $(PhO)_2P(O)N_3$, Et_3N, D.M.F. (iii) HCl, room temperature.

Treatment of the protected compound (212) or (13) with 3N HCl at reflux in ethanol overnight gave an acid soluble product. Inspection of the i.r. spectrum of this product revealed an absorption at 1720cm^{-1} corresponding to a lactone or ester carbonyl

stretch and no absorption corresponding to a lactam at 1650 - 1660cm^{-1}. Teleocidin B has been shown to undergo a ring opening/ring closure reaction to give the lactone (see Section 2)[3]. The structure of the new product is therefore thought to be the lactone (193) (Scheme 48).

SCHEME 48



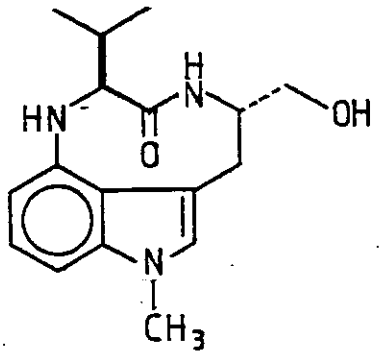
(13) R = H

(212) R = THP

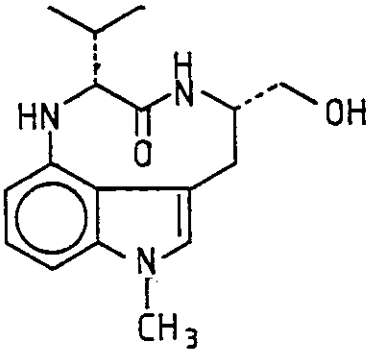
(193)

(i) 3N HCl, H_2O, EtOH, 85°C.

As previously mentioned (see Section 5 (ii)) the two diastereomers (125a) and (125b) have been unintentionally synthesised and details of the final stages of this synthesis are now discussed.



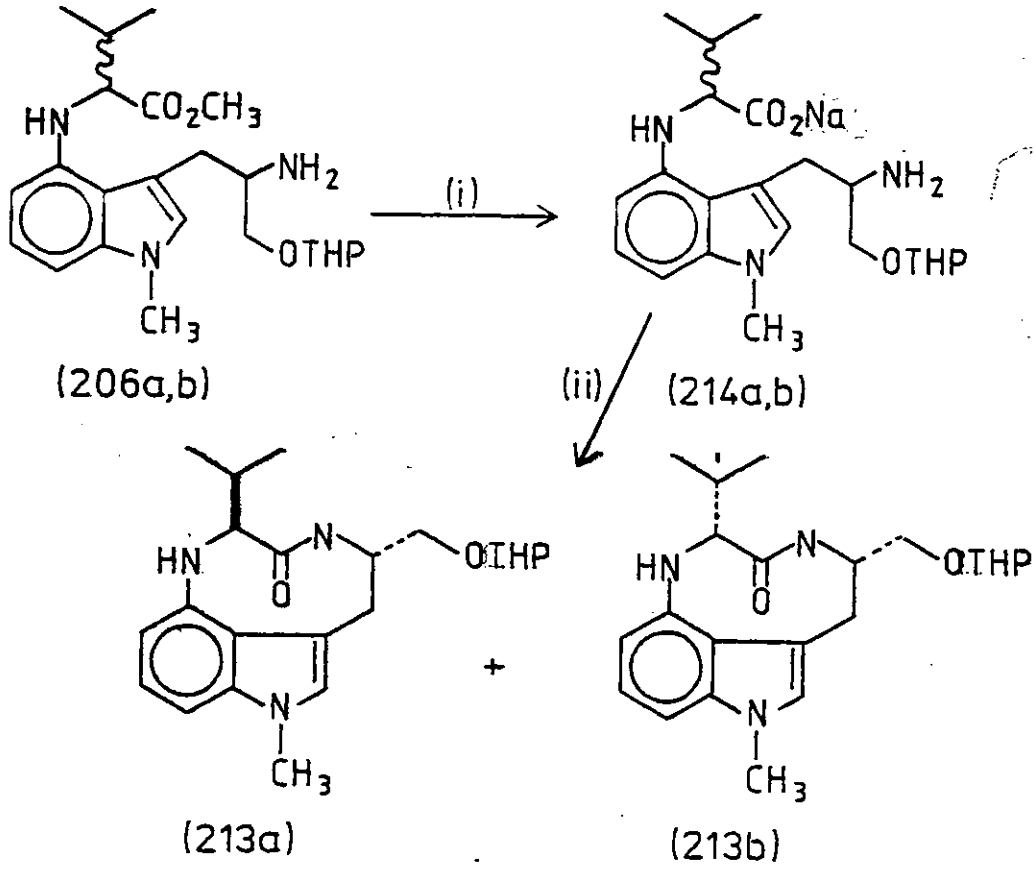
(125a)



(125b)

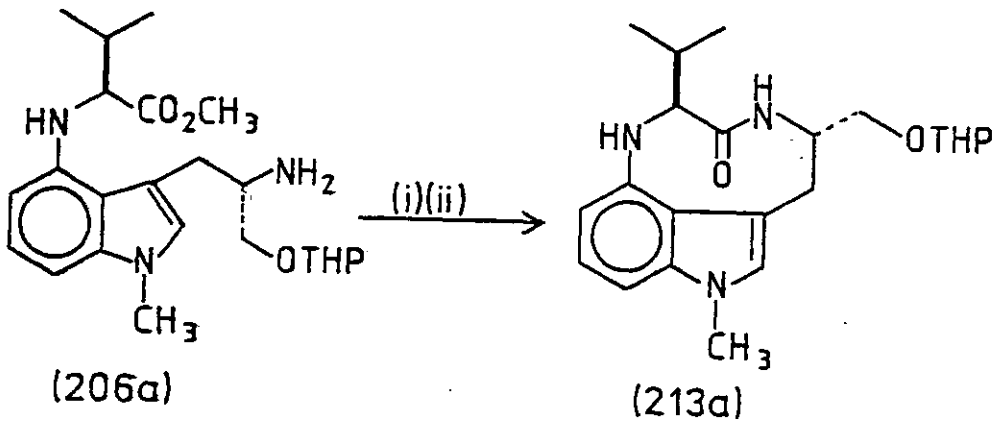
Treatment of the diastereomeric mixture of amino esters (206a,b) with base and subsequent cyclisation with diphenylphosphoryl azide gave a 1:1 mixture of the diastereomeric THP ethers (213a) and (213b) which were readily separated by chromatography (Scheme 49). It was noticeable that saponification of (206a,b) was much slower than was saponification of for example (202), reflux overnight being necessary. It had been thought that cyclisation of the diastereomeric mixture of the sodium salts (214a,b) would lead to formation of only one diastereomer, the trans isomer (213a). Epimerisation of the residual sodium salt (214b) and submission to cyclisation again would then lead to an additional yield of the trans product (213a). Evidently however since a 1:1 diastereomeric mixture of (213a) and (213b) was isolated no diastereoselection was obtained. Also it was found, surprisingly, that treatment of the diastereomerically pure amino ester (206a) with base at reflux and subsequent cyclisation gave the trans product (213a) with only minor quantities of the more polar cis product (213b) (Scheme 50). From this result it was clear that the valine moiety of (206a) was remarkably resistant to epimerisation.

SCHEME 49



(i) NaOH, EtOH, H_2O, reflux, 100%.
(ii) $(PhO)_2P(O)N_3$, Et_3N, D.M.F. 74%.

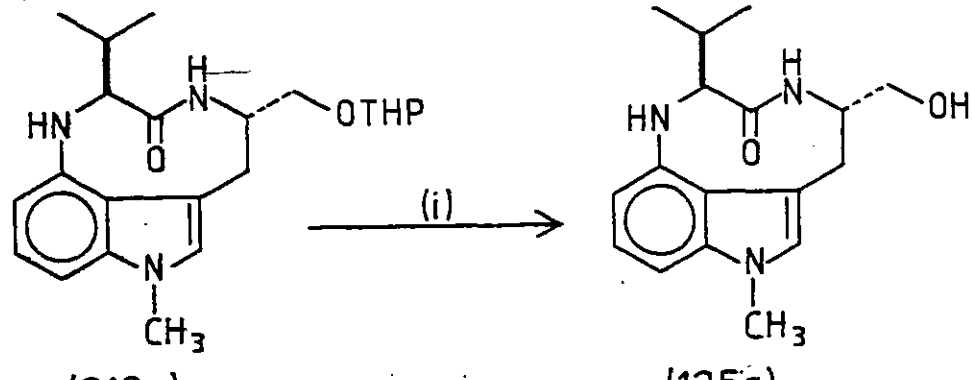
SCHEME 50



(i) NaOH, EtOH, H_2O, reflux. (ii) $(PhO)_2P(O)N_3$, Et_3N, D.M.F.

The THP ether (213a), isolated as a crystalline solid and (213b), an oil, were deprotected by an improved procedure[115]. Treatment of (213a) (Scheme 51) or (213b) with a catalytic quantity of 4-toluenesulphonic acid in warm methanol followed by removal of the bulk of the solvent and cooling gave in excellent yield (125a) and (125b) as colourless microneedles and pale yellow crystals respectively. X-ray crystallographic analysis of (125b) (Appendix 4) established its structure and relative cis stereochemistry. Variable temperature ^1H n.m.r. studies of both (125a) and (125b) were also undertaken and are illustrated in Appendices 5 and 6 respectively. The spectra of these two compounds demonstrated an improved resolution of resonances at room temperature relative to spectra of (12).

SCHEME 51

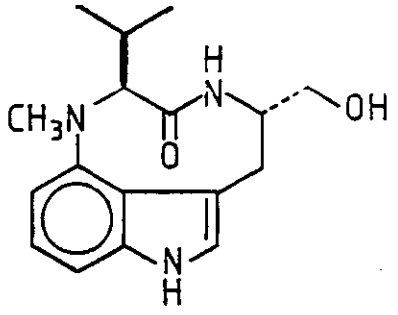


(213a) (125a)

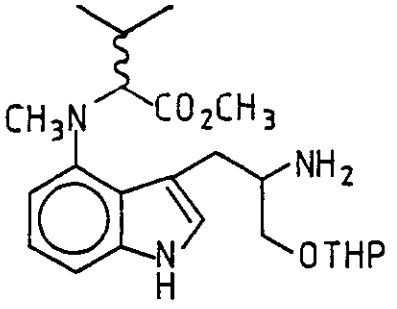
(i) CH_3OH, 4-$CH_3.C_6H_4SO_3H$, 60°C, 94%.

Finally in order to conclude this section we must consider the synthesis of the trans 'northern zone'

model (8) from the diastereomeric mixture of protected amino alcohols (205a,b).

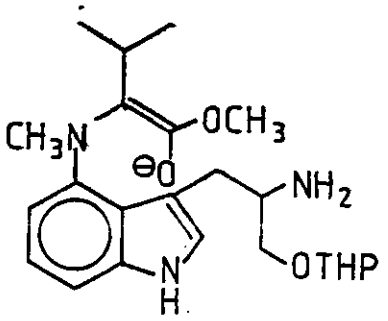


(8)

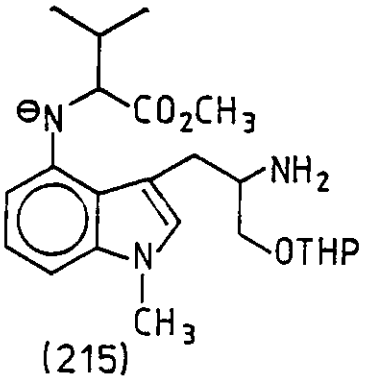


(205a,b)

Consequently it was found that (205a,b) was unaffected by treatment with four equivalents of NaOH in propan-2-ol at reflux temperature. Also it was shown that application of Gassman's hindered ester hydrolysis procedure[116] using ten equivalents of potassium tert butoxide in ether was also ineffective. Remarkably a considerable proportion of the amino ester was found to be extracted into the strongly basic aqueous phase on treating the ethereal reaction mixture with water. One possible explanation for this unexpected and disappointing result is that the proton α to the carboxylate ester is sufficiently acid to be removed under the basic reaction conditions resulting in an enolate ester (214). This enolate would not only deactivate the ester to normal base catalysed hydrolysis but would also solubilise the compound in a strongly basic aqueous medium.

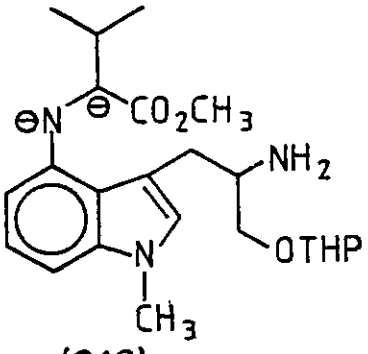


(214)

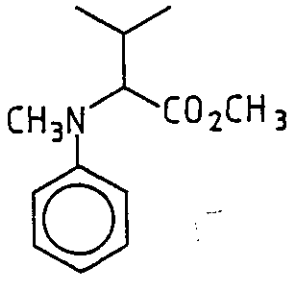


(215)

By contrast the 'rearranged' amino ester (206a,b) would be expected to deprotonate more readily on nitrogen than carbon to give the anion (215). This species can still undergo saponification by conventional means, albeit slowly. It would also be expected, as observed, to be resistant to epimerisation since this process requires the abstraction of the proton α to the carboxylate ester leading to a vicinal dianion (216) an obviously unfavoured species.



(216)

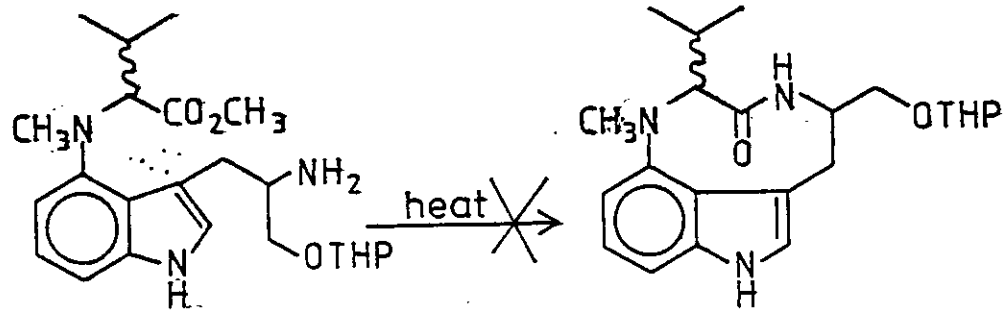


(122)

Finally it should be noted that N-phenyl-N-methyl valine methyl ester (122) undergoes a slow hydrolysis reaction on treatment with aqueous ethanolic sodium hydroxide. Evidently therefore, either the indole

ring or the tryptophanolyl substituent is influencing the acidity of the proton α to the ester functionality of (205a,b).

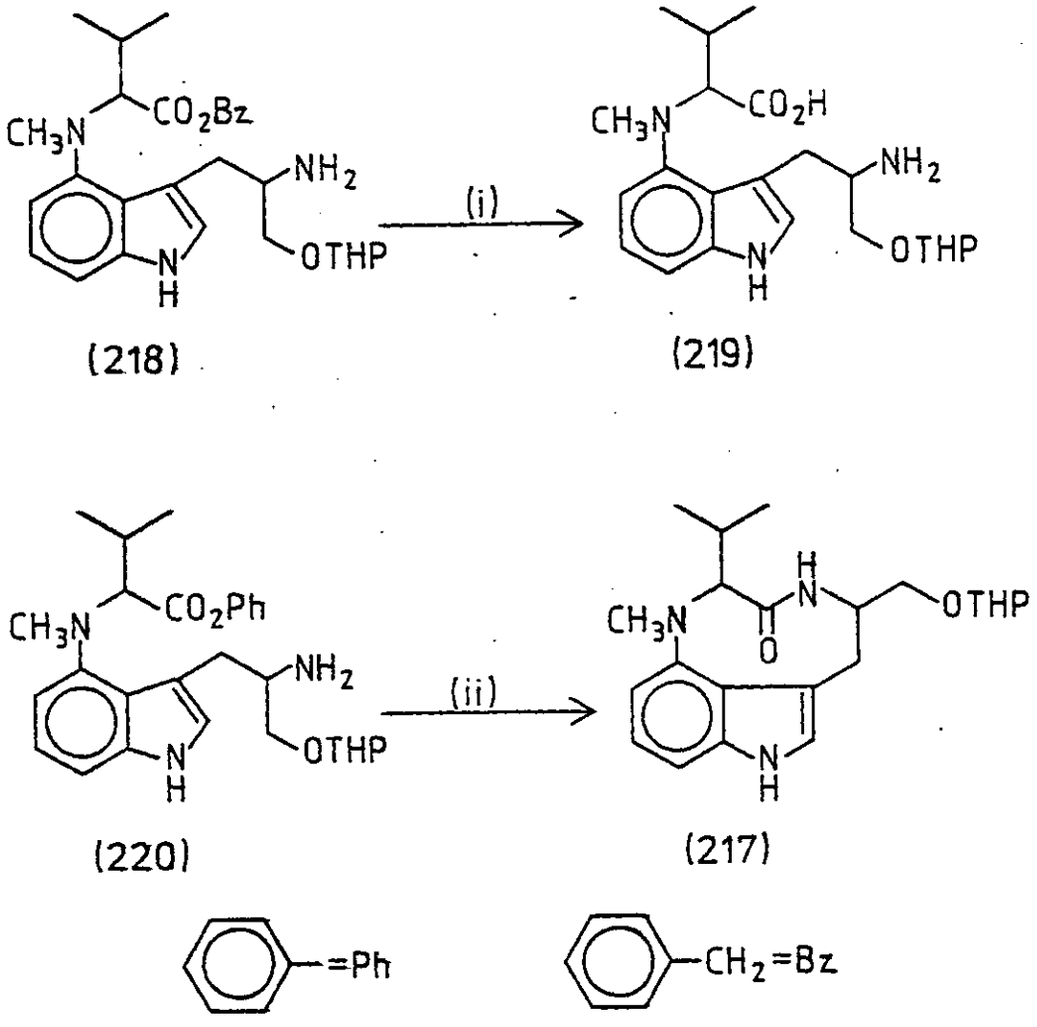
Direct intramolecular reaction of the diastereomeric mixture of amino esters (205a,b) by thermolysis as described for the formation of (12) resulted in the isolation of an intractable mixture of products, none of the protected compound (217a,b) being detected.



(205a,b) (217a,b)

Unfortunately due to lack of both material and time the further study of the hydrolysis of (205a,b) has not been possible. It is to be expected that esters such as the benzyl (218) or phenyl (220) would be more suitable than the methyl ester for synthesis of the tricylic lactam (8). The former should undergo a facile hydrogenolysis reaction to the amino acid (219) (Scheme 52). The latter is reported to be particularly effective in undergoing nucleophilic displacement by amines (Scheme 52) so that the tricycle (217) could be prepared in one step.

SCHEME 52



(i) H_2/Pd/C (ii) heat.

(ii) Conclusion

In this section we have shown that 9-membered lactam rings can be synthesised by using a conventional peptide coupling reaction. However the synthesis of the fully functionalised 'northern zone' model (8) has not proved possible due to the unusual stability towards hydrolysis of the methyl ester

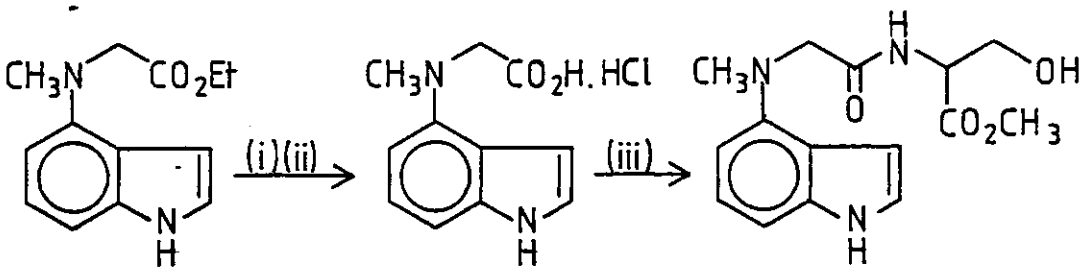
employed. It is thought however that variation of the ester functionality of the amino acid ester (205a,b) should make this important compound easily accessible and that the total synthesis of Teleocidin A is now in sight.

10. Alternative Strategy Towards 3H-Pyrrolo-1,4-benzodiazonin-3-ones

Having demonstrated in the previous section the feasability, using one approach, of the synthesis of the pyrrolo-1,4-benzodiazonin-3-one skeleton common to the Teleocidins a brief examination of an alternative strategy was also pursued. This approach (see Retrosynthesis) relies on intramolecular carbon-carbon bond formation at the indole 3-position of a dipeptide such as (221). This nine membered ring cyclisation process is favoured according to Baldwin's rules for ring closure[117]. An added attraction of this route was the potential for the simultaneous introduction of a chiral 5-substituent into the 3H-pyrrolo-1,4-benzodiazonin-3-one ring system.

Hydrolysis of the versatile 4-aminoindole derivative (113) and subsequent acidification with HCl gave the amino acid (222) as the hydrochloride salt. Subsequent reaction with dl-serine methyl ester[75], dicyclohexylcarbodiimide, triethylamine and 10mol% of 4-N,N-dimethylaminopyridine[118] gave the dipeptide (221) in a respectable 55% overall yield (Scheme 53).

SCHEME 53

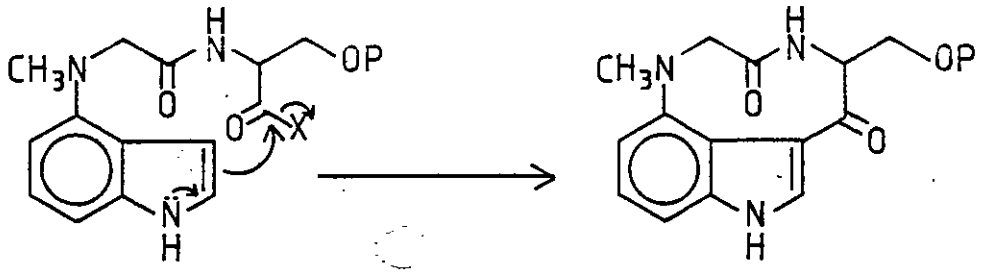


(113) (222) (221)

(i) NaOH, EtOH, H_2O. (ii) HCl (iii) dl-serine methyl ester hydrochloride, D.C.C., D.M.A.P., Et_3N, 55% overall

The serine moiety of the dipeptide (221) is potentially an ambident electrophile since reaction at the indole 3-position may either take place *via* acylation with the carboxylate group (223) (Scheme 54) or *via* displacement of an activated hydroxyl species (225) (Scheme 55). Subsequent elaboration of either product (224) or (226) would lead to the tricyclic lactam (13).

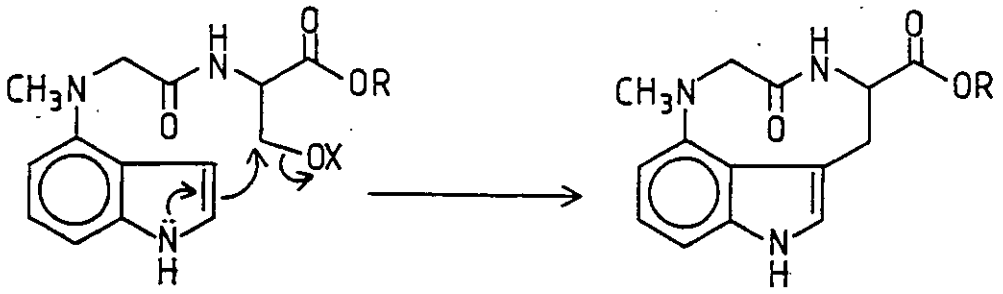
SCHEME 54



X = leaving group P = protecting group

(223) (224)

SCHEME 55

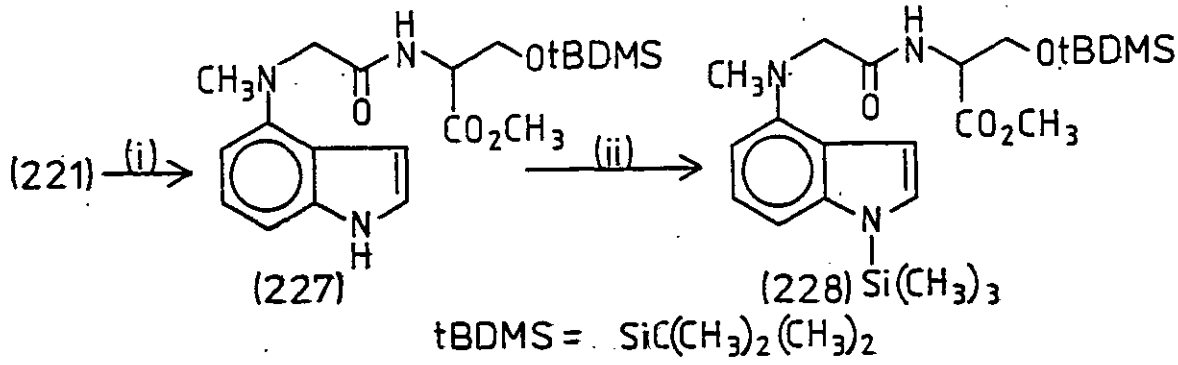


(225) (226)

In order to explore the first route, the tert butyldimethylsilyl ether (227) was prepared by standard means. No bis-silylation was observed. In an effort to exploit the unusual Friedel-Crafts chemistry of 1-trimethylsilyl-4-aminoindoles (see Section 7) attempts were directed towards the synthesis of the bis-silylated compound (228) (Scheme 56). Unfortunately this compound proved to be unexpectedly unstable and reverted rapidly to the monosilylated material (227) on rapid column

chromatography. Evidently therefore this compound (227) was not an ideal substrate for further chemical manipulation.

SCHEME 56



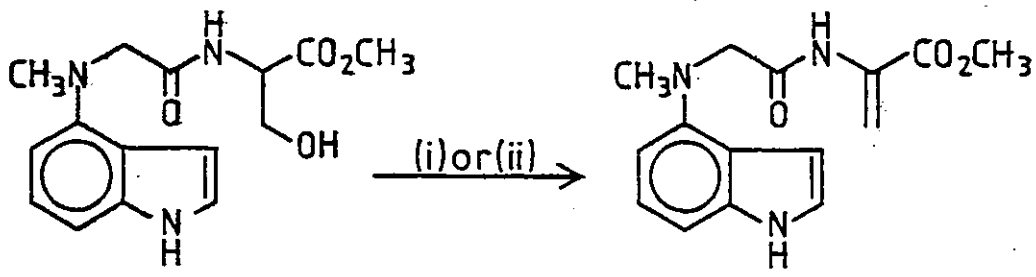
(i) $(CH_3)_2(CH_3)_3CSiCl$, D.M.A.P., Et_3N, 93%.
(ii) $(CH_3)_3SiCl$, Et_3N, D.M.A.P., 17% after chromatography.

The acylation of pyrroles and indoles by treatment of the parent heterocycle with a potassium carboxylate salt and methanesulphonyl chloride has been reported[97]. Saponification of (227) and treatment of the resultant sodium salt according to the literature procedure under high dilution conditions however, gave none of the desired tricyclic vinylogous amide (224, $P=Si(CH_3)_2C(CH_3)_3$).

Finally in this alternative approach to cyclisation, activation of the hydroxyl group to nucleophilic displacement was briefly investigated. Mitsonubu's approach to activating hydroxylic species with diethyl azodicarboxylate and triphenylphosphine is well known[119]. Application of this methodology to the dipeptide (221) did indeed result in the

formation of a new compound, which was however shown to be the glycylamidoacrylate ester (229). The same anhydro compound (229) was isolated quantitatively on treatment of the dipeptide (221) with one equivalent of methanesulphonyl chloride and excess triethylamine (Scheme 57).

SCHEME 57



(221) (229)

(i) Ph_3P, $EtO_2CN{=}NCO_2Et$, 76%. (ii) CH_3SO_2Cl, Et_3N 98%

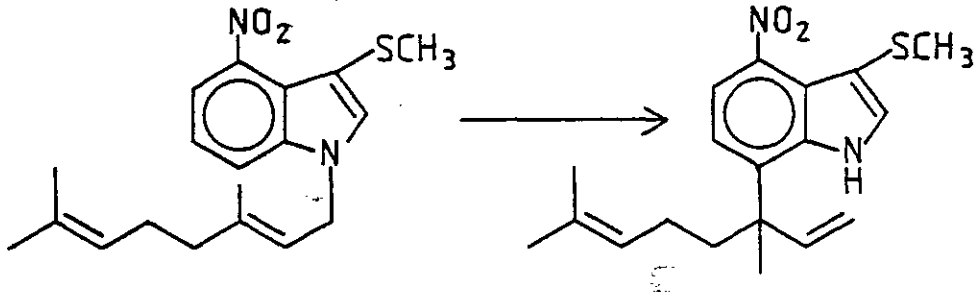
Although it was disappointing that intramolecular reaction had not occurred under these conditions the acrylate ester (229) is itself a potentially useful candidate for cyclisation since Michael additions at the indole 3-position are well documented[93,94(b),120]. Unfortunately however under a variety of acid conditions including both Brönsted and Lewis acids no cyclisation reaction was observed.

Although these initial results were discouraging further investigation of this approach is certainly warranted.

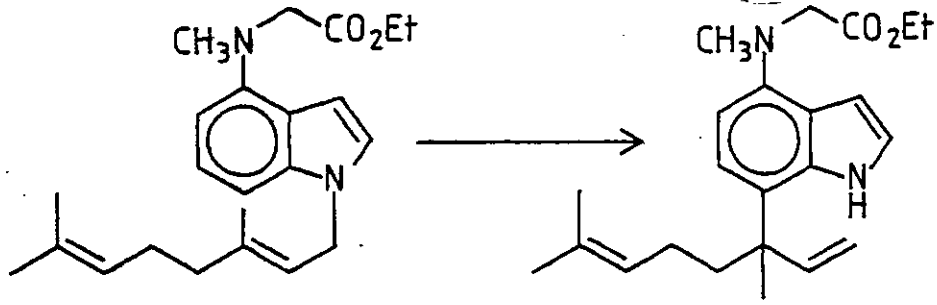
11. Approaches to the Introduction of the Linalyl 'Southern Zone'

(i) Introduction

The proposed route to the introduction of the 'southern zone' linalyl side chain of Teleocidin A (see Retrosynthesis) involved an aza-Claisen rearrangement of a 1-geranyl indole. The synthesis of two precursor model compounds (63) and (133) have already been described. Studies directed towards the rearrangement of these two compounds to (230) and (231) are discussed in this section.



(63) (230)



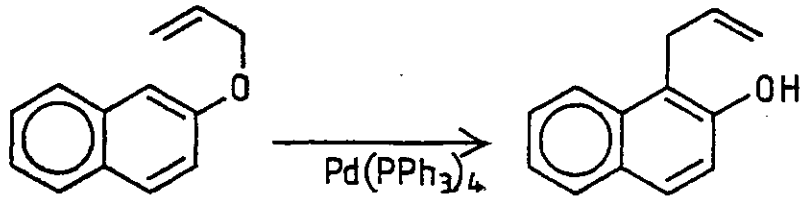
(133) (231)

(ii) The aza-Claisen reaction

The thermolysis of 1-crotylindoles at 460°C has been reported to give a mixture of 1-, 2- and 3-crotylindoles in low yield[121]. Also Inada's

group[122] and Gasnati[33] have reported the Lewis acid catalysed rearrangement of 1-allyl indoles to 2- or 3-substituted indoles. The very extensive applications of palladium complexes to organic chemistry also includes the mild Claisen rearrangement of aromatic allyl ethers (232)[123] (Scheme 58).

SCHEME 58



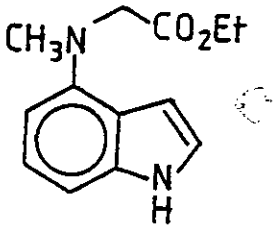
(232) (233)

Finally it has been shown that although the rates of Claisen rearrangement are only slightly affected by other substituents on the aromatic ring[124], solvent polarity plays a significant part in determining the rate of rearrangement[125]. A particularly suitable solvent is trifluoroacetic acid[126].

It was found however that on heating either (63) or (133) either neat at up to 230°C or at reflux in di-n-butyl phthalate for extended periods of time no useful products were produced. Treatment of (63) with $ZnCl_2$, $BF_3.Et_2O$, $AlCl_3$ or Et_2AlCl proved equally ineffective. The use of transition metal catalysts such as $Pd(PPh_3)_4$, $PdCl_2(MeCN)_2$, $Pd(OAc)_2(PPh_3)_2$, $RuCl_2(PPh_3)_3$ or the highly enophilic

$Pd(BF_4)_2MeCN(PPh_3)_3$[127] was also unsuccessful on this particular substrate.

Flash vacuum pyrolysis of (133) at 560°C and 680°C at a pressure of $5x10^{-2}$mmHg resulted in the complete recovery of starting material. At 800°C and 3.5 x 10^{-2}mmHg extensive decomposition occurred. The major product observed was the degeranyl material (113).

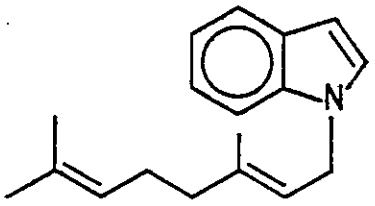


(113)

Finally it was observed that warming (133) in trifluoroacetic acid at reflux resulted in the isolation of a 60% yield of an unidentified product. Examination of the ^1H n.m.r. at 250MHz however revealed two doublets J 7.4Hz at δ 6.16 and 6.30. A triplet J 7.4Hz at δ 7.01 was also observed. These resonances were assigned to the indole 5,6 and 7 protons. The absence of a resonance corresponding to the indole NH indicated that no aza-Claisen reaction had taken place. Mass and i.r. spectroscopy revealed the presence of a trifluoroacetyl group. It was concluded therefore that a 1,2,3,4-tetrasubstituted indole had been generated and further exploration of the product was not undertaken. This result illustrated one of the problems of this approach to introducing the linalyl C-7 substituent. That is the

regioselectivity of the electrocyclic rearrangement of a 1-geranyl substituent in the 4-aminoindole system is uncertain.

Submission of 1-geranylindole (137) to the same reaction condition of refluxing trifluoroacetic acid resulted in a multitude of products. It is thought that the stability of the aminoindole (133) in strong acid is due to stabilisation of the indole ring by protonation of the amine functionality.

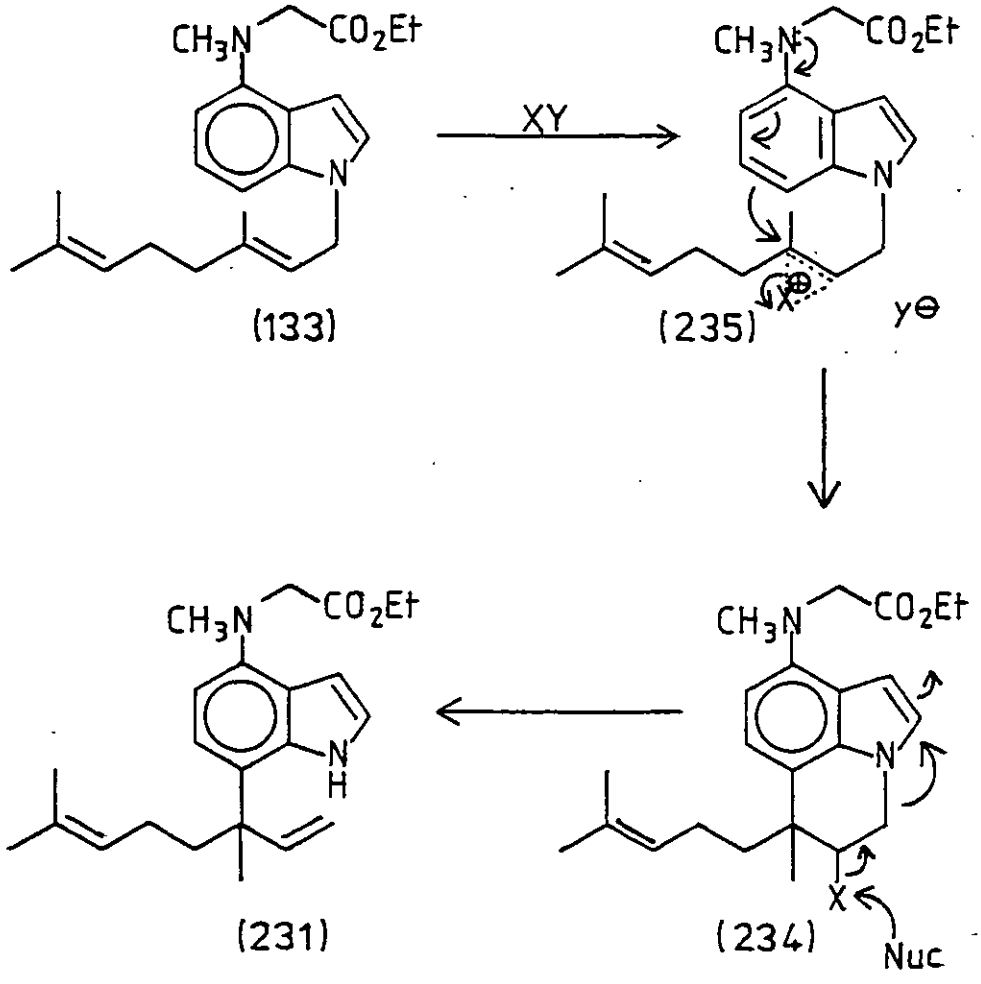


(137)

(iii) Alternative Approaches

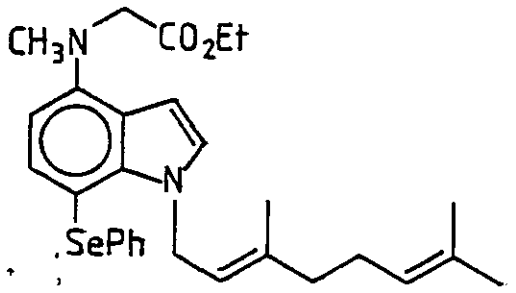
Direct aza-Claisen [3,3] sigmatropic rearrangement has so far proved unsuccessful on simple models. Multi-stage procedures using (133) have however also been briefly investigated. The general approach is outlined in Scheme 59 and involves the cationic activation of the olefinic bond allylic to the indole nitrogen and subsequent nucleophilic attack by the indole C-7 position a phenomenon that has already been discussed (Section 7). Reductive replacement of X from the intermediate tricycle (234) as indicated could lead to the required linalyl substituted indole (231).

SCHEME 59



Particularly attractive in this respect was the employment of a selenium reagent (X=SePh) since nucleophilic displacement of such a species is well known[128]. However treatment of (133) with either N-phenylselenophthalimide and $SnCl_4$ as catalyst, or with $PhSe^+SbF_6^-$ [129] generated <u>in situ</u> from phenylselenyl chloride and silver hexafluoroantimonate failed to provide the required tricylic adduct (234). Analysis of the mass spectra of these reactions revealed that selenium had been

incorporated into the molecule. Unfortunately loss of the geranyl group in the mass spectrum gave a peak at m/e 387 corresponding to a selenated indole. The structure of the indole generated by this methodology was therefore thought to be the 1,4,7-trisubstituted indole (236).

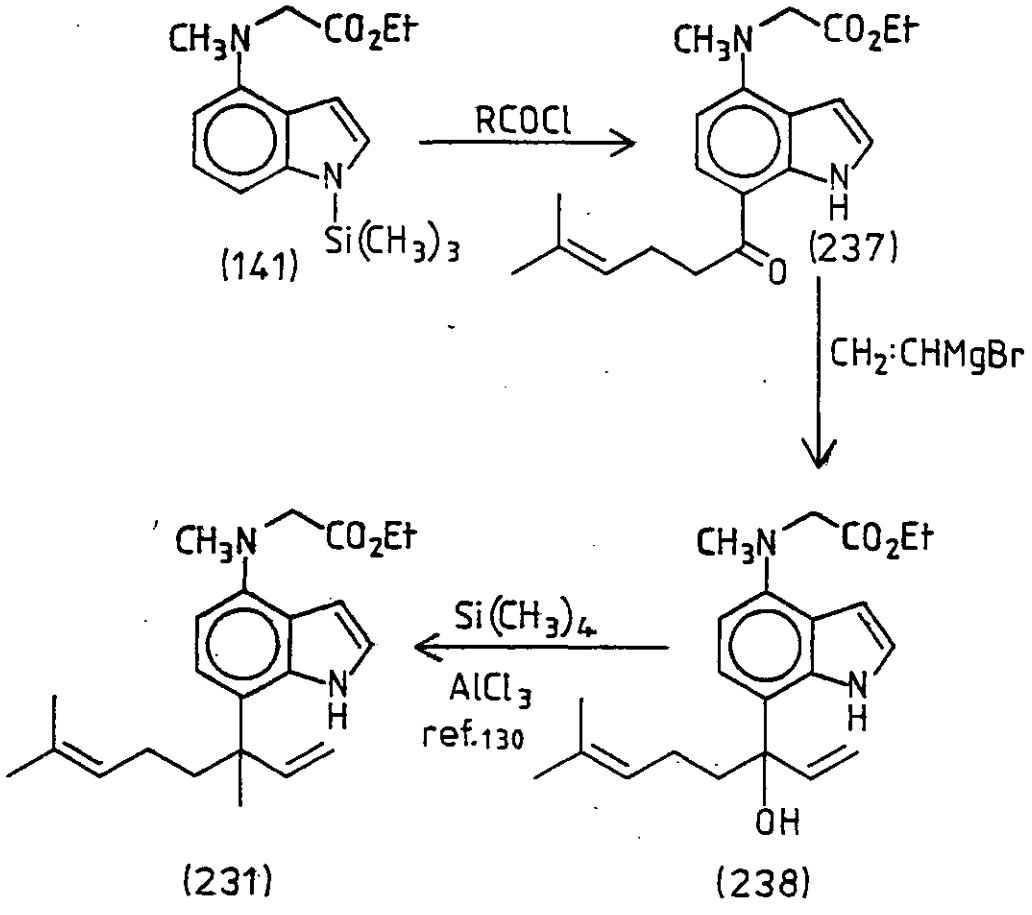


(236)

Similarly unsuccessful was the use of iodine, (X=I) and $Hg(OAc)_2$, (X=HgoAc).

A third approach to the introduction of a terpenoid 4-aminoindole C-7 substituent is of course by direct electrophilic substitution. One attractive version of this approach has already been discussed (see Section 7 (vi)) in which a suitable 7-acyl substituent (237) is introduced which on further manipulation could lead to the required linalyl substituent (Scheme 60). Unfortunately 7-acylation was shown to proceed in low yield with poor regioselectivity and this approach was not further pursued.

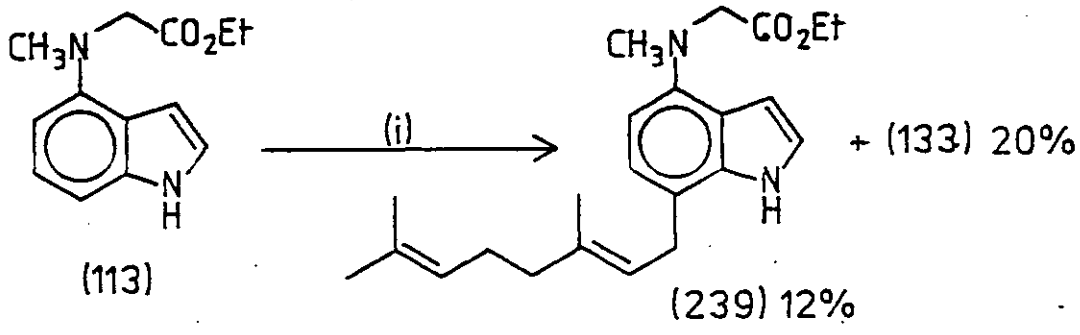
SCHEME 60



Friedel-Crafts alkylation of (133) with geranyl chloride under various conditions failed.

Finally in this section it was found that the methanesulphonate of geraniol gave a 12% yield of the 7-geranyl substituted 4-aminoindole (239). The 1-geranyl indole (133) was also isolated in low yield (Scheme 61). Replacement of geraniol with linalool led predictably to the recovery of starting material only.

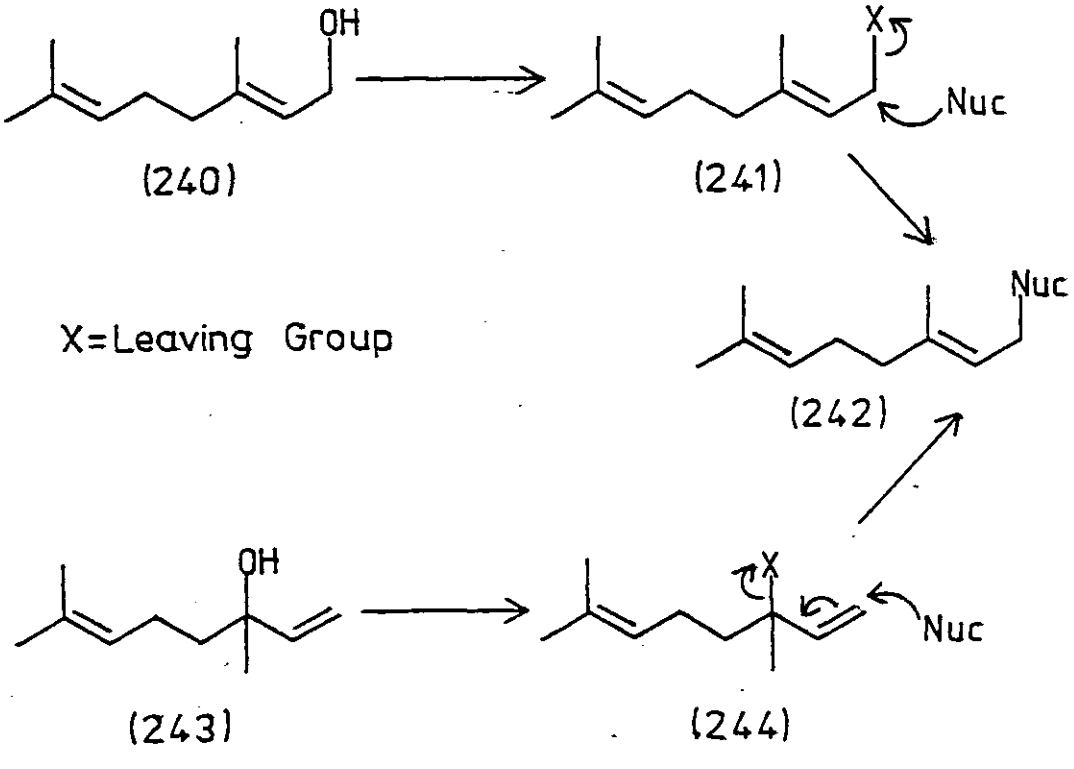
SCHEME 61



(i) geraniol, CH_3SO_2Cl, Et_3N, D.M.A.P., 12%

These two reactions highlight the major drawback to a direct electrophilic substitution procedure. The primary alcohol functionality of geraniol (240) is readily activated and undergoes SN2 substitution (Scheme 62). The tertiary alcohol linalool (243) is, however, less readily activated but would be expected to undergo S_N2^1 substitution with nucleophiles (Scheme 62) leading to the same product (242).

SCHEME 62



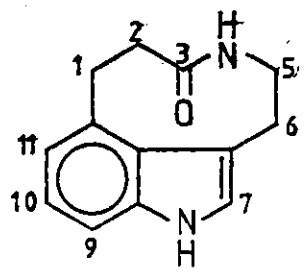
(iv) Conclusion

Results so far in the investigation of the introduction of an indole 7 linalyl substituent have been disappointing. However many alternatives still remain to be investigated and we are confident a suitable solution to the problem can be found. For example, photolysis of (133) or treatment of the same compound with tris(4-bromophenyl)amminium hexachloroantimonate[131], a stable radical cation reported to promote Diels Alder reactions, have not yet been studied. Also, a more extensive study of the attempted formation of the tricycle (234) is required. Finally the direct electrophilic substitution of 4-aminoindoles, needs further study.

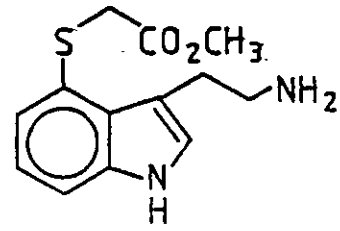
12 The Carbon Linked Analogue

(i) Introduction

As discussed in Section 3 (Retrosynthesis) a number of analogues of the Teleocidin A tricyclic lactam skeleton were proposed. These were designed to not only further investigate the chemistry of the lactam ring but also to explore the interesting biology of this unusual system. In this section the synthesis of one such compound, the 'carbon linked' analogue (15), is described. Additionally an approach to a 4-thio-substituted tryptamine (245) is briefly discussed.



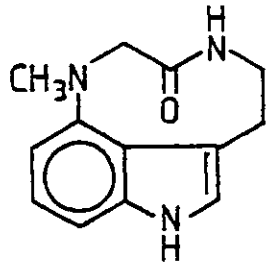
(15)



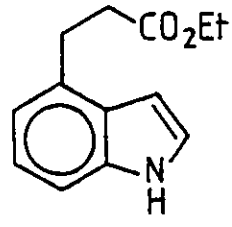
(245)

(ii) Synthesis of (15)

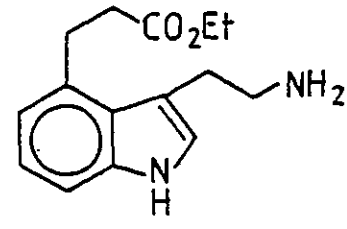
The approach to the preparation of (15) was similar to that used for the synthesis of (12). That is to say an appropriate 4-carbon substituted indole (246) was functionalised at the 3-position and this 3,4-disubstituted indole (247) was then cyclised to (15).



(12)



(246)

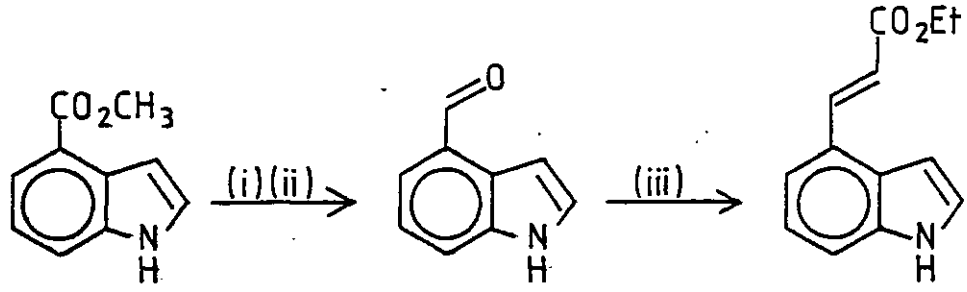


(247)

4-Carbon substituted indoles are of course well known from the extensive array of work in the field of ergot alkaloids[64]. In particular 4-methylindole carboxylate (88) the synthesis of which has already been discussed (see Section 4 (vi)) has proved to be particularly valuable. Kozikowski has recently reported the synthesis of the acrylate ester (248) from (88), which is a suitable precursor to (246), in

only three stages in excellent overall yield (Scheme 63)[65]. This same ester has been used recently by Oppolzer[132] in the synthesis of (±)Chanoclavine and (±)Isochanoclavine.

SCHEME 63

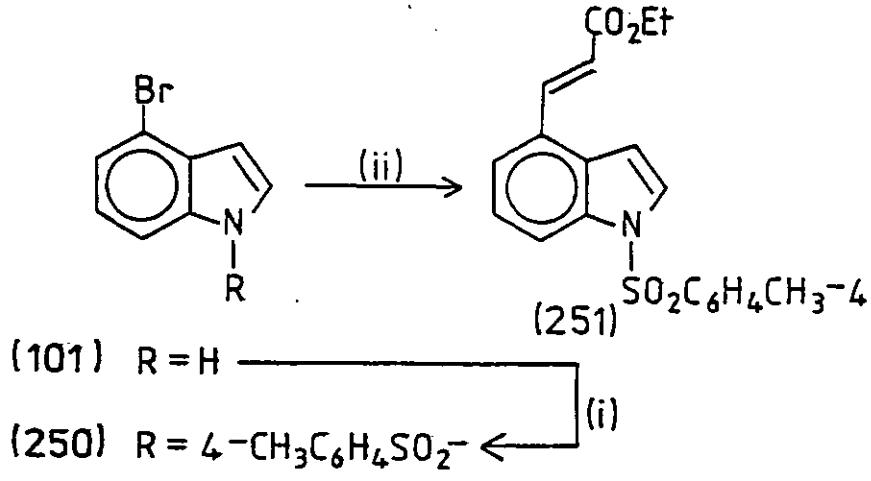


(88) (249) (248)

(i) $LiAlH_4$, THF, 99%. (ii) MnO_2, CH_2Cl_2, 92%.
(iii) $(C_6H_5)_3PCHCO_2Et$. 88%

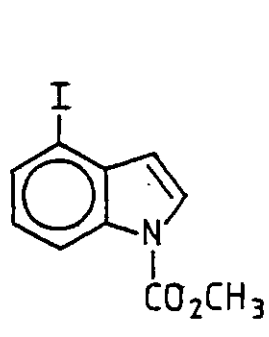
We also investigated an alternative route to the acrylate ester (248). Thus when 4-bromoindole (101) was treated under the usual Heck reaction conditions of palladium (II) acetate, triphenylphosphine, triethylamine and ethyl acrylate[133] no isolable product was realised. Deactivation of the indole ring however by introduction of the electron withdrawing 1-(4-toluenesulphonyl) group gave (250)[134]. Subsequent treatment under the same reaction conditions gave a 36% yield of the acrylate ester derivative (251) (Scheme 64).

SCHEME 64

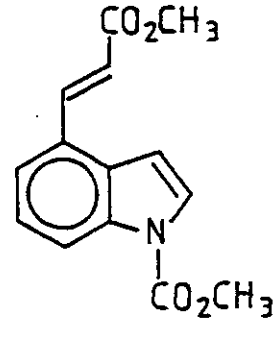


(i) butanone, K_2CO_3, $CH_3C_6H_4SO_2Cl$, 72% (ii) $Pd(OAc)_2$, PPh_3, Et_3N, methyl acrylate, 36%.

Somei's group have since reported a similar procedure for the preparation of (252) from the deactivated 4-iodoindole (253)[46]. As expected from Heck's findings[133b] the iodide (253) proved to be a better substrate giving an improved yield of 69% of (252).



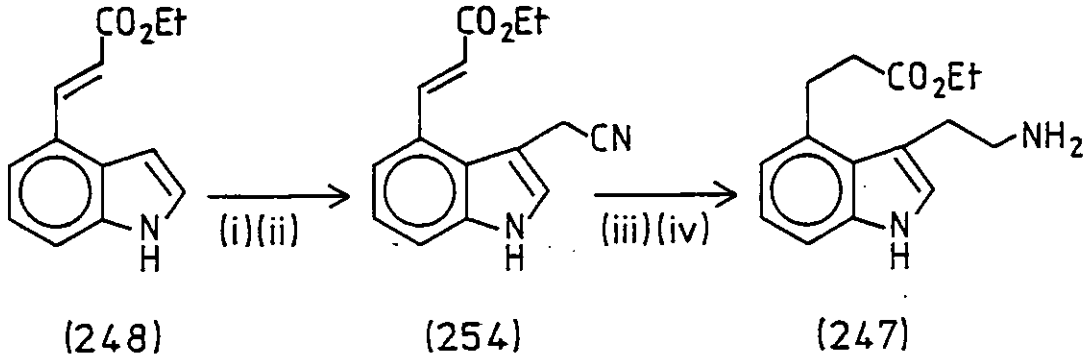
(253)



(252)

The key 3,4-disubstituted indole amino ester (247) was prepared by three routes. The nitrile ester (254) was synthesised according to Oppolzer's protocol[132] which on sequential reduction with hydrogen in the presence of palladium/charcoal followed by the mixed cobalt chloride/sodium borohydride[112] reagent gave in a 50% overall yield, (Scheme 65) the amino ester (247). Alternatively the acrylate ester (248) upon treatment with nitroethylene in the dark gave the unsaturated compound (255) as a crystalline solid in a 38% yield. Catalytic reduction converted (255) to the saturated indole (256) quantitatively. Under the same catalytic reduction conditions the acrylate ester (248) was converted smoothly to the saturated 4-substituted indole (257). Conversion of the indole (257) to (256) was accomplished in a 39% yield by treatment with nitroethylene. The nitro ester (256) was efficiently and cleanly reduced to the amino ester (247) by cobalt chloride/sodium borohydride (Scheme 66).

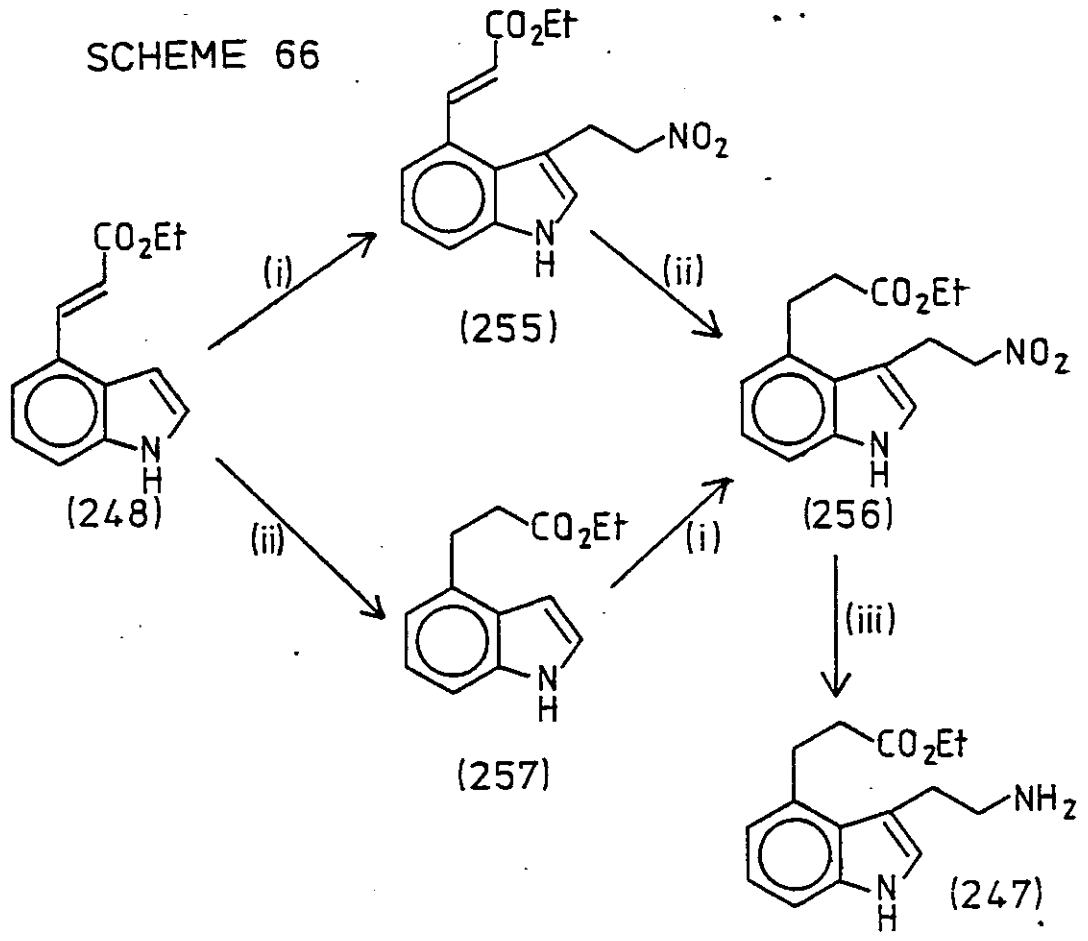
SCHEME 65



(248) (254) (247)

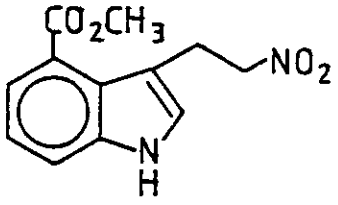
(i) $(CH_3)_2NH$, AcOH, HCHO. (ii) CH_3I, KCN, iPrOH. (iii) $H_2/Pd/C$, latm, EtOH. (iv) $CoCl_2.6H_2O/NaBH_4$, 50% overall.

SCHEME 66

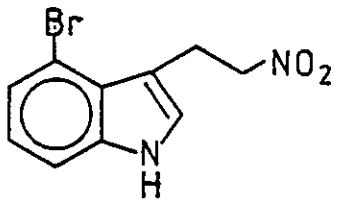


(i) $CH_2=CHNO_2$ 38%. (ii) $H_2/Pd/C$, EtOH, 100%. (iii) $CoCl_2$, $NaBH_4$, 65 - 75%

Although yields for the reaction of nitroethylene with the 4-substituted indoles (248) and (257) are not high this single stage reaction procedure is both simple and provides a concise route to the tryptamines. Two further 3-(2-nitroethyl)indoles (258) and (259) were synthesised in yields of 23% and 31% respectively. The latter compound is of particular interest since 4-bromoindole is reported to be inert to oxalyl chloride[135], a reagent classically used to prepare tryptamines by a three stage procedure (see review for examples).



(258)

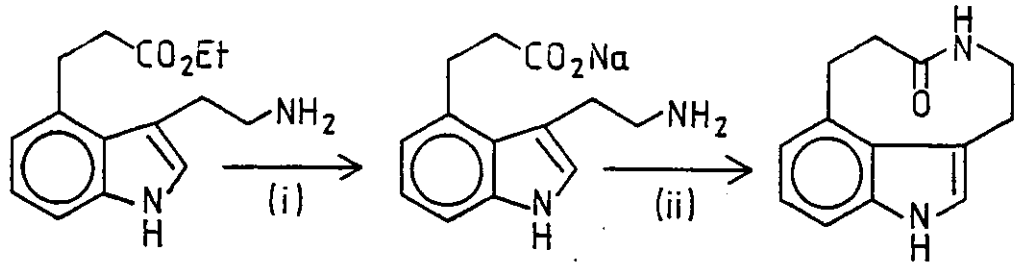


(259)

To complete the synthesis of (15) the amino ester (247) was readily saponified by treatment with one equivalent of sodium hydroxide. The sodium salt (260) isolated as an off white glass was readily cyclised to the tricyclic lactam (15) with diphenylphosphoryl azide (Scheme 67). The lactam (15) was isolated as a very insoluble colourless solid in a 47% yield.

Alternatives to the diphenylphosphoryl azide cyclisation procedures such as Mukaiyama's two phase procedure[136] or by warming the amino ester (247) in DMF failed.

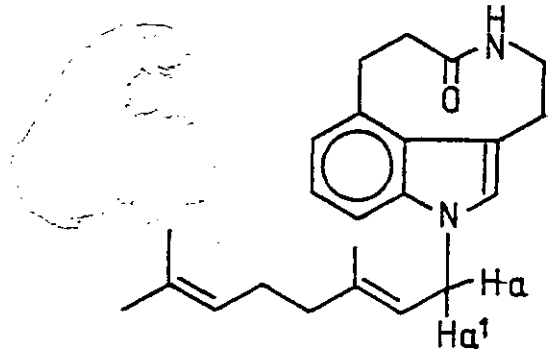
SCHEME 67



(247) (260) (15)

(i) NaOH, EtOH, H_2O, 94%. (ii) $(PhO)_2P(O)N_3$, Et_3N, 47%

The lactam (15) was successfully 8-mono alkylated with geranyl chloride and sodium hydride to give the 1-substituted lactam (261).



(261)

As has already been mentioned the synthetic lactams such as (15) reveal extensive broadening of peaks in the ^1H n.m.r. spectrum at room temperature. The lactam (15) is a particularly dramatic example of this conformational effect and is illustrated in Appendix 7. It can be seen that at room temperature

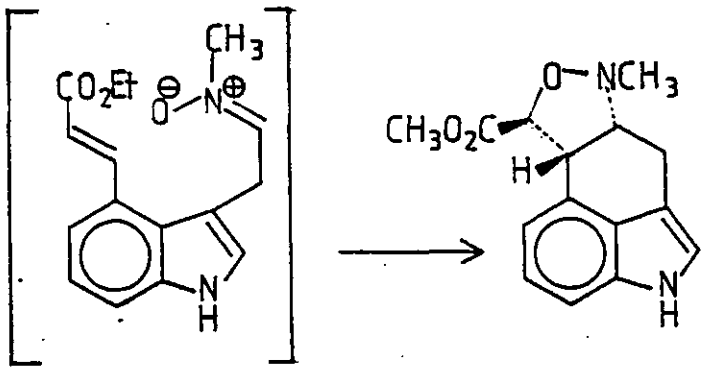
no significant structural information can be determined. At 120°C however the spectrum is resolved into the expected series of triplets which are readily assigned. The 1-substituted indole (261) demonstrated a further surprising effect in the ^1H n.m.r. spectrum. The two allylic protons a, a^1 (261) normally occur as a well resolved doublet at δ 4.60 J 6.3Hz. In (261) however two doublets corresponding to these protons occur at δ4.68 and 4.61, J 6Hz, due, it is thought, to the existence of two distinct conformers at room temperature. Additionally the ring methylene protons in (15) which, as previously stated, resonate as sharp triplets at 120°C, occur as resolved multiplets in (261) at room temperature. It is therefore evident that (15) is at its coalescence temperature at room temperature. The 1-substituted indole (261) however is below its coalescence temperature so that distinct resonances for two conformers occur. On warming, the resolved multiplets due to the ring methylene protons gradually collapse to broad unresolved peaks.

Further warming of the sample leads to a sharpening of these broad peaks until finally at 140°C the ring methylene protons resonate as well resolved triplets, as in (15).

(iii) <u>The Dienophilic Properties of (248)</u>

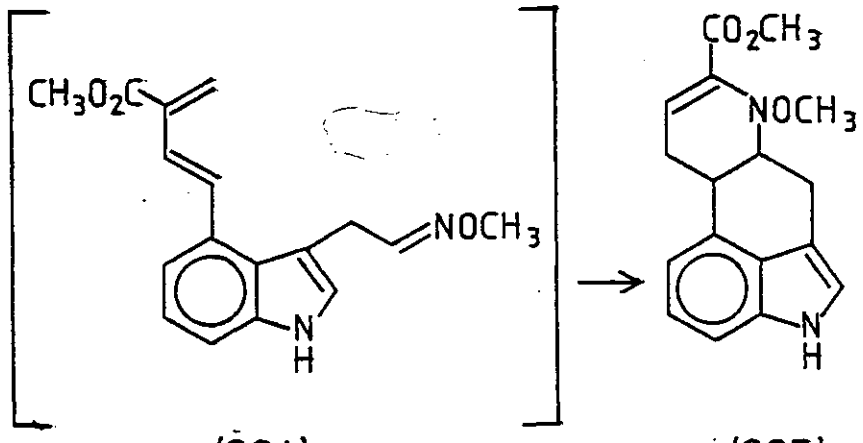
Oppolzer's (±)Chanoclavine synthesis[132] involved as the key step the intramolecular [2 + 3]

cycloaddition of the unstable N-methyloxime (262) to give the adduct (263).



(262) (263)

Likewise Oppolzer has also reported a synthesis of (±) Lysergic acid[91b] in which the key step is an intramolecular imino Diels-Alder reaction of (264) formed *in situ* to give the intermediate (265).

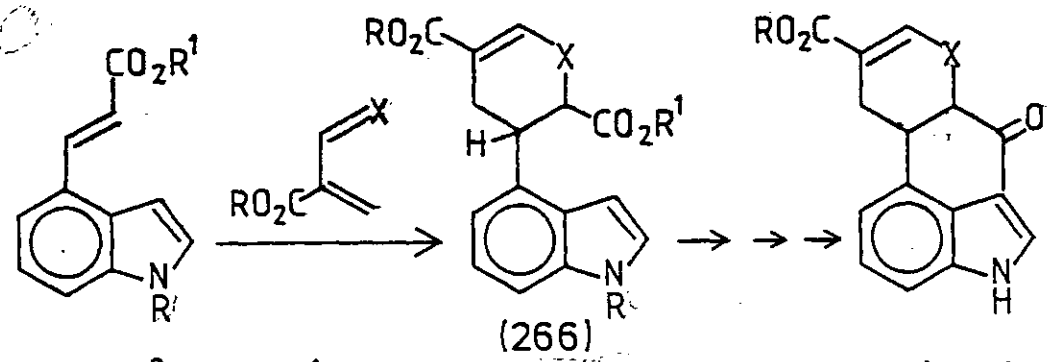


(264) (265)

Following this literature precedent it was anticipated that the acrylate ester (248) or the protected acrylate ester (251), would undergo Diels-Alder reaction with a suitable diene or

eneimine to give an adduct such as (266). Such an adduct might be expected to undergo further cyclisation after suitable functional group manipulation, to give the readily reduced tetracyclic vinylogous amide (267). Such an approach could lead to a novel route to the ergot alkaloids (Scheme 68).

SCHEME 68



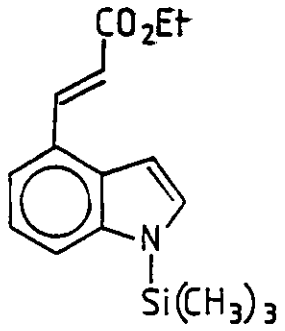
(248) R^2=H R, R^1=CH_3, CH_2CH_3

(267)

(251) R^2= 4-$CH_3C_6H_4SO_2$

X = CH_2, NCH_3

It was found however that when, in a model study, 1-methoxy-3-trimethylsilyloxybuta-1,3-diene (Danishefsky's diene)[138] and the acrylate ester (248) were warmed together, either neat, or at reflux in toluene, the sole product isolated proved to be the silylated indole (268) in low yield. Substitution of the 1-protected indole (251) for (248) in a similar reaction also failed.

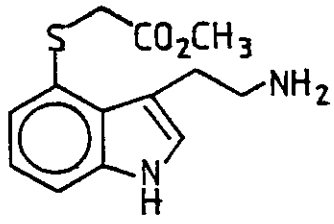


(268)

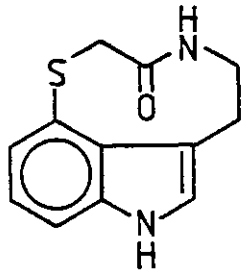
Although these initial results proved disappointing further study of this potentially viable approach would appear justified.

(iv) 4-Thiosubstituted Tryptamines

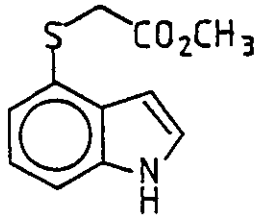
A further interesting analogue of the Teleocidin A skeleton that was discussed earlier (see Retrosynthesis) was the 4-thiosubstituted compound (14).



(245)



(14)



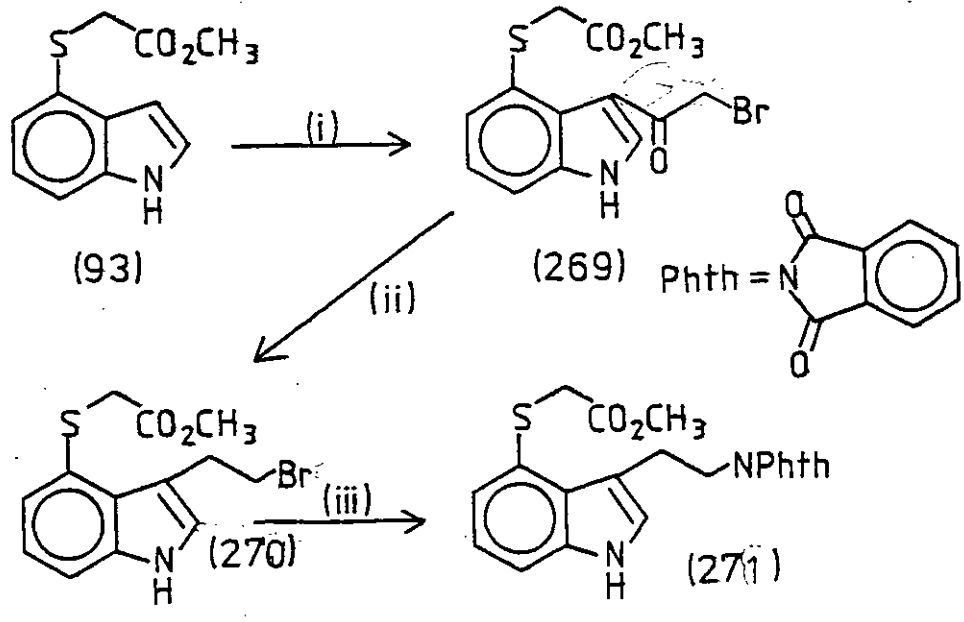
(93)

A synthesis of (14) through the 4-thioindole (93) whose synthesis has already been described (Section 4 (vi)) albeit in poor yield, was envisaged to follow the same route as that already described for the carbon linked analogue (15). It was therefore

evidently necessary to synthesise the 4-substituted tryptamine (245).

Kozikowski has reported[68] that (93) undergoes an efficient Friedel-Crafts acylation. In an effort to develop an alternative high yielding route to 4-substituted tryptamines the multi-stage sequence outlined in Scheme 69 was investigated. Unfortunately however Friedel-Crafts acylation of (93) with bromoacetyl bromide proceeded only poorly and subsequent reduction of the vinylogous amide (269) so formed to (270) was also inefficient. Although displacement of bromide from (270) with phthalimide was reasonably effective the overall yield to (271) from (93) was only 6%. This alternative approach to the synthesis of tryptamines was therefore abandoned.

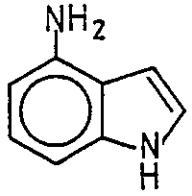
SCHEME 69



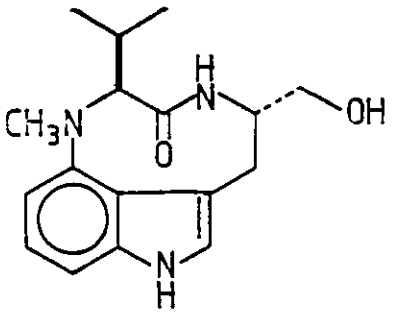
(i) $BrCH_2COBr$, $SnCl_4$, 42%. (ii) $BH_3.S(CH_3)_2$ 19%. (iii) K.Phthalimide 72%

13. Conclusion

In summary the work presented in this thesis represents a number of cojointly run studies directed towards the synthesis of Teleocidins A and B. Firstly three new routes to 4-aminoindole (9) have been developed. The best of these used the methodology of Leimgruber and Batcho. Secondly the N-alkylation of this compound was studied and a novel rearrangement of 4-N-alkylaminoindoles was discovered. Thirdly the unusual behaviour of 4-N,N-dialkylaminoindoles towards various electrophiles was investigated. The cumulative results of these studies has led to a viable route towards model 'northern zone' tricyclic lactams as outlined in Section 3 (Retrosynthesis). Although the synthesis of the correctly functionalised 'northern zone' lactam (8) has proved unsuccessful to date, it is considered to be within reach (see Section 10 for some alternative minor modifications that might prove successful at a later time). Additionally, of course, the ultimate target of this project, a total synthesis of Teleocidin A has not been possible. However (see Section 11 (iv)) many alternative variations on the basic strategy towards the linalyl 'southern zone' outlined in Section 3 (Retrosynthesis) still remain to be studied.



(9)



(8)

EXPERIMENTAL

Melting points were determined on a Kofler Heating Block and are uncorrected.

Infra-red spectra were recorded on a Perkin-Elmer 298 spectrometer and mass spectra on a V. G. Micromass 7070 instrument.

Proton nuclear magnetic resonance spectra were recorded on a Varian EM-360A instrument at 60MHz and on a Bruker 250 instrument at 250MHz. Deuteriochloroform was used for routine spectra unless otherwise stated, with tetramethylsilane as an internal reference. Variable temperature proton nuclear magnetic resonance spectra were performed in d^6 dimethylsulphoxide with the solvent multiplet centred at 2.49 as internal reference.

Microanalyses were carried out in the Microanalytical Department within the Department of Chemistry at Imperial College.

All reactions were performed under an inert atmosphere of nitrogen or argon.

Petrol refers to petroleum ether b.p. 40-60°C unless otherwise stated. Tetrahydrofuran was freshly distilled from a blue solution of sodium/benzophenone. Other solvents and reagents were purified by standard literature procedures[139].

Thin-layer analytical chromatography was performed on precoated aluminium backed Merck silica gel $60F_{254}$ plates with appropriate mixtures of petrol/chloroform, chloroform or chloroform/ethanol as eluant. Column chromatography was performed with 60H silica gel and with Merck silica gel 60 (partical size 0.040-0.063mm).

Abbreviations used:

D.M.F.	N,N-Dimethylformamide
D.M.S.O.	Dimethylsulphoxide
T.H.F.	Tetrahydrofuran
EtOAc	Ethyl Acetate
EtOH	Ethanol
MeOH	Methanol

CH_2Cl_2	Dichloromethane
$CHCl_3$	Chloroform
t.l.c.	Analytical Thin Layer Chromatography
mm	Millimoles

Teleocidin A-(4-Nitrobenzoyl) Ester (5) - Teleocidin A (4) (19mg, Ø.Ø44mm), 4-nitrobenzoyl chloride (8mg, Ø.Ø44mm) and 4-N,N-dimethylaminopyridine (5.4mg, Ø.Ø44mm) were stirred together in dichloromethane for 96 h at room temperature. An additional portion of 4-nitrobenzoyl chloride (4mg, Ø.Ø22mm) was then added and stirring continued for a further 48h. The clear solution was diluted with ether and extracted with 1N hydrochloric acid, sodium bicarbonate, water and brine. The solvent was removed at reduced pressure and the pale brown residue chromatographed (benzene/petrol, 3:1, eluant) to give Teleocidin A-(4-nitrobenzoyl) ester (5) (17mg, 66%) as an oil. All attempts to crystallise this material proved unsuccessful. (Found: M^+ 586.3155, $C_{34}H_{42}N_4O_5$ requires 586.3162); m/e 586 (M^+), 544, 46Ø, 419, 4Ø4, 376, and 15Ø; ν max. (thin film) 3445, 339Ø, 1723, 166Ø, 1525, 151Ø, 145Ø, 141Ø, 1345, 127Ø, 1213, 11ØØ, and 755cm^{-1}; δ ($CDCl_3$, 25ØMHz) major resonances 8.59 (1H, br s, 8-H), 8.29, 8.2Ø (4H, ABq, J_{AB} 8.1Hz, 4-Nitrobenzoyl ester), 7.ØØ (1H, d, J 8Hz, 1Ø-H), 6.87 (1H, d, J 1.4Hz, 7-H), 6.53 (1H, d, J 8Hz, 11-H), 6.18 (2H, m, 9^1-H and lactam NH), 5.31 (2H, m, $1Ø^1$-H), 5.Ø8 (1H, m, 4^1-H), 4.75 (1H, m, 5-H), 4.4Ø (2H, ABX system, J_{AX} 3.5Hz, J_{BX} 7.5Hz, J_{AB} 11.5Hz, 1^{111}-H), 4.36 (1H, d, J 1ØHz, 2-H), 3.24 (2H, m, 6-H), 2.93 (3H, s, 1-NCH_3), 2.61 (1H, m, 1^{11}-H), 1.75-2.ØØ (4H, m, 2^1, 3^1-H), 1.63 (3H, s, 7^1-H), 1.46 (3H, s, 6^1-H), 1.4Ø (3H, s, 8^1-H), Ø.92 (3H, d, J 6.9Hz, 2^{11}-H), and Ø.63 (3H, d, J 6.9Hz, 3^{11}-H). Minor resonances where different from above. δ 8.78 (1H, br s, 8-H), 7.29, 7.17 (4H, ABq, J_{AB} 8.8Hz, 4-nitrobenzoyl ester), 7.12, 7.Ø2 (2H, ABq, J_{AB} 7.5Hz, 1Ø, 11-H), 6.93 (1H, d, J 2.5Hz, 7-H), 6.18 (2H, m, 4, 9^1-H), 4.74 (1H, masked doublet, 2-H) 4.15 (2H, ABX system, J_{AX} 6Hz, J_{BX} 6.8Hz, J_{AB} 1Ø.5Hz, 1^{111}-H), 2.76 (3H,

s, 1-NCH_3), 2.30 (1H, m, 1^{11}-H), 1.67 (3H, s, 7^1-H), 1.49 (3H, s, 6^1-H), 1.25 (3H, d, J 6.9Hz, 3^{11}-H), and 0.94 (3H, d, J 6.9Hz, 2-H).

2-Chloro-6-Nitrophenylpyruvic Acid (37a) - 2-Chloro-6-nitrotoluene (37) (21.38g, 125mm) and diethyl oxalate (18.25g, 125mm) were dissolved in ethanol (50ml) containing sodium ethoxide (8.5g, 125mm). The deep red solution was warmed to reflux for 45 minutes and then steam distilled to remove residual 2-chloro-6-nitrotoluene. The cooled aqueous solution was acidified with HCl and extracted with ether (4 x 100ml). Removal of solvent from the combined organic phase gave 2-chloro-6-nitrophenylpyruvic acid (37a) (13g, 43%) as a semi-crystalline oil. Recrystallisation gave a pale yellow crystalline solid. m.p. 157.5 - 159°C (benzene), (lit. m.p. 114 - 115°C[41a]), semicarbazone m.p. 223 - 225°C (EtOH), (lit. m.p. 203 - 204°C[41a]), ν max. (nujol) 1700, 1660, and 1550cm^{-1}.

4-Chloroindole-2-carboxylic Acid (30) - **(i) Ferrous sulphate ammonium hydroxide reduction:** 2-Chloro-6-nitrophenylpyruvic acid (37a) (8.5g, 35mm) in aqueous ammonia (1M, 60ml) was added to a suspension of $Fe(OH)_2$ prepared from iron (II) sulphate heptahydrate (56g, 440mm) and conc. ammonium hydroxide (23ml) in water (200ml). The mixture was warmed on the steam bath for 5 minutes with stirring, cooled, filtered and the clear filtrate acidified with dilute hydrochloric acid. The pale yellow product (30) was filtered and recrystallised (4.9g, 72%) m.p. 258 - 260°C ($EtOH/H_2O$), (lit. m.p. 259 - 260°C[41a]), ν max. (nujol) 3350, 3270, 1728, and 1711cm^{-1}; δ ($(CD_3)_2SO$) 6.82 - 7.44 (4H, m, indole aromatics); m/e 195 and 197 (M^+). **(ii) Sodium dithionite reduction:** 2-Chloro-6-nitrophenylpyruvic acid (37a) (13g, 53mm) in aqueous sodium hydroxide (3%, 150ml) was treated with sodium dithionite (27g) in portions over 1 h. Acidification (conc. HCl) followed by degassing with a stream of nitrogen at 90°C for 2 h. and filtration gave the indole (30) as a pale brown powder (7.9g, 75%).

Attempted Preparation of 4-Aminoindole (9)[28] - 4-Chloroindole-2-carboxylic acid (30) (1.167g, 6.0mm), cuprous chloride (0.1g) and aqueous ammonium hydroxide (conc., 20ml) were heated together in a sealed container at 260°C for 5 h. After cooling overnight the dark solution was extracted with ether (3 x 30ml), the combined extracts evaporated and the residue column chromatographed ($CHCl_3$/petrol 4:1 eluant) to give as a pale yellow oil 4-chloroindole (38) (310mg, 34%), m/e 151, 153 (M^+), and 117 (M^+-Cl); ν max. (thin film) 3420, 1615, 1575, 1504, 1490, 1455, 1435, 1415, 1355, 1345, 1340, 1280, 1250, 1185, 1150, 1090, 1070, 930, 895, and 750cm^{-1}; δ ($CDCl_3$) 7.53 (1H, m, ArH), 7.03 (3H, m, 2 x ArH, NH), 6.70 (1H, m, ArH), and 6.36 (1H, m, ArH).

Methylthioacetaldehyde dimethylacetal (48) - Sodium sand (11.5g, 0.5M) in THF (150ml) was treated with dimethyl disulphide (22ml, 0.25M) over 5 minutes with ice cooling to control the vigorous reaction. When the reaction had subsided the solution was warmed to reflux for 150 minutes. After cooling the pale yellow suspension of sodium thiomethoxide was dissolved by the addition of dry ethanol (300ml). Bromoacetaldehyde dimethylacetal (49) (85g, 0.5M) in ethanol (40ml) was added over 10 minutes to the cooled (ice/salt) solution with stirring, followed by warming to 60°C for 1 h and stirring at room temperature for 36 h. Water (500ml) was added to dissolve the suspended sodium bromide and the clear solution extracted with ether (4 x 100ml). The combined organic extracts were washed with water (4 x 100ml), the solvent removed and the residue distilled at reduced pressure to give the liquid product (48) (47.0g, 69%); b.p. 70°C at 25mm (lit. b.p. 55°C at 10mm[51]); δ ($CDCl_3$) 4.45 (1H, t, J 5.5Hz, $-CH(OCH_3)_2$), 3.37 (6H, s, $CH(OCH_3)_2$), 2.63 (2H, d, J 5.5Hz, CH_3SCH_2CH), and 2.17 (3H, s, SCH_3).

Methylthiocetaldehyde (47) - (i) **HCl method:** Methylthioacetaldehyde dimethylacetal (48) (21g, 154mm) was warmed to reflux under nitrogen with dilute HCl (1%, 60ml)

for 35 minutes. After cooling the yellow homogeneous solution was neutralised with sodium bicarbonate and extracted with dichloromethane (6 x 30ml). After removal of solvent the residue was distilled to give the product (47) a pale yellow liquid (2.6g, 19%), b.p. 40°C at 13mm (lit. b.p. 35°C at 10mm[51]); δ ($CDCl_3$) 9.45 (1H, t, J 3.5Hz, CHO), 3.12 (2H, d, J 3.5Hz, CH_2CHO), and 2.00 (3H, s, SCH_3). (ii) **$S;O_2/H_2SO_4$ method[52]:** Silica gel (Merck 60H, 40g) was suspended in dichloromethane (100ml) and treated with dilute sulphuric acid (15%, 4g). After stirring for 5 minutes, methylthioacetaldehyde dimethyl-acetal (48) (10g, 74mm) was added and the solution stirred at room temperature for 24 h. Filtration and removal of solvent gave a yellow liquid (5.3g, 75%) containing 70% of the aldehyde (47) and 30% acetal (48) by ^1H n.m.r. This material was used without further purification.

3-Methylthio-4-nitroindole (40) and 3-Methylthio-6-nitroindole (50) - **(i) From methylthioacetaldehyde (47):** 3-Nitroaniline (6.4g, 50mm) in THF (50ml) was cooled to -65°C (acetone/cardice) and tert-butylhypochlorite (5.4g, 50mm freshly distilled) in THF (10ml) added. After 1h methylthioacetaldehyde (47) (from 7.8g, 60mm of the acetal (48)) was added in THF (10ml) over 10 minutes. Stirring was continued for a further 4 h at -65°C, triethylamine (5g, 50mm) added to the deep red suspension and the solution warmed over 1 h to room temperature. Addition of water, to dissolve precipitated salts, followed by removal of solvent gave a dark oil that was taken up in CH_2Cl_2 washed with 1N HCl (3 x 50ml) and water (2 x 50ml). Removal of solvent followed by chromatography (benzene eluant) gave (i) **3-methylthio-6-nitroindole (50)** (370mg, 4%) as a bright yellow crystalline solid m.p. 161.5 - 164°C ($CHCl_3$). (Found: C, 51.81; H, 3.84; N, 13.42; S, 15.25; $C_9H_8N_2O_2S$ requires C, 51.91; H, 3.87; N, 13.45; S, 15.39%); m/e 208 (M^+), 193 (M^+-CH_3), 162 (M^+-NO_2), and 147 ($M^+-NO_2-CH_3$); ν max. (nujol) 3320, 1500, 1463, 1455, 1372, 1321, 1298, and 1060; δ ($CDCl_3$) 7.60 - 8.36 (4H, m, ArH),

and 2.34 (3H, s, SCH_3). **(ii) 3-methylthio-4-nitroindole (40)**, (3.78g, 36%) as a very dark red crystalline solid m.p. 120.5 - 121.5°C (EtOH) (lit. m.p. 123 - 124°C[49]), (Found: C, 52.25; H, 3.93; N, 13.43; S, 15.49; $C_9H_8N_2O_2S$ requires C, 51.91; H, 3.87; N, 13.45; S, 15,39%); m/e 208 (M^+), 193 (M^+-CH_3), and 162 (M^+-NO_2); ν max. (nujol) 3360, 1560, 1500, 1490, 1465, 1375, 1365, 1320, 1310, 1260, 990, 980, 790, and 725cm^{-1}; δ ($CDCl_3$) 8.89 (1H, br s, indole NH), 7.02 - 7.72 (4H, m, ArH), and 2.39 (3H, s, SCH_3).
(ii) From methylthioacetaldehyde dimethylacetal (48): 3-Nitroaniline (414mg, 3mm) in THF at -78°C (acetone/cardice) was treated with tert-butylhypochlorite (354mg, 3mm) for 90 minutes followed by methylthioacetaldehyde dimethylacetal (48) (408mg, 3mm) for 6 h. The temperature was raised to -20°C and the solution stored overnight. Filtration gave the azasulphonium salt (44) (0.66g, 71%) which was refluxed in benzene (30ml) containing 1,8-diazabicyclo[5.4.0]undec-7-ene (450mg, 3mm) for 3 h. After cooling the solution was shaken with 2N HCl (30ml) overnight, the organic phase separated and solvent removed to give a dark oily residue. Chromatography (benzene eluant) gave 3-methylthio-6-nitroindole (50) (76mg, 12%) and 3-methylthio-4-nitroindole (40) (78mg, 13%).

3-Methylthio-4-bromoindole (52) and 3-Methylthio-6-bromoindole (53) - 3-Bromoaniline (51) (4.32g, 25mm) was dissolved in THF (40ml) and cooled to -78°C (acetone/cardice). tert-Butylhypochlorite (2.7g, 25mm) in THF (5ml) was added and the solution stirred for 1 h. Methylthioacetaldehyde (47) (from methylthioacetaldehyde dimethyl acetal (48) 3.9g, 30mm, crude) in THF was then added followed, after 5 h stirring at -78°C, by triethylamine (2.5g, 25mm) and by removal of the cooling bath. After stirring 1 h at room temperature water was added and solvent removed under reduced pressure. The residue was taken up in dichloromethane/water and the aqueous phase extracted with dichloromethane (3 x 50ml). The combined organic extracts were washed with 1N HCl (4 x

30ml) and water (2 x 50ml), solvent removed and the residue chromatographed ($CHCl_3$/petrol 3:2) to give, **(i)** **3-methylthio-6-bromoindole (53)** as a colourless crystalline solid (0.86g, 14%) m.p. 79 - 80°C (EtOH/H_2O), (Found: C, 44.45; H, 3.27; N, 5.70; Br, 33.28; C_9H_8NSBr requires C, 44.64; H, 3.33; N, 5.78; Br, 33.00%); m/e 240 (M^+-2), 207, 173, and 171; ν max. (nujol) 3360, 1600, 1465, 1450, 1440, 1380, 1325, 1300, 1090, 890, and 805cm^{-1}; δ ($CDCl_3$, 250MHz) 8.85 (1H, br s, indole NH) 8.59 (1H, d, J 8.0Hz, 4-H), 8.43 (1H, d, J 1.7Hz, indole 7-H), 7.28 (1H, dd, J 1.7, 8.0Hz, 5-H), 7.19 (1H, d, J 2.6Hz, irradiation of the indole NH causes the signal to collapse to a singlet, 2-H), and 2.34 (3H, s, SCH_3). **(ii)** **3-Methylthio-4-bromoindole (52)** (0.82g, 14%) as a pale yellow oil that solidified to an orange solid m.p. 57 - 59°C on cooling. (Found: C, 44.70; H, 3,31; N, 5.78; S, 13.17; C_9H_8NBrS requires C, 44.64; H, 3.33; N, 5.78; S, 13.24%); m/e 240 (M^+-2), 207, 173, and 171. ν max. (thin film) 3410, 1610, 1590, 1555, 1500, 1475, 1425, 1405, 1330, 1320, 1305, 1260, 1180, 1140, 1000, 965, 905, 805, 775, and 738cm^{-1}; δ ($CDCl_3$) 8.20 (1H, br s, indole NH), 6.76 - 7.28 (4H, m, ArH), and 2.33 (3H, s, CH_3S).

3-Methylthio-4-nitro-7-methylindole (55) - 2-Amino-4-nitrotoluene (54) (4.56g, 30mm) in THF (100ml) was treated at -78°C (acetone/cardice) with tert-butylhypochlorite (3.24g, 30mm) and stirred for 30 minutes. Methylthioacetaldehyde (47) (crude from methylthioacetaldehyde dimethylacetal (48) 4.76g, 35mm) was then added, followed after 5 h by triethylamine (3.0g, 30mm) and warming to room temperature. Addition of water, removal of solvent, extraction of the aqueous phase with dichloromethane (3 x 50ml) followed by repeated extraction with 3N HCl gave on removal of solvent an essentially pure product (2.34 g, 35%). Recrystallisation gave compound (55) m.p. 131 - 132°C (EtOH) as a brown-black crystalline material. (Found C, 54.16; H, 4.56; N, 12.51; S, 14.34; $C_{10}H_{10}N_2O_2S$ requires C, 54.04; H, 4.54; N, 12.61; S, 14.42%); m/e 222

(M^+), 176 (M^+-NO_2), and 130 (M^+-NO_2-SMe); ν max. (nujol) 3330, 1575, 1500, 1485, 1455, 1380, 1350, 1320, 1292, 1275, 1155, 1130, 980, 918, 820, 785, 755, and 735cm^{-1}; δ ($CDCl_3$, 250MHz) 8.65 (1H, br s, indole NH), 7.00, 7.68 (2H, ABq, J_{AB} 7.5Hz, 5-H, 6-H), 7.28 (1H, m, 2-H), 2.53 (3H, s, $ArCH_3$), and 2.38 (3H, s, SCH_3).

3-Methylthio-4-N-methyl-4-N-acetylaminoindole (57) - N-Methyl-N-acetyl-1,3-phenylenediamine (56) (328mg, 2mm) in THF (20ml) at -78°C (acetone/cardice) was treated with tert-butylhypochlorite (218mg, 2mm) for 30 minutes. Methylthioacetaldehyde (47) (crude, from methylthioacetaldehyde dimethyl acetal (48) 544mg, 4mm) was then added followed after 4 h by the addition of triethylamine (200mg, 2mm). The solution was allowed to warm to room temperature over 3 h, water added and solvent removed. The residue was taken up in chloroform, washed with water (2 x 20ml) and the residue, on removal of solvent, chromatographed ($CHCl_3/CCl_4$ eluant). 3-Methylthio-4-N-methyl-4-N-acetylaminoindole (57) and 3-methylthio-6-N-methyl-4-N-acetylaminoindole (57) (36mg, 7.7%) were isolated as an inseparable mixture. m/e 234 (M^+) and 219 (M^+-CH_3); δ ($CDCl_3$) 7.08 - 7.32 (4H, m, ArH), 3.32 (3H, s, NCH_3), 2.33 (3H, s, SCH_3), and 1.80 (3H, s, $COCH_3$).

1-Geranyl-3-methylthio-4-nitroindole (63) - Potassium hydroxide (1.12g, crushed pellets) was stirred in D.M.S.O. (15ml) for 5 minutes[53]. 3-Methylthio-4-nitroindole (40) (1g, 4.8mm) was then added followed, after 45 minutes stirring at room temperature, by geranyl chloride (830mg, 4.8mm) with ice cooling. The deep red solution was stirred for a further 45 minutes, diluted with water (50ml) and extracted with ether (4 x 50ml). The combined organic phases were washed with water (6 x 100ml), dried, solvent removed and the residue chromatographed (chloroform eluant) to give the product (63) (1.55g, 94%) as a deep red sweet smelling oil. (Found: C, 66.23; H, 7.33; N, 8.02; S, 9.19; $C_{19}H_{24}N_2O_2S$ requires C, 66.25; H, 7.02; N, 8.13; S, 9.31%); m/e 344 (M^+), 208 ($M^+-C_{10}H_{16}$),,

and 136; ν max. (thin film) 1520, 1440, 1350, 1280, 795, and 730; δ ($CDCl_3$) 6.82 - 7.43 (4H, m, ArH), 5.20 (1H, m, C=CH), 4.90 (1H, m, C=CH), 4.55 (2H, d, J 7Hz, NCH_2), 2.31 (3H, s, SCH_3), 2,06 (4H, m, allylic CH_2), 1.80 (3H, s, allylic CH_3), 1.64 (3H, s, allylic CH_3), and 1.56 (3H, s, allylic CH_3).

1-Benzyl-3-methylthio-4-nitroindole (62) - The procedure was identical to that used for the preparation of (63) using potassium hydroxide (1.12g, crushed pellets), 3-methylthio-4-nitroindole (40) (1g, 4.8mm) and benzyl chloride (595mg, 4.8mm). After the addition of benzyl chloride the deep coloured reaction mixture was stirred for 90 minutes. Aqueous work up and removal of solvent gave a crystalline residue (1.33g) which was chromatographed ($CHCl_3/CCl_4$, 1:1) to give the orange red compound (62), (1.12g, 88%). m.p. 111 - 113°C (benzene). (Found: C, 64.48; H, 4.73; N, 9.38; S, 10.75%; $C_{16}H_{14}N_2O_2S$ requires C, 64.41; H, 4.72; N, 9.39; S, 10.75%); m/e 298 (M^+), 283 (M^+-CH_3), 207 ($M^+-C_7H_7$), and 160 ($M^+-C_7H_7-SCH_3$); ν max. (nujol) 1520, 1498, 1370, 1350, and 730cm^{-1}; δ ($CDCl_3$) 6.80-7.67 (9H, m, ArH), 5.26 (2H, s, NCH_2Ar), and 2.33 (3H, s, SCH_3).

3-Dimethylsulphonium-4-nitroindolyl Iodide (64) - 3-Methylthio-4-nitroindole (40) (208mg, 1mm) in ether (5ml) was treated at room temperature with iodomethane (280mg, 2mm) for 140 h. The pale yellow solid formed was filtered and washed thoroughly with ether to give the product (64) (200mg, 57%). The analytical sample was prepared by recrystallisation. m.p. 146.5 - 147°C (with decomposition) ($EtOH/H_2O$). (Found: C, 34.45; H, 3.13; N, 8.07; I, 36.26; $C_{10}H_{11}N_2O_2S$ requires C, 34.29; H, 3.17; N, 8.00: I, 36.24%); ν max. (nujol) 3100, 1515, 1460, 1420, 1375, 1360, 1330, 1310, 1270, 1260, 1005, 805, and 730cm^{-1}; δ ($(CD_3)_2SO$) 8.72 (1H, s, 2-H), 7.97 - 8.20 (2H, m, 6-H and 5-H or 7-H), 7.53 (1H, m, 5-H or 7-H), and 3.40 (6H, s, $S(CH_3)_2$).

4-Aminoindole (9) - 3-Methylthio-4-nitroindole (40) (940mg, 4mm) and nickel (II) chloride (3.0g, 23mm) were

dissolved in hot ethanol (100ml) under nitrogen. Sodium borohydride (960mg, 25mm) was added in portions to the warm solution and after completion of the addition, the grey suspension was warmed to reflux for 30 minutes. Thin layer chromatography revealed a single product containing sulphur identified as 3-methylthio-4-aminoindole (69), m/e 178(M^+). Additional nickel (II) chloride (3.5g, 27mm) and sodium borohydride (1.04g, 27mm) were added and the reaction mixture boiled for a further 30 minutes. After cooling the solution was filtered (celite pad) and the residue thoroughly washed with chloroform. The filtrate was evaporated at reduced pressure and the residue dissolved in chloroform/water. Extraction of the aqueous phase with chloroform (3 x 50ml), washing of the combined organic phase with water (3 x 50ml) and removal of solvent gave 4-aminoindole (9) (400mg, 76%) as a pale yellow solid. m/e 132(M^+); ν max. (thin film) 3470, 3390, 1615, 1210, and 755cm^{-1}; δ ($CDCl_3$) 8.07 (1H, br s, indole NH), 6.12-7.04 (5H, m, ArH), and 3.60 (2H, br s, $ArNH_2$).

1-Benzyl-3-methylthio-4-aminoindole (70) and 1-Benzyl-4-aminoindole (71) - 1-Benzyl-3-methylthio-4-nitroindole (62) (260mg, 0.87mm) was boiled in ethanol (5ml), containing excess Raney nickel, under nitrogen for 2 h. Additional Raney nickel was then added and boiling continued for a further 1 h. The reaction mixture was filtered, the solvent evaporated at reduced pressure and the residue chromatographed ($CHCl_3$/petrol 4:1 eluant) to give (i) **1-Benzyl-3-methylthio-4-aminoindole (70)** (65mg, 28%) m.p. 118-119°C (EtOH). (Found: C, 71.69; H, 6.11; N, 10.35; $C_{16}H_{16}N_2S$ requires C, 71.61; H, 6.01; N, 10.44%); m/e 268(M^+), 250, 235, 177($M^+-C_7H_7$), 159, 130, and 117; ν max. (thin film) 3440, 3360, 1606, 1585, 1495, 1280, 1215, 760, and 730cm^{-1}; δ ($CDCl_3$) 6.60-7.40 (9H, m, ArH), 5.08 (2H, s, NCH_2Ar), 3.76 (2H, br s, $ArNH_2$), and 2.37 (3H, s, SCH_3); and (ii) **1-Benzyl-4-aminoindole** (71) (40mg, 21%) m.p. 113.5-115°C (EtOH/H_2O then $CHCl_3$/petrol). (Found: C, 81.07; H, 6.37; N, 12.61; $C_{15}H_{14}N_2$ requires C,

81.05; H, 6.35; N, 12.60%); m/e 222(M^+) and 131($M^+-C_7H_7$); ν max. (thin film) 3440, 3340, 1620, 1610, 1583, 1495, 1450, 1440, 1405, 1370, 1350, 1270, 1160, 910, and 730cm^{-1}; δ ($CDCl_3$) 6.20-7.34 (10H, m, ArH), 5.11 (2H, s, NCH_2), and 3.61 (2H, br s, NH_2).

1-Benzyl-4-aminoindole (71) - 1-Benzyl-3-methylthio-4-nitroindole (62) (260mg, 0.87mm) and nickel (II) chloride (250mg, 1.9mm) were dissolved in hot ethanol (30ml). Sodium borohydride (74mg, 2mm) was then added and the solution heated to reflux for 20 minutes. T.l.c. revealed the presence of 1-benzyl-3-methylthio-4-aminoindole (70) only. Additional nickel (II) chloride (250mg, 1.9mm) followed by sodium borohydride; (74mg, 2mm) were added and boiling continued for a further 45 minutes. The reaction mixture was cooled, filtered, the filtrate evaporated at reduced pressure, the residue taken up in chloroform, washed with water (3 x 20ml) and solvent removed to give a residue (140mg, 72%) identical by t.l.c., ^1H n.m.r. and i.r. with 1-benzyl-4-aminoindole (71) previously described.

1-(3,7-Dimethyloctyl)4-aminoindole (72) and 1-(3,7-Dimethyloctyl)4-N-propylaminoindole (73) - 1-Geranyl-3-methylthio-4-nitroindole (63) (110mg, 0.32mm) was boiled in propan-1-ol (3ml) with excess Raney nickel[59] for 50 minutes. After cooling, filtration and evaporation of the solvent under reduced pressure, the residue was chromatographed ($CHCl_3/CCl_4$ 1:1 eluant) to give **(i) 1-(3,7-dimethyloctyl)4-N-propylaminoindole** (73) as an oil (23mg, 23%). (Found: M^+ 314.2718 $C_{21}H_{34}N_2$ requires, 314.2722); m/e 314 (M^+), 285 ($M^+-C_2H_5$), 196, 187, and 145; ν max. (thin film) 3410, 1590, 1495, 1460, 1420, 1375, 1360, 1350, 1270, 905, and 730cm^{-1}; δ ($CDCl_3$) 6.10-7.23 (5H, m, ArH), 4.0 (2H, t, J 7.5Hz, NCH_2CH_2), 3.20 (2H, t, J 6Hz, $HNCH_2CH_2CH_3$), 3.0 (1H, br s, $HNCH_2$), and 0.76-2.06 (24H, m, aliphatics). **(ii) 1-(3,7-dimethyloctyl)4-aminoindole** (72) as an oil (29mg, 33%). (Found: M^+ 272.2250, $C_{18}H_{28}N_2$ requires, 272.2252); m/e 272 (M^+), 186 (M^+-

C_6H_{14}), 145, and 132 ($M^+-C_{10}H_{20}$); ν max. (thin film) 3450, 3360, 1610, 1580, 1490, 1460, 1445, 1375, 1360, 1345, 1270, 1150, and 725cm^{-1}; δ ($CDCl_3$) 6.20-7.00 (5H, m, ArH), 3.93 (2H, t, J 7.5Hz, NCH_2), 3.75 (2H, br s, NH_2), and 0.69-2.05 (19H, m, aliphatics).

1-1'-Digeranyl-3,3'-dithiomethyl-4,4'-hydrazoindole (74) - 1-Geranyl-3-methylthio-4-nitroindole (63) (700mg, 2.03mm) in T.H.F. (10ml) was treated with a solution of lithium aluminium hydride (350mg, 9.2mm) in T.H.F. (10ml) at reflux over 10 minutes. Boiling under nitrogen atmosphere was continued for a further 2.5 h after which the reaction was cooled and quenched with water. Filtration (celite pad), removal of solvent, dissolution of the residue in ethyl acetate/ether, washing with water (3 x 30ml) and removal of solvent gave compound (74) as a semi-crystalline deep red solid (419mg, 66%). Recrystallisation gave the analytical sample m.p. 131.5-133°C (Et_2O). (Found: C, 72.86; H, 7.76; N, 8.83; $C_{38}H_{50}N_4S_2$ requires C, 72.80; H, 8.00; N, 8.94%); m/e 626 (M^+), 624 (M^+-H_2), 314, 298, and 177; ν max. (nujol) 1505, 1460, 1444, 1385, 1375, 1347, 1286, 800, and 750cm^{-1}; δ ($CDCl_3$) 5.95-7.00 (8H, m, ArH), 4.00-5.17 (10H, m, 2 x NH, 4 x =CH, 2 x CH_2N), 2.20 (3H, s, SCH_3), 2.02 (3H, s, SCH_3), 1.74 (8H, m, 4 x allylic CH_2), 1.47 (6H, s, 2 x allylic CH_3), 1.35 (6H, s, 2 x allylic CH_3), and 1.30 (6H, s, allylic CH_3).

3-Methylthio-4-amino-7-methylindole (76) and 4-N-Ethylamino-7-methylindole (77) - 3-Methylthio-4-nitro-7-methylindole (55) (222mg, 1mm) and nickel (II) chloride (260mg, 2mm) were dissolved in hot ethanol (5ml). Sodium borohydride (152mg, 4mm) was added in portions over 5 minutes to the warm solution and boiled for 20 minutes. After the addition of further sodium borohydride (70mg, 2mm) and reflux for 20 minutes the solution was filtered, evaporated under reduced pressure, the residue taken up in ether, extracted with water (3 x 20ml) and the solvent removed. The dark residue was chromatographed ($CHCl_3$

eluant) to give 3-methylthio-4-amino-7-methylindole (76) (90mg, 47%). δ ($CDCl_3$) 7.90 (1H, br s, indole NH), 7.05 (1H, m, 2-H), 6.67, 6.17 (2H, ABq, J 8Hz 5-H and 6-H), 4.78 (2H, br s, NH_2), 2.35 (3H, s, SCH_3), and 2.30 (3H, s, $ArCH_3$). The chromatographed product (90mg, 0.47mm) was stirred with excess Raney nickel in ethanol (4ml) at room temperature for 6 h, the solution filtered, solvent removed and the residue chromatographed ($CHCl_3$ eluant) to give the product (77) (12mg, 14%). (Found: M^+ 174.1161, $C_{11}H_{14}N_2$ requires 174.1157); m/e 174 (M^+), 159 (M^+-CH_3), 144 ($M^+-C_2H_6$), and 131 ($M^+-C_2H_4-CH_3$). δ ($CDCl_3$, 250MHz) 8.05 (1H, br s, indole NH), 7.13 (1H, m, 3-H), 6.87, 6.27 (2H, ABq, J 6.5Hz, 5-H and 6-H), 6.49 (1H, m, 2-H), 3.31 (2H, q, J 7.5Hz, NCH_2CH_3), 2.41 (3H, s, $ArCH_3$), 1.60 (1H, br s, HNEt), and 1.35 (3H, t, J 7.5Hz, CH_2CH_3).

Trans-2-[β-(dimethylamino)vinyl]-2,6-dinitrobenzene (82) - 2,6-Dinitrotoluene (81) (36.4g, 200mm) and N,N-dimethylformamide dimethyl acetal (70ml, 530mm) in D.M.F. (200ml) were heated at 140°C for 5 h under argon. The deep red solution was cooled, diluted with ether (1L) and extracted with brine (3 x 250ml), water (5 x 500ml) and finally again with brine (250ml). Removal of solvent gave the essentially pure product (82) (44.0g, 93%) as a deep red solid that required no further purification. (Found: M^+ 237.0751, $C_{10}H_{11}N_3O_4$ requires 237.0749); ν max. (nujol) 1630, 1600, 1530, 1410, and 1350cm^{-1}; δ ($CDCl_3$ 7.80 (2H, d, J 7Hz, ArH), 7.08 (1H, m, ArH), 6.45, 5.32 (2H, ABq, J_{AB} 14Hz, CH≡CH), and 2.9 (6H, s, $N(CH_3)_2$)[45,47].

4-Aminoindole (9) - (i) Iron/acetic acid/ethanol reduction. trans-2-[β-(Dimethylamino)vinyl]-2,6-dinitrobenzene (82) (22.2g, 94mm) was dissolved in ethanol/acetic acid (200ml 1:1). Iron filings (25g) were added and the deep red reaction mixture cautiously warmed on the steam bath until reaction commenced. The steam bath was removed and additional iron (5g portions) was added at such a rate as to maintain a gentle reflux. (Total iron added, 100g). After the addition of iron was complete (about 30 minutes)

the reaction was warmed on the steam bath for 15 minutes, cooled, neutralised with sodium hydroxide (100g) in water (250ml), filtered (celite pad) and the residue thoroughly washed with ethanol (300ml) and ether (1L). The volume of the filtrate was reduced to 250ml and extracted with dichloromethane (4 x 100ml). The combined organic phase was washed with water (3 x 100ml) and solvent removed to give the semi crystalline red product (9) (9.07g, 69%). This material did not require further purification. An analytical sample was prepared by sublimation (0.1mm, 100°C) followed by recrystallisation. m.p. 108-109°C (benzene), (lit. m.p. 105-107°C[28]). (Found: C, 72.79; H, 6.09; N, 21.13; $C_8H_8N_2$ requires C, 72.70; H, 6.10; N, 21.20%). I.r., ^1H n.m.r. and mass spectral data were identical to those described above. **(ii) Catalytic hydrogenation** - trans-2-[β-(Dimethylamino)vinyl]-2,6-dinitrobenzene (82) (35g, 147mm) in T.H.F. (1L) containing 10% Pd/C (5g) was stirred under a hydrogen atmosphere at 60 p.s.i. at room temperature until hydrogen uptake was complete (about 2 h)[47]. The reaction mixture was filtered, solvent evaporated, the residue taken up in dichloromethane, dried ($MgSO_4$) and solvent again removed to give the product (9) (16.9g, 87%) as a deep red tacky solid. This was used without further purification.

2-(2,6-Dinitrophenyl)acrolein (85) - trans-2-[β-(Dimethylamino)vinyl]-2,6-dinitrobenzene (82) (2.2g, 9.4mm) in D.M.F. (5ml) was added to methanol (6ml) containing aqueous dimethylamine (26%, 2.4g) formalin (2.4g) and acetic acid (1.8ml) at 0°C over 1 h[63]. After the addition was complete the solution was stirred for an additional 30 minutes, methanol removed at reduced pressure and water (30ml) added. A dark oil precipitated that crystallised on standing overnight at 0°C to give compound (85) as a pale yellow solid; (1.8g, 92%). An analytical sample was prepared by recrystallisation. m.p. 74.5-75°C (EtOH/H_2O) (Found: C, 48.64; H, 2.72; N, 12.53;

$C_9H_6N_2O_5$ requires C, 48.66; H, 2.72; N, 12.61%); m/e No M^+ obtained at 180°C; ν max. (nujol) 1710, 1540, and 1348cm^{-1}; δ ($CDCl_3$ 9.7 (1H, s, CHO), 7.53-8.26 (3H, m, ArH), and 6.40 (2H, s CH_2=C).

3-(Dimethylamino)-2-(2,6-dinitrophenyl)acrolein (86) - trans-2-[β-(Dimethylamino)vinyl]-2,6-dinitrobenzene (82) (4.46g, 18.8mm) in D.M.F. (10ml) was added to a solution of phosphorous oxychloride (2.86g, 18.8mm) in D.M.F. (6.6ml) under argon at 0°C over 30 minutes[63]. The solution was warmed to room temperature and stirred for 1 h. Addition of ice (approx. 30g) and aqueous sodium hydroxide (5.2g in 20ml water) gave a rapid precipitation of the orange crystalline product. After warming at 65°C for 2 h the solution was cooled overnight and the filtered precipitate recrystallised ($CHCl_3$/petrol) to give compound (86) m.p. 191-192°C (4.10g, 82%). (Found: C, 49.90; H, 4.13; N, 15.70; $C_{11}H_{11}N_3O_5$ requires C, 49.81; H, 4.18; N, 15.84); m/e 265 (M^+) and 236 (M^+-CHO); ν max. (nujol) 1620, 1600, and 1526cm^{-1}; δ ($CDCl_3$) 8.93 (1H, s, CHO), 7.24-8.03 (3H, m, ArH), 7.10 (1H, s, =CH), and 2.97 (6H, s, $N(CH_3)_2$).

Methyl-trans-2-[β-(Dimethylamino)vinyl]-3-nitro benzoate (91) - A solution of methyl-2-methyl-3-nitro-benzoate (89) (48.75g, 250mm) and N,N-dimethylformamide dimethyl acetal (99.5ml, 750mm) in D.M.F. (200ml) was warmed at 150°C for 6.5 h. After cooling the solution was diluted with ether (1L), washed with brine (2 x 500ml), water (5 x 500ml) and finally again with brine (300ml). Removal of solvent gave the product (91) (58.4g, 93%) as a deep red oil that required no further purification. ν max. (thin film) 1720, 1630, 1594, 1520, and 1260cm^{-1}; δ ($CDCl_3$) 7.63 (2H, m, ArH), 7.00 (1H, m, ArH), 6.30, 5.59 (2H, ABq, J_{AB} 14Hz, CH≡CH), 3.80 (3H, s, CO_2CH_3), and 2.80 (6H, s, $N(CH_3)_2$)[65,66].

Methyl Indole-4-carboxylate (88)[65] - Methyl trans-2-[β-(dimethylamino)vinyl]-3-nitrobenzoate (91) (58.4g, 234mm) was dissolved in toluene (1L) containing 10% Pd/C

(12g) and stirred under a hydrogen atmosphere at 60 p.s.i. until hydrogen uptake was complete (about 2 h). The solution was filtered, extracted with 5% hydrochloric acid (2 x 300ml) and brine (2 x 200ml), solvent removed and the residue (32.1g) chromatographed using a Waters Prep. 500 H.P.L.C. system (petrol/CH_2Cl_2, 3:7 eluant). Methyl indole-4-carboxylate (88) (28.5g, 70%) was isolated as a crystalline solid m.p. 69-70°C (lit. 73-74°C[140]), ν max. (nujol) 3430, 3360, 1700, 1440, 1280, 1200, and 1150cm^{-1}; δ ($CDCl_3$) 9.15 (1H, br s, indole NH), 7.94 (1H, dd, J 1, 7Hz, 5-H or 7-H), 7.00-7.55 (4H, m, ArH), and 3.95 (3H, s, CO_2CH_3).

Indole-4-Carboxylic Acid (87) - Methyl indole-4-carboxylate (88) (350mg, 2mm) was refluxed in aqueous ethanol (1:1, 10ml) containing sodium hydroxide (2mm) under nitrogen for 15 h. The solvent was removed under reduced pressure and the residue taken up in water, extracted with chloroform (2 x 20ml) and acidified with conc. hydrochloric acid. The precipitated acid was collected by filtration and dried to give a colourless solid that was recrystallised to give (87) as fine white needles (257mg, 77%) m.p. 213-214°C (H_2O) (lit. 213-214°C[41a]). m/e 161 (M^+), 144 (M^+-OH) and 116 (M^+-CO_2H); ν max. (nujol) 3360, 1650, 1290, and 760cm^{-1}; δ ($(CD_3)_2SO$) 6.76-7.77 (5H, m, ArH).

4-N-tert-Butoxycarbonylaminoindole (92) - Indole-4-carboxylic acid (87) (187mg, 1.16mm), triethylamine (130mg, 1.3mm) and diphenylphosphoryl azide[67] (325mg, 1.18mm) were heated at reflux in tert-butanol (5ml) under argon for 6 h. The solvent was removed at reduced pressure and the brown semi-crystalline residue chromatographed ($CHCl_3$ eluant) to give compound (92) (164mg, 61%) as an off-white solid. An analytical sample was prepared by recrystallisation m.p. 142.5-143°C ($CHCl_3$/petrol). (Found: C, 67.02; H, 6.90; N, 12.05; $C_{13}H_{16}N_2O_2$ requires C, 67.22; H, 6.94; N, 12.06%); m/e 232 (M^+), 217 (M^+-CH_3), 176, 161, 144, 132 (M^+-$C_5H_8O_2$), and

116 ($M^+-C_5H_{10}NO_2$); ν max. (nujol) 3380, 3320, and 1678; δ ($CDCl_3$) 8.40 (1H, br s, indole NH), 6.33-7.56 (5H, m, ArH), 6.66 (1H, br s, HNCO-), and 1.52 (9H, s, $C(CH_3)_3$).

2-Amino-6-nitrotoluene (95)[69] - 2-Amino-6-nitrotoluene (95) was prepared according to Heck's procedure from 2,6-dinitrotoluene (81) (74g, 0.49M). Triethylamine (240ml) and formic acid (64ml, 1.8M) in the presence of 10% Pd/C (14.4g) were used for the reduction. 2-Amino-6-nitrotoluene was isolated as a pale yellow solid. Recrystallisation gave the product (40.0g, 66%) as a bright yellow material m.p. 87.5-88°C (EtOH/H_2O/ decolourising charcoal) (lit., m.p. 91.5°C[70]). ν max. (nujol) 3400, 3320, 3220, 1605, 1510, 1480, 1460, 1370, and 1350cm^{-1}; δ ($CDCl_3$) 6.71-7.22 (3H, m, ArH), 3.84 (2H, br s, $ArNH_2$), and 2.20 (3H, s, $ArCH_3$).

2-Bromo-6-Nitrotoluene (96) - The bromide was prepared from 2-amino-6-nitrotoluene (95) according to Noelting's procedure[70] m.p. 34-35°C (petrol) (lit., 41°C[70]). ν max. (thin film) 1590, 1525, 1445, 1370, 1350, 1275, 1215, 1090, 1010, 860, 795, 760, and 710cm^{-1}; δ ($CDCl_3$) 7.58 (2H, dd, J 2.5, 8Hz, ArH), 7.03 (1H, t, J 8Hz, ArH), and 2.45 (3H, s, $ArCH_3$).

trans-2-[β-(Dimethylamino)vinyl]-2-Bromo-6-nitrobenzene (102) - 2-Bromo-6-nitrotoluene (96) (6.48g, 30mm) and N,N-dimethylformamide dimethyl acetal (9.75ml, 90mm) were warmed to 140°C in D.M.F. (30ml) for 14 h. The deep red solution was cooled, diluted with ether (300ml) and washed with brine (2 x 100ml), water (4 x 100ml) and finally brine (100ml). Removal of solvent gave the product (102) as a deep red oil (6.9g, 85%) which required no further purification. (Found: M^+ 270.0001, $C_{10}H_{11}N_2O_2Br^{79}$ requires 269.9994); m/e 270, 272 (M^+), 251, and 253; ν max. (thin film) 1630, 1590, 1520, 1435, 1375, 1330, 1255, 1210, 1090, and 945cm^{-1}; δ ($CDCl_3$) 6.67-7.63 (3H, m, ArH) 8.47 (2H, ABq, J_{AB} 14Hz, $CH{=}CHN(CH_3)_2$), and 2.80 (6H, s, $N(CH_3)_2$).

4-Bromoindole (101)[39] - trans-2-[β-(Dimethylamino)-vinyl]-2-bromo-6-nitrotoluene (102) (6.9g, 25mm) in ethanol (150ml) containing Raney nickel[59] (2 teaspoons) was stirred under one atmosphere of hydrogen until hydrogen uptake ceased (about 3 h). The solution was filtered, solvent removed and the residue chromatographed (petrol/$CHCl_3$ 1:1) to give 4-bromoindole (101) as a pale yellow oil (3.41g, 69%). m/e 195, 197 (M^+), and 116 (M^+-Br); ν max. (thin film) 3420, 1610, 1560, 1500, 1490, 1475, 1430, 1410, 1330, 1270, 1175, 1140, 1090, 1065, 890, and 810cm^{-1}; δ ($CDCl_3$) 8.10 (1H, br s, indole NH), 6.98-7.34 (4H, m, ArH), and 6.53 (1H, m, 3-H).

General Procedure for the Preparation of 4-Formamido-indoles - The 4-aminoindole in T.H.F. or ether was cooled to 0°C (ice/salt) and a solution of freshly prepared formic acetic anhydride[72,73] (2-5 equiv.) in the same solvent added over 30 minutes - 1 h. The cooling bath was then removed and the reaction mixture stirred until the reaction was complete as indicated by t.l.c. T.H.F., when used as a solvent, was removed under reduced pressure and the residue taken up in ether. The ethereal phase was neutralised with excess potassium hydroxide and the organic phase thoroughly washed with water. Removal of solvent than gave the crude 4-N-formamidoindole which was reduced without further purification.

4-Formamidoindole (106) - 4-Aminoindole (9) (35.0g, 265mm) in T.H.F. (600ml) at 0°C (ice/salt) was treated with formic acetic anhydride (91ml, 700mm) in T.H.F. (100ml) over 1 h. Work up following the general procedure gave the compound (106) as a red semi-crystalline oil (34.8g, 82%). An analytical sample was prepared by recrystallisation m.p. 140-142°C (EtOH/H_2O). (Found: C, 67.35; H, 5.05; N, 17.34; $C_9H_8N_2O$ requires C, 67.49; H, 5.03; N, 17.49%); m/e 160 (M^+) and 131 (M^+-CHO); ν max. (nujol) 3410, 3270, 1648, 1580, 1525, 1460, 1430, 1415, 1380, 1350, 1240, 1185, 1150, 1110, 890, 820, and 750cm^{-1}; δ ($CDCl_3$) 9.59 (1H, br s, indole NH), 8.37 (1H, s, NCHO),

6.70-7.38 (5H, m, 4 x ArH and HNCHO), and 6.36 (1H, m, 2-H or 3-H).

1-Benzyl-4-Formamidoindole (107) - 1-Benzyl-4-aminoindole (71) (140mg, 0.63mm) was formylated in ether following the general procedure. The product (107) (121mg, 77%) was isolated as a semi-crystalline oil. ν max. (thin film) 3270, 1690, 1580, 1490, 1425, 1370, 1350, 1290, 1270, 910, and 730cm^{-1}; δ ($CDCl_3$) 8.60 (1H, s, NCHO), 6.33-7.15 (11H, m, 10 x ArH, HNCHO), and 4.95 (2H, s, NCH_2Ar).

General Procedure for the Reduction of 4-formamidoindoles - The 4-formamidoindole (1M) in T.H.F. was treated at room temperature under argon with lithium aluminium hydride (3-5M) and either stirred overnight or warmed to 60°C for 4 h and then stirred overnight at room temperature. Excess lithium aluminium hydride was destroyed with water, the precipitated salts removed by filtration, solvent removed at reduced pressure and the material either chromatographed or used, as isolated, without further purification.

4-N-Methylaminoindole (17) - 4-Formamidoindole (106) (34.8g, 0.217M) in T.H.F. (400ml) was treated at room temperature with lithium aluminium hydride (25g, 0.66M) in T.H.F. (200ml). The reaction mixture was stirred at 60°C for 4 h and worked up following the general procedure. The crude product was chromatographed using a Waters prep. 500 H.P.L.C. system (petrol/CH_2Cl_2 1:1, eluant) to give 4-N-methylaminoindole (17) (22.43g, 78%) as a dark green oil. Other batches of material were found to be sufficiently pure as to not require chromatography. The analytical sample was prepared by further chromatography of a portion ($CHCl_3$/petrol, 9:1 eluant) to give a pale green oil that rapidly darkened on standing. (Found: C, 73.88; H, 6.90; N, 18.76; $C_9H_{10}N_2$ requires C, 73.94; H, 6.89; N, 19.16%); m/e 146 (M^+), 131 (M^+-CH_3), and 116 (M^+-HNCH_3); ν max. (thin film) 3400, 3250, 1585, 1500, 1400, 1360, 1300, 1248, 1210, 1150, 1080, 894, and

730cm^{-1}; δ ($CDCl_3$, 250 MHz) 8.08 (1H, br s, indole NH), 7.10 (1H, dd, J 7.6, 8.3Hz, 6-H), 7.05 (1H, m, 2-H), 6.81 (1H, d, J 8.3Hz, 7-H), 6.43 (1H, m, 3-H), 6.29 (1H, d, J 7.6Hz, 5-H), 3.30 (1H, br s, ArNH), and 3.00 (3H, s, NCH_3). Irradiation at δ 8.08 collapsed the signals at 7.05 and 6.43 to a doublet J 3.4Hz and a double doublet J 0.8 and 3.4Hz respectively.

1-Benzyl-4-N-methylaminoindole (108) - 1-Benzyl-4-formamidoindole (107) (121mg, 0.48mm) was reduced at room temperature with lithium aluminium hydride (100mg, 2.6mm) following the general procedure. Chromatography of the residue after work up (benzene, eluant) gave compound (108) (47mg, 41%) as a semicrystalline oil. Recrystallisation gave the analytical sample m.p. 99-100°C (2 x $CHCl_3$/petrol). (Found: C, 81.61; H, 6.82; N, 11.85; $C_{16}H_{16}N_2$ requires C, 81.32; H, 7.07; N, 11.67%); ν max. (thin film) 3420, 1590, 1500, 1283, 910, and 730cm^{-1}; δ ($CDCl_3$) 6.15-7.33 (10H, m, ArH), 5.20 (2H, s, NCH_2Ar), 3.87 (1H, br s, NH), and 2.97 (3H, s, NCH_3).

4-N-Methylaminoindole (17) from Reduction of 4-N-tert-Butoxycarbonylaminoindole (92) - A solution of the tert-butoxycarbonylamine (92) (121mg, 0.52mm) in T.H.F. (5ml) was treated with lithium aluminium hydride (40mg, 1mm) at room temperature. After stirring at this temperature for 30 minutes the reaction mixture was warmed to 70°C for 1 h. The reaction mixture was cooled to room temperature and excess lithium aluminium hydride destroyed by the cautious addition of water. Filtration, evaporation of the filtrate, dissolution of the residue in ether followed by extraction with water (3 x 20ml) and brine (20ml) and evaporation of solvent at reduced pressure gave an oily residue. Chromatography ($CHCl_3$ eluant) of this residue gave 4-N-methylaminoindole (17) (28mg, 37%) identical by ^{1}H n.m.r., i.r. and t.l.c. with the previously described material.

4-N-Methyl-4-formamidoindole - 4-N-Methylaminoindole (17) (1.45g, 9.9mm) was formylated in ether according to

the general procedure to give the product (1.45g, 84%) as a dark oil. (Found: M^+ 174.0791, $C_{10}H_{10}N_2O$ requires, 174.0793); m/e 174 (M^+), 159 (M^+-CH_3), 146 (M^+-CO), 145 (M^+-CHO), and 116 (M^+-CH_3NCHO); ν max. (thin film) 3400, 3300, 1660, 1580, 1505, 1360, 1345, 1175, 1140, 1080, 1035, 910, 750, and 730cm^{-1}; δ ($CDCl_3$) 9.43 (1H, br s, indole NH), 8.41 (1H, s, NC<u>H</u>O), 6.67-7.37 (4H, m, Ar<u>H</u>), 6.37 (1H, m, 3-H), and 3.40 (3H, s, NC<u>H</u>$_3$).

<u>4-N,N-dimethylaminoindole (115)</u> - 4-N-Methyl-4-formamidoindole (1.305g, 7.5mm) was reduced in T.H.F. (30ml) with lithium aluminium hydride (800mg, 21mm) according to the general procedure to give <u>compound</u> (115) as a brown solid (1.135g, 95%). Chromatography ($CHCl_3$ eluant) gave a light brown crystalline solid (780mg, 65%). Recrystallisation gave the analytical sample m.p. 104-105.5°C ($CHCl_3$/petrol). (Found: C, 74.73; H, 7.58; N, 17.28; $C_{10}H_{12}N_2$ requires C, 74.97; H, 7.55; N, 17.49%); m/e 160 (M^+), 145 (M^+-CH_3), 131 ($M^+-C_2H_5$), and 117 ($M^+-NC_2H_5$); ν max. (thin film) 3470, 3400, 1600, 1580, 1500, 1470, 1450, 1430, 1410, 1360, 1340, 1310, 1260, 1220, 1195, 1180, 1145, 1080, 1050, 1015, 910, and 730cm^{-1}; δ ($CDCl_3$) 8.27 (1H, br s, indole NH), 6.38-7.13 (5H, m, Ar<u>H</u>), and 2.96 (6H, s, N(C<u>H</u>$_3$)$_2$).

<u>N-(4-Indolyl)glycine Ethyl Ester (109)</u> - 4-Aminoindole (9) (280mg, 2.1mm), ethyl bromoacetate (351mg, 2.1mm) and potassium carbonate (610mg, 4.4mm) were stirred in D.M.F. (5ml) containing potassium iodide (30mg, 0.18mm) at 65°C, under argon, overnight. After cooling the solution was diluted with ether, extracted with water (5 x 20ml) and brine (2 x 20ml), solvent removed and the residue chromatographed ($CHCl_3$ eluant) to give <u>compound</u> (109) (383mg, 84%) as an off-white crystalline solid. The analytical sample was prepared by recrystallisation m.p. 100-101°C (EtOH). (Found: C, 66.01; H, 6.63; N, 12.63; $C_{12}H_{14}N_2O_2$ requires C, 66.04; H, 6.47; N, 12.83%); m/e 218 (M^+), 157, 145 (M^+-CO_2Et), and 117 ($M^+-C_4H_7NO_2$); ν max.

(nujol) 3430, 3380, 1725, 1595, 1520, 1460, 1430, 1420, 1375, 1255, 1210, 1150, 1100, 1020, and 730cm^{-1}; δ ($CDCl_3$) 8.10 (1H, br s, indole NH), 6.50-7.05 (3H, m, ArH), 6.33 (1H, m, 3-H), 6.07 (1H, d, J 7.5Hz, 5-H), 4.10 (3H, q, J 7Hz and br s, OCH_2CH_3 and HNAr), 3.93 (2H, s, NCH_2CO), and 1.18 (3H, t, J 7Hz, CH_2CH_3).

N-(4-Indolyl)alanine Ethyl Ester (110) - 4-Aminoindole (9) (60mg, 0.45mm), ethyl 2-bromopropionate (90mg, 0.5mm) and silver oxide (120mg, 0.5mm) were stirred together in D.M.F. (2ml) under argon at room temperature for 15 h. After filtration, the solution was diluted with ether, extracted with water (5 x 10ml), the solvent removed at reduced pressure and the residue chromatographed ($CHCl_3$/petrol, 9:1 eluant) to give the oily product (110) (20mg, 19%). (Found: M^+ 232.1211, $C_{13}H_{16}N_2O_2$ requires 232.1212); m/e 232 (M^+), 159 ($M^+-C_3H_5O_2$), 132 ($M^+-C_5H_8O_2$), and 117 ($M^+-C_5H_9NO_2$); ν max. (thin film) 3480, 3400, 1728, 1665, 1610, 1590, 1505, 1375, 1365, 1300, 1180, 1155, 910, and 730cm^{-1}; δ ($CDCl_3$) 8.14 (1H, br s, indole NH), 6.70-7.14 (3H, m, ArH), 6.44 (1H, m, 3-H), 6.16 (1H, d, J 7.5Hz, 5-H), 4.16 (3H, 2 x q, J 7Hz, OCH_2CH_3 and $NCH(CH_3)CO$, 3.50 (1H, br s, HNAr), 1.55 (3H, d, J 7Hz, CH_3CH), and 1.23 (3H, t, J 7Hz, OCH_2CH_3).

4-N-Benzylaminoindole (111) and 4-N,N-Dibenzylaminoindole (112) - 4-Aminoindole (9) (130mg, 1mm) benzyl bromide (171mg, 1mm) and potassium carbonate (276mg, 2mm) were stirred at 70°C in D.M.F. (2ml) containing a catalytic quantity of potassium iodide for 16 h. After cooling to room temperature and dilution with ether, the solution was extracted with water (4 x 20ml) and brine (20ml) and the solvent removed at reduced pressure. The residue on subjection to column chromatography ($CHCl_3$/petrol, 3:2 eluant) gave (i) **4-N,N-Dibenzylaminoindole (112)** (73mg, 23%) as an oil. (Found: M^+ 312.1632, $C_{22}H_{20}N_2$ requires 312.1626); m/e 312 (M^+) and 221 ($M^+-C_7H_7$); ν max. (thin film) 3480, 1605, 1585, 1500, 1495, 1455, 1360, 1230, and 735cm^{-1}; δ ($CDCl_3$) 7.87 (1H,

br s, indole NH), 6.80-7.30 (13H, m, ArH), 6.27-6.53 (2H, m, ArH), and 4.50 (4H, s, 2 x NCH_2Ar). **(ii) 4-N-Benzylaminoindole (111)** (105mg, 47%). (Found: M^+ 222.1158, $C_{15}H_{14}N_2$ requires 222.1157); m/e 222 (M^+) and 137. ν max. 3480, 3400, 1595, 1510, 1455, 1428, 1410, 1370, 1360, 1305, 1250, 1095, and 735cm^{-1}; δ ($CDCl_3$) 7.73 (1H, br s, indole NH), 6.50-7.30 (8H, m, ArH), 6.09-6.29 (2H, m, ArH), 4.33 (2H, s, NCH_2Ar), and 3.92 (1H, br s, ArNH).

N-Methyl-N-(4-indolyl)glycine Ethyl Ester (113) - **(i) Potassium bicarbonate/potassium iodide method:-** 4-N-Methylaminoindole (17) (18.13g, 127mm) and ethyl bromoacetate (21.08g, 126mm) in D.M.F. (150ml), containing potassium bicarbonate (25g, 250mm) and potassium iodide (500mg, 3mm) were stirred at 60°C for 24 h. The solution was diluted with ether (800ml), extracted with water (5 x 500ml) and the solvent removed at reduced pressure to give an off-white solid. Recrystallisation gave compound (113) (20.3g, 69%) m.p. 79-79.5°C (EtOH). (Found: C, 67.22; H, 7.01; N, 12.00; $C_{13}H_{16}N_2O_2$ requires C, 67.22; H, 6.94; N, 12.06%); m/e 232 (M^+), 173 ($M^+-C_3H_7O$), 159 ($M^+-C_3H_5O_2$), and 130 ($M^+-C_5H_{10}O_2$); ν max. (nujol) 3320, 1720, 1580, 1510, 1465, 1435, 1415, 1380, 1225, 1200, 1045, and 735cm^{-1}; δ ($CDCl_3$, 250MHz) 8.33 (1H, br s, indole NH), 7.05 (2H, m, 2-H and 6-H), 6.93 (1H, d, J 7.8Hz, 7-H), 6.55 (2H, m, 3-H and 5-H), 4.23 (2H, q, J 7.3Hz, OCH_2CH_3), 4.18 (2H, s, NCH_2CO), 3.12 (3H, s, NCH_3), and 1.28 (3H, t, J 7.3Hz, CH_2CH_3). **(ii) Silver oxide method:-** 4-N-Methylaminoindole (17) (260mg, 1.78mm), ethyl bromoacetate (297mg, 1.78mm) and silver oxide (412mg, 1.78mm) were stirred in D.M.F. (5ml) for 2 h at room temperature. Silver oxide was removed by filtration and the filtrate, after dilution with ether, extracted with water (5 x 10ml). Removal of solvent at reduced pressure gave the product (113) as an oil (175mg, 42%) with identical i.r., ^{1}H n.m.r. and t.l.c. properties as those described above.

N-Methyl-N-[4-(1-benzyl)indolyl]glycine Ethyl Ester (114) - 1-Benzyl-4-N-methylaminoindole (108) (680mg,

2.88mm), ethyl bromoacetate (501mg, 3mm) and silver oxide (1g, 4.4mm) were stirred overnight at room temperature in D.M.F. (5ml). Filtration, dilution of the filtrate with chloroform, extraction with water (5 x 20ml) and removal of solvent at reduced pressure gave a dark brown oil. Chromatography (petrol/$CHCl_3$, 7:3 eluant) gave the product (114) as a yellow oil (230mg, 25%) that gradually turned dark on standing. (Found: M^+ 322.1684, $C_{20}H_{22}N_2O_2$ requires 322.1681); ν max. (thin film) 1740, 1575, 1492, 1190, 905, and 730cm^{-1}; δ ($CDCl_3$, 250MHz), 7.24 (3H, m, ArH), 7.05 (4H, m, ArH), 6.86 (1H, d, J 8.3Hz, 7-H), 6.56 (1H, dd, J 0.8, 3.3Hz, 3-H), 6.53 (1H, d, J 7.5Hz, 5-H), 5.27 (2H, s, NCH_2Ar), 4.22 (2H, q, J 7.6Hz, CH_2CH_3), 4.18 (2H, s, NCH_2CO), 3.12 (3H, s, NCH_3), and 1.28 (3H, t, J 7.6Hz, CH_2CH_3).

N-Methyl-N-(4-indolyl)glycine Ethyl Ester (113) from N-(4-Indolyl)glycine Ethyl Ester (109) - N-(4-Indolyl)-glycine ethyl ester (109) (100mg, 0.46mm) was stirred in D.M.F. (1ml) containing potassium carbonate (138mg, 1mm) and methyl iodide (100mg, 0.7mm) at room temperature for 72 h. The reaction mixture was diluted with ether, washed with water (5 x 10ml) and brine (2 x 10ml) and solvent removed at reduced pressure. ^1H n.m.r. data from the residue (72mg, 67%) indicated that despite being homogenous by t.l.c. the product only contained some 60% of the desired product (113) the remainder consisting of starting material (109).

Rearrangement of 4-N-Alkylaminoindoles to 1-Alkyl-4-aminoindoles - General Procedure - The appropriate 4-N-alkylaminoindole (1mm) was warmed to reflux temperature for 21 h in toluene (10ml) containing a catalytic quantity of 4-toluenesulphonic acid monohydrate. After the reaction had gone to completion, the solution was cooled to room temperature and diluted with ethyl acetate. Extraction with saturated sodium bicarbonate (2 x 20ml), water (3 x 20ml) and brine (20ml) followed by removal of solvent at reduced pressure gave

the oily crude product. Chromatography gave the pure sample.

1-Methyl-4-aminoindole (129) from 4-N-Methylaminoindole (17) - 1-Methyl-4-aminoindole (129) was prepared from 4-N-methylaminoindole (17) (196mg, 1.3mm) according to the general procedure. The product (129) (153mg, 75%) a pale green air sensitive oil, was purified by chromatography ($CHCl_3$/petrol, 4:1 eluant). (Found: M^+ 146.0849, $C_9H_{10}N_2$ requires 146.0844); m/e 146 (M^+) and 131 (M^+-CH_3); ν max. (thin film) 3460, 3360, 3230, 1620, 1588, 1500, 1456, 1425, 1350, 1310, 1285, 1210, 1160, 1085, and 730cm^{-1}; δ ($CDCl_3$, 250MHz) 7.02 (1H, dd, J 7.8, 8.1Hz, 6-H), 6.87 (1H, d, J 3.1Hz, 2-H), 6.73 (1H, d, J 8.1Hz, 7-H), 6.33 (1H, d, J 7.8Hz, 5-H), 6.32 (1H, dd, J 0.8, 3.1Hz, 3-H), 3.76 (2H, br s, $ArNH_2$), and 3.63 (3H, s, NCH_3).

Treatment of 4-N-Methylaminoindole (17) with water or anhydrous camphor-sulphonic acid according to the general procedure gave no rearranged product.

1-Benzyl-4-aminoindole (71) from 4-N-Benzyl-aminoindole (111) - 1-Benzyl-4-aminoindole (71) was prepared from 4-N-benzylaminoindole (111) (51mg, 0.23mm) according to the general procedure. The product (71) (46mg, 90%) was isolated as a crystalline solid after column chromatography ($CHCl_3$/petrol, 4:1 eluant). The ^1H n.m.r., i.r. and t.l.c. properties were identical with those of the previously described compound.

Ethyl-[1-(4-amino)indolyl]acetate (130) from N-(4-Indolyl)glycine Ethyl Ester (109) - N-(4-Indolyl)glycine ethyl ester (109) (86mg, 0.39mm) on treatment with 4-toluenesulphonic acid according to the general procedure for 24 h gave only partial reaction. ^1H n.m.r. of the crude reaction indicated a 60% conversion to ethyl-[1-(4-amino)indolyl]acetate (130). Reaction of this crude mixture according to the general procedure for a further 24 h followed by column chromatography ($CHCl_3$, eluant) gave (i) **N-(4-Indolyl)glycine ethyl ester (109)** (11.6mg,

13%) and (ii) **Ethyl-[1-(4-amino)indolyl]acetate (130)** (66mg, 77%) as an oil. (Found: M^+ 218.1058, $C_{12}H_{14}N_2O_2$ requires 218.1055); m/e 218 (M^+), 190 ($M^+-C_2H_4$), and 145 ($M^+-C_3H_5O_2$); ν max. (thin film) 3460, 3375, 1740, 1620, 1590, 1495, 1455, 1375, 1350, 1315, 1285, 1210, 1160, 1025, 910, and 730 cm^{-1}; δ($CDCl_3$) 6.19-7.10 (5H, m, ArH), 4.65 (2H, s, NCH_2CO), 4.08 (2H, q, J 7Hz, OCH_2CH_3), 3.66 (2H, br s, $ArNH_2$), and 1.20 (3H, t, J 7Hz, OCH_2CH_3).

N-[4-(1-Methyl)indolyl]dehydrovaline Methyl Ester (126) - 1-Methyl-4-aminoindole (129) (1.906g, 13mm) and methyl-2-keto-isovalerate (1.95g, 15mm) were warmed to reflux in toluene (40ml) containing a catalytic quantity of 4-toluenesulphonic acid under argon, for 9 h. This material was reduced without further purification. (See next experiment). Chromatography ($CHCl_3$/petrol 4:1 eluant) of an aliquot gave (126) as an unstable oil. (Found: M^+ 258.1372, $C_{15}H_{18}N_2O_2$ requires 258.1368); m/e 258 (M^+), 243 (M^+-CH_3), 211, and 198; ν max. (thin film) 3390, 1705, 1580, 1490, 1270, 1215, 1070, and 725cm^{-1}; δ ($CDCl_3$) 6.60-7.10 (3H, m, ArH), 6.35 (1H, d, J 3Hz, 3-H), 5.98 (1H, d, J 7Hz, 5-H), 5.29 (1H, br s, NH), 3.67 (3H, s, OCH_3), 3.60 (3H, s, NCH_3), 2.23 (3H, s, allylic CH_3), and 1.86 (3H, s, allylic CH_3).

N-[4-(1-Methyl)indolyl]valine Methyl Ester (127) - N-[4-(1-Methyl)indolyl]dehydrovaline methyl ester (126) (3.1g, 12mm) was dissolved in methanol (30ml) and magnesium powder (1.4g, 60mm) added. The solution was stirred at room temperature until a vigorous reaction started upon which an additional portion of magnesium powder (1.44g, 60mm) was added and the solution cooled (ice/salt) until the reaction had subsided (about 35 minutes). The reaction mixture was stirred for a further 1 h at room temperature, diluted with chloroform (200ml) and extracted with saturated ammonium chloride (4 x 100ml). Removal of solvent and chromatography ($CHCl_3$/ petrol 7:3 eluant) of the residue gave (i) **N-[4-(1-Methyl)indolyl]valine methyl ester (127)** (2.24g, 63% from

1-methyl-4-aminoindole) as an oil that slowly soldified on cooling. Recrystallisation of this solid gave an analytical sample m.p. 50.5-51°C (EtOH). (Found: C, 69.14; H, 7.89; N, 10.66; $C_{15}H_{20}N_2O_2$ requires C, 69.20; H, 7.74; N, 10.76%); m/e 260 (M^+), 217 ($M^+-C_3H_7$), and 201 ($M^+-C_2H_3O_2$); ν max. (thin film) 3390, 1725, 1578, 1490, 900, and 720cm^{-1}; δ ($CDCl_3$) 6.20-7.03 (4H, m, ArH), 6.10 (1H, d, J 7Hz, ArH), 4.30 (1H, br s, NH), 3.94 (1H, d, J 6Hz, NCHCO), 3.50 (3H, s, OCH_3), 3.40 (3H, s, NCH_3), 2.02 (1H, m, $CH(CH_3)_2$), 0.92 (3H, d, J 7Hz, $CHCH_3$), and 0.86 (3H, d, J 7Hz, $CHCH_3$). **(ii) 1-Methyl-4-aminoindole (129)** (400mg, 21%) identical by ^{1}H n.m.r. and t.l.c. with the previously described material.

N-Methyl-N-(4-indolyl)valine Methyl Ester (116) - A solution of 4-N-methylaminoindole (17) (885mg, 6.06mm) and methyl-2-ketoisovalerate (1.10g, 8.5mm) in toluene (60ml) containing camphor sulphonic acid (50mg) was boiled for 30 h under Dean-Stark conditions. Water formed during the reaction was absorbed by 4Å molecular sieve contained in the Dean-Stark apparatus. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and extracted with sodium bicarbonate (2 x 20ml) and water (3 x 20ml). Solvent was removed at reduced pressure and the crude dark green oil containing the dehydroamino acids (126) and (128) (1.5574g) dissolved in methanol (30ml). To the methanolic solution, magnesium powder (1.464g, 61mm) was added and the solution stood at room temperature. When a spontaneous reaction started the reaction mixture was stirred and cooled (ice bath) until the reaction had subsided, when the ice bath was removed. After stirring for a further 1h the reaction mixture was diluted with ethyl acetate (200ml) and the solution extracted with saturated ammonium chloride (3 x 50ml). Further extraction of the organic phase with water (3 x 50ml) and brine (50ml), removal of the solvent at reduced pressure and chromatography ($CHCl_3$/petrol 4:1 eluant) of

the dark residue gave (i) **N-[4-(1-Methyl)indolyl]valine methyl ester (127)** (280mg, 18%) identical by ^{1}H n.m.r., i.r. and t.l.c. with the previously described material and **(ii) N-Methyl-N-(4-indolyl)valine methyl ester (116)** (314mg, 20%) as a pale green oil that partially crystallised on standing. (Found: M^+ 260.1529, $C_{15}H_{20}N_2O_2$ requires 260.1525); m/e 260 (M^+), 231, 217 ($M^+-C_3H_7$), 201 ($M^+-C_2H_3O_2$), and 185; ν max. (thin film) 3420, 1725, 1610, 1585, 1505, 1470, 1440, 1390, 1370, 1300, 1255, 1170, 1150, 1125, and 735cm^{-1}; δ ($CDCl_3$, 250MHz) 8.14 (1H, br s, indole NH), 7.07 (2H, m, 2-H and 6-H), 6.94 (1H, complex d, J 8.3Hz, 7-H), 6.74 (1H, m, 3-H), 6.59 (1H, dd, J 0.8, 7.3Hz, 5-H), 4.15 (1H, d, J 10.8Hz, NCHCO), 3.66 (3H, s, OCH_3), 3.04 (3H, s, NCH_3), 2.49 (1H, m, $(CH_3)_2CH$), 1.05 (3H, d, J 6.4Hz, CH_3CH), and 0.95 (3H, d, J 6.4Hz, CH_3CH).

N-Methyl-N-[4-(1-geranyl)indolyl]glycine Ethyl Ester (133) - To a stirred suspension of sodium hydride (55mg of 50% in oil washed with petrol, 1.2mm) in D.M.F. (2ml) a solution of N-Methyl-N-(4-indolyl)glycine ethyl ester (113) (232mg, 1mm) and geranyl chloride (200mg, 1.1mm) in D.M.F. (2ml) was added over 5 minutes. Stirring was continued at room temperature for 45 minutes. After dilution with ether the solution was washed with water (5 x 20ml) and brine (10ml), the solvent removed at reduced pressure and the residue chromatographed ($CHCl_3$/petrol, 3:7 eluant). The compound (133) (310mg, 84%) was isolated as a pale yellow oil. (Found: C, 74.89; H, 8.97; N, 7.38; $C_{23}H_{32}N_2O_2$ requires C, 75.00; H, 8.76; N, 7.61%); m/e 368 (M^+), 295 ($M^+-C_3H_5O_2$), and 159 ($M^+-C_{10}H_{16}-C_3H_5O_2$); ν max. (thin film) 1750, 1595, 1575, 1495, 1440, 1375, 1340, 1290, 1255, 1185, 1115, 1030, 960, 750, and 730cm^{-1}; δ ($CDCl_3$) 6.40-7.17 (5H, m, ArH), 4.90-5.45 (2H, m, 2x=CH), 4.65 (2H, d, J 6Hz, NCH_2), 4.20 (2H, q, J 7Hz, CH_2CH_3), 4.12 (2H, s, NCH_2CO), 3.07 (3H, s, NCH_3), 2.05 (4H, m, allylic CH_2), 1.78 (3H, s, allylic CH_3), 1.68 (3H, s, allylic CH_3), 1.58 (3H, s, allylic CH_3), and 1.20 (3H, t, J 7Hz, CH_2CH_3).

N-Methyl-N-[4-(1-benzyl)indolyl]glycine Ethyl Ester (114) - N-Methyl-N-(4-indolyl)glycine ethyl ester (113) (232mg, 1mm) was benzylated according to the above procedure with benzyl bromide (180mg, 1.05mm) and sodium hydride (50mg, 50% in oil washed with petrol, 1.1mm). Chromatography of the residue after removal of solvent gave the product (114) as a dark oil (230mg, 71%), possessing the same ^{1}H n.m.r., i.r. and t.l.c properties as those previously described.

1-Geranyl-4-N,N-dimethylaminoindole (134) - Potassium hydroxide (250mg, 5mm, crushed pellets) was stirred in D.M.S.O. (3ml) for 5 minutes and 4-N,N-dimethylaminoindole (115) (200mg, 1.25mm) then added. After stirring for 45 minutes at room temperature geranyl chloride (260mg, 1.5mm) was added and stirring continued for 2h. Dilution with ether (50ml), extraction with brine (2 x 20ml), water (4 x 20ml) and brine (20ml) followed by evaporation of the solvent at reduced pressure and chromatography ($CHCl_3$/ petrol 3:7 eluant) gave the compound (134) as a yellow oil (174mg, 47%). (Found: C, 81.15; H, 9.71; N, 9.34; $C_{20}H_{28}N_2$ requires C, 81.03; H, 9.52; N, 9.45%); m/e 296 (M^+) and 159 ($M^+-C_{10}H_{17}$); ν max. (thin film) 1600, 1580, 1450, 1430, 1375, 1345, 1310, 1290, 1200, 1185, 1140, 1050, 995, 910, 755, and 730cm^{-1}; δ ($CDCl_3$) 6.35-7.16 (5H, m, ArH), 5.30 (1H, m, =CH), 5.00 (1H, m, =CH), 4.55 (2H, d, J 7Hz, NCH_2), 2.93 (6H, s, $N(CH_3)_2$), 2.01 (4H, m, allylic CH_2), 1.75 (3H, s, allylic CH_3), 1.65 (3H, s, allylic CH_3), and 1.57 (3H, s, allylic CH_3).

1-Acetyl-4-N,N-dimethylaminoindole (140) - 4-N,N-Dimethylaminoindole (115) (191mg, 1.19mm), triethylamine (175mg, 1.75mm) and acetic anhydride (160mg, 1.6mm) were stirred together in dichloromethane (2ml) containing a catalytic amount of 4-N,N-dimethylaminopyridine at room temperature for 36 h[87]. The solution was washed with water (3 x 20ml), brine (20ml) and solvent removed. Chromatography ($CHCl_3$ eluant) gave the product (140) as a pale brown crystalline solid (178mg, 74%). (Found: M^+

202.1110, $C_{12}H_{14}N_2O$ requires 202.1106); m/e 202 (M^+) and 160 (M^+-CH_2CO); ν max. (thin film) 1707, 1585, 1533, 1490, 1450, 1425, 1385, 1370, 1330, 1320, 1274, 1223, 1200, 1183, 1153, 1140, 930, 750, and 730cm^{-1}; δ ($CDCl_3$) 8.0 (1H, d, J 8Hz, 7-H), 7.03-7.36 (2H, m, ArH), 6.50-6.76 (2H, m, ArH), 2.93 (6H, s, $N(CH_3)_2$), and 2.53 (3H, s, CH_3CO).

N-Methyl-N-[4-(1-trimethylsilyl)indolyl]glycine Ethyl Ester (141) - N-Methyl-N-(4-indolyl)glycine ethyl ester (113) (1.16g, 5mm), chlorotrimethylsilane (0.864g, 8mm) and triethylamine (1.0g, 10mm) were stirred in dichloromethane (15ml) containing 4-N,N-dimethylaminopyridine (20mg) for 48 h. The dark green solution was diluted with dichloromethane (100ml) and washed with water (4 x 100ml) and brine (50ml). The solvent was removed at reduced pressure and the residue chromatographed ($CHCl_3$/petrol, 4:1 eluant). The compound (141) (1.525g, 100%) was isolated as a pale green oil. (Found: C, 62.83; H, 8.03; N, 8.80; $C_{16}H_{24}N_2O_2Si$ requires C, 63.12; H, 7.95; N, 9.20%); m/e 304 (M^+) and 216. ν max. (thin film) 1740, 1570, and 1480cm^{-1}; δ ($CDCl_3$) 6.90-7.10 (3H, m, ArH), 6.45-6.55 (2H, m, ArH), 4.13 (2H, q, J 7Hz, CH_2CH_3), 4.07 (2H, s, NCH_2CO), 3.03 (3H, s, NCH_3), 1.24 (3H, t, J 7Hz, CH_2CH_3), and 0.53 (9H, s, $NSi(CH_3)_3$).

N-Methyl-N-[4-(1-trimethylsilyl)indolyl]valine Methyl Ester (142) - A solution of N-methyl-N-(4-indolyl)valine methyl ester (116) (188mg, 0.72mm), chlorotrimethylsilane (130mg, 1.2mm) and triethylamine (200mg, 2mm) in dichloromethane containing a catalytic quantity of 4-N,N-dimethylaminopyridine was stirred for 48 h. After this period of time the reaction mixture was diluted with dichloromethane extracted with water (4 x 30ml) and brine (30ml). Removal of solvent at reduced pressure and chromatography ($CHCl_3$/petrol, 4:1 eluant) of the residue gave (142) (195mg, 82%) as a colourless oil. (Found: M^+ 332.1926, $C_{18}H_{28}N_2O_2Si$ requires 332.1920); m/e 332 (M^+), 302, 289 ($M^+-C_3H_7$), and 273; ν max. (thin film) 1725, 1575, 1485, 1425, 1390,

1260, 1160, 1140, and 730cm^{-1}; δ ($CDCl_3$, 250MHz) 7.02-7.12 (3H, m, ArH), 6.79 (1H, d, J 3.3Hz, 3-H), 6.62 (1H, dd, J 1.7, 8.5Hz, 5-H), 4.09 (1H, d, J 12.3Hz, NCHCO), 3.67 (3H, s, OCH_3), 3.03 (3H, s, NCH_3), 2.38 (1H, m, $(CH_3)_2CH$), 1.06 (3H, d, J 6.8Hz, CH_3CH), 0.94 (3H, d, J 6.8Hz, CH_3CH), and 0.54 (9H, s, $Si(CH_3)_3$).

4-N,N-Dimethylamino-7-N,N-dimethylaminomethylindole (153) - N,N-Dimethylmethyleneammonium iodide (126mg, 0.68mm) was added in one portion to a solution of 4-N,N-dimethylaminoindole (115) (100mg, 0.63mm) in dichloromethane (2ml) and the solution stirred for 10 minutes at room temperature[98]. Water (1ml) was then added, stirring continued for 2 minutes, the solution made alkaline with 10% sodium hydroxide, the organic phase washed with water (2 x 10ml) and brine (10ml) and the solvent removed at reduced pressure. The pale green residual oil (153) (130mg, 88%) showed no signs of impurity by ^1H n.m.r. and was used without further purification. (Found: M^+ 217.1582, $C_{13}H_{19}N_3$ requires 217.1579); m/e 216 (M^+-1), 201, 188, 187, 171, 159, 145, 130, and 117; δ ($CDCl_3$, 250MHz) 9.63 (1H, br s, indole NH), 6.93 (1H, m, 2-H), 6.72 (1H, d, J 7Hz, 6-H), 6.47 (1H, m, 3-H), 6.26 (1H, d, J 7Hz, 5-H), 3.57 (2H, s, $ArCH_2N$), 2.92 (6H, s, $ArN(CH_3)_2$), and 2.20 (6H, s, $CH_2N(CH_3)_2$).

N-Methyl-N-[4-(7-dimethylaminomethyl)indolyl]glycine Ethyl Ester (151) - N-Methyl-N-(4-indolyl)glycine ethyl ester (113) (232mg, 1mm) was treated with dimethylmethyleneammonium iodide (200mg, 1.1mm) under the same conditions described above. After work up the product (151) (260mg, 93%) was isolated as a green-brown oil that was used without further purification. (Found: M^+ 289.1784, $C_{16}H_{23}N_3O_2$ requires 289.1790); m/e 289 (M^+), 245 (M^+-$N(CH_3)_2$), 217 (M^+-$C_3H_4O_2$), 171, and 157; ν max. (thin film) 3390, 1740, 1600, 1520, 1500, 1455, 1370, 1190, 1020, 910, and 730cm^{-1}; δ ($CDCl_3$ 250MHz) 9.81 (1H, br s, indole NH), 7.10 (1H, m, 2-H), 6.83 (1H, d, J 7Hz, 6-H), 6.53 (1H, m, 3-H), 6.42 (1H, d, J 7Hz, 5-H), 4.21 (2H, q,

J 6.9Hz, OCH_2CH_3), 4.16 (2H, s, NCH_2CO), 3.66 (2H, s, $ArCH_2N$), 3.09 (3H, s, NCH_3), 2.23 (6H, s, $N(CH_3)_2$), and 1.26 (3H, t, J 6.9Hz, CH_2CH_3).

N-Methyl-N-{4-[5-(2-nitroethyl)]indolyl}glycine Ethyl Ester (157) and N-Methyl-N-{4-[7-(2-nitroethyl)]indolyl}-glycine Ethyl Ester (156) - N-Methyl-N-(4-indolyl)glycine ethyl ester (113) (120mg, 0.52mm) in benzene (1ml) at 5°C was treated with nitroethylene[94b] (1ml of 1M solution in benzene, 1mm) for 2 h and overnight at room temperature in the dark. Solvent was removed at reduced pressure and the dark residue chromatographed ($CHCl_3$ eluant) to give a product (80mg, 50%) homogeneous by t.l.c. (several solvent systems) but which revealed two regioisomers in a ratio of 4:1 by ^1H n.m.r. (Found: M^+ 305.1380, $C_{15}H_{19}N_3O_4$ requires 305.1375); m/e 305 (M^+), 259, and 232 ($M^+-C_2H_4NO_2$); ν max. (thin film) 3470, 3410, 1735, 1548, 1430, 1210, 1030, 910, 760, and 730cm^{-1}; δ ($CDCl_3$, 250MHz) major isomer (156) ; 8.58 (1H, br s, indole NH), 7.04-7.20 (2H, m, ArH), 6.90-7.00 (1H, m, ArH), 6.56 (1H, m, ArH), 4.80 (2H, t, J 7.8Hz, CH_2NO_2), 4.20 (2H, q, J 7Hz, OCH_2), 3.96 (2H, s, NCH_2CO), 3.51 (2H, t, J 7.8Hz, $ArCH_2CH_2$), 2.98 (3H, s, NCH_3), and 1.27 (3H, t, J 7Hz, CH_2CH_3); Minor isomer (157) (where different from above); δ 8.41 (1H, br s, indole NH), 6.82 (2H, m, ArH), 4.90 (2H, t, J 6.5Hz, CH_2NO_2) 3.85 (2H, s, NCH_2CO), and 2.85 (3H, s, NCH_3).

N-Methyl-N-{4-[5-(2-aminoethyl)]indolyl}glycine Ethyl Ester (159) and N-Methyl-N-{4-[7-(2-aminoethyl)]indolyl}-glycine Ethyl Ester (158) - The regiochemical mixture of (2-nitroethyl)indoles (156) and (157) (117mg, 0.38mm) and nickel (II) chloride (65mg, 0.5mm) were dissolved in hot ethanol (3ml). Sodium borohydride (30mg, 0.79mm) was added and the solution boiled for 20 minutes. An additional portion of sodium borohydride (10mg, 0.26mm) was then added, the solution boiled for a further 10 minutes, cooled, filtered and the solvent removed at reduced pressure. The residue was taken up in ether (20ml), extracted with water (3 x 15ml) and brine (10ml)

and solvent again removed to give the product (82mg, 78%) as a light brown oil, homogeneous by t.l.c. No further purification of the material was required. (Found: M^+ 275.1628, $C_{15}H_{21}N_3O_2$ requires 275.1634); m/e 275 (M^+), 246 ($M^+-C_2H_5$), 245 (M^+-CH_4N), and 173 ($M^+-CH_4N-C_3H_5O_2$); ν max. (thin film) 3400, 3360, 3210, and 1735cm^{-1}; δ ($CDCl_3$) major isomer 9.20 (1H, br s, indole NH), 6.70-7.20 (4H, m, ArH), 4.13 (2H, q, J 7Hz, OCH_2CH_3), 3.90 (2H, s, NCH_2CO), 2.95 (9H, m, $CH_2CH_2NH_2$, NCH_3), and 1.25 (3H, t, J 7Hz, CH_2CH_3).

3H-Pyrrolo-[2,3-j]-1,2,4,5,6-Pentahydro-1-Methyl-1,4-Benzo-[g]-diazocine-3-one (160) - The regiochemical mixture of amino esters (158) and (159) (60mg, 0.22mm) in xylene (10ml, 0.02M solution) was degassed with argon and warmed to reflux for 8 h. After cooling and removal of solvent at reduced pressure, the residue was chromatographed ($CHCl_3$ eluant) to give the tricyclic product (160) (6mg, 12%) as a pale brown oil. (Found: M^+ 229.1217, $C_{13}H_{15}N_3O$ requires 229.1215); m/e 229 (M^+) 171 ($M^+-C_2H_4NO$), 159 ($M^+-C_3H_4NO$), and 149; ν max. (thin film) 3480, 3410, 3300, and 1655; δ ($CDCl_3$, 250MHz) 8.19 (1H, br s, indole NH), 7.25 (1H, m, 2-H), 7.08, 6.88 (2H, ABq, J_{AB} 7.3HZ, 6-H and 7-H), 6.62 (1H, m, 3-H), 5.90 (1H, br s, CONH), 4.00 (2H, s, NCH_2CO), 3.80 (2H, m, NCH_2CH_2), 3.17 (2H, t, J 5Hz, CH_2CH_2Ar), and 3.13 (3H, s, NCH_3).

N-{4-[1-Methyl-3-(2-nitroethyl)]indolyl}valine Methyl Ester (165) - Indolyl valine methyl ester (127) (1.178g, 4.53mm) in benzene (2ml) was treated with nitroethylene (8ml, 1M solution in benzene, 8mm) in the dark, with cooling (ice). The solution was stirred overnight at room temperature, the solvent removed and the residue chromatographed ($CHCl_3$/petrol, 4:1 eluant) to give (i) N-{4-[1-Methyl-3-(2-nitroethyl)]indolyl} valine methyl ester (165) (770mg, 51%) as a pale yellow oil that solidified on cooling. m.p. 71.5-73.5°C; (Found: C, 61.12; H, 6.93; N, 12.49; $C_{17}H_{23}N_3O_4$ requires C, 61.25; H, 6.95; N, 12.60%); m/e 333 (M^+), 260, 217, and 201; ν max. (thin film) 3420,

1725, 1600, 1575, 1545, 1495, 1460, 1430, 1410, 1365, 1335, 1285, 1255, 1200, 1155, 1090, 900, and 730cm^{-1}; δ ($CDCl_3$, 250MHz) 7.06 (1H, t, J 7.5Hz, 6-H), 6.74 (2H, s + d, J 7.5Hz, 2-H and 7-H), 6.23 (1H, d, J 7.5Hz, 5-H), 4.70 (3H, t and br s, J 7.5Hz, NH and CH_2NO_2), 3.99 (1H, m, NCHCO), 3.70 (3H, s, OCH_3), 3.63 (3H, s, NCH_3), 3.60 (2H, t, J 7.5Hz, $ArCH_2CH_2$), 2.21 (1H, m, $(CH_3)_2CH$), 1.13 (3H, d, J 6.5Hz, CH_3CH), and 1.02 (3H, d, J 6.5Hz, CH_3CH).

(ii) N-{4-[1-Methyl-3-(2,4-dinitrobutyl)}indolyl]valine methyl ester - m/e 406 (M^+), 333 ($M^+-C_2H_3NO_2$), 217 ($M^+-C_3H_7$ - $C_4H_6N_2O_4$), and 201; ν max. (thin film) 3420, 1728, 1603, 1575, 1545, 1495, 1460, 1430, 1410, 1365, 1285, 1255, 1200, 1155, 900, and 730cm^{-1}; δ ($CDCl_3$) 6.93 (1H, d, J 8Hz, 7-H), 6.67 (2H, m, 2-H and 6-H), 6.16 (1H, d, J 8Hz, 5-H), 5.15 (1H, m, CH_2CHNO_2), 4.37 (2H, t, J 8Hz, CH_2NO_2), 4.0 (2H, m, NH, NCHCO), 3.67 (3H, s, OCH_3), 3.60 (3H, s, NCH_3), 3.50 (2H, t, J 8Hz, $ArCH_2$), 2.60 (3H, m, $CH(CH_2)NO_2$ and $(CH_3)_2CH$), and 1.07 (6H, m, $(CH_3)_2CH$).

N-Methyl-N-{4-(1-geranyl)[3-(2-nitroethyl)]indolyl}-glycine Ethyl Ester (164) - N-Methyl-N-[4-(1-geranyl)-indolyl]glycine ethyl ester (133) (1.803g, 4.9mm) in dichloromethane (6ml) at 0°C was treated in the dark with nitroethylene (4ml, 2M solution in dichloromethane, 8mm) over 5 minutes. The solution was stirred overnight in the dark, solvent removed at reduced pressure and the residue chromatographed ($CHCl_3$/petrol, 3:7 eluant) to give compound (164) (1.51g, 68%) as a pale yellow oil. (Found: C, 67.99; H, 8.07; N, 9.42; $C_{25}H_{35}N_3O_4$ requires C, 68.06; H, 7.99; N, 9.52%); m/e 441 (M^+), 395 ($M^+-C_2H_6O$), 368, 322, 259, and 185; ν max. (thin film) 1745, 1550, 1495, 1440, 1375, 1310, 1195, 910, and 730cm^{-1}; δ ($CDCl_3$, 250MHz) 7.04-7.14 (2H, m, 6-H and 7-H), 6.92 (1H, s, 2-H), 6.84 (1H, dd, J 1.2, 7.1Hz, 5-H), 5.34 (1H, t, J 6.9Hz, =CH), 5.06 (1H, m, =CH), 4.89 (2H, t, J 7.1Hz, CH_2NO_2), 4.61 (2H, d, J 6.9Hz, NCH_2), 3.52 (2H, t, J 7.1Hz, OCH_2CH_3), 3.84 (2H, s, NCH_2CO), 3.52 (2H, t, J 7.1Hz, $ArCH_2CH_2$), 2.88 (3H, s, NCH_3), 2.08 (4H, m, allylic CH_2),

1.79 (3H, s, allylic CH_3), 1.67 (3H, s, allylic CH_3), 1.60 (3H, s, allylic CH_3), and 1.24 (3H, t, J 7.3, CH_2CH_3).

Reaction of N-Methyl-N-[4-(1-trimethylsilyl)indolyl]-valine Methyl Ester (142) with Nitroethylene - To a solution of the silyl indole (142) (181mg, 0.55mm) in dichloromethane (0.5ml) cooled to 0°C (ice bath), a solution of nitroethylene in dichloromethane (1ml, 1M solution, 1mm) was added. The reaction mixture was stood in the dark at 5°C for 24 h and for a further 4 h at room temperature. The solvent was removed at reduced pressure and the dark oily residue submitted to column chromatography ($CHCl_3$/petrol, 4:1 eluant). **(i) N-Methyl-N-{4-[1-trimethylsilyl-3-(2-nitroethyl)]indolyl}valine methyl ester (163)** (10mg, 4.5%) was isolated as a colourless oil. (Found: M^+ 405.2089, $C_{20}H_{31}N_3O_4Si$ requires 405.2084); m/e 405 (M^+), 363 ($M^+-C_3H_6$), and 347; ν max. (thin film) 1730, 1560, 1470, 1430, 1380, 1265, and 1055cm^{-1}; δ ($CDCl_3$, 250MHz) 7.22 (1H, dd, J 0.8, 8.1Hz, 7-H), 7.17 (1H, t, J 8.1Hz, 6-H), 6.94 (1H, s, 2-H), 6.92 (1H, dd, J 0.8, 8.1Hz, 5-H), 4.94 (1H, m, $CHNO_2$), 4.73 (1H, dt, J 7.5, 12.9Hz, $CHNO_2$), 3.53-3.77 (3H, m, $ArCH_2$, $NCHCO$), 3.52 (3H, s, OCH_3), 2.81 (3H, s, NCH_3), 2.32 (1H, septet, $(CH_3)_2CH$), 1.08 (3H, d, J 6.2Hz, CH_3CH), 0.97 (3H, d, J 6.2Hz, CH_3CH), and 0.52 (9H, s, $Si(CH_3)_3$). **(ii) N-Methyl-N-{4-[3-(2-nitroethyl)]indolyl}valine methyl ester (162)** (91mg, 49%) as a pale yellow oil. (Found: M^+ 333.1687, $C_{17}H_{23}N_3O_4$ requires 333.1688); m/e 333 (M^+), 290 ($M^+-C_3H_7$), and 274 (M^+-CHNO_2); ν max. 3430, 1735, 1620, 1565, 1430, 1390, 1370, 1180, 1130, 1090, and 1045cm^{-1}; δ ($CDCl_3$, 250MHz) 8.06 (1H, br s, indole NH), 7.04-7.12 (2H, m, 6-H and 7-H), 7.00 (1H, d, J 2.9Hz, 2-H), 6.89 (1H, dd, J 6.8, 1.8Hz, 5-H), 4.91 (1H, m, $CHNO_2$), 4.78 (1H, dt, J 7.35, 12.9Hz, $CHNO_2$), 3.52-3.78 (3H, m, $ArCH_2$ and $NCHCO$), 3.50 (3H, s, OCH_3), 2.82 (3H, s, NCH_3), 2.35 (1H, m, $(CH_3)_2CH$), 1.09 (3H, d, J 6.7Hz, CH_3CH), and 0.97 (3H, d, J 6.7Hz, CH_3CH).

N-Methyl-N-[4-(1-benzyl-3-acetyl)indolyl]glycine Ethyl Ester (171) - N-Methyl-N-[4-(1-benzyl)indolyl]glycine ethyl ester (114) (110mg, 0.33mm) in dichloromethane (3ml) at -78°C (acetone/cardice) under argon was treated with acetyl chloride (55mg, 1mm) followed by stannic chloride (260mg, 1mm)[95]. After stirring at -78°C for 2 h the reaction temperature was raised to 0°C for 1h, quenched with water, diluted with dichloromethane and extracted with water (3 x 20ml) and brine (10ml). Removal of solvent and chromatography ($CHCl_3$ eluant) gave the product (171) (99mg, 83%) as a light yellow oil. (Found: M^+ 364.1787, $C_{22}H_{24}N_2O_3$ requires 364.1787); m/e 364 (M^+), 324, 291 ($M^+-C_3H_5O_2$), 278, 249, 230, and 223; ν max. (thin film) 1740, 1650, 1570, 1530, 1500, 1445, 1390, 1370, 1220, 1120, 1030, and 760cm^{-1}; δ ($CDCl_3$, 250MHz) 7.65 (1H, s, 2-H), 7.30 (3H, m, ArH), 7.15 (3H, m, 6-H and ArH), 6.95 (1H, d, J 7.9Hz, 7-H), 6.91 (1H, d, J 7.9Hz, 5-H), 5.27 (2H, s, NCH_2Ar), 4.09 (2H, q, J 6.7Hz, OCH_2CH_3), 3.96 (2H, s, NCH_2CO), 3.04 (3H, s, NCH_3), 2.68 (3H, s, CH_3CO), and 1.20 (3H, t, J 6.7Hz, OCH_2CH_3).

N-Methyl-N-[4-(7-bromo)indolyl]glycine Ethyl Ester (175) - To a solution of N-methyl-N-(4-indolyl)glycine ethyl ester (113) (116mg, 0.5mm) in D.M.F., N-bromo-succinimide (90mg, 0.51mm) was added at room temperature in one portion[103]. The solution immediately turned an intense deep blue. Stirring was continued for 24 h, the solution diluted with chloroform, extracted with water (5 x 15ml) and brine (10ml), solvent removed at reduced pressure and the residue chromatographed (CDCl3/petrol 3:1 eluant). The product (175) (63mg, 41%) was isolated as an unstable oil containing an intensely coloured blue impurity. (Found: M^+ 310.0314, $C_{13}H_{15}N_2Br^{79}O_2$ requires 310.0317); m/e 310, 312 (M^+), 253, 251, 239, and 237; ν max. (thin film) 3200 and 1745; δ ($CDCl_3$) 8.30 (1H, br s, indole NH), 7.11, 6.32 (2H, ABq, J_{AB} 9Hz, 5-H, 6-H), 7.02 (1H, m, 2-H), 6.53 (1H, m, 3-H), 4.14 (2H, q, J 7.5Hz, OCH_2CH_3), 4.10 (2H, s, NCH_2CO), 3.06 (3H, s, NCH_3), and

1.24 (3H, t, J 7.5Hz, CH_2CH_3).

N-Methyl-N-{4-[1-trimethylsilyl-3-(2-nitroethyl)]-indolyl}glycine Ethyl Ester (176) and N-Methyl-N-{4-[3-(2-nitroethyl)]indolyl}glycine Ethyl Ester (155) - To a stirred solution of N-Methyl-N-[4-(1-trimethylsilyl)-indolyl]glycine ethyl ester (141) (3.04g, 10mm) and nitroethylene (1.095g, 15mm) at -78°C (acetone/cardice), in dichloromethane (15ml), a solution of stannic chloride (2.86g, 11mm) in dichloromethane (11ml) was added over 10 minutes. The dark green solution was stirred at -78°C for 6 h, quenched with water and allowed to warm to room temperature. Stirring was continued for a further 2 h until all the precipitated, oily solid had dissolved. The organic phase was washed with water (3 x 50ml) and brine (50ml), the solvent removed at reduced pressure and the residue chromatographed ($CHCl_3$/petrol, 4:1 eluant) to give (i) N-Methyl-N-{4-[1-trimethylsilyl-3-(2-nitroethyl)]-indolyl}glycine Ethyl Ester (176) (1.61g, 43%) as a colourless oil. (Found: C, 56.90; H, 7.23; N, 11.01 $C_{18}H_{27}N_3O_4Si$ requires C, 57.27; H, 7.21; N, 11.13%); m/e 377 (M^+), 345, 343, 331, and 304 ($M^+-Si(CH_3)_3$); ν max. (thin film) 1732 and 1540cm^{-1}; δ ($CDCl_3$, 250MHz), 7.22 (1H, d, J 7.9Hz, 7-H), 7.10 (1H, dd, J 7.9, 8.3Hz, 6-H), 6.94 (1H, br s, 2-H), 6.87 (1H, d, J 8.3Hz, 5-H), 4.99 (2H, t, J 6.5Hz, CH_2NO_2), 4.16 (2H, q, J 7Hz, OCH_2CH_3), 3.82 (2H, s, NCH_2CO), 3.53 (2H, t, J 6.5Hz, $ArCH_2CH_2$), 2.85 (3H, s, NCH_3), 1.22 (3H, t, J 7Hz, CH_2CH_3), and 0.50 (9H, s, $Si(CH_3)_3$), and (ii) N-Methyl-N-{4-[3-(2-nitroethyl)]indolyl}glycine ethyl ester (155) (600mg, 20%) as a pale yellow oil. (Found: C, 58.87; H, 6.13; N, 13.57 $C_{15}H_{19}N_3O_4$ requires C, 59.01; H, 6.27; N, 13.76%); m/e 305 (M^+), 259 (M^+-NO_2), 246, 232 ($M^+-C_2H_3NO_2$), and 186; ν max. (thin film) 3480, 1740, and 1548cm^{-1}; δ ($CDCl_3$, 250MHz) 8.18 (1H, br s, indole NH), 7.10 (2H, m, ArH), 6.95 (1H, m, ArH), 6.83 (1H, m, ArH), 4.90 (2H, t, J 6.5Hz, CH_2NO_2), 4.17 (2H, q, J 7Hz, OCH_2CH_3), 3.84 (2H, s, NCH_2CO), 3.53 (2H, t, J 6.5Hz,

$ArCH_2CH_2$), 2.87 (3H, s, NCH_3), and 1.23 (3H, t, J 7Hz, CH_2CH_3).

Desilylation of N-Methyl-N-{4-[1-trimethylsilyl-3-(2-nitroethyl)]indolyl}glycine Ethyl Ester (155) - The 1-silyl indole (176) (40mg, 0.12mm) in dichloromethane (0.5ml) at 5°C (ice) was treated with tetrabutylammonium fluoride (0.13ml 1M solution in dichloromethane, 0.13mm) for 10 minutes. The solution was diluted with dichloromethane, extracted with ammonium chloride solution (2 x 10ml), water (2 x 10ml) and brine (10ml) and the solvent removed at reduced pressure to give the essentially pure product (155) (32mg, 88%) identical (^1H n.m.r., i.r. and t.l.c.) to the above product.

The procedure generally adopted was to treat the crude reaction mixture containing N-methyl-N-{4-[1-trimethylsilyl-3-(2-nitroethyl)]indolyl}glycine ethyl ester (176) and N-methyl-N-{4-[3-(2-nitroethyl)]indolyl}glycine ethyl ester (155) with one equivalent of tetrabutylammonium fluoride as described above giving a simple final chromatographic stage. Yields of up to 61% were obtained for nitroethylation followed by deprotection according to this protocol.

N-Methyl-N-{4-[1-trimethylsilyl-7-(2-nitroethyl)]-indolyl}glycine Ethyl Ester (177) - To a solution of N-methyl-N-[4-(1-trimethylsilyl)indolyl]glycine ethyl ester (141) (97mg, 0.22mm) and nitroethylene (22mg, 0.3mm) in dichloromethane (2ml) at -20°C (CCl_4/cardice), zinc iodide (68mg, 0.23mm) was added and the solution stirred for 150 minutes. After warming to room temperature and stirring for an additional 1 h the deep purple solution was quenched with water, diluted with dichloromethane and extracted with water (4 x 10ml) and brine (10ml). Evaporation of the solvent and chromatography gave the product (177) as a yellow-brown oil (32mg, 27%). m/e 377 (M^+), 343, 318, and 304 (M^+-$Si(CH_3)_3$); δ ($CDCl_3$, 250MHz), 7.27 (1H, dd, J 1.1, 7.6Hz, 6-H), 7.15 (1H, d, J 3.1Hz, 2-H), 6.98 (1H, d, J 7.6Hz, 2-H), 6.62 (1H, dd, J

3.1, 1Hz, 3-H), 4.80 (2H, t, J 6Hz, CH_2NO_2), 4.20 (2H, q, J 7Hz, OCH_2CH_3), 3.95 (2H, s, NCH_2CO), 3.52 (2H, t, J 6Hz, $ArCH_2CH_2$), 2.96 (3H, s, NCH_3), 1.28 (3H, t, J 7Hz, CH_2CH_3), 0.50 (9H, s, $Si(CH_3)_3$).

General Procedure for the Preparation of N-Methyl-N-[4-(3-acyl)indolyl]glycine Ethyl Esters - N-Methyl-N-[4-(1-trimethylsilyl)indolyl]glycine ethyl ester (141) (1M) in dichloromethane (3ml/mm) at -78°C (acetone/cardice) was treated sequentially with the appropriate acid chloride (or anhydride) (2M) and stannic chloride (3M) in dichloromethane (1ml/mm). The solution was stirred for 3 h at -78°C and 1 h at 0°C and quenched with water and sodium bicarbonate. Stirring was continued until the precipitated oily material dissolved, the solution diluted with dichloromethane and extracted with sodium bicarbonate, water and brine. Removal of solvent and chromatography (chloroform/petrol eluant) of the residue gave the desired product.

N-Methyl-N-[4-(3-acetyl)indolyl]glycine Ethyl Ester (180) - The silyl indole (141) (100mg, 0.33mm) was treated with acetyl chloride and stannic chloride according to the general procedure. The compound (180) (80mg, 88%) was isolated as a pale yellow brown oil. (Found: C, 55.72; H, 5.68; N, 8.45; $C_{15}H_{18}N_2O_3.0.5CHCl_3$ requires C, 55.74; H, 5.58; N, 8.39%; Found: M^+ 274.1321, $C_{15}H_{18}N_2O_3$ requires 274.1317); m/e 274(M^+) and 201($M^+-C_3H_5O_2$); ν max. (thin film) 3215, 1740, and 1640; δ ($CDCl_3$, 250MHz) 10.25 (1H, v br s, indole NH), 7.49 (1H, br s, 2-H), 7.09 (1H, dd, J 6.7, 7.1Hz, 6-H), 6.93 (1H, d, J 6.7Hz, 7-H), 6.79 (1H, d, J 7.1Hz, 5-H), 4.11 (2H, q, J 7Hz, OCH_2CH_3), 3.90 (2H, s, NCH_2CO), 2.95 (3H, s, NCH_3), 2.50 (3H, s, CH_3CO), and 1.20 (3H, t, J 7Hz, CH_2CH_3).

Acetic anhydride in lieu of acetyl chloride gave a product with identical ^1H n.m.r., i.r. and t.l.c. properties to those described above in a 78% yield.

N-Methyl-N-[4-(3-isobutyryl)indolyl]glycine Ethyl Ester (181) - The silyl indole (141) (108mg, 0.35mm) was

treated with isobutyryl chloride and stannic chloride according to the general procedure. The product (181) (39mg, 40%) was isolated as a pale brown oil. (Found: M^+ 302.1632, $C_{17}H_{22}N_3O_2$ requires 302.1630); m/e 302(M^+), 259($M^+-C_3H_7$), and 229 ($M^+-C_3H_5O_2$); ν max. (thin film) 3230, 1740, and 1645cm^{-1}; δ ($CDCl_3$) 7.29 (1H, s, 2-H), 6.64-7.03 (3H, m, ArH), 4.03 (2H, q, J 7.5Hz, OCH_2CH_3), 3.80 (2H, s, NCH_2CO), 3.32 (1H, m, $CH(CH_3)_2$), 2.91 (3H, s, NCH_3), and 1.16 (9H, t and d, J 7.5Hz, 7.5Hz, CH_2CH_3, $CH(CH_3)_2$).

N-Methyl-N-[4-(1,3-dibenzoyl)indolyl]glycine Ethyl Ester (183) and N-Methyl-N-[4-(3-benzoyl)indolyl]glycine Ethyl Ester (182) - The silyl indole (141) (115mg, 0.38mm) was treated with benzoyl chloride and stannic chloride according to the general procedure. Chromatography ($CHCl_3$/petrol 9:1) of the residue gave **(i) N-Methyl-N-[4-(1,3-dibenzoyl)indolyl]glycine ethyl ester (183)** (75mg, 45%) as a pale yellow oil (Found: M^+ 440.1733, $C_{27}H_{24}N_2O_4$ requires 440.1736); m/e 440(M^+), 381, 367($M^+-C_3H_5O_2$), and 245; ν max. (thin film) 1740, 1698, and 1655cm^{-1}; δ ($CDCl_3$) 6.95-8.20 (14H, m, ArH), 3.95 (2H, q, J 7.5Hz, CH_2CH_3), 3.50 (2H, s, NCH_2CO), 2.55 (3H, s, NCH_3), and 1.13 (3H, t, J 7.5Hz, OCH_2CH_3). **(ii) N-Methyl-N-[4-(3-benzoyl)indolyl]glycine ethyl ester (182)** (44mg, 34%) as a yellow oil. (Found: M^+ 336.1474, $C_{20}H_{20}N_2O_3$ requires 336.1475); m/e 336(M^+), 263($M^+-C_3H_5O_2$), and 246; ν max. (thin film) 3240, 1740, and 1625cm^{-1}; δ ($CDCl_3$) 10.10 (1H, br s, indole NH), 6.74-7.86 (9H, m, ArH), 3.96 (2H, q, J 7.5Hz, CH_2CH_3), 3.66 (2H, s, NCH_2CO), 2.80 (3H, s, NCH_3), and 1.10 (3H, t, J 7.5Hz, CH_2CH_3).

N-Methyl-N-[4-(7-acetyl)indolyl]glycine Ethyl Ester (184) - The silyl indole (141) (115mg, 0.38mm) and zinc (II) iodide (230mg, 1mm) in dichloromethane at -20°C (CCl_4/cardice) were treated with acetyl chloride (44mg, 0.57mm) for 3 h and for a further 1 h at 0°C. The dark solution was quenched with water and worked up as described in the general procedure. The residue was

chromatographed ($CHCl_3$ eluant) to give **(i) N-Methyl-N-[4-(7-acetyl)indolyl]glycine ethyl ester (184)** (16mg, 15%) as a colourless oil. (Found: M^+ 274.1317, $C_{15}H_{18}N_2O_3$ requires 274.1318); m/e 274(M^+), 201($M^+-C_3H_5O_2$), and 159($M^+-C_3H_5O_2-C_2H_2O$); ν max. (thin film) 3480, 3350, 1740, and 1660cm^{-1}; δ ($CDCl_3$, 250MHz) 8.52, (1H, br s, indole NH), 7.38, 7.10 (2H, ABq, J_{AB} 7.4Hz, 6-H, 5-H), 7.19 (1H, m, 2-H), 6.76 (1H, m, 3-H), 4.16 (2H, q, J 7Hz, OCH_2CH_3), 4.04 (2H, s, NCH_2CO), 3.13 (3H, s, NCH_3), 2.72 (3H, s, CH_3CO), and 1.25 (3H, t, J 7Hz, CH_2CH_3), and **(ii) N-Methyl-N-[4-(3-acetyl)indolyl]glycine ethyl ester (180)** (50mg, 48%) identical by t.l.c. and ^1H n.m.r. with the compound previously described.

N-Methyl-N-{4-[3-(2-nitro-3-hydroxypropyl)]indolyl}-glycine Ethyl Ester (189) - **(i) Potassium carbonate and formalin method:** N-Methyl-N-{4-[3-(2-nitroethyl)]indolyl}-glycine ethyl ester (155) (336mg, 1.1mm) and potassium carbonate (75mg, 0.55mm) in ethanol/water (4ml/2:1) at 0°C were treated with formalin (0.09ml, 1.1mm) for 2 h. The solvent was removed at reduced pressure, the oily residue taken up in chloroform and extracted with water (3 x 20ml) and brine (20ml). Removal of the solvent at reduced pressure and chromatography ($CHCl_3$ eluant) of the residue (402mg) gave (i) **N-Methyl-N-{4-[3-(2-nitro-3-hydroxypropyl)]indolyl}glycine ethyl ester (189)** (68mg, 19%) as a pale yellow oil. (Found: C, 53.38; H, 5.94; N, 11.43 $C_{16}H_{21}N_3O_5.0.25\ CHCl_3$ requires C, 53.44; H, 5.87; N, 11.51%); m/e 335 (M^+) and 305 (M^+-CH_2O); ν max. (thin film) 3410, 1730, and 1560cm^{-1}; δ ($CDCl_3$) 8.30 (1H, br s, indole NH), 6.40-7.05 (4H, m, ArH), 5.32 (1H, m, $CHNO_2$), 4.14 (2H, q, J 7.5Hz, OCH_2CH_3), 3.70-4.00 (5H, m, NCH_2CO, CH_2OH), 3.39 (2H, d, J 8Hz, CH_2Ar), 2.76 (3H, s, NCH_3), and 1.23 (3H, t, J 7.5Hz, CH_2CH_3) and (ii) **N-Methyl-N-{4-[3-(2-nitro-2-hydroxymethyl-3-hydroxypropyl)]indolyl}-glycine ethyl ester (190)**, (160mg, 40%) as an oil. (Found: M^+ 365.1582, $C_{17}H_{23}N_3O_6$ requires 365.1587); m/e 365 (M^+), 335 (M^+-CH_2O), 318, and 306; ν max. (thin film)

3400, 3280, 1735, and 1540cm^{-1}; δ ($CDCl_3$) 8.82 (1H, br s, indole NH), 6.80-7.16 (4H, m, ArH), 3.53-4.40 (12H, m, OCH_2CH_3, CH_2OH x 2, NCH_2CO, $ArCH_2$), 2.86 (3H, s, NCH_3), and 1.27 (3H, t, J 7.5Hz, CH_2CH_3).

(ii) Sodium methoxide and paraformaldehyde method:- A suspension of paraformaldehyde (118mg, 3.94mm) in D.M.F. (8ml) containing N-methyl-N-{4-[3-(2-nitroethyl)]indolyl}-glycine ethyl ester (155) (1.1973g, 3.94mm) and sodium methoxide (15mg) was warmed to 70°C under argon until a clear solution was formed (about 10 minutes). The cooled solution was diluted with ethyl acetate (150ml), extracted with water (5 x 100ml) and brine (50ml). Removal of the solvent at reduced pressure and chromatography ($CHCl_3$ eluant) gave N-methyl-N-{4-[3-(2-nitro-3-hydroxypropyl)]-indolyl}glycine ethyl ester (189) (903mg, 68%) identical by t.l.c., ^1H n.m.r. and i.r. with the material described above. N-Methyl-N-{4-{3-(2-nitro-2-hydroxymethyl-3-hydroxypropyl)]indolyl}glycine ethyl ester (190) (235mg, 16%) was also isolated.

An additional quantity of the monohydroxymethylated product (189) was obtained by treating the bishydroxy-methylated material (190) (235mg, 0.65mm) with sodium methoxide (10mg) in D.M.F. at 70°C for 10 minutes. Work up as described above followed by chromatography ($CHCl_3$ eluant) gave the monohydroxymethylated product (189) (91mg, 42% or 75% overall from (155)) and bishydroxy-methylated product (190) (116mg, 50%).

N-Methyl-N-{4-[3-(2-nitro-3-hydroxypropyl)]indolyl}-valine Methyl Ester (191a,b) - N-Methyl-N-{4-[3-(2-nitro-ethyl)]indolyl}valine methyl ester (162) (34.7mg, 0.10mm) was treated with paraformaldehyde (3.1mg, 0.10mm) and sodium methoxide (catalytic portion) according to the above procedure. Chromatography ($CHCl_3$ eluant) of the residue after work up gave the product (191a,b) (20mg, 55%) as an oil. Treatment of the residual material with a further catalytic quantity of sodium methoxide resulted in a further yeild of (191a,b) (total yield 25mg, 70%). It

was not found possible to separate the diastereomeric mixture by chromatography. (Found: M^+ 363.1789, $C_{18}H_{25}N_3O_5$ requires 363.1794); m/e 363 (M^+), 334 (M^+-CHO), and 274 (M^+-$C_2H_3NO_3$); ν max. (thin film) 3420-3500, 1735, 1560, 1185, 1095, and 1045cm^{-1}; δ ($CDCl_3$, 250MHz, diastereomeric mixture), 8.10 (1H, br s, indole NH), 6.84-7.17 (4H, m, ArH), 4.55 and 4.11 (1H, m, NO_2CH), 3.72-4.09 (5H, m, $CH_2CH(NO_2)CH_2OH$, NCHCO), 3.58 and 3.50 (3H, s, OCH_3), 2.83 and 2.80 (3H, s, NCH_3), 2.35 (1H, m, $(CH_3)_2CH$), 1.15 (3H, D, J 7.5HZ, CH_3CH), 1.07 (3H, d, J 7.5Hz, CH_3CH), and 0.94 (3H, m, $(CH_3)_2CH$).

N-{4-[1-Methyl-3-(2-nitro-3-hydroxypropyl)]indolyl}-valine Methyl Ester (192a,b) - N-{4-[1-methyl-3-(2-nitroethyl)]indolyl}valine methyl ester (165) (770mg, 2.3mm) and paraformaldehyde (70mg, 2.3mm) in D.M.F. (4ml) containing sodium methoxide (10mg) were warmed at 70°C for 10 minutes, cooled and worked up as described above. Chromatography ($CHCl_3$ eluant) gave the product (192a,b,) as two enantiomeric mixtures. (Found: C, 51.29; H, 6.03; N, 9.43; $C_{18}H_{25}N_3O_5$ 0.6 $CHCl_3$ requires C, 51.39; H, 5.93; N, 9.66; Found: M^+ 363.1803, $C_{18}H_{25}N_3O_5$ requires 363.1794); m/e 363 (M^+), 334 (M^+-CHO), and 274 (M^+-$C_2H_3NO_3$); ν max. (thin film) 3590, 1725, 1600, 1575, 1540, 1495, 1450, 1430, 1410, 1380, 1360, 1290, 1255, 1205, 1155, 1045, 900, and 720cm^{-1}. Careful chromatography ($CHCl_3$/petrol 72:28 then $CHCl_3$/petrol 74:26 eluant) gave the two pure enantiomeric mixtures referred to as 'more polar' (192b) and 'less polar' (192a) from their t.l.c. behaviour. (i) Less polar (192a) δ ($CDCl_3$, 250MHz) 7.05 (1H, dd, J 7.6, 8Hz, 6-H), 6.73 (2H, s + d, J 8Hz, 2-H and 7-H), 6.23 (1H, d, J 7.6Hz, 5-H), 4.94 (1H, m, $CHNO_2$), 3.95-4.06 (4H, m, ArNH, CH_2OH and NCHCO), 3.73 (3H, s, OCH_3), 3.65 (3H, s, NCH_3), 3.58 (2H, d, J 7Hz, $ArCH_2$), 3.24 (1H, br s, OH), 2.20 (1H, septet, J 6.7Hz, $(CH_3)_2CH$), 1.11 (3H, d, J 6.7Hz, CH_3CH), and 1.03 (3H, d, J 6.7Hz, CH_3CH). (ii) More polar (192b) δ ($CDCl_3$, 250MHz) 7.05 (1H, dd, J 7.5, 8.8Hz, 6-H), 6.74 (1H, d, J 8.8Hz,

7-H), 6.72 (1H, s, 2-H), 6.24 (1H, d, J 7.5Hz, 5-H), 5.05 (1H, m, $CHNO_2$), 4.87 (1H, br s, ArNH), 3.96-4:04 (3H, m, CH_2O, NCHCO), 3.72 (3H, s, OCH_3), 3.64 (3H, s, NCH_3), 3.62 (1H, dd, J 6.25, 15.5Hz, ArCH), 3.50 (1H, dd, J 7.5, 15.5Hz, ArCH), 3.08 (1H, br s, OH), 2.22 (1H, m, $(CH_3)_2CH$), 1.12 (3H, d, J 6.8Hz, CH_3CH), and 1.05 (3H, d, J 6.8Hz, CH_3CH).

N-Methyl-N-{4-[3-(2-nitro-3-(2-tetrahydropyranyl-oxy)propyl)]indolyl}glycine Ethyl Ester (196) - A solution of N-Methyl-N-{4-[3-(2-nitro-3-hydroxypropyl)]indolyl}-glycine ethyl ester (189) (994mg, 3.0mm), dihydropyran (500mg, 6mm) and pyridinium tosylate (262mg, 1.05mm) in dichloromethane[100] (20ml) was stirred overnight at room temperature. After extraction with water (3 x 50ml) and brine (50ml) and removal of solvent at reduced pressure the residue was chromatographed ($CHCl_3$/petrol 4:1 eluant) to give compound (196) (1.07g, 86%) as an oil. (Found: C, 57.37; H, 6.92; N, 9.25; $C_{21}H_{29}N_3O_6$ 0.2$CHCl_3$ requires C, 57.43; H, 6.64; N, 9.48%; Found: M^+ 419.2060, $C_{21}H_{29}N_3O_6$ requires 419.2056); m/e 419 (M^+), 346 ($M^+-C_3H_5O_2$), 271, and 199: ν max. (thin film) 3410, 1740, 1548, 910, and 730cm^{-1}; δ ($CDCl_3$) 8.36 (1H, br s, indole NH), 6.69-7.05 (4H, m, ArH), 5.36 (1H, m, $CHNO_2$), 4.57 (1H, m, OCHO), 4.10 (2H, q, J 7Hz, OCH_2CH_3), 3.36-4.00 (4H, m, (OCH_2 x 2), 3.77 (2H, s, NCH_2CO), 3.36 (2H, d, J 7Hz, $ArCH_2$), 2.82 (3H, s, NCH_3), 1.35-1.80 (6H, m, $CH_2CH_2CH_2$), and 1.19 (3H, t, J 7Hz, CH_2CH_3).

N-[4-[1-Methyl-3-(2-nitro-3-(2-tetrahydropyranyl-oxy)propyl)]indolyl}valine Methyl Ester (198a,b) - N-{4-[1-Methyl-3-(2-nitro-3-hydroxypropyl)]indolyl}valine methyl ester (192a,b) (diastereomeric mixture, 190mg, 0.52mm) was treated in the same manner as described above with dihydropyran (84mg, 1mm) and pyridinium tosylate (59mg, 0.25mm). Chromatography ($CHCl_3$/petrol 9:1 eluant) gave the product (198a,b) (200mg, 86%) as a yellow oil. (Found: M^+ 447.2380, $C_{23}H_{33}N_3O_6$ requires 447.2369); m/e 447 (M^+), 363, 345, 320, 304, 274, 229, and 213; ν max

(thin film) 3440, 1735, 1610, 1580, 1550, 1504, 1465, 1440, 1420, 1370, 1345, 1290, 1260, 1200, 1165, 1130, 1070, 1030, 965, 910, and 740cm^{-1}; δ ($CDCl_3$) 6.54-6.93 (3H, m, ArH), 6.15 (1H, d, J 7.5Hz, 5-H), 5.15 (1H, m, $CHNO_2$), 4.53 (1H, m, OCHO), 3.26-4.20 (7H, m, $ArCH_2CH(NO_2)CH_2O$, NCHCO, OCH_2CH_2), 3.69 (3H, s, OCH_3), 3.59 (3H, s, NCH_3) 2.16 (1H, septet, J 6.5Hz, $(CH_3)_2CH$), 1.36-1.76 (6H, br m, $CH_2CH_2CH_2$), 1.05 (3H, d, CH_3CH), and 0.98 (3H, d, CH_3CH).

The less polar enantiomeric mixture (192a) (122mg, 0.33mm) was treated in the same way with dihydropyran (44mg, 0.5mm) and pyridinium tosylate (20mg, 0.1mm) to give the product (198a) (143mg, 97%) identical by t.l.c. and ^{1}H n.m.r. with the above product.

Reduction of 3-(2-Nitroethyl)indoles to 3-(2-Amino)-indoles - General Procedure - A solution of the appropriate 3-(2-nitroethyl)indole (1M) and cobalt (II) chloride hexahydrate (2M) in methanol (4ml/mm) or T.H.F./methanol 1:1 (4ml/mm) was cooled to 0°C and treated over 5 minutes with sodium borohydride (10M)[112]. The black solution was stirred for 30 minutes at 0°C and 30 minutes at room temperature and worked up. If there was no 2-tetrahydropyranyloxy ether present in the molecule, the black suspended material was dissolved by the addition of 6N HCl, neutralised with excess ammonium hydroxide, the solution extracted with ethyl acetate (3 times) and the combined organic phases washed with water and evaporated at reduced pressure. If the molecule contained a 2-tetrahydropyranyloxy ether moiety, the reaction mixture was diluted with ethyl acetate, extracted with brine (twice), water (4 times) and brine and the solvent removed at reduced pressure. In either case the product could be purified by chromatography ($Et_2NH/EtOH/CHCl_3$) although purification was not generally necessary.

N-Methyl-N-{4-[3-(2-aminoethyl)]indolyl}glycine Ethyl Ester (202) - N-Methyl-N-{4-[3-(2-nitroethyl)]indolyl}-glycine ethyl ester (155) (248mg, 0.82mm) was reduced

according to the general procedure with cobalt (II) chloride hexahydrate (387mg, 1.64mm) and sodium borohydride (312mg, 8.2mm) to give the product (202) (185mg, 82%) homogeneous by t.l.c. (Found: M^+ 275.1638, $C_{15}H_{21}N_3O_2$ requires 275.1634); m/e 275 (M^+), 246, and 173; ν max, (thin film) 3480, 3370, and 1745cm^{-1}; δ ($CDCl_3$) 9.05 (1H, br s, indole NH), 6.65-7.05 (4H, m, ArH), 4.06 (2H, q, J 7.5Hz, OCH_2CH_3), 3.74 (2H, s, NCH_2CO), 2.96 (6H, m, $ArCH_2CH_2NH_2$), 2.80 (3H, s, NCH_3), and 1.25 (3H, t, J 7.5Hz, CH_2CH_3).

Hydrolysis of 3-(2-Aminoethyl)indole Amino Acid Esters and Preparation of 3H-Pyrrolo-[4,3,2-g,h]1,2,4,5,6,8-hexahydro-1-methyl-1,4-benzodiazonin-3-ones - General Procedure - The appropriate 3-(2-aminoethyl)indole amino acid ester (1M) in aqueous ethanol (1:2) (4ml/mm) containing 1N NaOH (1ml/mm) was stirred at room temperature overnight (glycine ethyl ester derivatives) or refluxed 36 h (valine methyl ester derivatives). The solvent was removed at reduced pressure and the amino acid sodium salt, so formed, dried overnight at room temperature in vacuo over phosphorous pentoxide.

The crude, dry amino acid sodium salt (1M) was dissolved in D.M.F. (2mg/ml) and treated with diphenylphosphorylazide[67] (1.1M) and triethylamine (1.5M) at room temperature under argon for 72 h. The solvent was removed at reduced pressure and the residue taken up in ethyl acetate/water. The organic phase was washed with water (4 times) and brine, solvent removed at reduced pressure and the residue chromatographed to give the desired hexahydro-1,4-benzodiazonin-3-one.

3H-Pyrrolo[4,3,2-g,h]-1,2,4,5,6,8-hexahydro-1-methyl-1,4-benzodiazonin-3-one (12) - N-Methyl-N-{4-[3-(2-aminoethyl)]indolyl}glycine ethyl ester (202) (60mg, 0.22mm) was hydrolysed according to the general procedure to give N-methyl-N-{4-[3-(2-aminoethyl)]indolyl}glycine sodium salt (210) (58mg, 98%) as a pale brown glass δ (D_2O) 6.95-7.46 (4H, m, ArH), 4.23 (2H, s, NCH_2CO), 3.28 (4H, m, CH_2CH_2), 3.16 (3H, s, NCH_3).

The amino acid sodium salt (210) (58mg, 0.21mm) was cyclised according to the general procedure and gave after chromatography ($CHCl_3$ eluant) the product (12) (27mg, 57%) as a colourless foam. (Found: M^+ 229.1214, $C_{12}H_{15}N_3O$ requires 229.1214); m/e 229 (M^+), 119, and 117; ν max. (thin film) 3475, 3400, 3290, 1655, 1610, 1545, 1500, 1470, 1445, 1425, 1355, 1235, 1225, 1185, 1160, 1100, 1040, 1025, 905, and 730cm^{-1}; δ ($CDCl_3$, 250MHz, 50°C) 8.13 (1H, br s, indole NH), 7.04-7.15 (2H, m, 6-H and 7-H), 6.88 (1H, d, J 2.2Hz, 2-H), 6.78 (1H, d, J 6.1Hz, 5-H), 6.21 (1H, br s, CONH), 3.80 (4H, m, CH_2NHCO, NCH_2CO), 3.24 (2H, t, J 6Hz, $ArCH_2$), and 2.97 (3H, s, NCH_3).

3H-Pyrrolo-[4,3,2-g,h]-1,2,4,5,6,8-hexahydro-8-geranyl-1-methyl-1,4-benzodiazonin-3-one (211) - 3H-Pyrrolo[4,3,2-g,h]-1,2,4,5,6,8-hexahydro-1-methyl-1,4-benzodiazonin-3-one (12) (22.4mg, 0.12mm) and geranyl chloride (30mg, 0.15mm) in D.M.F. (0.5ml) were added to a stirred suspension of sodium hydride (6mg, 50% dispersion in oil, 0.13mm, washed with petrol) at 0°C and stirred for a further 2 h. After dilution with ether, the organic phase was extracted with water (5 x 15ml) and brine, the solvent removed at reduced pressure and the residue chromatographed ($CHCl_3$ eluant) to give compound (211) (18.2mg, 41%) as a colourless solid. Recrystallisation gave the analytical sample m.p. 173-174°C ($CHCl_3$/petrol). (Found: C, 75.30; H, 8.54; N, 11.39; $C_{23}H_{31}N_3O$ requires C, 75.58; H, 8.55; N, 11.50%; Found: M^+ 365.2458, $C_{23}H_{31}N_3O$ requires 365.2467); m/e 365 (M^+) and 228 ($M^+-C_{10}H_{17}$); ν max. (thin film) 1644, 1425, 1200, and 735cm^{-1}; δ ($CDCl_3$, 250MHz) 7.12 (1H, dd, J 8, 8.5Hz, 6-H), 6.99 (1H, d, J 8Hz, 7-H), 6.77 (1H, s, 2-H), 6.75 (1H, d, J 8.5Hz, 5-H), 6.27 (1H, br t, NHCO), 5.35 (1H, t, J 6.8Hz, =CH), 5.06 (1H, m, =CH), 4.60 (2H, d, J 6.8Hz, NCH_2), 3.68-4.06 (4H, br m, NCH_2CO, NCH_2CH_2), 3.17-3.32 (2H, br t, $ArCH_2CH_2$), 2.95 (3H, s, NCH_3), 2.08 (4H, m, allylic CH_2), 1.80 (3H, s, allylic CH_3), 1.68 (3H, s, allylic CH_3), and 1.59 (3H, s, allylic CH_3).

N-Methyl-{4-[3-(2-amino-3-hydroxypropyl)]indolyl}-glycine Ethyl Ester (203) - N-Methyl-N-{4-[3-(2-nitro-3-hydroxypropyl)]indolyl}glycine ethyl ester (189) (34mg, 0.1mm) was reduced with cobalt (II) chloride and sodium borohydride according to the general procedure to give the amino alcohol (203) (21mg, 68%) as an oil. (Found: M^+ 305.1730, $C_{16}H_{23}N_3O_3$ requires 305.1739); m/e 305 (M^+), 246 ($M^+-C_2H_5NO$), and 173 ($M^+-C_2H_5NO-C_3H_5O_2$); ν max. (thin film) 3100-3400, 1720, 1565, 1420, 1340, 1180, 1020, 895, and 720cm^{-1}; δ ($CDCl_3$) 6.56-7.10 (5H, m, ArH, and indole NH), 4.13 (2H, q, J 7Hz, OCH_2CH_3), 3.73 (2H, s, NCH_2CO), 2.80-3.55 (8H, m, $ArCH_2CH(NH_2)CH_2OH$), 2.80 (3H, s, NCH_3), and 1.23 (3H, t, J 7Hz, CH_2CH_3).

Hydrolysis and cyclisation of N-Methyl-N-{4-[3-(2-amino-3-hydroxypropyl)]indolyl}glycine Ethyl Ester (203) - The amino alcohol (203) (21mg, 0.068mm) was hydrolysed with aqueous ethanolic sodium hydroxide (0.068mm) according to the general procedure to give the sodium salt (20mg, 100%). Treatment with diphenylphosphoryl azide and triethylamine according to the general cyclisation procedure gave a single product (13) after work up, whose crude i.r. revealed an absorption at 1640cm^{-1} CONH and no absorption at 1710cm^{-1} corresponding to lactone formation. It was not possible to purify this product by chromatography.

N-Methyl-N-{4-[3-(2-amino-(2-tetrahydropyranyloxy)-propyl)]indolyl}glycine Ethyl Ester (204) - N-Methyl-N-{4-[3-(2-nitro-(2-tetrahydropyranyloxy)propyl)]indolyl}-glycine ethyl ester (196) (229mg, 0.54mm) was reduced with cobalt (II) chloride and sodium borohydride according to the general procedure to give compound (204) (158mg, 76%) as a pale brown oil. No further purification after aqueous workup was necessary. An analytical sample was prepared by chromatography ($CHCl_3$/EtOH/Et_2NH, 84:15:1): (Found: M^+ 389.2305, $C_{21}H_{31}N_3O_4$ requires 339.2314); m/e 389 (M^+), 246 ($M^+-C_7H_{13}NO_2$), and 173 ($M^+-C_7H_{13}NO_2-C_3H_5O_2$); ν max. (thin film) 3460, 3300, 1730, 1570, 1500, 1440,

1370, 1345, 1210, 1115, 1020, and 745cm^{-1}; δ ($CDCl_3$) 9.36 (1H, br s, indole NH), 6.60-7.03 (4H, m, ArH), 4.50 (1H, br s, OCHO), 4.07 (2H, q, J 7Hz, OCH_2CH_3), 3.13-4.00 (5H, m, $CH_2CH(NH_2)CH_2CH_2OCH_2CH_2$), 3.73 (2H, s, NCH_2CO), 2.75-3.04 (5H, m + s, $ArCH_2$, NCH_3), 2.73 (2H, br s, NH_2), 1.45-1.70 (6H, br m, $CH_2CH_2CH_2$), and 1.22 (3H, t, J 7Hz, CH_2CH_3).

3H-Pyrrolo-[4,3,2-g,h]-1,2,4,5,6,8-hexahydro-5-[(2-tetrahydropyranyloxy)methyl]-1,4-benzodiazonin-3-one (212) - The amino alcohol (204) (138mg, 0.35mm) was hydrolysed to the sodium salt (124mg, 93%) and cyclised according to the usual procedure to give, after chromatography, the desired tricyclic product (212) (71mg, 63%) as an oil. (Found: M^+ 343.1888, $C_{19}H_{25}N_3O_3$ requires 343.1896); m/e 343 (M^+), 260, 258 ($M^+-C_5H_9O$), and 171; ν max. (thin film) 3460, 3370, 1640, 1492, 1430, 1350, 1230, 1110, 1020, 900, and 720cm^{-1}; δ ($CDCl_3$, 250MHz) 8.34 (1H, br s, indole NH), 7.02-7.13 (2H, m, 7-H and 6-H), 6.84 (1H, dd, J 1.5, 6.5Hz, 5-H), 6.76 (1H, m, 2-H), 6.28 (1H, br dd, J 7, 16Hz, NHCO), 4.62 (1H, m, OCHO), 3.74-3.93 (4H, m, OCH_2 x 2) 3.47-3.62 (3H, m, $NCHCH_2$, NCH_2CO), 3.05-3.20 (2H, br m, $ArCH_2$), 2.96 (3H, s, NCH_3), and 1.45-1.90 (6H, br m, $CH_2CH_2CH_2$).

Deprotection of 3H-Pyrrolo-[4,3,2-g,h]-1,2,4,5,6,8-hexahydro-5-[(2-tetrahydropyranyloxy)methyl]-1-methyl-1,4-benzodiazonin-3-one (13) - The protected tricyclic indole (212) (45mg, 0.13mm) was treated in ethanol (1ml) with 3N HCl (1ml) at 0°C for 20 minutes and at room temperature for 1 h. The solution was diluted with ethyl acetate (30ml), basified with sodium hydroxide solution and the organic phase extracted with water (3 x 30ml) and brine (30ml). Removal of solvent at reduced pressure gave 3H-pyrrolo-[4,3,2-g,h]-1,2,4,5,6,8-hexahydro-5-[(hydroxymethyl]-1-methyl-1,4-benzodiazonin-3-one (13) (22.4mg, 59%) as an essentially pure glass insoluble in standard organic solvents. (Found: M^+ 259.1314, $C_{14}H_{17}N_3O_2$ requires 259.1321); m/e 259 (M^+), 228 (M^+-CH_3O), 215, 185,

171, and 117; ν max. (thin film) 3300-3450, 1640, 1450, 1380, 1215, 1080, 1045, 880, and 760cm^{-1}; δ ($(CD_3)_2SO$, 250MHz, 102°C), 10.50 (1H, br s, indole NH), 6.92-7.08 (3H, m, ArH), 6.69 (1H, dd, J 1.5, 6.5Hz, 5-H), 6.58 (1H, d, J 7.2Hz, NHCO), 4.25 (1H, br s, OH), 3.45-3.60 (3H, m, $CHCH_2OH$), 2.95-3.05 (4H, m, $ArCH_2$, NCH_2CO), and 2.86 (3H, s, NCH_3). At room temperature the absorption due to NCH_2CO is a sharp singlet at δ 3.32 but NCH_3 is very broad.

Rearrangement of Lactam (13) to the Lactone (193) - 3H-Pyrrolo-[4,3,2-g,h]-1,2,4,5,6,8-hexahydro-5-(hydroxymethyl)-1-methyl-1,4-benzodiazonin-3-one (13) (10mg, 0.039mm) was warmed to 85°C, under argon with stirring, in ethanol (2ml) and conc. HCl (2ml) overnight. After cooling the solution was diluted with ethyl acetate, the solution basified with sodium hydroxide and the organic phase extracted with water (3 x 20ml) and brine (20ml). Removal of the solvent at reduced pressure and chromatography ($CHCl_3$/EtOH/Et_2NH 89:10:1 eluant) gave 3H-pyrrolo-[4.3.2-h,i]-1,2,4,5,6,7,9-heptahydro-6-amino-1-methyl-1,4-benzoxecin-3-one (193) (6.7mg, 67%). No molecular ion was obtained. ν max. (thin film) 3330, 3250, 1720, 1595, 1560, 1490, 1425, 1365, 1340, 1200, 1100, 1020, and 740cm^{-1}. Attempted determination of the ^1H n.m.r. spectrum in $(CD_3)_2SO$ at elevated temperatures gave decomposition of material. No meaningful spectrum was obtained at room temperature.

N-{4-[1-Methyl-3-(2-amino-3-(2-tetrahydropyranyloxy)-propyl]indolyl}valine Methyl Ester (206a,b) Reduction of N-{4-[1-Methyl-3-(2-nitro-3-(2-tetrahydropyranyloxy)-propyl]indolyl}valine methyl ester (198a,b) (88mg, .20mm) according to the general procedure gave the desired diastereomeric mixture of amines (206a,b) as a yellow oil (66mg, 79%) which required no further purification. (Found: M^+ 417.2637, $C_{23}H_{35}N_3O_4$ requires 417.2627); m/e 417 (M^+), 375, 274, and 215; ν max. (thin film) 3440,

3380, 1730, 1610, 1580, 1070, 1030, 970, 900, and 725cm^{-1}; δ ($CDCl_3$) 6.55-6.98 (3H, m, ArH), 6.09 (1H, d, J 8Hz, 5-H), 4.58 (1H, br s, OCHO), 2.97-4.13° (10H, m, $CH_2CH(NH_2)CH_2O$, CH_2O, NCHCO), 3.66 (3H, s, OCH_3), 3.61 (3H, s, NCH_3), 2.17 (1H, m, $(CH_3)_2CH$), 1.40-1.76 (6H, m, $CH_2CH_2CH_2$), and 1.10 (6H, 2 superimposed doublets, $(CH_3)_2CH$).

Reduction of the less polar enantiomeric mixture (198a) (148mg, 0.33mm) gave the amine (206a) without isomerisation as an oil (127mg, 92%) which required no further purification. This material was indistinguishable by t.l.c. and ^1H n.m.r. with the above material.

cis and trans 3H-Pyrrolo-[4,3,2-g,h]-1,2,4,5,6,8-hexahydro-5-[(2-tetrahydropyranyloxy)methyl]-8-methyl-2-(1-methylethyl)-1,4-benzodiazonin-3-one (213a,b) - Hydrolysis of the diastereomeric mixture of amines (206a,b) (23mg, 0.063mm) with sodium hydroxide and cyclisation of the crude sodium salt (26.6mg, 100%) according to the general procedure, gave the desired tricyclic products (213a,b) (17.9mg, 74%) after chromatography ($CHCl_3$/petrol eluant) as an oil. (Found: M^+ 385.2369, $C_{22}H_{31}N_3O_3$ requires 385.2365); m/e 385 (M^+), 300 ($M^+-C_5H_9O$), 214, 213 and 171. Careful chromatography ($CHCl_3$/petrol 4:1) of the mixture of the diastereoisomers (213a,b) gave in equal quantities **(i) the less polar enantiomeric mixture compound (213a) as a crystalline solid.** Recrystallistion gave the analytical sample m.p. 179-180°C (MeOH) (Found: C, 68.03; H, 8.18; N, 10.84 $C_{22}H_{31}N_3O_3$ requires C, 68.03; H, 8.11; N, 10.90%); ν max. (thin film) 3380, 3320, 1650, 1545, 1490, 1460, 1440, 1410, 1380, 1350, 1320, 1300, 1245, 1210, 1120, 1060, 1040, and 750cm^{-1}; δ ($(CD_3)_2SO$, 250MHz, 122°C) 6.98 (3H, m, ArH), 6.65 (1H, m, ArH), 4.56-4.61 (3H, m, OCHO, OCNHCHNCH), 4.11 (1H, br s, NHAr), 3.81 (1H, m, NCH O), 3.59-3.75 (2H, m, CH_2O), 3.67 (3H, s, NCH_3), 3.37-3.52 (2H, m, OCH_2CH_2), 3.13 (1H, dd, J 4.6, 14.6Hz, ArCH), 2.94 (1H, dd, J 6.5Hz, ArCH), 2.21 (1H, m, $(CH_3)_2CH$), 1.46-1.84

(6H, m, $CH_2CH_2CH_2$), 1.18 (3H, d, J 6.6Hz, CH_3CH), and 0.97 (3H, d, J 6.6Hz, CH_3CH); **(ii) the more polar enantiomeric mixture (213b) as an oil.** ν max. (thin film) 3370, 3300, 1665, 1610, 1570, 1545, 1490, 1470, 1440, 1410, 1370, 1320, 1250, 1220, 1195, 1160, 1120, 1070, 1030, and 750cm^{-1}; δ ($(CD_3)_2SO$, 250MHz, 122°C), 6.86-6.92 (3H, m, ArH), 6.60 (1H, m, ArH), 6.42 (1H, dd, J 6.9, 21Hz, NHCO), 4.67 (1H, br s, OCHO), 4.40 (1H, br m, OCNHCH), 3.81-3.94 (3H, m, $CH_2ONCHCO$), 3.65 (3H, s, NCH_3), 3.46-3.63 (2H, m, CH_2O), 3.21 (1H, dd, J 4.9, 14.6Hz, ArCH), 2.95 (1H, dd, J 5.1, 14.6Hz), 2.14 (1H, m, $(CH_3)_2CH$), 1.44-1.80 (6H, m, $CH_2CH_2CH_2$), 1.11 (3H, d, J 6.6Hz, CH_3CH), and 0.93 (3H, d, J 6.6Hz, CH_3CH).

The hydrolysis of the less polar enantiomeric mixture of amines (206a) (127mg, 0.30mm) and cyclisation of the sodium salt so formed gave a single product (73mg, 64%) corresponding to the less polar tricyclic enantiomeric mixture (213a).

3H-Pyrrolo-[4,3,2-g,h]-1,2,4,5,6,8-hexahydro-5-hydroxymethyl-8-methyl-2-(1-methylethyl)-1,4-benzodiazonin-3-one (125a,b) - (i) The trans tricyclic tetrahydropyranyl ether (213a) (6.2mg, 0.016mm) was warmed to 65°C in methanol (2ml) containing 4-toluenesulphonic acid for 4 h[115]. The reaction was cooled to room temperature, the solvent volume reduced by one half and cooled to -30°C for 24 h. trans 3H-Pyrrolo-[4,3,2-g,h]-1,2,4,5,6,8-hexahydro-5-hydroxymethyl-8-methyl-2-(1-methylethyl)-1,4-benzodiazonin-3-one (125a) (4.2mg, 87%) was isolated by centrifugation as a microcrystalline colourless solid m.p. 271.5-272.5°C. (Found: M^+ 301.1785, $C_{17}H_{23}N_3O_2$ requires 301.1790); m/e 301 (M^+), 283, 270, 256, 227, 213, 198, 185, 171, and 144; ν max. (nujol mull) 3410, 3350, 3310, 1638, 1550, 1515, 1495, 1415, 1375, 1355, 1250, 1215, 1040, and 755cm^{-1}; δ ($(CD_3)_2SO$, 250MHz, 142°C) 6.94 (3H, m, ArH), 6.63 (1H, dd, J 2.5, 6.0Hz, 11-H), 6.06 (1H, br s, 4-H), 4.38 (1H, m, 5-H), 3.69 (3H, s, 8-NCH_3), 3.48 (3H, m, 2,1^{111}-H), 3.03 (2H, ABX system, J_{AB} 15.5Hz, J_{AX}

5.4Hz, J_{BX} 7.2Hz, collapses to an AB system J 15.5Hz on irradiation at 4.38, 6-H), 2.21 (1H, m, 1^{11}-H), 1.14 (3H, d, J 6.5Hz, 2^{11}), and 0.96 (3H, d, J 6.5Hz, 3^{11}-H). At room temperature additional resonances were observed at δ 4.87 (1H, t, J 5.5Hz, $CH_2O\underline{H}$) and 4.78 (1H, d, J 6.8Hz, $N\underline{H}$).

(ii) The cis tetrahydropyranyl ether (213b) (9.1mg, 0.024mm) was treated with a catalytic quantity of 4-toluenesulphonic acid as described above. On completion of the reaction, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (30ml). Extraction with sodium bicarbonate (2 x 20ml) and water (2 x 20ml) and evaporation of the solvent at reduced pressure gave cis 3H-Pyrrolo-[4,3,2-g,h]-1,2,4,5,6,8-hexahydro-5-hydroxymethyl-8-methyl-2-(1-methylethyl)-1,4-benzodiazonin-3-one (125b) (6.8mg, 96%) as a yellow crystalline solid. Recrystallisation gave a sample suitable for X-ray crystallographic analysis (Appendix 4) m.p. 216-218°C (EtOH). (Found: M^+ 301.1791, $C_{17}H_{23}N_3O_2$ requires 301.1790); m/e 301 (M^+), 283, 270, 256, 227, 213, 198, 185, 171, and 144; ν max. (nujol mull) 3330, 3320, 3200, 1635, 1560, 1550, 1525, 1485, 1465, 1440, 1415, 1380, 1335, 1280, 1260, 1210, 1060, and 750cm^{-1}; δ ($(CD_3)_2SO$, 250MHz, 139°C) 6.89 (3H, m, aromatics), 6.58 (1H, dd, J 2.0, 7.2Hz, 11-H), 6.27 (1H, br s, 4-H), 3.54-3.80 (4H, m, 2, 5, 1^{111}-H), 3.66 (3H, s, 8-$NC\underline{H}_3$), 3.20 (1H, part ABX system J_{AB} 13.6Hz, J_{AX} 4.1Hz, 6-H, the remainder of this system is masked by H_2O), 2.14 (1H, m, 1^{11}-H), 1.09 (3H, d, J 6.5Hz, 2^{11}-H), and 0.94 (3H, d, J 6.5Hz, 3^{11}-H).

N-Methyl-N-(4-indolyl)glycine Hydrochloride (222) - N-Methyl-N-(4-indolyl)glycine ethyl ester (113) (930mg, 4mm) was stirred overnight at room temperature in ethanol (8ml) containing 1N sodium hydroxide (4ml, 4mm). The dark green solution was evaporated at reduced pressure, the residue taken up in water, extracted with dichloromethane (3 x 20ml), acidified with 1N HCl (8ml, 8mm), filtered and solvent removed. The glycine hydrochloride salt (222)

(790mg, 86%) was isolated as a brown foam. ν max. (nujol) 3400, 3200, 1740, 1400, 1375, and 1340cm^{-1}; δ (D_2O) 6.80-7.40 (5H, m, ArH), 4.43 (2H, s, NCH_2CO), and 3.20 (3H, s, NCH_3).

dl-[N-Methyl-N-(4-indolyl)glycyl]serine Methyl Ester (221) - A solution of N-Methyl-N-(4-indolyl)glycine hydrochloride (222) (216mg, 0.9mm), dl serine methyl ester hydrochloride[75] (186mg, 1.2mm), dicyclohexylcarbodiimide (270mg, 1.3mm) and triethylamine (250mg, 2.5mm) in dichloromethane (5ml) containing 4-N,N-dimethylamino-pyridine [118] (12mg, 0.09mm) was stirred at room temperature overnight. After filtration to remove precipitated dicyclohexylurea, the solution was extracted with water (3 x 20ml) and evaporated at reduced pressure. The residue on chromatography ($CHCl_3$ eluant) gave the dipeptide (221) (171mg, 62%) as a light green oil. (Found M^+ 305.1370, $C_{15}H_{19}N_3O_4$ requires 305.1375); m/e 305 (M^+), 287 (M^+-H_2O), and 259; ν max. (thin film) 3340, 1735, 1655, 1210, and 745cm^{-1}; δ ($CDCl_3$) 8.62 (1H, br s, indole NH), 8.06 (1H, d, J 8Hz, CONH), 6.93-7.10 (3H, m, ArH), 6.40-6.60 (2H, m, ArH), 4.67 (1H, m, $NCHCH_2OH$), 3.89 (5H, br s, CO_2CH_3, $CHCH_2OH$), 3.68 (2H, s, NCH_2CO), and 2.91 (3H, s, NCH_3).

dl-[N-Methyl-N-(4-indolyl)glycyl]O-t-Butyldimethylsilyl Serine Methyl Ester (227) - The dipeptide methyl ester (221) (100mg, 0.33mm) t-butyldimethylsilyl chloride (60mg, 0.40mm) and triethylamine (60mg, 0.60mm) were stirred in dichloromethane (2ml) containing 4-N,N-dimethylamino pyridine (5mg) at room temperature overnight. The solution was diluted with dichloromethane, extracted with water, the solvent removed at reduced pressure and the residue chromatographed ($CHCl_3$/EtOH, 97:3 eluant) to give the silyl ether (227) (117mg, 85%) as an oil. (Found: M^+ 419.2239, $C_{21}H_{33}N_3O_4Si$ requires 419.2240); m/e 421 (M^+ + 2), 391, and 364; ν max. (thin film) 3370, 3300, 1745, and 1665cm^{-1}; δ ($CDCl_3$) 8.85, (1H, br s, indole NH), 8.16 (1H, d, J 8Hz, NHCO), 7.00-7.18 (3H, m, ArH), 6.50-6.65 (2H, m,

ArH), 4.81 (1H, m, CONHCH), 3.95-4.12 (4H, m, NCH_2CO and CH_2O), 3.72 (3H, s, $COCH_3$), 2.96 (3H, s, NCH_3), 0.80 (9H, s, $C(CH_3)_3$), and 0.10 (6H, s, $Si(CH_3)_2$).

dl-[N-Methyl-N-[4-(1-trimethylsilyl)indolyl]glycyl]O-t-Butyldimethylsilyl Serine Methyl Ester (228) - A solution of dl [N-Methyl-N-(4-indolyl)glycyl]t-butyldimethylsilyl serine methyl ester (227) (190mg, 0.45mm), chlorotrimethylsilane (73mg, 0.68mm) and triethylamine (90mg, 0.90mm) were stirred together in dichloromethane containing 4-N,N-dimethylaminopyridine (10mg) for 8 days. Dilution with dichloromethane, extraction with water (3 x 20ml) and brine (20ml), removal of solvent at reduced pressure and chromatography ($CHCl_3$ eluant) gave the product (228) (38mg, 17%) as an oil. (Found: M^+ 491.2644, $C_{24}H_{41}N_3O_4Si_2$ requires 491.2635); m/e 491 (M^+), 435, 419 ($M^+-Si(CH_3)_3$), and 231; ν max. (thin film) 3370, 1740, 1668, 1570, 1510, 1480, 1280, 1255, 905, 845, and 830cm^{-1}; δ ($CDCl_3$) 8.12 (1H, d, J 9Hz, lactam NH), 7.02-7.20 (3H, m, ArH), 6.60-6.73 (2H, m, ArH), 4.84 (1H, m, CONHCH), 3.95-4.14 (4H, m, NCH_2CO and CH_2O), 3.77 (3H, s, OCH_3), 3.00 (3H, s, NCH_3), 0.83 (9H, s, $(CH_3)_3C$), 0.60 (9H, s, $NSi(CH_3)_3$), and 0.10 (6H, s, $Si(CH_3)_2$).

Methyl-2-[N-methyl-N-(4-indolyl)glycylamido]acrylate (229) - (i) Mitsonubu procedure[119]:- Diethyl azodicarboxylate (73mg, 0.42mm) and triphenylphosphine (110mg, 0.45mm) were added to a stirred solution of dl-[N-methyl-N-(4-indolyl)glycyl]serine methyl ester (221) (52mg, 0.17mm) in T.H.F. (25ml). After stirring for 4 h the solvent was removed at reduced pressure and the residue chromatographed to give the product (229) (38mg, 58%) as an oil. (Found: M^+ 287.1271, $C_{15}H_{17}N_3O_3$ requires 287.1270); m/e 287 (M^+), 173, 159, 144, 131, and 117; ν max. (thin film) 3300-3380, 1720, 1682, 1630, 1580, 1510, 1435, 1365, 1325, 1200, 905, and 730cm^{-1}; δ ($CDCl_3$) 9.63 (1H, br s, lactam NH), 8.84 (1H, br s, indole NH), 6.98-7.12 (3H, m, ArH), 6.50-6.74 (2H, m, ArH and =CH), 6.42 (1H, m, 3-H), 5.91 (1H, br s, =CH), 3.96 (2H, s,

NCH_2CO), 3.76 (3H, s, OCH_3), and 2.97 (3H, s, NCH_3). **(ii) Methanesulphonyl chloride/triethylamine procedure:-** The dipeptide (221) (81mg, 0.28mm) in dichloromethane (2ml) was treated in turn with triethylamine (100mg, 1mm) and methanesulphonyl chloride (35mg, 0.3mm) at room temperature. The solution was stirred for 1 h, diluted with chloroform and extracted with water (3 x 20ml) and brine (20ml) followed by removal of solvent at reduced pressure to give the product (229) (80mg, 100%) essentially pure by t.l.c. and ^1H n.m.r. The product had identical ^1H n.m.r., i.r. and t.l.c. properties as the compound prepared by Mitsonubu's procedure.

N-Methyl-N-[4-(7-geranyl)indolyl]glycine Ethyl Ester (239) - A solution of geraniol (92mg, 0.6mm) in dichloromethane (2ml) was treated, at room temperature with triethylamine (70mg, 0.7mm) and methanesulphonyl chloride (68mg, 0.6mm) for 10 minutes. N-Methyl-N-[4-indolyl]glycine ethyl ester (113) (116mg, 0.5mm) was then added and the solution stirred for 5 h. After dilution with dichloromethane the solution was extracted with water (3 x 100ml) and brine (10ml), the solvent removed at reduced pressure and the residue chromatographed ($CHCl_3$/petrol 1:3 eluant). The product (239) (12mg, 6.5%) was isolated as a light brown oil. (Found: M^+ 368.2475, $C_{23}H_{32}N_2O_2$ requires 368.2464); m/e 368 (M^+), 309, and 295 ($M^+-C_3H_5O_2$); ν max. (thin film) 3460, 1735, 1600, 1500, 1445, 1370, 1210, 1190, 1020, 900, and 730cm^{-1}; δ ($CDCl_3$, 250MHz) 8.18 (1H, br s, indole, NH), 7.12 (1H, t, J 2.8Hz, 2-H), 6.58 (1H, t, J 2.8Hz, 3-H), 6.89, 6.51 (2H, ABq, J_{AB} 7.5Hz, 5-H and 6-H), 5.09 (2H, m, =CH), 4.21 (2H, q, J 7.3Hz, OCH_2CH_3), 4.14 (2H, s, NCH_2CO), 3.52 (2H, d, J 6.7Hz, NCH_2CH=), 3.06 (3H, s, NCH_3), 2.10 (4H, m, allylic CH_2), 1.80 (3H, s, allylic CH_3), 1.69 (3H, s, allylic CH_3), 1.60 (3H, s, allylic CH_3), and 1.27 (3H, t, J 7.3Hz, OCH_2CH_3).

Indole-4-methanol - Methyl indole-4-carboxylate (88) (10.5g, 60mm) in T.H.F. (150 ml) at 0°C was treated with

lithium aluminium hydride (2.28g, 60mm) in T.H.F. (100ml). After stirring at 0°C for 2 h an additional portion of lithium aluminium hydride (500mg, 13mm) was added, the solution warmed to 60°C for 4 h and stirred at room temperature overnight. Excess lithium aluminium hydride was destroyed by the careful addition of water and the solution filtered to remove aluminium salts. Solvent was removed at reduced pressure, the residue taken up in dichloromethane, dried ($MgSO_4$) and solvent again removed at reduced pressure. The product (8.80g, 99%) was isolated as a pale yellow solid and required no further purification. ν max. (nujol) 3480, 3420, 3340, 1500, 1435, 1410, 1340, 1155, 1110, 1050, 1025, 985, 910, and 730cm^{-1}; δ ($CDCl_3$) 8.47 (1H, br s, indole NH), 6.87-7.20 (4H, m, ArH), 6.47 (1H, m, 3-H), 4.80 (2H, s, $ArCH_2OH$), and 2.33 (1H, br s, OH)[65].

Indole-4-carboxaldehyde (249) - Indole-4-methanol (8.80g, 59.9mm) and activated manganese dioxide (30g, Aldrich) were stirred together for 14 h at room temperature. An additional portion of activated manganese dioxide (30g) was then added and stirring continued for a further 48 h. Filtration and removal of solvent gave the carboxaldehyde (249) (8.05g, 92%) as a pale yellow solid. No further purification of the product was required. m/e 145 (M^+), 144 (M^+-1), 127, and 126; ν max. (nujol) 3480, 1670, 1570, 1500, 1485, 1440, 1420, 1390, 1350, 1265, 1225, 1155, 1110, 1075, 1025, 905, and 730cm^{-1}; δ ($CDCl_3$) 10.28 (1H, s, CHO), 7.50-7.72 (2H, m, ArH), and 7.07-7.40 (3H, m, ArH)[65].

Ethyl (E)-3-(4-indolyl)propenoate (248) - Indole-4-carboxaldehyde (249) (8.05g, 55.5mm) and [(carboethoxy)-methylene]triphenylphosphorane (28g, 80mm) were stirred together in T.H.F. (240ml) for 72 h. The solvent was removed at reduced pressure and the residue chromatographed ($CHCl_3$/petrol 3:7 Waters HPLC) to give the product (248) (10.6g, 88%) as a pale yellow solid. Recrystallisation gave a colourless sample m.p.

69.5-70.5°C (EtOAc/petrol) (lit. 72-73.5°C[65]); m/e 215 (M^+); ν max. (nujol) 3340, 1680, 1620, 1180, and 745cm^{-1}; δ ($CDCl_3$) 8.42 (1H, br s, indole NH), 6.55, 8.05 (2H, ABq, J_{AB} 16Hz, C<u>H</u>=C<u>H</u>), 7.07-7.47 (4H, m, Ar<u>H</u>), 6.75 (1H, m, 3-H), 4.28 (2H, q, J 6.5Hz, $OC\underline{H}_2CH_3$), and 1.33 (3H, t, J 6.5Hz, $CH_2C\underline{H}_3$).

<u>Ethyl(E)-3-{4-[1-(4-toluenesulphonyl)]indolyl}-propenoate (251)</u> - To a stirred suspension of sodium hydride (60mg, 50% in oil, washed with petrol, 1.2mm) in D.M.F. (3ml), ethyl(E)-3-(4-indolyl)propenoate (248) (215mg, 1mm) and 4-toluenesulphonyl chloride (190mg, 1mm) were added. After stirring for 20 h at room temperature the reaction mixture was diluted with ether, extracted with water (5 x 50ml) and brine (50ml), the solvent removed at reduced pressure and the residue chromatographed ($CHCl_3$/petrol) to give (i) **<u>Ethyl(E)-3-{4-[1-(4-toluenesulphonyl)]indolyl}propenoate</u> (251)** (65mg, 18%) as a solid. Recrystallisation ($CHCl_3$/petrol) gave the analytical sample m.p. 129.5-130°C (Found: C, 65.09; H, 5.18; N, 3.79; $C_{20}H_{19}NSO_4$ requires C, 65.02; H, 5.18; N, 3.79%); ν max. (nujol) 1714, 1635, 1595, 1520, 1478, 1425, 1415, 1370, 1360, 1310, 1300, 1290, 1265, 1180, 1170, 1160, 1120, 1080, 905, and 730cm^{-1}; δ ($CDCl_3$) 7.30-8.00 (6H, m, Ar<u>H</u>), 6.40, 7.73 (2H, ABq, J_{AB} 16Hz, ArC<u>H</u>=C<u>H</u>CO), 7.10 (2H, .5 ABq, J 9Hz), 6.79 (1H, d, J 3.5Hz, 3-H), 4.20 (2H, q, J 7Hz, $OC\underline{H}_2CH_3$), 2.30 (3H, s, $ArC\underline{H}_3$), and 1.33 (3H, t, J 7Hz, $OCH_2C\underline{H}_3$). (ii) **Ethyl(E)-3-(4-indolyl)propenoate (248)** (91mg, 42%) identified by ^{1}H n.m.r., i.r. and t.l.c.

<u>1-(4-toluenesulphonyl)4-bromoindole (250)</u> - 4-Bromoindole (101) (1.62g, 8.3mm), 4-toluenesulphonyl chloride (3.14g, 16.5mm) and potassium carbonate (4.416g, 32mm) were warmed to reflux in butanone[134] under argon for 5 h. After cooling the solution was diluted with ethyl acetate, extracted with water (5 x 50ml) and brine (50ml) and solvent removed at reduced pressure to give the crude crystalline product. Recrystallisation gave <u>compound</u>

(250) (2.015g, 70%) m.p. 119.5-120°C (EtOAc/petrol) (Found: C, 51.34; H, 3.43; N, 4.00; S, 9.32 $C_{15}H_{12}NO_2SBr$ requires C, 51.44; H, 3.45; N, 4.00; S, 9.15%); m/e 351, 349 (M^+), 196 ($M^+-C_7H_7O_2S$), 194, and 155; ν max. (thin film) 1595, 1560, 1520, 1470, 1410, 1370, 1350, 1280, 1220, 1190, 1160, 1125, 1090, 995, 900, 810, and 725cm^{-1}; δ ($CDCl_3$) 7.43-7.90 (4H, m, ArH), 6.90-7.30 (4H, m, ArH), 6.59 (1H, d, J 4Hz, 3-H), and 2.27 (3H, s, $ArCH_3$).

Reaction of 1-(4-Toluenesulphonyl)-4-bromoindole (250) with Ethyl Acrylate - 1-(4-Toluenesulphonyl)-4-bromoindole (250) (308mg, 0.88mm), palladium (II) acetate (20mg, 0.088mm), triphenylphosphine (92mg, 0.35mm), triethylamine (100mg, 1mm) and ethyl acrylate (0.13ml) were warmed to 100°C in acetonitrile (2ml) under argon for 48 h[133]. The dark solution was evaporated at reduced pressure and the residue chromatographed ($CHCl_3$/petrol 7:3 eluant) to give ethyl(E)-3-{4-[1-(4-toluenesulphonyl)]indolyl}propenoate (251) (102mg, 34%) identical by ^{1}H n.m.r., i.r. and t.l.c. with the previously described material.

Ethyl-3-(4-Indolyl)propanoate (257) - A solution of Ethyl(E)-3-(4-indolyl)propenoate (248) (215mg, 1mm) in ethanol (40ml) containing 10% Pd/C (30mg) was stirred at room temperature under one atmosphere of hydrogen until hydrogen uptake ceased (about 4 h). The solution was filtered (celite pad) and the solvent removed at reduced pressure to give the product (257) (216mg, 100%) as an oil that was not purified further. m/e 217 (M^+), 143 ($M^+-C_3H_6O_2$), and 130 ($M^+-C_4H_7O_2$); δ ($CDCl_3$) 8.35 (1H, br s, indole NH), 6.70-7.30 (4H, m, ArH), 6.50 (1H, m, 3-H), 4.12 (2H, q, J 7Hz, OCH_2CH_3), 3.25 (2H, t, J 6.5Hz, CH_2CH_2CO), 2.73 (2H, t, J 6.5Hz, $ArCH_2CH_2$), and 1.21 (3H, t, J 7Hz, CH_2CH_3).

General Procedure for the 3-(2-Nitroethylation) of 4-Carbon Substituted Indoles[94b] - The appropriate 4-substituted indole (1M) was stirred in dichloromethane (3ml/mm) with nitroethylene (2M) in the dark, under argon until the reaction was shown to be complete by t.l.c.

Solvent was then removed at reduced pressure and the residue chromatographed ($CHCl_3$/petrol eluant) to give the product. Analytical samples were prepared by recrystallisation.

Methyl-{4-[3-(2-Nitroethyl)]indolyl}carboxylate (258) - Methyl indole-4-carboxylate (88) (531mg, 3mm) was treated according to the general procedure with nitroethylene (440mg, 6mm) for 48 h. Removal of solvent and chromatography ($CHCl_3$ eluant) gave compound (258) (173mg, 23%) as a crystalline solid. Recrystallisation gave the analytical sample m.p. 102-102.5°C ($CHCl_3$/petrol) (Found: C, 58.15; H, 4.88; N, 11.33 $C_{12}H_{12}N_2O_4$ requires C, 58.06; H, 4.87; N, 11.29%); m/e 248 (M^+), 201, and 170; ν max. (thin film) 3470, 1712, and 1552cm^{-1}; δ ($CDCl_3$) 8.53 (1H, br s, indole NH), 6.90-7.73 (4H, m, ArH), 4.61 (2H, t, J 7Hz, CH_2NO_2), 3.90 (3H, s, OCH_3), and 3.54 (2H, t, J 7Hz, $ArCH_2$).

Ethyl(E)-3-{4-[3-(2-Nitroethyl)]indolyl}propenoate (255) - Ethyl(E)-3-(4-indolyl)propenoate (248) (2.15g, 10mm) was treated with nitroethylene (1.46g, 20mm) according to the general procedure. Chromatography ($CHCl_3$/petrol eluant) of the dark residue after removal of solvent from the reaction mixture gave compound (255) as an orange yellow crystalline solid (1.0888g, 38%). Recrystallisation gave the analytical sample m.p. 117.5-119°C (CH_2Cl_2/petrol) (Found: C, 62.25; H, 5.55; N, 9.63 $C_{15}H_{16}N_2O_4$ requires C, 62.49; H, 5.59; N, 9.72%); m/e 288 (M^+), 255, and 197; ν max. (nujol) 3310, 1690, 1625, 1610, and 1540cm^{-1}; δ ($CDCl_3$) 8.30, 6.40 (2H, ABq, J_{AB} 15Hz, $CH^{t}{=}CH$), 8.10 (1H, br s, indole NH), 7.0-7.45 (4H, m, ArH), 4.65 (2H, t, J 6.7Hz, CH_2NO_2), 4.28 (2H, q, J 7Hz, OCH_2CH_3), 3.59 (2H, t, J 6.7Hz, $ArCH_2$), and 1.34 (3H, t, J 7Hz, CH_2CH_3).

Ethyl-3-{4-[3-(2-nitroethyl)]indolyl}propanoate (256) - Ethyl-3-(4-indolyl)propanoate (257) (216mg, 1mm) was treated with nitroethylene (140mg, 2mm) according to the general procedure for 23 h. Chromatography ($CHCl_3$/petrol 4:1 eluant) gave compound (256) as an oil that solidified

when cooled to give a pale yellow solid (95mg, 33%) m.p. 82.5-83°C (Found: C, 61.93; H, 6.25; N, 9.53 $C_{15}H_{18}N_2O_4$ requires C, 62.06; H, 6.25; N, 9.65%); m/e 290 (M^+), 243, and 170; ν max. (thin film) 3410, 1723, and 1549cm^{-1}; δ ($CDCl_3$) 8.35 (1H, br s, indole NH), 6.82-7.25 (4H, m, ArH), 4.63 (2H, t, J 6.7Hz, CH_2NO_2), 4.18 (2H, q, J 6.8Hz, OCH_2CH_3), 3.60 (2H, t, J 6.7Hz, $ArCH_2CH_2NO_2$), 3.27 (2H, m, CH_2CO), 2.70 (2H, $ArCH_2CH_2CO$), and 1.24 (3H, t, J 6.8Hz, CH_2CH_3).

Reduction of Ethyl-3-{4-[3-(2-nitroethyl)]indolyl}-Propenoate - A solution of ethyl-3-{4-[3-(2-nitroethyl)]-indolyl}propenoate (255) (300mg, 1.04mm) in ethanol (25ml) containing 10% Pd/C (50mg) was stirred at room temperature under hydrogen at atmospheric pressure until the uptake of gas was complete (about 2 h). The solution was filtered (celite pad) and solvent removed at reduced pressure to give ethyl-3-{4-[3-(2-nitroethyl)]indolyl}propanoate (256) (298mg, 99%) identical by ^{1}H n.m.r., i.r. and t.l.c. with the previously described compound.

Ethyl-3-{4-[3-(2-aminoethyl)]indolyl}propanoate (247) - A solution of ethyl-3-{4-[3-(2-nitroethyl)]indolyl}-propanoate (256) (290mg, 1mm) was reduced with cobalt (II) chloride and sodium borohydride according to the general procedure to give compound (247). Chromatography ($CHCl_3$/EtOH/Et_2NH 80:20:0.5 eluant) gave the analytical sample (220mg, 85%) as an oil. (Found: C, 68.99; H, 7.82; N, 10.68 $C_{15}H_{20}N_2O_2$ requires C, 69.20; H, 7.74; N, 10.76%); m/e 260 (M^+) and 231 (M^+-CH_3N); ν max. (thin film) 3460, 3400, 3360, 1720, 1610, 1570, 1420, 1370, 1340, 1290, 1280, 1260, 1185, 1155, 1050, 1030, 905, and 730cm^{-1}; δ ($CDCl_3$) 9.48 (1H, br s, indole NH), 6.60-7.17 (4H, m, ArH), 4.05 (2H, q, J 7Hz, OCH_2CH_3), 3.03-3.40 (2H, m, CH_2CO), 2.97 (4H, m, $ArCH_2CH_2NH_2$), 2.40 (2H, m, $ArCH_2$), 1.70 (2H, br s, NH_2), and 1.20 (3H, t, J 7Hz, CH_2CH_3).

3H-Pyrrolo-[4,3,2-q,h]-1,2,4,5,6,8-hexahydro-4-benzazonin-3-one (15) - Ethyl-3-{4-[3-(2-aminoethyl)]-indolyl}propanoate (247) (148mg, 0.57mm) was hydrolysed to

the amino acid sodium salt (26Ø) (142mg, 96%) isolated as a pale brown glass. Cyclisation of the amino acid sodium salt (43mg, Ø.16mm) with diphenylphosphoryl azide according to the general procedure gave after chromatography (CH_2Cl_2 -> CH_2Cl_2/EtOH 96:4, 1% increments, 1ØØml each increment) the tricyclic product (15) (16mg, 47%) as a colourless solid insoluble in standard organic solvents. An analytical sample was prepared by recrystallisation m.p. 282-282.5°C with sublimation (EtOH). (Found: C, 72.73; H, 6.65; N, 12.89 $C_{13}H_{14}N_2O$ requires C, 72.87; H, 6.59; N, 13.Ø7%; Found: M^+ 214.1113, $C_{13}H_{14}N_2O$ requires 214.11Ø6); m/e 214 (M^+) and 156 ($M^+-C_2H_4NO$); ν max: (nujol) 33ØØ, 1635, 1475, 9ØØ, and 73Øcm^{-1}; δ ($(CD_3)_2SO$, 25ØMHz, 122°C) 1Ø.44 (1H, br s, indole NH), 7.19 (1H, dd, J 1.1, 7.8Hz, 7-H), 7.Ø1 (1H, d, J 2.5Hz, 2-H), 6.94 (1H, dd, J 7.2, 7.8Hz, 6-H), 6.76 (1H, dd, J 1.1, 7.2Hz, 5-H), 6.43 (1H, br s, NHCO), 3.46 (2H, m, $CONHCH_2CH_2$, sharpened by decoupling of NHCO), 3.22 (2H, t, J 6.7Hz, $COCH_2CH_2$), 3.Ø3 (2H, t, J 5.8Hz, NCH_2CH_2Ar), and 2.54 (2H, t, J 6.7Hz, $ArCH_2CH_2CO$).

3H-Pyrrolo-[4,3,2-g,h]-1,2,4,5,6,8-hexahydro-8-geranyl-4-benzazonin-3-one (261) - To a stirred suspension of sodium hydride (4mg, 5Ø% suspension in oil washed with petrol, Ø.Ø87mm) in D.M.F. (Ø.5ml) a solution of 3H-pyrrolo-[4,3,2-g,h]-1,2,4,5,6,8-hexahydro-4-benzazonin-3-one (15) (15mg, Ø.Ø7mm) and geranyl chloride (14mg, Ø.Ø81mm) in D.M.F. (Ø.5ml) was added at room temperature. Stirring was continued for 3 h and the brown solution diluted with ethyl acetate. The organic phase was extracted with water (5 x 2Øml) and brine (2Øml), the solvent removed and the residue chromatographed (CH_2Cl_2 -> CH_2Cl_2/EtOH, 49:1 eluant). The product (261) (2Ømg, 6Ø%) was isolated as a colourless solid, from which the analytical sample was prepared by recrystallisation m.p. 1Ø6-1Ø7°C (EtOAc/petrol) (Found: C, 78.68; H, 8.47; N, 7.95 $C_{23}H_{3Ø}N_2O$ requires C, 78.82; H, 8.63; N, 7.99%; Found: M^+ 35Ø.2356 $C_{23}H_{3Ø}N_2O$ requires 35Ø.2358); m/e 35Ø

(M^+) and 214 ($M^+-C_{10}H_{16}$); ν max. (thin film) 1645, 1430, 900, and 720cm^{-1}; δ ($(CD_3)_2SO$, 250MHz, 140°C), 7.20 (1H, d, J 7.4Hz, 7-H), 6.99 (1H, dd, J 7.5, 7.4Hz, 6-H), 6.97 (1H, s, 2-H), 6.81 (1H, d, J 7.5Hz, 5-H), 6.40 (1H, br s, NHCO), 5.36 (1H, t, J 6.5Hz, =CH), 5.10 (1H, m, =CH), 4.65 (2H, d, J 6.5Hz, NCH_2), 3.46 (2H, m, $CONHCH_2CH_2$), 3.23 (2H, t, J 6.9Hz, CH_2CH_2CO), 3.04 (2H, t, J 6.2Hz, $ArCH_2CH_2N$), 2.55 (2H, t, J 6.9Hz, $ArCH_2CH_2CO$), 2.09 (4H, m, allylic CH_2), 1.80 (3H, s, allylic CH_3), 1.65 (3H, s, allylic CH_3), and 1.59 (3H, s, allylic CH_3).

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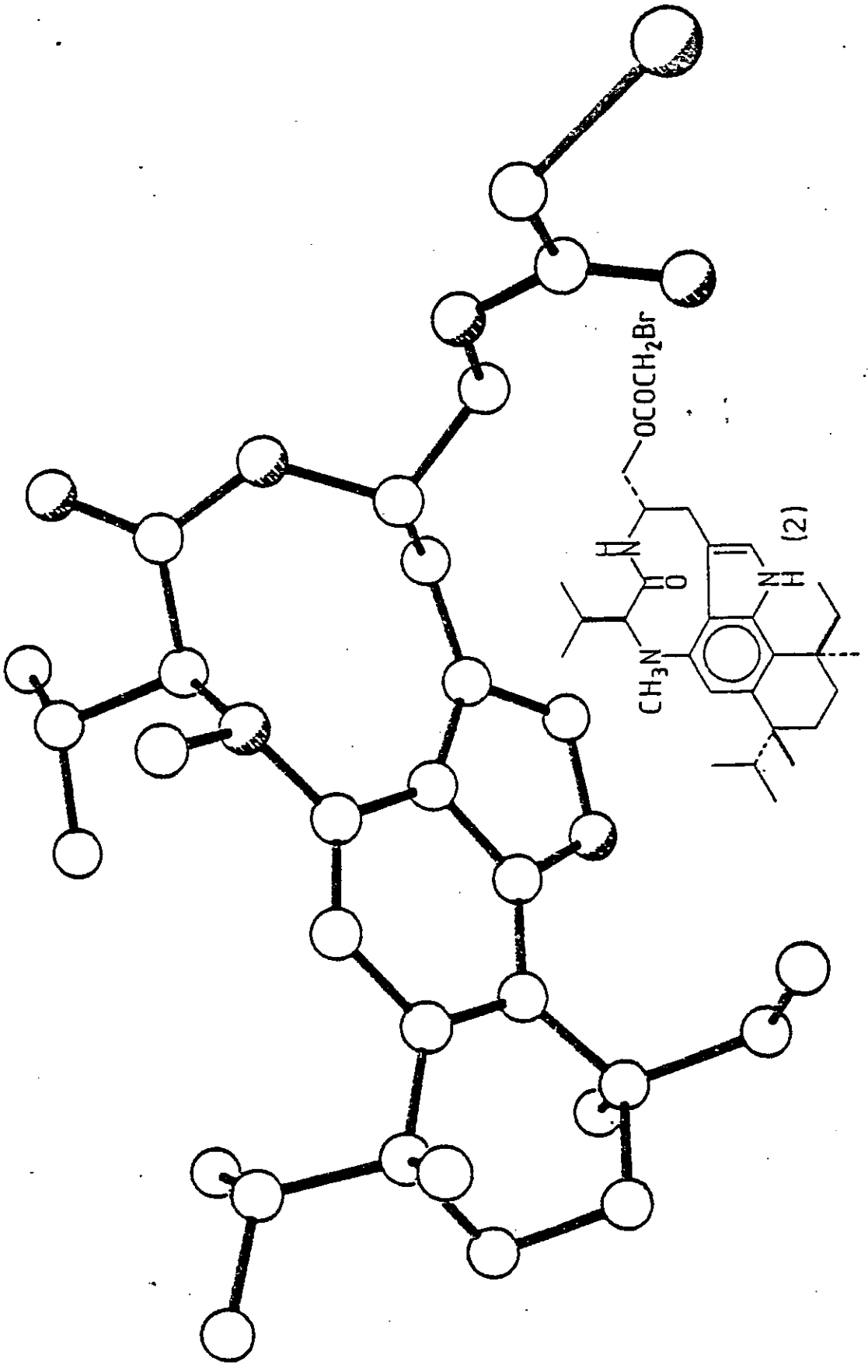
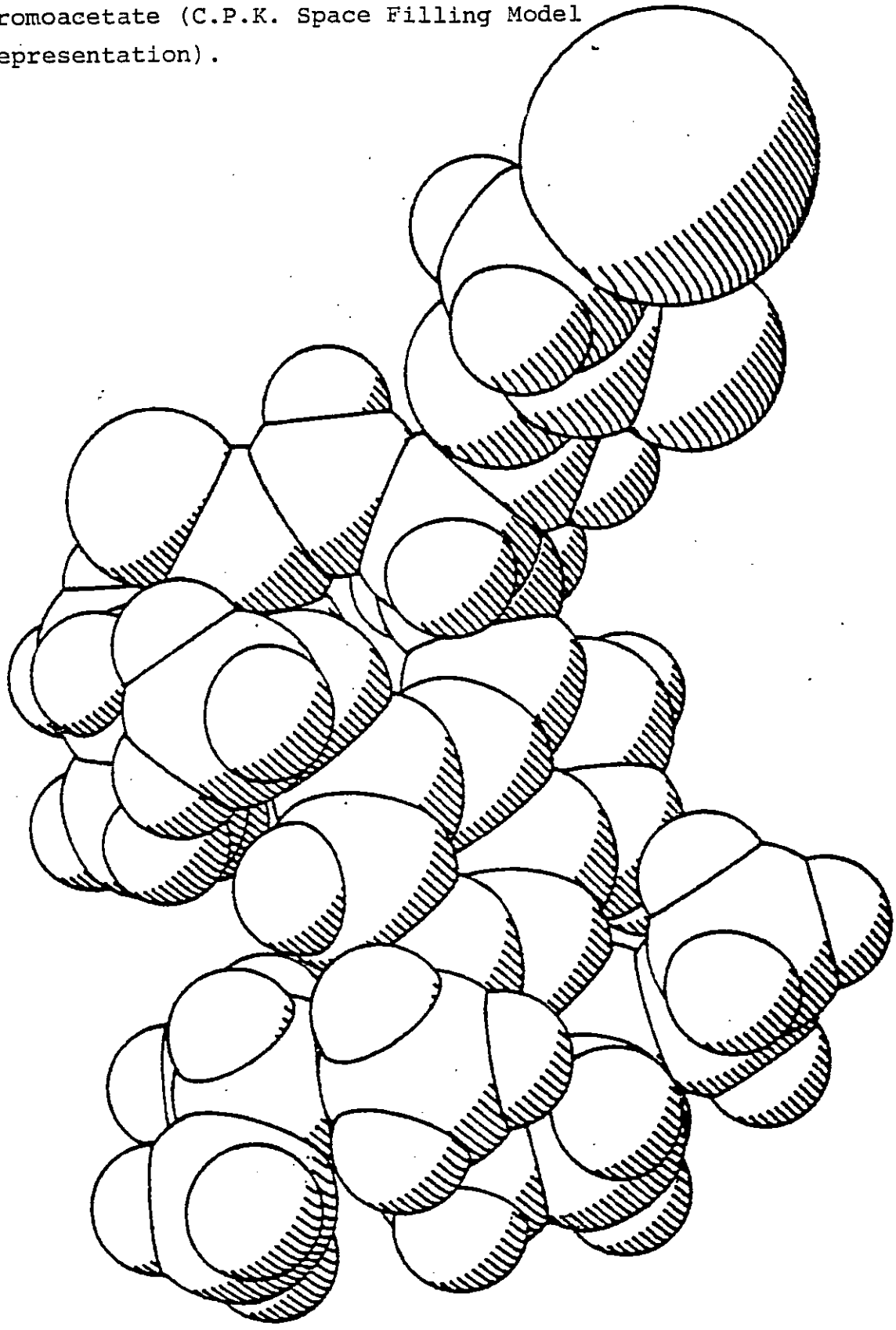
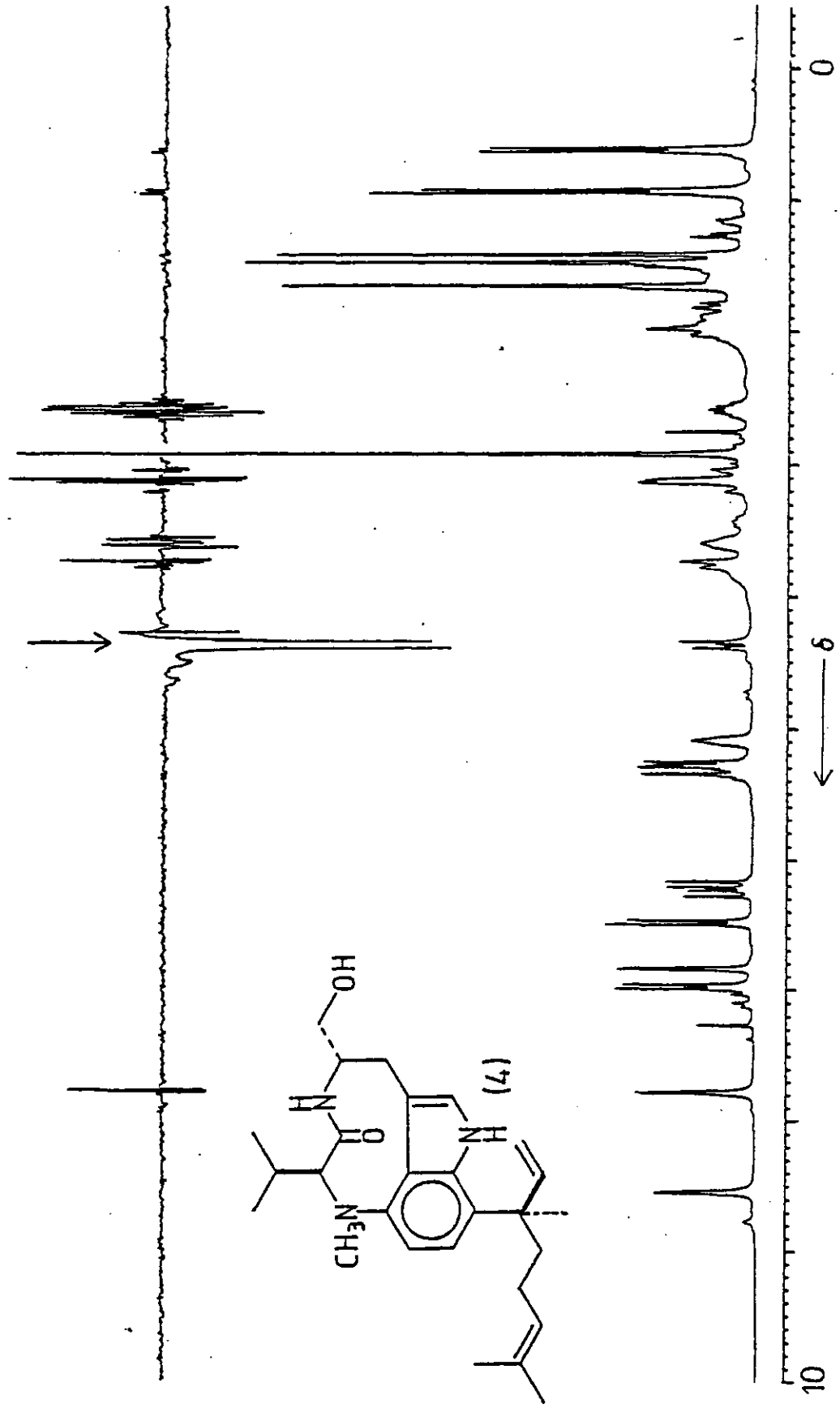
Appendix 1(a) X-Ray Crystallographic Study of Teleocidin B Bromoacetate (Dreiding Model Representation).



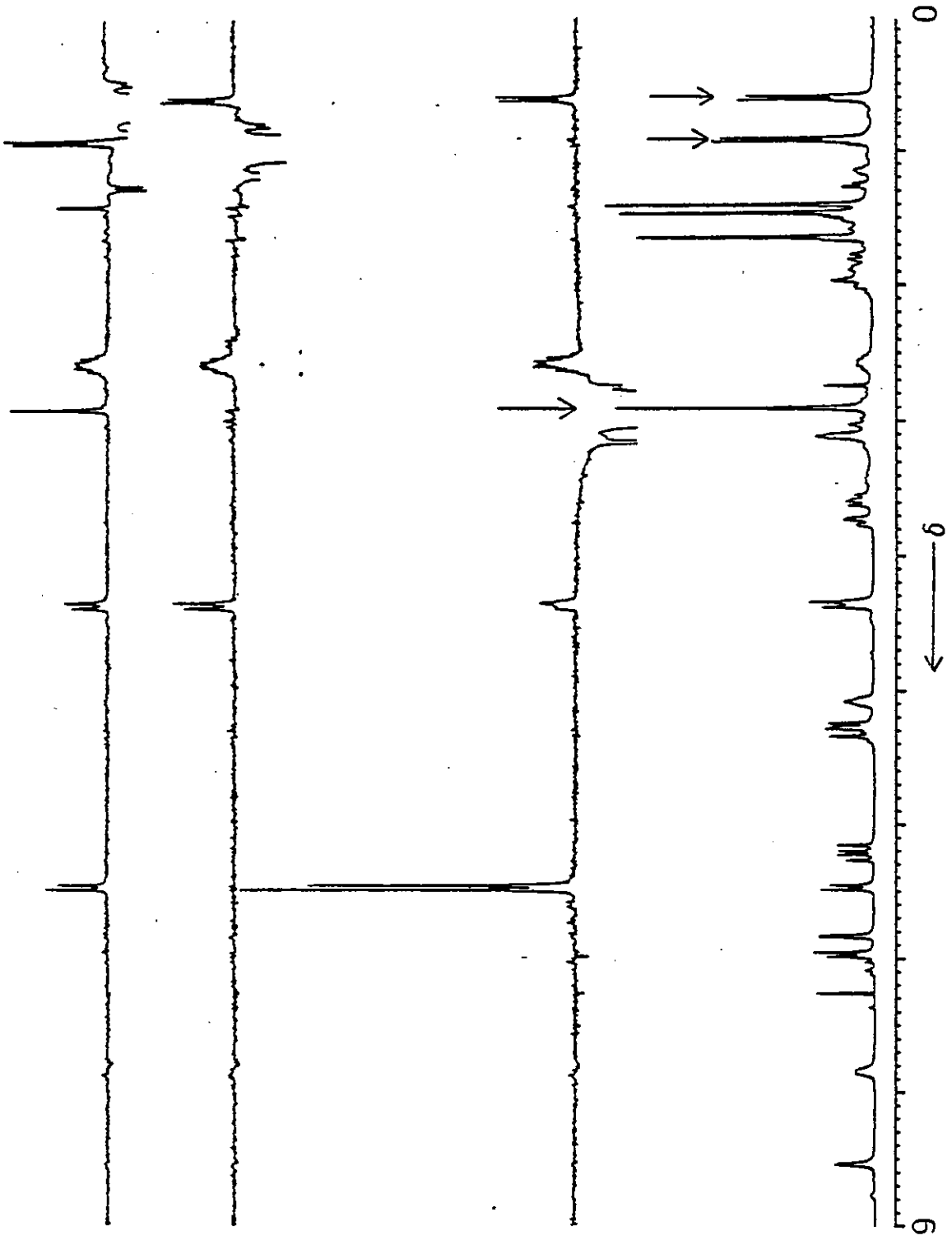
Appendix 1(b) X-Ray Crystallographic Study of Teleocidin B Bromoacetate (C.P.K. Space Filling Model Representation).



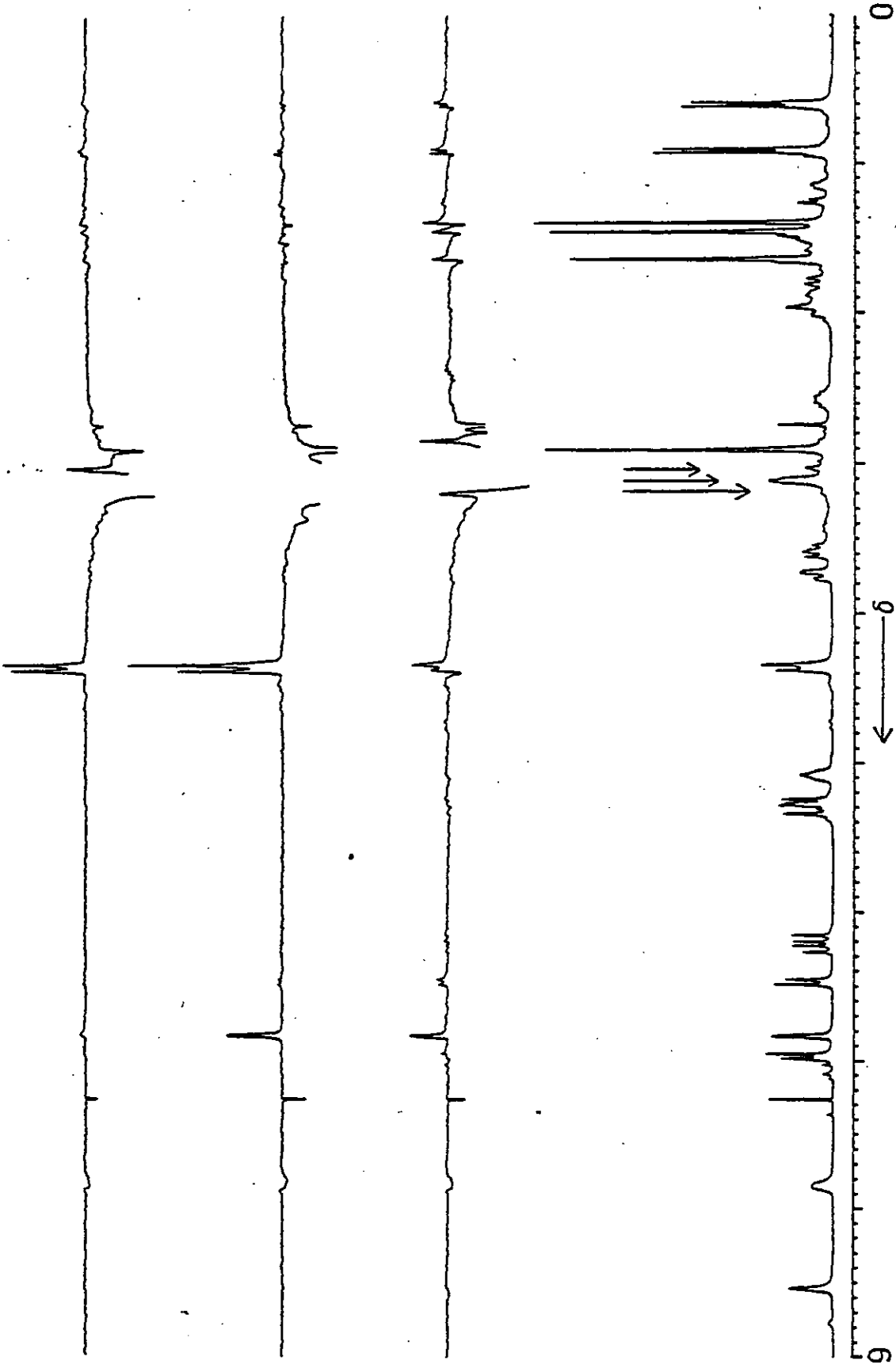
Appendix 2 Teleocidin A: Difference Decoupling Study (Irradiation at 4.34, $CDCl_3$ solvent).



Appendix 3 Teleocidin A: Nuclear Overhauser Effect Study ($CDCl_3$ solvent).



Appendix 3 (Cont.)



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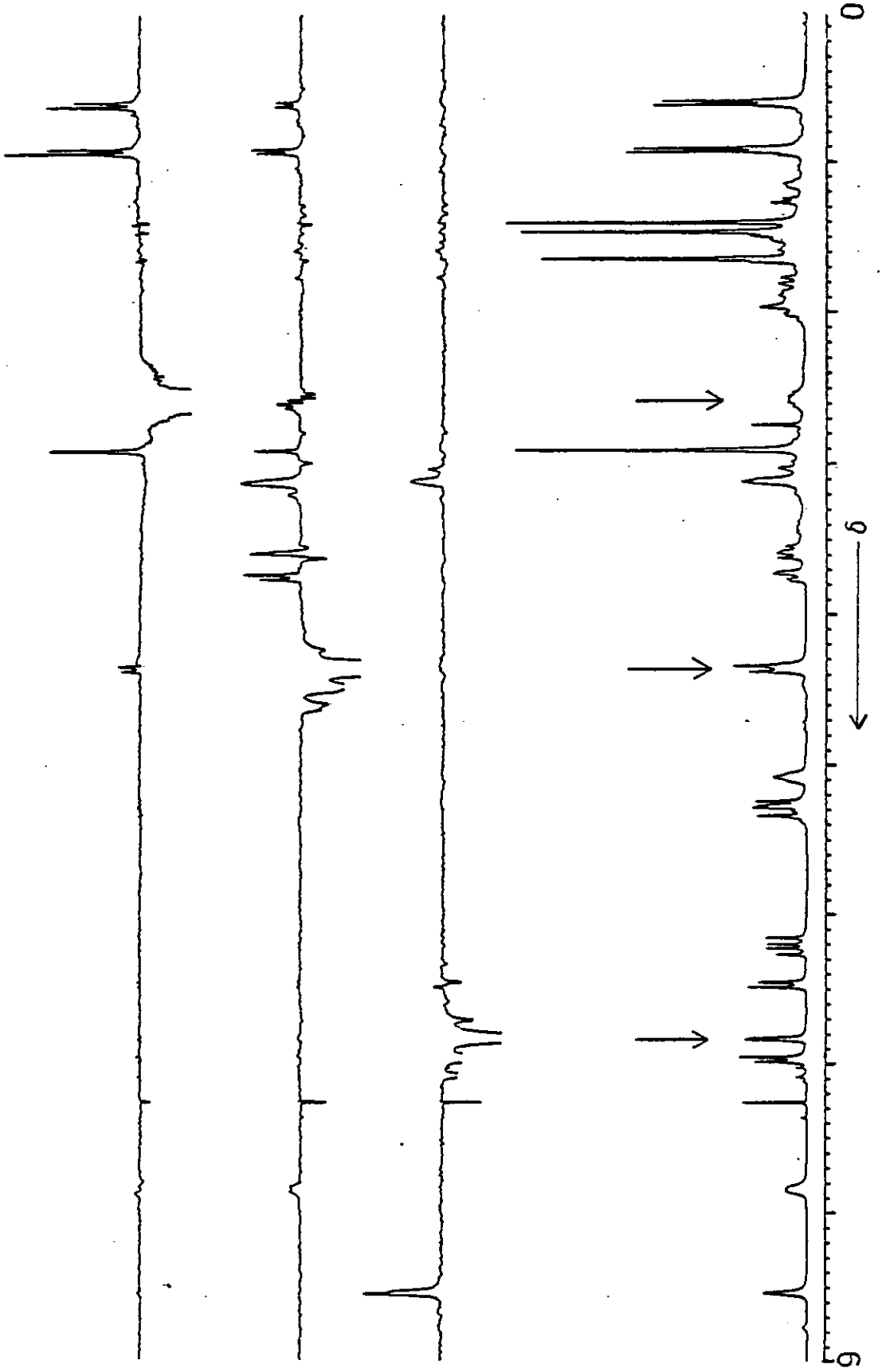
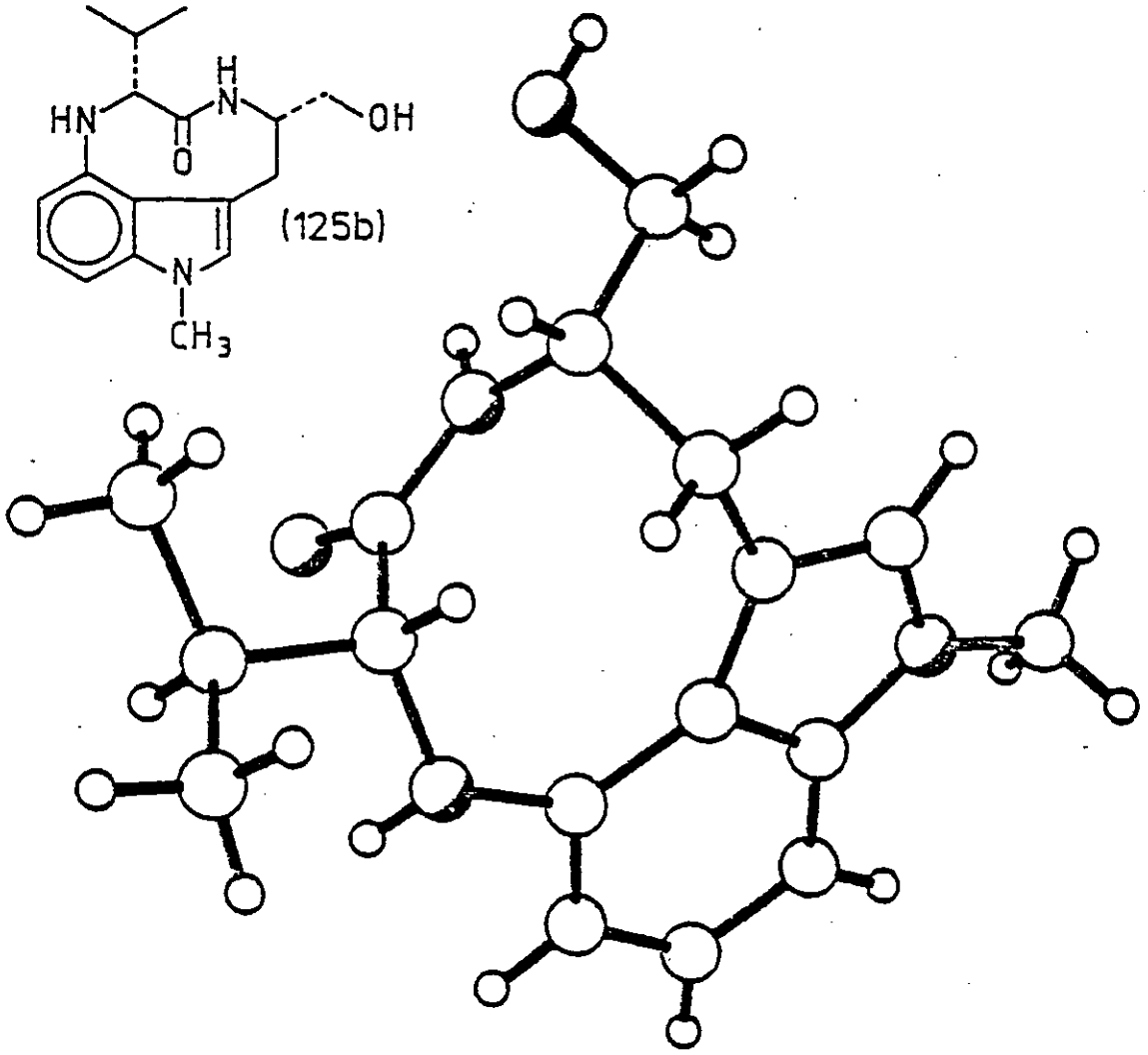
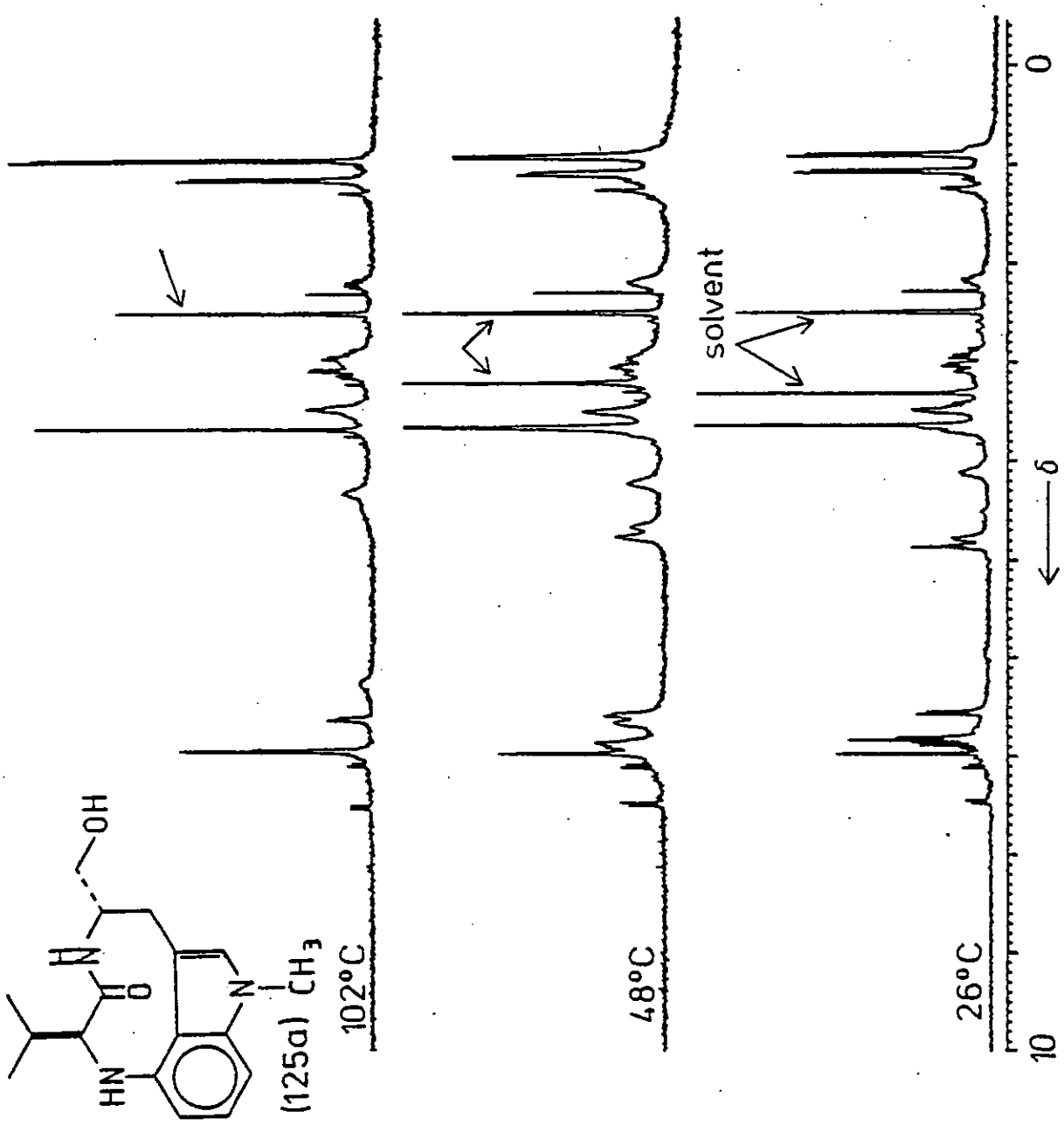


Appendix 4 X-Ray Crystallographic Analysis of the "Rearranged" cis Lactam (125b).



(125b)

Appendix 5 Variable Temperature ^1H n.m.r. Study on the Rearranged <u>trans</u> Lactam (125a) ($(CD_3)_2SO$ Solvent).



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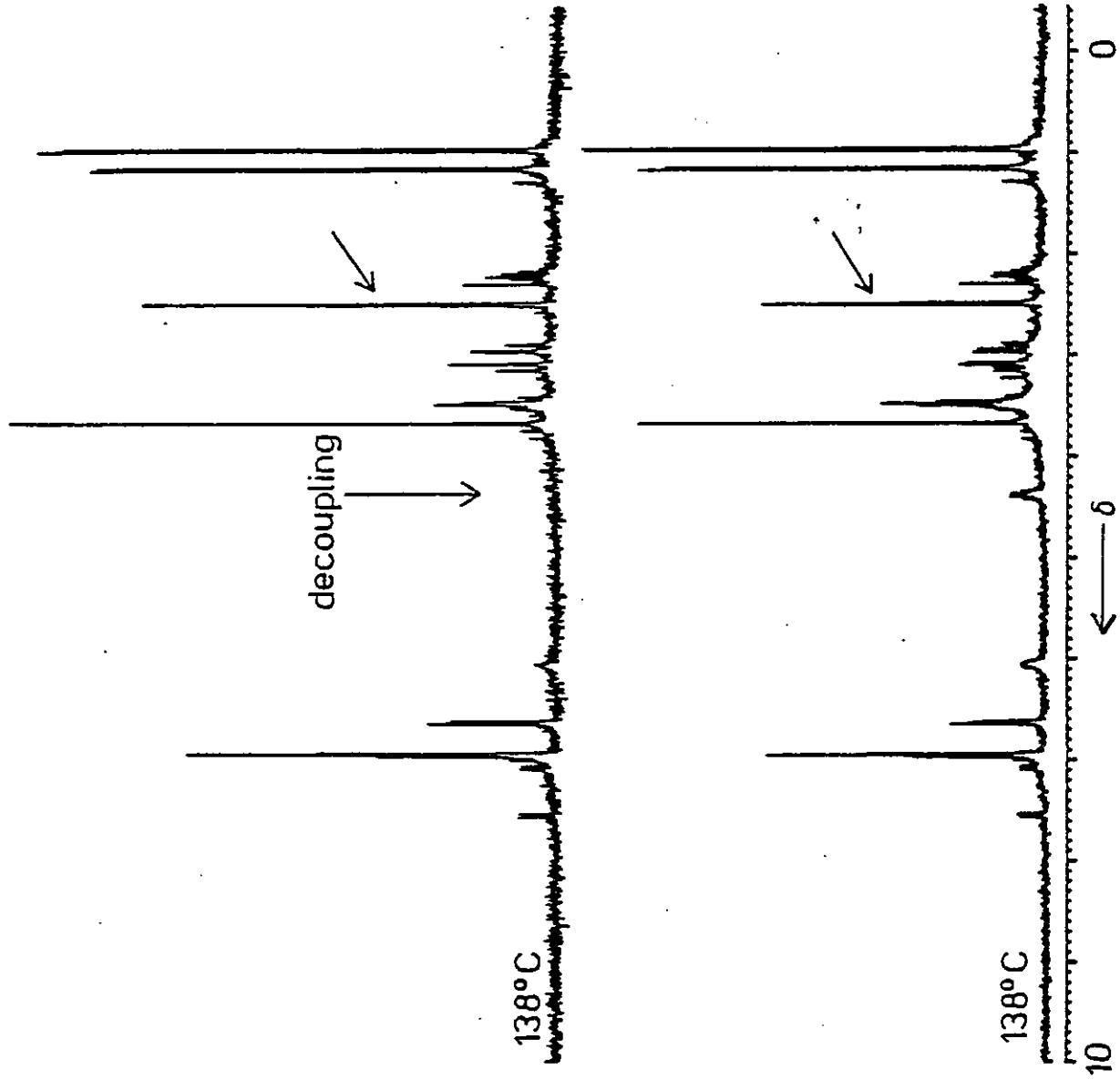
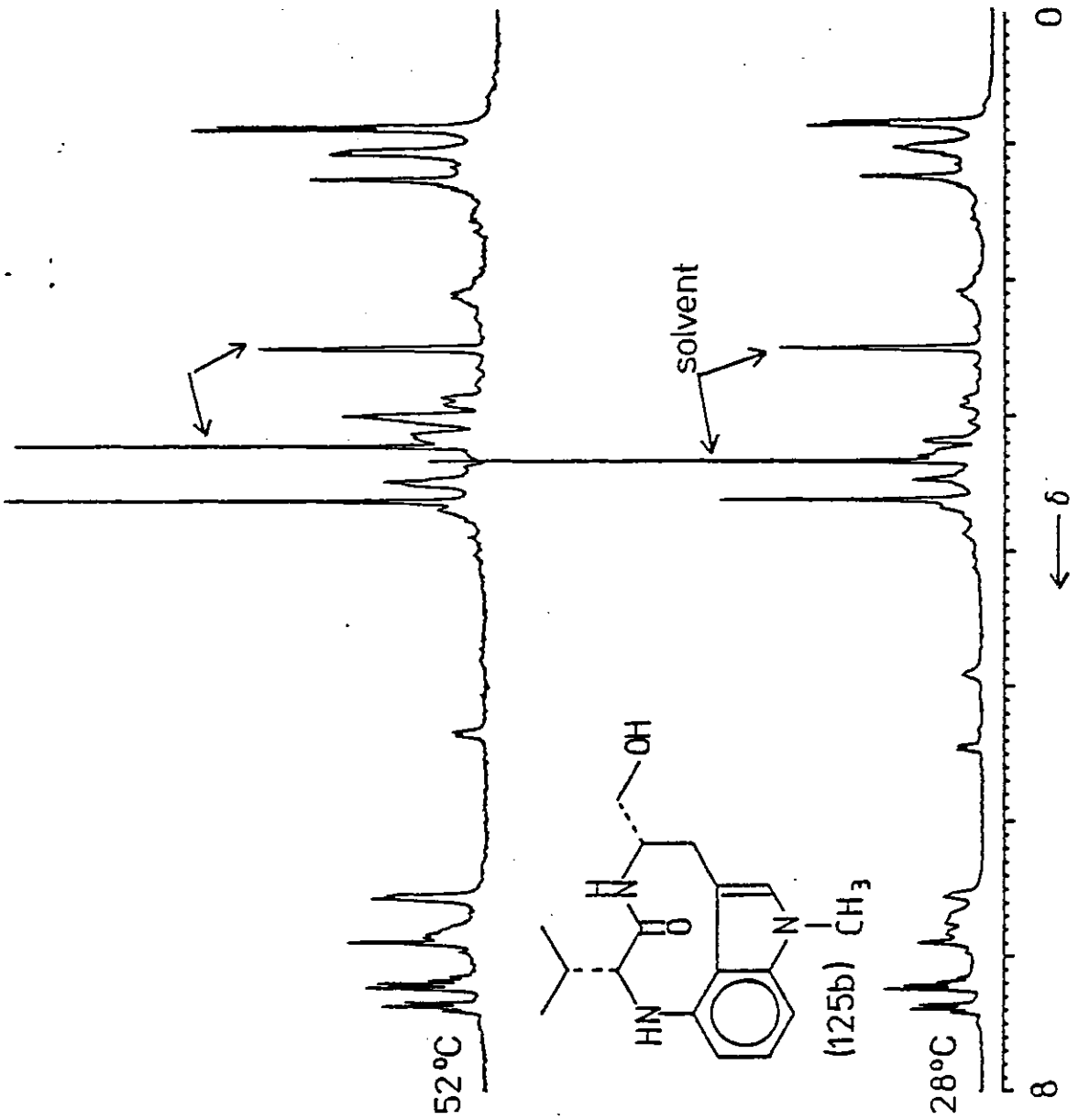


Appendix 6 Variable Temperature ^1H n.m.r. Study on the Rearranged <u>cis</u> Lactam (125b) ($(CD_3)_2SO$ Solvent).



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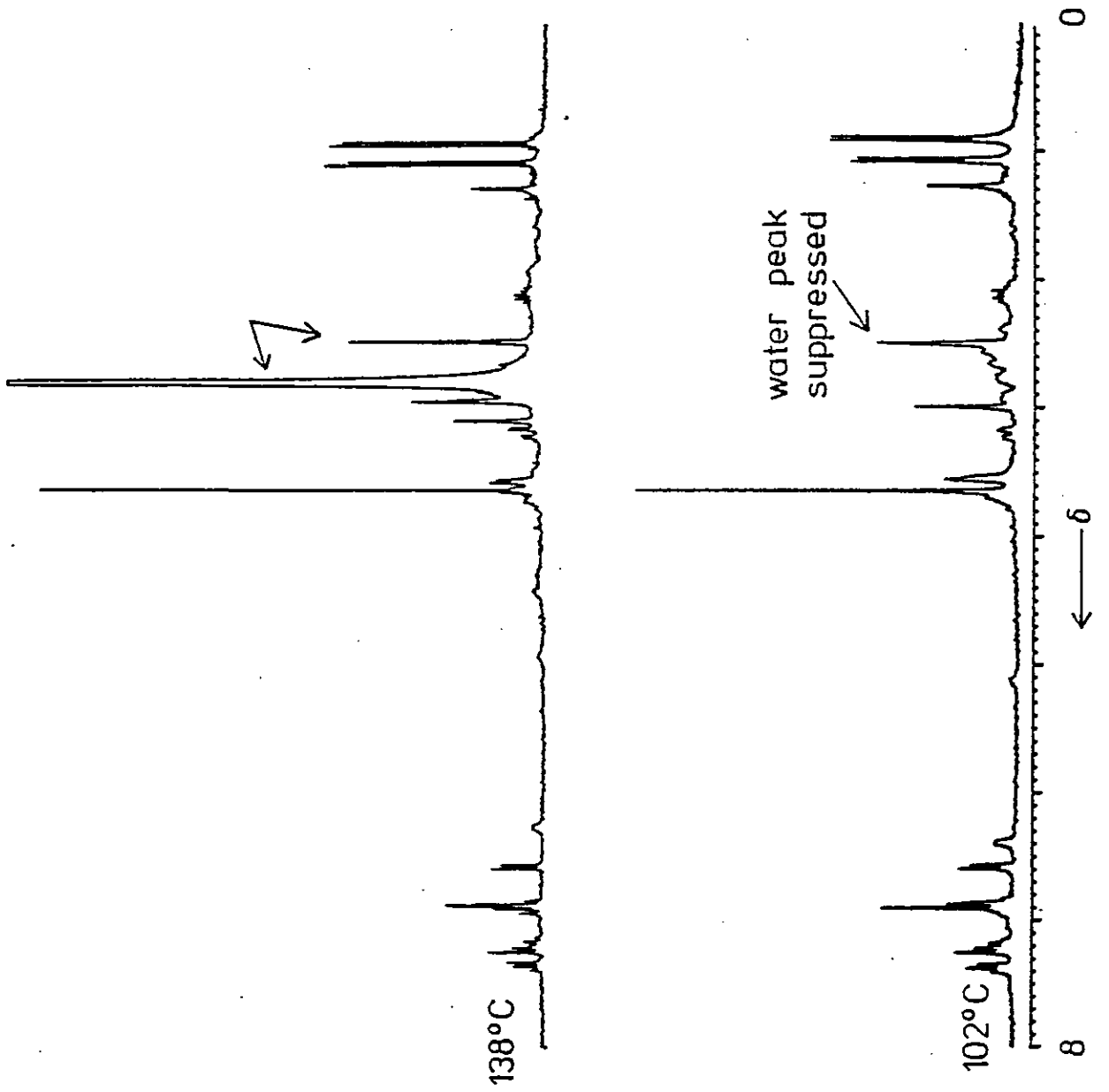
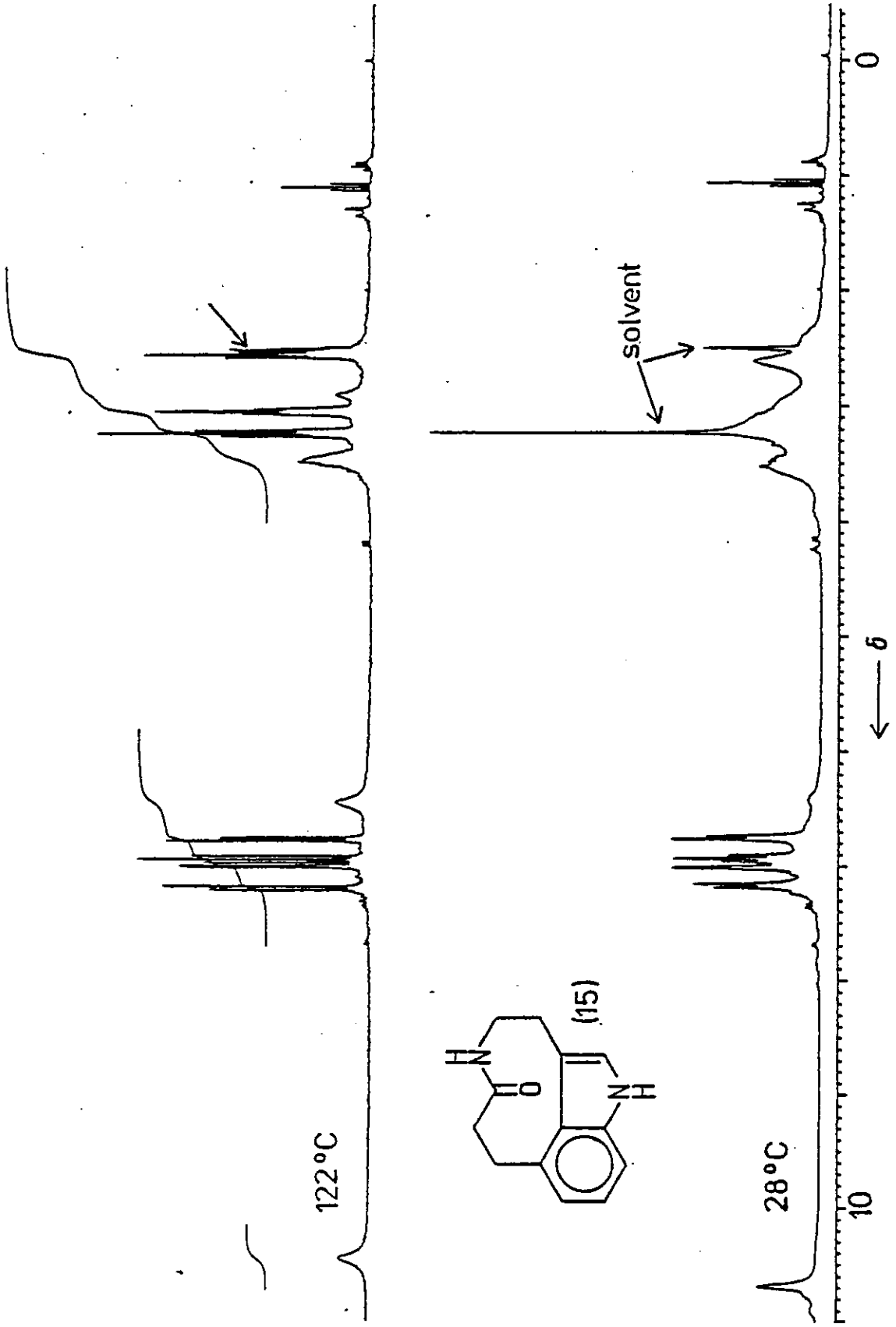


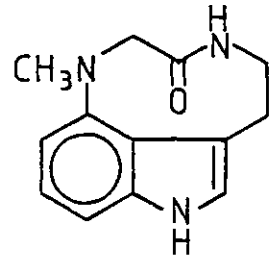
Appendix 7 Variable Temperature ^{1}H n.m.r. Study on the Carbon Linked Analogue (15) ($(CD_3)_2SO$ Solvent).



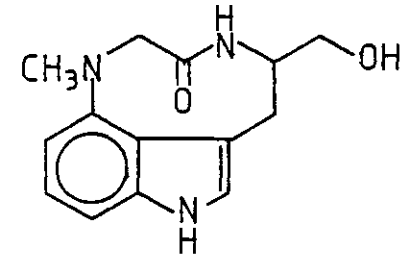
Appendix 8 Biological Studies

A recurring theme in this thesis has been the anticipated biological activity of the tricyclic model compounds (12), (13) and (15). It was found, however, that none of these compounds displayed any activity in a cattle tick screen at Pfizer Central Research, Sandwich, Kent. Teleocidin A (4) had previously been shown to be effective in the same screen. Increasing lipophilicity of (12) by introduction of a C-10 geranyl unit to give (211) was ineffective. The rearranged tricyclic compounds (125a) and (125b) were also inactive.

From these results it is evident that a biologically active molecule requires the following characteristics: (i) a hydrophilic 'northern region' lactam ring, (ii) a lipophilic 'southern region' and (iii) a free indole NH position.



(12)



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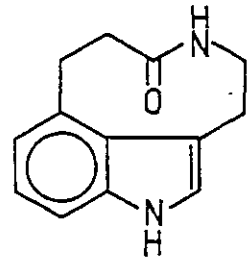

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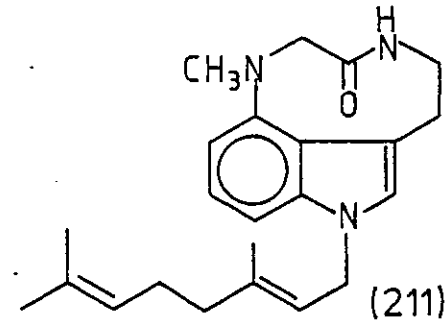

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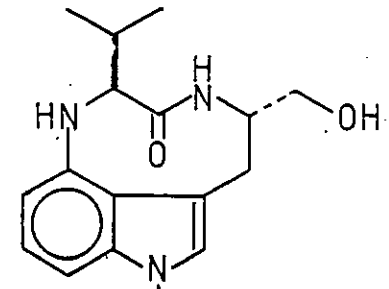
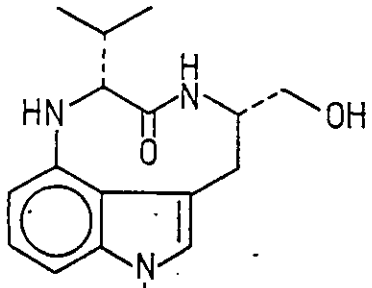


(125a)



(125b)