SYNTHESIS OF [2,3]-FUSED INDOLES

VIA VINYL AZIDES

A thesis presented by

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ABSTRACT

The synthesis of [2,3]-fused indoles from an existing indole unit is reviewed.

Several alkyl 2-azido-3-(indol-3-yl)azidopropenoates with various substituents were prepared,and their thermolyses in refluxing hydrocarbon and other solvents were investigated. It was shown that depending on the indole-2-substituent, pyrrolo[2,3-b]indoles, pyrido-[3,4-b]indoles (β-carbolines) or azepino[4,5-b]indoles could be obtained from these reactions. A mechanistically revealing intermediate in the formation of azepino[4,5-b]indoles was isolated. Some of the chemistry of these fused indoles was also investigated.

Numerous unsuccessful attempts to develop an alternative route to the azidopropenoates are described, some of which gave unexpected products.

To Carol, and my parents in

gratitude for their patience

ACKNOWLEDGEMENTS

The work described herein was carried out in the Hofmann Laboratory, Imperial College, between October 1980 and July 1983. No part of this work is being submitted for any other degree.

My thanks are due to my supervisor, Dr. Christopher J. Moody for his continuing enthusiasm and guidance throughout the three years of my Ph.D. project. His encouragement was particularly appreciated during those inevitable periods of stagnation when every reaction fails. I would also like to thank Professor Charles W. Rees, F.R.S., with whose group I worked in close association.

I offer my thanks to my Hofmann Laboratory colleagues, past and present, for making the "Hofmann" a laboratory of which I am proud to have been a member, and which in many ways I am sorry to leave.

Mr. Peter Sulsh has my thanks for his friendly and efficient services as Hofmann Laboratory Technician, and for his sense of humour.

I am also obliged to the following for the provision of excellent analytical, n.m.r., mass spectroscopic and X-ray crystallographic services: Mr. K.I. Jones (microanalysis); Mr. Richard Sheppard, Dr. David Neuhaus and Mr. Richard Young (250 MHz p.m.r. and ^{13}C c.m.r.); Mr. John Bilton, Mr. Nick Davies and Mrs. J. Challis (mass spectroscopy); and Dr. David Williams (X-ray crystallography).

Finally, I would like to thank Mrs. Betty Pinn for typing this thesis so accurately and efficiently, and Mr. Rod MacKenzie for proof-reading it.

CONTENTS

LIST OF ABBREVIATIONS

DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAD	Dimethyl acetylenedicarboxylate
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulphoxide
HMPA	Hexamethylphosphoramide
i.r.	Infrared
LAH	Lithium aluminium hydride
NBS	*N*-Bromosuccinimide
n.m.r.	Nuclear magnetic resonance
p.l.c.	Preparative layer chromatography
THF	Tetrahydrofuran
t.l.c.	Thin layer chromatography
u.v.	Ultra violet

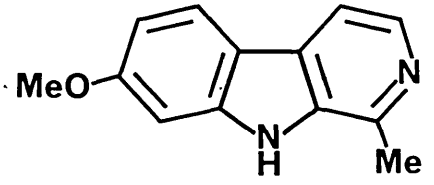
PART 1 : INTRODUCTION

Chapter 1

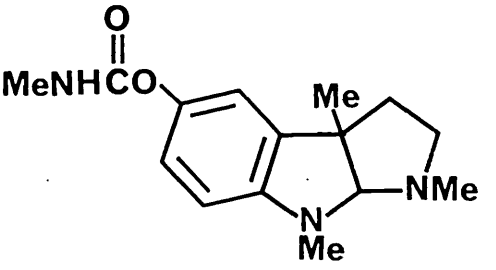
Synthesis of [2,3]-fused indoles from an existing indole unit

1.1 Introduction

[2,3]-Fused indoles are frequently found in Nature. Examples range from the relatively simple β-carboline alkaloids such as harmine (1) and the reduced pyrrolo[2,3-b] indole system found in, for example physostigmine (2), to more complex systems exemplified by catharanthine (3) and vindoline (4).



(1)



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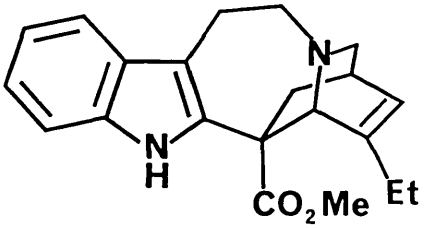

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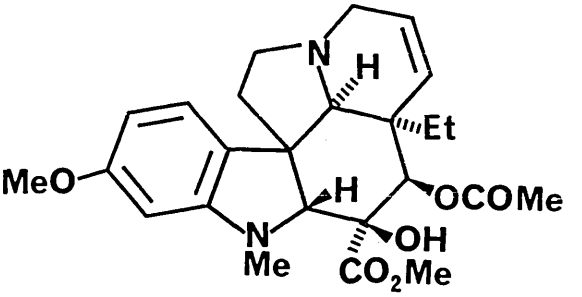


(4)

Since numerous examples of other systems could be cited, it is obvious that routes to [2,3]-fused indoles will be of importance to the synthetic alkaloid chemist, and many of the examples in this review come from the field of alkaloid synthesis.

Only reactions in which a new ring is fused to an existing indole moiety will be considered in this review, and these will be categorized according to reaction mechanism thus:

Section 1.2: Formal electrophilic attack at the indole 2-position.

Section 1.3: Electrophilic attack at the indole 3-position.

Section 1.4: Nucleophilic attack at the 2-position following an initial electrophilic attack at the 3-position.

Section 1.5: Cycloadditions.

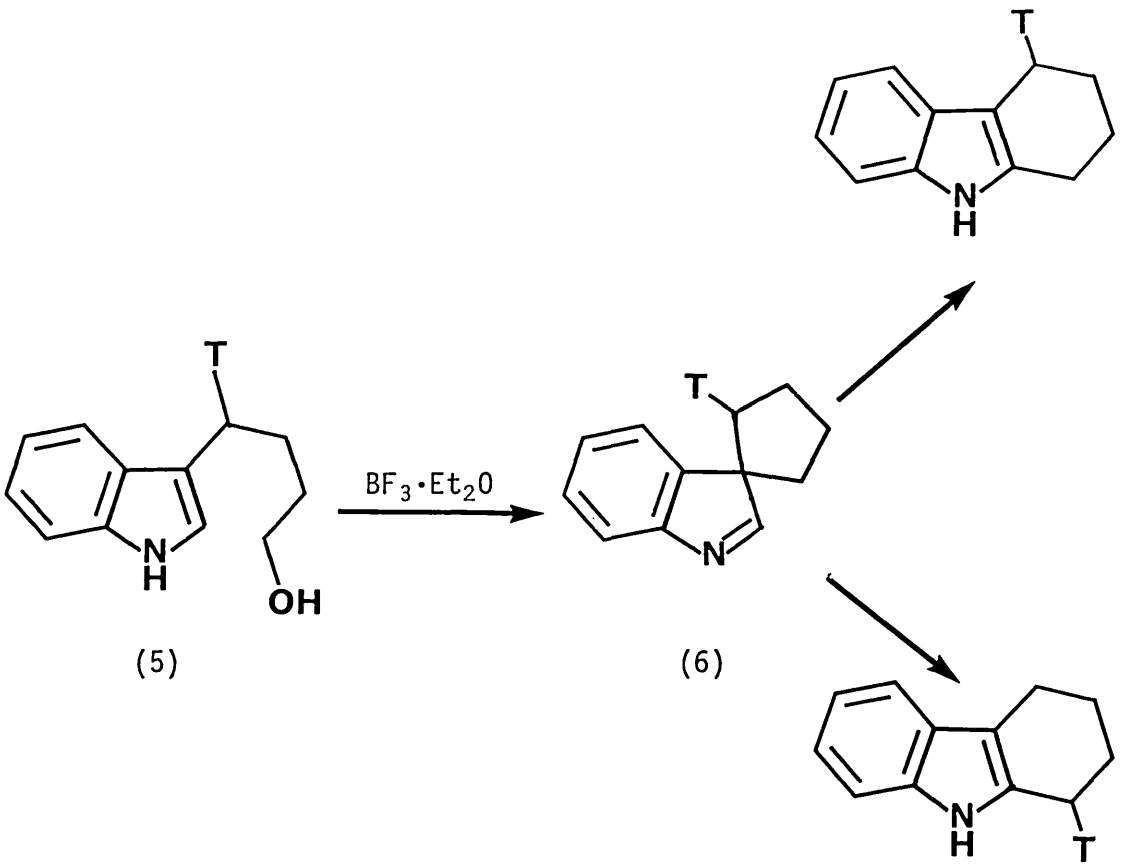
Section 1.6: Interactions between two side-chains.

Section 1.7: Miscellaneous.

The literature in this area is so voluminous that it would require far more space than is available, for the review to be comprehensive. The intention is rather, to systematize and exemplify the kinds of reaction which appear to be the most useful routes into these important compounds.

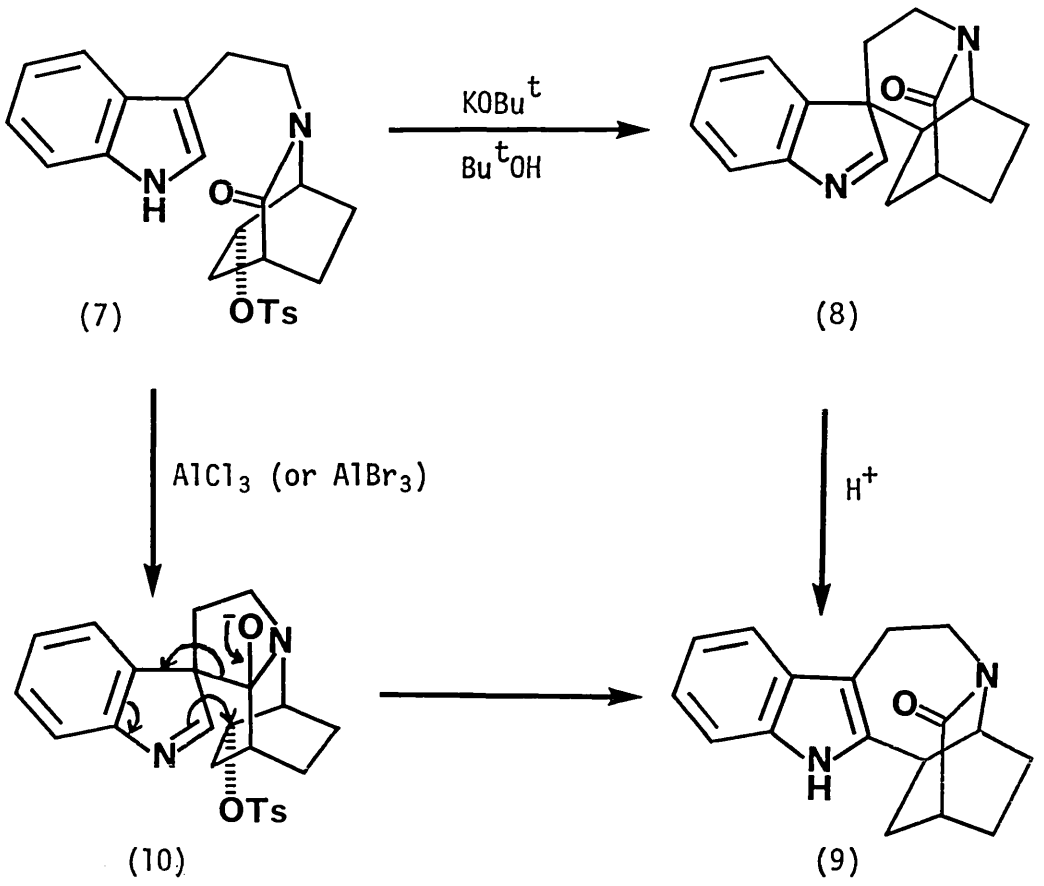
1.2 Formal electrophilic substitution at the indole 2-position

Formal electrophilic substitution of the indole 2-position is in many cases the result of initial attack at the 3-position followed by rearrangement of the resulting indolenine or indoleninium cation, such as in the case of the 3-indolyl butanol (5). The roughly equal distribution of the tritium label in the products suggests the intermediacy and subsequent migration of the indolenine (6).[1]



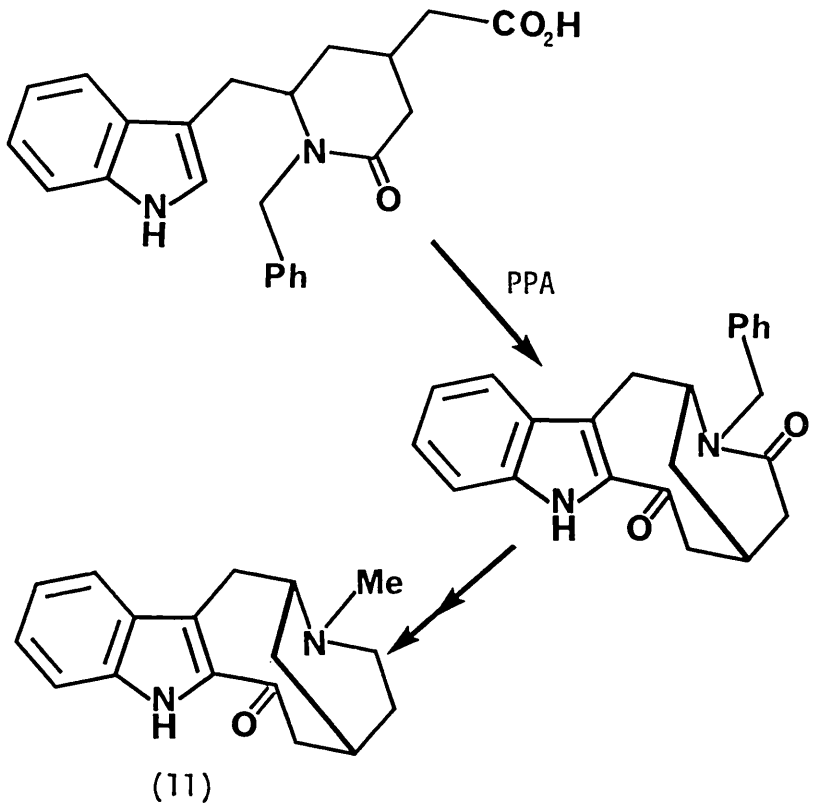
(5) (6)

Many examples of cyclizations of this nature are encountered in alkaloid synthesis. The isoquinuclidine tosylate (7) for example, gave the indolenine (8) upon base treatment. Dilute acid treatment of (8) then effected rearrangement to the ibogamine lactam (9). Alternatively (9) is available from (7) by treatment with aluminium chloride or bromide.[2] The author suggests that the Lewis acid catalysed cyclizations are likely to proceed *via* a different pathway, since it is probable that treatment of (7) with *protic* acids gives a carbonium ion, and in such reactions no trace of (9) could be observed. An alternative (non-carbonium ion) mechanism for the Lewis acid catalysed reactions must therefore be sought. One possible rationale would be to assume initial cyclization at the indole 3-position, giving (10), followed by rearrangement as shown:

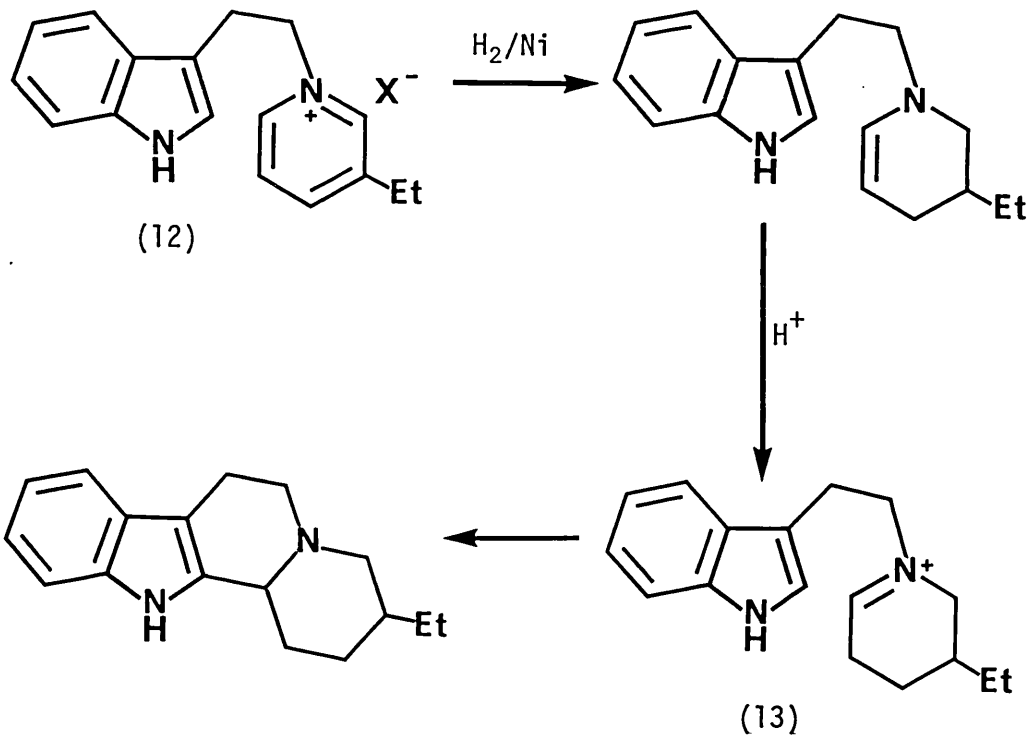


A Lewis acid catalysed cyclization of the Friedel Crafts type has been described by Japanese workers, whereby 3-indolyl alkanoic acids were treated with PPA, to give cycloalkan[b]indolones.[3] This method has been employed in the synthesis of the alkaloid model (11).[4]

Many examples of cyclizations in both the 2- and 3-positions involve electrophilic attack by an imine or iminium species (normally generated *in situ*), on an indole. A simple example is the cyclization in acid, of the product of hydrogenation of (12), *via* (13).[5]


CO2H
N
H
O
Ph
PPA
Ph
N
O
N
H
O
Me
N
N
H
O

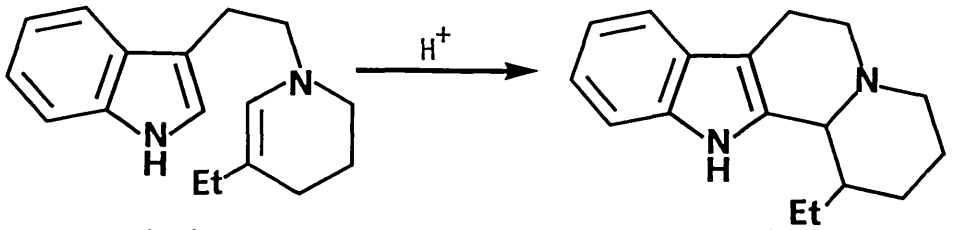
(11)


N
H
X-
N+
Et
H2/Ni
N
H
N
Et
H+
N
H
N
Et
N+
H
Et

(12)

(13)

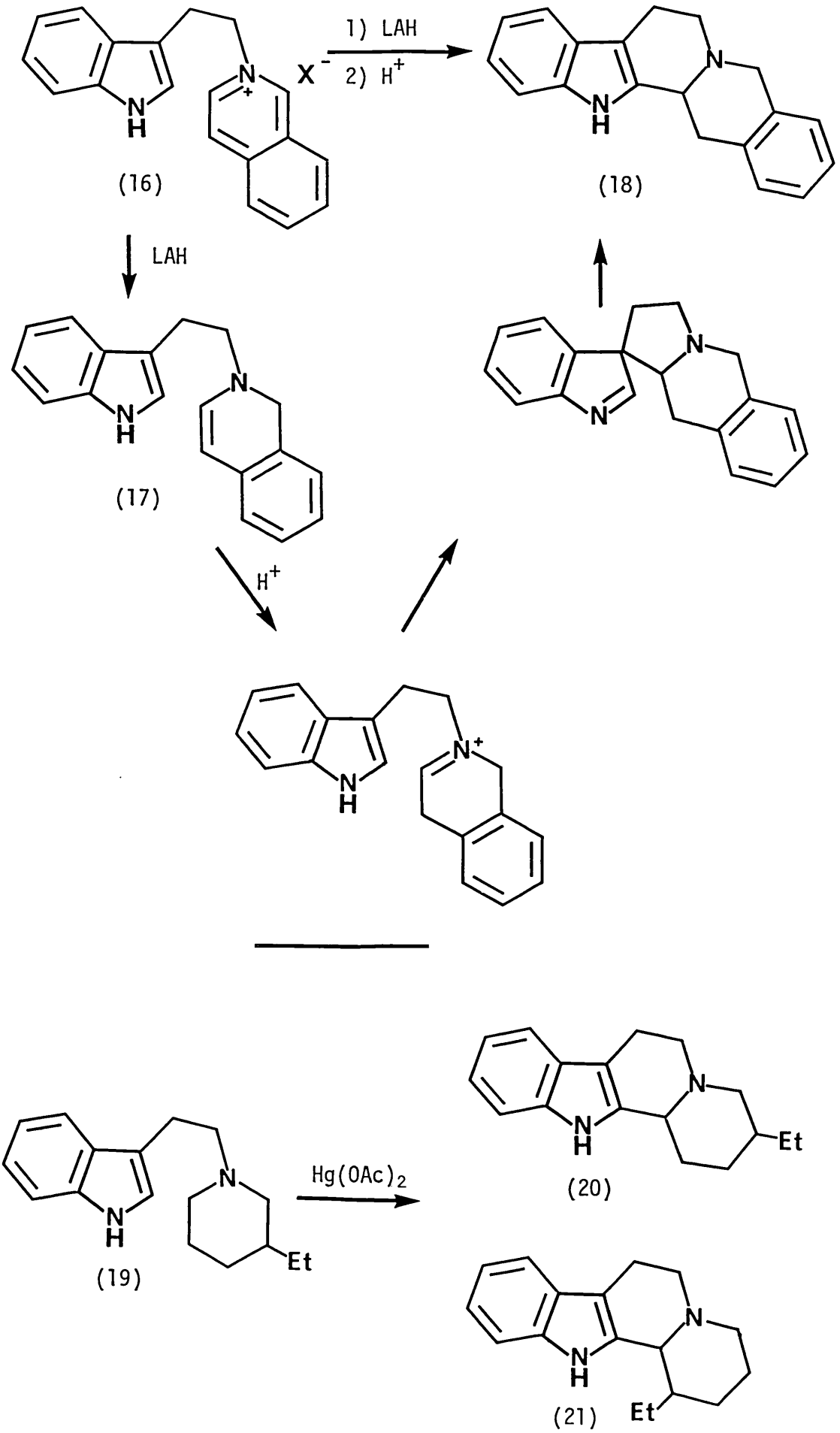
The authors make no mention of obtaining any of the product (14) which would be obtained by a similar cyclization of the other possible hydrogenation product (15).



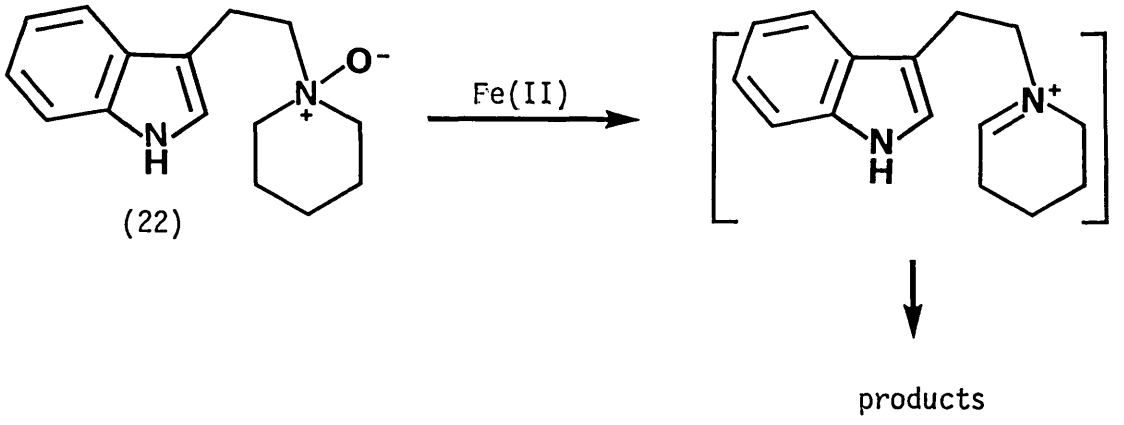
(15) (14)

Huffman has reported a similar sequence,[6] in which the isoquinolinium salt (16) was cyclized by treatment with LAH, followed by acid. The intermediate dihydroisoquinoline (17) was isolated and shown to give the same cyclized product (18) upon acid treatment. The dihydroisoquinoline is thought to give the iminium species by protonation. As in the previous example cyclization follows, presumably *via* the pathway shown.

Oxidative methods may also be used to furnish the tetrahydropyridinium species necessary for such cyclizations. The oxidative cyclization of piperidine (19) with mercuric acetate has been reported[7] to give mixtures of both epimers of (20) and (21) after work-up with hydrogen sulphide and acid. Since mercuric acetate is known to oxidize *N*-alkyl piperidines to tetrahydropyridine species, the assumed intermediate is again an iminium cation such as (13). This method has been used in the synthesis of ajmalicine, and other heteroyohimbine alkaloids.[8]

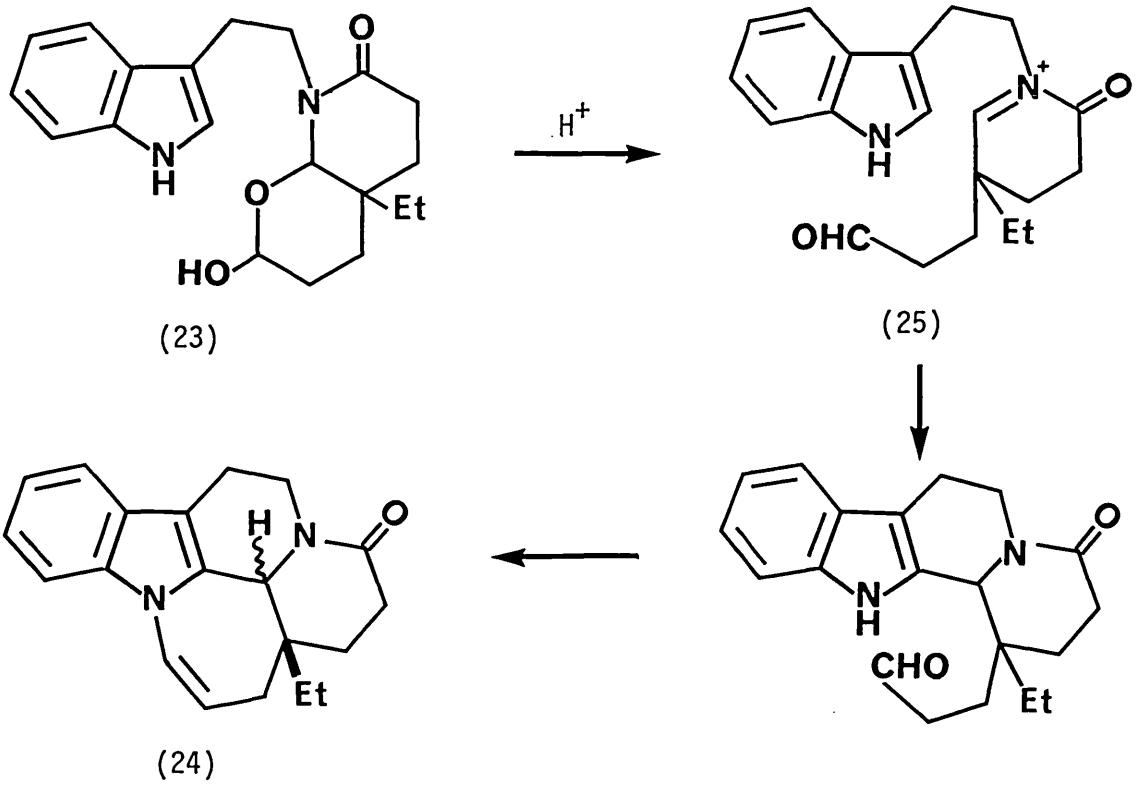

1) LAH
2) H+
X-
(16)
(18)
LAH
(17)
H+
(19)
Hg(OAc)2
Et
(20)
(21)
Et

More recently, a method of producing such iminium species by catalytic treatment of *N*-oxides such as (22) with ferrous salts, has been reported.[9]



(22)

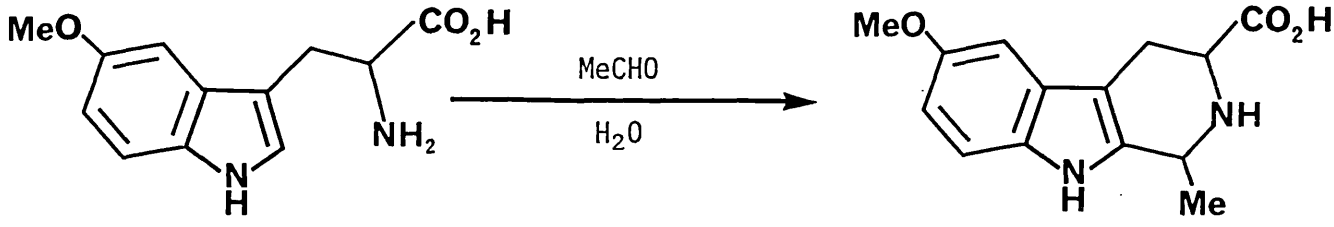
In the elegant cyclization of (23) to the pentacycle (24) under the influence of acid, the intermediate species (25) is in this instance produced by hydrolytic cleavage (assisted by the nitrogen lone pair) of a cyclic hemiacetal unit.[10]



(23) (25)

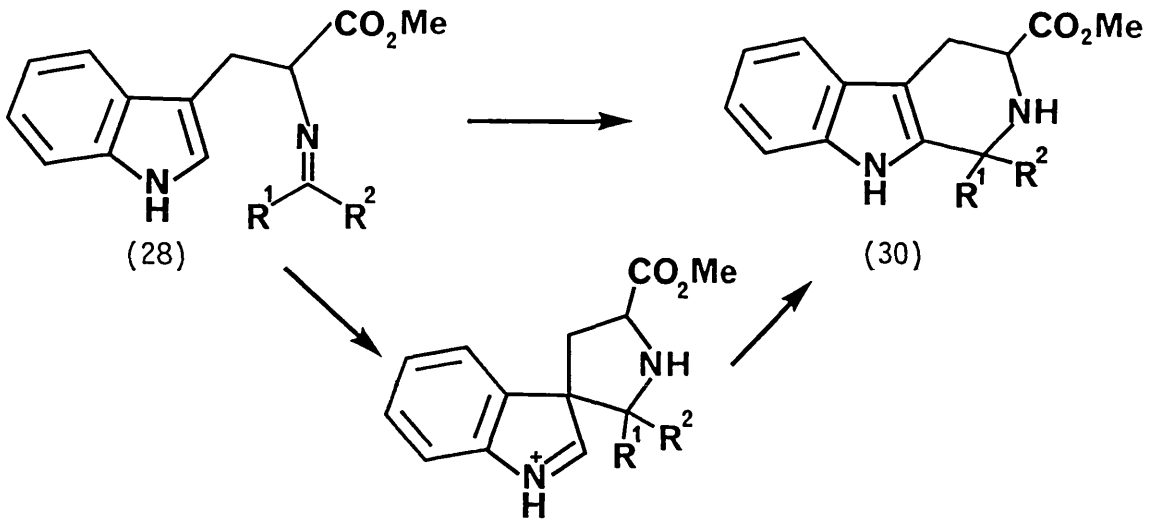
(24)

The well-known cyclization of tryptophans and tryptamines, when condensed with aldehydes[12] or ketones[13] may be exemplified by the reaction of (26) with acetaldehyde in water, to give tetrahydro-β-carboline (27),[11] *via* an intermediate imine.



(26) (27)

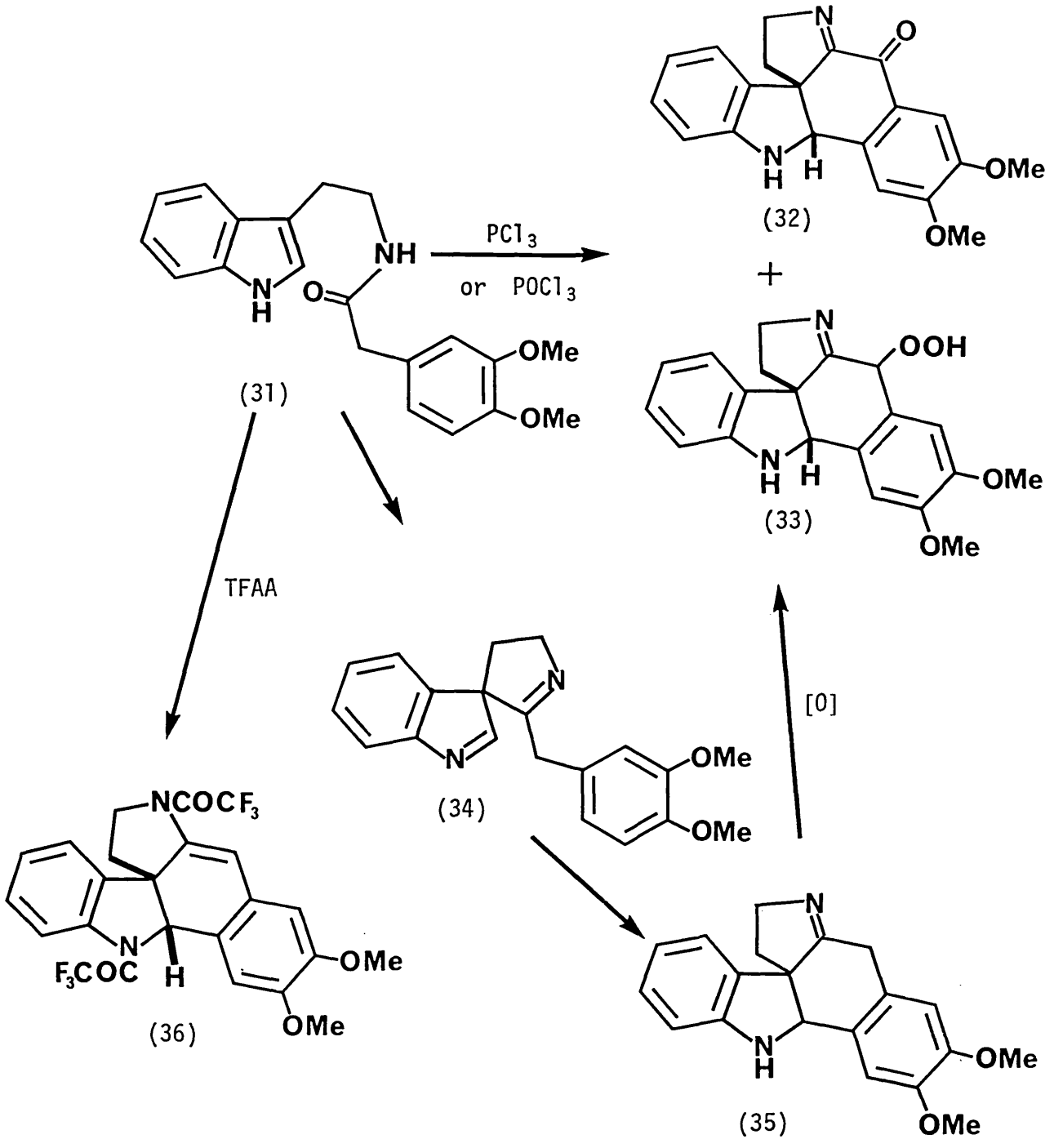
This reaction has received some attention recently. Grigg *et al*[14] have shown that the reaction does not proceed in aprotic solvents even at elevated temperatures in the absence of acids, and moreover that the rate of cyclization is directly related to the pK_a of the acid catalyst. This is contrary to the assertion of Cook *et al*[15] who describe such cyclizations taking place without any acid catalyst. Grigg[14] concludes that cyclization under Cook's conditions must have been catalysed by adventitious acidic impurities. He also speculates, without reaching any apparent conclusion, as to whether the cyclization goes *via* spiro imine (29) implying a disfavoured 5-*endo trig* process or directly, *viz* (28) → (30), a geometrically favoured 6-*endo trig* process.



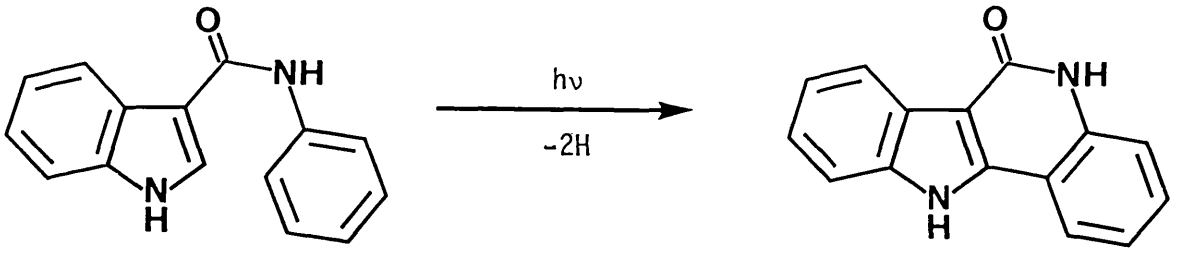
(28) (29) (30)

N-Acyltryptamines may be cyclized to 3,4-dihydro-β-carbolines by treatment with phosphorus oxychloride, under the conditions of the Bischler-Napieralski reaction.[12] However, the cyclization of amide (31) with phosphorus trichloride, phosphorus oxychloride or trifluoroacetic anhydride gave contrasting results.[16] The phosphorus trichloride and phosphorus oxychloride mediated reactions both gave moderate yields of (32) as well as traces of β-carboline products and of the hydroperoxide (33).

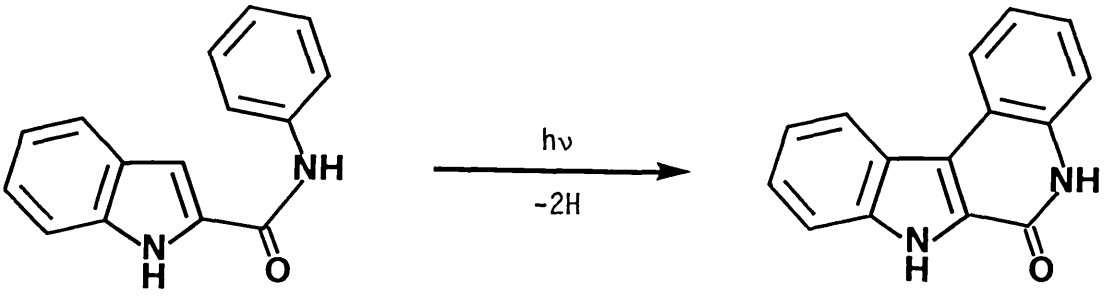
The overall sequence seemingly involves formation of the spirocyclic indolenine intermediate (34) which further cyclizes by intramolecular attack of the nucleophilic dimethoxyphenyl residue. Jackson asserts that air autoxidation of the species (35) thus produced, affords (33) which subsequently gives (32) by loss of water. The trifluoroacetic anhydride mediated reaction gave a quantitative yield of (36).



A photochemical cyclization applicable to introduction of bonds at either *C*-2 or *C*-3 of an indole nucleus involves preparation and photolysis of amides (37) or (38) to give cyclized derivatives (39) and (40) respectively.[17] The authors propose that double bond character in the amide C-N bond furnishes some stilbene-type properties in the substrate, facilitating photocyclization. Dehydrogenation occurs spontaneously, but unfortunately the overall yields are somewhat low.

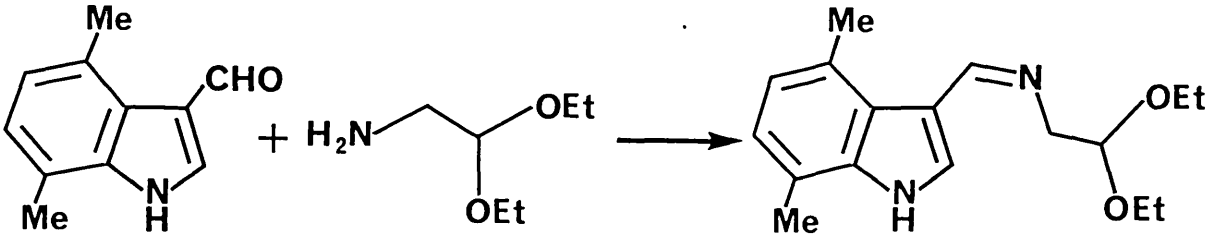


(37) (39)

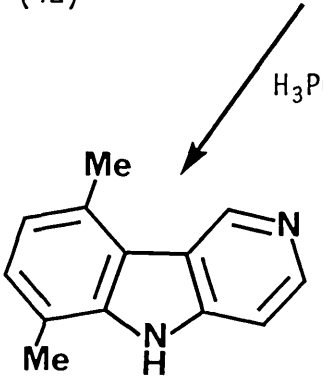


(38) (40)

The imine (41) resulting from condensation of 4,7-dimethylindole-3-carbaldehyde with the aminoacetal (42), may be cyclized in high yield (*ca* 90%) by treatment with phosphoric acid, to give the γ-carboline (43).[18]

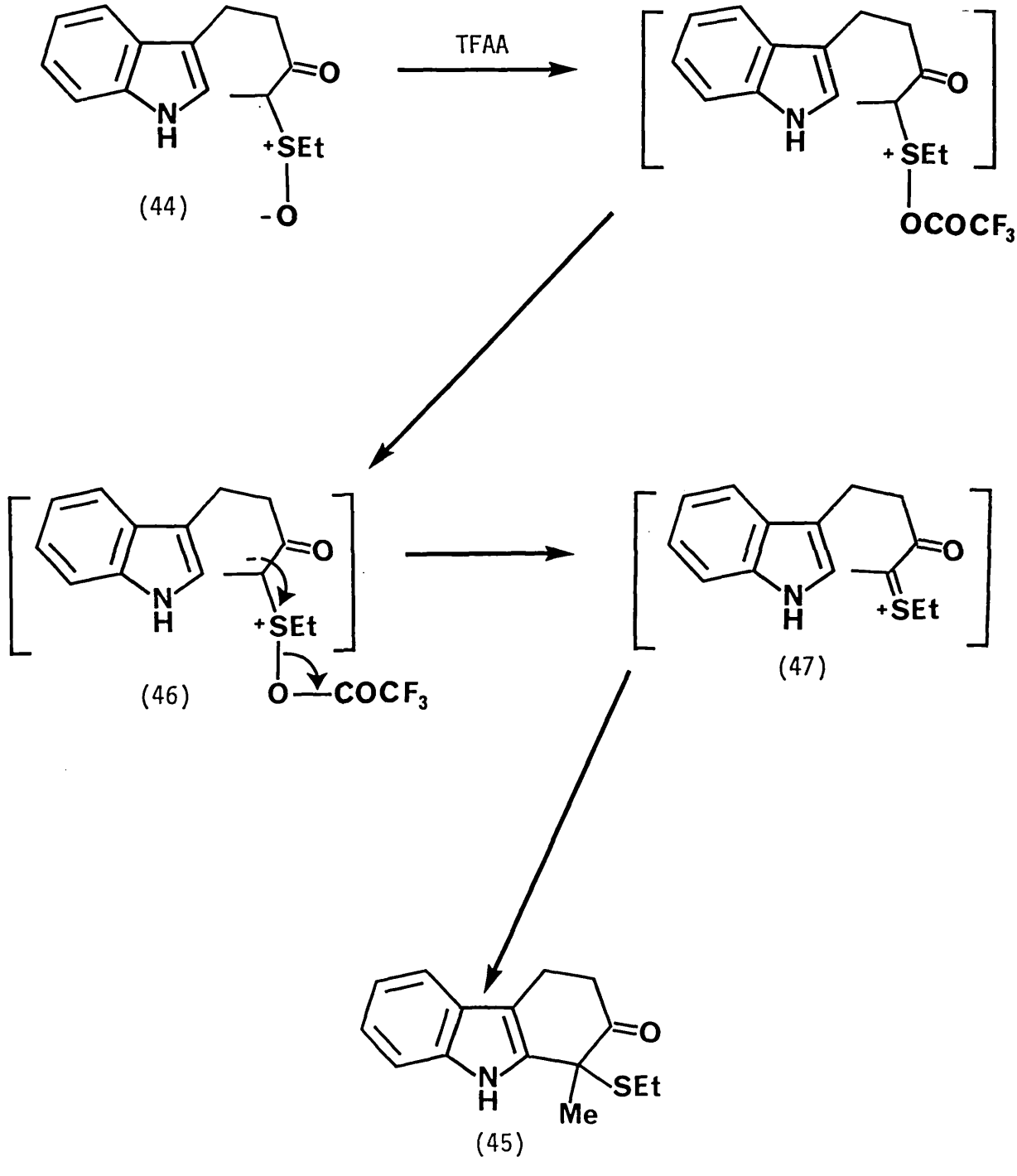


(42) (41)

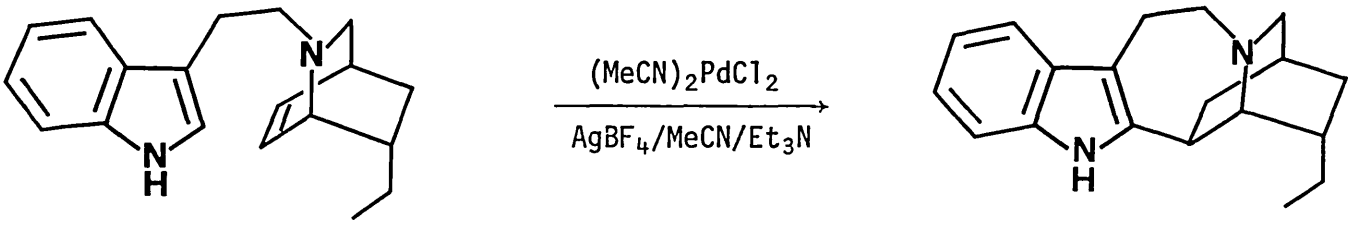


(43)

A very attractive application of the Pummerer rearrangement has been reported by Japanese workers,[19] who cyclized sulphoxides such as (44) by treatment with trifluoroacetic anhydride in benzene, to give (45) evidently *via* ylid (46) and subsequently, sulphenium ion (47).



Palladium induced cyclizations have received some attention of late. An example of such is Trost's use of $(MeCN)_2PdCl_2/AgBF_4$ to produce the ibogamine ring system (49) from substrate (48). Deuteration studies provided strong evidence of the involvement of a 2-metallated indole species in the reaction pathway.[20]



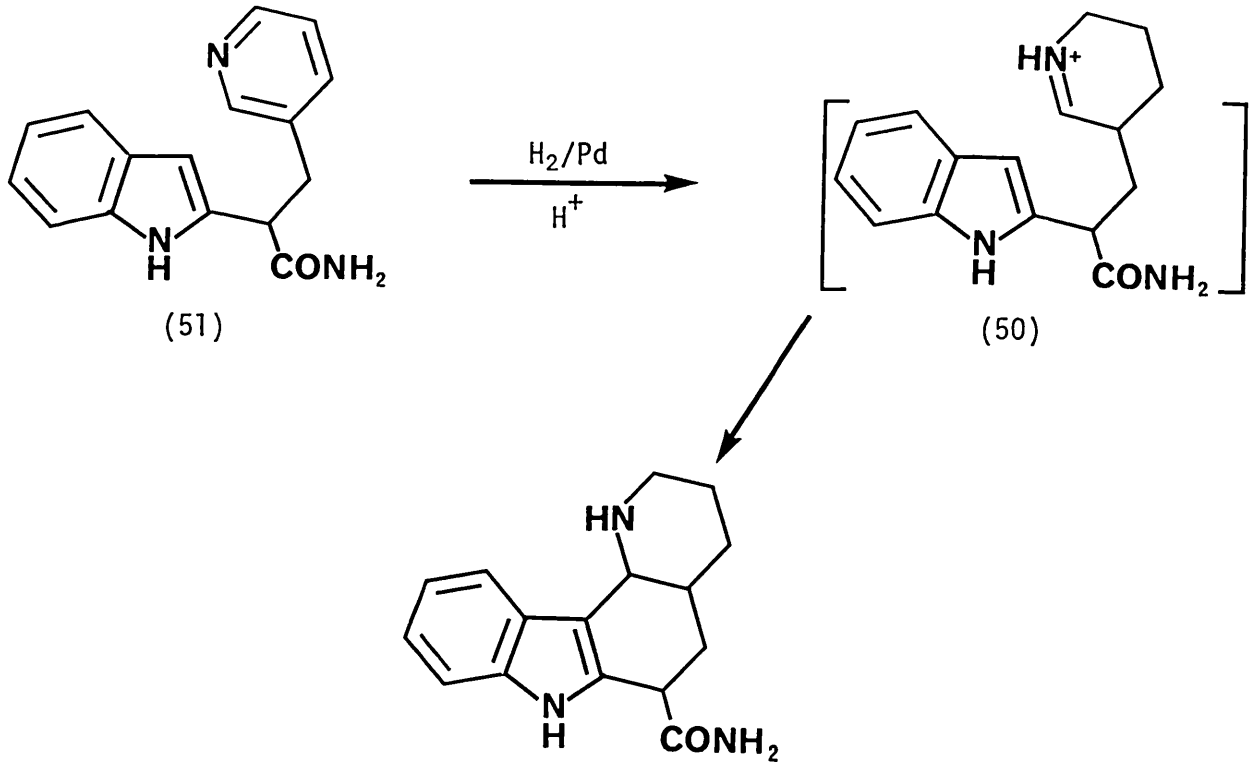
(48) (49)

1.3 Electrophilic attack on the indole-3-position

Reactions involving electrophilic attack at the 3-position dominate indole chemistry, and hence only representative examples of this type of cyclization will be given. As already discussed in Section 1.2, formal electrophilic attack in the 2-position by an iminium cation on an indole is a very common and useful ring forming reaction, and many cyclizations in the 3-position likewise involve attack by such species. Electrophiles such as carbonyl groups, may also be induced to attack the 3-position intramolecularly.

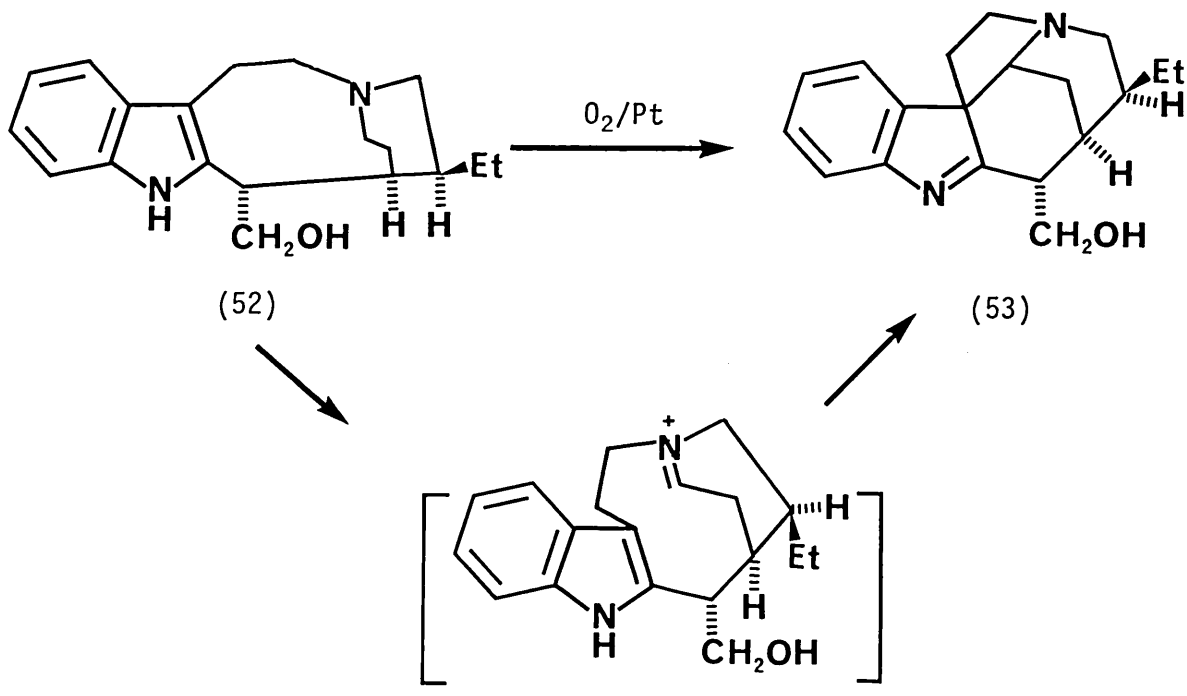
An example of the former type is the acid catalysed ring closure of (50), the hydrogenation product of (51).[21]

Oxidative routes to iminium species suitable for cyclization at the indole-3-position have been applied to alkaloid synthesis. For instance, cyclization of the hydroxymethyl amide (52), to (53) proceeds



(51) (50)

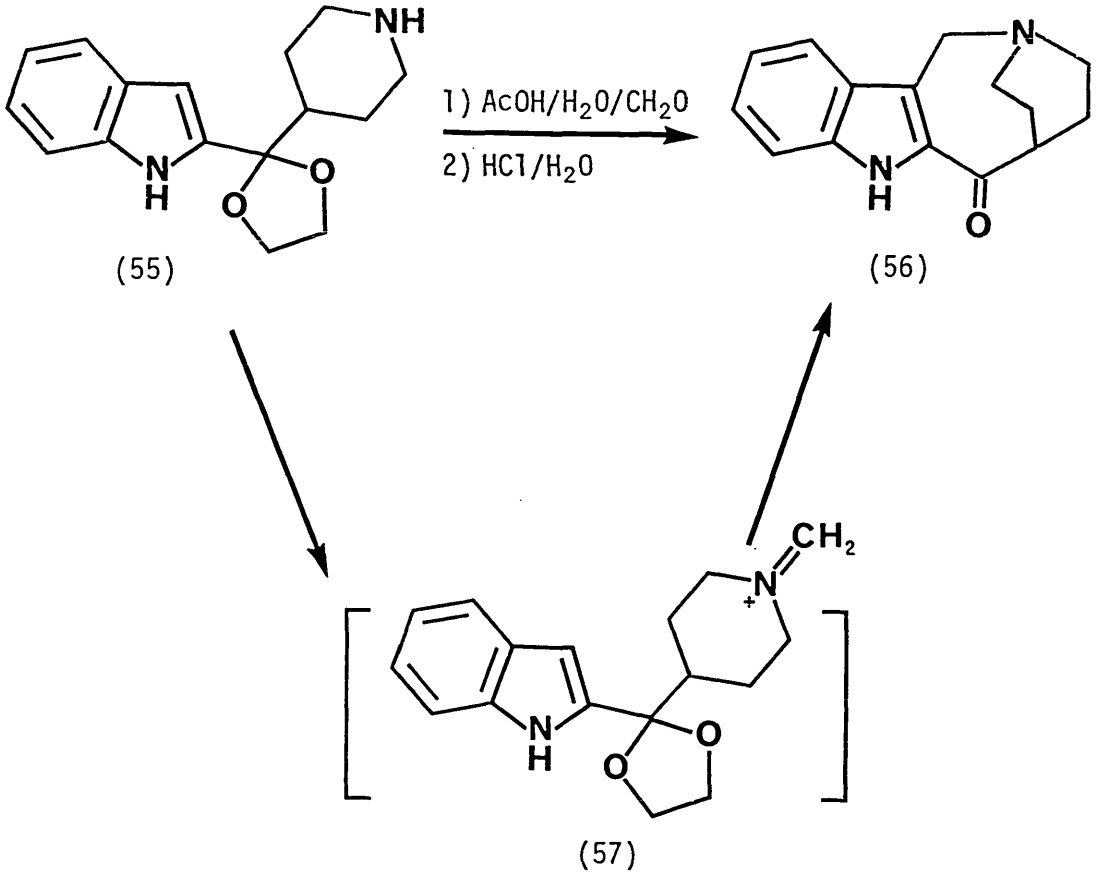
via (54) which is produced by a platinum catalysed oxidation.[22]



(52) (53)

(54)

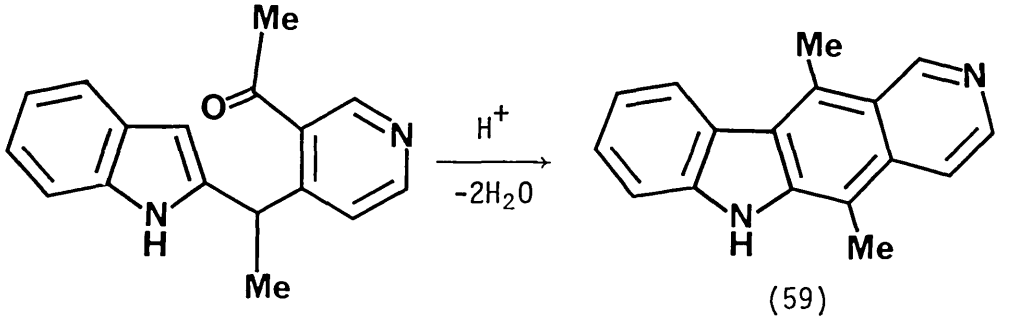
An example of an intramolecular Mannich reaction used to furnish a [2,3]-fused indole arises in the work of Joule *et al* on the ring skeleton of the alkaloid appariciné.[23] The ketal (55), upon treatment with formaldehyde in acetic acid, followed by dilute hydrochloric acid gave (56), as a result of attack at the indole-3-position by the intermediate Mannich base (57).



(55) (56)

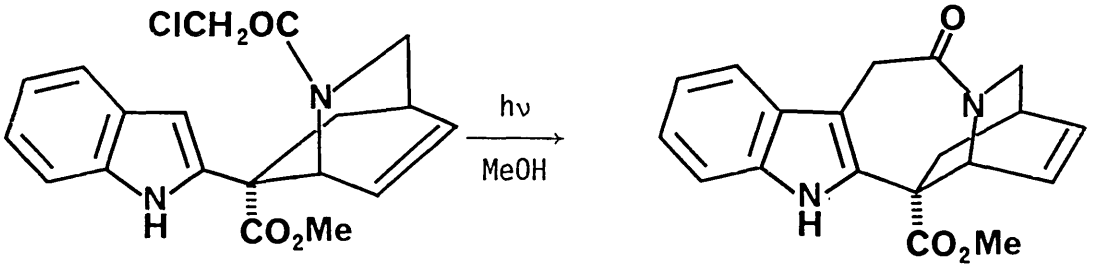
(57)

The electrophilic attack of a carbonyl group in the indole-3-position has been employed by Joule[24] in the last step of a synthesis of ellipticine. Acid catalysed cyclization of (58) followed by loss of water, gave ellipticine (59).



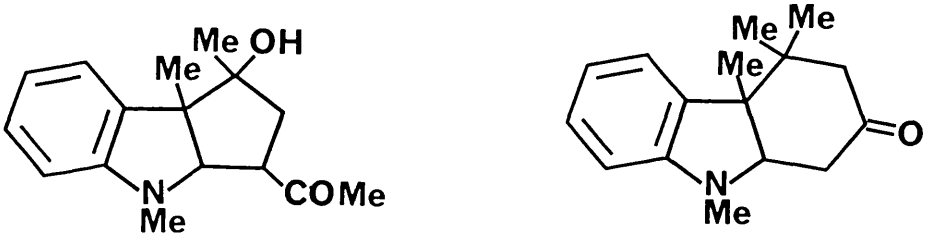
(58) (59)

A photochemical cyclization of chloroacetamides at the indole-3-position[25] has recently been applied to alkaloid synthesis by Sundberg *et al*[26], in the preparation of desethyl catharanthine derivative (60). The chloroacetamide (61) was photocyclized in methanol, evidently *via* homolytic cleavage of the C-Cl bond and subsequent cyclization of the resulting free radical.



(61) (60)

Numerous cyclizations of indoles with 1,4-diketones were reported in the 1950's by Robinson *et al*.[27,28] Indole itself condensed with acetonylacetone to give 1,4-dimethylcarbazole, while 1,3-dimethylindole was found to give (62). It is reasonable to suppose that a conventional series of electrophilic attacks on indole is involved. Another reaction in a similar vein is that between mesityl oxide and 1,3-dimethylindole. Again, the author suggests that initial attack is at the indole 3-position, followed by cyclization *via* the enolized side chain to give (63).[29]

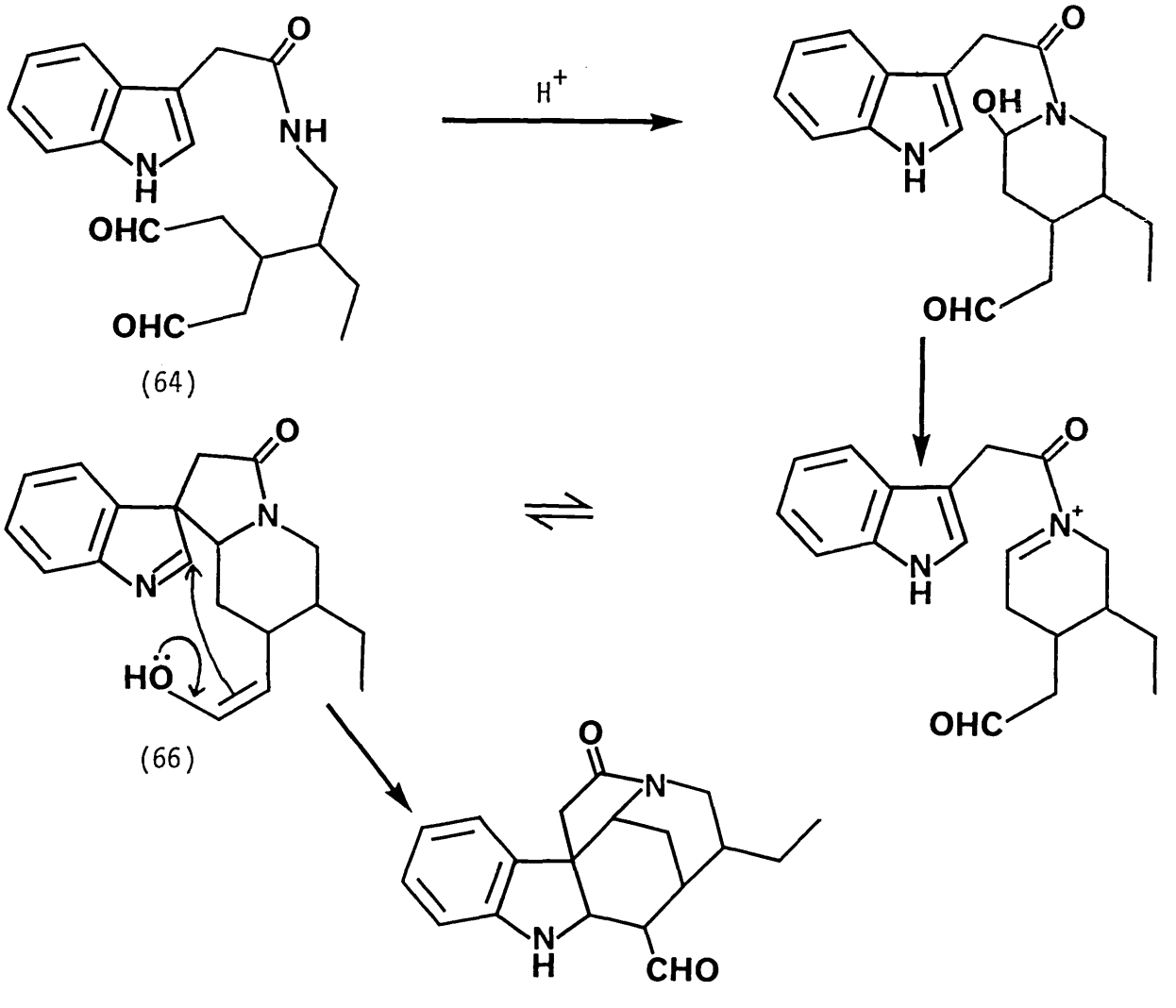


(62) (63)

1.4 Nucleophilic attack at the indole-2-position, following an initial electrophilic attack at the 3-position.

Another large and useful category of cyclizations are those involving initial electrophilic attack at the 3-position to form an indolenine, followed by intramolecular nucleophilic attack at the 2-position, and thus resulting in ring formation. One such reaction has already been mentioned in Section 1.2,[16] because of its contrast to the normal course of reaction of *N*-acyl tryptamines with phosphorus halides. Some other examples will now be given.

The cyclization of (64) by acid treatment to give (65) is thought to proceed *via* the pathway shown, presumably through the enol (66).[30]

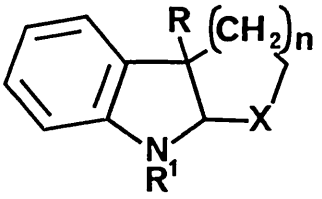


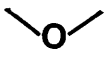
(64)

(66)

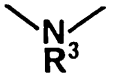
(65)

Systems having the general structure (67) are widely found in Nature especially where n = 1 and X = N — R^3. Numerous methods for their synthesis are to be found in the literature, many being variations on the idea described in the introduction to this section. The necessary indolenine intermediates for cyclization have been generated oxidatively, by alkylation and by halogenation, and the most common intramolecular nucleophiles are alcohols, amines and amides.



X = 

or



(67)

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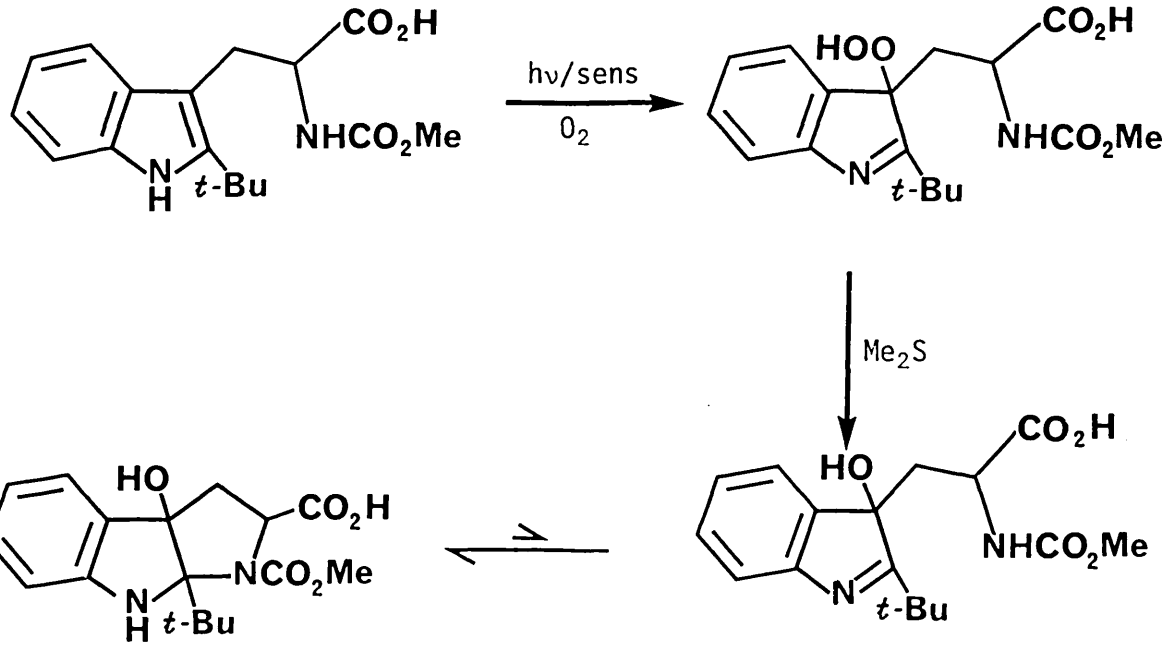
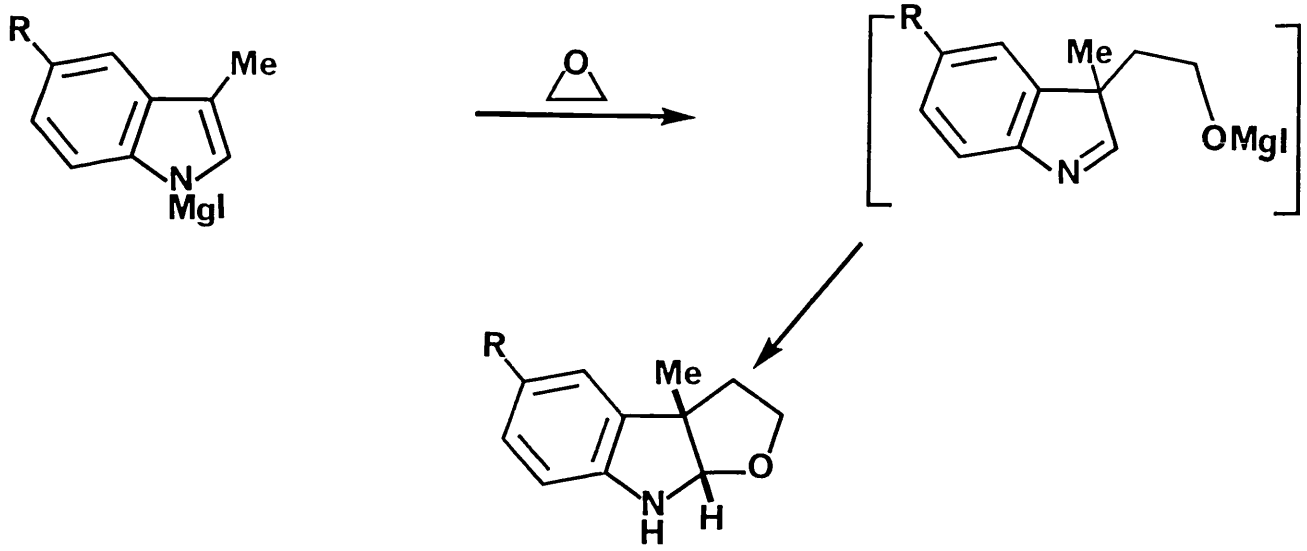
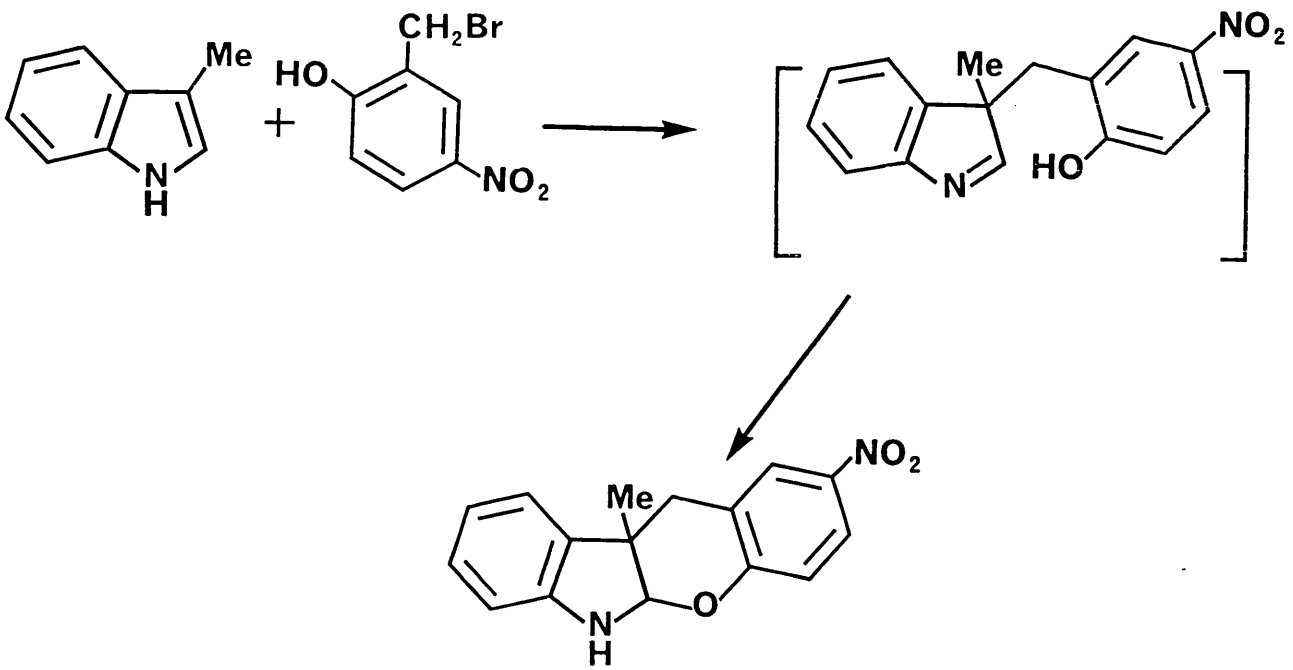
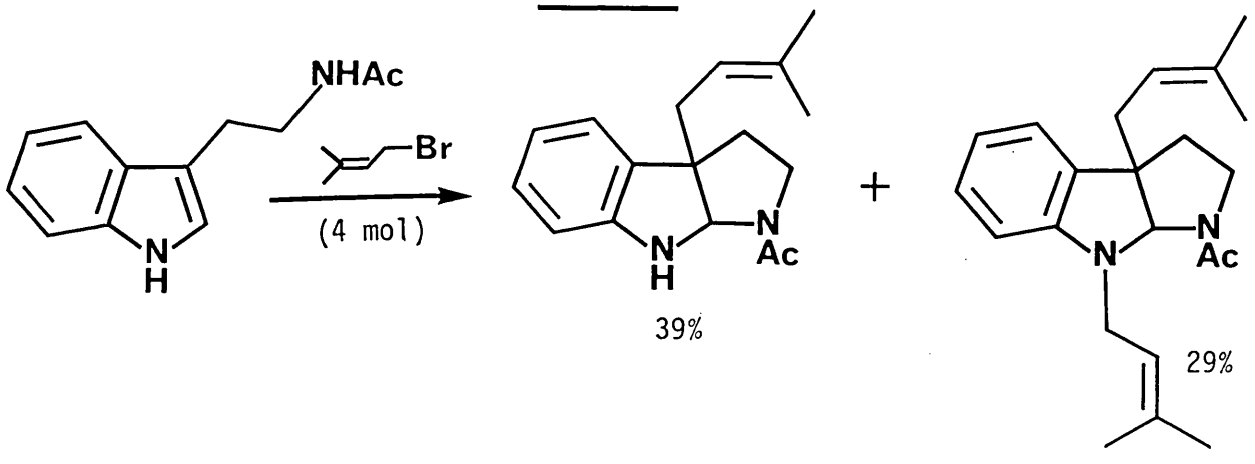
a) oxidatively[31,32]



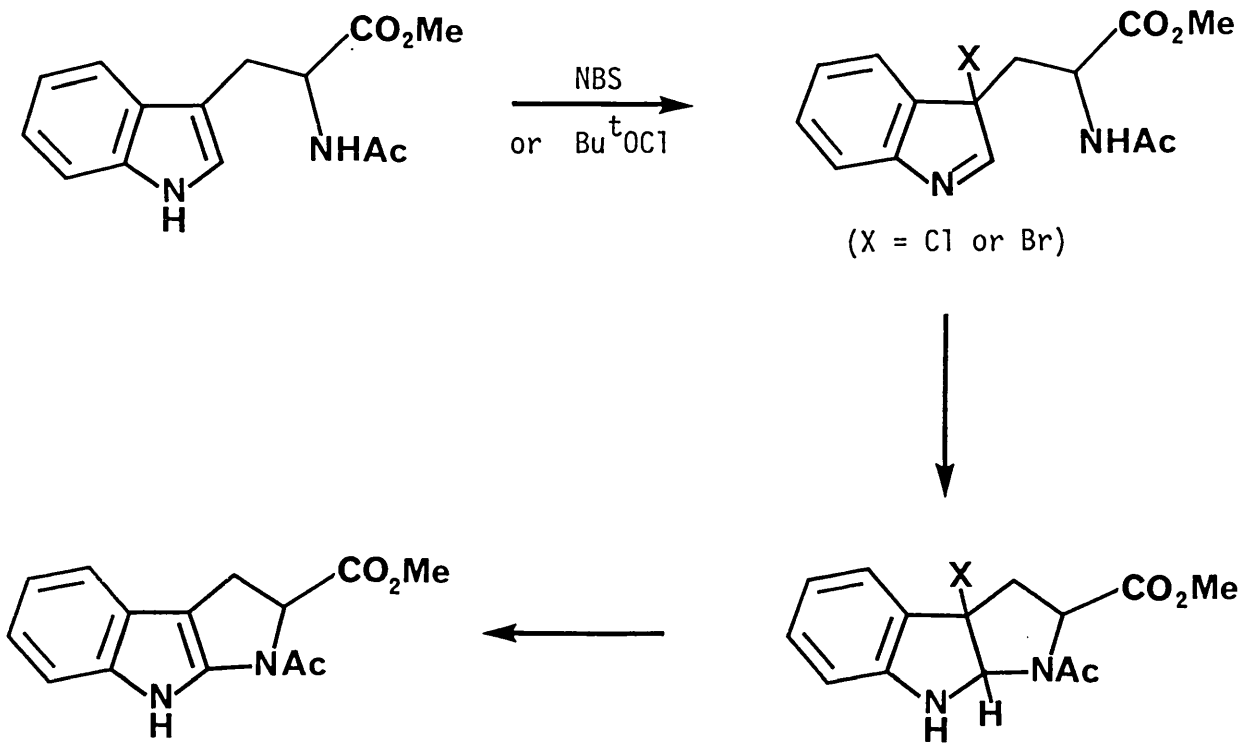
b) by alkylation,[33,34,35]







c) by halogenation,[36]



1.5 Cycloadditions

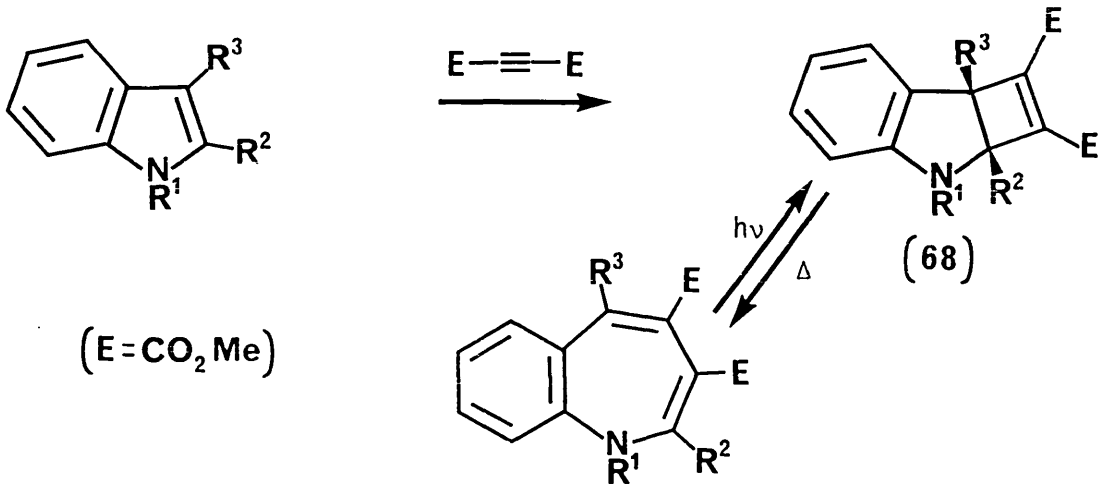
Numerous cycloadditions leading to [2,3]-fused indoles are described in the literature, these may be divided into three basic categories:

a) direct cycloaddition to an indole 2,3-double bond.

b) cycloaddition to a 2- or 3-vinyl indole or its derivatives.

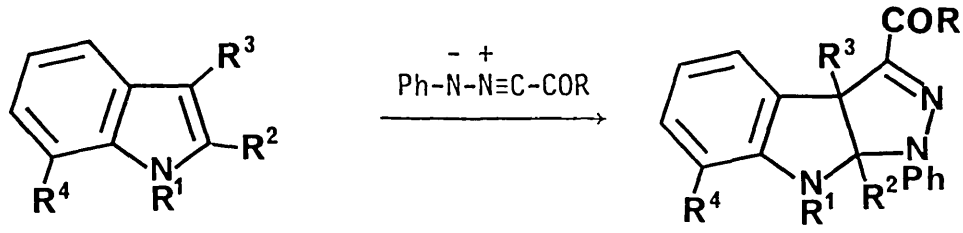
c) cycloaddition to indole-2,3-quinonoid systems.

An example of the first category is the [2π + 2π] photochemical cycloaddition of dimethyl acetylenedicarboxylate to indoles. This constitutes a useful synthetic route to compounds of the type (68), thermal ring opening of which, affords benzazepines (69).[37]



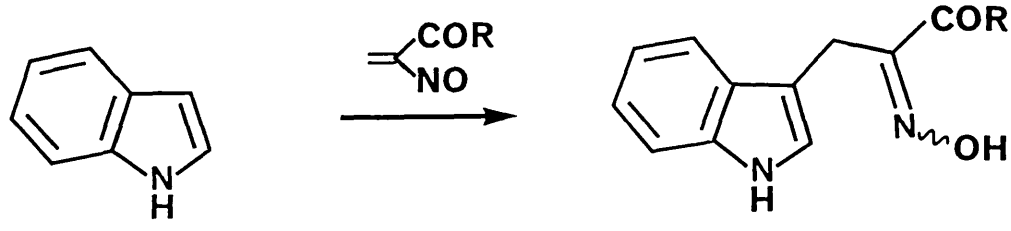
(69)

The cycloaddition of 1,3-dipoles to indoles has also been reported.[38] Adducts such as (70) were obtained by what is claimed to be a concerted process, although the authors offer very little evidence for this assertion.

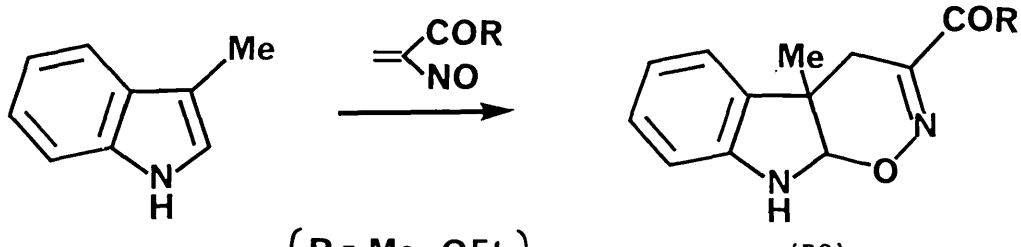


(70)

Gilchrist has recently reported the addition of activated nitroso-alkenes to indoles.[39] In the case of indoles unsubstituted in the 3-position, oximes such as (71) were obtained. However, when 3-methylindole was used as a substrate, the dihydro-oxazine (72) was the product. It is not yet possible to deduce whether the cycloadducts are formed *via* a genuine cycloaddition, or *via* a 3-alkylation followed by a ring closure at the 2-position,in the manner of the reactions discussed in Section 1.4.



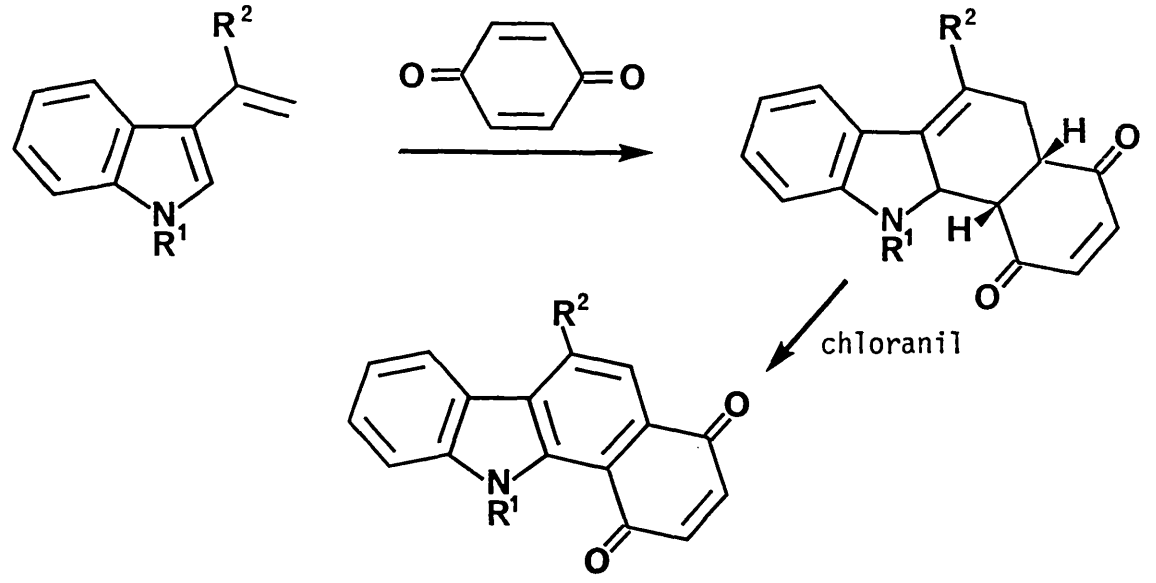
(71)

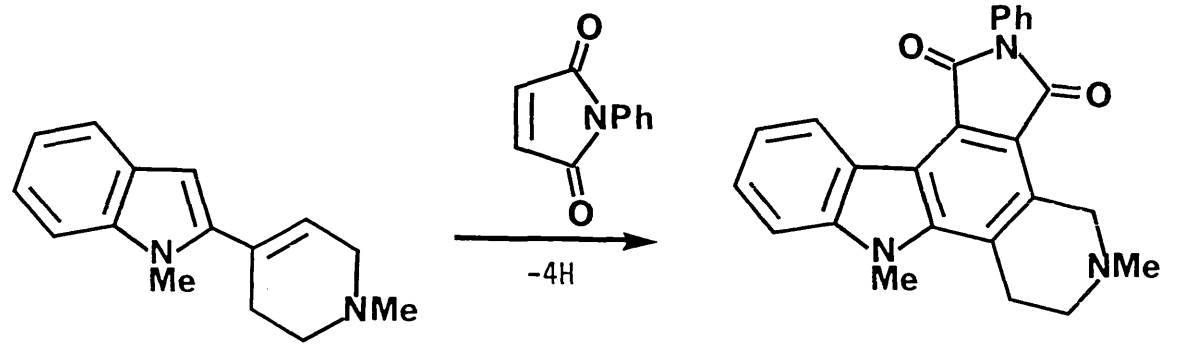


(R = Me, OEt)

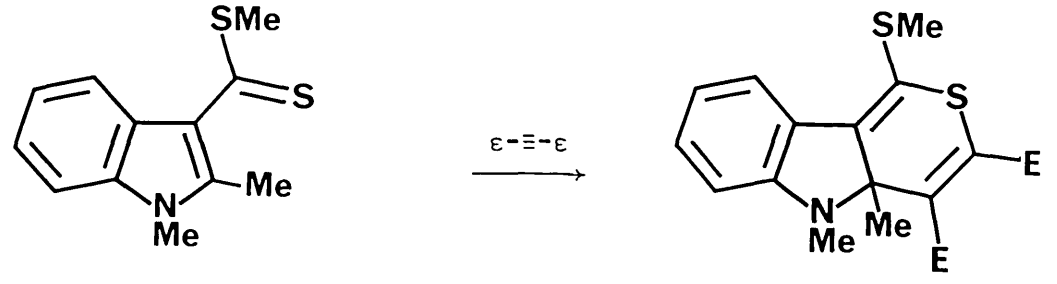
(72)

Both 2- and 3-vinyl indoles undergo [4+2] cycloadditions with dienophiles, exemplified by the reactions shown below.[40,41]





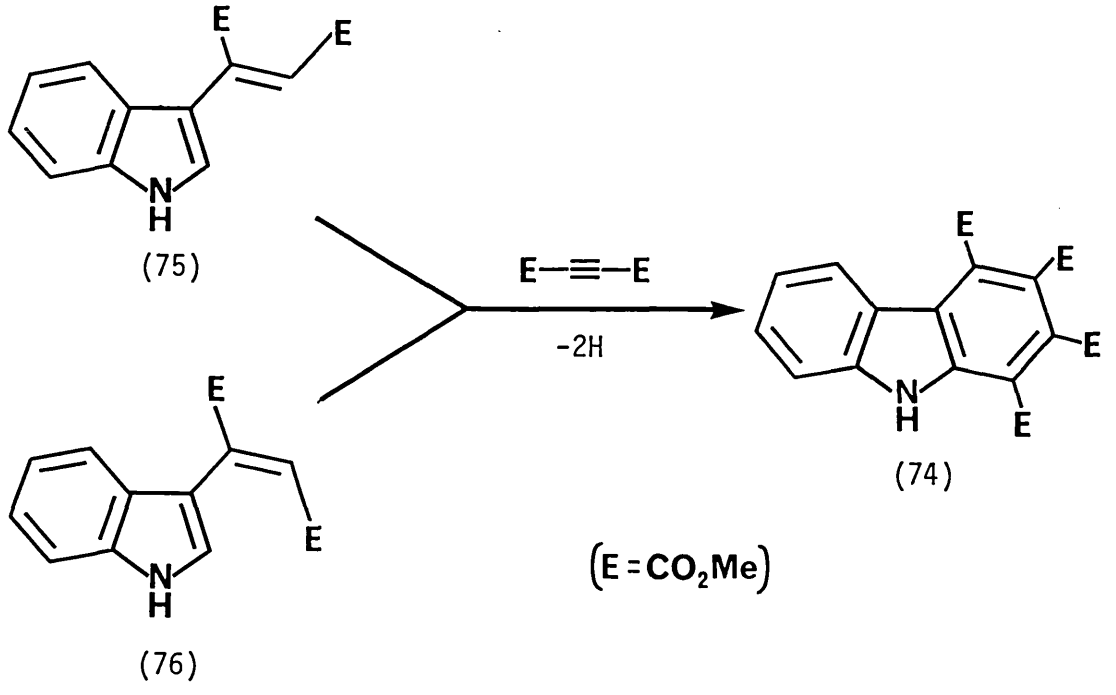
Heterosubstituted double bonds can also take part in such cycloadditions, as in the case of the addition of dimethyl acetylenedicarboxylate to (73).[42]



(73)

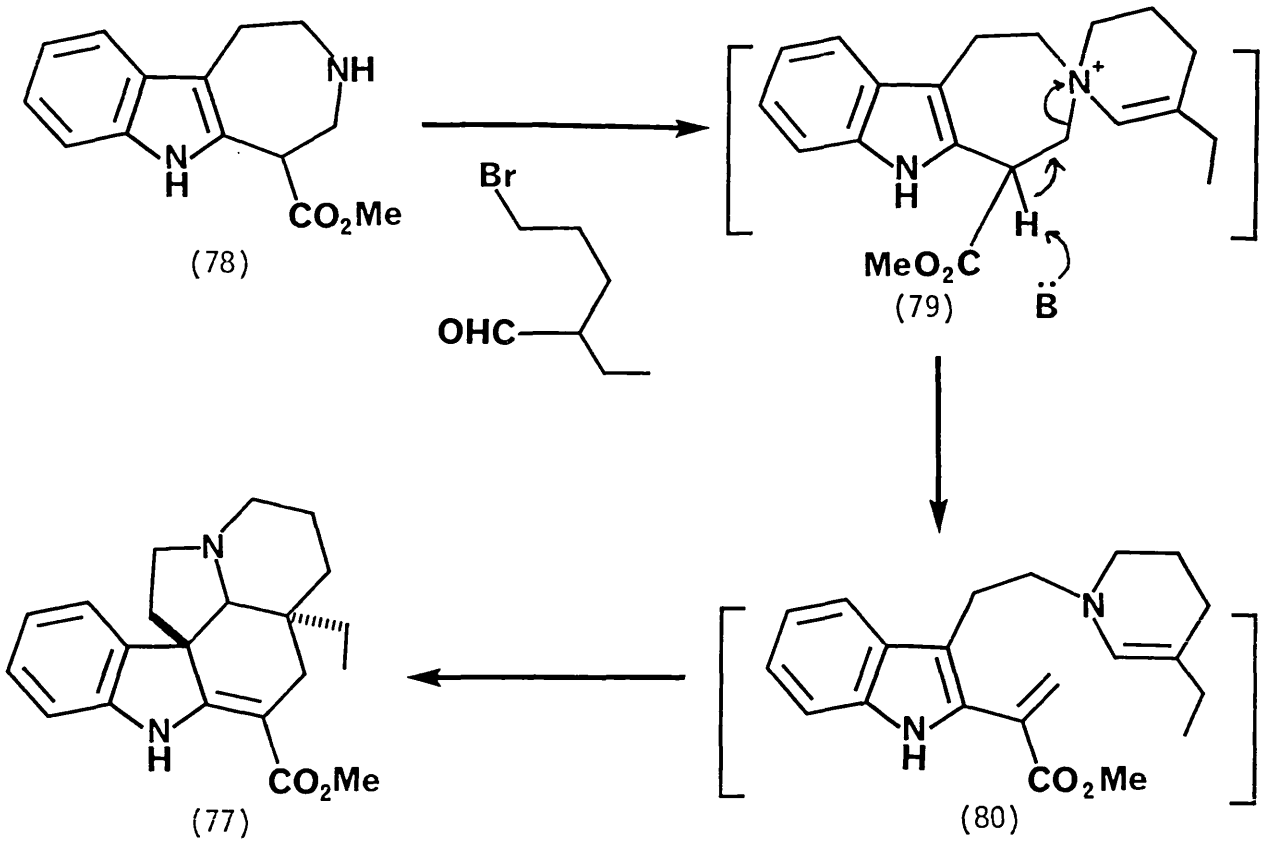
It is interesting to compare the thermal reaction between indole and dimethyl acetylenedicarboxylate with the corresponding photochemical reaction discussed above. The former has been examined numerous times, and Acheson,[43] operating on a large scale, obtained fourteen products after chromatography of the complex reaction mixture. One of the chief constituents of the reaction mixture was found to be the carbazole (74). Reaction of dimethyl acetylenedicarboxylate with indole in various solvents (rather than neat, as above) gave mixtures containing (75) and/or (76) as chief constituents. It is thought that (74) is produced by cycloaddition of further dimethyl acetylenedicarboxylate to (75) or (76) and subsequent dehydrogenation, presumably by air oxidation.

The reaction is however a great deal more complex than reported by other workers, and constitutes something of a curiosity, rather than a viable synthetic method of preparing [2,3]-fused indoles.



An example of a formal intramolecular (4+2) cycloaddition applied to alkaloid synthesis is the elegant construction of (77) from (78) *via* the spiroammonium salt (79), which ring opens to give (80). The closure of this species is probably not concerted, but proceeds *via*

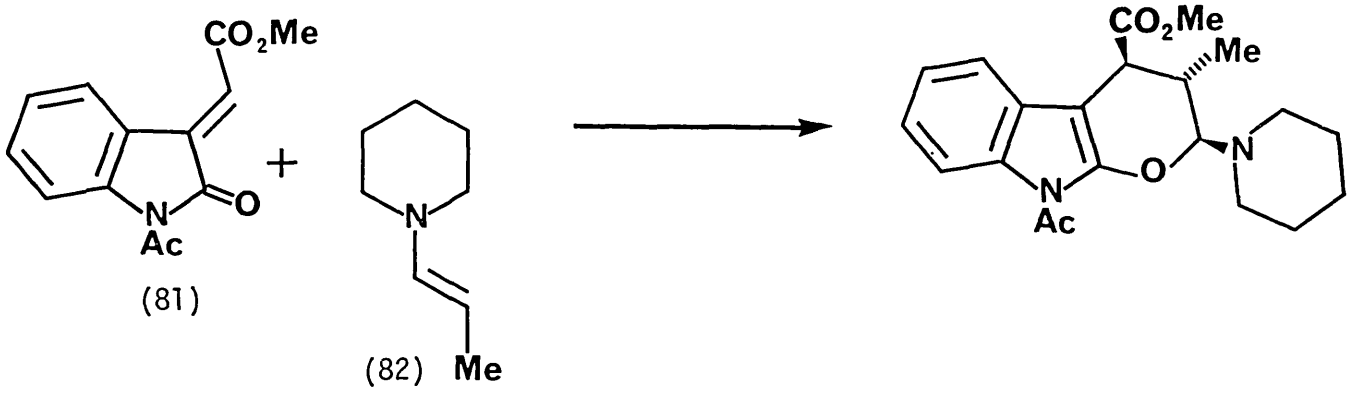
initial attack of the enamine into the conjugated 2-vinyl group, followed by intramolecular trapping of the resultant iminium species.[44]

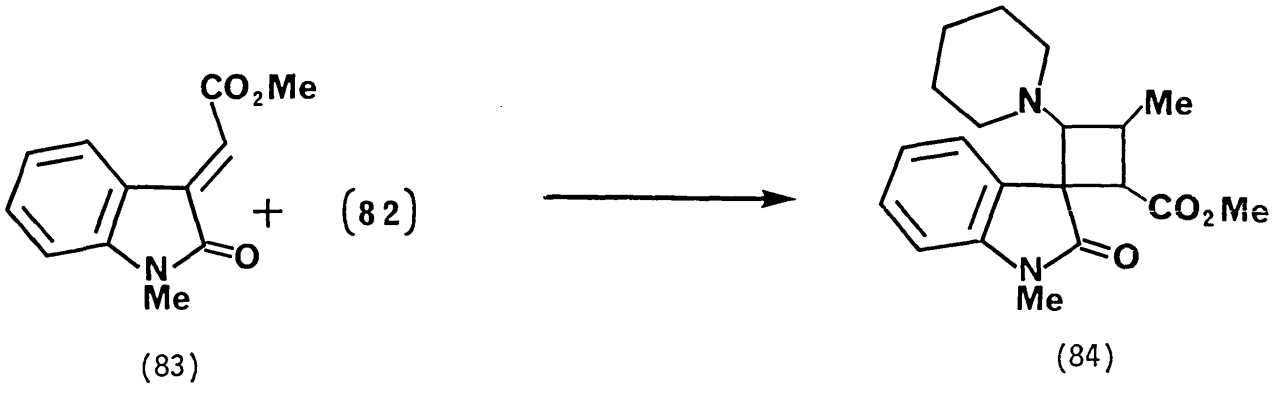


There has been great interest in *o*-quinonoid systems recently.[45] Indole-2,3-quinonoids may undergo cycloaddition reactions to give [2,3]-fused indoles, and although this type of reaction has been known for some time, it has only received much attention in the last few years.

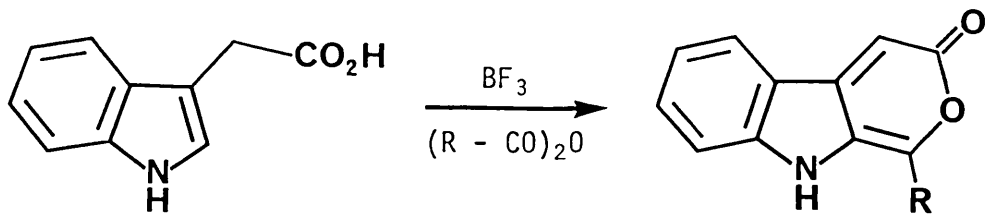
The system (81) added to the enamine (82) as shown,[46] however with *N*-alkyl, (rather than *N*-acyl) 2-oxoindolin-3-ylidene derivatives, such as (83), a 1,2-cycloadduct was generated *viz* (84). This is rationalized by assuming that in the *N*-acyl compounds, the lone pair is preferentially delocalized into the acyl group, and does not perturb the 1,4-ring closure which follows initial attack of the enamine into the α,β-unsaturated system. In contrast, when the lone pair is free,

as in the *N*-alkyl compounds, it causes the 3-position in the oxindole ring to be the position of greater electron density, and hence 1,2-closure results.[47]



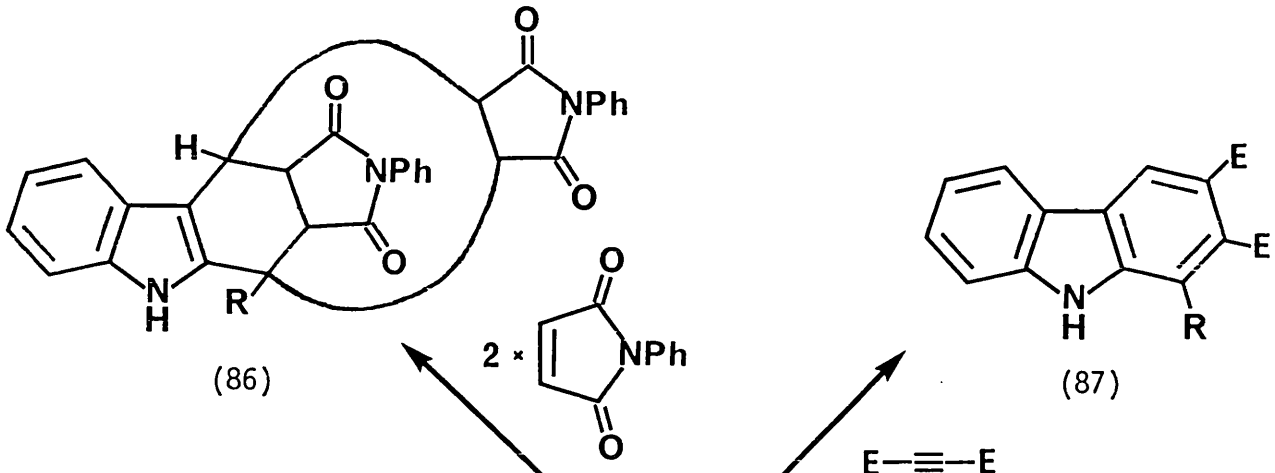


The cycloaddition of indole-2,3-quinodimethanes is potentially a very elegant way of constructing [2,3]-fused indoles. Some twenty years ago, German workers reported the preparation of (85) by Lewis acid catalysed reaction of indoleacetic acid with anhydrides.[48] This compound may react in a number of ways with dienophiles. For instance, with *N*-phenylmaleimide, a first molecule cycloadds, with concomitant loss of carbon dioxide, reforming a quinodimethane system which adds to a further molecule of *N*-phenylmaleimide to give a *bis* adduct (86). With dimethyl acetylenedicarboxylate, the carbazole (87) was formed. The system (85) may also be reduced by hydrogenation to (88). Heating of this compound with dienophiles gave cycloadducts such as (89), resulting from trapping of the *o*-quinodimethane intermediate generated by extrusion of carbon dioxide.



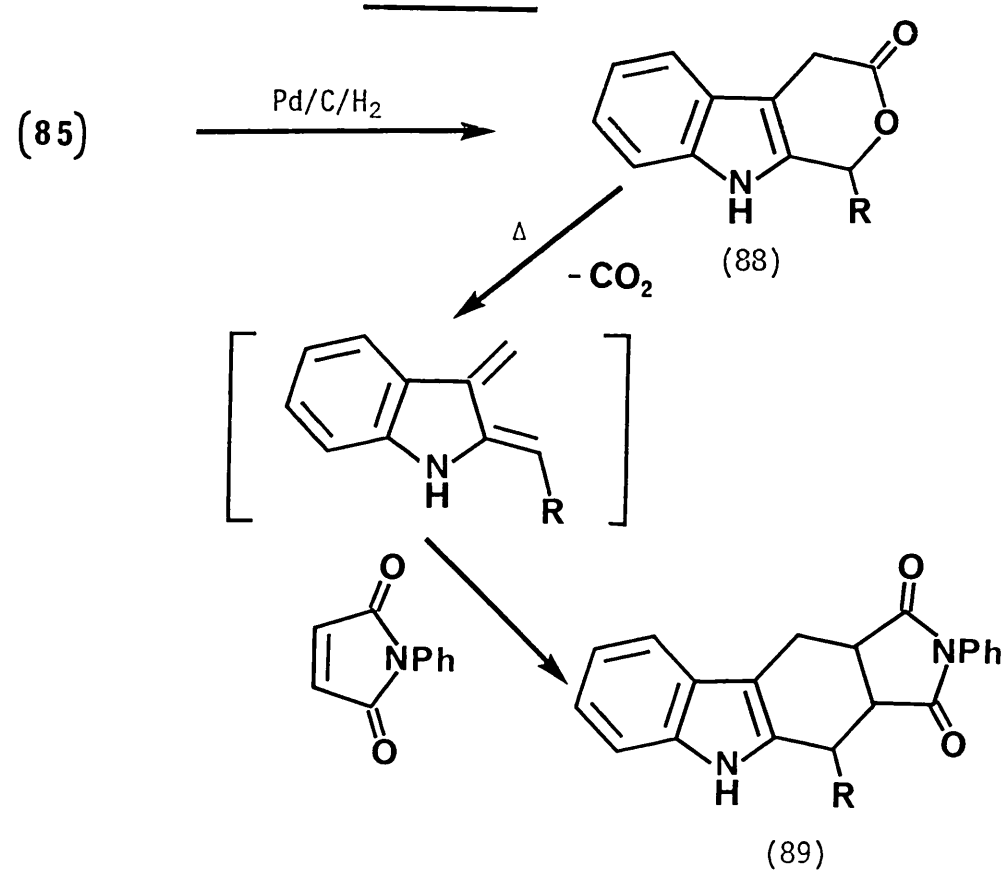
(85)

R = Me, Et, ^{n}Pr, Ph



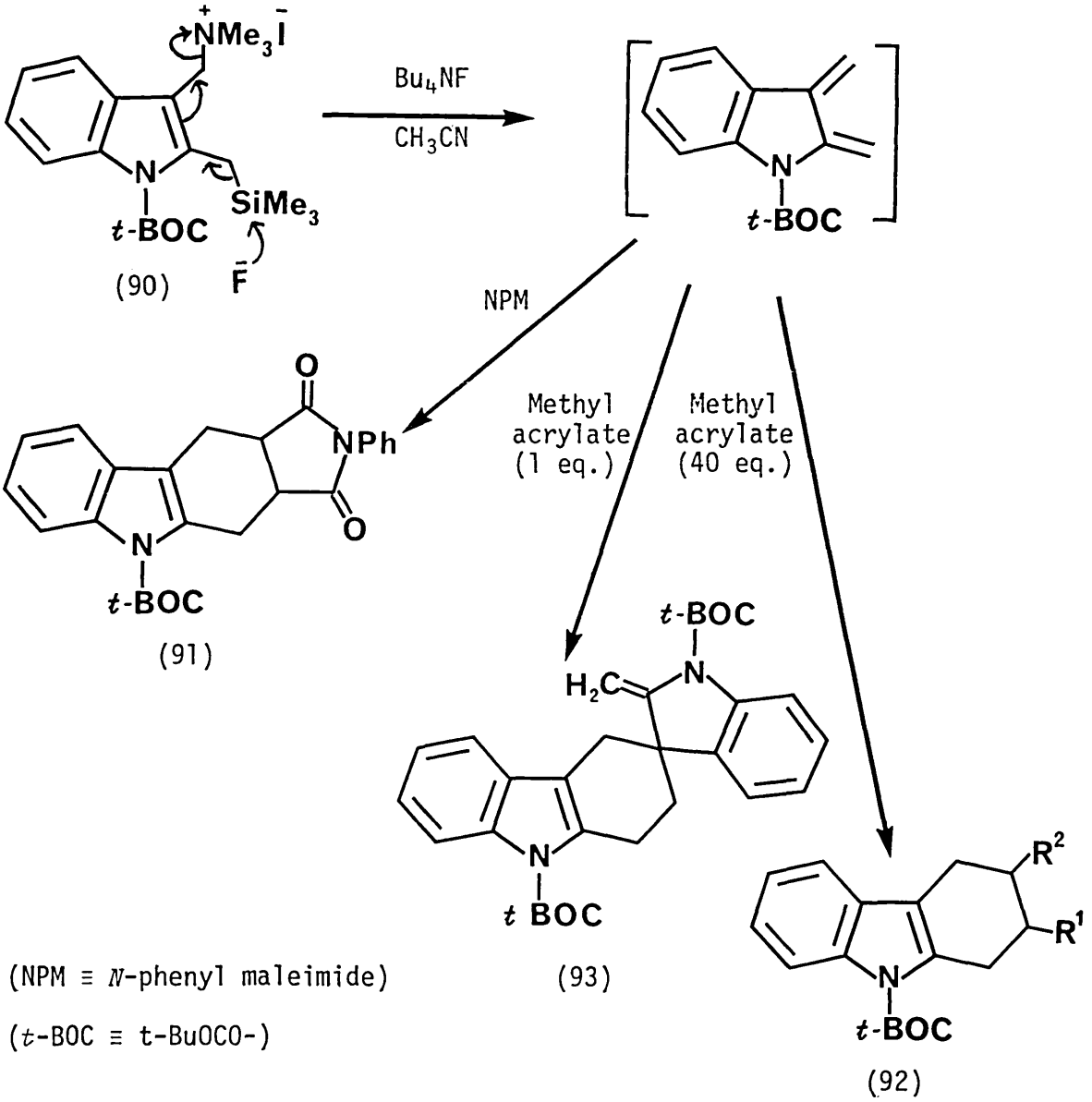
(86) (87)

(85) (E=CO_2Me)



(89)

More recently, a similar intermolecular cycloaddition of an indole-2,3-quinodimethane has been reported.[49] In this case however, the reactive intermediate quinodimethane was prepared by treatment of the trimethylsilylammonium salt (90) with tetrabutylammonium fluoride. Reaction with *N*-phenylmaleimide in acetonitrile gave the cycloadduct (91). In the presence of one equivalent of methyl acrylate, the quinodimethane dimerised to give (93) in preference to reaction with the added dienophile. Use of excess acrylate (40 equivalents) resulted in the isolation of a 3:1 mixture of (92a) and (92b) along with a minor amount of the dimer (93).



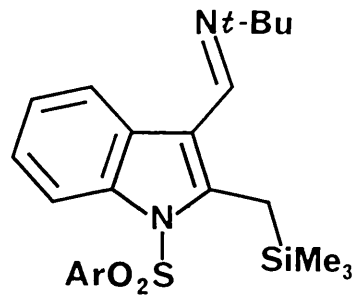
(NPM ≡ *N*-phenyl maleimide)

(*t*-BOC ≡ t-BuOCO-)

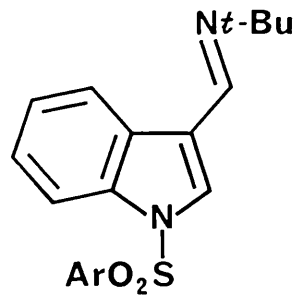
a) $R^1 = CO_2Me$, $R^2 = H$

b) $R^1 = H$, $R^2 = CO_2Me$

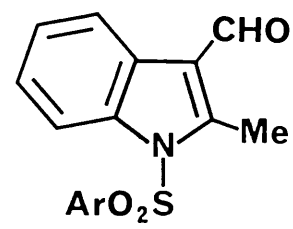
Recent reports from Magnus *et al*[50] describe work directed at effecting intramolecular cycloadditions to indole-2,3-quinodimethanes. Initially Magnus attempts to utilize the strategy described above, having as an initial synthetic target the model trimethylsilylimine (94). This compound was not easily prepared, and amongst other attempts at its synthesis, the imine (95) was treated with n-butyllithium/HMPA and $CF_3SO_3CH_2SiMe_3$. N.m.r. indicated that the required product was formed in low yield, but that extensive desilylation had occurred, and the only isolable product was the indole-3-carbaldehyde (96). This extensive protodesilylation suggests that the methyl trimethylsilyl group is highly labile, and that a logical extension might be the exclusion of the trimethylsilyl group, and formation of the quinodimethane by a pathway involving deprotonation, rather than desilylation. Before this extension was investigated, however, the compound (97) was synthesised from the imine (98). Treatment with caesium fluoride in glyme did not however give any of the required cyclized product, and only the desilylated imine (99) could be isolated from the reaction mixture. It is suggested that the required quinodimethane is formed, but at the temperature of refluxing glyme (70°C) it does not undergo [4+2] cycloaddition. Since the related species discussed earlier are reactive enough to undergo intermolecular cycloadditions in refluxing acetonitrile (82°C), it is perhaps surprising that this quinodimethane does not react intramolecularly at the temperature described.



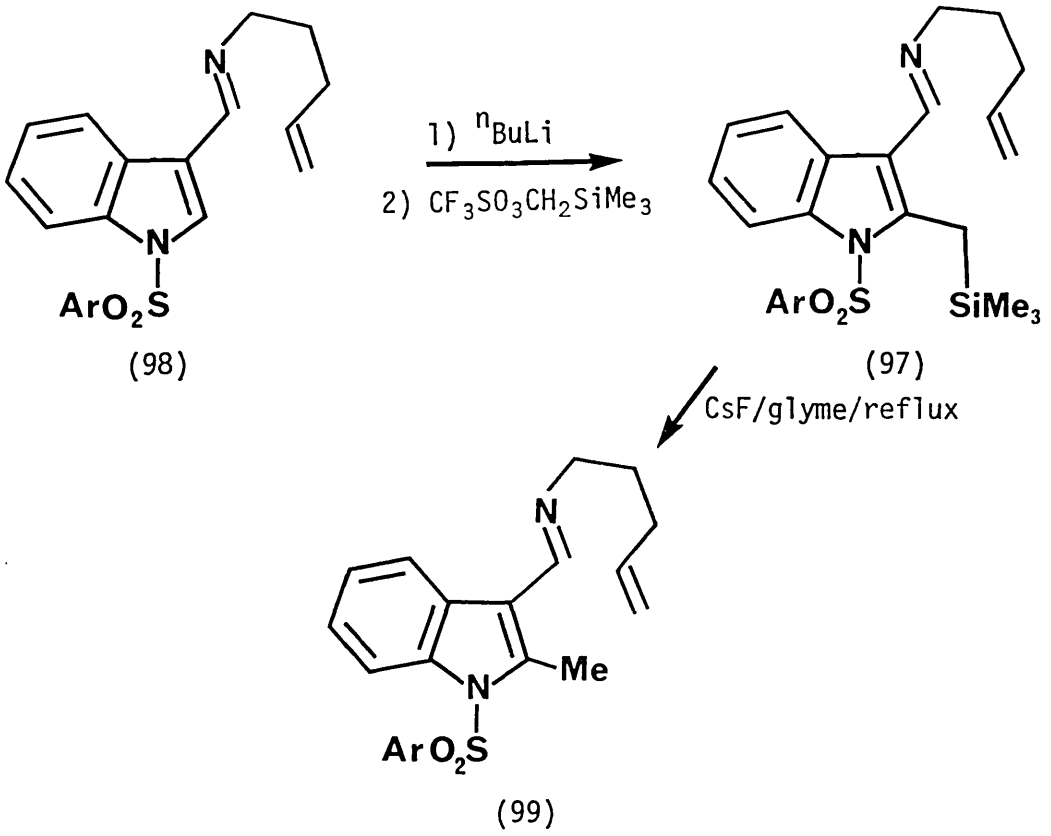
(94)



(95)



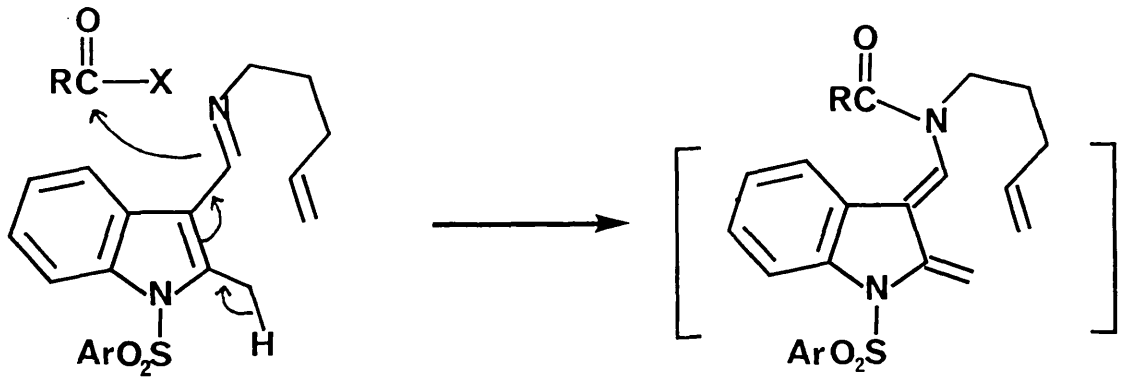
(96)



(98) (97) (99)

It was therefore decided to exclude the trimethylsilyl group, and it was found that treatment of imine (99) with boiling acetic anhydride (140°C) or boiling ethyl chloroformate (93°C) cleanly gave cyclized products (100a) and (100b) respectively *via* (101).

This method has since been applied to the synthesis of aspidosperma alkaloids.[51]

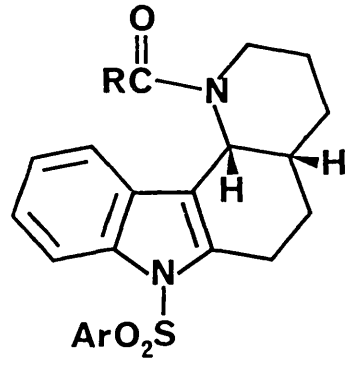


(99)

(101)

R = EtO, Me

X = Cl , $OCOCH_3$



(100)

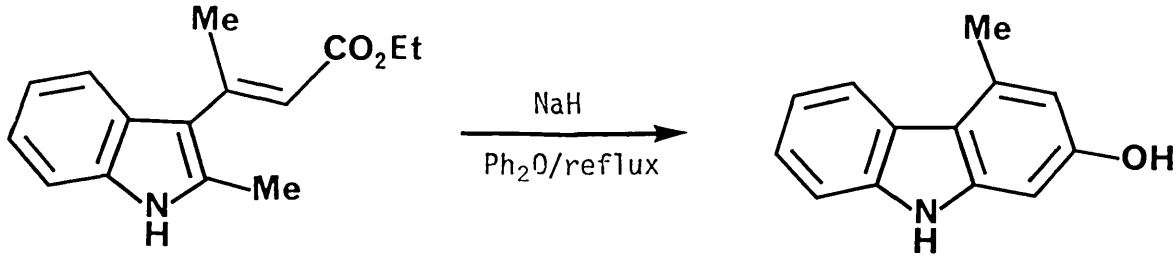
a) R = Me

b) R = OEt

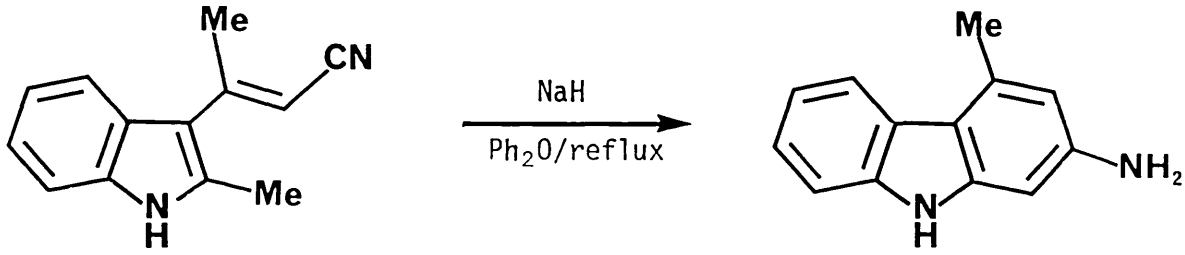
1.6 Interactions between two side-chains

The formation of [2,3]-fused indoles by interaction of two side chains (normally involving interactions with 2-alkylindole substituents, the α protons of which are somewhat acidic) constitute another extensive group of reactions, and again, only a representative selection will be discussed.

The indole-3β-methacrylate derivative (102) can be cyclized by refluxing with sodium hydride in diphenyl ether. Similarly (103) may be cyclized under these conditions.[52]

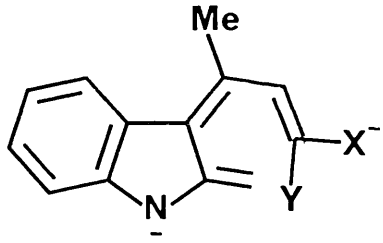


(102)

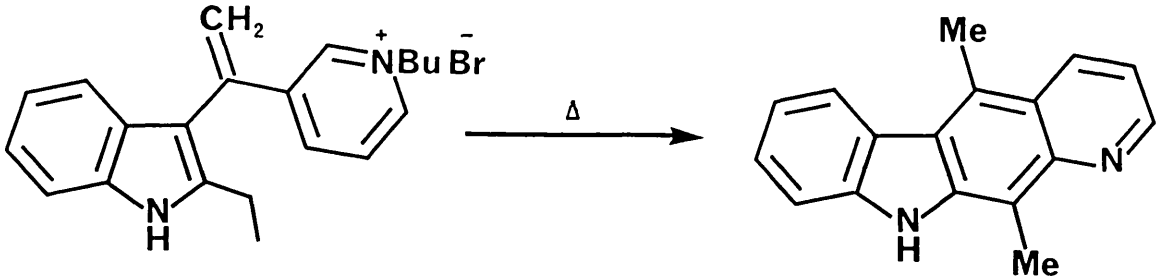


(103)

These cyclizations which proceed *via* the exocyclic tautomer (104) were developed as a part of an independent synthesis of (105) the minor product in the pyrolysis of (106) to give ellipticine (59).[53]



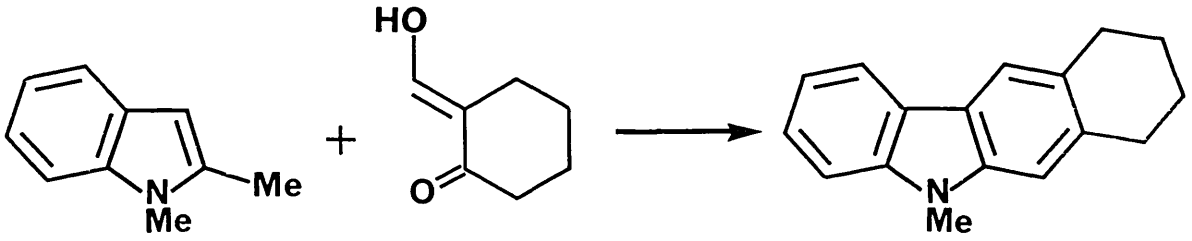
(104)



(106) (105)

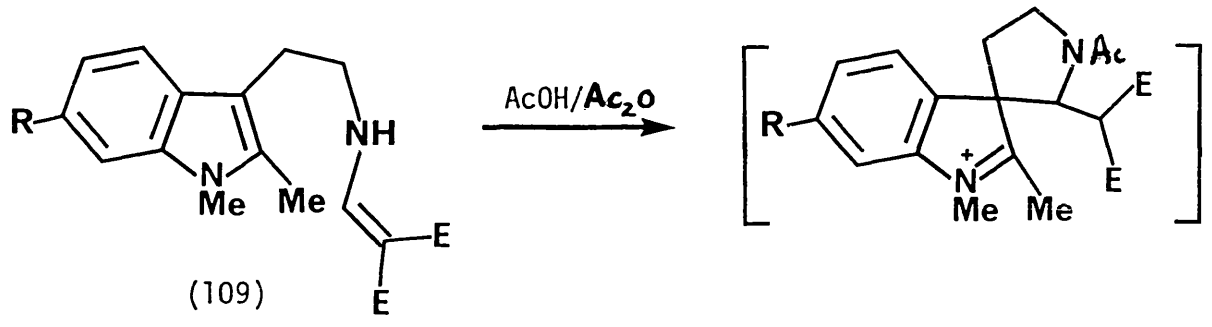
+ (59)

Another example of a cyclization demonstrating the reactivity of 2-alkylindole substituents is the interaction of the hydroxymethylene ketone (107) with 1,2-dimethylindole, and subsequent dehydration to afford the carbazole (108).[54]



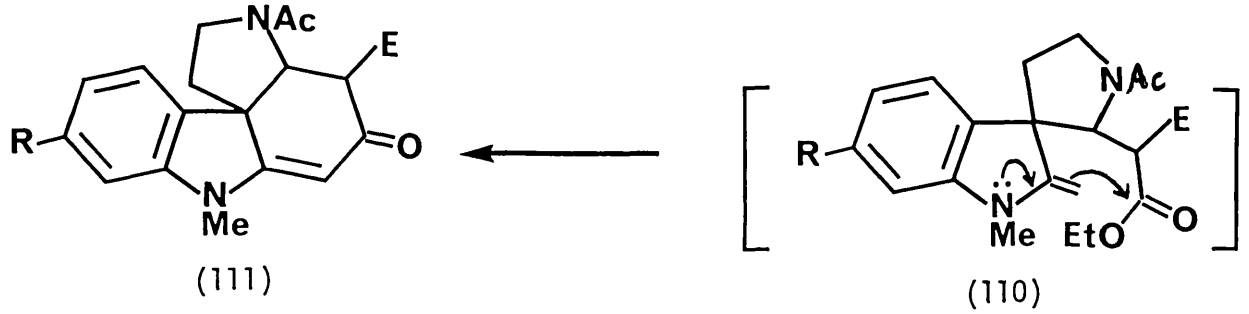
(107) (108)

This kind of reactivity is again evident in the step (109) → (111) *via* (110) which is part of a synthesis of the alkaloid vindoline.[55]



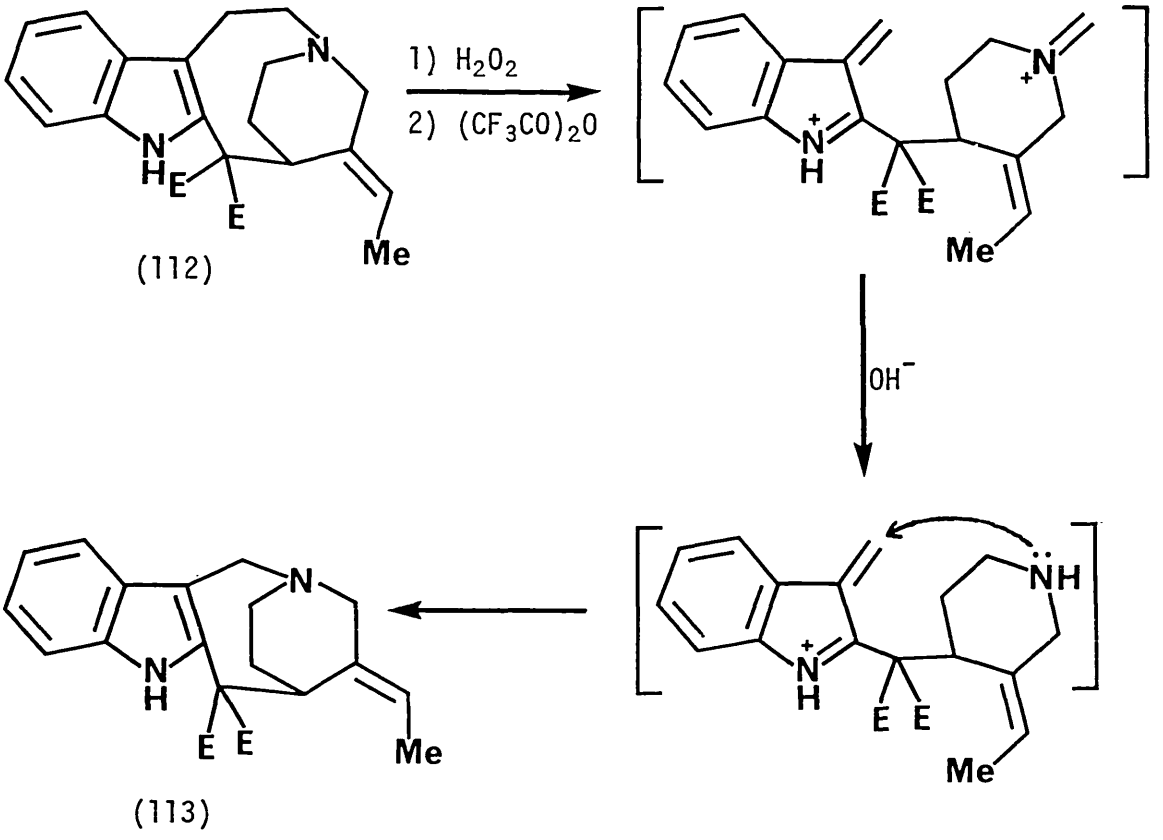
(109)

$(E = CO_2Et)$



(111) (110)

The conversion of (112) to (113) using the Polonovski reaction appears to proceed *via* a 3-exomethylene species.[56]



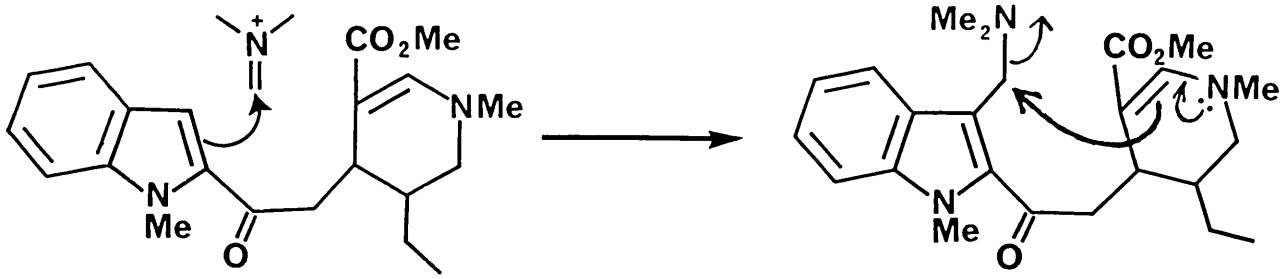
(112)

(113)

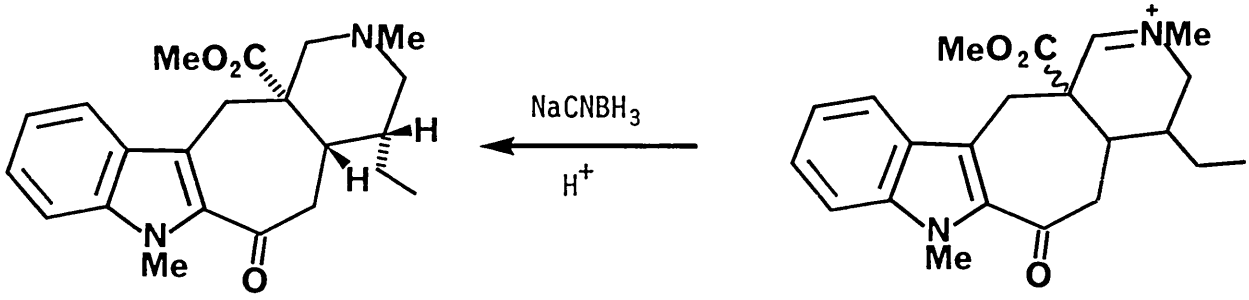
The well-known nucleophilic substitution of gramines may be carried out in an intramolecular fashion, as in the cyclization of (114) to (115).[57]

The dehydrative cyclization of (116) to (117) upon heating has been reported by Clemo.[58]

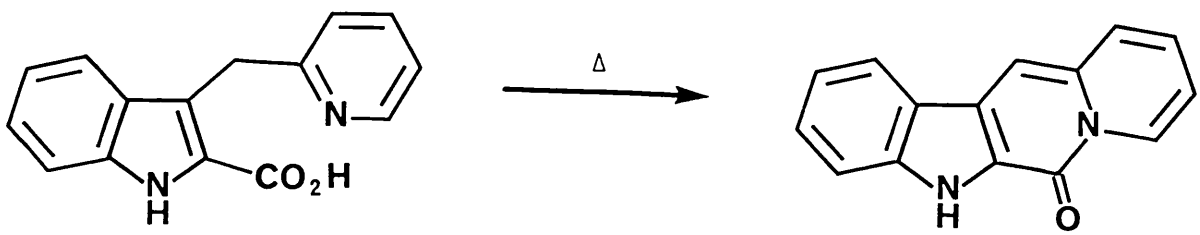
The interaction between the two side chains in tryptamines having a 2-acyl substituent on the indole ring, to form β-carbolines,[59] is in effect an intramolecular version of the condensation between carbonyl compounds and tryptamines (or tryptophans) discussed in Section 1.2.



(114)



(115)

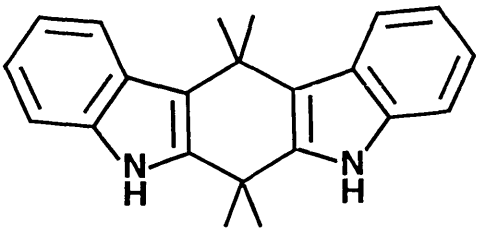


(116)

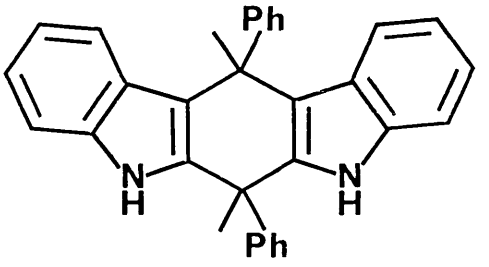
(117)

1.7 Miscellaneous

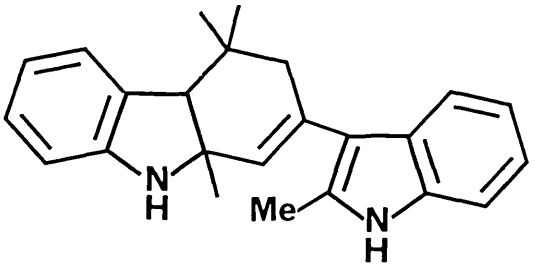
It has long been known that indoles react with aldehydes and ketones to give rather complex condensation products. Noland *et al*, in the 1960's examined many of these reactions, proposing structures for numerous products. For instance, indole reacts with acetone under various conditions, giving (the authors claim), compound (118),[60] and with acetophenone to give (119).[60] Reaction of 2-methylindole with mesityl oxide, phorone, or acetone gives (120).[61] Compounds (118) and (119) are thought to be formed by the action of further acetone or acetophenone on the initially formed alkylidene bis indoles (121).



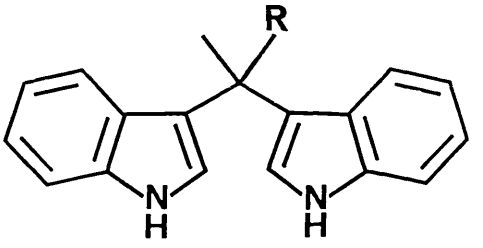
(118)



(119)

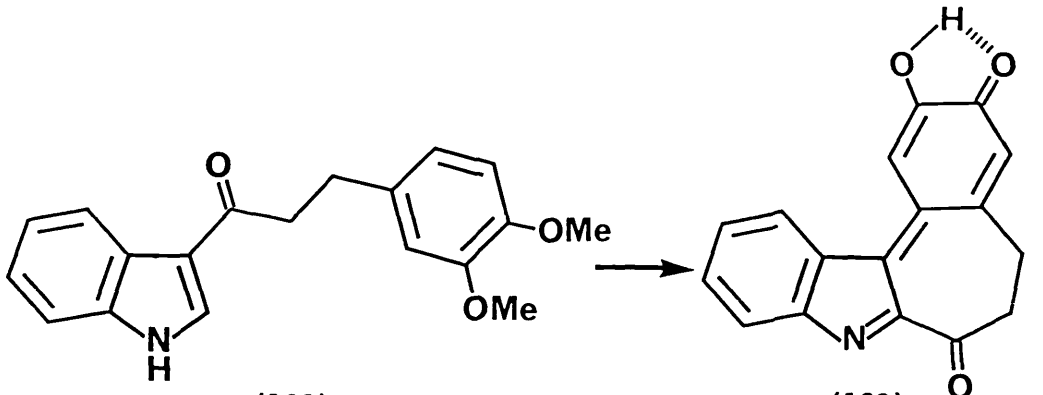


(120)



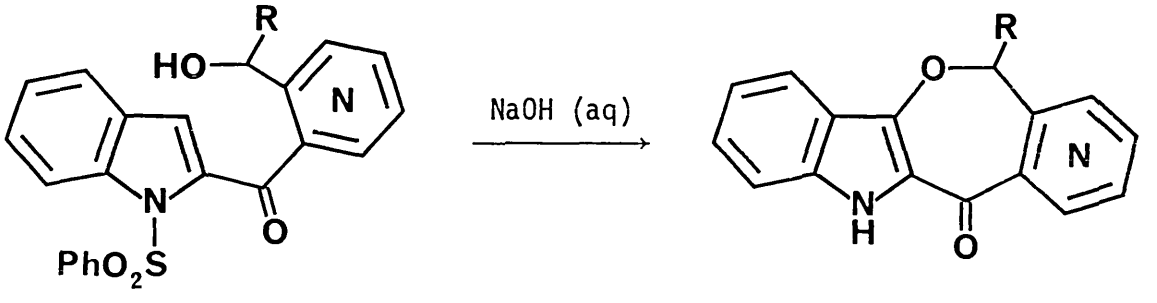
(121)

The anodic cyclization of (122) has been reported,[62] whereby the fused indolenine (123) is produced.

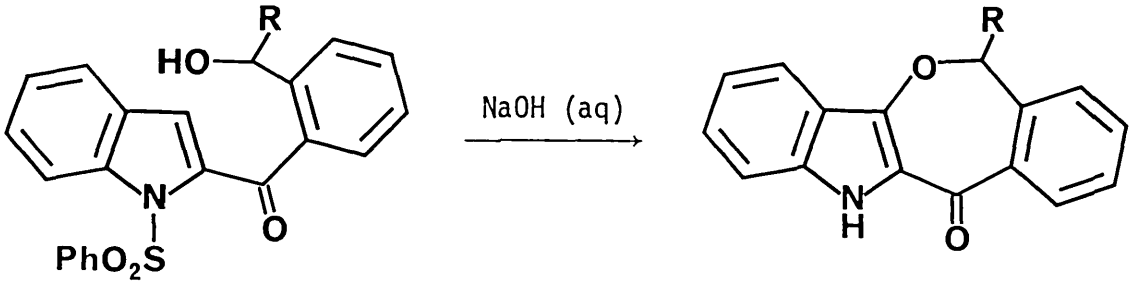


(122) (123)

A putative nucleophilic attack on the indole 3-position has been claimed. Compounds such as (124) and (125) are cyclized to pyrido- or benzo-oxepinoindoles respectively, by briefly boiling in ethanolic sodium hydroxide.[63]



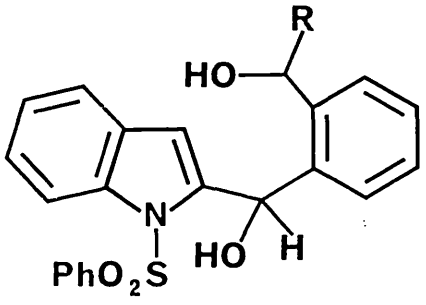
(124)



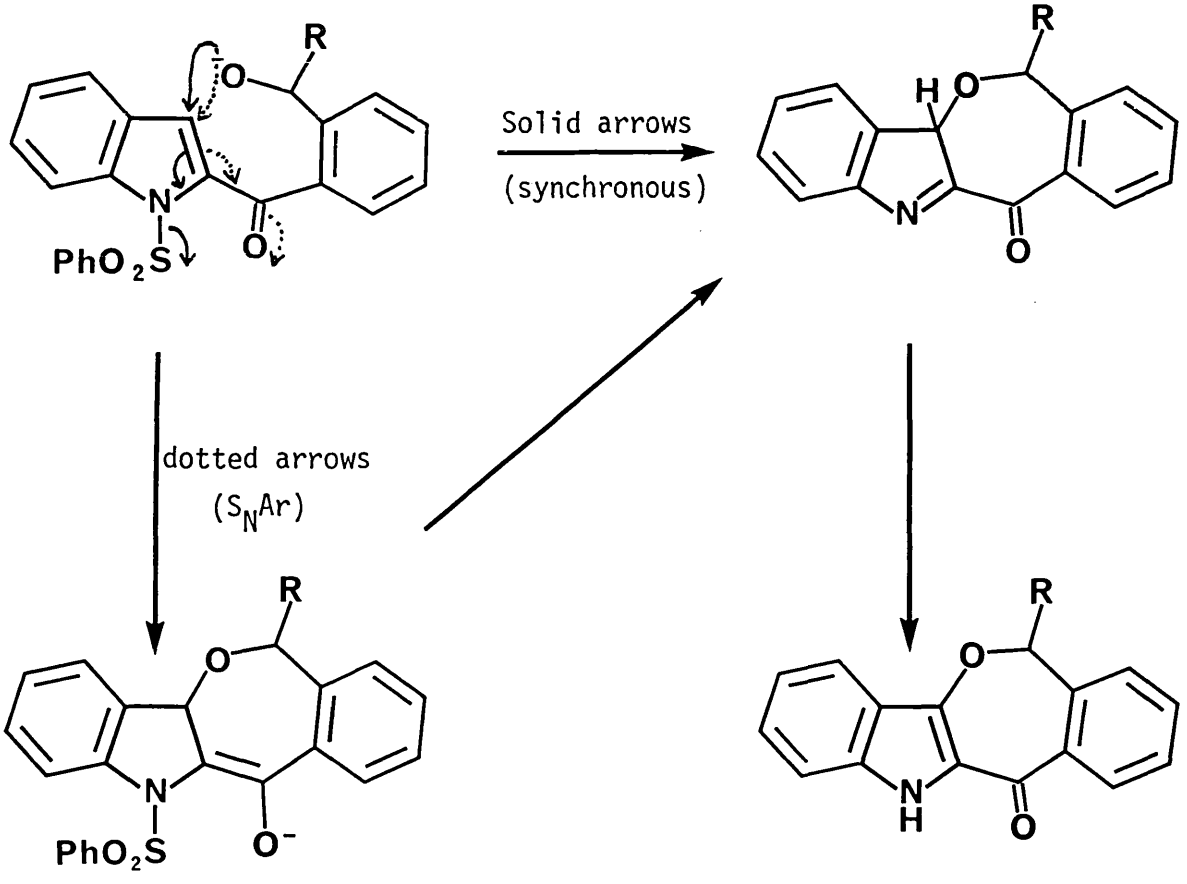
(125)

The presence of the carbonyl group was shown to be essential, as (126) does not cyclize and only hydrolysis of the benzenesulphonyl group

occurs when this compound is treated under the aforementioned conditions. Whether the mechanism is synchronous or goes *via* a conjugate addition (through enolate (127)), the carbonyl group would still be necessary. Obviously, for the S_NAr type mechanism the carbonyl group would be intrinsically so, but the synchronous mechanism would also be aided by the reduction of electron density at the indole-3-position which would be effected by this group.



(126)



(127)

1.8 Conclusion

In conclusion to this survey of indole-2,3-cyclizations it must again be said that the literature on the subject, being so copious necessitates selectivity in reviewing it. However, certain trends do emerge. The electrophilic attack of imines, iminium cations and other electrophiles is still by far the most commonly encountered mode of cyclization both in the 2- and 3-positions, finding employment in many alkaloid syntheses. The intramolecular nucleophilic attacks on indolenines described in Section 1.4 have received much attention in the literature recently not primarily from a synthetic viewpoint, but in connection with biologically orientated studies on the oxidation of tryptophans and tryptamines. Finally, the advent of several new cycloadditions, especially the Magnus quinodimethane route adds some important tools to the indole chemist's workshop. These methods are to be welcomed because of their elegance and potential for stereochemical control.

PART 2 : RESULTS AND DISCUSSION

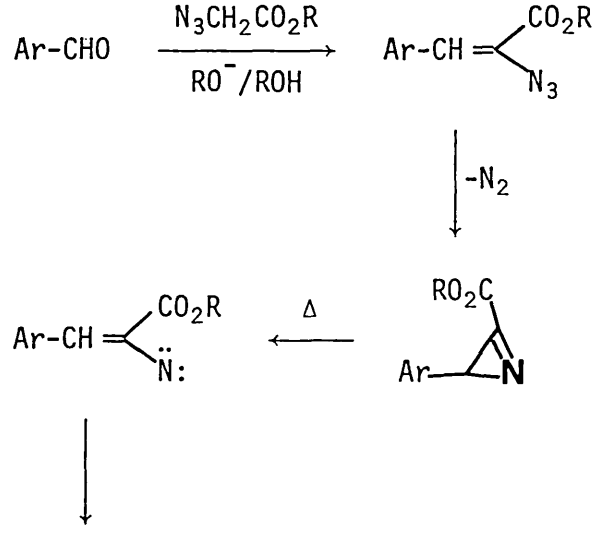
Chapter 2

Preparation, formylation and *N*-alkylation of indoles, and preparation of the derived azidopropenoates

2.1 Introduction

The preparation of alkyl 2-azido-3-aryl propenoates by condensation of alkyl azidoacetates with aromatic aldehydes in an alcoholic solution of the appropriate sodium alkoxide has been described by Hemetsberger,[64,81] and further investigations of the scope of this reaction have recently been carried out.[66,67,68] Thermal or photochemical decompositions of these vinyl azides often constitute useful preparative routes to fused heterocyclic systems. The thermal route outlined in Scheme 1 allows preparation of indoles, from benzaldehydes with at least one free *ortho* position,[81] and also isoquinolines from 2,6-dialkylbenzaldehydes.[66] If other aromatic aldehydes (*e.g.* thiophene or naphthalene carbaldehydes) are employed, the corresponding pyrrolo- or pyrido-fused systems may be obtained.[65,66] Photochemical decompositions yield entirely different products[67] and will not be discussed further.

Scheme 1

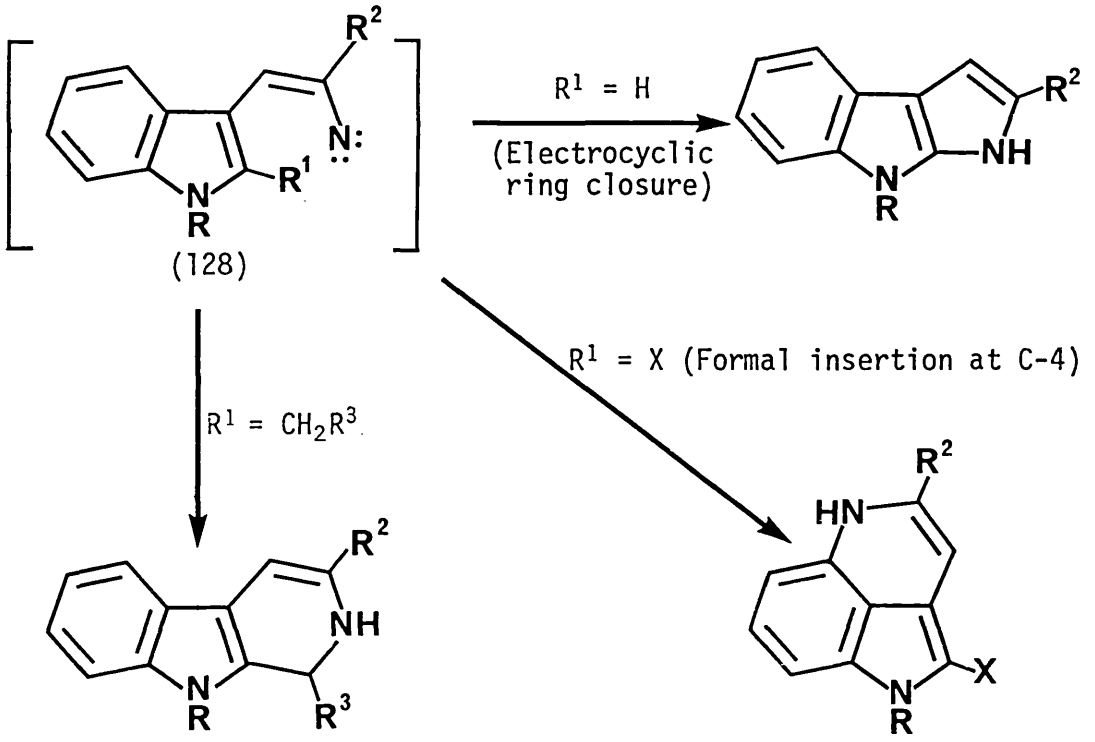


products.

The purpose of this investigation is to ascertain if the reactions delineated above may be applied when Ar-CHO is an indole-3-carbaldehyde, and to examine some of the chemistry of the systems thus produced.

Scheme 2 shows a conjectural outline of the possible modes of collapse of the nitrene (128) which is the expected intermediate if a generalized 1-azido-2-(3-indolyl)ethene is thermolysed.

Scheme 2

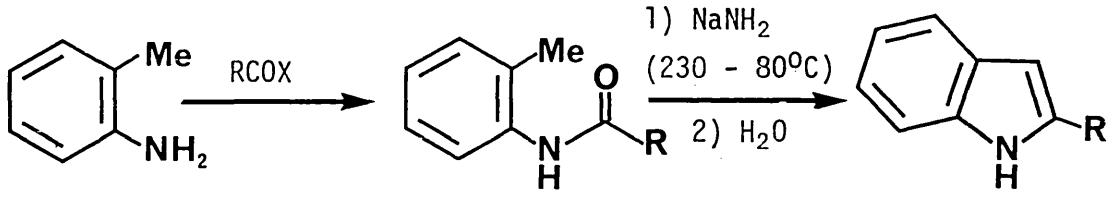


This report will describe how pyrroloindoles and pyridoindoles were in fact obtained by this route, and although no products corresponding to the insertion at C-4 were obtained, another new reaction of vinyl azides was observed.

2.2 Synthesis of starting indoles

Two of the starting indoles (indole itself, and 2-methylindole) were commercially available, and the remainder were synthesised by the Madelung route,[69] (Scheme 3). The requisite *o*-toluidides were prepared by standard methods from *o*-toluidine and the appropriate acid chloride or anhydride.

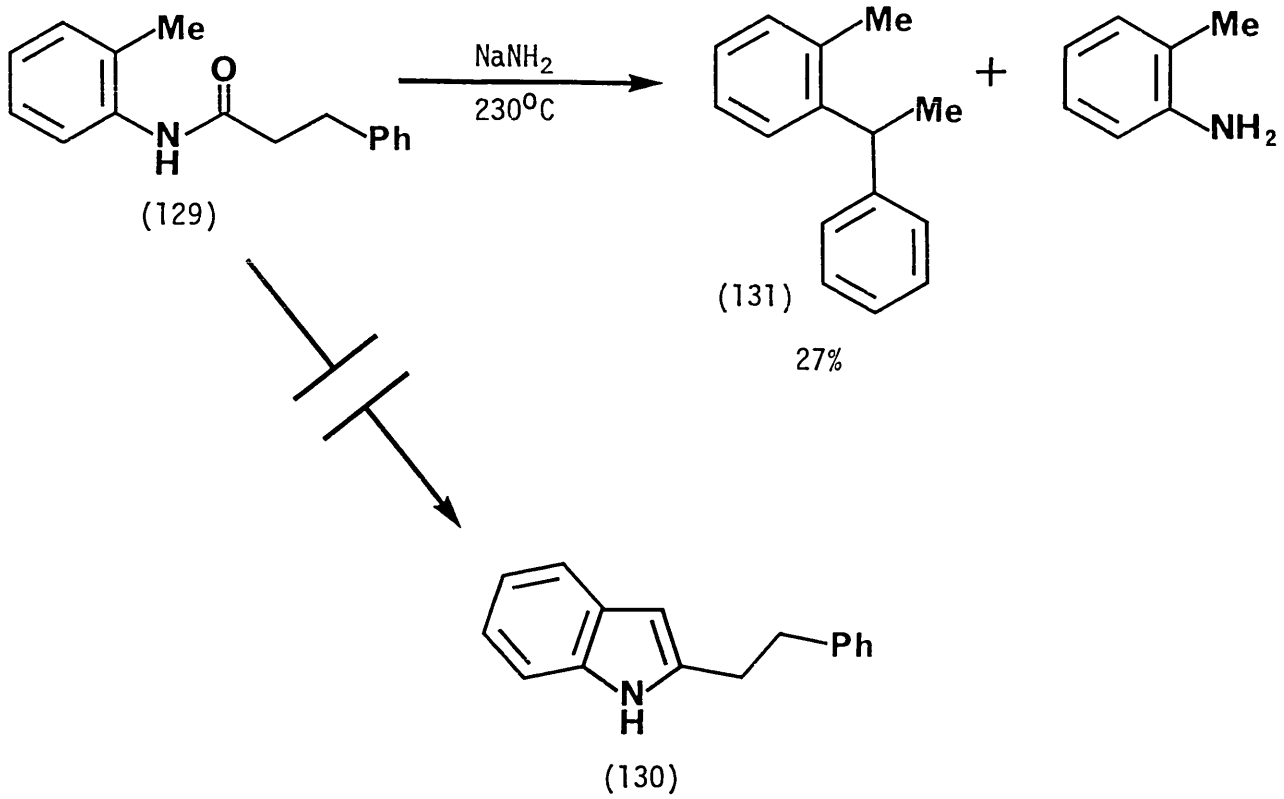
Scheme 3



One notable anomaly was observed in the attempted synthesis of 2-phenethylindole. The product obtained from treatment of amide (129) with sodamide at 230°C for 1h showed none of the expected characteristics of the indole (130). It was finally identified as 1-phenyl-1-(2-methylphenyl)ethane (131), m.p. 37-8°C (lit.,[70] 40-1°C). The only other isolable product was *o*-toluidine, formed by cleavage of the amide (129).

It must be assumed that the protons α to the phenyl group in the phenethyl side-chain are more acidic than those of the aryl methyl group. The anion formed under the conditions of the Madelung reaction is thus (132), and a Smiles-type process followed by extrusion of cyanate may then be invoked to rationalize the formation of (131).

3-Formylation of the indoles was efficiently carried out by the Vilsmeier-Haack reaction,[71] which gave yields varying from 75-97%, (Table 1). The crude material obtained from such reactions was

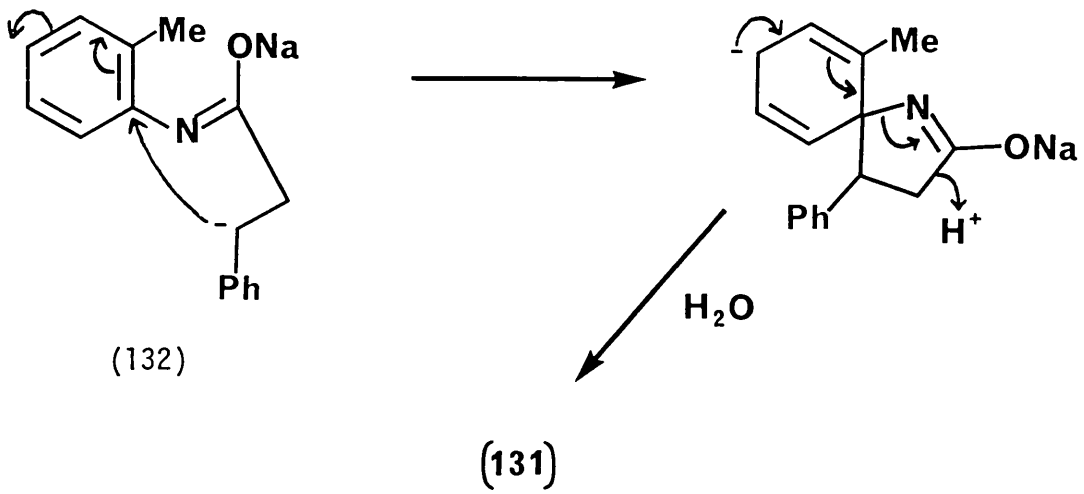


(129)

(131)

27%

(130)



(132)

(131)

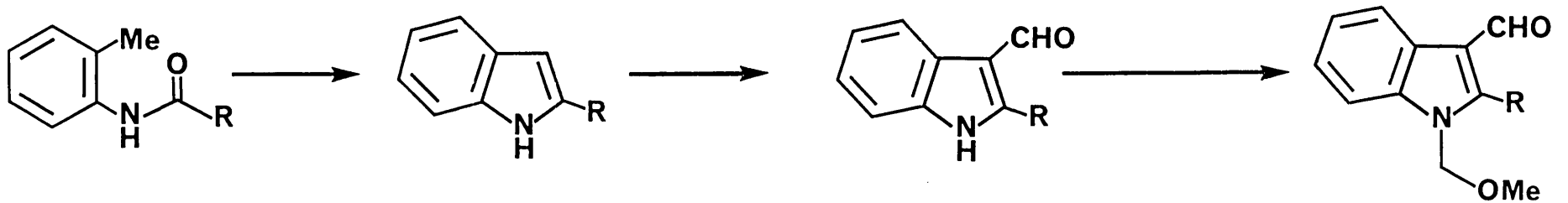
generally clean enough for immediate use, without further purification.

In the early experiments methyl or benzyl groups were used to protect the indole nitrogen, as it was ascertained that condensation with ethyl azidoacetate did not take place with *N*-unsubstituted indole-3-carbaldehydes. These groups could be introduced by refluxing the required indole-3-carbaldehyde with methyl iodide or benzyl bromide in acetone, over anhydrous potassium carbonate.[72] (Table 2).

Use of *N*-methyl protected substrates however, limited the scope of the reaction, since the indole nitrogen could not be subsequently deprotected. 1-Benzylindole-3-carbaldehydes also proved to be unsatisfactory because of the difficulty of effecting deprotection of the *N*-benzylated products.

The use of the *N*-methoxymethyl group ($-CH_2OCH_3$) for the *N*-protection of indole-3-carbaldehydes has been described in the literature,[73] and this group is very easily introduced by treatment of the appropriate carbaldehyde with sodium hydride in DMF at room temperature, and subsequently quenching with chloromethyl methyl ether. Protection with this group afforded crystalline compounds, which were easily purified. It was also found that the final products derived from these aldehydes, could be deprotected in aqueous acid, and hence, this group was adopted as the protecting group of choice for the remainder of the work, (Table 1).

TABLE 1: Indoles, Indole-3-carbaldehydes and *N*-methoxymethylindole-3-carbaldehydes

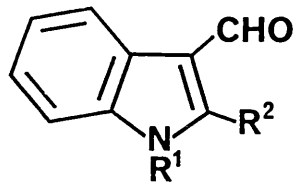


R	Yield(%)	m.p.(°C)	Yield(%)	m.p.(°C)	Yield(%)	m.p.(°C)
H	*	-	93	193-5 (lit.,[71] 194-6)	86	77-8
Me	*	-	96	199-202 (lit.,[79] 202-3)	78	87-90
Et	45	44-6 (lit.,[74] 44-5)	70	167-71	82	72-4
^{n}Pr	63	30-1 (lit.,[75] 33-4)	75	154-55	73	49-51
^{i}Pr	58	65-72 (lit.,[76] 73-5)	88	179-80	75	104-7
^{c}Hexyl	84	105-8 (lit.,[77] 103-5)	79	202-5	72	77-80
Ph	82[†]	188-92 (lit.,[78] 187-8)	97	256-85 (lit.,[80] 250-5)	90	109.5-10

* Commercially available

[†] Prepared by Fischer indole synthesis[78]

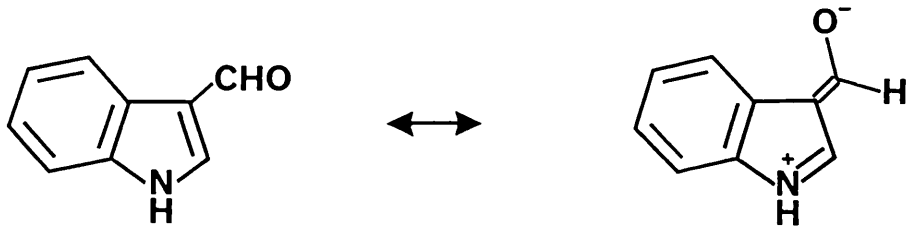
TABLE 2: *N*-Methyl and *N*-benzylindole-3-carbaldehydes



R^1	R^2	Yield(%)	m.p.(^oC)
Me	H	65	65-8 (lit.,[72] 68-9)
CH_2Ph	H	79	107-10
CH_2Ph	Me	76	135

2.3 Condensations of indole-3-carbaldehydes with alkyl azidoacetates

Indole-3-carbaldehydes are known to be considerably less reactive than for instance, benzaldehydes. The vinylogous amide character of the carbonyl group, shown in resonance structure (133b) is responsible for its low electrophilicity. A physical indication of this effect is given by the low frequency of the i.r. absorption corresponding to the C=O stretch in indole-3-carbaldehydes (1630-1650 cm^{-1}). Benzaldehydes in comparison exhibit a C=O stretching signal at 1680-1710 cm^{-1}.[99]



(133a) (133b)

It was envisaged therefore, that the condensation of these aldehydes with azidoacetates would be problematic, and this was indeed the case. Attempted condensation of the *N*-unsubstituted indole-3-

carbaldehyde under the standard conditions (*cf.* experimental) at -10°C resulted only in the aldehyde crystallizing out of solution.

Initial attempts to condense *N*-protected indoles with ethyl azidoacetate, using 1-methylindole-3-carbaldehyde, were carried out at -20°C in accordance with literature methods.[67,81] This temperature was however too low for reaction to occur, and the reaction had to be warmed to -10 - -5°C before product formation was observed (t.l.c.). Because of this, a much enhanced rate of base induced decomposition of the azidoacetate had to be tolerated.

Very concentrated solutions of the aldehyde were found to be desirable, and it was preferable to dissolve the aldehyde in neat ethyl (or methyl) azidoacetate and add this to the alkoxide solution. This was not always possible however, since some of the aldehydes employed, notably the *N*-benzyl compounds, required relatively large amounts of co-solvents (ethanol or THF) to effect solution. These rather dilute solutions frequently afforded little or no product.

The problem of solubility was effectively solved by employing the *N*-methoxymethyl protecting group, and under optimum conditions, acceptable yields (60-80%) of vinyl azides could be obtained from the condensation of **1**-methoxymethylindole-3-carbaldehyde with ethyl (or methyl) azidoacetate. The introduction of 2-alkyl substituents into the indole-3-carbaldehydes caused dramatic lowering of yields in the condensation. The optimum yield in the condensation of **1**-methoxymethyl-2-methylindole-3-carbaldehyde with ethylazidoacetate was 36% (47% based on recovery of starting material). The regularly decreasing yields obtained, as the bulk of the 2-substituent increases seems to indicate that these low yields are an inherent problem, and caused by steric hindrance of the carbonyl centre.

In none of the cases could the reaction be driven to completion, but separation of the azides from unreacted starting material was easily effected by silica gel chromatography. Table 3 lists all the azides prepared in this investigation.

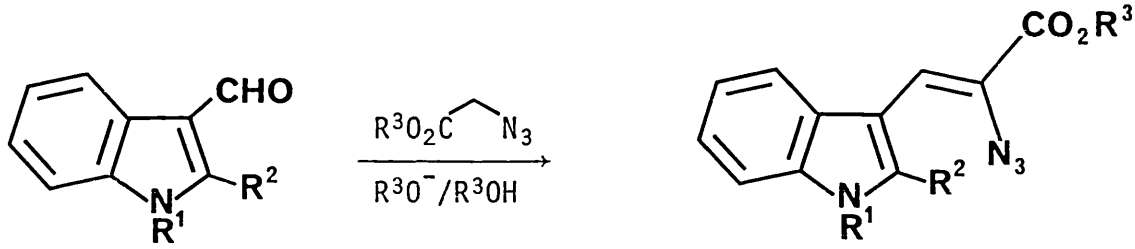
Some of the azides could be crystallized to analytical purity, and gave acceptable microanalyses (marked † in the table), the remainder however, gave microanalyses which were consistently low in nitrogen. These azides also darkened rapidly to an orange colour (whereas when freshly chromatographed they were pale yellow), and it is assumed that some decomposition, with loss of nitrogen occurred in these cases. These azides could be stored without extensive decomposition, for weeks if necessary, in a refrigerator.

The stereochemistry about the vinyl bond in these compounds has not been investigated, but is assumed to be *Z*, the thermodynamically more stable isomer, and will be drawn as such in the remainder of this work.

This is based on analogy with α-azidovinyl ketones which have the *Z* configuration and also on consideration of the instability of certain vinyl azides which have two bulky groups (*e.g.* phenyl and ester) cis to one another.[82]

Two simple strategies to increase the reactivity of the indole-3-carbaldehydes were cursorily examined. Initially, it was hoped that *N*-acetylation of the indole-3-carbaldehyde would result in decreasing the electron release to the aldehyde carbonyl group, this would be expected on the basis of contribution from resonance structure (134b).[83]

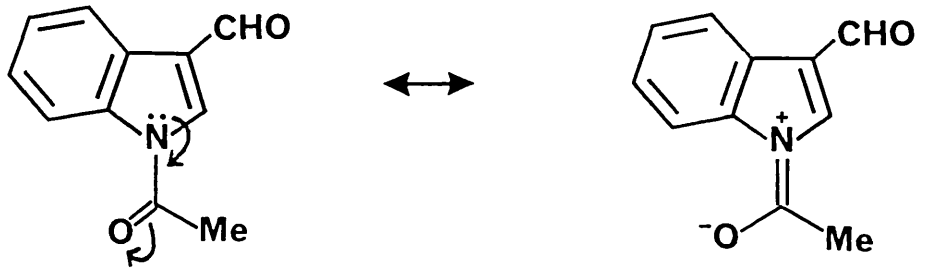
TABLE 3: Condensations of indole-3-carbaldehydes with alkyl azidoacetates



R_1	R_2	R_3	Optimum yield(%)	Yield based on recovery of starting material. (%)	m.p.(^{o}C)
Me	H	Et	50-70	*ca.* 80	100-2 dec.
CH_2Ph	H	Et	25-30	*ca.* 80	85-9 dec.
CH_2OMe	H	Et	81	-	90-2.5 dec.
CH_2OMe	H	Me	55-60	83	113.5-16 dec.†
CH_2Ph	Me	Et	20-30	*ca.* 45	90-2 dec.
CH_2OMe	Me	Et	36	47	90 dec.†
CH_2OMe	Et	Et	24	40	-*
CH_2OMe	^{n}Pr	Et	25	-	-*
CH_2OMe	^{i}Pr	Et	6	-	-*
CH_2OMe	$^{c}Hexyl$	Et	4	28	-*
CH_2OMe	Ph	Et	1	4	-*

* oil, did not crystallize

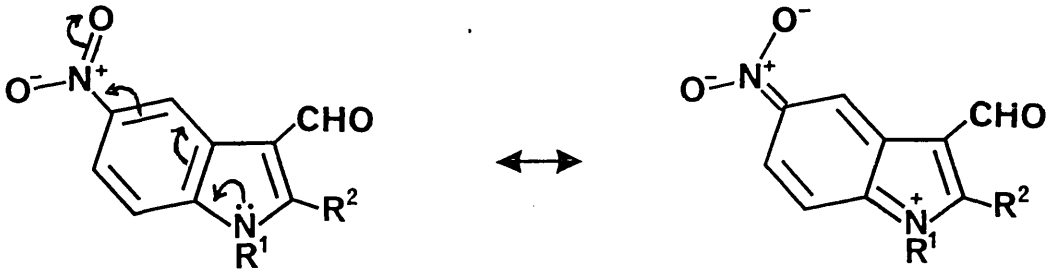
† microanalysis obtained



(134a) (134b)

It was thought that because of the low temperature of the condensation reaction, cleavage of the *N*-acetyl group would be suppressed. This was not the case, and only indole-3-carbaldehyde could be isolated from the reaction mixture.

It was then envisaged that the normal mode of electron release in indole-3-carbaldehydes might be diverted to some extent if a 5-nitro substituent were to be introduced into the indole 6-ring, by virtue of resonance structure (135b).



(135a) (135b)

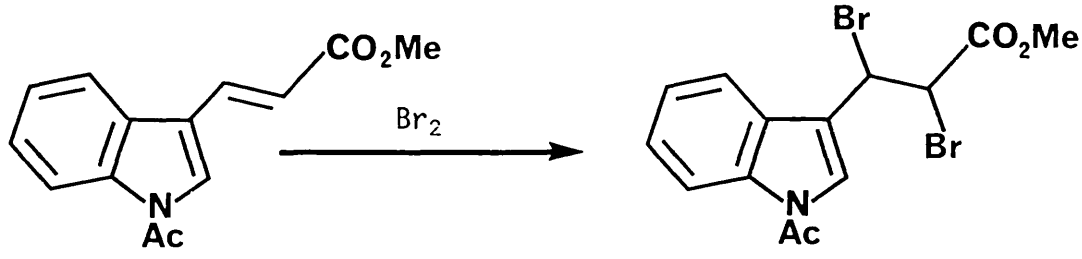
Accordingly, 1-benzyl-2-methyl-5-nitroindole-3-carbaldehyde was prepared. This however proved to be so insoluble in virtually all cold organic solvents (except DMF or DMSO), that this strategy was abandoned.

2.4 Other attempted syntheses of vinyl azides

In the absence of a strategy for improving the yields of the azido-acetate condensations, it was decided to seek an alternative route to the azidopropenoates.

The first effort to develop an alternative synthesis of these vinyl azides involved an attempted addition-elimination to a 3-indolyl-bromopropenoate.

Russian workers have described the preparation of 1,2-dibromide (136) by bromination of propenoate ester (137).[84]

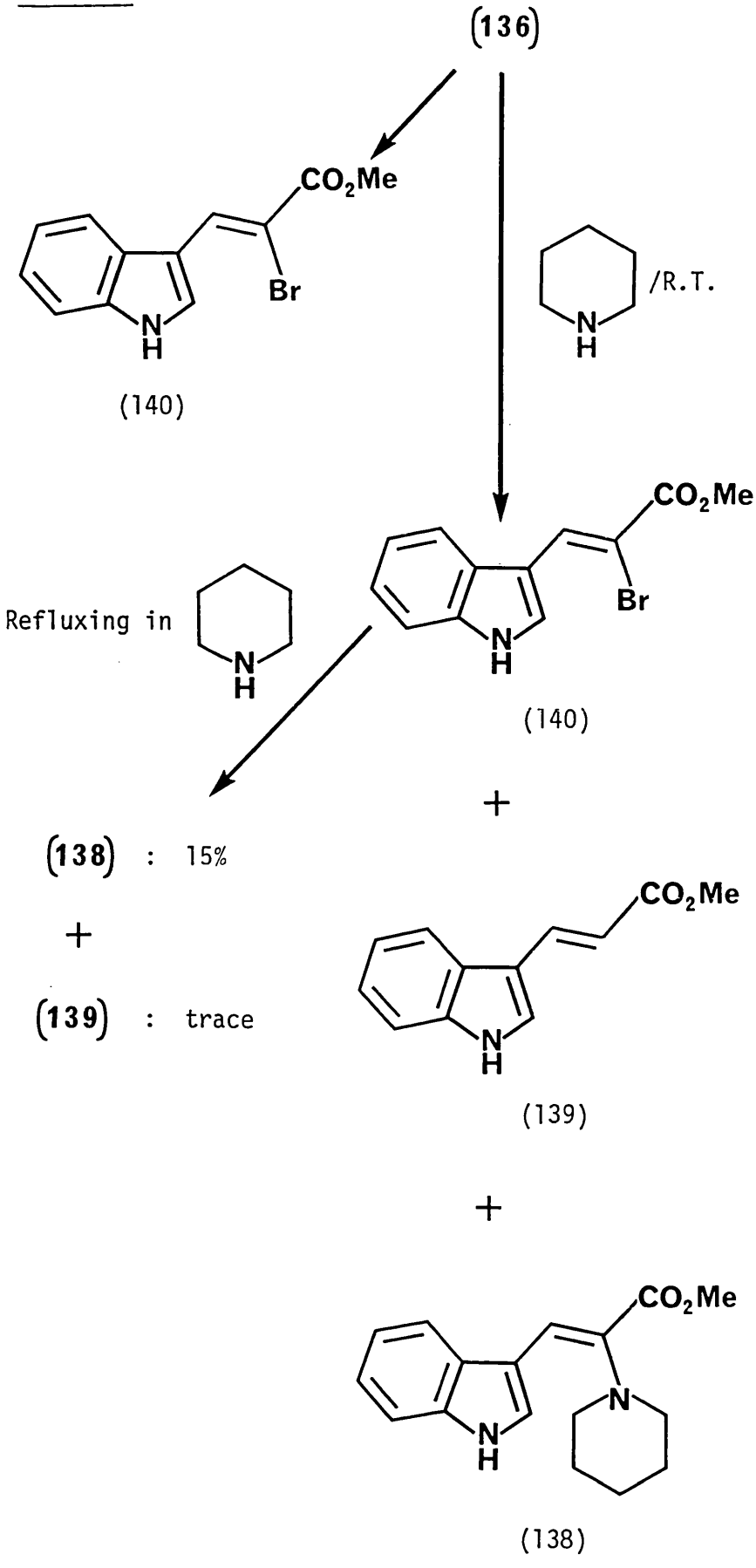


(137) (136)

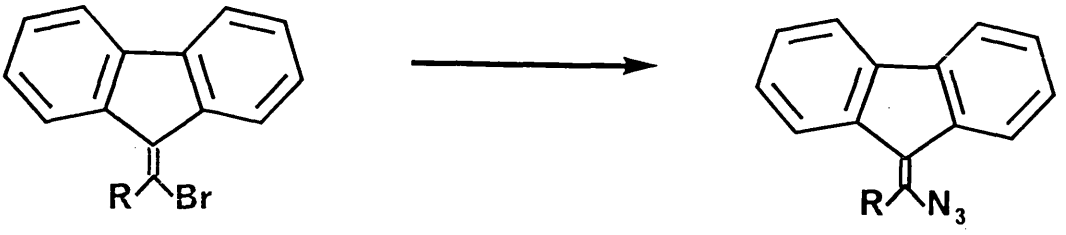
This dibromide underwent base catalysed elimination of HBr, and concomitant deacetylation when treated with methanolic methoxide.[85] With piperidine at room temperature, compounds (138) - (140) were formed, whereas in boiling piperidine only (138) could be isolated, although (139) could be detected in the reaction mixture by t.l.c. Furthermore, the 2-bromopropenoate (140) gave the same products as the dibromide (136) when refluxed in excess piperidine, (Scheme 4).[86]

This precedent for nucleophilic addition-elimination type reactions with 2-bromopropenoates such as (140), coupled with the knowledge that vinyl bromides such as (141a) and (141b) may be converted into vinyl azides (142a) and (142b) by treatment with sodium azide in DMF,[87] seemed to suggest that treatment of bromopropenoates such as (143a) or

Scheme 4


(136)
CO2Me
Br
N
H
/R.T.
(140)
Refluxing in
CO2Me
Br
(140)
+
(138) : 15%
+
(139) : trace
CO2Me
(139)
+
CO2Me
N
(138)

(143b) with sodium azide in polar solvents might lead to the formation of vinyl azides of the required type.



(141)

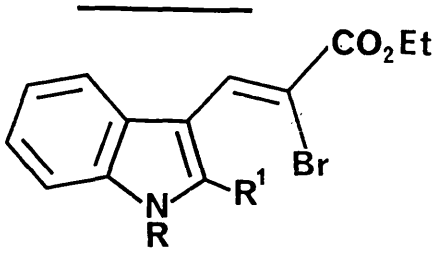
a) R = H

b) R = Me

(142)

a) R = H

b) R = Me

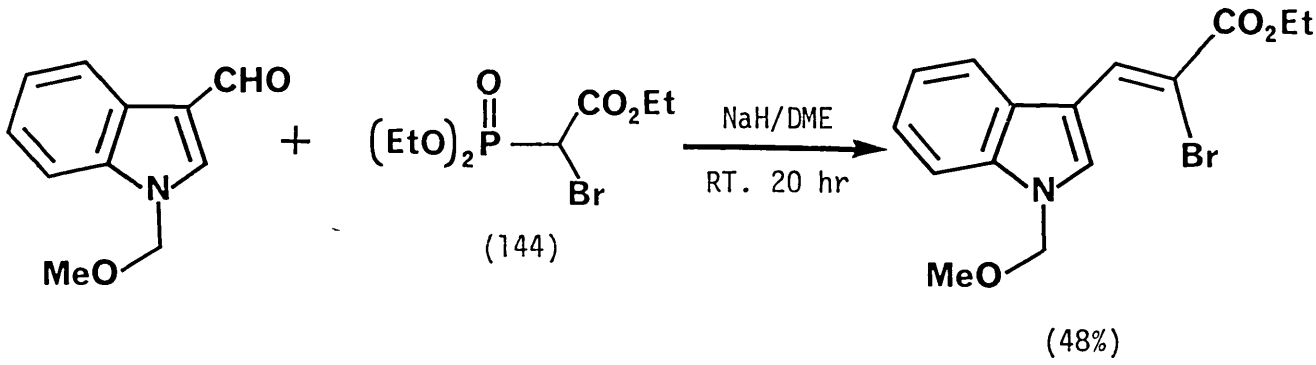


(143)

a) R = $-CH_2OMe$, R^1 = H

b) R = $-CH_2OMe$, R^1 = Me

A convenient preparation of (143a) employs the Wadsworth-Emmons reaction. Bromophosphonate (144) was reacted with 1-methoxymethyl-indole-3-carbaldehyde under standard conditions.[88] The reaction did not go to completion, and some starting aldehyde could be recovered. The bromopropenoate (143a) thus obtained was assumed to have the geometry shown, *viz.* the two largest groups being *trans* to one another, which is the expected geometry for olefins formed thus. A small amount of the other isomer was detected by n.m.r. of the oily material obtained by chromatography of the crude reaction product. Crystallization from petrol afforded the pure major isomer (m.p. 77-9°C).

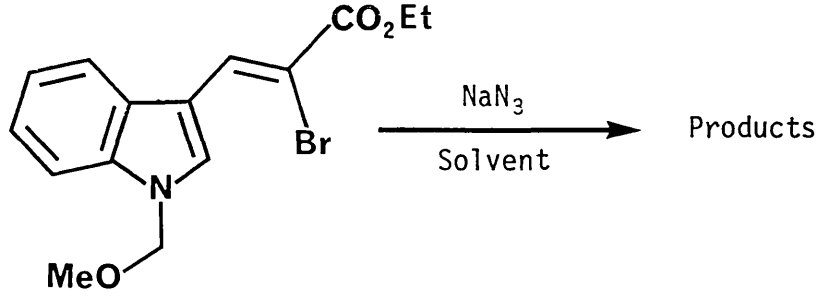


(48%)

An attempt to effect the analogous formation of (143b) from 1-methoxymethyl-2-methylindole-3-carbaldehyde was unsuccessful, and even after refluxing the reaction mixture, only starting material could be detected by n.m.r.

Initial attempts to carry out an addition elimination reaction with azide resulted only in recovery of the starting bromopropenoate, or formation of intractable materials. These abortive attempts are outlined in Table 4.

TABLE 4:

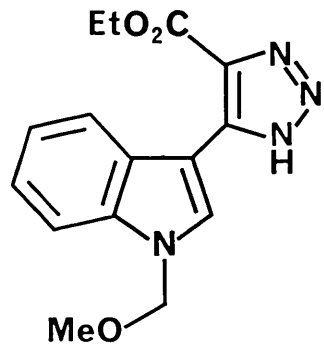


Amount of NaN_3	Solvent	Reaction Temp	Reaction Time	Result
1.1 eq.	DMSO	Ambient	20 hr	No Reaction
1.1 eq.	DMSO	60°C	24 hr	No Reaction
1.1 eq.	DMSO	120°C	48 hr	Complex mixture*
3 eq.	60% aqueous acetone	Reflux	18 hr	No Reaction
3 eq.	HMPA	Ambient	18 hr	No Reaction

*Probably due to oxidation of the system by hot DMSO.

Treatment with 3 equivalents of sodium azide in HMPA at 65°C for 48 hr, or with 1 equivalent of sodium azide in the same solvent at 120°C for 2.5 hr, resulted in the formation of two new compounds which were separated by chromatography on silica gel. The less polar compound, obtained in 10% yield from the reaction at 65°C, was an oil which could not be obtained analytically pure either by chromatography or by short-path distillation, the presence of minor impurities being indicated by n.m.r.. The n.m.r. spectrum consists of only the methyl and methylene singlets corresponding to the *N*-methoxymethyl group, and five aromatic protons, one of which is a singlet (δ 7.44). The i.r. spectrum exhibits peaks at 3290, 2110 and 1535 cm^{-1}. No useful information could be obtained from the mass spectrum. It was not found possible to propose a structure on the basis of these data and the compound was not investigated further.

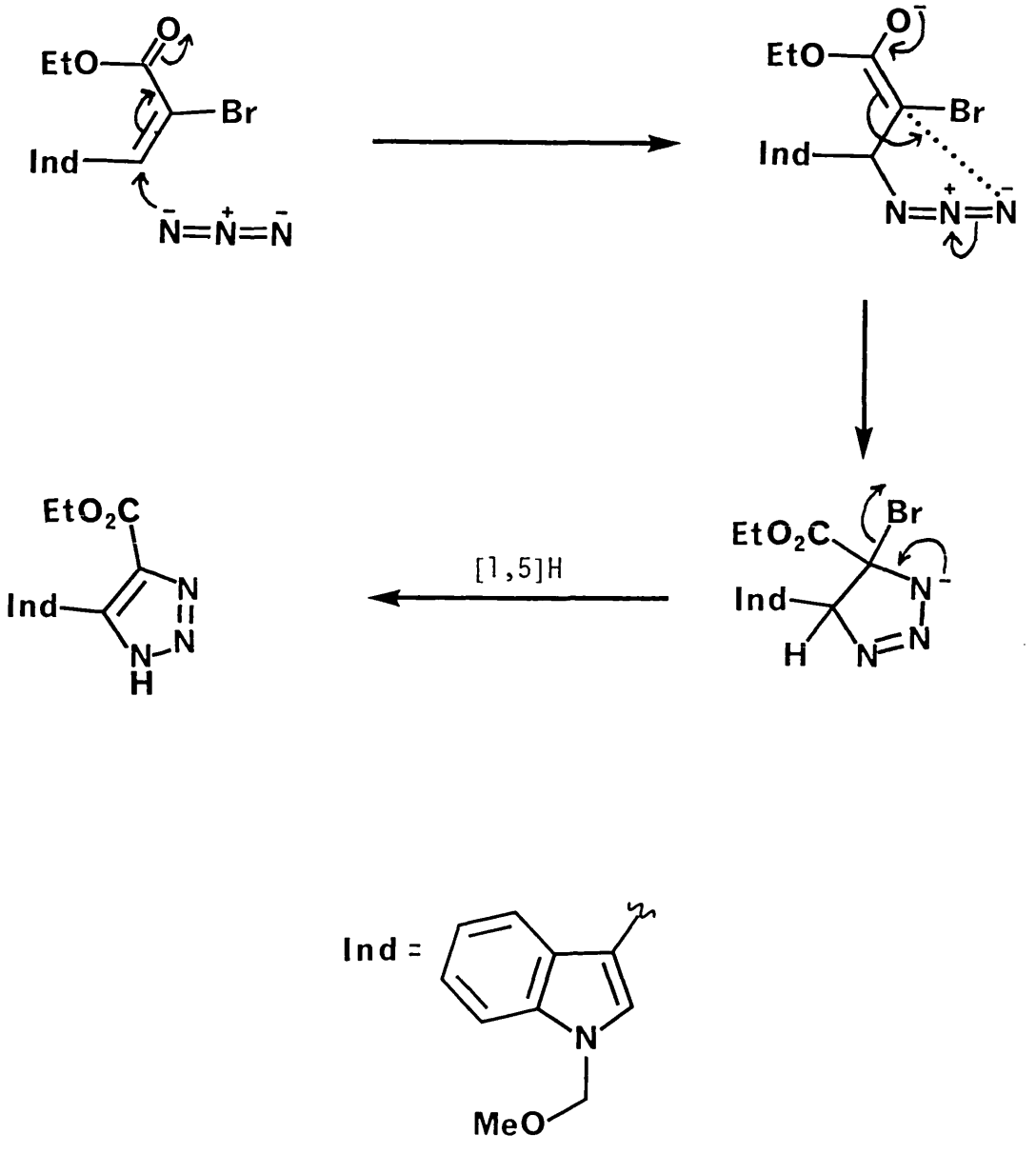
The more polar compound, obtained in 16% yield, is a crystalline solid (m.p. 106-8.5°C). The n.m.r. spectrum contains signals corresponding to an ethyl ester group, an *N*-methoxymethyl group, and five aromatic protons, one of which is a singlet at δ 8.47. Signals are observed at 3140 and 1720 cm^{-1} in the i.r., and in the mass spectrum at 300 (100%) and 272 (8%). These data appear to be consistent with the structure (145).



(145)

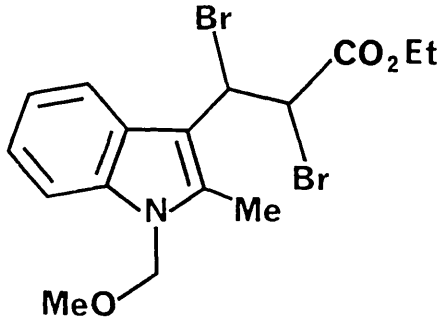
This is not altogether surprising, since olefins with a strongly electron withdrawing group are known to react with azide ion to give triazoles. One possible mechanism involves conjugate addition of azide to the double bond, cyclization of the resulting anion and aromatization, (Scheme 5).[89]

Scheme 5



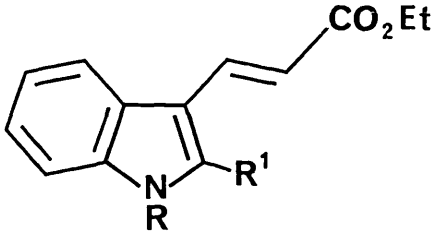
It seemed unlikely in the light of the above observations, that vinyl azides could be formed by this methodology.

By consideration of the Russian work previously described, it appeared worthwhile to attempt the preparation of dibromide (146). It was felt that in analogy with the formation of (138) from (136), as shown in Scheme 4, a vinyl azide might be obtained upon treatment of (146) with azide ion.



(146)

It was decided to prepare this dibromide by bromination of indolyl-3-propenoate (147c).[84] A selection of these propenoates was synthesised, since they were also required for other purposes.



(147)

a) R = H, R' = H
b) R = H, R' = Me
c) R = CH_2OMe, R' = Me
d) R = CH_2OMe, R' = Et

Heating indole-3-carbaldehyde or 2-methylindole-3-carbaldehyde with excess monoethyl malonate in pyridine with a trace of piperidine, gave the propenoates (147a) and (147b) respectively, in 50-70% yield.[90]

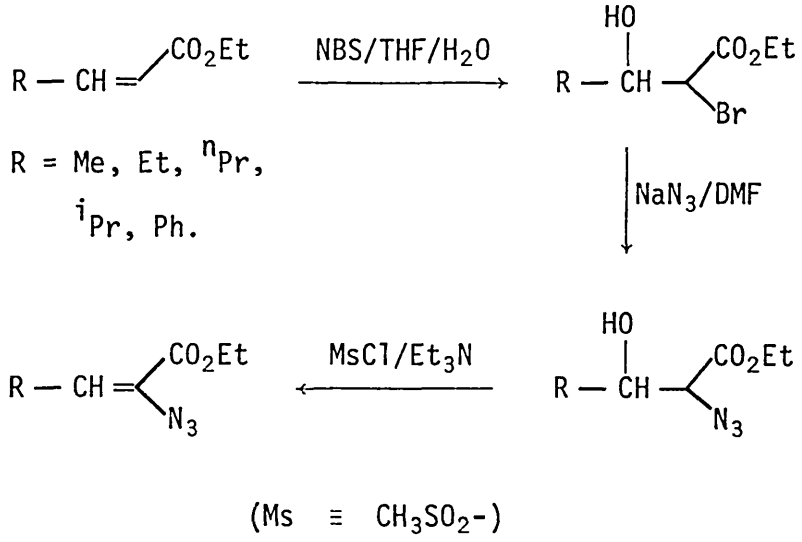
When preparing the *N*-protected propenoates (147c) and (147d) from the corresponding *N*-protected aldehydes, it was found that the reaction could not be driven to completion, even by employing large excesses of monoethyl malonate and long periods of refluxing. The propenoates could, however, be separated easily from unreacted starting material by chromatography on silica gel.

The bromination attempts were carried out on (147c) in the hope that a fully substituted indole 5-ring would minimize the chance of attack by bromine on the indole nucleus. Addition of a solution of bromine in carbon tetrachloride to a solution of the propenoate in the same solvent, at room temperature, until a faint orange colour persisted, resulted in the formation of a complex mixture as evidenced by t.l.c. and n.m.r. Chromatography of the mixture gave only unidentifiable gums. It would appear that (146) was never formed, since, in view of the stability claimed for compound (136) by the Russian group, it would almost certainly not decompose under the conditions described. Evidently, electrophilic attack by bromine on the indole 5-ring is implicated, notwithstanding the attempt made to block this ring to such attack.

Despite the failure to prepare (146), synthesis of 2-azidopropenoates *via* the propenoates (147) still seemed viable, and an alternative route was sought to effect this transformation.

Shin *et al*[91] have described a sequence whereby propenoates were treated with NBS in aqueous THF to give bromohydrins, which could be converted to azidohydrins and subsequently to vinyl azides, (Scheme 6).

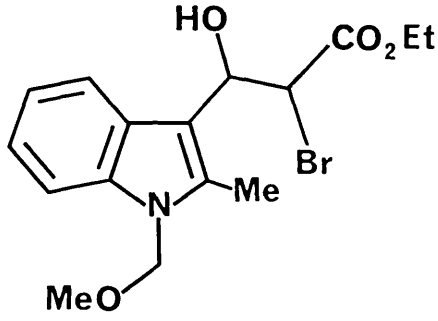
Scheme 6



(Ms ≡ CH_3SO_2-)

Initially, propenoates (147a) and (147b) were treated with NBS in aqueous THF for varying time periods, but even short exposure to these conditions gave highly coloured gums, which appeared to consist only of intractable materials.

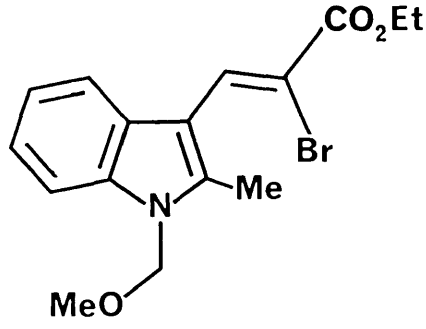
Treatment of the *N*-protected propenoate (147c) with NBS in aqueous THF at 0^oC for 8 minutes, followed by quenching in a large excess of ice-water, gave crude material which exhibited a doublet at δ 4.8 and what appeared to be another, partially hidden doublet at *ca.* δ 5.5 the coupling between which was approximately 9 Hz. This seemed to point to the formation of the required bromohydrin (148).



(148)

Also observed were doublets corresponding to traces of unreacted propenoate, and a small sharp singlet at δ 8.5.

The crude material was treated with sodium azide in DMF at 76°C for 1.5h, followed by an aqueous work-up. The two doublets previously alluded to, were absent in the n.m.r. of the material resulting from this treatment, the compound responsible for the sharp singlet at δ 8.5 having become the major component. A part of this material was in turn treated with methanesulphonyl chloride and triethylamine in dichloromethane. The crude material from this reaction possessed an n.m.r. spectrum identical with that of the material prior to such treatment. Chromatography of this mixture resulted in the isolation of a small amount of a substance having a complex n.m.r. spectrum, and exhibiting an i.r. signal at 2104 cm^{-1}, which was discarded, along with a trace of propenoate (147c). The major component was isolated in 29% yield (from propenoate (147c)) as an oil, which subsequently solidified (m.p. 90-3°C). This was the material responsible for the δ 8.5 singlet in the n.m.r., along with which, resonances corresponding to ethyl ester, *N*-methoxymethyl, 2-methylindole and aromatic protons are observed. The i.r. spectrum shows no evidence of the compound being an azide, and the mass spectrum shows it to be a monobromo compound. These data point to the structure (143b).



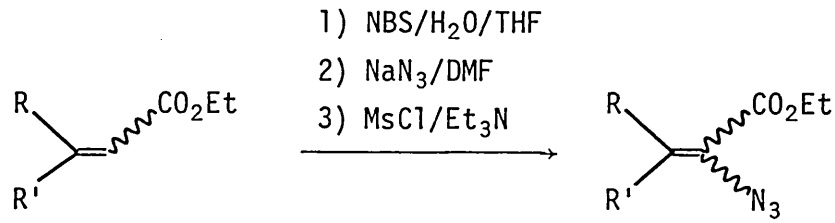
(143b)

This compound could also be isolated in comparable yield from the remainder of the crude material resulting from the sodium azide/DMF reaction, which had not been submitted to methanesulphonyl chloride/triethylamine treatment.

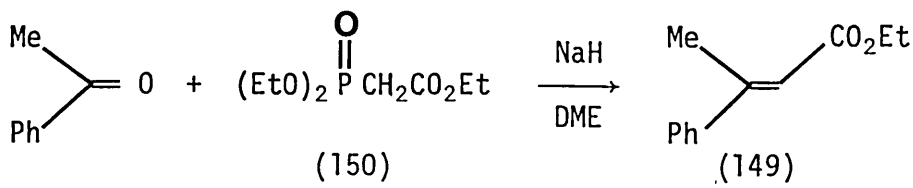
It appears that dehydration of the bromohydrin (148) is so facile, due to the acidity of the proton α to the ethyl ester group, and to the driving force of conjugation of the ester group and the indole nucleus, that in the preferred mode of reaction, the rôle of azide is that of a base rather than a nucleophile. The ease with which this dehydration takes place, is apparent from the presence of traces of (143b) in the reaction mixture from the treatment with NBS in aqueous THF, prior to treatment with sodium azide.

The failure of the bromohydrin route to indolyl-3-(2-azidopropenoates) prompted a brief investigation of alternative uses for this sequence of reactions. It was thought that by using 3,3-disubstituted propenoates, as starting materials, the 2-azidopropenoates formally derived from condensation of ethyl azidoacetate with ketones might be accessible. This would be useful, since the condensation with ketones does not proceed, (Scheme 7).

Scheme 7

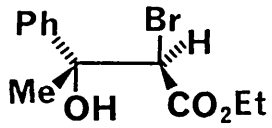


The propenoate (149) was employed as a model system to investigate this idea. This was easily prepared by the Wadsworth-Emmons reaction of acetophenone with phosphonate (150), and was obtained isomerically pure in 54% yield after distillation.[88]

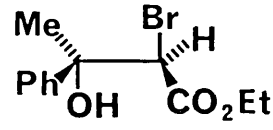


(150) (149)

Treatment of (149) with NBS in aqueous THF gave a mixture of the two diastereomers (151a) and (151b) in 73% overall yield, in a 9:2 ratio after chromatography.

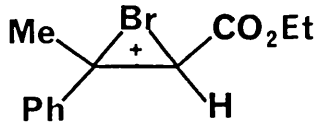


(151a)

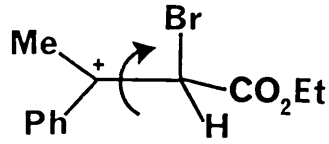


(151b)

Presumably some epimerization occurs because of the large degree of carbonium ion character in the bromonium intermediate (152a). This is due to the high stability of carbonium ion (152b), and has the effect of lowering the energy required for rotation about the central bond.



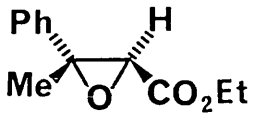
(152a)



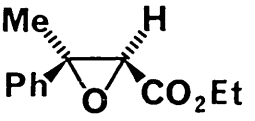
(152b)

When this diastereomeric mixture was treated with sodium azide in DMF at 64°C for 18 hr a mixture of two diastereomeric products was obtained, in a 9:2 ratio. The major isomer could be obtained pure by chromatography on silica gel. The later fractions contained a mixture of the two isomers. After further purification by short-path distillation, spectroscopic analysis showed that these diastereomers were not azides, the only significant i.r. absorption being at 1735 cm^{-1}. The n.m.r. spectrum (major isomer) shows the presence of ethyl ester,

methyl, and aromatic protons, and also, a one proton singlet at δ 3.46. The structures (153a) and (153b) were thus proposed for these diastereomers. This assignment was confirmed by treatment of the epimeric



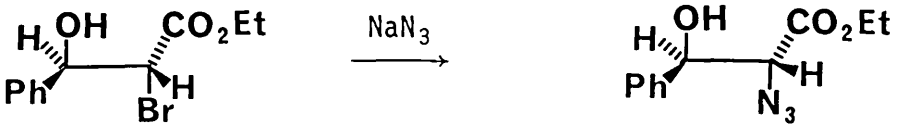
(153a)



(153b)

mixture (151a and b) with sodium hydride in dry ether, whereby the same epimeric mixture of epoxides (153a and b), as that formed by the azide treatment was obtained. The epoxide mixtures formed from both reactions were identical spectroscopically and chromatographically.

It is still unclear why sodium azide should apparently behave as a base rather than as a nucleophile in this reaction. This behaviour being in sharp contrast to the report of Shin, as regards the closely related systems (154) - (155).[91]

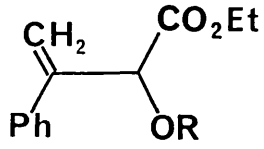


(154) (155)

One possible explanation is that in the sterically more crowded systems (151a and b) conformational locking in an *anti* periplanar conformation operates, this being the favoured conformation for the intramolecular

nucleophilic displacement leading to the epoxides. In the less sterically congested (154), one of the conformations in which hydroxyl and bromo substituents are not *anti* periplanar may be preferred. Intermolecular nucleophilic displacement by azide ion would then be far more favourable.

Treatment of the mixture of epoxides (153a and b) with sodium ethoxide in ethanol resulted in the formation of acetophenone, *via* a ring opening and retro-aldol sequence. Catalytic pTSA in dichloromethane, or acetic anhydride containing catalytic sulphuric acid gave (156a) or (156b) respectively.

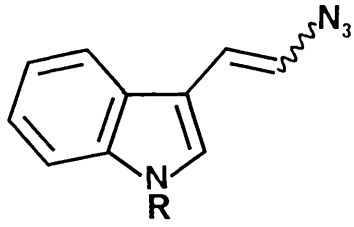


(156)

a) R = H

b) R = Ac

A route was also sought, whereby azides such as (157), without the alkoxycarbonyl group, might be prepared.

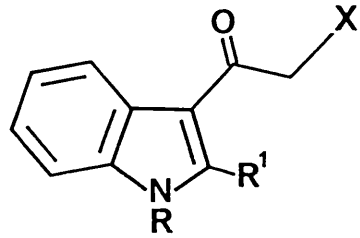


(157)

a) R = H

b) R = Me

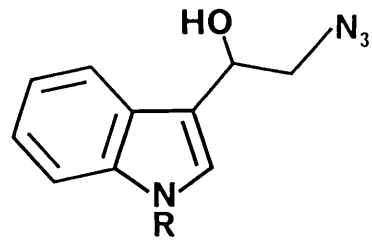
The conversion of phenacyl bromide to 2-azidostyrene *via* formation of an α-azidoketone, reduction to an azidohydrin and elimination, has been reported.[92] This suggested that the chloroketone (158a) would be an appropriate starting material.



(158)

a) R = H , X = Cl, R' = H
b) R = H , X = N_3, R' = H
c) R = Me, X = N_3, R' = H
d) R = Me, X = N_3, R' = Me

This compound was accordingly prepared by treatment of indole with chloroacetyl chloride in toluene containing 1 equivalent of pyridine.[93] Treatment of (158a) with sodium azide in refluxing aqueous acetone afforded the azidoketone (158b) quantitatively. This was reduced to the azidohydrin (159a) by treatment with sodium borohydride in ethanol containing a trace of acetic acid. Finally, treatment with methanesulphonyl chloride and triethylamine in dichloromethane gave the vinyl azide (157a) as an approximately 50:50 mixture of double bond isomers. The n.m.r. spectrum of the *trans* isomer exhibits an AB quartet centred at δ 6.55 (J 14 Hz) and the *cis* at δ 6.12 (J 7.4 Hz).



(159)

a) R = H
b) R = Me

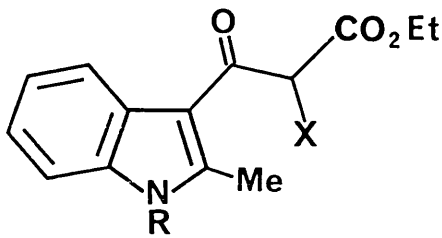
The *N*-methyl azide (157b) was prepared in an exactly similar manner, from the *N*-methylazidoketone (158c), obtained by treating (158b) with methyl iodide and potassium carbonate in refluxing acetone. The *cis/trans* isomer ratio of (157b) obtained by dehydration of (159b), was estimated by n.m.r. as being approximately 70:30, assuming again, that the AB quartet with the larger J value corresponds to the *trans* isomer.

The success of the above route initiated renewed efforts to prepare the 2-azidopropenoates already described, by a similar methodology. An initial attempt was made to form the enolate anion of (158d), (prepared from 2-methylindole by a sequence exactly analogous to the preparation of (158c)), with sodium hydride in DMF. Reaction of this with ethyl chloroformate, it was hoped, would give azidoketoester (160f). The crude material from this reaction, however, appeared to be complex by n.m.r., and furthermore showed no azide signal in the i.r.

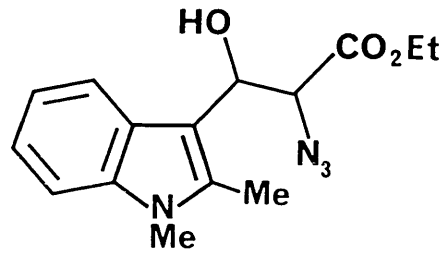
It was then decided that the bromoketoester (160e) would be required as the key intermediate. It was hoped that treatment of this with sodium azide would give azidoketoester (160f). Reduction of this with borohydride was expected to give azidohydrin (161). The apparent ease of dehydration of the analogous bromohydrin already described, was expected to be a favourable effect in this case, and to lead to facile formation of the required 2-azidopropenoate. It was decided to work with the 2-methylindole derivatives, since it was in the indole-2-substituted series of azidopropenoates that improvement in yields was most desirable. For the sake of simplicity, an *N*-methyl protecting group was employed. The original strategy for the preparation of (160e) involved bromination of the enolate anion of (160c), the preparation of which was thus undertaken.

Initially, the ketoester (160a) was prepared in 35% yield by treatment of 2-methylindole with ethylmalonyl chloride in toluene containing 1 equivalent of pyridine.[93] Attempts to *N*-methylate this compound using excess methyl iodide and potassium carbonate in refluxing acetone, led to dimethylation, giving compound (160d), a colourless solid (m.p. 105.5-7°C). Treatment of (160a) with 1 equivalent of sodium hydride in DMF, followed by quenching with methyl iodide gave a mixture of (160b) and(160c) in a 75:25 ratio, as estimated by n.m.r.

Treatment of 1,2-dimethylindole with ethylmalonyl chloride under the aforementioned conditions gave a mixture of starting material and (160c) which was easily separable by chromatography on silica gel. A 30% yield of (160c) was obtained, along with 55% recovery of 1,2-dimethylindole.



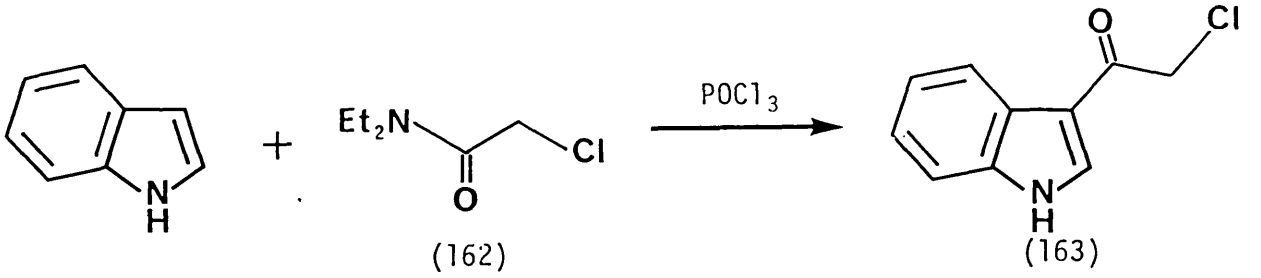
(160)



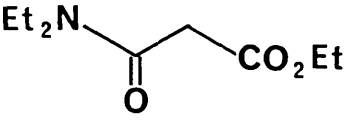
(161)

a) R = H , X = H
b) R = H , X = Me
c) R = Me, X = H
d) R = Me, X = Me
e) R = Me, X = Br
f) R = Me, X = N_3

Due to the rather low yields of (160c) obtained by this method, an alternative preparation was sought. It is known that the Vilsmeier-Haack reaction of indole with amide (162), gives chloroketone (163).[94] A modified version of this reaction could be envisaged, in which Vilsmeier reaction of amide (164) with 1,2-dimethylindole would give (160c). Amide (164) was easily prepared by treatment of ethyl malonyl

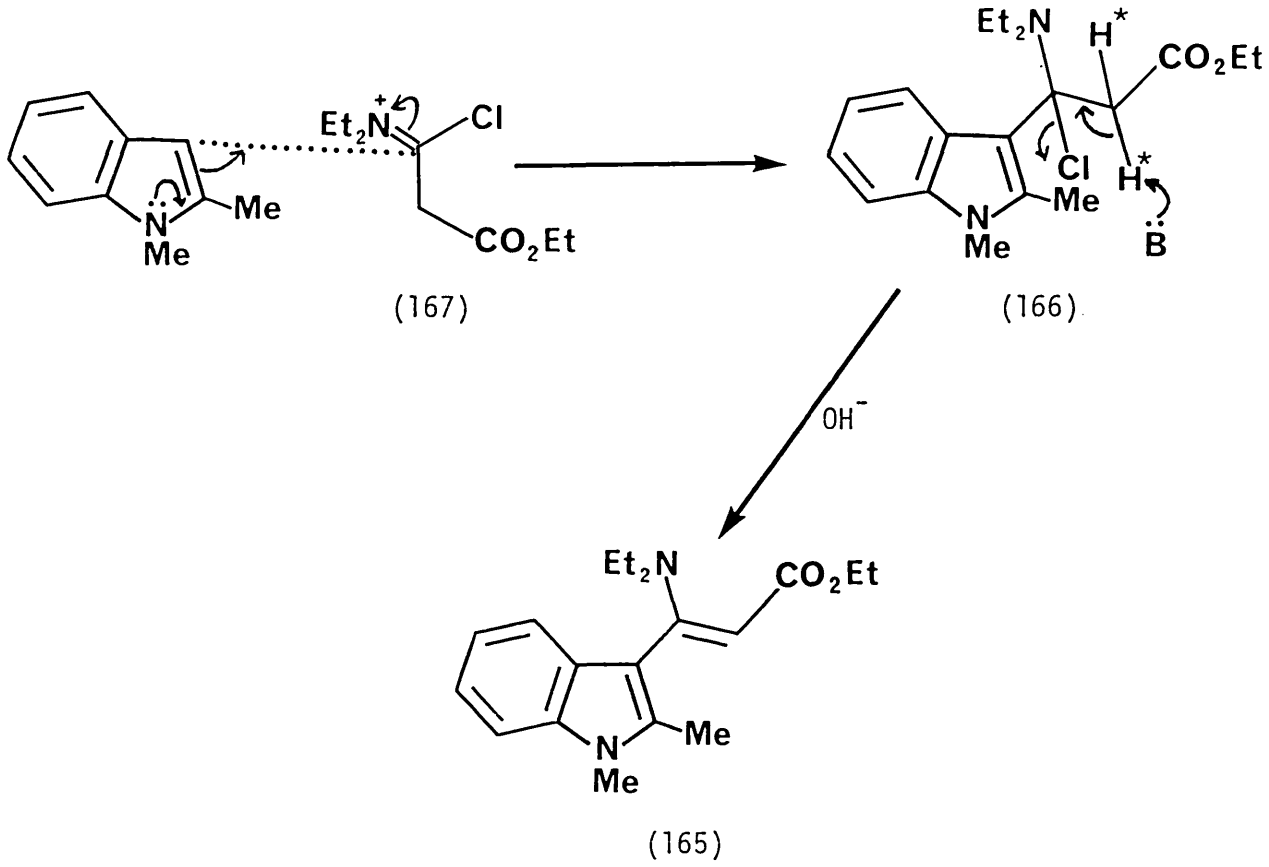


(162) (163)

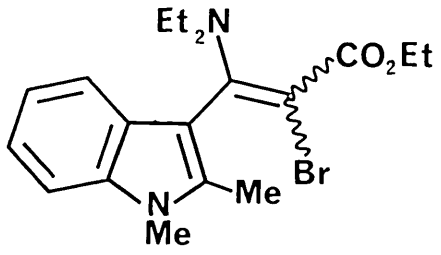


(164)

chloride with 2 equivalents of diethylamine in dry ether at 0°C. The Vilsmeier reaction was carried out as normal, using (164) as reaction solvent as well as reagent. The product of this Vilsmeier reaction, a pale yellow solid (m.p. 117 - 9.5°C) was not however, (160c). In the n.m.r. spectrum, along with ethyl ester, *N*-methyl, 2-methyl and aromatic signals were multiplets δ 0.8 - 1.5 (6H) and δ 3.0 - 3.5 (4H), as well as a sharp singlet 5.05 (1H). These data are consistent with the structure (165). Its formation is easily rationalised by consideration of the intermediate (166), formed by attack of 1,2-dimethylindole on the Vilsmeier reagent (167). The normal course of the reaction, *viz* displacement of chloride ion by the nitrogen lone pair, subsequent nucleophilic attack by hydroxide ion and elimination of diethylamine, is not followed due to the acidity of the α protons (marked with an asterisk in (166)). Instead, elimination of HCl results in formation of the enamine (165), which was formed isomerically pure, and is assumed to have the geometry shown. Although the enamine (165) could be hydrolysed with dilute sulphuric acid in ethanol to the ketoester (160c), another possibility



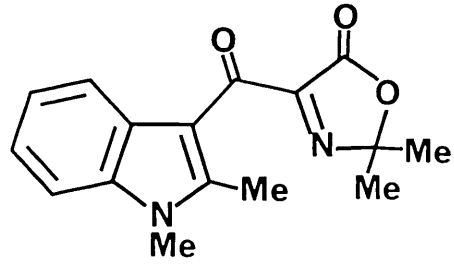
was considered, *viz* direct bromination of enamine (165). Accordingly, this enamine was treated with bromine in dry ether at -78°C. Treatment of the resultant buff precipitate of the iminium bromide with water, and isolation of the product by chromatography, gave a yellow gum in 69% yield. Spectroscopic examination showed this to consist of an approximately 40:60 mixture of double bond isomers of the bromoenamine (168).



(168)

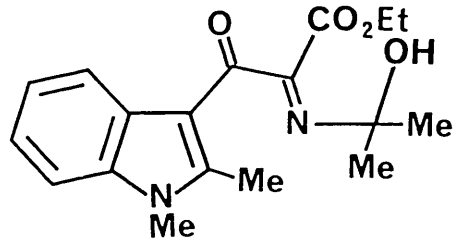
The yield of this reaction was somewhat variable in subsequent runs. Bromoenamine (168) could be hydrolysed with dilute sulphuric acid in ethanol, giving the required bromoketone (160e) in 83% yield.

The first attempt at nucleophilic substitution of (160e) with azide, involved heating with 2 equivalents of sodium azide in 60% aqueous acetone. The resulting gum, after chromatography, appeared to consist of two compounds. One of this pair of compounds was an ethyl ester, but no more could be concluded about it with certainty, as it appeared to transform to the other compound during chromatography. The other compound was obtained as a yellow crystalline solid (m.p. 144-6^{o}C), in low yield, by crystallization of the mixture from ethanol/petrol. The n.m.r. spectrum of this compound is simple, consisting of aromatic protons, *N*-methyl and 2-methylindole resonances, and one other singlet at δ 1.78 (6H). This six proton singlet points to the incorporation of acetone, while it is also obvious that the loss of the ester group has occurred. Consideration of these data, as well as i.r. and mass spectral information leads to the structure (169).



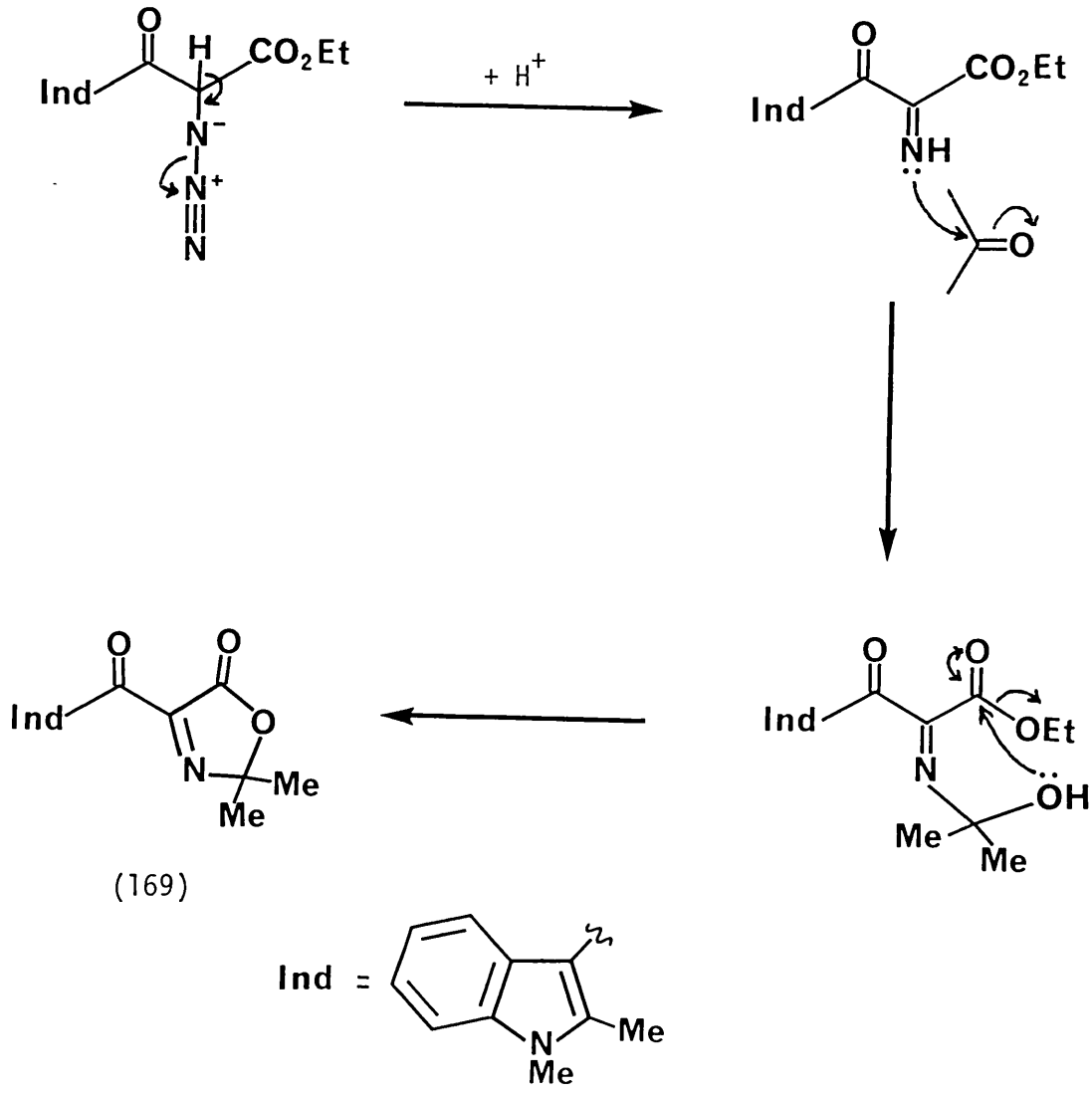
(169)

One possible structure for the other compound alluded to above would be that of alcohol precursor (170), although there is no firm evidence for this assertion. The mode of formation of (169) is thought to involve initial nucleophilic displacement of bromine, followed by loss of nitrogen as shown. Incorporation of one molecule of acetone, and cyclization then gives (169), (Scheme 8).



(170)

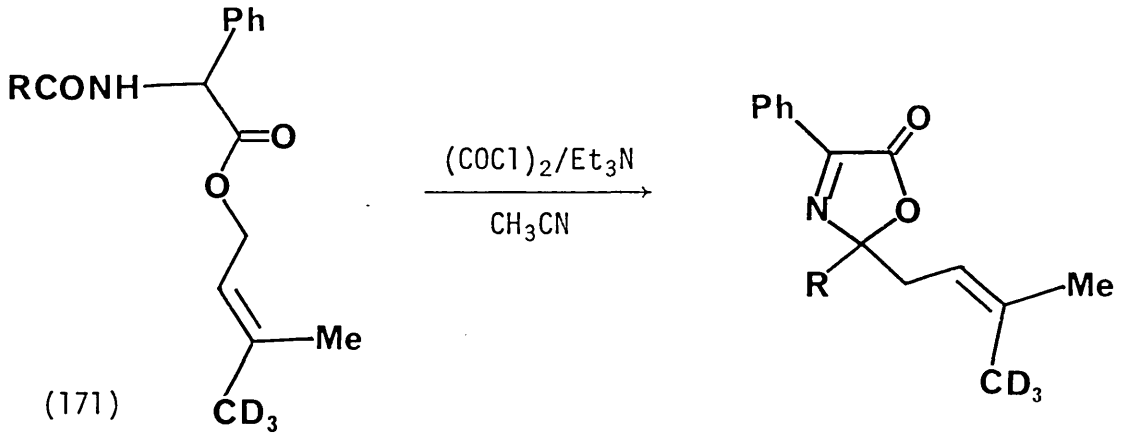
Scheme 8



(169)

Ind =

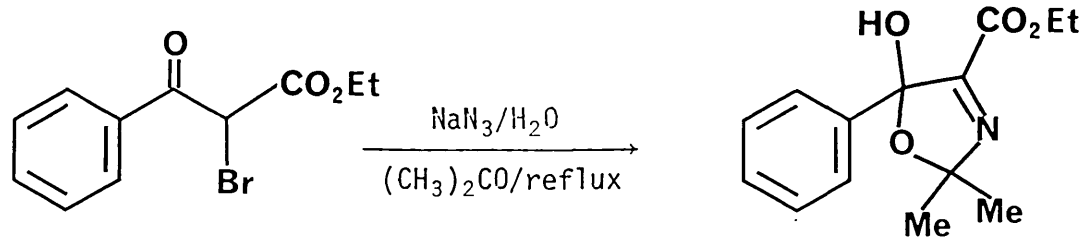
Oxazolones such as (169) are known in the literature, where they have been prepared for instance by treatment of amidoesters such as (171) with oxalyl chloride and triethylamine.[95]



(171)

The thermal extrusion of carbon dioxide from these oxazolones to give nitrile ylids has been extensively studied.[96,97]

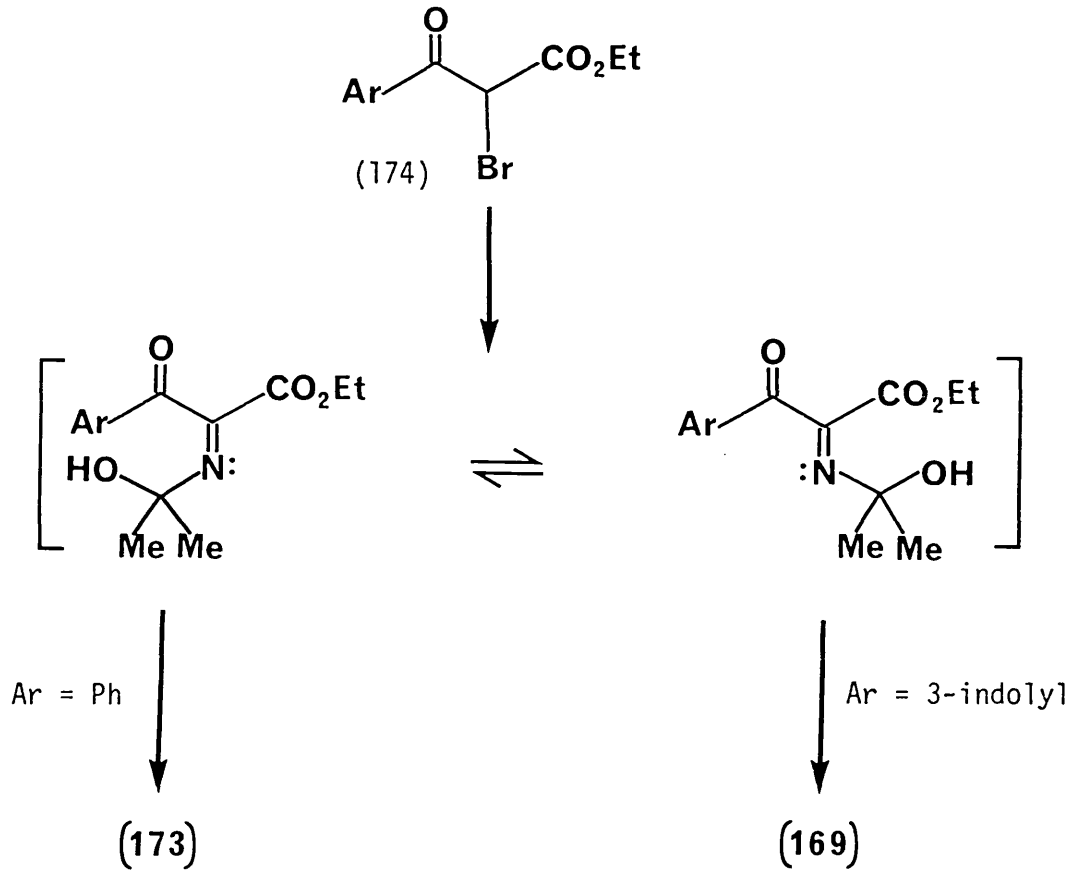
In an attempt to assess the generality of this reaction, bromoketoester (172) was treated with sodium azide in aqueous acetone.[98] Instead of an oxazolone analogous to (169) however, a 2,5-dihydrooxazole (173) was obtained.



(172) (173)

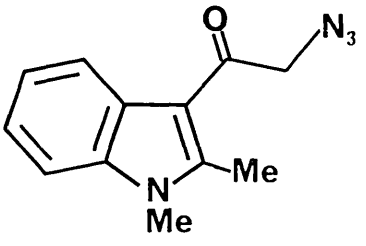
Consideration of the relative reactivities of the keto groups in (160e) and (172) affords a rationale for this difference in behaviour. When Ar in species (174) is a 3-indolyl group, the vinylogous amide

character of the keto function causes it to be of lower reactivity than the ester carbonyl, ring closure into the ester group results. If Ar is a phenyl group however, there is no electron release into the keto group, and in this instance it is more reactive than the ester carbonyl, resulting in the opposite mode of ring closure.



Nucleophilic substitution of (160e) was then attempted in other solvents. Treatment of (160e) with one equivalent of sodium azide in DMF, DMSO or HMPA at room temperature, gave after work-up, crude mixtures which were identical by i.r. and t.l.c. The combined mixtures were chromatographed, resulting in the isolation in low yield of a crystalline solid (m.p. 138.5 - 142^{o}C). The other fractions appeared to contain several compounds, one of which was an ethyl ester. Attempts to isolate this ester were unsuccessful, and further chromatography only

led to decomposition. Examination of the crystalline material showed it to be an azide, with the characteristic i.r. band at 2110 cm^{-1}. In the n.m.r. spectrum are aromatic, *N*-methyl and 2-methyl signals, as well as a singlet corresponding to 2 protons at δ 4.54. Consideration of this and the other spectral data leads to the structure (158d), and this assignment was confirmed by comparison with an authentic sample of (158d) prepared as described earlier.



(158d)

The mode of hydrolysis and decarboxylation is assumed to involve neighbouring group assistance from the azide function.

It was also shown that (160e) may be reductively dehalogenated by treatment with sodium borohydride or DIBAL, to give ketoester (160c).

Evidently, there are some subtle effects in operation, which preclude the simple nucleophilic substitution of (160e) with azide ion.

2.5 Conclusion

Although the yields of the azidoacetate condensations were not satisfactory in some cases, an alternative route to the 2-azidopropenoates was not found, and thus it was decided that these low yields would have to be tolerated in order to investigate the thermolyses of these azides. The next chapters describe these thermolyses, and the chemistry of the resulting products.

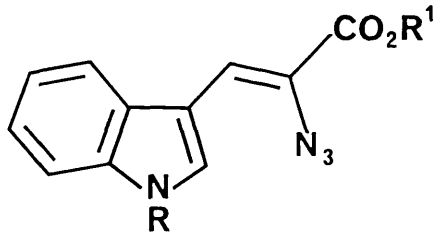
Chapter 3

Thermolyses of azidopropenoates unsubstituted in the indole-2-position, and chemistry of the resulting pyrroloindoles

3.1 Thermolyses of azidopropenoates unsubstituted in the indole-2-position

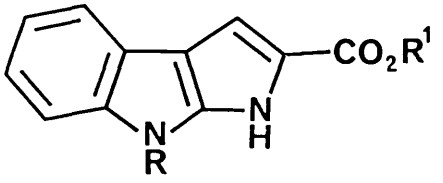
In Chapter 2 some conjectures were made as to the fate of 2-azido-3-(indol-3-yl)propenoates on thermolysis. Herein it is intended to describe studies on the thermolyses of the simplest type of these compounds, that is those bearing no 2-substituent in the indole ring, and some simple chemistry of the products thus obtained.

When the azides (175a-d) were thermolysed as *ca.* 0.5% solutions in refluxing toluene,[67,81] under a nitrogen atmosphere for approximately 1.5 hr, the formation of one new compound was in each case detectable by t.l.c.. These could be isolated and purified, by evaporation of the solvent, and recrystallization from toluene, ethanol or methanol. Yields of 70-90% could be obtained. The compounds may be shown to have structures (176a-d), the i.r. spectra having characteristic bands for *N*-H and aromatic ester groups, and the n.m.r. showing the presence of five aromatic protons, one being a singlet. The resonance due to the indole-2-proton, observed in the starting azide, is now absent. Mass spectroscopic and microanalytical data are in all cases consistent with the proposed structures.



(175)

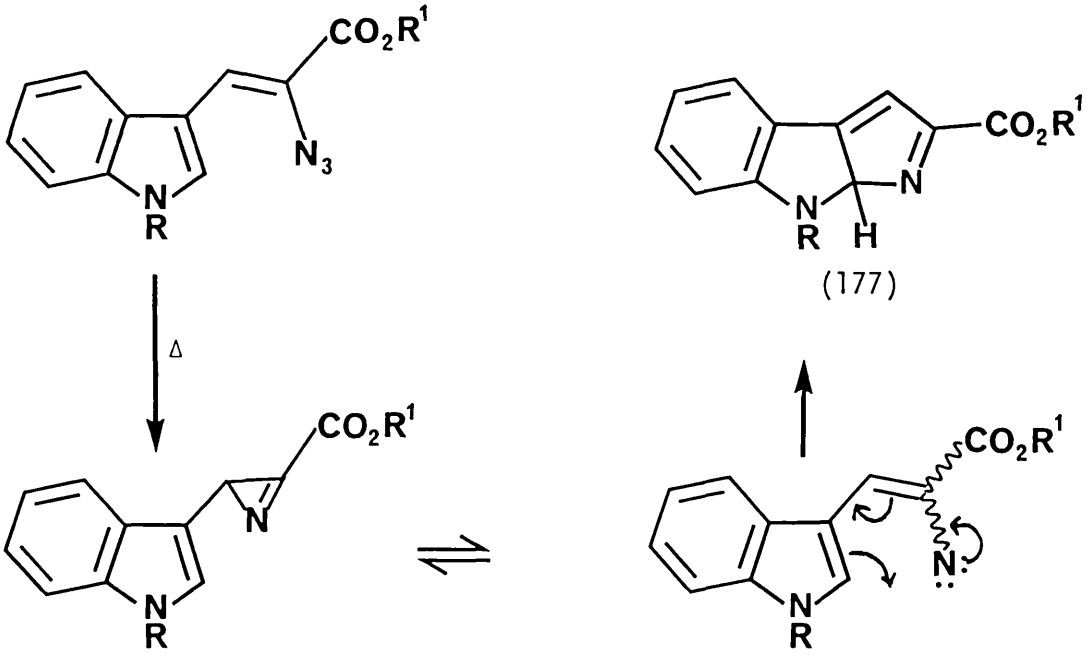
a) R = Me R^1 = Et
b) R = CH_2Ph R^1 = Et
c) R = CH_2OMe R^1 = Et
d) R = CH_2OMe R^1 = Me



(176)

a) R = Me R^1 = Et
b) R = CH_2Ph R^1 = Et
c) R = CH_2OMe R^1 = Et
d) R = CH_2OMe R^1 = Me

These [2,3-b] pyrroloindoles are thought to be formed as the result of a 6π electrocyclic ring closure of the intermediate nitrene (178b), to give an 8aH-pyrroloindole (177), and subsequent [1,5] prototropic shift.[67]

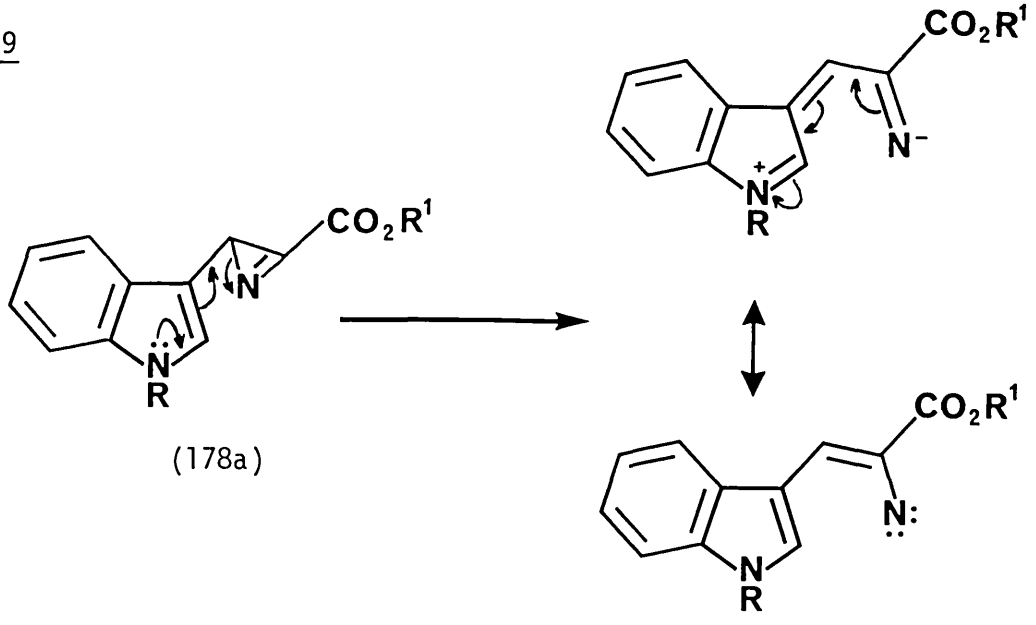


(178a) (178b) (177)

Because of the intermediacy of the azirine (178a) the double bond stereochemistry of the starting azide is immaterial, since such stereodifferentiation between *cis* and *trans* groups is destroyed upon formation of the azirine. Thus if the azirine ring opens to give the nitrene in which the indole nucleus and the ester group are *trans*, ring closure will result, if not re-formation of the azirine may be expected until all of the azirine-nitrene equilibrium system has gone to product *via* the nitrene of required stereochemistry.[67]

Neither the azirine (178a) which is supposed to be in equilibrium with nitrene (178b), nor the 8aH-pyrroloindole intermediate were ever detected in the thermolysis reaction mixtures. In the latter case this is not in the least surprising, since the 8aH-pyrroloindole species may be imagined to be highly unstable, aromatizing rapidly. In the case of the azirines however, it was thought that detection might be possible, since such species have been detected in and indeed isolated from reaction mixtures of thermolyses of other 2-azidopropenoates.[67] It may be supposed that electron release from the indole nitrogen weakens the C-N single bond in the azirine, making this a very transient species, (Scheme 9).

Scheme 9

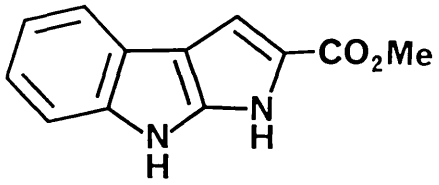


(178a)

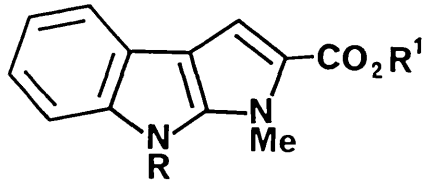
3.2 Simple chemistry of the pyrroloindoles

The debenzylation of (176b) was attempted, using excess sodium in liquid ammonia. This resulted only in the isolation of a very small amount of decomposed material, and since later attempts to effect a dissolving metal reduction, using sodium in liquid ammonia on a related compound, resulted in similar decomposition, it was assumed that the pyrroloindole system is unstable to such conditions. Attempted debenzylation by hydrogenolysis also failed. Later, when the *N*-methoxymethyl compounds (176c) and (176d) had been obtained, it was found possible to effect deprotection by treatment, for fairly extended periods (2-4 weeks) with cold dilute aqueous HCl in ethanol or methanol. Attempts to use harsher acid conditions or higher temperatures in order to accelerate the deprotection rate, resulted only in decomposition. The compound (179) thus formed has been described by Witkop *et al*,[36] although only melting point and u.v. data are given. These correspond closely with the data recorded on samples of (179) prepared as outlined above.

N-Alkylation of the unsubstituted nitrogen atom in the systems (176) may be efficiently carried out. Treatment with sodium hydride in DMF at room temperature, followed by quenching with an alkylating agent such as methyl iodide, leads to *N*,*N*'-disubstituted compounds. Pyrroloindoles such as (180a) and (180b) were generated in this manner.



(179)

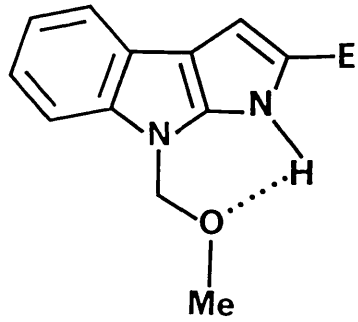


(180)

a, R = Me, R^1 = Et

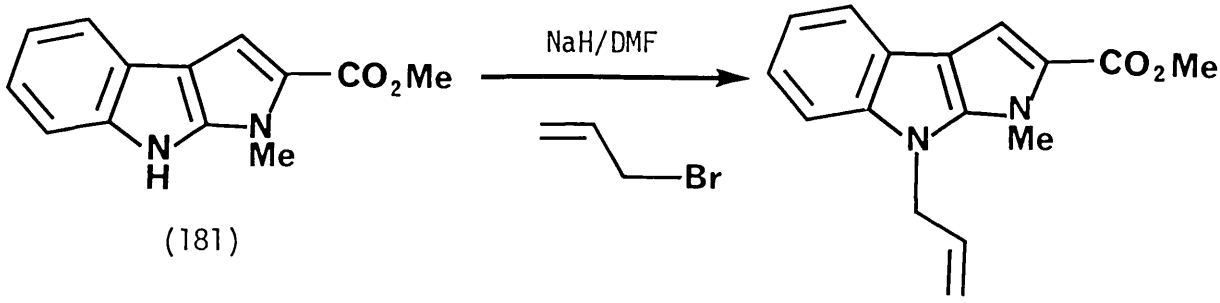
b, R = CH_2OMe, R^1 = Me

Removal of the *N*-methoxymethyl group from system (180b) may be effected as before, by treatment with aqueous HCl in methanol, to give (181). Curiously, the period of time necessary for complete deprotection of (180b) under identical conditions to those employed in the deprotection of (176d), was only 3-5 days as opposed to 4 weeks in the latter case. The reason for this difference is unclear, it may be related to the capacity for hydrogen bonding which exists in (176d) but not in (180b). The implication being that electron density is released from the oxygen atom in the formation of the hydrogen bond, making protonation on oxygen (the first step in the deprotection mechanism) less facile.



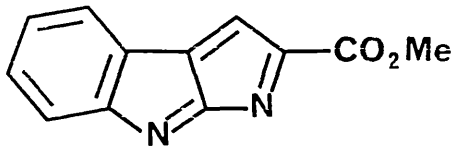
(176d)

The system (181) may also be alkylated by NaH/DMF treatment and subsequent quenching with *e.g.* allyl bromide to afford compound (182).



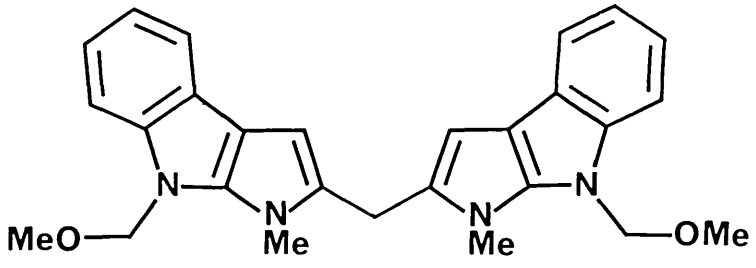
(181) (182)

In a rather speculative attempt to oxidize the compound (179) to the benzodiazapentalene (183), a solution of DDQ in THF was added to a solution of (179) in the same solvent at room temperature. Only highly coloured decomposition products were formed.



(183)

Treatment of (180b) with LAH in THF at room temperature was expected to give the 2-hydroxymethyl pyrroloindole. Separation of the resulting crude material by p.l.c. resulted in the isolation of one slow running band, a solid (m.p. 220-5°C) which was shown not to be the expected compound. No -OH or carbonyl signals are observed in the i.r. spectrum, and the n.m.r. shows aromatic, *N*-methoxymethyl and *N*-methyl signals, and also two other one proton singlets. The molecular ion is at 440 mass units. On the basis of these data structure (184) is proposed. Its mode of formation is not certain. The reduction of simple 2-carbonyl

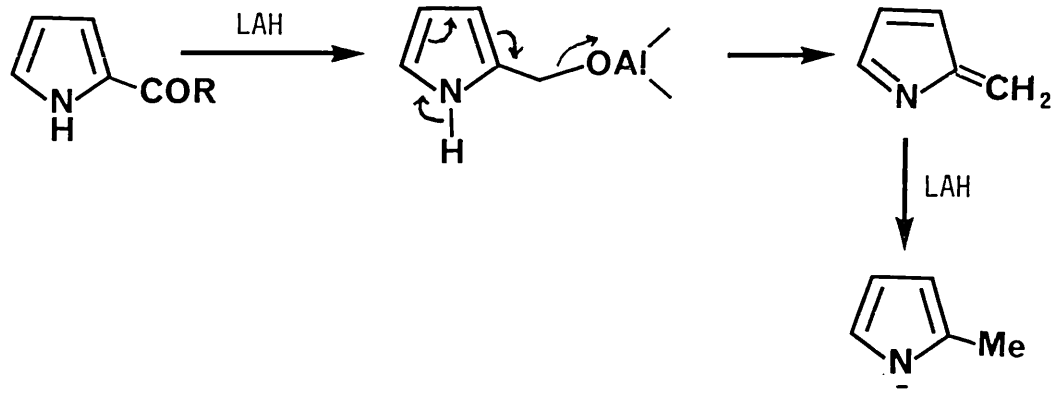


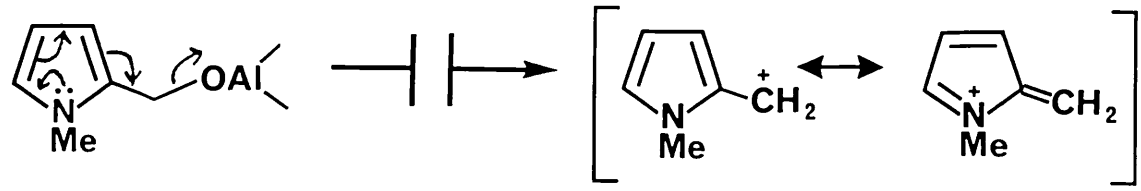
(184)

pyrroles with LAH has been well studied, and it is known that reduction of pyrrole-2-carboxylic acids and esters gives 2-methylpyrroles when large excesses of LAH are used. With equimolar amounts of LAH,

dipyrromethanes and polymers are also obtained due to the facile polymerization of the intermediate hydroxymethylpyrrole (or rather the aluminium alkoxide derivative).[100] Reduction of 1-methylpyrrole-2-carbaldehyde or 1-methylpyrrole-2-carboxylic acid even with large excesses of LAH gives only the 2-hydroxymethyl-1-methylpyrrole.[101a] This is seen to be a reflection of the fact that while base catalyzed elimination in the N-H compounds can give a 1-azafulvene intermediate which is subsequently reduced to a 2-methylpyrrole, the analogous *exo*-methylene species is not formed from the N-Me compound,[101b] Scheme 10.

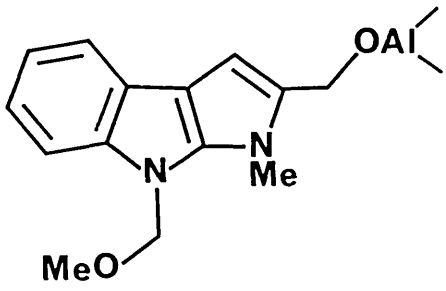
Scheme 10



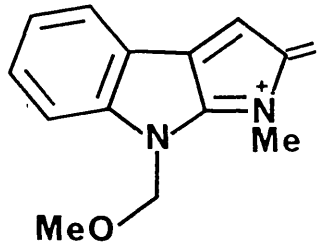


The LAH reduction of (180b) provides something of a contrast, since although an excess of LAH was used, only dark blue polymers and the isolated compound (184) were observed. The formation of (184) must involve displacement of an O-Al leaving group from the putative inter-

mediate (185a) by a nucleophilic pyrroloindole species, possibly another molecule of (185a) itself, followed by loss of a one-carbon fragment with concomitant rearomatization. The possibility of intermediacy of exomethylene species (185b) seems remote since this would surely be reduced by hydride to the 2-methyl compound.



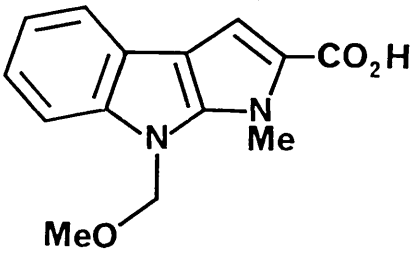
(185a)



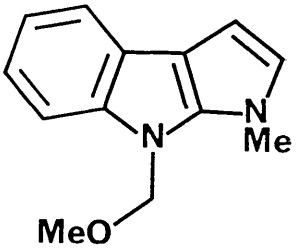
(185b)

The base catalyzed hydrolysis of the ester group in (180b) was effected by heating with 5.6 equivalents of sodium hydroxide in water/methanol at reflux, for 2.5 hr. Acidification and work-up gave a pale blue oily solid which was shown to consist of two compounds by t.l.c.. Washing with hot petrol removed one of the compounds, leaving a pale blue powder which could be recrystallized from methanol/nitromethane (m.p. 124-6^{o}C). This was characterized as the acid (186), having i.r. signals at 2560-3120 and 1665 cm^{-1}, and showing only two methyl resonances in the n.m.r. spectrum. The other compound was obtained as a colourless oil (becoming blue-green on exposure to the atmosphere at room temperature) by silica gel chromatography. In its i.r. are no carbonyl or O-H absorptions, and its n.m.r. displays aromatic, *N*-methoxymethyl and *N*-methyl resonances, as well as an AB quartet (δ 6.45). Consideration

of the full data* indicates strongly that this compound is the decarboxylated pyrroloindole (187).



(186)



(187)

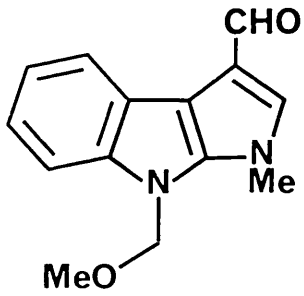
In another experiment, the pyrroloindole (180b) was heated in methanol/water at reflux with 30 equivalents of sodium hydroxide for 24 hr. On this occasion the decarboxylated compound was isolated in 37% yield, but none of the acid was detected. However, a compound was obtained in low yield, the m.p., n.m.r., and t.l.c. of which, indicated it to be identical with (184).

The pyrroloindole (187) could be formylated by the Vilsmeier-Haack reaction. The product being tentatively identified as the 3-aldehyde (188) by nuclear Overhauser difference spectroscopy. The nOe difference spectra and normal ^1H spectrum are reproduced in Appendix 1 (Figure 1), the bottom trace being the normal spectrum. Irradiation of the formyl proton (middle trace) causes a large enhancement of the signal corresponding

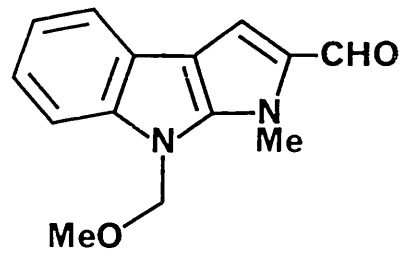
---

*The AB quartet (δ 6.45) is observed when the spectrum is run in $CDCl_3$. When d_6-acetone is employed, the chemical shifts are sufficiently different to resolve this into a simple AX system. The 250 MHz spectrum of (187) was run in d_6-acetone, and this is the one which will be reported in the experimental section.

to the lone proton in the 5-ring but virtually no other enhancements. If the compound were the 2-formyl isomer (189) an enhancement of the *N*-methyl signal would also be expected. Irradiation of the *O*-methyl protons of the methoxymethyl group gives the expected modest enhancements which may be observed in the figure. The formation of the 3-formyl compound is in some contrast with results to be discussed later, which suggest that the terminal 5-ring of these pyrroloindoles behaves like an isolated pyrrole ring. This would, of course, lead one to expect 2-formylation.



(188)

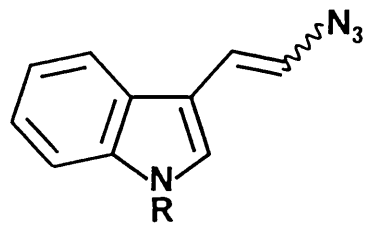


(189)

3.3 Thermolyses of 1-azido-2-(indol-3-yl)alkenes

The preparation of the vinyl azides (157) was discussed in Chapter 2. These rather unstable compounds darkened rapidly at room temperature, but could be stored at $-18^{o}C$ for periods of months.

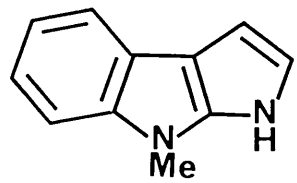
Thermolysis of (157a) in toluene for 5 min resulted in rapid and dramatic darkening. Analysis of the resulting tarry material by n.m.r. showed it to consist only of complex decomposition products.



(157)

a) R = H
b) R = Me

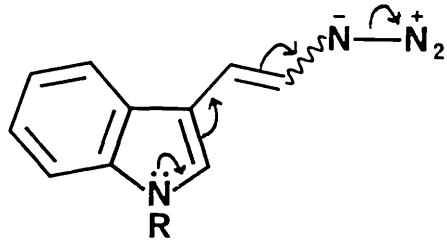
Similar thermolysis of the *N*-methyl compound (157b) gave a dark purple oil, and amongst other signals in the crude n.m.r. of this material (in deuterochloroform), a distinct AB quartet was observed, having an almost identical chemical shift and J value to the AB quartet of compound (187). This was taken as strong evidence of the formation of pyrroloindole (190).



(190)

Attempted isolation by p.l.c. resulted in complete decomposition, and only dark tarry gums could be obtained.

It must be assumed that the pyrroloindoles not having an electron withdrawing 2-substituent are only tolerably stable when both nitrogen atoms are alkylated. It is interesting to compare the relative stabilities of the azides (175) and (157). Whereas 2-azidostyrene[102] and ethyl 2-azidocinnamate[64] are both of comparable stability the azides (157) are very much less stable than their alkoxycarbonyl counterparts (175). This effect is presumably attributable to electron release from the indole nitrogen, which weakens the $\bar{N}-\overset{+}{N}_2$ bond in the azide group, assisting loss of nitrogen as shown below. In the azides (175) much

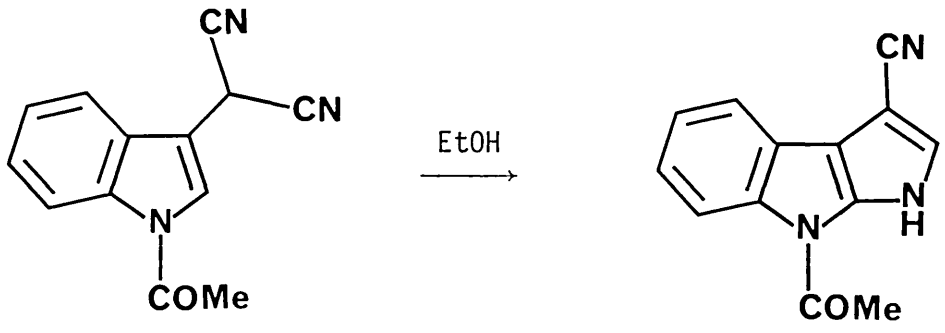


of this electron release would be diverted into the alkoxycarbonyl group. Another relevant comparison to be drawn between 2-azidostyrene and ethyl 2-azidocinnamate is that of product distribution upon thermolysis. This reveals another important effect of the alkoxycarbonyl group on the reactivity of these vinyl azides. 2-Azidostyrene when thermolysed at 290°C gave in mediocre yield, a mixture of indole and phenylacetonitrile.[102] At the far lower temperature of 140°C ethyl 2-azidocinnamate gave very high yields of 2-ethoxycarbonylindole.[81] The thermolysis reaction mixture of (157b) contained numerous minor products, although it was not determined if any of these was a nitrile, while the reaction mixtures resulting from thermolysis of azides (175) generally were very clean.

Thus the alkoxycarbonyl group exerts a strong influence on the product distribution, but the nature of this effect is not quite clear. An observation which may be relevant in rationalizing this, is that the intermediate azirine in the thermolysis of 2-azidostyrene is unstable and could only be detected by spectroscopic means or by reduction to the aziridine,[103] while the analogous azirine in the thermolysis of ethyl 2-azidocinnamate is reasonably stable up to *ca.* 100°C.[81] This stabilization of the azirine by the ester group might be expected to lead to increased selectivity in its mode of reaction. This effect may also be assumed to operate in the azirines derived from vinyl azides (175), although for reasons stated earlier, the azirines derived from the azides (175) are not expected to be as stable as that derived from ethyl 2-azidocinnamate

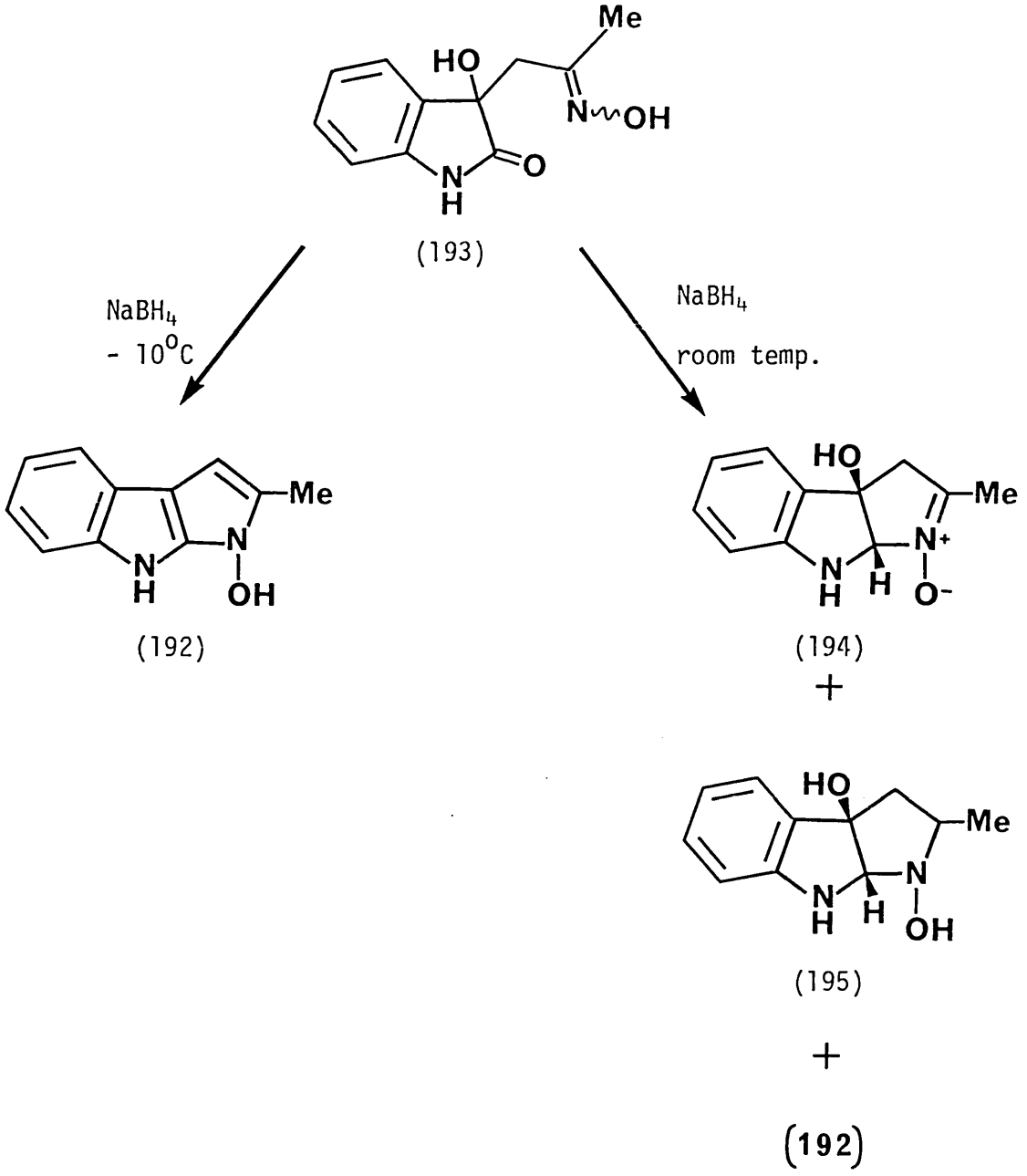
3.4 Brief survey of the literature on pyrrolo[2,3-b]indoles

There are very few references in the literature to pyrrolo[2,3-b] indoles in the same high oxidation level as the compounds described in the previous section. The preparation of (179) by Witkop *et al*[36] has already been cited, and Russian workers claim to have prepared the 3-cyanopyrroloindole (191).[104]

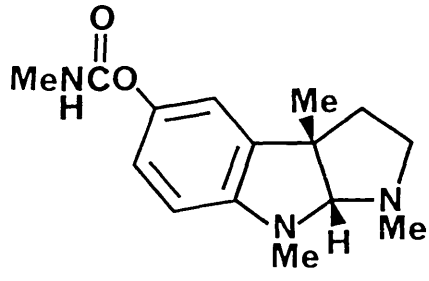


(191)

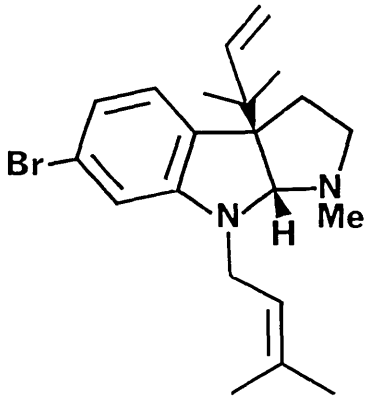
The compound (192) may be prepared by borohydride reduction of the oxime (193) at -10°C. If the reaction is carried out at higher temperatures, mixtures containing (192) as well as (194) and (195) result.[105]



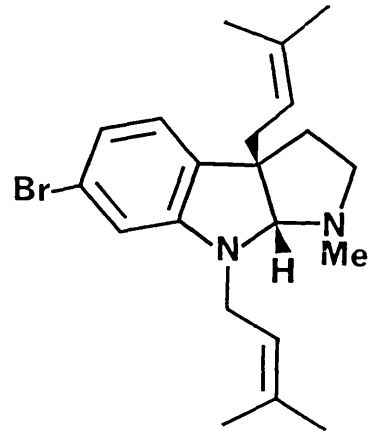
This ring system is well known however, in the reduced form, and as such is found in many natural products. Physostigmine (196) is a well known example. Recently, structurally related brominated compounds such as (197) and (198) have been isolated from marine sources.[106]



(196)

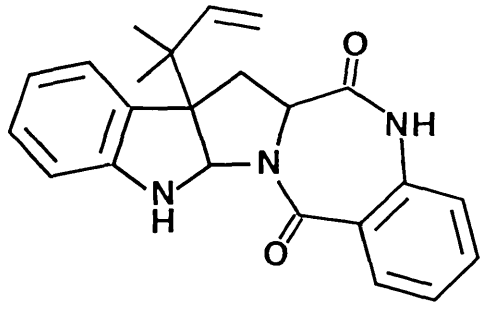


(197)

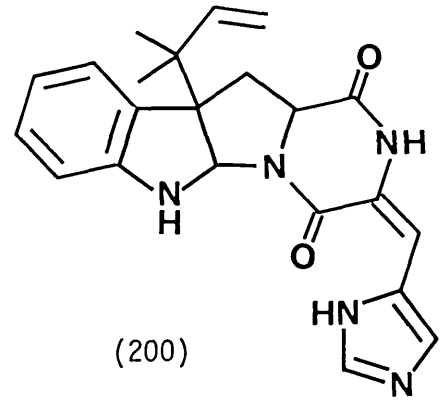


(198)

Aszonalenin (199)[107] and roquefortine (200)[108] are other examples of recently isolated natural products containing the pyrrolo[2,3-b] indole skeleton. The stereochemistry was not reported in either case.



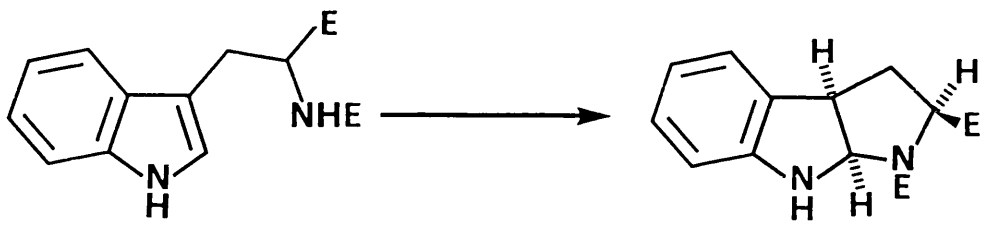
(199)



(200)

These may be envisaged as arising from enzymic alkylation of a tryptophan or tryptamine and subsequent nucleophilic ring closure, as described in Chapter 1. Various syntheses of pyrrolo[2,3-b]indoles also depend on this principle, some of which have already been discussed, and amongst the most important of which are oxidations, photochemical or otherwise of tryptophans and tryptamines.[31,109]

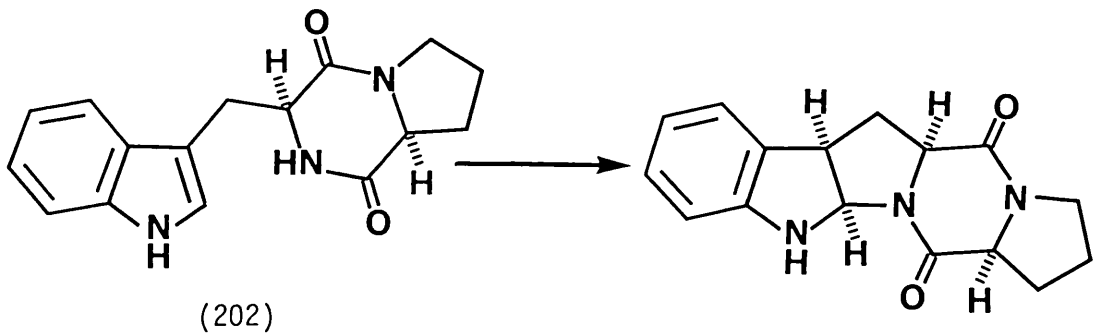
Stable cyclic tautomers of tryptophans obtained by treatment of the tryptophan with 85% phosphoric acid have been described by Taniguchi *et al.*[110] A simple example of this is the acid induced cyclization of (201).



(201)

$(E=CO_2Me)$

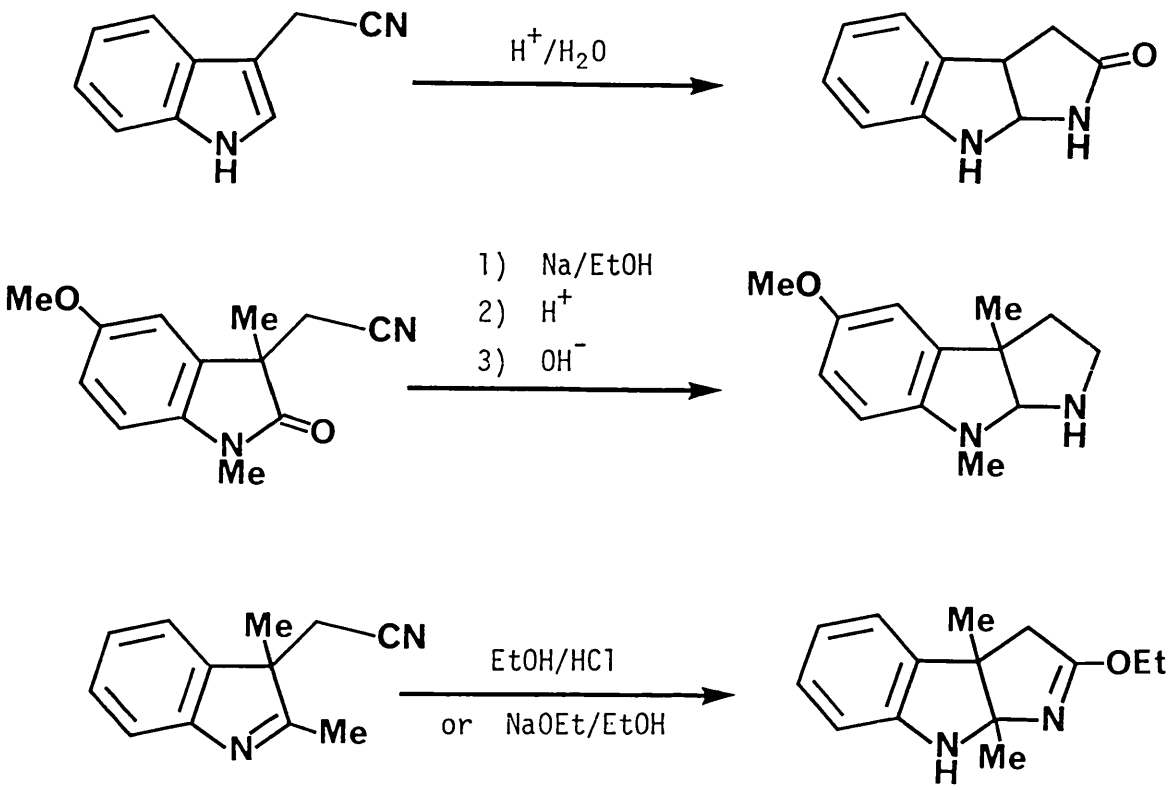
The diketopiperazine (202) may be cyclized in a similar manner.[111]



(202)

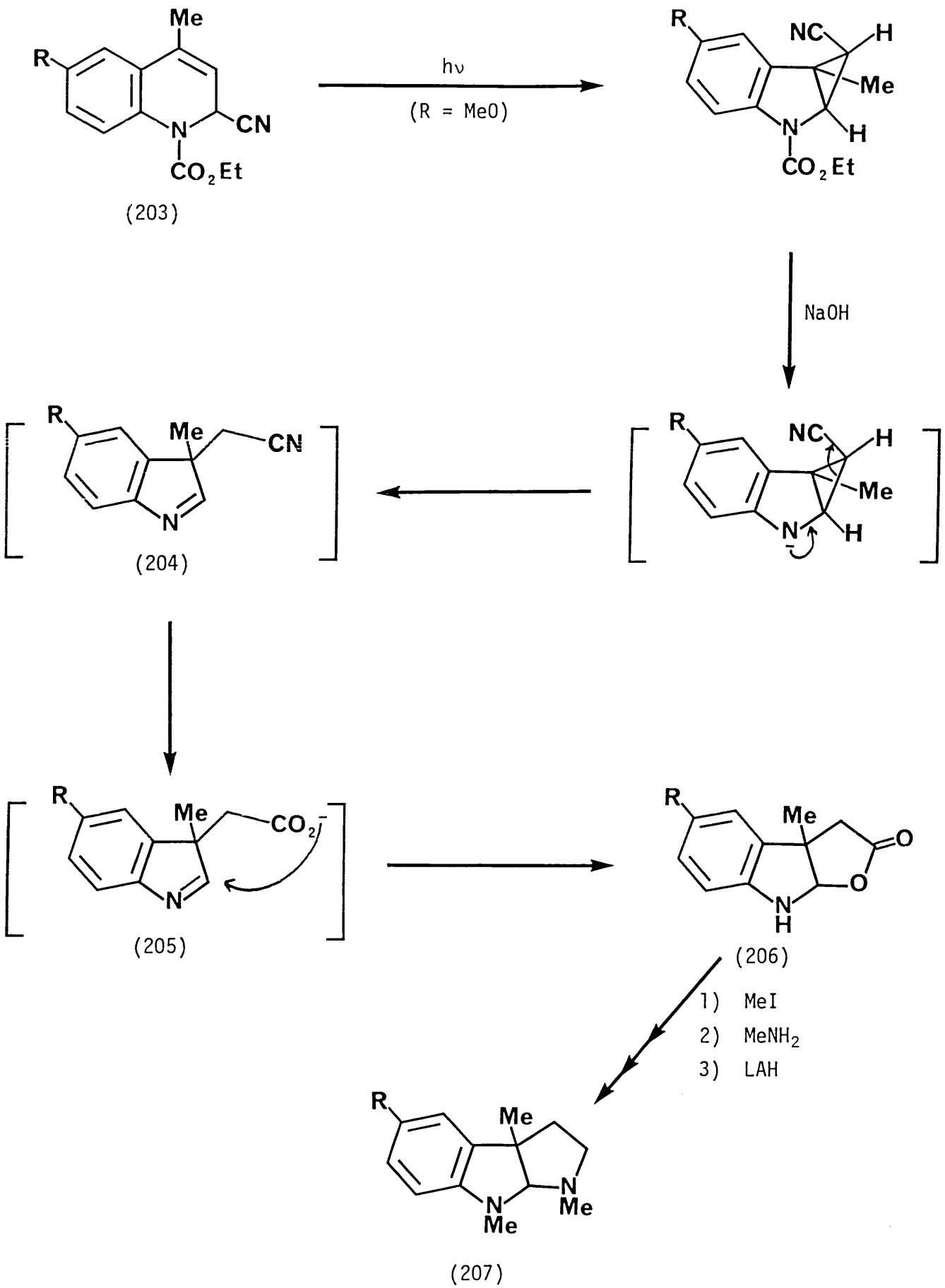
Classical syntheses of this system frequently employ, as the key intermediate, a 3-cyanomethyl indole, oxindole or indolenine, as in the examples below, (Scheme 11).[112,113,114]

Scheme 11

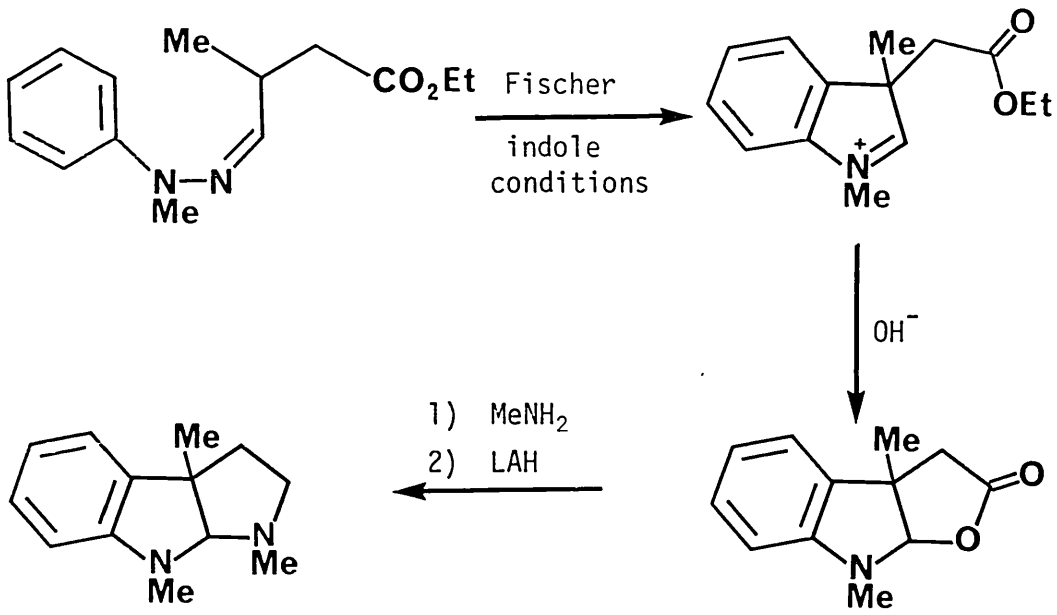


More recently, the photolysis of Reissert compound (203) to give a cyclopropa[*b*]indole, followed by base treatment, has been used to generate 3-cyanomethyl indolenine (204). This hydrolyses *in situ* to give carboxylate (205). Cyclization gives lactone (206) which may be converted to (±)esermethole (207) by the steps summarized below.[115,116]

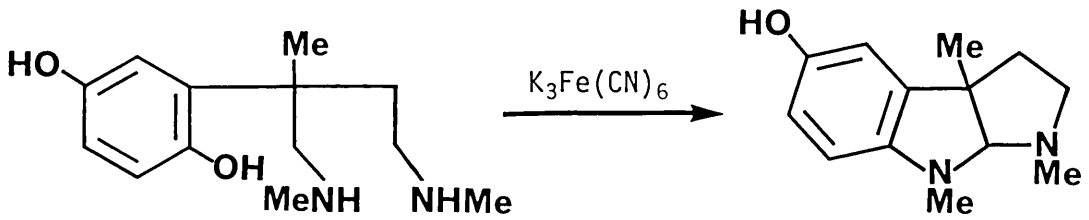
Fischer indolization has also been used to synthesise this ring system, (Scheme 12).[117]


Me
R
CN
N
CO2Et
hν
(R = MeO)
NC
H
Me
H
NaOH
CN
(204)
(205)
CO2
O
(206)
1) MeI
2) MeNH2
3) LAH
(207)

Scheme 12



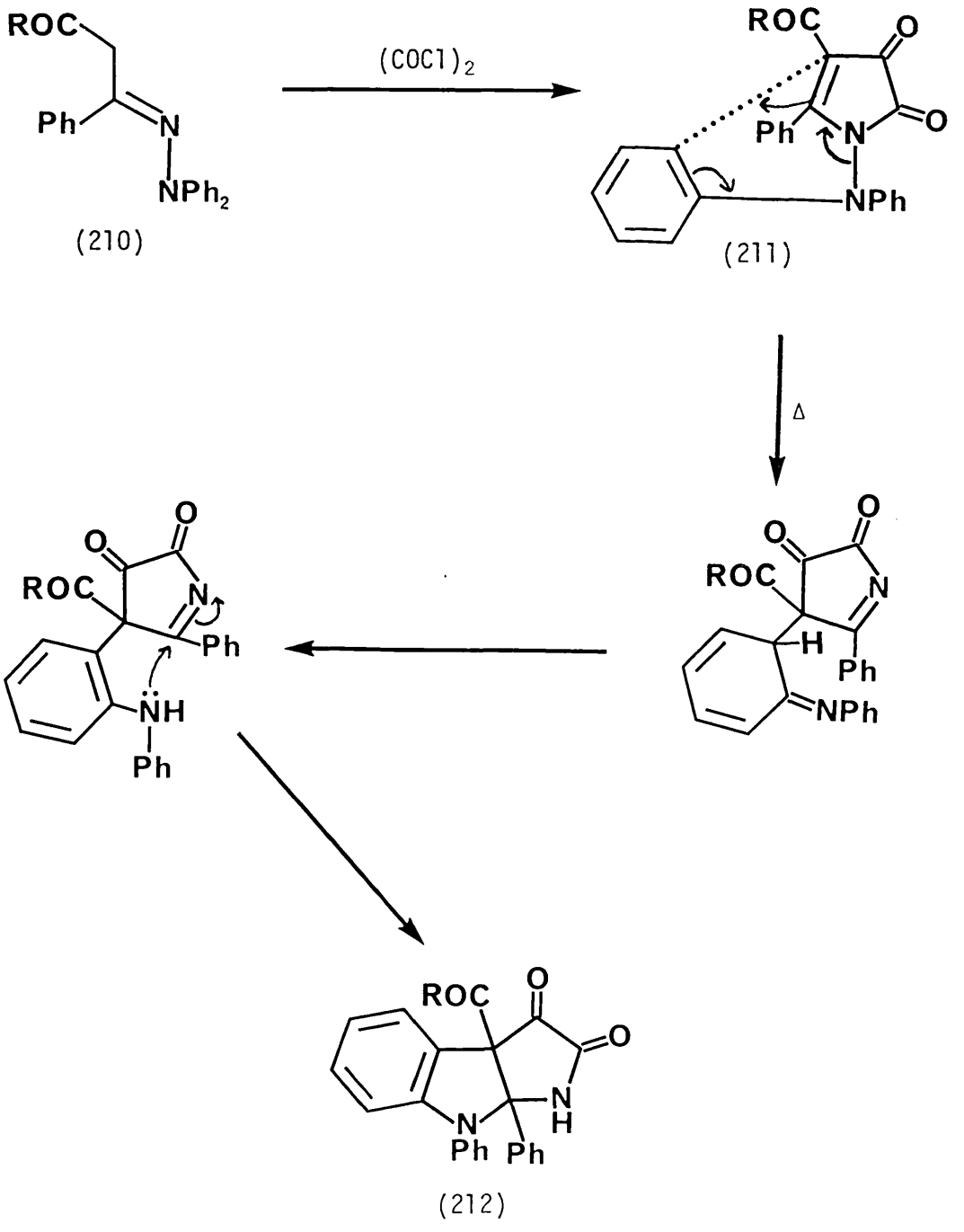
Harley-Mason *et al* have obtained the physostigmine precursor (208), by oxidative cyclization of the diamine (209).[118]



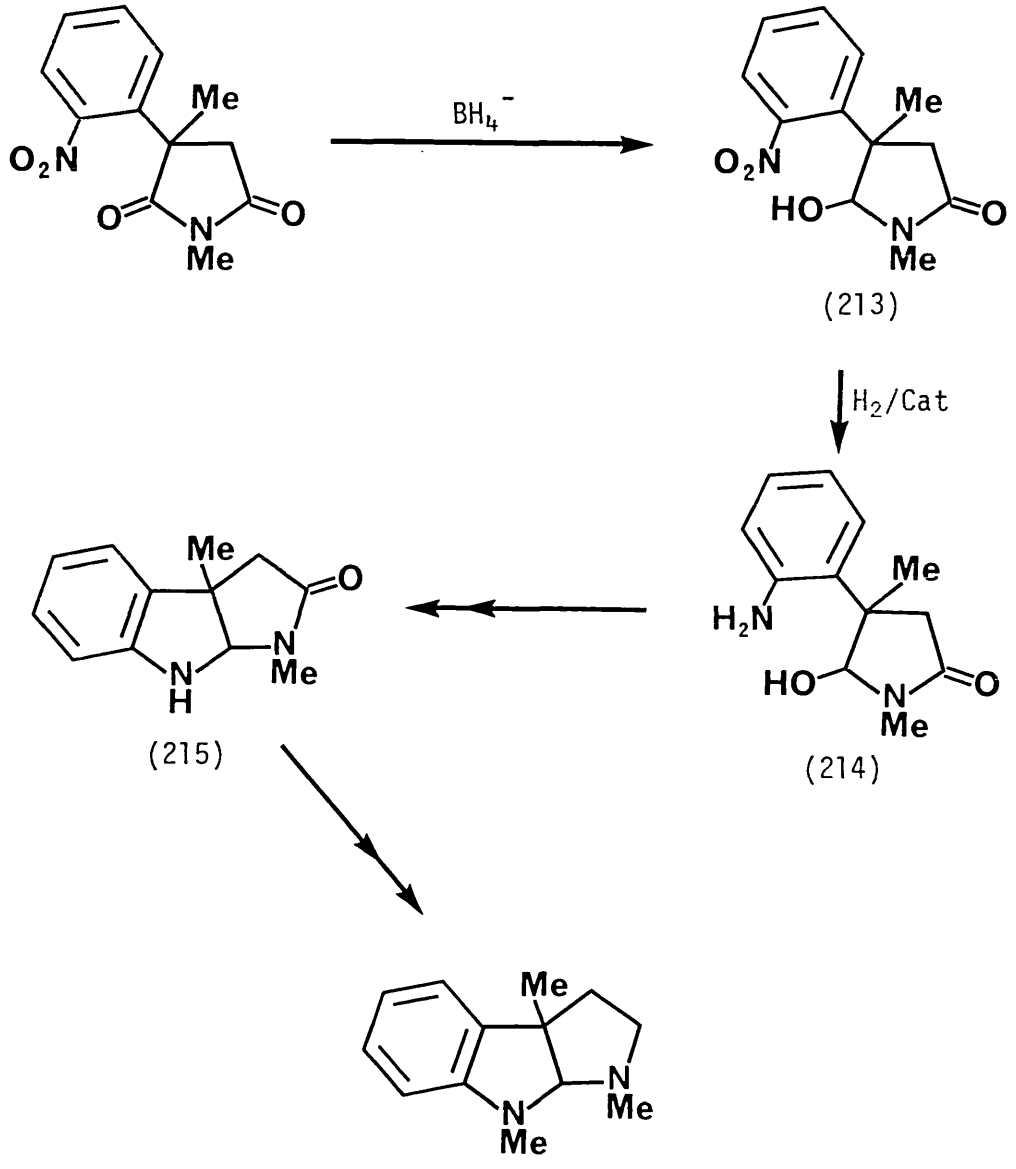
(209) (208)

More recent synthetic routes which have been used to obtain this ring system include treatment of the hydrazone (210) with oxalyl chloride to afford the cyclized product (211), which upon thermolysis in decalin gives the dioxopyrrolo[2,3-b]indole (212). This presumably comes about *via* a [3,3] sigmatropic shift, rearomatization and nucleophilic attack, as shown, (Scheme 13).[119]

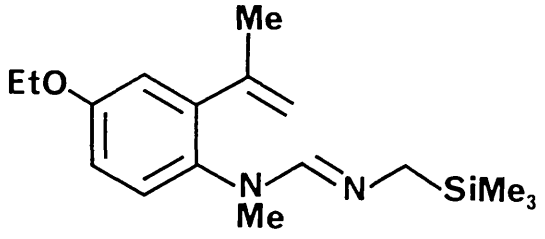
Scheme 13



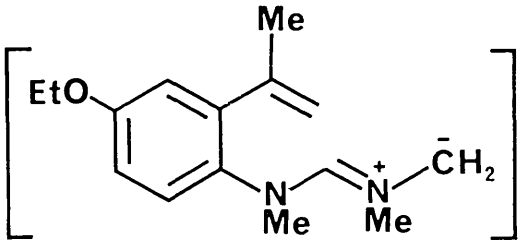
Wijnberg *et al* describe the synthesis of (±)desoxyeseroline (216), as an application of their previously reported regiospecific reduction of substituted succinimides with borohydride.[120] The compound (213) was thus prepared, and catalytic reduction of the nitro group afforded amino compound (214). This may be cyclized to the amide (215), and standard steps (as described above) were used to convert this to (216).[121]



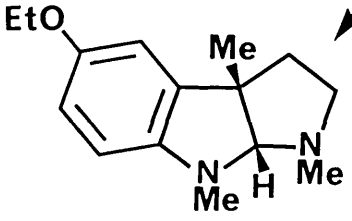
Possibly the most elegant synthesis of the physostigmine ring system to be found in the literature is the recently reported cyclization of trisubstituted benzene (217). This was treated with methyl trifluoromethanesulphonate followed by TBAF, giving the dipolar ylid (218). This subsequently closes *via* an intramolecular (4+2) cycloaddition.[122]



(217)



(218)



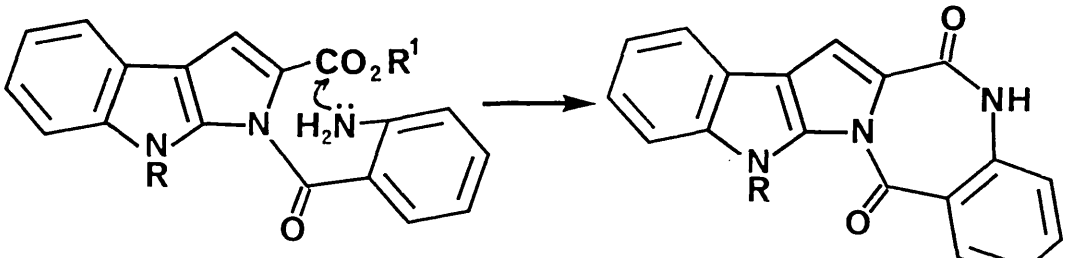
3.5 Further chemistry of the pyrrolo[2,3-b]indole systems

Having studied some simple chemistry of the pyrrolo[2,3-b]indoles as described earlier, it was hoped that these systems might be used as a starting point for approaches to natural products. It was decided to investigate reactions which could lead from a pyrrolo[2,3-b]indole to the aszonalenin ring system (199).

Three considerations had to be borne in mind:

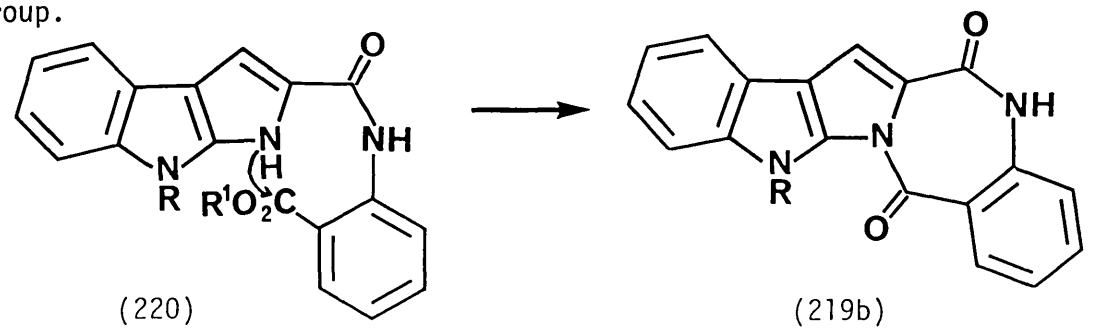
(i) The formation of the 7-membered cyclic diamide (219b). Two modes of effecting this goal could be envisaged *viz*

a) Formation of a 1-anthranoyl pyrrolo[2,3-b]indole such as (219a), and cyclization *via* nucleophilic attack of the amine upon the 2-carboxymethyl group.



(219a) (219b)

b) Initial formation of an amide such as (220), and cyclization by attack of the pyrrolic nitrogen upon the anthranilate carboxymethyl group.

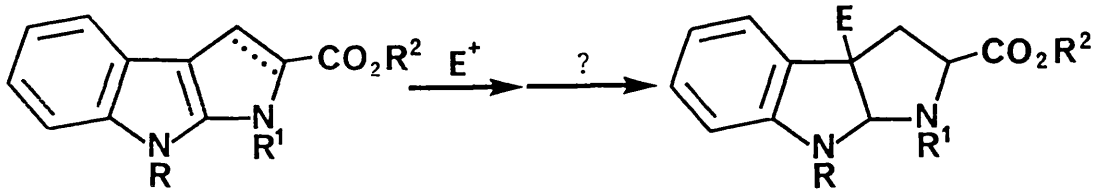


(220) (219b)

(ii) Reduction of the 2,3-double bond of the pyrrolo[2,3-b]indole system.

(iii) Introduction of a substituent at the bridgehead of the two 5-membered rings, as shown schematically below, (Scheme 14).

Scheme 14

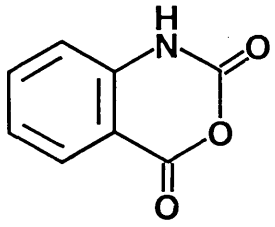


(i) Attempts directed at the construction of the 7-membered cyclic diamide (219b) where R = $-CH_2OMe$

In the first attempt to construct the cyclic diamide (219b), methyl anthranilate was heated with the pyrroloindole (176d) and sodium methoxide, in refluxing benzene.[123] Only starting materials could be obtained from this reaction mixture. Likewise, treatment of a DMF solution of (176d) with sodium hydride followed by methyl anthranilate, afforded only starting material on work-up, as evidenced by t.l.c. and n.m.r.. Several simple experiments were then carried out to assess the likelihood of formation of an amide by nucleophilic attack of an amine on the carboxymethyl group of the pyrroloindole systems (176d) or (180b). Treatment of (176d) with excess aqueous ammonia in refluxing methanol, or (180b) with excess hydrazine hydrate under the same conditions resulted only in the recovery of the respective starting materials. Heating of (176d) in neat aniline gave the deprotected

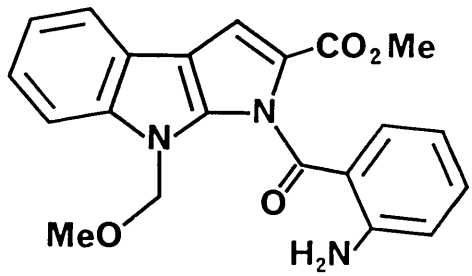
compound (179) in 46% yield as the only product. Presumably this deprotection comes about *via* nucleophilic attack by aniline at the methylene centre of the methoxymethyl group.

Since the ester group in methyl anthranilate appeared to be insufficiently electrophilic, an alternative anthranoylating agent was sought. One such reagent in common use is isatoic anhydride (221).[124,125]

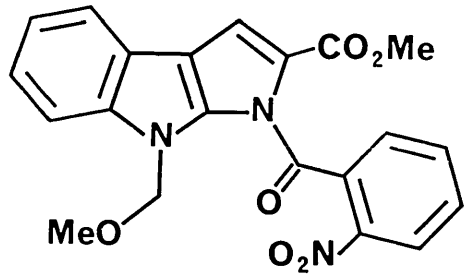


(221)

The pyrroloindole (176d) was heated with (221) in refluxing pyridine for 8h.[125] No compounds other than (176d) and (221) could be detected in the reaction mixture after this time. Likewise, treatment of (176d) with sodium hydride in DMF or THF/HMPA, followed by a solution of (221) in the appropriate solvent, did not result in anthranoylation. The *N*-anthranoylated compound (222) was eventually prepared, albeit in low yield, by treatment of (176d) with sodium hydride in THF followed by *o*-nitrobenzoyl chloride to give (223) in 65% yield, and subsequent reduction of the nitro compound. It was recognised that the *o*-nitrobenzoyl group is used as a protecting group for alcohols since it may be easily removed by reductive cleavage,[126] the intermediate hydroxylamine species (224) assisting such cleavage as shown, (Scheme 15). Thus it was expected that some cleavage would occur during hydrogenation of (223), and indeed this was the case. When this nitro compound was hydrogenated in methanol over palladium-charcoal, yields of the amine (222) varying between 9 and 27% were obtained as well as the cleaved product (176d).

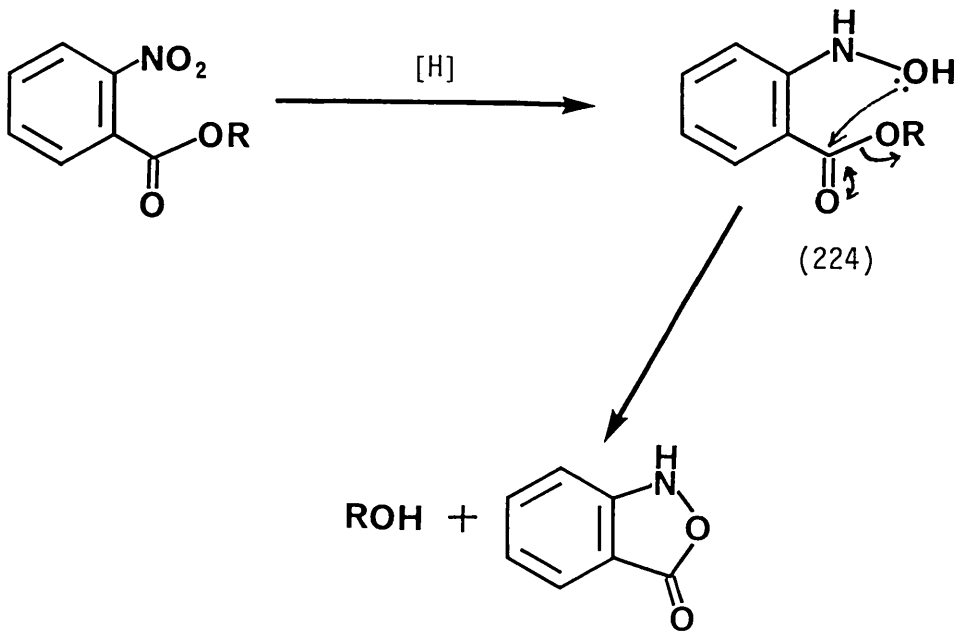


(222)



(223)

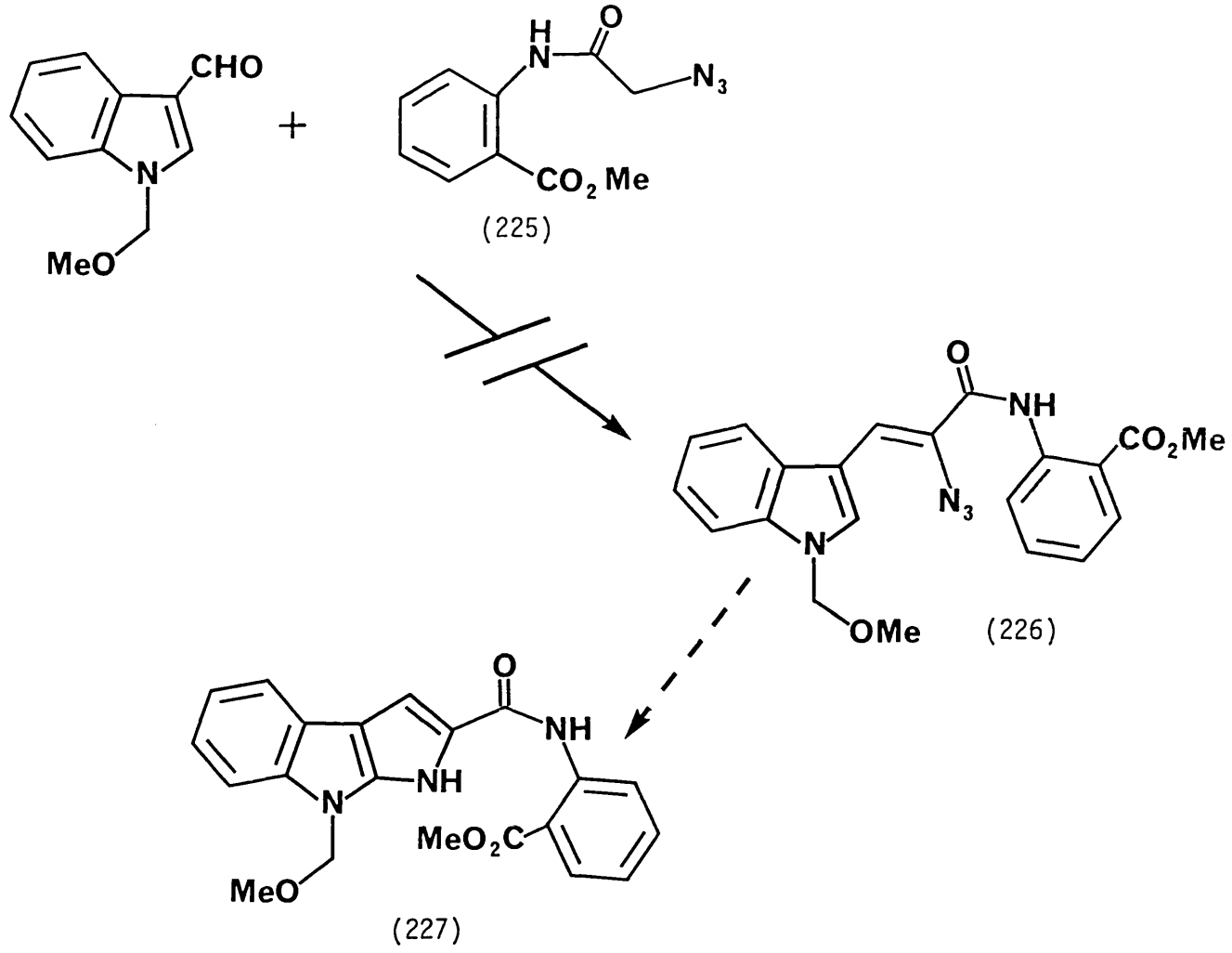
Scheme 15



Attempts to reduce the nitro compound by catalytic transfer hydrogenation with palladium on charcoal and cyclohexa-1,4-diene were unsuccessful.[127] Reduction of (223) with sodium dithionite in aqueous THF gave a *ca.* 50:50 mixture of (222) and (176d) as estimated by n.m.r.[128]

It was hoped that intramolecular nucleophilic attack by the amine group in (222) would be more facile than the corresponding intermolecular reaction. Heating of (222) in xylene for 20h or in toluene with a catalytic amount of sodium methoxide[123] did not however effect cyclization. Acid catalysed cyclization of (222)[125] was also attempted on a very small scale due to lack of material, but n.m.r. appeared to indicate that only cleavage of the **1**-methoxymethyl group had occurred.

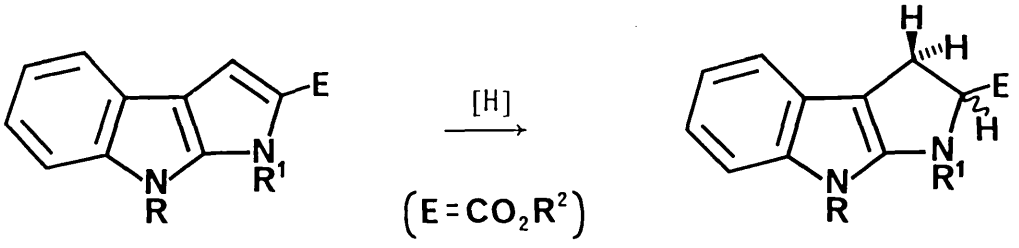
In a somewhat speculative attempt to produce a species such as (220), the azidoamide (225) and **1**-methoxymethylindole-3-carbaldehyde were added as a methanol solution to a cooled solution of sodium methoxide under the conditions of the azidoacetate condensation. It was hoped that vinyl azide (226) would be formed, which on thermolysis would afford (227). Numerous products were formed in the reaction, and separation was effected by silica gel chromatography. These compounds were all shown by n.m.r. to be anthranilate derivatives, and since none of the required compound was obtained these were not investigated further.

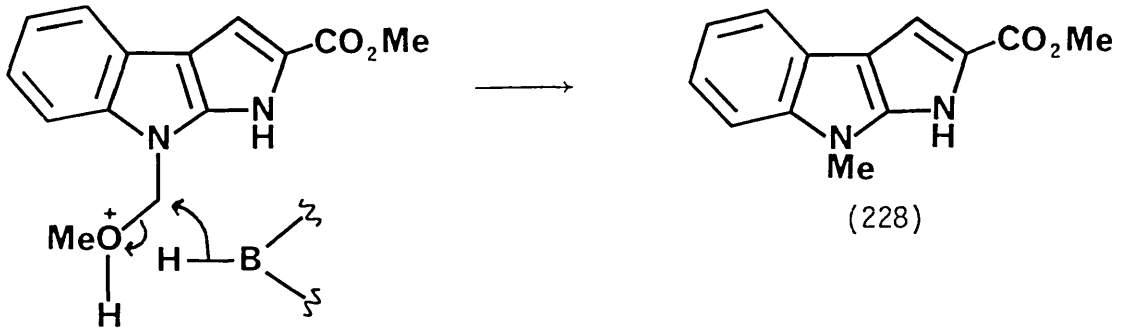


(ii) Attempts to reduce the 2,3-double bond

Attempts to effect the transformation summarised in Scheme 16 commenced with treatment of the pyrroloindole (176d) with borane-trimethylamine complex and aqueous hydrochloric acid in dioxan.[129] A compound was isolated which appeared by its i.r. and n.m.r. to be the *N*-methyl compound (228), the methoxy group presumably having been reductively replaced by hydrogen.

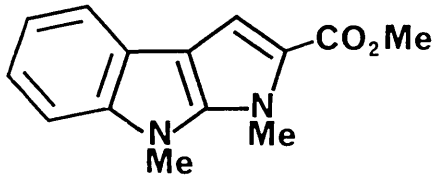
Scheme 16





(228)

Similar reactivity was observed when (180b) was treated with excess sodium cyanoborohydride in glacial acetic acid[130] at 60-70°C for 2h, the *N*,*N*'-dimethyl compound (229) being isolated in good yield, as the only product.

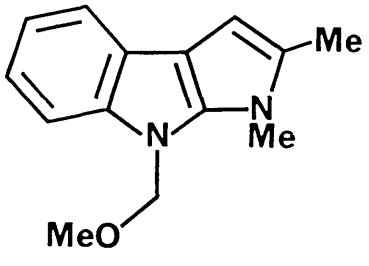


(229)

An attempt to reduce (180b) with zinc and phosphoric acid[131] resulted only in cleavage of the *N*-methoxymethyl group, giving (181). High pressure catalytic hydrogenation of (176d) in methanol over palladium-charcoal at 50 p.s.i. also failed and starting material was recovered. Treatment of (180b) with excess sodium in liquid ammonia gave, after work-up, a gum having a complex n.m.r. spectrum indicating complete conversion to intractable material which was not investigated further. The failure of hydride transfer, or nucleophilic reducing agents to reduce the pyrroloindole system under acidic conditions led to the question as to whether this ring system is indeed protonated in acidic

media. This protonation is a necessary condition for such reductions, and if the system were not being protonated this would explain the lack of reactivity under such conditions. Thus the u.v. spectrum of pyrroloindole (180a) was recorded in methanol and subsequently in methanol containing sulphuric acid. No appreciable changes in λ_{max} or ε values were observed, indicating that in fact no significant degree of protonation had taken place.

Reduction of (180b) with the "cuprous hydride" reagent described by Paquette *et al*[132] gave a three component mixture. Separation by silica gel chromatography afforded starting material (17% recovery) as well as a rather impure rear band, appearing by its n.m.r. spectrum to consist chiefly of the bis(pyrrolo[2,3-b]indolyl)methane (184) already described. The front band, isolated in 17% yield was identified as the 2-methyl pyrroloindole (230) on the basis of its n.m.r. spectrum which exhibited the expected aromatic, *N*-methyl and *N*-methoxymethyl signals as well as a 1 proton quartet at δ 6.20 and a 3 proton doublet at δ 2.39 (J *ca.* 1.0 Hz).



(230)

The reduction of the 2-methoxycarbonyl group to a methyl group runs contrary to the known mode of LAH reduction of 1-methyl-2-carbonyl pyrroles as discussed earlier, as in these cases no 2-methyl compound may be obtained.[101a, 101b] Whether the exomethylene species (185b)

is actually formed in this instance or whether displacement of an O-Cu leaving group by a nucleophilic hydride species is involved, cannot be said for certain. Presumably (184) is formed *via* a similar pathway to that discussed earlier, only in this case an O-Cu species is displaced as leaving group.

(iii) Attempts to introduce a bridgehead substituent

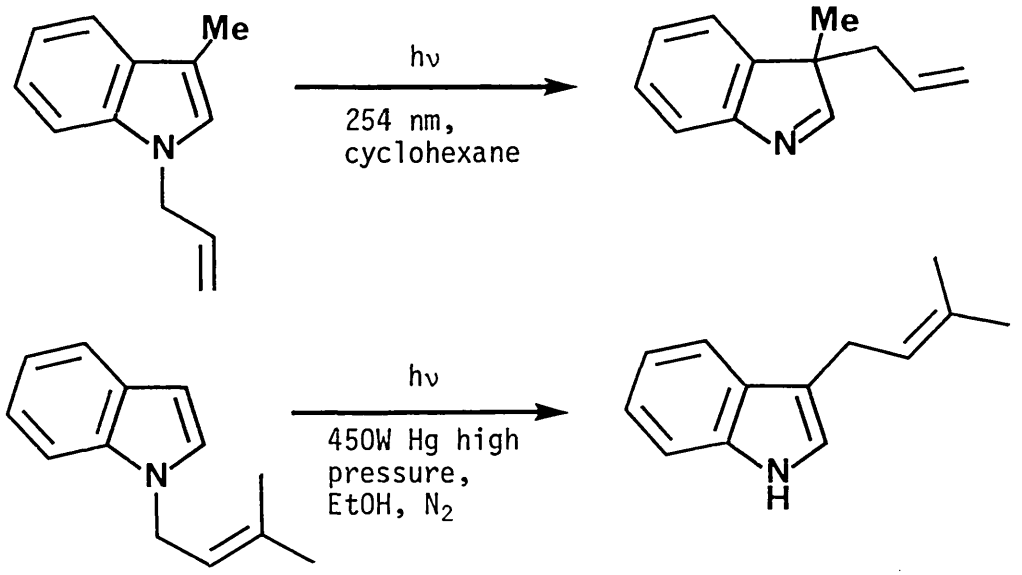
Considering the direction of electron release in the central double bond of these pyrroloindole systems, it might be supposed that the 3a-position would be activated to electrophilic attack. Indolic Grignard reagents formed by treatment of *N*-H indoles with alkyl magnesium halides can be alkylated in the 3-position,[133] and 3-substituted indoles treated thus, afford indolenines. It was hoped that the *N*-Grignard reagents of either (176a) or (181) could be alkylated in this manner at the 3a-position. The system (181) seemed more likely to behave so, as it appeared to approximate more closely to the simple indoles which are known to undergo this reaction. It was suspected that the terminal 5-membered ring in (176a) would behave more like an isolated pyrrole.

In the event, both (176a) and (181) were treated with ethylmagnesium bromide in THF, and although a red colouration developed in both cases, no reaction was observed by t.l.c. when methyl iodide was added. Both reactions gave only recovered starting material on work-up. Repeating the above treatment with (176d) but using allyl bromide instead of methyl iodide also resulted in recovery of starting material. It is not certain if the required *N*-Grignard reagents were formed. The red colouration imparted to the reaction mixture by addition of ethylmagnesium bromide was not discharged when water was added, and was therefore possibly due not to the required Grignard, but to a trace impurity or to a small amount of polymerization. The failure of these

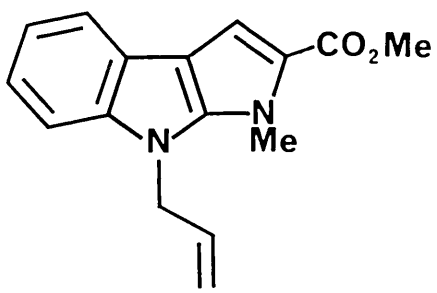
model systems to react in the required fashion led to the abandonment of this approach.

Another approach to the introduction of a bridgehead substituent was based on the known migrations of allyl and related groups from nitrogen to carbon in indoles. Thus *N*-allylindole gives 3-allylindole upon F.V.P. at 500°C, or by refluxing in benzene with aluminium chloride.[134,135] Photolytic rearrangements are also known, Scheme 17.[136,137]

Scheme 17

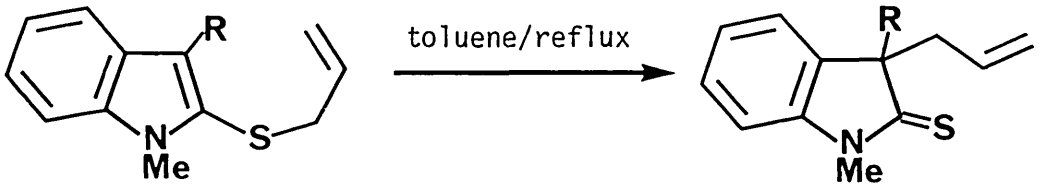


It was thought that the *N*-allyl compound (182) would be a suitable model substrate, but refluxing in *o*-dichlorobenzene for 24h or photolysis at 300 or 254 nm left this compound unchanged. Treatment with aluminium chloride in refluxing benzene resulted in complete decomposition.

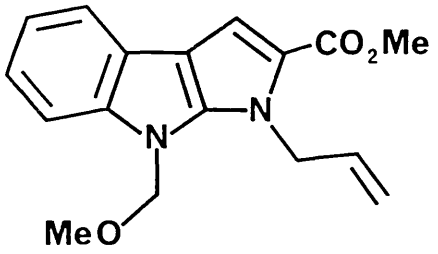


(182)

Another known reaction related to those mentioned above, is the migration of the allyl group in the compound (231).[138] If the pyrroloindole system is regarded as an indole with a heteroatom substituent in the 2-position, then it might be envisaged that the system (232) would undergo a similar rearrangement.



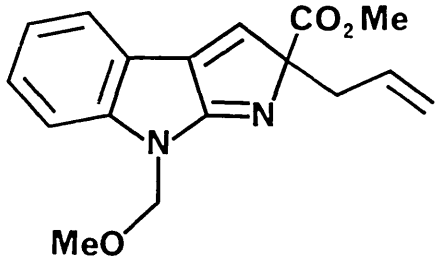
(231)



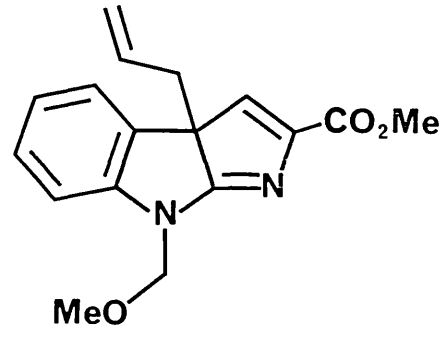
(232)

This compound was prepared in a similar fashion to (182), by treatment of (176d) with sodium hydride and subsequent quenching with allyl bromide. A yield of 71% was obtained, along with a minor amount of another compound, appearing as an intensely fluorescent, slower running spot on t.l.c.. Thermolysis of (232) in decalin left this compound unchanged, but photolysis at 300 nm in cyclohexane for 40 minutes resulted in almost complete consumption of the starting material, and formation of two new products, the major product being identical by t.l.c. and spectroscopically with the minor compound from the allylation reaction described above. The minor photolysis product was shown to be (176d), presumably the result of photolytic cleavage, and was obtained in 11% yield, while the yield of the major product was 62%. The major photolysis product

has a molecular ion of the same mass as (232) *viz* 298, and is therefore isomeric with (232). The presence in its n.m.r. spectrum of a two-proton multiplet at δ 2.93, corresponding to the methylene protons of the allyl group, was taken as evidence that N to C migration had indeed taken place. In the starting compound (232) these protons resonate at δ 5.40. The methylene protons of the *N*-methoxymethyl group appear as an AB quartet in the n.m.r. of the rearranged compound, and this points to the formation of a chiral centre, which is also fully consistent with N to C migration. Further evidence for this migration is obtainable from the ^{13}C n.m.r. spectrum of this material, in which a high field quaternary resonance at δ 92.95 indicates the presence of an sp^3 quaternary centre. The data so far described could be equally consistent with either of structures (233a) or (233b). The i.r.



(233a)



(233b)

spectrum of the rearrangement product seems to provide some slight evidence in favour of structure (233a) since the ester carbonyl signal comes at 1730 cm^{-1} while that of the starting compound (232) is at 1690 cm^{-1}. The higher frequency of the ester carbonyl signal in the photolysis product could be seen as an indication that the methoxycarbonyl group is now attached to an sp^3 centre as in structure (233a), rather than to an sp^2 centre which would be the case in structure (233b). This could not be taken as conclusive evidence however, and comparison of the u.v. spectrum of (232) with that of the rearranged product, although revealing

considerable differences, did not afford any further means of distinguishing which of the two possible structures was correct. Nuclear Overhauser difference spectroscopy showed only the expected enhancements for each centre irradiated, and did not lead to any concrete assignment of structure. The structure was finally elucidated by X-ray crystallography, the crystal data being as follows:

For $C_{17}H_{18}N_2O_3$, triclinic, $\underline{a}$ = 8.175 (3), $\underline{b}$ = 9.732 (3), $\underline{c}$ = 10.863 (4) Å; α = 115.62 (2), β = 92.56 (3), γ = 93.88 (3)°; $\underline{u}$ = 775 Å^3; space group $P\bar{1}$; Z = 2; D_c = 1.28 g cm^{-3}. Data were collected on a Nicolet R3m diffractometer with Cu-K_α radiation. The structure was solved by direct methods and refined anisotropically to give R = 0.054 for 1321 independent observations. The structure was thus determined to be (233a) as shown in the computer generated drawing reproduced in Appendix 2 (Figure 2). A full list of bond angles and lengths is also included in Appendix 2.

This result is not altogether surprising in the light of work by Patterson *et al.*,[139,140] who have investigated the photolyses at 254 nm, of simple *N*-alkyl and *N*-allylpyrroles, and have obtained 2H-pyrroles as the major components, along with 3-substituted pyrroles, and *N*-H pyrroles which are the result of photocleavage. Comparison with these literature results suggests that the terminal 5-ring of the pyrroloindole system behaves at least to some extent as if it were an isolated pyrrole ring. The analogy with Patterson's work is not complete, since no products of migration to the 3-position were obtained.

Photolysis of the *N*-methyl compound (180b) at 300 nm for 2h left this compound unchanged.

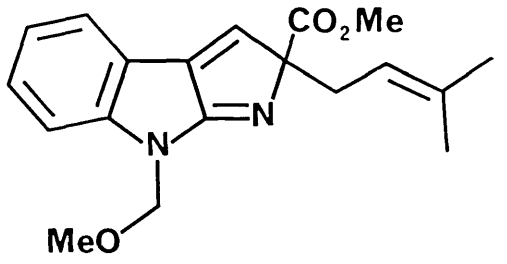
It is also known from the literature that treatment of pyrrylmagnesium halides with alkylating agents frequently results in the formation of 2H-pyrroles,[140] although pyrroles bearing an ester group cannot be

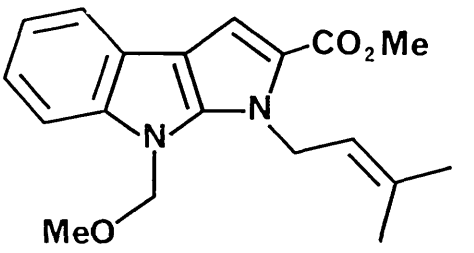
alkylated in this fashion[141] (this is also true of the pyrroloindoles, and unsuccessful attempts to alkylate the pyrroloindoles bearing alkoxycarbonyl groups *via* the *N*-Grignard compounds have been described earlier). It has been seen however that treatment of the *N*-sodium salt of (176d) with allyl bromide gives a minor amount of the 2H-pyrroloindole (233a).

Treatment of the *N*-sodium salt of (176d) with prenyl bromide results in the formation of the analogous 2H-pyrroloindole (234) as the major product, in 60% yield. In this instance only a 6% yield of the *N*-alkylated compound (235) could be isolated. The structure (234) was assigned by comparison of its i.r., u.v. and n.m.r. spectra with those of (233a). The reason for this great difference in the ratio of N to C alkylation when compared with the ratio for alkylation with allyl bromide is not clear.

Photolysis of (235) in cyclohexane at 254 nm gave a compound having an identical n.m.r. spectrum to (234), indicating that these rearrangements take place without inversion of the allylic group, although there is no evidence to suggest that a direct migration to the 2-position takes place, and a series of sigmatropic shifts may be responsible for the gross result.

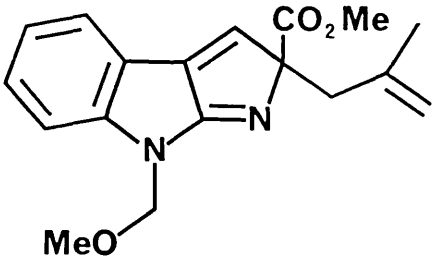
The *N*-potassium salt of (176d) was also treated with prenyl bromide and in this case the 2H-pyrroloindole (234) was obtained in 56% yield, while the yield of the *N*-prenyl compound was 18%. This rise in the yield of the *N*-alkylation product is in accord with the known reactivity of *N*-potassium and *N*-sodium salts of simple pyrroles, since the *N*-potassium species are known to have a higher tendency towards *N*-alkylation.[142]

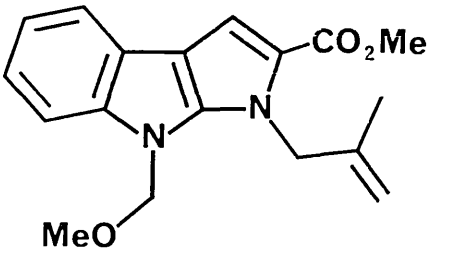




(234) (235)

Treatment of the *N*-sodium salt of (176d) with 3-chloro-2-methylprop-1-ene gave the expected *N*-alkylated compound (237) in 72% yield as well as a minor amount (11%) of the corresponding 2H-pyrroloindole (236). Photolysis of (237) in cyclohexane gave a 50% yield of (236) as well as 15% of the photocleaved product (176d).

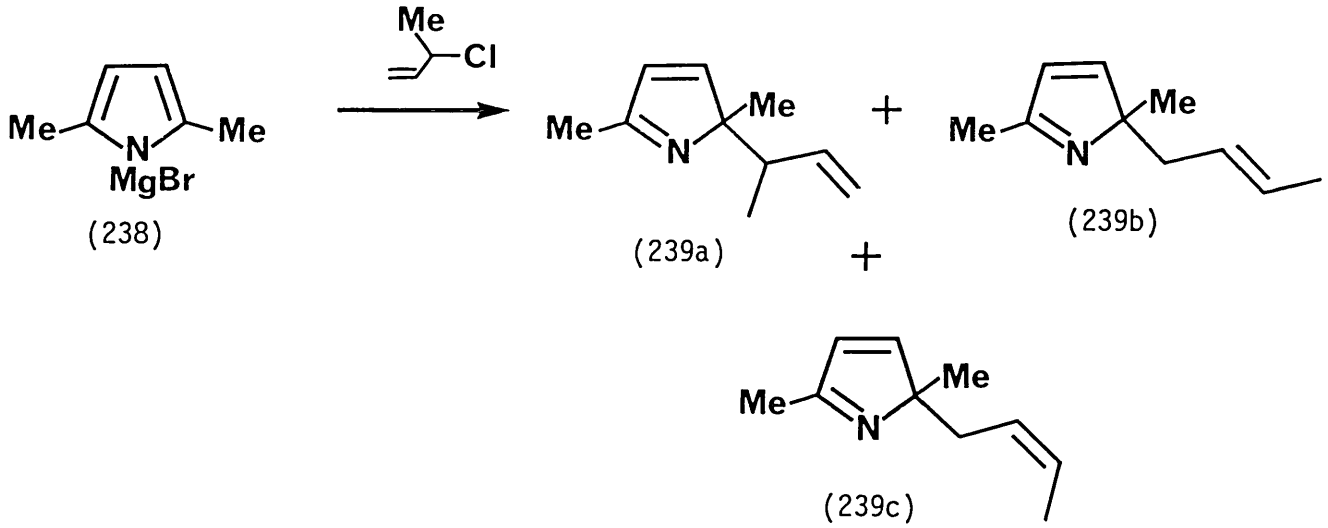


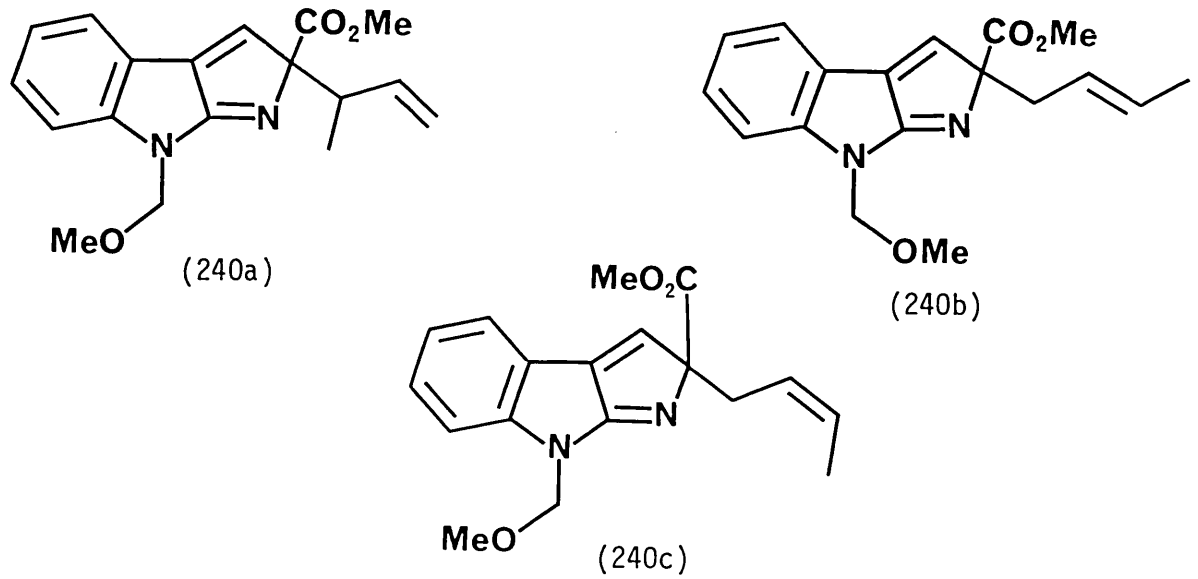


(236) (237)

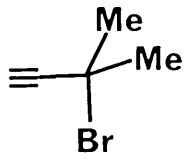
Reaction of the secondary halide 3-chlorobut-1-ene with the *N*-sodium salt of (176d) gave a small amount of an apparently *N*-alkylated compound which was not the expected *N*-alkylation product. The major fraction was the product of C-alkylation, and appeared to be chromatographically homogeneous, but examination by n.m.r. showed this band to consist of three compounds. These were tentatively assigned the structures (240 a, b and c) by analogy with the report by Patterson[140] of treatment of the pyrrylmagnesium halide (238) with this same alkylating agent to afford

(239 a, b and c), and also by comparison of the n.m.r. spectra of the 2H-pyrroloindoles already prepared with the n.m.r. spectrum of the mixture.



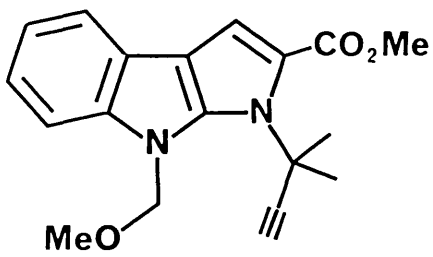


Treatment of the *N*-sodium salt of (176d) with the acetylenic bromide (241)[143] gave a mixture of four compounds which were separated by silica gel chromatography.

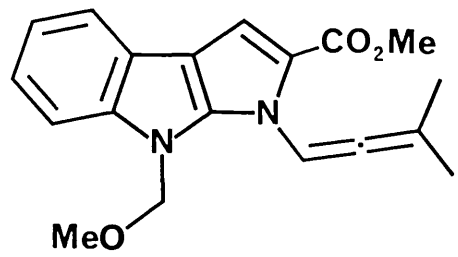


(241)

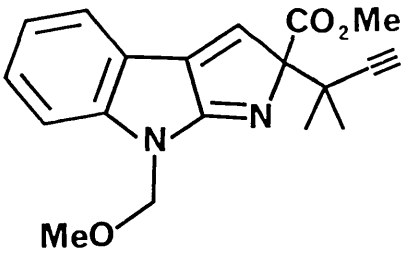
The two front running bands were crystalline, although the faster of the two appeared to be a mixture by n.m.r. (even though it was chromatographically homogeneous). Both bands exhibited molecular ions at 324, but neither seemed to be the expected *N*-alkylated compound (242), or the allene (243) which would result from the alternative mode of nucleophilic attack upon (241). Fully consistent structures for these compounds were not easily proposed, and they were not examined any further. The two other bands were both shown to be 2H-pyrroloindoles by comparison of their u.v., i.r. and n.m.r. spectra with those of authentic 2H-pyrroloindoles. The faster running band which was obtained in low yield (2%) was identified as the compound (244), having i.r. signals at 3310 and 2120 (very weak) cm^{-1} and the expected pattern of aromatic protons as well as a one-proton singlet at δ 2.20 in its n.m.r.. Its u.v. spectrum was characteristic for a 2H-pyrroloindole. The slower running band was tentatively identified as the allene (245).



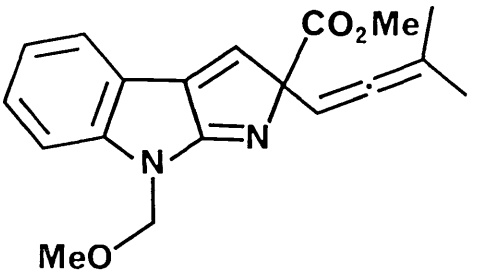
(242)



(243)

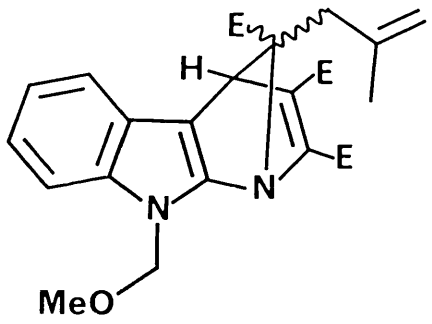


(244)



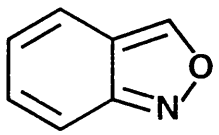
(245)

Clearly, these 2H-pyrroloindoles are examples of indole-2,3-quinone methide imines. Species containing the *o*-quinone methide imine functionality are known in the literature,[144] and some of these are relatively stable, such as the benzoisoxazole (246). Others, exemplified by (247) are highly reactive intermediates which rapidly dimerize *via* [4+2] cycloaddition. Intramolecular trapping of the *o*-quinonoid system may be effected in such cases, as shown below (248) → (249). Even the relatively stable benzoisoxazole (246) rapidly undergoes [4+2] cycloadditions with dienophiles. Analogous cycloaddition reactions of indole-2,3-quinonoid species have already been described in chapter 1, and in the light of these considerations it was decided to investigate briefly the behaviour of the 2H-pyrroloindole system with dienophiles. Heating of the 2H-pyrroloindole (236) with DMAD in toluene for 2h gave a material which appeared to consist of one major and one minor product. Examination of the crude n.m.r. indicated that the major product was a 1:1 adduct, there being 4 × 3H, s, and signals at δ 4.81 (2H, m, possibly CH_2-C(Me) = CH_2) and 6.40 (1H, s, possibly the bridgehead proton), *inter alia*. The structure (250) was tentatively assigned on the basis of these data, but lack of time precluded a more thorough investigation.

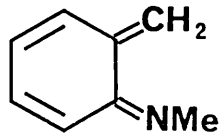


(E = CO_2Me)

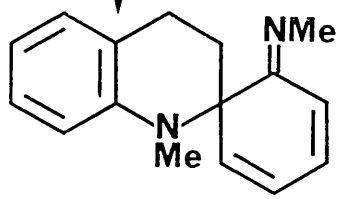
(250)

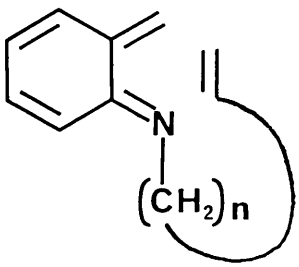


(246)

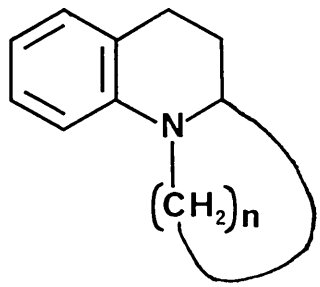


(247)



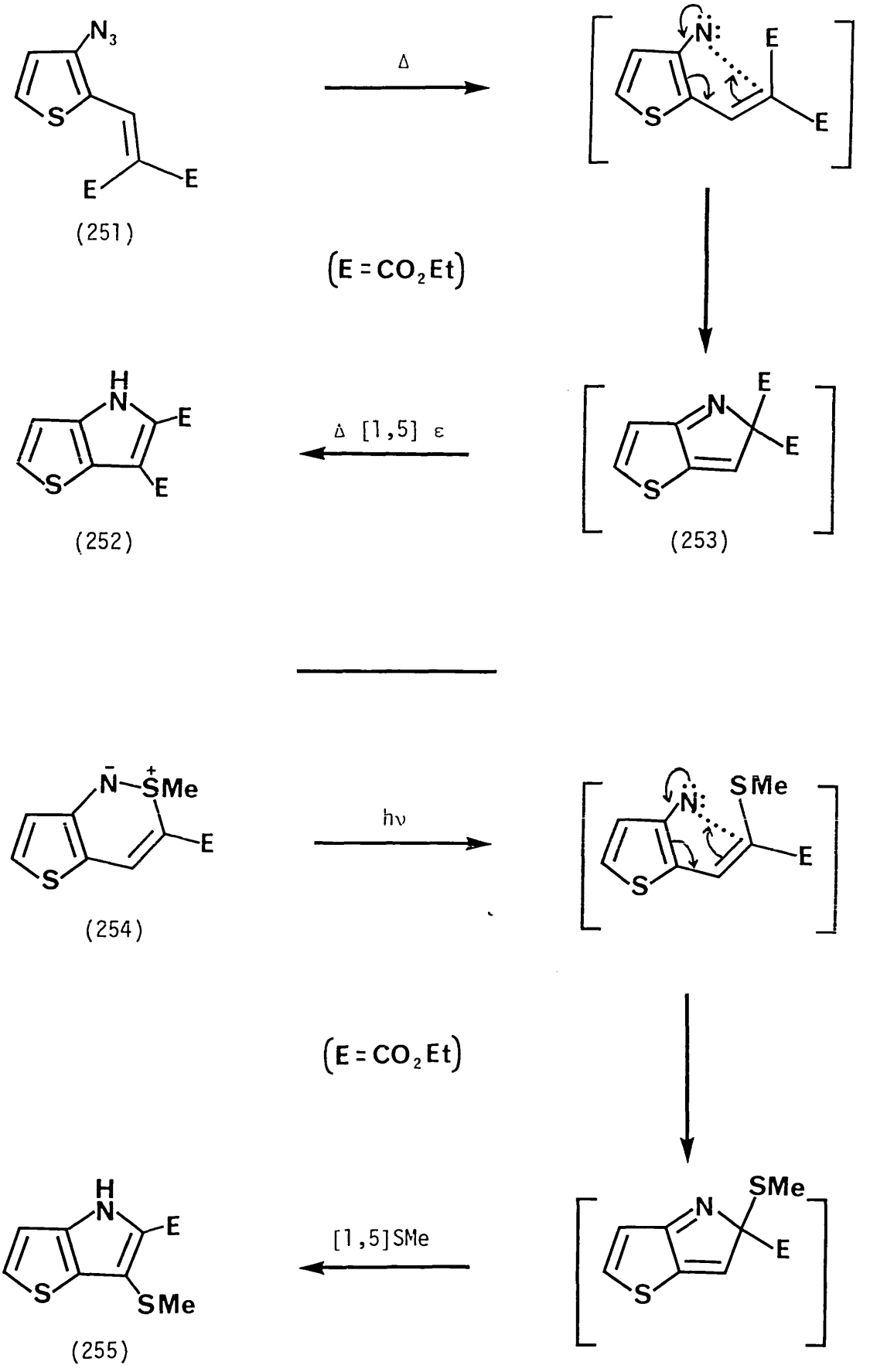


(248)



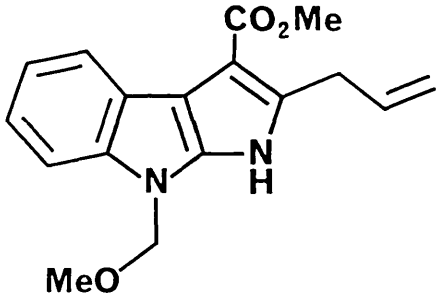
(249)

The thermal rearrangement of these 2H-pyrroloindoles was also examined rather briefly. Literature precedent,[145] and in particular the work of Tsoi[68] seemed to indicate that substituent migration should take place in these compounds. Tsoi thermolysed the azide (251) and obtained the thienopyrrole (252) presumably *via* the intermediate (253), and a seemingly related thermal rearrangement is also implicated as the

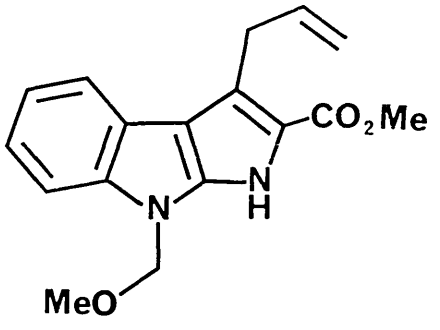

N3
S
E
E
(251)
Δ
(E = CO2Et)
N:
E
E
H
N
E
E
Δ [1,5] ε
(252)
(253)
N
SMe
E
hν
SMe
[1,5]SMe
(254)
(255)

final step in the formation of the thienopyrrole (255) by photolysis of the cyclic sulphimide (254).

Thermolysis of the 2H-pyrroloindole (233a) in toluene at reflux for 12h gave a mixture of two compounds in unequal proportion, which could not be chromatographically separated. The crude n.m.r. contained broad singlets at δ 8.91 and 9.76 the higher field signal corresponding to the major product. These peaks were presumed to represent NH protons. The crude u.v. spectrum was considerably different from those of both the starting 2H-pyrroloindole and the *N*-allyl compound (232). Structure (256) was tentatively assigned to the major product, while it was thought possible that the minor component could be the alternative migration product (257). Again, however, time did not allow a fuller investigation.



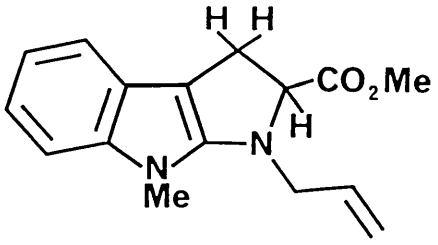
(256)



(257)

Although these reactions were considered interesting enough in their own right to be worth examining, they were unfruitful as regards the initial aim of introduction of a bridgehead substituent at the 3a-position of the pyrroloindole system, and seem rather to reflect the inclination of the terminal 5-ring to react as an isolated pyrrole which has already been remarked on.

It may be speculated that if the dihydro compound (258) were available, the analogy with compound (231) might be closer, and indeed sufficiently close for the desired rearrangement to take place.



(258)

Chapter 4

Thermolyses of 2-indolyl substituted azidopropenoates

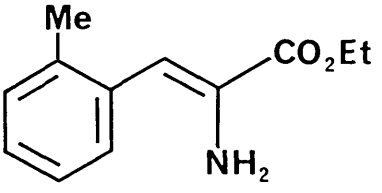
4.1 Introduction

At the beginning of chapter 2, some possible modes of collapse of nitrenes derived from 2-indolyl substituted azides were considered. The synthesis of these azides has been described in chapter 2 and their thermolyses are now to be discussed.

It is known in the literature that the 2,4,6-trimethylphenyl azidopropenoate (259) may be thermally decomposed in boiling toluene or xylene open to the atmosphere, to give the isoquinoline (261), presumably *via* the dihydroisoquinoline (260), which is dehydrogenated either by air oxidation or possibly by more nitrene.[66]

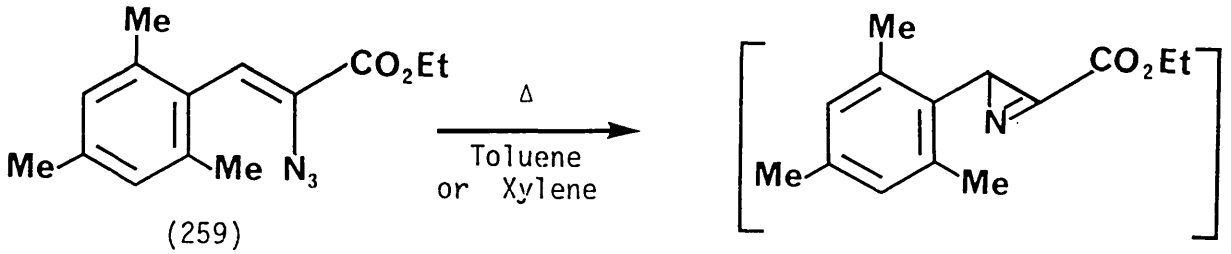
Such dihydroisoquinolines have indeed been isolated, for example, in the thermolysis of the 2-benzylazidocinnamate (262).[67]

Enamines such as (263) have also been isolated and are thought to be the result of hydrogen abstraction from dihydroisoquinolines by the nitrene precursor.[67] In some cases, the intermediate azirines may also be isolated.[67]



(263)

It was initially hoped that thermolysis of 2-indolyl substituted vinyl azides would afford pyrido[3,4-b]indoles (β-carbolines) in an analogous manner to the formation of isoquinolines briefly described above.



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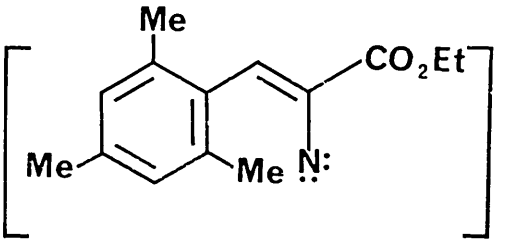

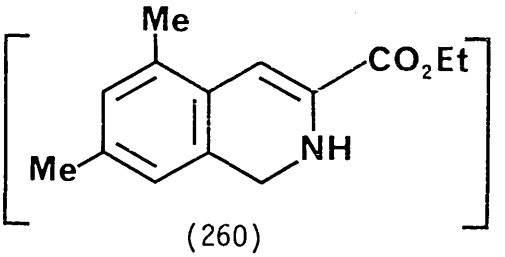

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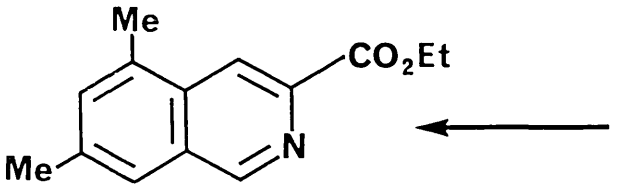

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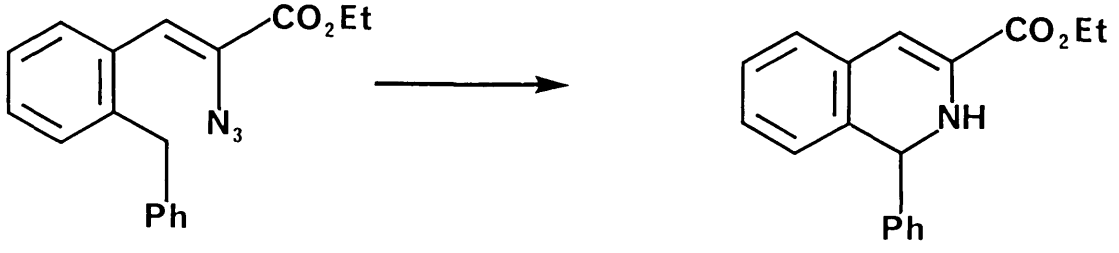


(262)

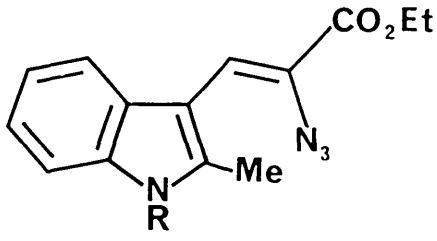
4.2 Thermolyses of 2-methylindolyl azidopropenoates

The vinyl azide (264a) was initially thermolysed on a small scale under a variety of conditions. Depending on these conditions, products could be obtained which were spectroscopically identified as the expected β-carboline (266a) and the dihydro-β-carboline (265). The results of these experiments are summarized in Table 5.

Table 5

(264) ⟶ (266a) + (265)

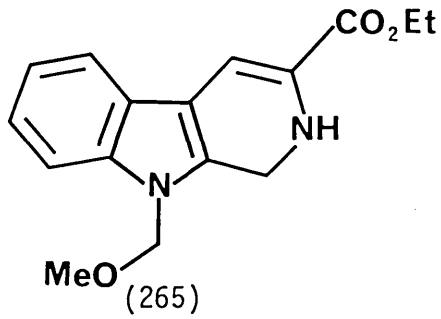
	Experimental Conditions	Time h	Refluxing Solvent	Result (from n.m.r.)
1)	Open to atmosphere	4.5	Benzene	Only (266a) detected, plus decomposition products.
2)	"	2.5	Toluene	(266a) plus a somewhat smaller amount of decomposition products.
3)	"	1.5	Xylene	high yield of (266a)
4)	"	0.75	Bromobenzene	high yield of (266a)
5)	Under N_2	1.5	Xylene	approximately 40:60 ratio of (265) and (266a)
6)	With added I_2	1.5	Xylene	only complex decomposition products



(264)

a) R = CH_2OMe

b) R = CH_2Ph



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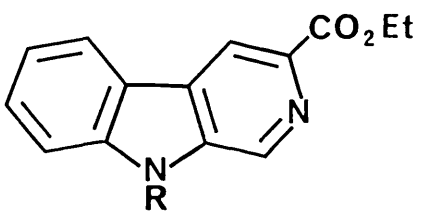
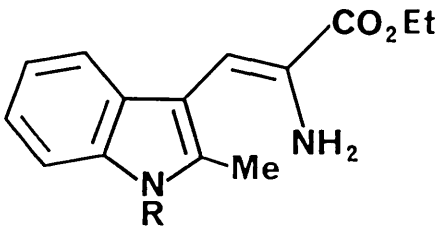


(266)

a) R = CH_2OMe
b) R = CH_2Ph
c) R = H



(267)

a) R = CH_2OMe
b) R = CH_2Ph

In preparative scale experiments, thermolysis of (264a) in xylene for 1.5h open to the atmosphere, gave a 59% isolated yield of the β-carboline (266a), along with trace amounts of 1-methoxymethyl-2-methyl-indole-3-carbaldehyde and another faster running compound having spectral data consistent with the structure (267a). Thermolysis of (264a) in degassed xylene under nitrogen, gave a *ca.* 55:45 mixture of (265) and (266a), (265) being identified by n.m.r. signals at δ 5.0 (2H, s), 5.38 (2H, s) and 6.73 (1H, s). Attempted isolation of (265) by silica gel chromatography resulted in its complete dehydrogenation, and only (266a) could be isolated, in 85% yield.

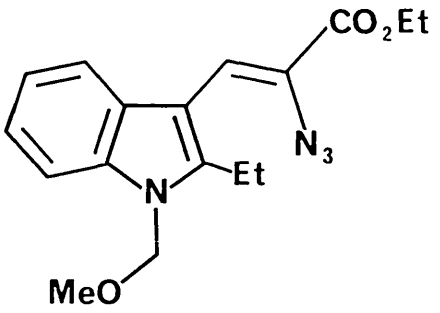
The *N*-benzyl vinyl azide (264b) was also thermolysed, and yields of up to 76% of the β-carboline (266b) were obtained. Traces of a compound tentatively assigned the structure (267b) were also obtained. Attempted debenzylations of (266b) were not successful, but (266a) could be deprotected by treatment with hot 90% formic acid, giving (266c) in 75% yield. Comparison of the (266c) so prepared, with an authentic sample[159] confirmed its identity.

Considerable interest in compound (266c) has been evinced in the biochemical literature recently, since it has been shown to have a high

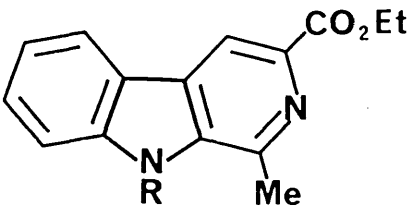
affinity for benzodiazepine-binding brain proteins.[146,147]

4.3 Thermolyses of 2-ethyl and 2-*n*-propylindolyl azidopropenoates

The 2-ethyl substituted vinyl azide (268) was initially thermolysed in xylene, at reflux for 2h, open to the atmosphere. At this stage the crude n.m.r. indicated the presence of three compounds. The material was thermolysed under identical conditions for a further 22h, after which time only two compounds were present. These were separated by silica gel chromatography. The slow running band, isolated in 35% yield was spectroscopically identified as the expected β-carboline (269a), which exhibited the characteristic intense violet fluorescence on t.l.c. when observed under the u.v. lamp. The other compound isolated in 24% yield, was assigned the structure (270a) on the basis of its spectral properties, having i.r. signals at 3380 and 1690 cm^{-1} and in the n.m.r., resonances at δ 3.29 (2H, t, J 5.1 Hz), 3.48 (2H, t, J 5.1 Hz) and 6.93 (1H, s). The isolation of this surprising product led to further investigations to ascertain its mode of formation. A somewhat suggestive observation was made when (268) was thermolysed for 3h in benzene, without the exclusion of air. One new compound was formed as indicated by n.m.r., which was neither (269a) nor (270a). It was eventually identified as the enamine (271), having i.r. signals at 3480 and 3380 cm^{-1}, characteristic of an NH_2 group, and n.m.r. signals characteristic of a monosubstituted ethene as well as a sharp singlet corresponding to one olefinic proton. Enamine (271) was thermolysed (without further purification) in xylene for 20h, giving a mixture containing (269a) and (270a) in very similar proportions to that obtained when the azide (268) was thermolysed under those conditions.



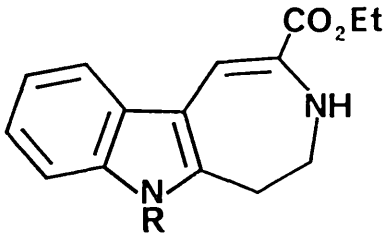
(268)



(269)

a) R = CH_2OMe

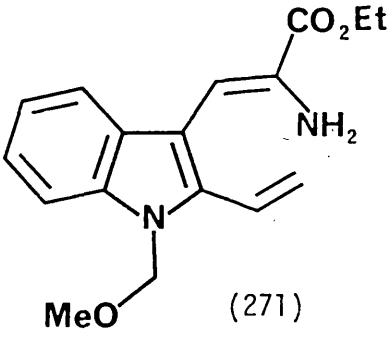
b) R = H



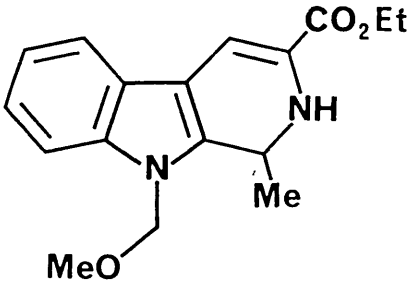
(270)

a) R = CH_2OMe

b) R = H



(271)



(272)

Further small scale thermolyses which were carried out to investigate this reaction are described in Table 6. Thermolysis of (271) under the conditions described in the Table gave very similar results in all cases.

Table 6

(268) ⟶ (269a), (270a), (271) and (272)

	Experimental Conditions	Time h	Refluxing Solvent	Result (from n.m.r.)
1)	Open to atmosphere	2	Xylene	approximately 60:35:5 ratio of (270a), (271) and (269a).
2)	"	24	Xylene	approximately 70:30 ratio of (270a) and (269a) plus decomposition products.
3)	"	4	Bromobenzene	(269a) plus decomposition products.
4)	"	1.5	*o*-dichloro-benzene	(269a) plus decomposition products.
5)	"	3	DMF	high yield of (270a).
6)	Under N_2	3	Xylene	approximately 10:35:20:35 ratio of (269a), (270a), (272) and (271).*

In preparative scale experiments, thermolysis of (268) in DMF gave a 60% isolated yield of (270a). Thermolysis in *o*-dichlorobenzene resulted in the isolation of (269a) in 43% yield.

Attempted purification of enamine (271) by silica gel chromatography resulted in ring closure, and only (270a) could be isolated, in 54% yield (*ex* starting azide). Likewise, stirring of an ethereal solution of (271) over silica gel for 17h, was found to effect complete and clean ring closure.

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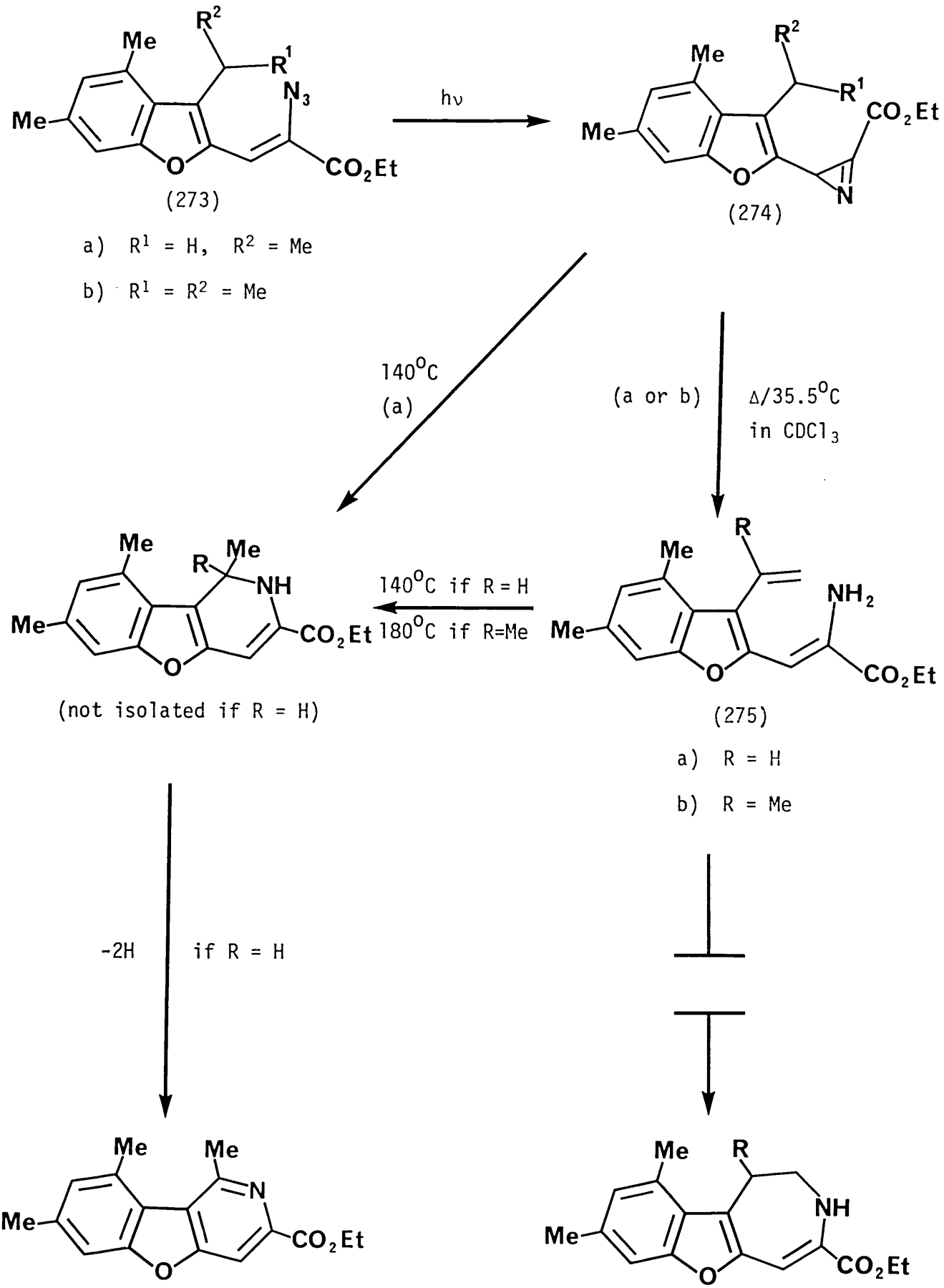
*The reaction mixture was left open to the air overnight after which time n.m.r. showed an approximately 30:40:30 ratio of (269a), (270a) and (271).

In rationalising these observations, the work of Taniguchi *et al.*[148] was considered. These workers obtained azirines (274) by photolysis of azides (273). Thermolysis of (274) under the conditions indicated in Scheme 18 gave a variety of products as shown. The pathway proposed by Taniguchi[148] to accommodate these results would also accommodate the observations described earlier, even though no benzofuroazepines were isolated by Taniguchi.

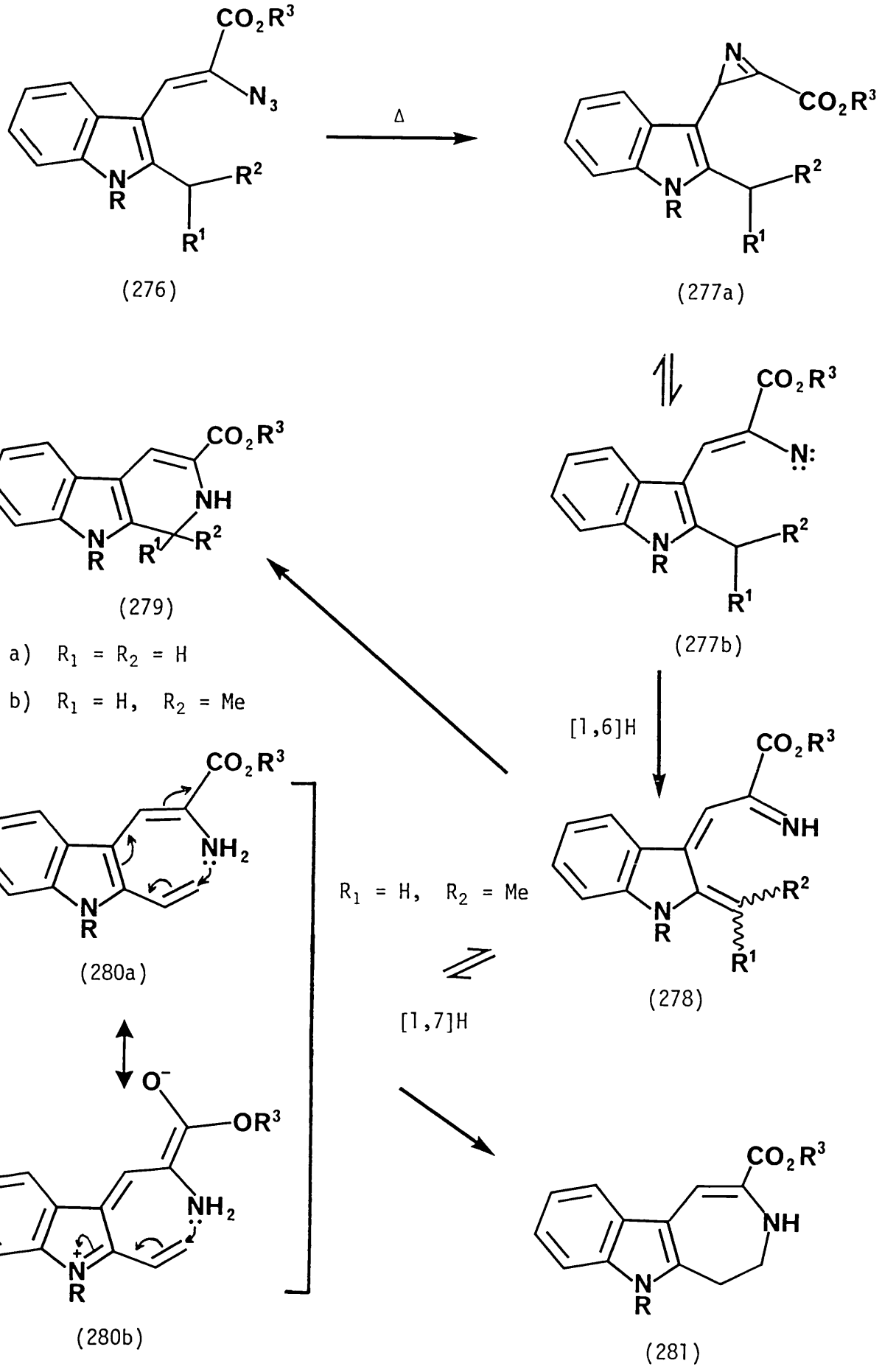
Considering a generalised azide (276) which upon thermolysis initially gives azirine (277a) in equilibrium with nitrene (277b), it may be seen that a [1,6] hydrogen shift in this nitrene could lead to a conjugated imine intermediate such as (278). In the simplest case, when $R_1 = R_2 = H$, electrocyclic ring closure gives dihydro-β-carboline (279a). If $R_1 = Me$ and $R_2 = H$ another possibility arises, namely, a further [1,7] hydrogen shift to give the enamine (280a). Since this process occurs at low temperature (280a) may be assumed to be a kinetically controlled product. At higher temperatures the imine-enamine equilibrium system* may either give the electrocyclic ring closure product (279b), or the azepinoindole (281) *via* conjugate attack by the $-NH_2$ of the enamine on the terminal carbon of the vinyl group, Scheme 19. The polarization of the 3-substituted indole system promotes such reactivity owing to contributions from resonance structures such as (280b). The possibility of dipolar character in the transition state which leads to the azepinoindole is suggested by its almost exclusive formation when azide (268) or enamine (271) are thermolysed in DMF. The conjugate addition mechanism is also suggested by the fact that mild acid catalysis (silica gel) promotes ring closure even at room temperature.

---

*Evidence that this is an equilibrium system has been provided by Taniguchi,[148] who thermolysed *N*-deuterated enamine (275a) in benzene. This treatment resulted in the deuteration of the terminal carbon of the vinyl group.

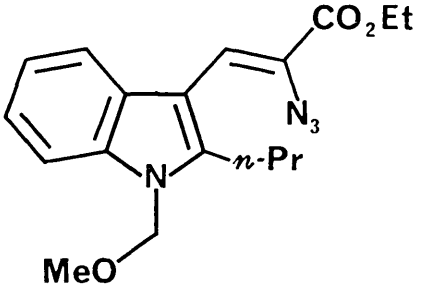

Me
R2
R1
N3
CO2Et
O
hν
(273)
a) R1 = H, R2 = Me
b) R1 = R2 = Me
(274)
140°C
(a)
(a or b)
Δ/35.5°C
in CDCl3
140°C if R = H
180°C if R=Me
NH
NH2
R
(not isolated if R = H)
(275)
a) R = H
b) R = Me
-2H
if R = H
N

Scheme 19

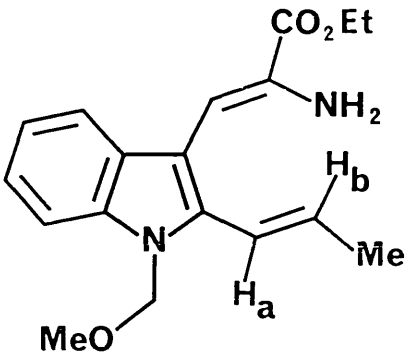

CO2R3
N3
R2
R1
N
R
Δ
(276)
(277a)
(277b)
(279)
a) R1 = R2 = H
b) R1 = H, R2 = Me
[1,6]H
(278)
R1 = H, R2 = Me
[1,7]H
(280a)
(280b)
O−
OR3
NH2
NH
(281)

As in the case of β-carboline (266a), treatment of (269a) with hot 90% formic acid afforded the deprotected compound (269b) which was isolated in 95% yield.

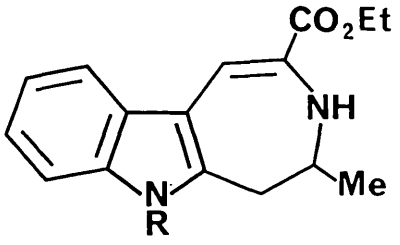
The 2-*n*-propylindolylazidopropenoate (282) was thermolysed under a variety of conditions. The expected products *viz* enamine (283), (the *trans* geometry of the disubstituted vinylic system shown, being implied by the coupling constant J_{ab} which is 16 Hz), azepinoindole (284a) and β-carboline (285) were obtained as shown in Table 7. The β-carboline was never obtained in more than trace amounts, and was never isolated.



(282)



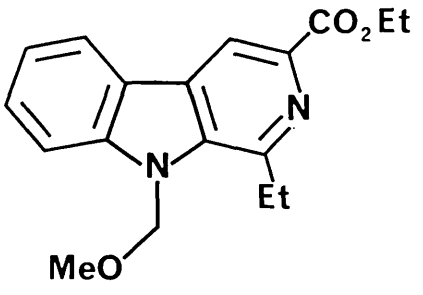
(283)



(284)

a) R = CH_2OMe

b) R = H



(285)

Table 7

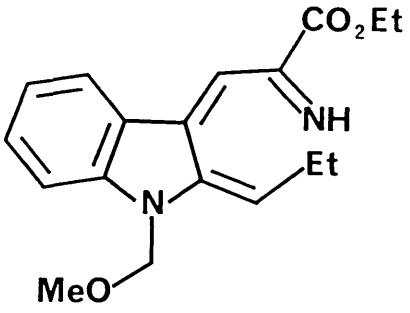
(282) ⟶ (283), (284a) + (285)

	Experimental Conditions	Time h	Refluxing Solvent	Result (from n.m.r. unless indicated)
1)	Open to atmosphere	2	Benzene	(283) in 65% isolated yield.
2)	Open to atmosphere	2	Xylene	(283) and (284a) in an approximately 80:20 ratio.
3)	Open to atmosphere	24	Xylene	high yield of (284a) plus trace of (285)
4)	Open to atmosphere	5	DMF	(284a) isolated in 51% yield.

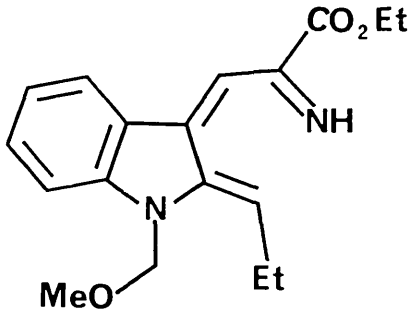
The enamine (283) was also thermolysed under the conditions indicated in the table, giving on each occasion, very similar results to those observed when the azide (282) was thermolysed. When an ethereal solution of enamine (283) was stirred at room temperature over silica gel for 20h, a mixture estimated by n.m.r. to contain (283) and (284a) in 75:25 ratio was the result. It was thus found possible to purify (283) by flash chromatography on silica gel. The slower rate of ring closure of the enamine (283) in comparison with (271), may be due to steric hindrance of the site of conjugate attack in (283) by the terminal methyl group.

It would also appear that some effect is in operation which discourages the formation of the dihydro-β-carboline from which (285) is derived, explaining the miniscule yields of this compound which are observed. A credible rationalization for this may be derived from the work of Taniguchi.[148] Considering the two possible stereoisomers of the intermediate imine (286a) or (286b), it seems likely that (286a)

would be formed preferentially, due to steric repulsion between the ethyl group and the methoxymethyl group. The disinclination to form the dihydro-β-carboline may then be seen as a reflection of the unfavourability of a 6π disrotatory ring closure of (286a), due to steric hindrance and possibly to partial destruction of the coplanarity of the 6π conjugated system by the ethyl group.



(286a)



(286b)

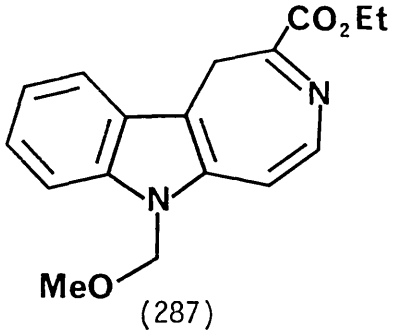
Owing to the smaller steric bulk of a methyl group, this effect is not so pronounced in the imine precursor of (272).

Both of the azepinoindoles (270a) and (284a) may be deprotected, giving (270b) and (284b) respectively, by treatment with aqueous hydrochloric acid in ethanol. The enamine functionality in these compounds is apparently totally stable to these mild acid conditions.

The enamines (271) and (283) were characterized as the *N*-acetyl compounds,[158] obtained by treatment with acetic anhydride in pyridine. The *N*-acetyl compounds when pure were pale yellow crystalline solids giving correct mass spectral and microanalytical results. Some of their other physical properties were however curious. Their melting points for instance, were not sharp, and melting ranges of up to 11°C were recorded on analytically pure samples. Their n.m.r. spectra exhibited sharp signals for all the protons excepting the *N*-acetyl methyl group and the vinyl proton of the enamine system, which were considerably broadened. Although restricted rotation effects were considered, no

really satisfactory explanation for these phenomena could be advanced.

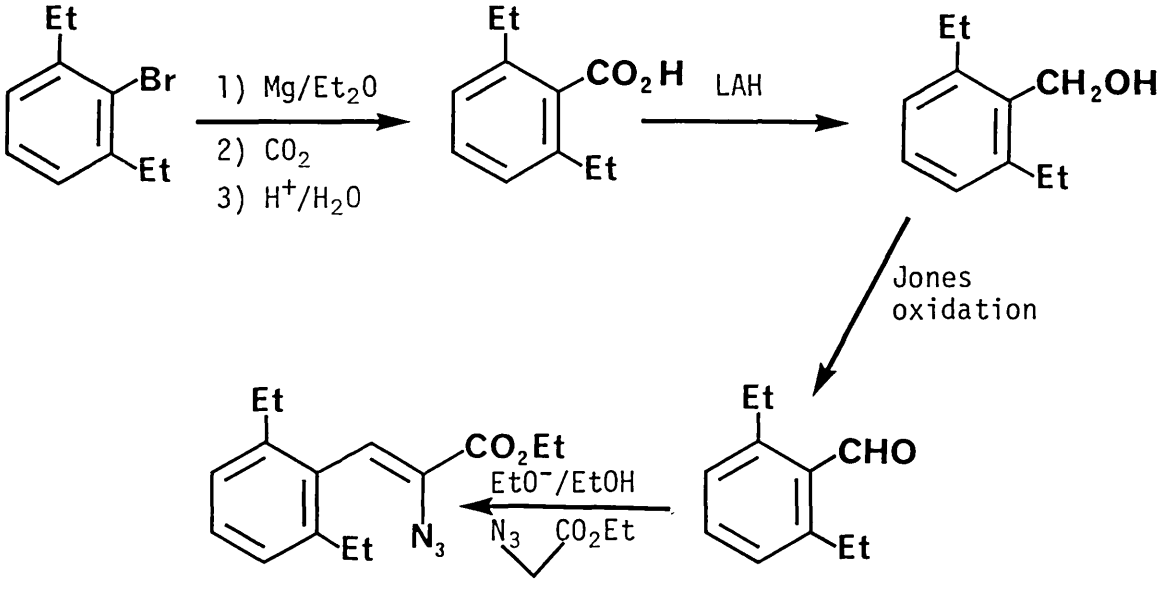
Attempts to reduce the azepinoindole (270a) with sodium borohydride in ethanol containing acetic acid were unsuccessful. This compound could be dehydrogenated giving (287), by treatment with t-butyl hypochlorite in methylene chloride at -22°C followed by DBU.



(287)

In an attempt to discover the generality of this azepine formation, it was decided to prepare and thermolyse the azide (288), in order to ascertain if benzazepines could be thus obtained. The required 2,6-diethylbenzaldehyde was prepared from 2,6-diethylbromobenzene[149] by a standard approach summarized in Scheme 20.

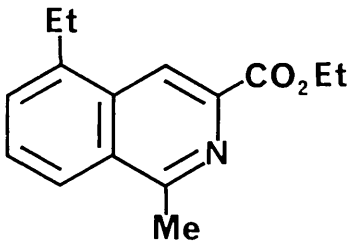
Scheme 20



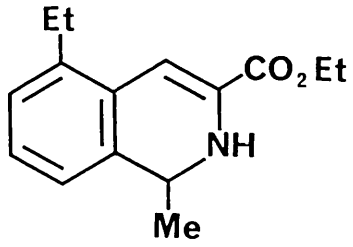
(288)

The condensation of this aldehyde with ethyl azidoacetate did not go to completion, and separation of the vinyl azide (288) from the unreacted aldehyde proved to be very difficult. Therefore, samples of the azide contaminated with *ca.* 10% of the aldehyde had to be employed in the thermolyses. The aldehyde could be recovered from the products after thermolysis, by chromatography on silica gel, and its presence did not appear to affect the results of these reactions.

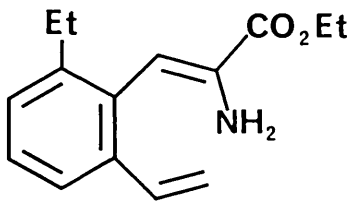
An initial thermolysis of (288) was carried out in xylene for 2h, after which time the n.m.r. of the crude material showed the presence of isoquinoline (289) as well as appreciable quantities of dihydroisoquinoline (290). Separation by p.l.c. was attempted, but gradual air oxidation always caused samples of (290) to be contaminated with the aromatized compound. A small amount of another compound, assigned the structure (291) was also obtained. The rate of oxidation of the dihydroisoquinoline (290) appeared to be considerably slower than that of the dihydro-β-carbolines already described. Thermolyses under other conditions, some using external oxidants, were carried out, and these are summarized in Table 8.



(289)



(290)



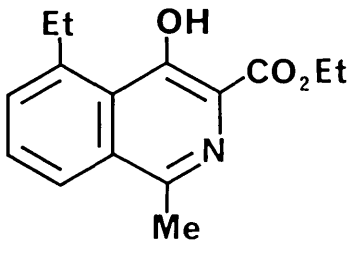
(291)

Table 8

(288) ⟶ (289), (290) + (291)

	Experimental Conditions	Time h	Refluxing Solvent	Result (isolated)
1)	Thermolysed open to atmosphere, cooled and iodine (one molar equiv.) added.	2	Xylene	(289); 35%
2)	Under N_2	2	Toluene	(290); 75% (291); 25% (by n.m.r.)
3)	Reaction mixture *ex* (2) above is dissolved in toluene and air drawn through for 48h, and then refluxed in toluene with sulphur overnight			(289); 27% (291); 13%
4)	Thermolysed open to atmosphere, cooled, and reaction mixture exposed to air for 7 days at 3°C.	2.5	DMF	(289); 26% (291); 5% plus a trace of another compound.*

*The spectral data of this compound suggest the structure (292). Its mode of formation is not known.



(292)

In no case was there any indication of azepine formation, and this is further evidence that formation of azepines is peculiarly favoured in the indole systems, due to the particular type of bond polarization found in these molecules.

The generation of azepines from vinyl azides in the manner described is previously unreported, although its scope for use in other systems may be limited. Azepino[4,5-b]indoles in the higher oxidation states are sparsely represented in the literature, although there are numerous references[44,150-156] to compounds with the same ring skeleton in reduced states.

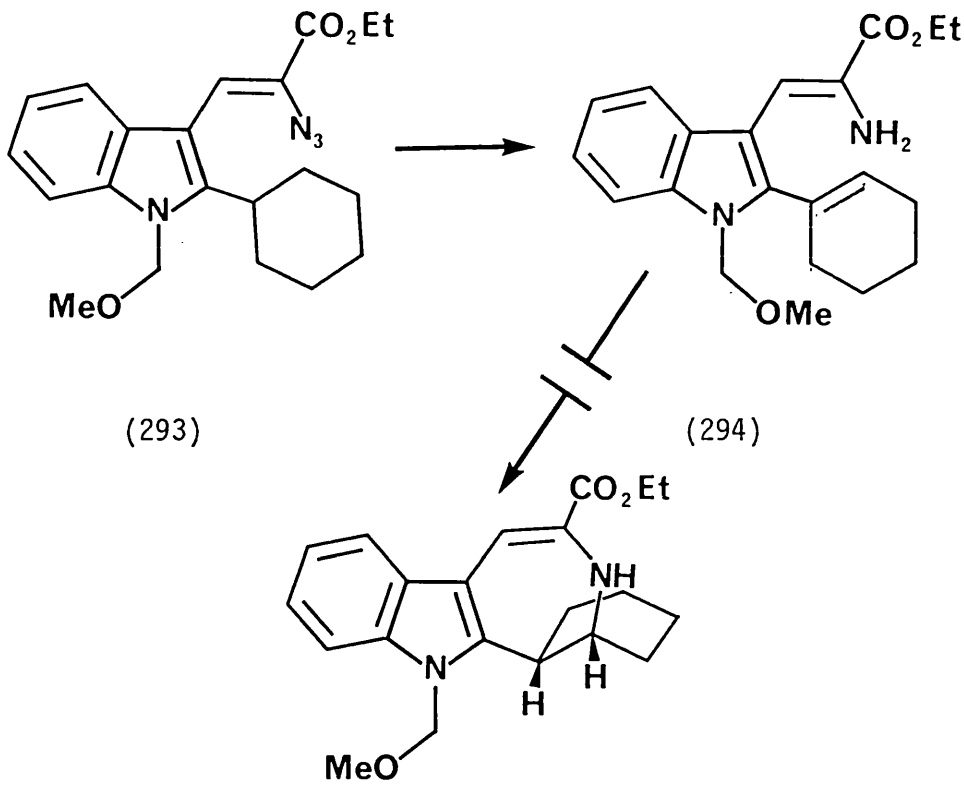
The reaction described above is thus a useful mode of entry into systems which are unknown in the literature. It was decided therefore, to ascertain if this method could be used to prepare some slightly more complex azepinoindoles.

4.4 Thermolyses of 2-cyclohexyl and 2-isopropyl azidopropenoates

It was hoped that thermolysis of the 2-cyclohexylindolyl azidopropenoate (293) would lead to azepinoindole (295) *via* the expected enamine (294). The reason for interest in (295) being its close relationship to the ring skeleton of the catharanthine alkaloids.

The azide (293) was thermolysed in refluxing xylene, and n.m.r. spectra were recorded after 1.5, 4.5 and 17h. The enamine (294), which had apparently formed after refluxing for 1.5h, proved to be thermally stable, and was still unchanged after 17h. Refluxing the crude material for a further 2h in *o*-dichlorobenzene, caused some decomposition, but the only detectable compound present after this treatment was the enamine (294).

Refluxing for 2h in DMF gave a complex crude mixture which was not investigated further.



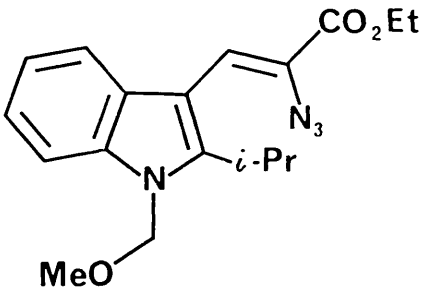
(293) (294)

(295)

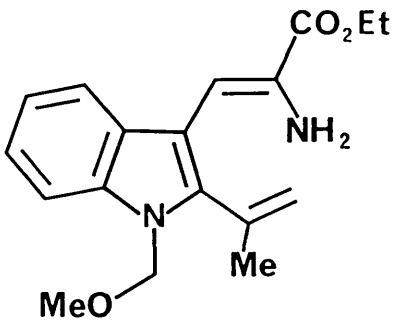
A sample of the enamine (294) prepared by heating the azide (293) in refluxing benzene for 3h was *N*-acetylated as described previously. The solid *N*-acetyl compound gave as expected, fully consistent micro-analytical and mass spectral data, but as before the melting point range was large (11°C), and the n.m.r. peak broadening effects already alluded to in section 4.3 were again observed.

Thermolysis of the 2-isopropyl azide (296) in benzene for 5h gave the enamine (297) which could be *N*-acetylated as before. The *N*-acetyl compound had similar physical properties to the *N*-acetyl enamines previously described.

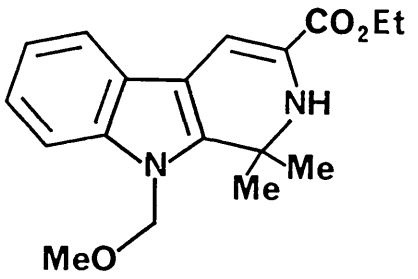
Thermolysis of the azide (296) in refluxing xylene resulted in the gradual formation of a compound which was assigned the dihydro-β-carboline structure (298).



(296)

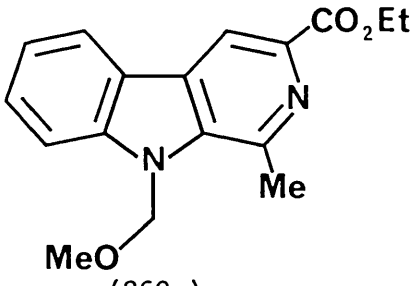


(297)



(298)

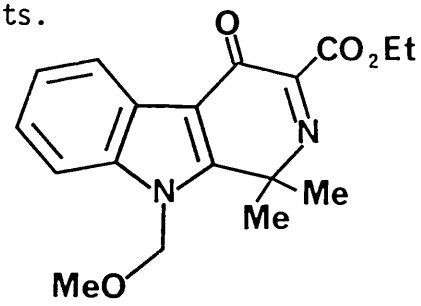
This structure was postulated on the basis of n.m.r. spectroscopy, although the compound could never be obtained completely pure. The spectrum consisted of, *inter alia*, a singlet at δ 1.61 (6H) and a singlet at δ 6.8 (1H). Prolonged heating of this compound in bromobenzene resulted in the formation of the β-carboline (269a), identical with an authentic sample, although the mode of demethylation is not known.



(269a)

Storage of the impure sample of (298) in a refrigerator in contact with air, for 10 weeks, resulted in its clean conversion to another compound having in its n.m.r. a singlet at δ 1.8 (6H) as well as ethyl

ester, *N*-methoxymethyl and four aromatic protons. There was however, no low field one proton singlet. Consideration of this and the other spectral data led to the postulation of structure (299), formed presumably by the same mode of oxidation by which hydroxy compound (292) is formed from (290). No azepinoindole was ever detected or isolated in any of these experiments.



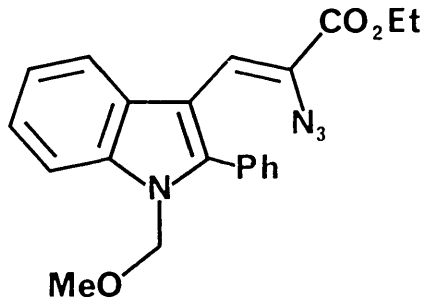
(299)

It is not easy to rationalise the difference in behaviour between the 2-ethyl and 2-*n*-propyl azides and their derived enamines on one hand, and the corresponding 2-cyclohexyl and 2-isopropyl compounds on the other, in the matter of azepinoindole formation. It is impossible to argue simple steric hindrance at the site of conjugate attack since this site in the 2-isopropenyl enamine (297) is surely considerably less hindered than the corresponding site in the 2-*n*-prop-2-enyl enamine (283), and yet no azepinoindole is formed by thermolysis of (282). Presumably some more subtle effect is in operation, but it has not proved possible to advance an explanation of the nature of this effect.

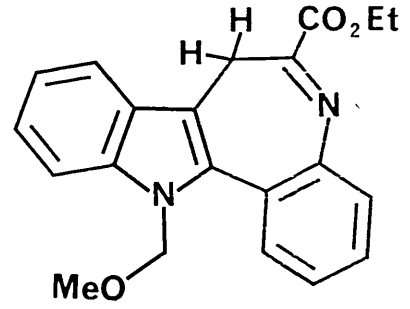
4.5 Thermolysis of the 2-phenylindolyl azidopropenoate

The azide (300) was thermolysed in refluxing xylene for 1h. This treatment resulted in the formation of one compound, which was obtained after chromatography and crystallization from ethanol/petrol as yellow prisms. It proved somewhat difficult to assign a structure based on spectroscopic data, and recourse was made to X-ray crystallography. Crystal data were obtained as follows: for $C_{21}H_{21}N_2O_3$, triclinic,

$\underline{a}$ = 8.371 (1), $\underline{b}$ = 10.274 (1), $\underline{c}$ = 11.948 (2)Å, α = 114.47 (1), β = 104.09 (1), γ = 90.38 (1)°, u = 900 Å^3, space group $P\bar{1}$, Z = 2, D_c = 1.29 g cm^{-3}. Data were collected on a Nicolet R3m diffractometer with Cu-K_α radiation. The structure was solved by direct methods and refined anisotropically to give R = 0.050 for 1725 independently observed reflections. The structure was thus determined to be (301) as shown in the computer generated drawing (Figure 3) reproduced in Appendix 3. A full list of bond angles and lengths is also included in Appendix 3.



(300)



(301)

This was in fact the product expected from thermolysis of (300) both intuitively and by analogy with the literature.[157] The difficulty in assigning its structure by spectroscopic means was due to the fact that in the n.m.r. spectrum of (301) no signal is observed corresponding to the two protons indicated. A two proton singlet had been expected, by analogy with compound (287). The reason for this somewhat strange effect is obscure.

4.6 Conclusion

The interesting and unexpected formation of azepino[4,5-b]indoles as well as the formation of the expected β-carbolines may be rationalized in the manner described in the foregoing chapter. The formation of azepino[4,5-b]indoles however is not general for all 2-alkyl indoles as has been demonstrated. The synthetic utility of this reaction is somewhat diminished by low yields in the preparation of the azidopropenoates, but since this is the only route to these compounds, as yet reported, comparison with other preparations is impossible.

PART 3 : EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES

Petrol refers to the light petroleum fraction boiling in the range 40-60°C, and was redistilled prior to use. Ether was dried by distillation from sodium or calcium hydride; THF and DME were dried by distillation from potassium-benzophenone; DMF, DMSO and HMPA were dried by distillation from calcium hydride, and methylene chloride was dried by distillation from phosphorus pentoxide. Benzene, toluene, xylene, *o*-dichlorobenzene and bromobenzene which were used as thermolysis solvents, were distilled prior to use. Pyridine, diethylamine and triethylamine were distilled from calcium hydride. Dried solvents were stored in septum-sealed vessels under nitrogen.

Chromatography was carried out at medium pressure on Merck 60H silica gel using hand-bellows to apply the pressure to the column-head. Samples were normally applied as a dry, pre-adsorbed mixture with a small amount of adsorbent. Reactions were monitored by t.l.c. using Merck Kieselgel 60 F_{254} aluminium backed silica gel plates cut to the appropriate size. Plates were visualised under u.v. light at 254 or 306 nm. P.l.c. employed glass backed plates (20 × 20 or 20 × 40 cm) coated to a thickness of 2 mm with Merck Kieselgel Type 60 GF_{254}.

I.r. spectra were recorded in the range 4000 - 600 cm^{-1} using a Perkin Elmer 257 grating spectrophotometer. Solid samples were run as Nujol mulls. Liquids and gums were run either as thin films or in chloroform solution. U.v. spectra were recorded on a Pye-Unicam SP 800 recording spectrophotometer in the range 200 - 450 nm, and points of inflexion are abbreviated (sh). Proton n.m.r. spectra were recorded using Varian EM 360 (60 MHz), Perkin Elmer R 32 (90 MHz) or Bruker WM 250 (250 MHz) instruments. All spectra included tetramethylsilane

(TMS) as an internal standard; most of those recorded at 90 MHz employed a heteronuclear lock (TMS), while all of those run at 250 MHz employed a homonuclear lock (deuterium of the solvent). Signals are described as singlets (s), doublets (d), triplets (t), multiplets (m), broad (br), double doublets (dd), etc.

Broad band decoupled ^{13}C n.m.r. spectra were recorded using a Bruker WM 250 spectrometer operating at 62.9 MHz. Mass spectra were recorded at low resolution using A.E.I. MS 12 and VG Micromass 7070B instruments, the latter being used also for high resolution determinations. Samples were mostly recorded at 70 eV using a direct insertion probe.

Photolyses were carried out in a Rayonet photochemical reactor using lamps of 254 or 300 nm. Solutions were contained in quartz vessels and a thin stream of nitrogen was passed through the solutions for the duration of the photolyses.

Melting points were determined on a Kofler hot stage apparatus and are uncorrected.

EXPERIMENTAL FOR CHAPTER TWO

1. Synthesis of the indoles

(i) This was carried out by a standard literature procedure,[69] see Table 1.

(ii) Attempted synthesis of 2-phenethylindole

N-Hydrocinnamoyl-*o*-toluidine (5g, 20.92 mmol) and sodamide (3g, 76.92 mmol, 3.68 equiv.) were mixed together intimately as a paste with ether. The ether was distilled off using gentle heating, and then the mixture was heated to 230°C on a fusible metal bath and maintained there for 1h, with occasional stirring using a long metal spatula. After cooling, aqueous ethanol was added and the resulting slurry was poured into water (200 ml) and extracted with ether. The combined dried ($MgSO_4$) ethereal extracts were evaporated to give a dark oil which was distilled under reduced pressure. The early fractions contained *o*-toluidine, and were discarded. The later fractions contained one compound which was further purified by short path distillation and crystallization from petrol, giving as large colourless prisms, 1-(2-methylphenyl)-1-phenylethane (131) (1.1g, 27%), m.p. 37-8°C (lit.,[70] 40-1°C);

ν_{max} (thin film): 2830 - 3100 cm^{-1} (CH) cm^{-1};

δ_H (250 MHz; $CDCl_3$): 1.54 (3H, d, *J* 7.3 Hz, $CHCH_3$), 2.14 (3H, s, Ar-*Me*), 4.23 (1H, q, *J* 7.3 Hz, $CHCH_3$), 7.0 - 7.25 (9H, m, Ar-H);

$\delta_{^{13}C}$ (62.9 MHz; $CDCl_3$): 19.58 (45%), 22.00 (59), 41.05 (55), 125.74 (51), 126.07 (71), 126.65 (50), 127.60 (88), 128.24 (100), 130.42 (41), 135.86 (17), 143.80 (12), 146.18 (20);

m/z: 196 (M^+, 44%), 181 (100), 166 (19), 165 (18).

2. Formylation of the indoles

This was carried out by the method of James and Snyder,[71] and the following compounds were prepared:

(i) Indole-3-carbaldehyde (93%), m.p. 193-5°C (lit.,[71] 194-6°C).

(ii) 2-Methylindole-3-carbaldehyde (96%), m.p. 199-202°C (lit.,[79] 202-3°C).

(iii) *2-Ethylindole-3-carbaldehyde* (70%), m.p. 167-71°C. (Found: C, 76.47; H, 6.43; N, 8.10. $C_{11}H_{11}NO$ requires C, 76.28; H, 6.40; N, 8.09%);

ν_{max} (nujol): 3185 (NH), 1639, 1633 and 1590 cm^{-1};

δ_H(90 MHz; d_6-DMSO): 1.28 (3H, t, *J* 8 Hz, CH_2CH_3), 3.02 (2H, q, *J* 8 Hz, CH_2CH_3), 7.10 (2H, m, 5-H and 6-H), 7.33 (1H, m, 4-H or 7-H), 7.98 (1H, m, 7-H or 4-H), 10.02 (1H, s, CHO), NH not observed;

m/z: 173 (M^+, 100%), 158 (35), 144 (35), 130 (13), 77 (10).

(iv) *2-n-propylindole-3-carbaldehyde* (75%), m.p. 154-55.5°C. (Found: C, 76.71; H, 6.98; N, 7.44. $C_{12}H_{13}NO$ requires C, 76.97; H, 7.00; N, 7.48%);

ν_{max} (nujol): 3180 (NH), 1620, 1580 cm^{-1};

δ_H (90 MHz; d_6-DMSO): 1.0 (3H, t, *J* 7.5 Hz, $CH_2CH_2CH_3$), 1.83 (2H, sextet, *J* 7.5 Hz, $CH_2CH_2CH_3$), 3.10 (2H, t, *J* 7.5 Hz, $CH_2CH_2CH_3$), 7.20 (2H, m, 5-H and 6-H), 7.46 (1H, m, 4-H or 7-H), 8.13 (1H, m, 7-H or 4-H), 10.14 (1H, s, CHO), NH not observed;

m/z: 187 (M^+, 100%), 172 (91), 158 (51), 144 (26), 130 (26).

(v) *2-isopropylindole-3-carbaldehyde* (88%), m.p. 179-80°C. (Found: C, 76.78; H, 6.97; N, 7.46. $C_{12}H_{13}NO$ requires C, 76.97; H, 7.00; N, 7.48%);

ν_{max} (nujol): 3200 (NH), 1634 and 1590 cm^{-1};

δ_H (90 MHz; d_6-DMSO/$CDCl_3$): 1.44 (6H, d, *J* 7 Hz, $CH(CH_3)_2$), 3.77 (1H, septet, *J* 7 Hz, $CH(CH_3)_2$), 7.25 (2H, m, 5-H, and 6-H), 7.44 (1H, m, 4-H or 7-H), 8.26 (1H, m, 7-H or 4-H), 10.27 (1H, s, CHO), 11.33 (1H, br s, NH);

(vi) *2-cyclohexylindole-3-carbaldehyde* (79%), m.p. 202-5°C. (Found: C, 79.23; H, 7.54; N, 6.19. $C_{15}H_{17}NO$ requires C, 79.26; H, 7.54; N, 6.16%);

ν_{max} (nujol): 3180 (NH), 1622 and 1582 cm^{-1};

δ_H (90 MHz; d_6-DMSO): 1.2 - 2.1 (10H, br m, $-(CH_2)_5-$), 7.18 (2H, m, 5-H and 6-H), 7.43 (1H, m, 4-H or 7-H), 8.08 (1H, m, 7-H or 4-H), 10.18 (1H, s, CHO), 11.83 (1H, br s, NH);

m/z: 227 (M^+, 100%), 210 (27).

(vii) 2-phenylindole-3-carbaldehyde (97%), m.p. 256 - 58.5°C (lit.,[80] 250 - 55°C).

(viii) *2-methyl-5-nitroindole-3-carbaldehyde*

This compound was prepared by Vilsmeier formylation of 2-methyl-5-nitroindole (98%), m.p. 306-11°C dec. (Found: C, 58.77; H, 3.87; N, 13.70. $C_{10}H_8N_2O_3$ requires C, 58.82; H, 3.95; N, 13.72%);

ν_{max} (nujol): 3110 (NH), 1631, 1587, 1340 cm^{-1};

δ_H (90 MHz; d_6-DMSO): 2.71 (3H, s, 2-Me), 7.46 (1H, d, *J* 9 Hz, 7-H), 7.97 (1H, dd, *J* 9 and 3 Hz, 6-H), 8.75 (1H, d, *J* 3 Hz, 4-H), 10.18 (1H, s, CHO), NH not observed;

m/z: 204 (M^+, 100%), 158 (39), 157 (43), 103 (48).

3. *N*-protection of the indole-3-carbaldehydes

(i) 1-methyl and benzylindole-3-carbaldehydes.

General Procedure

The indole-3-carbaldehyde was refluxed for 17-24h in acetone (250 ml per 5g) with anhydrous potassium carbonate (10 equiv.) and either methyl iodide (5-10 equiv.) or benzyl bromide (1.1 equiv.). Filtration and evaporation gave the required *N*-alkylated compounds, which were recrystallized from ethanol.

a) 1-methylindole-3-carbaldehyde (65%), m.p. 65-8°C (lit.,[72] 68-9°C).

b) *1-benzylindole-3-carbaldehyde* (79%), m.p. 108-9°C.

ν_{max} (nujol): 1664 (C = O) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 5.22 (2H, s, CH_2Ph), 7.0 - 7.35 (8H, m, 5-H, 6-H, 4-H or 7-H and Ph), 7.56 (1H, s, 2-H), 8.28 (1H, m, 7-H or 4-H), 9.84 (1H, s, CHO);

m/z: 235 (M^+, 49), 91 (100).

c) *1-benzyl-2-methylindole-3-carbaldehyde* (76%), m.p. 135°C. (Found: C, 82.00; H, 6.22; N, 5.68. $C_{17}H_{15}NO$ requires C, 81.90; H, 6.06; N, 5.62%);

ν_{max} (nujol): 1645 (C = O), 1585 cm^{-1};

δ_H (60 MHz; $CDCl_3$): 2.63 (3H, s, 2-Me), 5.33 (2H, s, CH_2Ph), 6.83 - 7.5 (8H, m, 5-H, 6-H, 7-H and Ph), 8.40 (1H, m, 7-H), 10.25 (1H, s, CHO);

m/z: 249 (M^+), 91.

d) *1-benzyl-2-methyl-5-nitroindole-3-carbaldehyde* (61%), m.p. 182-4°C. (Found: C, 69.33; H, 4.74; N, 9.56. $C_{17}H_{14}N_2O_3$ requires C, 69.38; H, 4.79; N, 9.52%);

ν_{max} (nujol): 1655 (C=O), 1580, 1505, 1415, 1395, 1332, 1300 cm^{-1};

δ_H (90 MHz; d_6-DMSO): 2.77 (3H, s, 2-Me), 5.65 (2H, s, CH_2Ph), 7.02 - 7.41 (5H, m, Ph), 7.74 (1H, d, *J* 9 Hz, 7-H), 8.09 (1H, dd, *J* 9 and 3 Hz, 6-H), 8.93 (1H, d, *J* 3 Hz, 4-H), 10.26 (1H, s, CHO);

m/z: 294 (M^+, 100%), 278 (4), 264 (8), 248 (4).

(ii) 1-acetylindole-3-carbaldehyde

This compound was prepared by a literature procedure, m.p. 165-66°C (lit.,[83] 161-64°C).

(iii) 1-methoxymethylindolyl-3-carbaldehydes[73]

General Procedure

The indole-3-carbaldehyde (5-50 mmol) was added as a solution in DMF, to a suspension of sodium hydride (1.5 - 2 equiv.) in DMF, at room temperature. After stirring for *ca.* 0.5h, chloromethyl methyl ether (1.1 - 1.3 equiv.) was added, and stirring continued for 4-20h. The solution was then poured into water and extracted three times with ether or ethyl acetate. The combined organic layers were washed three times with water, dried ($MgSO_4$) and evaporated. The resulting crude *N*-methoxymethyl compounds were recrystallized from ethanol or ether/petrol. The following compounds were prepared:

a) *1-methoxymethylindole-3-carbaldehyde* (86%), m.p. 77-8°C. (Found: C, 69.81; H, 5.86; N, 7.38. $C_{11}H_{11}NO_2$ requires C, 69.82; H, 5.86; N, 7.40%);

ν_{max} (nujol): 1640 (C = O) and 1527 cm^{-1};

δ_H (90 MHz; $CDCl_3$): 3.27 (3H, s, CH_2OMe), 5.48 (2H, s, CH_2OMe), 7.25 - 7.6 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.79 (1H, s, 2-H), 8.31 (1H, m, 7-H or 4-H), 10.00 (1H, s, CHO);

m/z: 189 (M^+, 100%), 158 (52).

b) *1-methoxymethyl-2-methylindole-3-carbaldehyde* (78%), m.p. 87-90°C. (Found: C, 70.98; H, 6.41; N, 6.86. $C_{12}H_{13}NO_2$ requires C, 70.92; H, 6.45; N, 6.89%);

ν_{max} (nujol): 1640 (C = O), 1426 cm^{-1};

δ_H (90 MHz; $CDCl_3$): 2.64 (3H, s, 2-Me), 3.27 (3H, s, CH_2OMe), 5.40 (2H, s, CH_2OMe), 7.20 - 7.50 (3H, m, 5-H, 6-H and 4-H or 7-H), 8.25 (1H, m, 7-H or 4-H), 10.10 (1H, s, CHO);

m/z: 203 (M^+, 100%), 172 (50).

c) *2-ethyl-1-methoxymethylindole-3-carbaldehyde* (82%), m.p. 72-4°C. (Found: C, 71.96; H, 7.01; N, 6.44. $C_{13}H_{15}NO_2$ requires C, 71.87; H, 6.96; N, 6.45%);

ν_{max} (nujol): 1635 (C = O), 1605, 1425 cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.34 (3H, t, *J* 7.5 Hz, CH_2CH_3), 3.17 (2H, q, *J* 7.5 Hz, CH_2CH_3), 3.32 (3H, s, CH_2OMe), 5.50 (2H, s CH_2OMe), 7.25 - 7.55 (3H, m, 5-H, 6-H and 4-H or 7-H), 8.30 (1H, m, 7-H or 4-H), 10.24 (1H, s, CHO);

m/z: 217 (M^+, 100%), 202 (38), 186 (46).

d) *1-methoxymethyl-2-n-propylindole-3-carbaldehyde* (73%), m.p. 49-51°C. (Found: C, 72.46; H, 7.37; N, 5.99. $C_{14}H_{17}NO_2$ requires C, 72.70; H, 7.41; N, 6.06%);

ν_{max} (nujol): 1646 (C = O), 1530 cm^{-1};

δ_H (90 MHz, $CDCl_3$): 1.0 (3H, t, *J* 7.5 Hz, $CH_2CH_2CH_3$), 1.72 (2H, sextet, *J* 7.5 Hz, $CH_2CH_2CH_3$), 3.08 (3H, t, *J* 7.5 Hz, $CH_2CH_2CH_3$), 3.28 (3H, s, CH_2OMe), 5.42 (2H, s, CH_2OMe), 7.20 - 7.50 (3H, m, 5-H, 6-H and 4-H or 7-H), 8.23 (1H, m, 7-H or 4-H), 10.20 (1H, s, CHO).

m/z: 231 (M^+, 100%), 216 (62), 200 (38).

e) *2-isopropyl-1-methoxymethylindole-3-carbaldehyde* (75%), m.p. 104-7°C. (Found: C, 72.69; H, 7.49; N, 6.02. $C_{14}H_{17}NO_2$ requires C, 72.70; H, 7.41; N, 6.06%);

ν_{max} (nujol): 1639 (C = O), 1606 cm^{-1};

δ_H (90 MHz, $CDCl_3$): 1.54 (6H, d, *J* 7 Hz, $CH(CH_3)_2$), 3.32 (3H, s, CH_2OMe), 3.63 (1H, septet, *J* 7 Hz, $CH(CH_3)_2$), 5.56 (2H, s, CH_2OMe), 7.2 - 7.55 (3H, m, 5-H, 6-H and 4-H or 7-H), 8.39 (1H, m, 7-H or 4-H), 10.53 (1H, s, CHO);

m/z: 231 (M^+, 100%), 216 (70), 200 (45), 186 (23).

f) *2-cyclohexyl-1-methoxymethylindole-3-carbaldehyde* (72%), m.p. 77-80°C. (Found: C, 75.43; H, 7.85; N, 5.24. $C_{17}H_{21}NO_2$ requires C, 75.24; H, 7.80; N, 5.16%);

ν_{max} (nujol): 1640 (C = O), 1515 cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.20 - 1.60 and 1.60 - 2.10 (10H, br m, $-(CH_2)_5-$), 3.20 (1H, br m, $CH(CH_2)_5$), 3.29 (3H, s, CH_2OMe), 5.54 (2H, s, CH_2OMe), 7.20 - 7.55 (3H, m, 5-H, 6-H and 4-H or 7-H), 8.40 (1H, m, 7-H or 4-H), 10.53 (1H, s, CHO);

m/z: 271 (M^+, 100%), 256 (36).

g) *1-methoxymethyl-2-phenylindole-3-carbaldehyde* (68%), m.p. 109.5 - 110°C. (Found: C, 76.82; H, 5.72; N, 5.25. $C_{17}H_{15}NO_2$ requires C, 76.96; H, 5.70; N, 5.28%);

ν_{max} (nujol): 1647 (C=O), 1480 cm^{-1};

δ_H (90 MHz; $CDCl_3$): 3.21 (3H, s, CH_2OMe), 5.33 (2H, s, CH_2OMe), 7.20 - 7.60 (8H, m, 5-H, 6-H, 4-H or 7-H and 2-Ph), 8.40 (1H, m, 7-H or 4-H), 9.70 (1H, s, CHO);

m/z: 265 (M^+, 100%), 165 (53).

4. Condensation of indole-3-carbaldehydes with alkyl azidoacetates

General Procedure[67,81]

The aldehyde was dissolved in ethyl or methyl azidoacetate, using the least amount of THF necessary to effect complete solution. This was then added over *ca.* 1h to a solution of sodium ethoxide or methoxide made by dissolving sodium metal (4 equiv.) in ethanol or methanol, (300 mg/10 ml). During the addition, the mixture was kept at between -15 and -5°C, and after the completion of addition it was maintained there for *ca.* 6h, after which time it was stirred at 3°C for a further 10-15h. The reaction mixture was then warmed to room temperature over 1h, t.l.c. at this juncture normally showing the presence of starting material (as a slower running spot) and product (as a faster running yellow spot). The viscous reddish reaction mixture was then poured into saturated ammonium chloride solution and extracted thoroughly with ether. The ethereal extracts were washed with water, dried ($MgSO_4$) and evaporated. The crude mixtures were then separated by column chromatography on silica gel. Normally, gradient elution was employed commencing with light petrol, and increasing the polarity with ether as required to

effect clean separation. The following reactions were carried out:

(i) Attempted condensation of 2-methylindole-3-carbaldehyde with ethyl azidoacetate

The aldehyde (1g, 6.28 mmol) was dissolved in ethyl azidoacetate (3.24g, 25.16 mmol, 4 equiv.) and THF (15 ml), and this solution added to a solution of sodium (0.58g, 25.16 mmol, 4 equiv.) in ethanol (12 ml) as described above. The aldehyde appeared to crystallize out of solution, and only starting material could be detected by t.l.c. and n.m.r. of the crude reaction product after work-up.

(ii) Condensation of 1-methylindole-3-carbaldehyde with ethyl azidoacetate

The aldehyde (1g, 6.28 mmol) was dissolved in ethyl azidoacetate (3.24g, 25.16 mmol, 4 equiv.) and added to a solution of sodium (0.58g, 25.16 mmol, 4 equiv.) in ethanol (12 ml). The reaction was carried out as described above, the temperature of addition being -15°C. Work-up and chromatography gave *ethyl 2-azido-3-(1-methylindol-3-yl)propenoate* (175a) (1.162g, 68%), m.p. 100-102°C (from ether/petrol);

ν_{max} (nujol): 2110 and 1990 (N_3), 1693 (C = O) and 1611 (C = C) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.39 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 3.82 (3H, s, N-Me), 4.39 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 7.33 (4H, m, 5-H, 6-H, 4-H or 7-H and $CH = C(N_3)\varepsilon$), 7.78 (1H, m, 7-H or 4-H), 8.04 (1H, s, 2-H);

m/z: 270 (M^+, 100%), 242 (6), 196 (8).

(iii) Condensation of 1-benzylindole-3-carbaldehyde with ethyl azidoacetate

The aldehyde (1g, 4.26 mmol) was dissolved in ethyl azidoacetate (2.20g, 17.02 mmol, 4 equiv.) and THF (3 ml), and added at -15°C to a

solution of sodium (0.391g, 17.02 mmol, 4 equiv.) in ethanol (10 ml). The remainder of the process was as described above, chromatography of the crude product giving *ethyl 2-azido-3-(1-benzylindol-3-yl)propenoate* (175b) (0.455g, 31%), m.p. 85-9^{o}C dec. (from ether/petrol);

ν_{max} (nujol): 2110 cm^{-1} (N_3), 1691 (C = O), 1650 and 1615 (C = C) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.39 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 4.40 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.40 (2H, s, CH_2Ph), 7.30 (9H, m, 5-H, 6-H, 4-H or 7-H, $CH = C(N_3)\varepsilon$ and Ph), 7.83 (1H, m, 7-H or 4-H), 8.18 (1H, s, 2-H);

m/z: 346 (M^+, 3%), 318 (22), 272 (15), 245 (28), 91 (100).

(iv) Condensation of 1-benzyl-2-methylindole-3-carbaldehyde with ethyl azidoacetate

The aldehyde (1g, 4.02 mmol) was dissolved in ethyl azidoacetate (5.18g, 40.20 mmol, 10 equiv.) and THF (7 ml). This solution was added to a solution of sodium (0.40g, 16.08 mmol, 4 equiv.) in ethanol (11 ml). The reaction was carried out as described previously, chromatography of the crude reaction product giving *ethyl 2-azido-3-(1-benzyl-2-methylindol-3-yl)propenoate* (264b), which was recrystallized from ether/petrol (0.222g, 15%), m.p. 90-92^{o}C dec.;

ν_{max} (nujol): 2104 (N_3), 1702 (C = O) and 1615 (C = C) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.39 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 2.41 (3H, s, 2-Me), 4.40 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.37 (2H, s, CH_2Ph), 6.95 - 7.30 (9H, m, 5-H, 6-H, 4-H or 7-H, $CH = C(N_3)\varepsilon$ and Ph), 8.05 (1H, m, 7-H or 4-H);

m/z: 334 ($M^+ - 26$, 50%), 330 ($M^+ - 30$, 18), 258 (45), 249 (30), 243 (17), 234 (9), 169 (17), 91 (100).

(v) Condensation of 1-methoxymethylindole-3-carbaldehyde with ethyl azidoacetate

The aldehyde (1g, 5.29 mmol) was dissolved in ethyl azidoacetate (2.73g, 21.16 mmol, 4 equiv.), and added to a solution of sodium (0.49g, 21.16 mmol, 4 equiv.) in ethanol (14 ml) at -20 - -15°C. The crude product was chromatographed yielding *ethyl 2-azido-3-(1-methoxymethyl-indol-3-yl)propenoate* (175c) (1.29g, 81%), m.p. 90 - 2.5°C dec. (from ether/petrol);

ν_{max} (nujol): 2120 (N_3), 1690 (C = O) and 1611 (C = C) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.40 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 3.27 (3H, s, CH_2OMe), 4.40 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.51 (2H, s, CH_2OMe), 7.25 - 7.40 (2H, m, 5-H and 6-H), 7.32 (1H, s, $CH=C(N_3)\varepsilon$), 7.55 (1H, m, 4-H or 7-H), 7.79 (1H, m, 7-H or 4-H), 8.16 (1H, s, 2-H);

m/z: 300 (M^+, 0.1%), 272 (M^+-28, 100), 241 (10), 227 (29), 199 (26), 196 (21), 195 (40), 181 (16), 168 (43), 153 (16), 140 (16), 127 (18).

(vi) Condensation of 1-methoxymethyl-2-methylindole-3-carbaldehyde with ethyl azidoacetate

The aldehyde (4.49g, 22.11 mmol) was dissolved in ethyl azidoacetate (11.41g, 88.44 mmol, 4 equiv.), and added to a solution of sodium (2.035g, 88.44 mmol, 4 equiv.) in ethanol (50 ml) at between -12 and -5°C. Chromatography of the crude product gave *ethyl 2-azido-3-(1-methoxy-methyl-2-methylindol-3-yl)propenoate* (264a) (2.52g, 36%), m.p. 90°C dec.; (Found: C, 61.21; H, 5.77; N, 17.69. $C_{16}H_{18}N_4O_3$ requires C, 61.13; H, 5.77; N, 17.82%);

ν_{max} (nujol): 2110 (N_3), 1700 (C = O) and 1616 (C = C) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.40 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 2.49 (3H, s, 2-Me), 3.21 (3H, s, CH_2OMe), 4.33 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.37 (2H, s, CH_2OMe), 7.07 - 7.40 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.17 (1H, s, $CH=C(N_3)\varepsilon$), 7.80 (1H, m, 7-H or 4-H).

(vii) Condensation of 2-ethyl-1-methoxymethylindole-3-carbaldehyde with ethyl azidoacetate

The aldehyde (5.1g, 23.50 mmol) was dissolved in ethyl azidoacetate (12.2g, 94.66 mmol, 4 equiv.) and added to a cooled solution of sodium (2.16g, 94.66 mmol, 4 equiv.) in ethanol (72 ml). Chromatography of the crude product gave *ethyl 2-azido-3-(2-ethyl-1-methoxymethylindol-3-yl)propenoate* (268) (1.87g, 24%) as a yellow oil;

ν_{max} (thin film): 2105 (N_3), 1700 (C=O) and 1615 (C=C) cm^{-1};

δ_H (90 MHz, $CDCl_3$): 1.26 (3H, t, *J* 7.7 Hz, 2-CH_2CH_3), 1.40 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 2.96 (2H, q, *J* 7.7 Hz, 2-CH_2CH_3), 3.30 (3H, s, CH_2OMe), 4.42 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.50 (2H, s, CH_2OMe), 7.20 - 7.50 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.28 (1H, s, $CH=C(N_3)\varepsilon$), 8.02 (1H, m, 7-H or 4-H).

(viii) Condensation of 1-methoxymethyl-2-*n*-propylindole-3-carbaldehyde with ethyl azidoacetate

The aldehyde (2.34g, 10.13 mmol) was dissolved in ethyl azidoacetate (5.23g, 40.54 mmol, 4 equiv.) and added to a cooled solution of sodium (0.93g, 40.54 mmol, 4 equiv.) in ethanol (30 ml). Chromatography of the crude product gave *ethyl 2-azido-3-(1-methoxymethyl-2-n-propylindol-3-yl)propenoate* (282) (900 mg, 26%) as a yellow oil;

ν_{max} (thin film): 2106 (N_3), 1702 (C=O) and 1613 (C=C) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 0.99 (3H, t, *J* 7.5 Hz, $CH_2CH_2CH_3$), 1.40 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 1.66 (2H, sextet, *J* 7.5 Hz, $CH_2CH_2CH_3$), 2.90 (2H, t, *J* 7.5 Hz, $CH_2CH_2CH_3$), 3.28 (3H, s, CH_2OMe), 4.42 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.47 (2H, s, CH_2OMe), 7.20 - 7.50 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.30 (1H, s, $CH=C(N_3)\varepsilon$), 8.04 (1H, m, 7-H or 4-H).

(ix) Condensation of 2-isopropyl-1-methoxymethylindole-3-carbaldehyde with ethyl azidoacetate

The aldehyde (5g, 21.64 mmol) was dissolved in ethyl azidoacetate (11.17g, 86.58 mmol, 4 equiv.) and added to a cooled solution of sodium (2.0g, 86.58 mmol, 4 equiv.) in ethanol (60 ml). Chromatography of the crude product yielded *ethyl 2-azido-3-(2-isopropyl-1-methoxymethylindol-3-yl)propenoate* (296) (0.43g, 6%) as an oil;

ν_{max} (thin film): 2120 cm^{-1} (N_3), 1710 (C=O) and 1615 (C=C) cm^{-1};

δ_H (90 MHz, $CDCl_3$): 1.39 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 1.43 (6H, d, *J* 7 Hz, $CH(CH_3)_2$), 3.28 (3H, s, CH_2OMe), 3.41 (1H, septet, *J* 7 Hz, $CH(CH_3)_2$), 4.41 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.52 (2H, s, CH_2OMe), 7.20 - 7.55 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.46 (1H, s, $CH=C(N_3)\varepsilon$), 7.79 (1H, m, 7-H or 4-H).

(x) Condensation of 1-methoxymethyl-2-cyclohexylindole-3-carbaldehyde with ethyl azidoacetate

The aldehyde (2.56g, 9.44 mmol) was dissolved in ethyl azidoacetate (4.87g, 37.75 mmol, 4 equiv.) and added to a cooled solution of sodium (0.87g, 37.75 mmol, 4 equiv.). Chromatography of the crude product yielded *ethyl 2-azido-3-(2-cyclohexyl-1-methoxymethylindol-3-yl)propenoate* (293) (0.146g, 4%) as an oil;

ν_{max} ($CHCl_3$): 2105 (N_3), 1697 (C = O), 1605 (C = C) cm^{-1};

δ_H (250 MHz; $CDCl_3$): 1.43 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 1.7 - 2.0 (10H, br m, $-(CH_2)_5-$), 3.0 (1H, br m, $CH(CH_2)_5$), 3.29 (3H, s, CH_2OMe), 4.41 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.50 (2H, s, CH_2OMe), 7.22 (2H, m, 5-H and 6-H), 7.42 (1H, m, 4-H or 7-H), 7.48 (1H, s, $CH = C(N_3)\varepsilon$), 7.74 (1H, m, 7-H or 4-H).

(xi) Condensation of 1-methoxymethyl-2-phenylindole-3-carbaldehyde with ethyl azidoacetate

The aldehyde (1.3g, 4.91 mmol) was dissolved in ethyl azidoacetate (2.53g, 19.61 mmol, 4 equiv.) and added to a cooled solution of sodium (0.45g, 19.61 mmol, 4 equiv.). The crude product was washed with petrol which dissolved the azide leaving unreacted starting material (0.947g, 73% recovery). Chromatography of the petrol washings gave *ethyl 2-azido-3-(1-methoxymethyl-2-phenylindol-3-yl)propenoate* (300) (0.022g, 1.2%) as yellow prisms;

ν_{max} (nujol): 2100 (N_3), 1700 (C = O), 1617 (C = C) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.26 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 3.18 (3H, s, CH_2OMe), 4.23 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.30 (2H, s, CH_2OMe), 6.96 (1H, s, $CH = C(N_3)\varepsilon$), 7.16 - 7.54 (8H, m, 5-H, 6-H, 4-H or 7-H and Ph), 8.04 (1H, m, 7-H or 4-H).

(xii) Condensation of 1-methoxymethylindole-3-carbaldehyde with methyl azidoacetate

The aldehyde (6.08g, 32.17 mmol) was dissolved in methyl azidoacetate (14.80g, 128.7 mmol, 4 equiv.) and added to a cooled solution of sodium (2.96g, 128.7 mmol, 4 equiv.) in methanol (100 ml). Chromatography of the crude product gave *methyl 2-azido-3-(1-methoxymethylindol-3-yl)*

propenoate (175d) (5.5g, 60%) yellow needles from methanol, m.p. 113.5 - 6°C. (Found: C, 58.54; H, 4.86; N, 19.46. $C_{14}H_{14}N_4O_3$ requires C, 58.74; H, 4.93; N, 19.57%);

ν_{max} (nujol): 2140 (N_3), 1697 (C = O), 1618 (C = C), 1609 cm^{-1};

δ_H (90 MHz, $CDCl_3$): 3.30 (3H, s, CH_2OMe), 3.92 (3H, s, CO_2Me), 5.48 (2H, 2, CH_2OMe), 7.2 - 7.35 (2H, m, 5-H and 6-H), 7.27 (1H, s, $CH = C(N_3)\varepsilon$), 7.48 (1H, m, 4-H or 7-H), 7.73 (1H, m, 7-H or 4-H), 8.10 (1H, s, 2-H);

m/z: 286 (M^+, 2%), 258 (100), 226 (27), 196 (28), 195 (55), 181 (55), 168 (24).

5. Attempted alternative azidopropenoate syntheses

(i) Wadsworth-Emmons reaction of triethylbromophosphonate with 1-methoxymethylindole-3-carbaldehyde[88]

Triethyl bromophosphonate (4.33g, 14.29 mmol, 1.32 equiv.) was added dropwise over 10 min. to a DME suspension of sodium hydride (50% suspension in paraffin oil, 1.02g, 21.25 mmol, 1.96 equiv.) at room temperature. The sodium hydride was de-oiled prior to suspension in DME, by washing with petrol. 1-Methoxymethylindole-3-carbaldehyde (2.05g, 10.85 mmol), in DME solution was added, and the mixture was stirred at room temperature under a nitrogen atmosphere for 20h. T.l.c. after this time showed the formation of a product running considerably faster than the aldehyde, and also some unreacted starting material. Work-up was effected by pouring into water, extraction with ether (3 times), washing and drying ($MgSO_4$) of the combined ethereal layers and evaporation. Silica gel chromatography of the resulting brown gum, gave an almost colourless gum (1.74g, 47%) consisting chiefly of the expected (*Z*)-isomer and a minor amount of the (*E*)-isomer (*ca.* 20% by n.m.r.). Crystallization from

petrol gave the pure *(Z)-ethyl 2-bromo-3-(1-methoxymethylindol-3-yl) propenoate* (143a) as colourless prisms, m.p. 79-80°C. (Found: C, 53.17; H, 4.76; N, 4.07; Br, 23.60. $C_{15}H_{16}BrNO_3$ requires C, 53.27; H, 4.77; N, 4.14; Br, 23.63%);

ν_{max} (nujol): 1700 (C=O), 1610 sh, 1600, 1510, 730 cm^{-1};

δ_H (90 MHz, $CDCl_3$): 1.37 (3H, t, *J* 7.5 Hz, $CO_2CH_2CH_3$), 3.26 (3H, s, CH_2OMe), 4.32 (2H, q, *J* 7.5 Hz, $CO_2CH_2CH_3$), 5.48 (2H, s, CH_2OMe), 7.24 (2H, m, 5-H and 6-H), 7.49 (1H, m, 4-H or 7-H), 7.71 (1H, m, 7-H or 4-H), 8.38 (1H, s, $CH=C(Br)\varepsilon$), 8.49 (1H, s, 2-H);

m/z: 339 and 337 (M^+, 100%), 308 and 306 (21).

The other fraction from chromatography consisted of recovered 1-methoxymethylindole-3-carbaldehyde (0.77g, 38% recovery).

(ii) Attempted Wadsworth-Emmons reaction of triethyl bromophosphonate with 1-methoxymethyl-2-methylindole-3-carbaldehyde[88]

Triethyl bromophosphonate (0.746g, 2.46 mmol) was added dropwise over 10 minutes to a DME suspension of sodium hydride (50% suspension in paraffin oil, 0.125g, 2.60 mmol, 1.06 equiv.) at room temperature. The sodium hydride was de-oiled as described previously. 1-Methoxymethyl-2-methylindole-3-carbaldehyde (0.50g, 2.46 mmol) was added as a DME solution. The mixture was stirred at room temperature under an atmosphere of nitrogen for 3h, after which time no reaction was indicated by t.l.c.. The mixture was refluxed for 0.5h, but t.l.c. still did not show any product formation. The mixture was partitioned between water and ether and the ethereal layer was washed, dried ($MgSO_4$) and evaporated. N.m.r. of the resulting gum showed it to consist essentially of 1-methoxymethyl-2-methylindole-3-carbaldehyde.

(iii) Attempts to react the bromopropenoate (143a) with sodium azide

a) The bromopropenoate (143a) (0.50g, 1.48 mmol) was stirred in DMSO (3 ml) with sodium azide (0.128g, 1.97 mmol, 1.33 equiv.) for 24h at room temperature. After this time no reaction was indicated by i.r. examination of a small aliquot which was removed from the reaction mixture and worked up. The mixture was then heated to 60°C for a further 24h and a similar examination after this period still did not show the presence of any new compound. Thus the mixture was heated to 120°C for 48h. Spectroscopic examination of the crude mixture at this juncture showed only complex decomposition products, and the material was discarded.

b) The bromopropenoate (143a) (0.215g, 0.64 mmol) was treated with sodium azide (0.124g, 1.91 mmol, 3 equiv.) in refluxing 66% aqueous acetone (15 ml), for 20h. Concentration of the solution followed by ethereal extraction etc. gave a light yellow gum which was shown, spectroscopically, to be starting material.

c) The bromopropenoate (143a) (0.22g, 0.65 mmol) was stirred with sodium azide (0.126g, 1.94 mmol, 3 equiv.) in HMPA (3 ml) at room temperature for 72h under an atmosphere of nitrogen. The solution was then poured into water and extracted with ether. The combined ethereal layers were washed with water and dried ($MgSO_4$). Evaporation gave a yellow gum, which was shown to consist of starting material, by spectroscopic methods.

d) The bromopropenoate (143a) (0.218g, 0.645 mmol) was stirred with sodium azide (0.126g, 1.94 mmol, 3 equiv.) in HMPA (5 ml) for 48h at 60°C. The solution was then poured into water and extracted with ether. The combined ethereal layers were washed with water and dried ($MgSO_4$). Evaporation gave a gum, spectroscopic and t.l.c. examination of which, showed the formation of two new compounds. Chromatography on silica

gel resulted in the isolation of two bands. The rear band was the triazole (145) (0.031g, 16%), m.p. 106 - 8.5°C (from petrol). (Found: M^+ = 300.1219. $C_{15}H_{16}N_4O_3$ requires M^+ = 300.1222);

ν_{max} (nujol): 3140 (NH), 1720 (C = O) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.41 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 3.32 (3H, s, CH_2OMe), 4.50 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.57 (2H, s, CH_2OMe), 7.31 (2H, m, 5-H and 6-H), 7.56 (1H, m, 4-H or 7-H), 8.25 (1H, m, 7-H or 4-H), 8.47 (1H, s, 2-H);

m/z: 300 (M^+, 100%), 272 (8), 269 (55).

The front band was an oil which could not be completely freed from impurities by chromatography or short path distillation, and was not identified (0.016g);

ν_{max} (thin film): 3290, 2810 - 3000, 2110, 1535, 1465, 1090, 745 cm^{-1};

δ_H (250 MHz; $CDCl_3$): 3.25 (3H, s), 5.47 (2H, s), 7.28 (2H, m), 7.44 (1H, s), 7.50 (1H, m), 7.76 (1H, m);

m/z: 267 (3%), 265 (3), 236 (3), 234 (3), 215 (4), 185 (100).

e) The bromopropenoate (143a) (0.203g, 0.60 mmol) was stirred with sodium azide (0.043g, 0.66 mmol, 1.1 equiv.) in HMPA (5 ml) for 3h at 120°C. Work-up of the cooled solution as described above gave a three component mixture which was separated by chromatography on silica gel. The front band consisted of the same unidentified oil already described (0.03g), the middle band was unreacted starting material (0.029g, 14%) and the rear band contained the triazole (145) (0.052g, 29%).

(iv) Preparation of the indol-3-yl propenoates (147)[90]

a) Indole-3-carbaldehyde (2.0g, 13.8 mmol) and monoethyl malonate (2.5g, 18.9 mmol, 1.37 equiv.) were heated in a refluxing mixture of pyridine (15 ml) and piperidine (1 ml) for 16h. The cooled solution was then poured into cold water and the precipitate collected. Recrystallization from benzene (charcoal) gave two crops of buff crystals of *(E)-ethyl 3-(indol-3-yl)propenoate* (147a) (2.12g, 72%), m.p. 119-21°C (lit.,[90] 122°C);

ν_{max} (nujol): 3280 (NH), 1665 (C = O), 1616 cm^{-1};

δ_H (90 MHz, $CDCl_3/d_6$-DMSO): 1.33 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 4.26 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 6.42 (1H, d, *J* 16 Hz, $CH = CH\varepsilon$), 7.23 (2H, m, 5-H and 6-H), 7.53 (2H, m, 2-H and 4-H or 7-H), 7.86 (1H, m, 7-H or 4-H), 7.92 (1H, d, *J* 16 Hz, $CH = CH\varepsilon$), 11.24 (1H, br s, NH);

b) 2-methylindole-3-carbaldehyde (4.0g, 25.15 mmol) and monoethyl malonate (3.32g, 25.15 mmol, 1 equiv.) were heated in a refluxing mixture of pyridine (40 ml) and piperidine (2 ml). After 20h the n.m.r. spectrum of a small sample worked up for examination, showed that there was still roughly 50% of unreacted starting material present. More monoethyl malonate (4 ml) was added and refluxing continued for a further 30h, after which time the reaction was found to have gone to completion. The cooled solution was poured into water and the precipitate collected and recrystallized from ethanol giving *(E)-ethyl 3-(2-methylindol-3-yl) propenoate* (147b) (2.71g, 47%), m.p. 180-3°C;

ν_{max} (nujol): 3390 (NH), 1683 (C = O), 1605 cm^{-1};

δ_H (90 MHz; $CDCl_3/d_6$-DMSO): 1.32 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 2.56 (3H, s, 2-Me), 4.24 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 6.33 (2H, d, *J* 16 Hz, CH = CHε), 7.17 (2H, m, 5-H and 6-H), 7.37 (1H, m, 4-H or 7-H), 7.81 (1H, m, 7-H or 4-H), 7.94 (1H, d, *J* 16 Hz, CH = CHε), 11.13 (1H, br s, NH).

c) 1-methoxymethyl-2-methylindole-3-carbaldehyde (3.43g, 16.9 mmol) and monoethyl malonate (13.4g, 101.51 mmol, 6 equiv.) were heated in a refluxing mixture of pyridine (40 ml) and piperidine (10 ml) for 24h. The resulting solution, once cool, was poured into 1N hydrochloric acid (400 ml) and extracted with ether. The combined ethereal layers were washed with sodium bicarbonate solution, dried (Na_2SO_4) and evaporated, to give a brownish gum, t.l.c. examination of which indicated the presence of unreacted starting material. Chromatography on silica gel, eluting with petrol-ether, gave *(E)-ethyl 3-(1-methoxymethyl-2-methyl-indol-3-yl)propenoate* (147c) as a gum (1.49g, 32%) which was distilled (Kugelrohr) and crystallized from petrol, m.p. 52.5 - 5°C. (Found: C, 70.18; H, 7.04; N, 5.05. $C_{16}H_{19}NO_3$ requires C, 70.31; H, 7.01; N, 5.12%);

ν_{max} (nujol): 1697 (C = O), 1610 cm^{-1};

δ_H (90 MHz, $CDCl_3$): 1.34 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 2.60 (3H, s, 2-Me), 3.28 (3H, s, CH_2OMe), 4.31 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.51 (2H, s, CH_2OMe), 6.52 (1H, d, *J* 16 Hz, CH = CHε), 7.35 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.91 (1H, m, 7-H or 4-H), 8.01 (1H, d, *J* 16 Hz, CH = CHε);

m/z: 273 (M^+, 100%), 242 (43), 228 (25), 168 (36), 154 (25).

d) 2-ethyl-1-methoxymethylindole-3-carbaldehyde (0.73g, 3.36 mmol) and monoethyl malonate (1.78g, 13.48 mmol, 4 equiv.) were heated in a refluxing mixture of pyridine (15 ml) and piperidine (1 ml) for 24h. T.l.c. after this time showed the presence of a considerable amount of starting material. Monoethyl malonate (0.89g, 6.74 mmol, 2 equiv.) was added and refluxing continued for a further 48h. Even though t.l.c. still showed the presence of starting material, the reaction mixture was worked up as described above, yielding a yellow gum from which was isolated by column chromatography, *(E)-ethyl 3-(2-ethyl-1-methoxymethylindol-3-yl) propenoate* (147d) as a colourless gum (0.503g, 52%) and starting aldehyde (0.126g, 17%). The product was distilled (Kugelrohr) and crystallized from petrol, m.p. 81-3°C. (Found: C, 70.84; H, 7.37; N, 4.90. $C_{17}H_{21}NO_3$ requires C, 71.06; H, 7.37; N, 4.87%);

ν_{max} (nujol): 1695 (C=O), 1617 cm^{-1};

^{H} (90 MHz; $CDCl_3$): 1.29 (3H, t, *J* 7.7 Hz, 2-CH_2CH_3), 1.36 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 3.03 (2H, q, *J* 7.7 Hz, 2-CH_2CH_3), 3.31 (3H, s, CH_2OMe), 4.31 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.51 (2H, s, CH_2OMe), 6.53 (1H, d, *J* 16 Hz, CH=CHε), 7.35 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.92 (1H, m, 7-H or 4-H), 8.00 (1H, d, *J* 16 Hz, CH=CHε);

m/z: 287 (M^+, 100%), 256 (43), 242 (21), 182 (96), 168 (21).

(v) Attempted formation of the dibromo compound (146)[84]

The indolyl propenoate (147c) (0.455g, 1.67 mmol) was dissolved in carbon tetrachloride (5 ml). Bromine (85 µl, 1.66 mmol, 1 equiv.) in carbon tetrachloride (3 ml) was added at room temperature over 10 minutes. A slight orange colouration persisted in the solution when the last few drops were added, and at this time t.l.c. examination showed the presence of two compounds. The crude n.m.r. showed that starting material had

been completely consumed. Attempted chromatographic separation of the mixture gave three fractions which were gums, and had complex and uninformative n.m.r. spectra. These were thus discarded.

(vi) Reactions of the indolyl propenoates (147) with NBS in aqueous THF[91]

a) The indolyl propenoate (147a) (1.0g, 4.65 mmol) was dissolved in aqueous THF (13:17 by volume, 30 ml). NBS (1.0g, 5.62 mmol, 1.2 equiv.) was added to the solution, which had been cooled to $0^{o}C$. The resulting mixture was stirred at $0^{o}C$ for 12h and then at $20^{o}C$ for 24h. The whole mixture was then extracted with ether and the extracts combined and washed with water, dried ($MgSO_4$) and evaporated, yielding a dark red gum (1.22g). The n.m.r. and t.l.c. showed this to consist of a complex intractable mixture and it was not investigated further.

b) The indolyl propenoate (147b) (0.20g, 0.87 mmol) was dissolved in aqueous THF (1:1 by volume, 20 ml) and allowed to react with NBS (0.187g, 1.05 mmol, 1.2 equiv.) at $0^{o}C$ for a period of 2 minutes. Quenching with a large excess of ice followed by extraction with ether, drying ($MgSO_4$) and evaporation, gave a brown gum. This was in turn treated with sodium azide (0.143g, 2.2 mmol, 2.5 equiv.) in DMF (10 ml) at $60^{o}C$ for 20h. Aqueous work-up and extraction etc. gave a dark gum which appeared to consist of two major compounds by t.l.c. Attempted separation by chromatography gave only complex tarry materials which were discarded.

c) The indolyl propenoate (147c) (0.315g, 1.15 mmol) was dissolved in aqueous THF (5:8 by volume, 13 ml), and NBS (0.246g, 1.38 mmol, 1.2 equiv.) was added to the solution, which had been cooled to $0^{o}C$. After 8 minutes a large excess of ice was added, and the whole mixture was extracted with ether. The combined extracts were dried ($MgSO_4$) and evaporated giving a

brownish gum (0.445g), the n.m.r. of which exhibited a doublet at δ 4.8 and a partially hidden doublet at *ca.* δ 5.5, $J \simeq 9$ Hz. This material, without further purification, was dissolved in DMF (20 ml) and treated with sodium azide (0.595g, 9.15 mmol) for 1.5h at 76°C. After this time t.l.c. showed 3 bands. The mixture was poured into water, and extracted with ether. The combined ethereal extracts were washed with water, dried ($MgSO_4$) and evaporated to give a gum. Part of this material (0.126g), was dissolved in methylene chloride (20 ml) and treated with methanesulphonyl chloride (35 μl, 0.45 mmol) at 0°C. Subsequently triethylamine (158 μl, 1.13 mmol, 2.5 equiv.) was added, and stirring at 0°C was continued for 0.75h. The solution was then washed with 3N hydrochloric acid, and subsequently with water. Drying ($MgSO_4$) and evaporation gave a gum which had crude i.r. and n.m.r. spectra almost identical to those of the crude material prior to treatment with methanesulphonyl chloride and triethylamine. Chromatographic separation of the mixture yielded 3 bands, the front running band (8 mg) was a buff gummy material; ν_{max} (thin film) 2104, 1730, 1720, 1460, 740 cm^{-1}; the n.m.r. was complex and uninformative, and mass spectroscopy suggested strongly that this was not the required azide, and thus it was discarded. The middle band was *ethyl 2-bromo-3-(1-methoxymethyl-2-methylindol-3-yl) propenoate* (143b) (0.033g, 29% from (147c)) which was crystallized from petrol, m.p. 90-3°C. (Found: C, 54.78; H, 5.18; N, 3.97; Br, 22.97. $C_{16}H_{18}BrNO_3$ requires C, 54.56; H, 5.15; N, 3.98; Br, 22.69%);

ν_{max} (nujol): 1699 (C=O), 1602, 1230, 1044, 754 cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.40 (3H, t, J 7 Hz, $CO_2CH_2CH_3$), 2.50 (3H, s, 2-Me), 3.30 (3H, s, CH_2OMe), 4.40 (2H, q, J 7 Hz, $CO_2CH_2CH_3$), 5.51 (2H, s, CH_2OMe), 7.15 - 7.55 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.66 (1H, m, 7-H or 4-H), 8.50 (1H, s, $CH=C(Br)\varepsilon$);

m/z: 353 and 351 (M^+, 100%), 322 and 320 (30), 272 (32), 218 (41), 205 (40).

The third band (13 mg) consisted of the starting indolylpropenoate (147c). Chromatography of the remaining material from the sodium azide in DMF reaction also gave the bromopropenoate (143b) and starting indolylpropenoate (147c).

(vii) Wadsworth-Emmons reaction of triethylphosphonoacetate with acetophenone[88]

Triethylphosphonoacetate (10.27g, 45.8 mmol) was added to a suspension in DME (30 ml) of sodium hydride (50% suspension in paraffin oil, 2.45g, 51.0 mmol, 1.11 equiv.) the sodium hydride had been previously de-oiled by washing with petrol. The mixture was stirred at room temperature for 0.25h after which, acetophenone (5.0g, 41.67 mmol) was added, and the resulting mixture was stirred overnight. The mixture was then poured into water and extracted three times with ether. The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated yielding a yellow oil. Short path distillation gave the required (*E*)-ethyl 3-phenylbut-2-enoate (149) (4.24g, 54%);

ν_{max} (thin film): 1710 (C = O), 1630 (C = C) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.30 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 2.59 (3H, d, *J* 1.3 Hz, $CH_3C(Ph)$), 4.23 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 6.18 (1H, q, *J* 1.3 Hz, $C(Me) = CH\varepsilon$), 7.30 - 7.60 (5H, m, Ph).

(viii) Reaction of butenoate (149) with NBS in aqueous THF[91]

The butenoate (149) (2.0g, 10.52 mmol) was dissolved in aqueous THF (1:4 by volume, 25 ml) and cooled to 3°C. NBS (3.75g, 21.06 mmol, 2 equiv.) was added and the mixture was stirred at 3°C for 36h. Some starting material was still present after this time, as evidenced by

t.l.c., and thus NBS (1.88g, 10.56 mmol, 1 equiv.) was added, and stirring continued at room temperature for 48h. The mixture was then evaporated *in vacuo* to remove most of the THF and the resulting emulsion was extracted with ether. The ethereal extracts were washed with water, dried ($MgSO_4$) and evaporated to give an orange oil (3.17g). Column chromatography gave the required *ethyl 2-bromo-3-hydroxy-3-phenylbutanoates* (151a) and (151b) as a 9:2 mixture (2.595g, 86%).

ν_{max} (thin film): 3500 (OH), 2850 - 3100, 1720 (C = O), 763 and 700 cm^{-1};

δ_H (90 MHz, $CDCl_3$; major isomer): 0.97 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 1.67 (3H, s, PhC(OH)*Me*), 3.96 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 4.32 (1H, br s, OH), 4.68 (1H, s, BrC*H*ε), 7.20 - 7.60 (5H, m, Ph);

δ_H (90 MHz, $CDCl_3$; minor isomer): 1.23 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 1.80 (3H, s, PhC(OH)*Me*), 4.21 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 4.32 (1H, br s, OH), 4.57 (1H, s, BrC*H*ε), 7.20 - 7.60 (5H, m, Ph);

m/z: 288 and 286 (M^+, 0.14%), 273 and 271 (0.48), 190 (12), 145 (19), 121 (100), 105 (38), 77 (24).

(ix) Reaction of bromobutanoates (151) with sodium azide

The mixture of bromobutanoates (151a) and (151b) (2.0g, 7.0 mmol) was dissolved in DMF (50 ml), and sodium azide (1.13g, 17.38 mmol, 2.5 equiv.) was added. The mixture was stirred at 63°C for 14h. The solution was then poured into water and extracted with ether. The combined ethereal layers were washed with water, dried ($MgSO_4$) and evaporated leaving a yellow oil (1.44g, 83%) which was a 9:2 mixture of the *ethyl 3-methyl-3-phenyloxirane-2-carboxylates* (153a) and (153b). Column

chromatography of the mixture resulted in the isolation of the almost pure major isomer (153a) and another fraction containing both isomers. This was distilled (Kugelrohr) giving a colourless oil;

ν_{max} (thin film): 2830 - 3100, 1735 (C = O) cm^{-1};

δ_H (90 MHz; $CDCl_3$; major isomer): δ 1.33 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 1.78 (3H, s, PhC*Me*), 3.46 (1H, s, *H*Cε), 4.31 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 7.2 - 7.5 (5H, m, Ph);

δ_H (90 MHz; $CDCl_3$; minor isomer): 0.90 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 1.74 (3H, s, PhC*Me*), 3.67 (1H, s, *H*Cε), 3.91 (2H, q, *J* = 7 Hz, $CO_2CH_2CH_3$), 7.2 - 7.5 (5H, m, Ph);

m/z: 206 (M^+, 6.5%), 205 (9), 190 (5), 178 (4), 160 (16), 149 (19), 132 (100).

(x) Independent synthesis of the oxiranes (153)

The mixture of bromobutanoates (151a) and (151b) (0.250g, 0.87 mmol) was added as an ethereal solution to a suspension of sodium hydride (50% suspension in paraffin oil, 0.139g, 2.90 mmol, 3.3 equiv.) in ether. The mixture was stirred at room temperature for 2h, after which the mixture was poured into water and the ethereal layer separated, dried ($MgSO_4$) and evaporated. The crude n.m.r. of the resulting material showed this to be a mixture of the two isomers (153a) and (153b) in an almost identical ratio as that obtained by sodium azide treatment of bromobutanoates (151). Column chromatography gave two fractions. The front band being the almost pure major isomer (153a) and the rear band being a mixture of the two isomers, (total yield 0.147g, 82%).

(xi) Reactions of the oxiranes (153)

a) The mixture of oxiranes (153) (0.052g, 0.25 mmol) was added as an ethanolic solution to a solution of sodium (0.01g, 0.43 mmol, 1.74 equiv.) in ethanol (2 ml). The mixture was stirred at room temperature for 2h, after which time a brown colouration had developed. More sodium metal (0.01g) in ethanol (2 ml) was added, and the mixture was stirred for 18h at room temperature. The mixture was then poured into water and extracted with ether. The combined ethereal layers were washed with water, dried and evaporated, leaving almost pure acetophenone, which was identified by spectroscopic comparison with an authentic sample.

b) The mixture of oxiranes (153) (0.156g, 0.76 mmol) was dissolved in methylene chloride (25 ml), and pTSA (10 mg) was added. Stirring at room temperature for 48h resulted in the formation of one new compound as evidenced by t.l.c. The solution was then washed with saturated sodium bicarbonate solution, dried ($MgSO_4$) and evaporated. Purification was effected by p.l.c. and short path distillation giving *ethyl 2-hydroxy-3-phenylbut-3-enoate* (156a) (141 mg, 90%) as a colourless oil;

ν_{max} (thin film): 3490 (OH), 1730 (C = O) cm^{-1};

δ_H (250 MHz; $CDCl_3$): 1.11 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 3.29 (1H, d, *J* 6 Hz, OH), 4.16 (2H, ABqq, *J* 11, 7 Hz, $CO_2CH_2CH_3$), 5.04 (1H, d, *J* 6 Hz with some fine splitting, $CH(OH)CO_2Et$), 5.45 (1H, finely split m, one of $PhC=CH_2$), 5.49 (1H, d, J *ca.* 0.8 Hz, one of $PhC=CH_2$), 7.34 (5H, m, Ph).

Irradiation of the δ 3.29 doublet resulted in collapse of the δ 5.04 doublet (with fine splitting) to a fine doublet, *J ca.* 0.8 Hz and collapse of the δ 5.45 multiplet to a fine doublet, *J ca.* 0.6 Hz. Irradiation of the δ 5.04 doublet resulted in the collapse of the δ 3.29 doublet to a singlet and collapse of the δ 5.45 multiplet to a fine doublet, *J ca.* 0.6 Hz;

m/z: 206 (M^+, 22%), 189 (22), 160 (24), 133 (100), 105 (80).

c) The mixture of oxiranes (153) (0.059g, 0.29 mmol) was dissolved in acetic anhydride (15 drops), and conc. sulphuric acid (1 drop) was added. The solution was brought to 50°C and kept at that temperature for 1.5h. The mixture was then poured into saturated sodium bicarbonate solution, and extracted with ether/benzene (50:50). The organic layer was washed twice with saturated sodium bicarbonate solution, once with water and then dried ($MgSO_4$). Evaporation gave an oil which was separated into two components by p.l.c. The front band (0.005g, 10%) was shown to be the butenoate (149) by n.m.r. spectroscopy. The rear band was shown to be *ethyl 2-acetoxy-3-phenylbut-3-enoate* (156b) (0.019g, 27%);

ν_{max} (thin film): 1710 - 1770 br (C = O) cm^{-1};

δ_H (250 MHz; $CDCl_3$): 1.13 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 2.18 (3H, s, OAc), 4.15 (2H, ABqq, *J* 11, 7 Hz, $CO_2CH_2CH_3$), 5.53 (1H, s, slightly broadened, one of $PhC=CH_2$), 5.63 (1H, s, one of $PhC=CH_2$), 5.94 (1H, d, *J ca.* 0.8 Hz, $CH(OAc)CO_2Et$), 7.30 - 7.50 (5H, m, Ph);

m/z: 248 (M^+, 2), 230 (1), 206 (8), 189 (100), 175 (7), 161 (29), 160 (27), 133 (27).

(xii) Preparation of the ketone (158a)[93]

A solution of indole (2.26g, 19.3 mmol) in toluene (50 ml) containing pyridine (1.62 ml, 19.3 mmol) was heated to 60°C, and to this was added chloroacetyl chloride (1.6 ml, *ca.* 20 mmol) over a period of 1h. The resulting cloudy solution was heated at 60°C for a further 1h, with stirring, and then poured into water (60 ml) and allowed to stand at 3°C for 0.5h. The yellow solid found to have been deposited after this time was collected by filtration, dried and recrystallized from methanol, giving crystalline *3-chloroacetyl indole* (158a) (1.77g, 51%), m.p.

220 - 30°C dec. (Found: C, 62.37; H, 4.20; N, 7.21. $C_{10}H_8ClNO$ requires C, 62.03; H, 4.16; N, 7.23%);

ν_{max} (nujol): 3190 (NH), 1635 (C = O) cm^{-1};

δ_H (90 MHz; $CDCl_3/d_6$-DMSO): 4.59 (2H, s, $COCH_2Cl$), 7.04 (2H, m, 5-H and 6-H), 7.26 (1H, m, 4-H or 7-H), 7.98 (2H, m, 2-H and 7-H or 4-H), 11.87 (1H, br s, NH);

m/z: 195 (M^+, 9%) and 193 (M^+, 24), 144 (100).

(xiii) Treatment of (158a) with sodium azide

Chloroketone (158a) (0.30g, 1.55 mmol) and sodium azide (0.202g, 3.1 mmol, 2 equiv.) were refluxed overnight in a mixture of acetone (20 ml) and water (10 ml). The resulting solution was poured into water (200 ml) and extracted with methylene chloride. Drying and evaporation of the combined organic layers gave a pale yellow solid in quantitative yield which was recrystallized from methanol giving fine needles of *3-azidoacetyl indole* (158b), m.p. 172.5 - 5°C. (Found: C, 59.82; H, 4.01; N, 27.73. $C_{10}H_8N_4O$ requires C, 60.00; H, 4.03; N, 27.99%);

ν_{max} (nujol): 3320 (NH), 2103 (N_3), 1637 (C = O) cm^{-1};

δ_H (90 MHz; $CDCl_3/d_6$-DMSO): 4.39 (2H, s, $COCH_2N_3$), 7.12 (2H, m, 5-H and 6-H), 7.35 (1H, m, 4-H or 7-H), 7.89 (1H, d, *J* 2 Hz, 2-H), 8.12 (1H, m, 7-H or 4-H), 11.78 (1H, br s, NH);

m/z: 200 (M^+, 8%), 172 (4), 144 (100), 106 (19), 89 (19).

(xiv) Borohydride reduction of (158b)

The azidoketone (158b) (0.20g, 1.0 mmol) was dissolved in ethanol (40 ml) and treated with excess sodium borohydride, and glacial acetic acid (10 drops) at room temperature. After *ca.* 2h, t.l.c. indicated complete consumption of starting material, and the mixture was poured into brine

and extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4) and evaporated, yielding as a yellow gum, *2-azido-1-(indol-3-yl)ethanol* (159a) (0.18g, 89%);

ν_{max} (thin film): 3510 sh, 3410 (OH and NH), 2102 (N_3) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 2.9 (1H, br s, OH), 3.44 (2H, m, $CH(OH)CH_2N_3$), 4.96 (1H, dd, *J* 7.5, 5 Hz, $CH(OH)CH_2N_3$), 6.81 (1H, d, *J* 2 Hz, 2-H), 7.07 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.50 (1H, m, 7-H or 4-H), 8.23 (1H, br s, NH);

(xv) Elimination of water from the alcohol (159a)

The azidoalcohol (0.18g, 0.89 mmol) was dissolved in methylene chloride (20 ml) and cooled to 0^oC under a nitrogen atmosphere. Methanesulphonyl chloride (90 µl, 1.16 mmol, 1.3 equiv.) was added and after 5 minutes, triethylamine (0.39 ml, 2.8 mmol, 3.1 equiv.) was introduced into the reaction. The mixture was stirred under nitrogen for 1h, after which it was poured onto ice, and when the ice had melted ethereal extraction was carried out. The combined extracts were dried (Na_2SO_4) and evaporated, giving a brown gum which was rapidly chromatographed on alumina, eluting with petrol/ether, to yield a rather unstable oily yellow crystalline material which rapidly darkened at room temperature in contact with air and light. This was a mixture (in approximately 50:50 proportion) of the *(Z)- and (E)-1-azido-2-(indol-3-yl)ethenes* (157a) (0.082g, 50%);

ν_{max} (thin film): 3400 (NH), 2110 (N_3), 1630 (C = C) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 6.12 (2H, ABq, *J* 7.4 Hz, $CH = CHN_3$ in (*Z*)-isomer), 6.56 (2H, ABq, *J* 14 Hz, $CH = CHN_3$ in (*E*)-isomer), 7.0 - 7.4 (m, Ar-H), 7.45 - 7.65 (m, Ar-H), 7.9 (br s, NH).

(xvi) *N*-methylation of (158b)

The azidoketone (158b) (0.892g, 4.46 mmol) and methyl iodide (2.78 µl, 44.6 mmol, 10 equiv.) were heated together in acetone at reflux, over potassium carbonate (3.0g, 21.7 mmol, 4.9 equiv.) for 16h. Filtration of the resulting mixture to remove the potassium carbonate, followed by evaporation of the solvent *in vacuo* gave a reddish gum which was purified by filtration through a pad of silica gel, eluting with ether. Evaporation of the resulting ethereal solution gave a yellow gum which solidified upon storage at 3°C for 24h. Recrystallization from ethanol/petrol gave fine beige needles of *3-azidoacetyl-1-methylindole* (158c) (0.787g, 82%), m.p. 77-8.5°C. (Found: C, 61.73; H, 4.64; N, 26.14. $C_{11}H_{10}N_4O$ requires C, 61.67; H, 4.71; N, 26.15%);

ν_{max} (nujol): 2100 (N_3), 1660 (C = O) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 3.76 (3H, s, NMe), 4.21 (2H, s, $COCH_2N_3$), 7.30 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.53 (1H, s, 2-H), 8.26 (1H, m, 7-H or 4-H);

m/z: 214 (M^+, 2%), 186 (18), 158 (100).

(xvii) Reduction of azidoketone (158c)

The azidoketone (158c) (0.30g, 1.4 mmol) was dissolved in methanol containing 5 drops of glacial acetic acid, and the resulting solution was treated with excess sodium borohydride over a period of 1.5h at room temperature. When t.l.c. indicated complete consumption of starting material, the solution was partitioned between saturated aqueous sodium hydrogen carbonate and ether. The combined ethereal layers were washed with water, dried ($MgSO_4$) and evaporated, yielding as a yellow gum, *2-azido-1-(1-methylindol-3-yl)ethanol* (159b) (0.29g, 96%);

ν_{max} (thin film): 3410 (OH), 2100 (N_3) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 2.70 (1H, br s, OH), 3.50 - 3.70 (2H, m, AB part of ABX system, $CH(OH)CH_2N_3$), 5.09 (1H, dd, *J* 7.5, 5 Hz, $CH(OH)CH_2N_3$), 6.97 (1H, s, 2-H), 7.0 - 7.30 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.60 (1H, m, 7-H or 4-H).

(xviii) Elimination of water from azidoalcohol (159b)

The azidoalcohol (159b) (0.29g, 1.34 mmol) was dissolved in methylene chloride (5 ml) and cooled to 0^oC under a nitrogen atmosphere. Methanesulphonyl chloride (125 µl, 1.62 mmol, 1.2 equiv.) was added, and after 5 minutes, triethylamine (0.559 ml, 4.02 mmol, 3 equiv.) was introduced into the reaction. The resulting mixture was stirred at 0^oC for 20 minutes and was then allowed to warm to room temperature over a further 40 minutes. A similar work-up procedure to that employed in experiment (xv) was used, and as before, rapid chromatography of the crude product on alumina, eluting with petrol/ether, gave the expected *(Z)- and (E)-1-azido-2-(1-methylindol-3-yl)ethenes* (157b) as a yellow oil, rapidly darkening.

ν_{max} (thin film): 3060 - 2900 (OH), 2110 (N_3), 1631 (C=C) cm^{-1};

δ_H (90 MHz; $CDCl_3$, (*Z*)-isomer (major product)): 3.63 (3H, s, NMe), 6.02 (2H, ABq, *J* 8 Hz, $CH=CHN_3$), 7.0 - 7.25 (m, Ar-H), 7.45 - 7.70 (m, Ar-H);

((*E*)-isomer, (minor product)): 3.54 (3H, s, NMe), 6.44 (2H, ABq, *J* 15 Hz, $CH=CHN_3$), 7.0 - 7.25 (m, Ar-H), 7.45 - 7.70 (m, Ar-H).

(xix) Preparation of 3-chloroacetyl-1,2-dimethylindole

This was prepared in an exactly similar fashion to (158a) by treating 1,2-dimethylindole (4.83g, 33.3 mmol) with 1 equivalent of chloroacetyl

chloride in toluene, containing 1 equivalent of pyridine at 60°C. The required *3-chloroacetyl-1,2-dimethylindole* was recrystallized from ethanol (4.01g, 54%), m.p. 138-40°C. (Found: C, 64.35; H, 5.50; N, 6.13; Cl, 16.35. $C_{12}H_{12}ClNO$ requires C, 65.01, H, 5.45; N, 6.32; Cl, 15.99%);

ν_{max} (nujol): 1660 (C = O), 1510, 1400 cm^{-1};

δ_H (90 MHz; $CDCl_3$): 2.72 (3H, s, 2-Me), 3.62 (3H, s, NMe), 4.56 (2H, s, $COCH_2Cl$), 7.22 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.74 (1H, m, 7-H or 4-H);

m/z: 223 (M^+, 11%), 221 (M^+, 22), 172 (100).

(xx) Reaction of 3-chloroacetyl-1,2-dimethylindole with sodium azide

The chloroketone (1.0g, 4.51 mmol) and sodium azide (0.35g, 5.38 mmol, 1.2 equiv.) were heated together in refluxing 60% aqueous acetone for 24h. The reaction was worked up exactly as in experiment (xii) giving a solid which was recrystallized from ether to give fluffy pale yellow needles of *3-azidoacetyl-1,2-dimethylindole* (158d) (0.70g, 68%), m.p. 139-41°C. (Found: C, 63.40; H, 5.30; N, 24.32. $C_{12}H_{12}N_4O$ requires C, 63.14; H, 5.30; N, 24.55%);

ν_{max} (nujol): 2110 (N_3), 1645 (C = O) cm^{-1};

δ_H (250 MHz; $CDCl_3$): 2.81 (3H, s, 2-Me), 3.73 (3H, s, NMe), 4.50 (2H, s, $COCH_2N_3$), 7.28 (2H, m, 5-H and 6-H), 7.35 (1H, m, 4-H or 7-H), 7.69 (1H, m, 7-H or 4-H);

m/z: 228 (M^+, 8%), 200 (11), 172 (100).

(xxi) Attempted formation of the enolate anion of (158d) and subsequent quenching with ethyl chloroformate

The azidoketone (158d) (0.10g, 0.44 mmol) was added as a solution in DMF (4 ml) to a suspension of sodium hydride (1 equivalent) in DMF

(5 ml) at -12°C. A deep red colouration developed instantly, and after 10 minutes ethyl chloroformate (1 equivalent) was added, and the red colour was discharged. Aqueous work-up and extraction etc. gave a brown gum. The i.r. showed no azide signal, and the n.m.r. revealed the material to be a complex mixture. It was thus discarded.

(xxii) Treatment of 2-methylindole with ethylmalonyl chloride

2-Methylindole (2.0g, 15.3 mmol) was dissolved in toluene (40 ml) containing pyridine (1.30 ml, 16.1 mmol, 1.05 equiv.). The resulting solution was heated with stirring to 50°C, at which temperature ethyl malonyl chloride (1.90 ml, 14.8 mmol, 0.97 equiv.) was added over a period of 1h. When addition was complete, the solution was heated at 50-60°C for a further 1.5h. Water (40 ml) was then added and the mixture was extracted with ether. The combined organic layers were washed with sodium carbonate solution, dried ($MgSO_4$) and evaporated to give a brown gum which solidified upon standing overnight at 3°C. This material was triturated twice with petrol/ether and then recrystallized from methylene chloride giving fine crystals of *ethyl 3-(2-methylindol-3-yl)-3-oxopropanoate* (160a) (1.32g, 35%), m.p. 90 - 1.5°C. (Found: C, 68.82; H, 6.30; N, 5.77.. $C_{14}H_{15}NO_3$ requires C, 68.57; H, 6.12; N, 5.71%);

ν_{max} (nujol): 3360, 3266 (NH), 1741, 1730 (C = O), 1629, 1605 (C = O) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.26 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 2.67 (3H, s, 2-Me), 4.06 (2H, s, $COCH_2CO_2Et$), 4.26 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 7.1 - 7.5 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.95 (1H, m, 7-H or 4-H), 9.67 (1H, br s, NH);

m/z: 245 (M^+, 20%), 199 (16), 158 (100).

(xxiii) Attempted *N*-methylation of (160a)

The ketoester (160a) (0.50g, 2.16 mmol) and methyl iodide (0.5 ml, 8.03 mmol, 3.7 equiv.) were heated together in refluxing acetone (20 ml), over potassium carbonate (0.34g, 2.46 mmol, 1.14 equiv.) for 20h. The mixture was then filtered to remove the potassium carbonate and the resulting solution was evaporated leaving a yellow gum, which was chromatographed on silica gel to give *ethyl 3-(1,2-dimethylindol-3-yl)-2-methyl-3-oxopropanoate* (160d) (0.287g, 52%) white prisms from petrol/ether, m.p. 105.5 - 7°C. (Found: C, 70.29; H, 7.05; N, 5.16. $C_{16}H_{19}NO_3$ requires C, 70.31; H, 7.01; N, 5.12%);

ν_{max} (nujol): 1745 (C = O, ester), 1631 (C = O, ketone) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.20 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 1.54 (3H, d, *J* 8 Hz, $COCH(Me)CO_2Et$), 2.8 (3H, s, 2-Me), 3.72 (3H, s, NMe), 4.22 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 4.47 (1H, q, *J* 8 Hz, $COCH(Me)CO_2Et$), 7.20 - 7.50 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.95 (1H, m, 7-H or 4-H);

m/z: 273 (M^+, 19%), 172 (100).

(xxiv) Attempted methylation of (160a)

The ketoester (160a) (0.50g, 2.16 mmol) in DMF solution was treated with sodium hydride (50% suspension in paraffin oil, 0.095g, 1.98 mmol, 0.92 equiv.) which was added portionwise over 5 minutes. After stirring for a further 15 minutes at room temperature, methyl iodide (0.35 ml, 5.62 mmol, 2.6 equiv.) was added, and the mixture was stirred at room temperature for 1h. Aqueous work-up and extraction with ether etc. gave a gum, which by n.m.r. was shown to be essentially a mixture of (160b) and (160c) in a 75:25 ratio. The mixture was discarded.

(xxv) Treatment of 1,2-dimethylindole with ethyl malonyl chloride

1,2-dimethylindole (2.0g, 13.8 mmol) was treated with ethyl malonyl chloride (1.77 ml, 13.8 mmol, 1 equiv.) in toluene (50 ml) containing pyridine (1.11 ml, 13.7 mmol, 1 equiv.) in the same manner as described in experiment (xxii). A similar aqueous work-up and ethereal extraction gave a brown gum which was chromatographed on silica gel, eluting with petrol/ether. Two bands were isolated, the faster, running in neat petrol, proved to be recovered starting material (1.09g, 55% recovery). The rear band was the required *ethyl 3-(1,2-dimethylindol-3-yl)-3-oxo-propanoate* (160c) (1.05g, 30%) which gave fine needles upon recrystallization from ethanol/petrol, m.p. 133-5°C. (Found: C, 69.82; H, 6.57; N, 5.41. $C_{15}H_{17}NO_3$ requires C, 69.48; H, 6.61; N, 5.40%);

ν_{max} (nujol): 1732 (C = O, ester), 1624 (C = O, ketone) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.29 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 2.76 (3H, s, 2-Me), 3.70 (3H, s, NMe), 4.06 (2H, s, $COCH_2CO_2Et$), 4.28 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 7.20 - 7.50 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.90 (1H, m, 7-H or 4-H);

m/z: 259 (M^+, 19), 213 (12), 172 (100).

(xxvi) Preparation of ethoxycarbonyl-*N*,*N*-diethylacetamide (164)

A solution of diethylamine (6.90 ml, 66.4 mmol, 2 equiv.) in ether (40 ml) was cooled to 0°C. Ethyl malonyl chloride (5.0g, 33.21 mmol) was added dropwise. A thick white precipitate of diethylammonium chloride was formed, and upon the completion of addition, this was filtered off. The filtrate was evaporated and the resulting yellowish liquid was distilled (b.p. 94°C at 1.2 mm Hg) yielding, as a slightly viscous colourless liquid, ethoxycarbonyl-*N*,*N*-diethylacetamide (164) (2.84g, 46%);

δ_H (60 MHz; $CDCl_3$): 1.0 - 1.5 (9H, m, $CO_2CH_2CH_3$ and $CON(CH_2CH_3)_2$), 3.1 - 3.6 (4H, 2 q, *J* 7 Hz, $CON(CH_2CH_3)_2$), 3.42 (2H, s, $Et_2NCOCH_2CO_2Et$), 4.20 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$).

(xxvii) Vilsmeier reaction of (164) with 1,2-dimethylindole[94]

Phosphorus oxychloride (0.38 ml, 4.15 mmol, 1.42 equiv.) was added to the *N*,*N*-diethylamide (164) (1.5g, 8 mmol) at 0°C. The resulting bright yellow solution was stirred for 1.5h at 0°C, after which time 1,2-dimethylindole (0.423g, 2.9 mmol) as a solution in the *N*,*N*-diethylamide (164) (1.0 ml) was added. The solution was allowed to warm to room temperature, and after stirring for 4h, when the solution had become deep red and somewhat viscous, it was treated with excess saturated sodium carbonate solution for 0.5h. Extraction with ether, washing and drying ($MgSO_4$) of the combined organic layers and evaporation, gave a yellow-orange solid which was recrystallized from ether/petrol giving pale yellow prisms of *ethyl 3-(N,N-diethylamino)-3-(1,2-dimethylindol-3-yl)propenoate* (165) (0.776g, 83%) only one stereoisomer was obtained, but the stereochemistry was not investigated, m.p. 117 - 9.5°C. (Found: C, 72.57; H, 8.28; N, 8.92. $C_{19}H_{26}N_2O_2$ requires C, 72.58; H, 8.33; N, 8.91%);

ν_{max} (nujol): 1696 (C = O), 1554 cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.0 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 0.8 - 1.5 (6H, m, $N(CH_2CH_3)_2$), 2.33 (3H, s, 2-Me), 3.0 - 3.5 (4H, m, $N(CH_2CH_3)_2$), 3.72 (3H, s, NMe), 3.87 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.05 (1H, s, $Et_2N-C=CH\varepsilon$), 7.0 - 7.50 (4H, m, H-4, H-5, H-6 and H-7);

m/z: 314 (M^+, 100%), 299 (80).

(xxviii) Hydrolysis of the enamine (165)

The enamine (165) (0.402g, 1.28 mmol) was dissolved in ethanol (30 ml) and 3N sulphuric acid (5 ml). The resulting solution was stirred at room temperature for 48h, when t.l.c. indicated complete consumption of starting material. The acid was then neutralized with solid sodium hydrogen carbonate, and the mixture was partitioned between ether and brine. The organic layer was dried and evaporated yielding a solid which was recrystallized from ethanol, giving fine needles, m.p. 132 - 5°C, which had an identical i.r. spectrum to the ketoester (160c) (0.132g, 40%).

(xxix) Bromination of the enamine (165)

The enamine (165) (0.222g, 0.71 mmol) was dissolved in ether (10 ml) and the resulting solution was cooled to -78°C. Bromine (37 µl, 0.71 mmol, 1 equiv.) was then added as a solution in ether (5 ml). A buff coloured precipitate was rapidly formed, and stirring at -78°C was continued for 0.5h. The mixture was then allowed to warm to room temperature, and water (10 ml) was added. Extraction with ether, washing, drying ($MgSO_4$) and evaporation of the combined extracts, gave a red material which was chromatographed on silica gel to give as a yellow gum, *ethyl 2-bromo-3-(N,N-diethylamino)-3-(1,2-dimethylindol-3-yl)propenoate* (168) (0.19g, 69%) in an approximately 60:40 ratio of double bond isomers.

ν_{max} (thin film): 1670 (C = O) cm^{-1};

δ_H (90 MHz; $CDCl_3$, major isomer): 1.12 (6H, t, *J* 8 Hz, $N(CH_2CH_3)_2$), 1.33 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 2.46 (3H, s, 2-Me), 3.23 (4H, q, *J* 8 Hz, $N(CH_2CH_3)_2$), 3.70 (3H, s, NMe), 4.26 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 7.10 - 7.30 (3H, m, 5-H, 6-H and 4-H or 7-H), 8.45 - 8.65 (1H, m, 7-H or 4-H);

δ_H (90 MHz; $CDCl_3$, minor isomer): 0.58 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 1.13 (6H, t, *J* 8 Hz, $N(CH_2CH_3)_2$), 2.37 (3H, s, 2-Me), 3.33 (4H, q, *J* 8 Hz, $N(CH_2CH_3)_2$), 3.40 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 3.66 (3H, s, NMe), 7.10 - 7.30 (3H, m, 5-H, 6-H and 4-H or 7-H), 8.45 - 8.65 (1H, m, 7-H or 4-H);

m/z: 394 (M^+, 7%); 392 (M^+, 7), 313 (28), 242 (100).

(xxx) Hydrolysis of the bromoenamines (168)

The bromoenamine mixture (168) (0.19g, 0.48 mmol) was dissolved in THF (15 ml), 3N sulphuric acid (6 ml) and water (2 ml). The resulting solution was stirred at room temperature for 48h, when t.l.c. indicated complete consumption of starting material. The acid was neutralized with solid sodium hydrogen carbonate and the THF was removed by evaporation *in vacuo*. The resulting emulsion was extracted with ether and the combined extracts were dried ($MgSO_4$) and evaporated, yielding a brownish gum which was chromatographed on silica gel. The resulting *ethyl 2-bromo-3-(1,2-dimethylindol-3-yl)-3-oxopropanoate* (160e) (0.136g, 83%) was obtained as an almost colourless gum which solidified on storage at 3°C for some time. Recrystallization from ethanol/petrol gave colourless prisms, m.p. 124.5 - 6.5°C. (Found: C, 53.40; H, 4.79; N, 4.09; Br, 23.36. $C_{15}H_{16}BrNO_3$ requires C, 53.27; H, 4.77; N, 4.14; Br, 23.63%);

ν_{max} (nujol): 1766 (C = O, ester), 1645 (C = O, ketone) cm^{-1};

δ_H (250 MHz; $CDCl_3$): 1.30 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 2.82 (3H, s, 2-Me), 3.75 (3H, s, NMe), 4.32 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.74 (1H, s, $COCHBrCO_2Et$), 7.33 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.87 (1H, m, 7-H or 4-H);

m/z: 339 (M^+, 5%), 337 (M^+, 5), 259 (6), 213 (6), 172 (100).

(xxxi) Treatment of bromoketoester (160e) with sodium azide

a) The bromoketoester (160e) (0.136g, 0.40 mmol) and sodium azide (0.052g, 0.80 mmol, 2 equiv.) were heated together in refluxing 60% aqueous acetone for 15h. The acetone was then removed by evaporation *in vacuo*, and the resulting emulsion was extracted with ether. Drying ($MgSO_4$) and evaporation of the combined ethereal layers gave a gum which had a somewhat complex n.m.r. spectrum, and appeared to be a mixture. Attempted separation by p.l.c. resulted in the isolation of a band apparently containing two compounds, one of which appeared to be an ethyl ester, δ_H (90 MHz; $CDCl_3$): 1.18 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$) and 4.22 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), *inter alia*. The other compound appeared to be without an ester group. Attempted isolation of the ethoxycarbonyl compound by further p.l.c. always led to samples which were contaminated with the other material. Crystallization of the combined crude gums from ethanol, and recrystallization from the same solvent gave yellow needles of the *oxazolone* (169) (0.01g, 9%), m.p. 144 - 6°C. (Found: M^+ = 284.1154. $C_{16}H_{16}N_2O_3$ requires M^+ = 284.1161);

ν_{max} (nujol): 1775 (C = O, oxazolone), 1604 (C = O, ketone), 1582 cm^{-1};

δ_H (250 MHz; $CDCl_3$): 1.78 (6H, s, CMe_2), 2.74 (3H, s, 2-Me), 3.76 (3H, s, NMe), 7.30 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.75 (1H, m, 7-H or 4-H);

m/z: 284 (M^+, 13%), 172 (100).

b) Solutions of the bromoketoester (160e) (in each case 0.08g, 0.24 mmol) were made in DMF (4 ml) DMSO (4 ml) and HMPA (4 ml). To each solution was added sodium azide (0.016g, 0.24 mmol, 1 equiv.). The resulting solutions were stirred at room temperature for 40h. Standard aqueous work-up and extraction with ether etc. gave gums having identical t.l.c. and i.r.

spectral properties. Chromatography of the combined crude gums gave in the early fractions, a small amount of a gum which could be crystallized from ethanol, giving fine white needles, m.p. 138.5 - 42°C and having identical spectral properties to the azidoketone (158d) (0.01g, 19%). In subsequent fractions and also in the mother liquors from the crystallization, a compound presumed to be an ethyl ester was shown by n.m.r. to be present (90 MHz; $CDCl_3$): 1.28 (3H, t, *J ca.* 7 Hz), 2.68 (3H, s), 3.66 (3H, s), 4.40 (2H, q, J *ca.* 7 Hz), *inter alia*. The i.r. showed signals at 1720 and 1615 cm^{-1} but no azide peak. Attempts to purify this material by further chromatography only resulted in its further decomposition, and thus the crude mixture was discarded.

(xxxii) Treatment of the bromoketone (160e) with reducing agents

a) The bromoketone (160e) (0.058g, 0.17 mmol) was dissolved in ethanol (15 ml) and over a period of 3h excess sodium borohydride and glacial acetic acid (15 drops) were added, the reaction being all the time at 0°C, and consumption of starting material being followed by t.l.c.. The mixture was then poured into ice-water and treated with solid sodium hydrogen carbonate. Extraction with ether etc. gave a solid (0.048g, 100%) which was recrystallized from ethanol/petrol giving fine needles, m.p. 127 - 32°C, having identical i.r. and n.m.r. spectra to ketoester (160c).

b) The bromoketone (160e) (0.085g, 0.25 mmol) was dissolved in toluene and cooled to 0°C. DIBAL (1M solution in hexane, 0.26 ml, 0.26 mmol, 1.04 equiv.) was added and the mixture stirred at 0-5°C for 80 minutes. The mixture was then warmed to room temperature and methanol (1 ml) was added, followed by water (1 ml). Filtration through celite, washing the filter cake with hot methanol, gave a cloudy solution which was evaporated to dryness. The crude n.m.r. of the resulting semi-solid material showed this to consist essentially of the ketoester (160c).

EXPERIMENTAL FOR CHAPTER THREE

1. Thermolysis of azidopropenoates (175).[67,81]

(i) Thermolysis of azidopropenoate (175a)

The azidopropenoate (175a) (1.174g, 4.35 mmol) was dissolved in toluene (235 ml), and the resulting solution was added dropwise, over 1h to refluxing toluene (235 ml) under an atmosphere of nitrogen. The solution was allowed to reflux for an additional 10 minutes after addition was complete, and then it was allowed to cool. The toluene was then evaporated and the resulting brown material was purified by filtration through a thin pad of silica gel, eluting with petrol/ether. Evaporation of the filtrate gave off-white microcrystals of *ethyl 1,8-dihydro-8-methylpyrrolo[2,3-b]indole-2-carboxylate* (176a) (0.987g, 94%) which was recrystallized from toluene/petrol/ethyl acetate (70:20:10) m.p. 234-9°C (Found: C, 69.25; H, 5.85; N, 11.32. $C_{14}H_{14}N_2O_2$ requires C, 69.41; H, 5.82; N, 11.56%);

ν_{max} (nujol): 3240 (NH), 1665 (C=O), 1625 cm^{-1};

λ_{max} (EtOH): 336 (log ε 4.55), 279 nm (4.35);

δ_H (90 MHz; d_6-DMSO): 1.31 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 3.81 (3H, s, N-Me), 4.30 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 7.15 (2H, m, 5-H and 6-H), 7.17 (1H, s, 3-H), 7.40 (1H, m, 4-H or 7-H), 7.65 (1H, m, 7-H or 4-H), (NH not observed);

m/z: 242 (M^+, 73%), 196 (100), 168 (66), 127 (23).

(ii) Thermolysis of azidopropenoate (175b)

The azidopropenoate (175b) (0.50g, 1.45 mmol) was dissolved in toluene (100 ml) and the resulting solution added dropwise to refluxing toluene (100 ml) under an atmosphere of nitrogen. Upon completion of addition the solution was allowed to reflux for a further 10 minutes

and then allowed to cool. The toluene was then evaporated leaving a brown solid which was triturated with petrol/ether (4:1). The resulting yellowish powder was collected by filtration. This was *ethyl 8-benzyl-1,8-dihydropyrrolo[2,3-b]indole-2-carboxylate* (176b) (0.419g, 91%) which was recrystallized from ether/ethyl acetate, m.p. 217-8°C (Found: C, 75.27; H, 5.78; N, 8.68. $C_{20}H_{18}N_2O_2$ requires: C, 75.46; H, 5.70; N, 8.80%);

ν_{max} (nujol): 3275 (NH), 1663 (C = O), 1630, 1598 cm^{-1}.

δ_H ($CDCl_3/d_6$-DMSO): 1.33 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 4.30 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.48 (2H, s, CH_2Ph), 7.20 (9H, m, 3-H, 5-H, 6-H, Ph and 4-H or 7-H), 7.67 (1H, m, 7-H or 4-H), (NH not observed);

m/z: 318 (M^+, 99%), 272 (84), 91 (100).

(iii) Thermolysis of azidopropenoate (175c)

The azidopropenoate (175c) (1.144g, 3.81 mmol) was dissolved in toluene (230 ml) and added dropwise over 80 minutes to refluxing toluene (230 ml) under a nitrogen atmosphere. The procedure described above was followed except that after evaporation of the toluene the crude material was recrystallized from ethanol, giving needles of *ethyl 1,8-dihydro-8-methoxymethylpyrrolo[2,3-b]indole-2-carboxylate* (176c) (0.828g, 80%), m.p. 173-80°C (Found: C, 66.19; H, 5.96; N, 10.30. $C_{15}H_{16}N_2O_3$ requires C, 66.15; H, 5.92; N, 10.29%);

ν_{max} (nujol): 3250 (NH), 1650 (C = O), 1615, 1579 cm^{-1}.

δ_H (90 MHz; d_6-DMSO): 1.32 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 3.23 (3H, s, CH_2OMe), 4.32 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.72 (2H, s, CH_2OMe), 7.10 - 7.30 (2H, m, 5-H and 6-H), 7.21 (1H, s, 3-H), 7.55 (1H, m, 4-H or 7-H), 7.71 (1H, m, 7-H or 4-H), 12.20 (1H, br s, NH);

m/z: 272 (M^+, 100%), 226 (33), 195 (37), 168 (33).

(iv) Thermolysis of the azidopropenoate (175d)

The azidopropenoate (175d) (7.50g, 26.22 mmol) was dissolved in toluene (500 ml) and added dropwise to refluxing toluene (500 ml) over 1h. The solution was refluxed for an additional 0.5h after addition was complete. The solution was then reduced in volume to *ca.* 100 ml and cooled to 3^oC. The deposited solid was collected and recrystallized from methanol, giving white needles of *methyl 1,8-dihydro-8-methoxymethylpyrrolo[2,3-b]indole-2-carboxylate* (176d) (4.72g, 70%), m.p. 214-8^oC dec. (Found: C, 64.87; H, 5.43; N, 10.77. $C_{14}H_{14}N_2O_3$ requires C, 65.11; H, 5.46; N, 10.85%);

ν_{max} (nujol): 3300, 3290 sh, 3260 (NH), 1662 (C = O), 1620, 1588 cm^{-1}.

δ_H (250 MHz; $CDCl_3$): 3.32 (3H, s, CH_2OMe), 3.94 (3H, s, CO_2Me), 5.60 (2H, s, CH_2OMe), 7.23 (2H, m, 5-H and 6-H), 7.26 (1H, s, 3-H), 7.41 (1H, m, 4-H or 7-H), 7.73 (1H, m, 7-H or 4-H), 9.87 (1H, br s, NH);

m/z: 258 (M^+, 100%), 227 (23), 195 (25), 168 (33).

2. Simple chemistry of the pyrrolo[2,3-b]indole systems (176)

(i) Attempted debenzylations of (176b).

a) The pyrroloindole (176b) (0.05g, 0.16 mmol) was dissolved in THF (3 ml) and added to anhydrous liquid ammonia (8 ml). Small pieces of sodium were added until the blue-black colouration became permanent. Treatment of this solution with solid ammonium chloride and aqueous hydrochloric acid gave a pale yellow solution from which the liquid ammonia was allowed to evaporate. The remaining liquid was extracted with chloroform, and the dark chloroform extracts were combined dried ($MgSO_4$) and evaporated to give a dark tarry material. The n.m.r.

showed this to be a complex mixture of decomposition or polymerization products and it was discarded. The aqueous layer was then evaporated and the resulting solid was extracted with boiling ethyl acetate. No organic material could however be obtained.

b) The pyrroloindole (176b) (0.062g, 0.19 mmol) was dissolved in ethanol (20 ml) and the solution was hydrogenated over (10%) palladium-charcoal (0.02g) for 20h. Filtration through celite and evaporation gave a solid which was shown to be starting material by n.m.r. and t.l.c.

(ii) Deprotection of pyrroloindole (176d)

The pyrroloindole (176d) (0.10g, 0.39 mmol) was dissolved in a mixture of methanol (40 ml), water (6 ml) and 2.4M hydrochloric acid (4 ml). The solution was kept at room temperature for 7 days. After this time t.l.c. showed the presence of a new compound as well as a considerable amount of unreacted starting material. Water (6 ml) and 2.4M hydrochloric acid (4 ml) were added, and after 24h more 2.4M hydrochloric acid (8 ml) was added. The solution was stirred at room temperature for a further 7 days, after which t.l.c. indicated almost complete reaction. The reddish solution was neutralised with solid sodium hydrogen carbonate and most of the methanol evaporated *in vacuo*. The aqueous suspension was then extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$) and evaporated, and the resulting reddish material was chromatographed on silica gel, eluting with petrol/ether. Two bands were obtained, the faster band (4 mg, 4%) proved to be unreacted starting material. The slower band was the deprotected compound: *methyl 1,8-dihydropyrrolo[2,3-b]indole-2-carboxylate* (179) (33 mg, 40%) which was recrystallized from methanol/nitromethane giving small prisms, m.p. 230-6°C (lit.,[36] 229 - 31°C) (Found: C, 67.10; H, 4.73; N, 12.92. $C_{12}H_{10}N_2O_2$ requires: C, 67.28; H, 4.71; N, 13.08%);

ν_{max} (nujol): 3370 (NH), 3280 (NH), 1655 (C = O), 1626, 1597 cm^{-1};

δ_H (250 MHz; d_6-DMSO): 3.78 (3H, s, CO_2Me), 7.06 (2H, m, 5-H and 6-H), 7.13 (1H, s, 3-H), 7.33 (1H, m, 4-H or 7-H), 7.62 (1H, m, 7-H or 4-H), 11.11 (1H, br s, NH), 11.90 (1H, br s, NH);

m/z: 214 (M^+, 82), 182 (100), 154 (69), 127 (44).

(iii) *N*-methylation of pyrroloindole (176a)

Sodium hydride (50% suspension in paraffin oil, 0.026g, 0.54 mmol, 1.3 equiv.) was de-oiled by washing with petrol and suspended in DMF (2 ml). The pyrroloindole (176a) (0.10g, 0.41 mmol) was added at room temperature as a solution in DMF (1 ml), and the mixture was stirred at room temperature under a nitrogen atmosphere for 10 minutes. Methyl iodide (0.43g, 190 µl, 7.2 equiv.) was added, and stirring was continued at room temperature for 4h. The mixture was then poured into water and extracted with ether. The combined ethereal extracts were washed with water, dried ($MgSO_4$) and evaporated, and the resulting oily solid was recrystallized from ether giving needles of *ethyl 1,8-dihydro-1,8-dimethylpyrrolo[2,3-b]indole-2-carboxylate* (180a) (0.093g, 82%), m.p. 134.5-6°C (Found: C, 70.60; H, 6.29; N, 11.11. $C_{15}H_{16}N_2O_2$ requires C, 70.29; H, 6.29; N, 10.93%);

ν_{max} (nujol): 1697 (C = O), 1624, 1585, 1573 cm^{-1}.

δ_H (90 MHz, $CDCl_3$): 1.32 (3H, t, *J* 7.4 Hz, $CO_2CH_2CH_3$); 3.77 (3H, s, NMe), 4.14 (3H, s, NMe), 4.28 (2H, q, *J* 7.4 Hz, $CO_2CH_2CH_3$), 7.18 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.29 (1H, s, 3-H), 7.66 (1H, m, 7-H or 4-H);

m/z: 256 (M^+, 100%), 228 (84), 184 (52).

(iv) *N*-methylation of pyrroloindole (176d)

The pyrroloindole (176d) (1.0g, 3.88 mmol) was added as a solution in DMF (10 ml) to a suspension of sodium hydride (50% suspension in paraffin oil, 0.466g, 9.71 mmol, 2.5 equiv.) in DMF (5 ml). The mixture was warmed to 70°C and stirred for 2h. After this time, methyl iodide (0.91g, 0.40 ml, 1.66 equiv.) was added, and the mixture was stirred for a further 0.5h, after which it was poured into water and extracted with ether. The combined ethereal extracts were dried ($MgSO_4$) and evaporated and the resulting off-white gum was triturated with petrol, giving as a solid, *methyl 1,8-dihydro-8-methoxymethyl-1-methylpyrrolo[2,3-b]indole-2-carboxylate* (180b) (0.882g, 84%) which was recrystallized from methanol giving prisms, m.p. 106-7.5°C (Found: C, 66.13; H, 5.90; N, 10.28. $C_{15}H_{16}N_2O_3$ requires C, 66.16; H, 5.92; N, 10.29%);

ν_{max} (nujol): 1704 (C=O), 1615, 1580, 1575 sh cm^{-1};

δ_H (250 MHz, $CDCl_3$): 3.30 (3H, s, CH_2OMe), 3.84 (3H, s, NMe), 4.23 (3H, s, CO_2Me), 5.56 (2H, s, CH_2OMe), 7.20 (2H, m, 5-H and 6-H), 7.29 (1H, s, 3-H), 7.37 (1H, m, 4-H or 7-H), 7.67 (1H, m, 7-H or 4-H);

δ_C (62.9 MHz; $CDCl_3$): 32.95 (69%), 50.68 (78), 55.79 (65), 74.39 (92), 108.87 (86), 109.20 (100), 109.32 (28), 119.41 (79), 120.79 (95), 121.56 (19), 121.75 (26), 122.15 (77), 142.72 (27), 143.83 (17), 162.23 (17);

m/z: 272 (M^+, 91%), 241 (29), 227 (100).

(v) Deprotection of the pyrroloindole (180b)

The pyrroloindole (180b) (0.75g, 2.76 mmol) was dissolved in a mixture of methanol (225 ml), water (75 ml) and 2.4M hydrochloric acid (30 ml). The solution was stirred at room temperature for 5 days, when

t.l.c. showed complete consumption of all starting material. The solution was neutralized with solid sodium hydrogen carbonate and concentrated *in vacuo*. The resulting suspension was extracted with ethyl acetate, and the combined extracts were dried ($MgSO_4$) and evaporated. The resulting brownish solid was purified by filtration through a thin pad of silica gel, eluting with ether. Evaporation of the ethereal solution gave as a buff powder *methyl 1,8-dihydro-1-methylpyrrolo[2,3-b]indole-2-carboxylate* (181) (0.575g, 91%) which was recrystallized from methanol, m.p. 185-90°C dec. (Found: C, 68.11; H, 5.32; N, 12.09. $C_{13}H_{12}N_2O_2$ requires C, 68.41; H, 5.30; N, 12.27%);

ν_{max} (nujol): 3230, 3190 sh (NH), 1645 (C = O), 1623, 1602 cm^{-1}.

δ_H (250 MHz, d_6-DMSO): 3.74 (3H, s, NMe), 3.96 (3H, s, CO_2Me), 7.09 (2H, m, 5-H and 6-H), 7.21 (1H, s, 3-H), 7.36 (1H, m, 4-H or 7-H), 7.64 (1H, m, 7-H or 4-H), 11.41 (1H, br s, NH);

m/z: 228 (M^+, 100%), 197 (32), 170 (35).

(vi) *N*-allylation of pyrroloindole (181)

The pyrroloindole (181) (0.250g, 1.38 mmol) was dissolved in DMF (5 ml) and added at room temperature to a suspension of sodium hydride (50% suspension in paraffin oil, 0.158g, 3.29 mmol, 2.4 equiv.) in DMF (5 ml). Upon completion of addition, the suspension was stirred for 1h, and then allyl bromide (180 µl, 2.07 mmol, 1.5 equiv.) was added. Further stirring for 1h was followed by aqueous work-up, extraction with ether, drying ($MgSO_4$), and evaporation of the ether. The resulting gum was purified by filtration through a pad of silica gel, eluting with petrol/ether. Evaporation of the resulting solution gave a light yellow gum (0.284g, 97%) which was distilled (Kugelrohr) and crystallized from petrol giving colourless plates of *methyl 8-allyl-1,8-dihydro-1-*

methylpyrrolo[2,3-b]indole-2-carboxylate (182), m.p. 85-7°C (Found: C, 71.78; H, 6.08; N, 10.43. $C_{16}H_{16}N_2O_2$ requires C, 71.62; H, 6.01; N, 10.44%);

ν_{max} (nujol): 1703 (C=O), 1624, 1586, 1578 cm^{-1};

δ_H (250 MHz; $CDCl_3$): 3.83 (3H, s, NMe), 4.16 (3H, s, CO_2Me), 4.89 (2H, m, CH_2-CH=CH_2), 4.97 (1H, d, *J* 17 Hz with some fine splitting, *trans* proton of CH_2-CH=CH_2), 5.20 (1H, d, *J* 10.5 Hz with some fine splitting, *cis* proton of CH_2-CH=CH_2), 6.04 (1H, ddt, *J* 17, 10.5, 4.2 Hz, CH_2-CH=CH_2), 7.17 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.31 (1H, s, 3-H), 7.69 (1H, m, 7-H or 4-H);

m/z: 268 (M^+, 87%), 227 (100).

(vii) Attempted dehydrogenation of (179) with DDQ

The pyrroloindole (179) (0.025g, 0.12 mmol) was dissolved in THF (15 ml), and to this solution at room temperature was added a solution of DDQ (0.026g, 0.11 mmol, 1 equiv.) in THF (5 ml). The mixture was stirred at room temperature for 10 minutes during which time it became very dark. Examination of the material produced, by t.l.c. and n.m.r., showed the presence of highly complex polymeric materials only.

(viii) Reduction of pyrroloindole (180b) with LAH

A solution of pyrroloindole (180b) (0.228g, 0.84 mmol) in THF (7 ml) was added to a suspension of LAH (0.064g, 1.68 mmol, 2 equiv.) in THF. The resulting mixture was stirred overnight under an atmosphere of nitrogen, at room temperature. Careful addition of water destroyed any excess LAH. Extraction with ethyl acetate, drying of the organic solution ($MgSO_4$) and evaporation gave a semi-solid material which was

chromatographed on silica yielding one major band, a solid (0.081g, 44%). This was recrystallized from methanol/nitromethane, to give small plates of *bis(1,8-dihydro-8-methoxymethyl-1-methylpyrrolo[2,3-b]indol-2-yl) methane* (184), m.p. 220-5°C dec. (Found: C, 73.56; H, 6.33; N, 12.80. $C_{27}H_{28}N_4O_2$ requires C, 73.61; H, 6.41; N, 12.72%);

ν_{max} (nujol): 1610w, 1573, 1561 sh, 1557, 1513, 1291, 1104, 1065, 1045 cm^{-1}.

δ_H (250 MHz, $CDCl_3/d_6$-DMSO): 3.26 (6H, s, CH_2OMe), 3.86 (6H, s, NMe), 4.18 (2H, s, $-CH_2-$), 5.67 (4H, s, CH_2OMe), 6.12 (2H, s, 3-H), 7.05 (4H, m, 5-H and 6-H), 7.48 (4H, m, 4-H and 7-H);

m/z: 440 (M^+, 100%), 395 (25).

(ix) Base hydrolyses of pyrroloindole (180b)

a) The pyrroloindole (180b) (0.392g, 1.44 mmol) was dissolved in methanol (50 ml), 1M sodium hydroxide solution (8 ml) and water (17 ml). The mixture was heated on an oil bath at 100°C for 2.5h, after which careful acidification to *ca.* pH 6 caused the solution to become cloudy. Extraction with ethyl acetate, drying ($MgSO_4$) of the organic solution and evaporation gave a pale blue oily solid. Washing of this material with hot petrol left a pale blue powder (0.166g, 45%) which could be recrystallized from methanol/nitromethane, affording tiny crystals of *1,8-dihydro-8-methoxymethyl-1-methylpyrrolo[2,3-b]indole-2-carboxylic acid* (186), m.p. 124-6°C (Found: M^+ = 258.1010. $C_{14}H_{14}N_2O_3$ requires M^+ = 258.1004);

ν_{max} (nujol mull): 2560-3120 (OH), 1665 (C=O), 1620, 1584, 1577 cm^{-1};

δ_H (90 MHz; d_6-DMSO): 3.21 (3H, s, CH_2OMe), 4.16 (3H, s, NMe), 5.71 (2H, s, CH_2OMe), 7.16 (2H, m, 5-H and 6-H), 7.19 (1H, s, 3-H), 7.60 (2H, m, 4-H and 7-H);

m/z: 258 (M^+, 35%), 214 (62), 169 (100).

The petrol washings were chromatographed on silica and yielded, as a colourless oil *1,8-dihydro-8-methoxymethyl-1-methylpyrrolo[2,3-b]indole* (187) (0.075g, 24%) (Found: M^+ = 214.1110. $C_{13}H_{14}N_2O$ requires: M^+ = 214.1106);

ν_{max} ($CHCl_3$): 1608w, 1561, 1449, 1106 cm^{-1};

δ_H (250 MHz; $(CD_3)_2CO$): 3.23 (3H, s, CH_2OMe), 3.91 (3H, s, NMe), 5.69 (2H, s, CH_2OMe), 6.31 (1H, d, *J* 3.1 Hz, 3-H), 6.54 (1H, d, *J* 3.1 Hz, 2-H), 7.06 (2H, m, 5-H and 6-H), 7.54 (2H, m, 4-H and 7-H).

b) The pyrroloindole (180b) (0.10g, 0.37 mmol) was dissolved in methanol (24 ml) and 1M sodium hydroxide solution (11 ml, 30 equiv.). The resulting solution was refluxed for 24h, after which it was allowed to stand at room temperature for 24h. Acidification and extraction with ethyl acetate gave a dark blue organic solution which was dried ($MgSO_4$) and evaporated, giving a dark blue semi-solid. This material did not seem to be very stable on analytical silica gel t.l.c. plates, but rapid p.l.c. of this material, eluting with petrol/ether led to the isolation of two bands. The faster band proved to be the decarboxylated pyrroloindole (187) (0.029g, 37%), while the other band was the bis(pyrrolo[2,3-b]indolyl) methane (184) (0.006g, 7%).

(x) Formylation of (187)

To phosphorus oxychloride (0.056g, 0.36 mmol), was added DMF (0.3 ml) and the solution stirred, with cooling in an ice bath, for 1h. The pyrroloindole (187) (0.075g, 0.35 mmol) in DMF (0.5 ml) was then added, and the mixture was allowed to warm to room temperature, and then heated at 40°C for 0.5h. Sodium hydroxide solution (10%, 3 ml) was

then added, and the mixture heated to 70°C and kept at that temperature for 0.5h. Pouring into water, ethereal extraction, washing and drying ($MgSO_4$) of the organic layers gave the crude *1,8-dihydro-8-methoxymethyl-1-methylpyrrolo[2,3-b]indole-3-carbaldehyde* (188) as an oil which was crystallized from ethanol/petrol, m.p. 104.5 - 106.5°C. (Found: C, 69.12; H, 5.81; N, 11.50. $C_{14}H_{14}N_2O_2$ requires C, 69.41; H, 5.82; N, 11.56%).

ν_{max} (nujol): 1645 (C = O), 1619, 1584 cm^{-1};

δ_H (250 MHz; $CDCl_3$): 3.33 (3H, s, CH_2OMe), 4.30 (3H, s, NMe), 5.59 (2H, s, CH_2OMe), 7.14 (1H, s, 2-H), 7.26 (2H, m, 5-H and 6-H), 7.40 (1H, m, 4-H or 7-H), 7.72 (1H, m, 7-H or 4-H), 9.47 (1H, s, CHO);

m/z: 242 (M^+, 100%), 211 (24), 197 (33), 169 (19), 168 (14).

3. Thermolysis of 1-azido-2(indol-3-yl)alkenes (157)

(i) Thermolysis of 1-azido-2(indol-3-yl)ethene (157a)

The 1-azido-2(indol-3-yl)ethene (157a) (0.082g, 0.45 mmol) was heated in refluxing toluene (16 ml). Over a period of 5 minutes the solution darkened dramatically to a deep violet. Evaporation of the toluene left a dark gummy residue. Analysis by n.m.r. and t.l.c. showed this to be a complex, presumably polymeric material, and it was discarded.

(ii) Thermolysis of 1-azido-2(*N*-methylindol-3-yl)ethene (157b)

The 1-azido-2(1-methylindol-3-yl)ethene (157b) (0.05g, 0.25 mmol) was heated in refluxing toluene (10 ml). Over a period of 5 minutes darkening to a violet colour occurred. Evaporation of the toluene left a gum. The n.m.r. showed this to consist of one major compound having δ (90 MHz; $CDCl_3$) 3.49 (s, NMe) and 6.44 (2H, ABq, $J \simeq 3$ Hz) *inter alia*. Attempted purification of this material by p.l.c. on silica gel resulted in its complete decomposition.

4. Attempts to construct the cyclic diamide (219b)

(i) Using methyl anthranilate

a) The pyrroloindole (176d) (0.05g, 0.19 mmol) and methyl anthranilate (0.046g, 0.30 mmol, 1.6 equiv.) were heated in refluxing benzene (10 ml) containing sodium methoxide[123] (0.014g, 0.26 mmol, 1.5 equiv.), under a Dean-Stark trap, the limb of which was filled with calcium chloride. After 6h, examination by t.l.c. showed only the presence of starting materials.

b) To a suspension of sodium hydride (50% suspension in paraffin oil, 0.023g, 0.48 mmol, 1.2 equiv.) in DMF (5 ml), was added a solution in

DMF (5 ml) of the pyrroloindole (176d) (0.10g, 0.39 mmol), after heating at 70°C for 2h, methyl anthranilate (0.064g, 0.42 mmol, 1.1 equiv.) was added, and the mixture was heated at 70-90°C overnight. Aqueous work-up and ethereal extraction etc. gave a material which proved to contain only starting materials when examined by n.m.r.

(ii) Attempted reaction of amines with pyrroloindoles (176d) and (180b)

a) pyrroloindole (176d) (0.10g, 0.39 mmol) was suspended in methanol (15 ml) and treated with excess concentrated aqueous ammonia. The resulting mixture was heated at reflux for 20h. When it was allowed to cool a solid precipitated, and this was collected by filtration, and dried. It was shown to be the starting pyrroloindole by n.m.r.

b) Pyrroloindole (180b) (0.03g, 0.11 mmol) was suspended in methanol (10 ml) and treated with excess hydrazine hydrate. The mixture was heated at reflux for 3h, after which time t.l.c. showed no new compound.

c) The pyrroloindole (176d) (0.10g, 0.39 mmol) was heated at 120°C in aniline (15 ml) overnight under a nitrogen atmosphere, and then for a further 7h at 180°C. The solution was poured into 3M hydrochloric acid and extracted with ether. The combined ethereal layers were washed twice with 3N hydrochloric acid and then three times with water. Drying ($MgSO_4$) and evaporation gave a dark solid which was chromatographed on a silica gel p.l.c. plate eluting with petrol/ether. One band was isolated, and was shown by n.m.r. and mass spectroscopy to be the pyrroloindole (179) (0.038g, 46%).

(iii) Using isatoic anhydride[124,125]

a) Isatoic anhydride (221) (0.114g, 0.70 mmol, 1 equiv.) and the pyrroloindole (176d) (0.181g, 0.70 mmol) were heated in refluxing pyridine (10 ml) for 8h. Work-up was effected by pouring into aqueous hydrochloric acid, extraction with ethyl acetate etc. Examination of the

resulting solid by t.l.c. and n.m.r. indicated that only the starting pyrroloindole was present.

b) A solution of pyrroloindole (176d) (0.25g, 0.97 mmol) in DMF (10 ml) was added to a suspension of sodium hydride (50% suspension in paraffin oil, 0.06g, 1.26 mmol, 1.3 equiv.) in DMF (5 ml). The mixture was stirred for 1h, and then a solution of isatoic anhydride (0.158g, 0.97 mmol, 1 equiv.) in DMF (5 ml) was added. This mixture was heated at $80^{o}C$ for 4h, after which it was poured into water and extracted with ethyl acetate. Drying ($MgSO_4$) and evaporation of the combined organic extracts gave a solid. Examination of this by n.m.r. and t.l.c. showed that only starting material was present.

c) A solution of pyrroloindole (176d) (0.20g, 0.78 mmol) in THF (10 ml) was added to a suspension of sodium hydride (50% suspension in paraffin oil, 0.041g, 0.85 mmol, 1.1 equiv.) in THF (7 ml) and HMPA (2 ml). After stirring at room temperature for 0.5h, a solution of isatoic anhydride (0.127g, 0.78 mmol, 1 equiv.) in a mixture of THF (3 ml) and HMPA (1 ml) was added. The mixture was stirred at room temperature for 1h and then at reflux for 4h. Examination by t.l.c. showed only the presence of starting material after this time.

(iv) Using 2-nitrobenzoyl chloride

a) The pyrroloindole (176d) (0.954g, 3.70 mmol) was dissolved in THF (12 ml) and the solution was added to a suspension of sodium hydride (50% suspension in paraffin oil, 0.53g, 11.10 mmol, 3 equiv.) in THF (5 ml). The mixture was refluxed for 1h and then 2-nitrobenzoyl chloride (0.824g, 4.44 mmol, 1.2 equiv.) was added. After stirring at room temperature for 5h, t.l.c. showed the presence of a new yellow compound as well as unreacted starting material. More 2-nitrobenzoyl chloride (0.21g, 1.11 mmol, 0.3 equiv.) was added, and stirring continued

overnight. The mixture was then poured into water and extracted with ether. The combined ethereal extracts were washed with water, dried ($MgSO_4$) and evaporated, giving a brownish solid. Chromatography on silica gel gave the intensely yellow *methyl 1,8-dihydro-8-methoxymethyl-1-(2-nitrobenzoyl)pyrrolo[2,3-b]indole-2-carboxylate* (223) (0.955g, 65%). This compound darkened on storage at room temperature in contact with air and light, and thus necessary precautions had to be taken. It was used without further purification.

ν_{max} (nujol): 1727 (C = O), 1715 (C = O) cm^{-1};

δ_H (60 MHz; $CDCl_3$): 3.22 (3H, s, CH_2OMe), 3.42 (3H, s, CO_2Me), 5.90 (CH_2OMe), 7.15 - 8.10 (8H, m, Ar-H), 7.42 (1H, s, 3-H);

m/z: 407 (M^+, 2%), 391 (2), 362 (3), 361 (2), 300 (3), 258 (14), 257 (12), 140 (100).

b) The 1-(2-nitrobenzoyl)pyrroloindole (223) (0.10g, 0.25 mmol) was dissolved in methanol, and hydrogenated over 10% palladium-charcoal (0.05g) at atmospheric pressure for 3.5h. After this time t.l.c. (on alumina) indicated the presence of the cleaved pyrroloindole (176d) and a new compound running significantly faster. Isolation was effected by repeated p.l.c. on silica gel and crystallization from methanol, whereby yellow prisms could be obtained of *methyl 1-(2-aminobenzoyl)-1,8-dihydro-8-methoxymethylpyrrolo[2,3-b]indole-2-carboxylate* (222) (0.022g, 24%), m.p. 185-7°C (Found: C, 66.64; H, 4.98; N, 11.09. $C_{21}H_{19}N_3O_4$ requires: C, 66.83; H, 5.07; N, 11.13%);

ν_{max} (nujol): 3470, 3330 (NH_2), 1690 (C = O), 1673 (C = O), 1624, 1562, 1555 cm^{-1};

δ_H (250 MHz, $CDCl_3$): 2.98 (3H, s, CH_2OMe), 3.67 (3H, s, CO_2Me), 5.38 (2H, br s, CH_2OMe), 6.11 (2H, br s, NH_2), 6.45 (1H, ddd, *J* 7.9, 6.9, 0.9 Hz, 5-H of benzoyl ring), 6.71 (1H, d, *J* 8.3 Hz, 3-H of benzoyl ring), 6.83 (1H, dd, *J* 7.9, 1.7 Hz, 6-H of benzoyl ring), 7.26 (3H, m, 4-H of benzoyl ring, 5-H and 6-H), 7.41 (1H, m, 4-H or 7-H), 7.41 (1H, s, 3-H), 7.77 (1H, m, 7-H or 4-H);

m/z: 377 (M^+, 29%), 258 (100).

c) The 1-(2-nitrobenzoyl)pyrroloindole (223) was dissolved in aqueous THF (3:7 by volume, 10 ml) and treated with excess sodium dithionite (*ca* 6 equiv.) for 2h.[128] The whole mixture was extracted with ether, and the ethereal extracts dried ($MgSO_4$) and evaporated. The n.m.r. of the crude product showed an approximately 1:1 ratio of (222) and 176d).

(v) Attempts to ring close the amine (222)

a) The 1-(2-aminobenzoyl)pyrroloindole (222) (0.011g, 0.03 mmol) was heated in refluxing toluene (10 ml) with a catalytic amount of sodium methoxide for 18h. Aqueous work-up, drying of the organic layer and evaporation gave a gum. The n.m.r. spectrum gave no useful information and the material was discarded.

b) The 1-(2-aminobenzoyl)pyrroloindole (222) (0.015g, 0.04 mmol) was heated in refluxing xylene (5 ml) for 18h. After this time t.l.c. examination showed only the presence of starting material.

c) The 1-(2-aminobenzoyl)pyrroloindole (222) (0.007g, 0.019 mmol) was dissolved in water (2 ml) and THF (2 ml)) to which 1M hydrochloric acid (10 drops) had been added. The mixture was stirred at 70°C for 18h.[125] One new slower running compound was observed on t.l.c. This was isolated after basic work-up, by p.l.c. (0.003g). Its n.m.r., though

weak, appeared to indicate simple cleavage of the methoxymethyl group.

(vi) Synthesis of azidoamide (225)

To an ice-cooled solution of methyl anthranilate (3.41g, 22.6 mmol) and triethylamine (3.147 ml, 22.6 mmol, 1 equiv.) in ether (50 ml), was added chloroacetyl chloride (1.80 ml, 22.6 mmol, 1 equiv.) over 5 minutes, with constant stirring. The resulting slurry was allowed to warm to room temperature, and the triethylammonium chloride was collected by filtration. The ethereal solution was evaporated, and the residue crystallized from methanol/petrol, giving needles of *methyl 2-chloroacetamidobenzoate*.

ν_{max} (nujol): 3200 (NH), 1703 (C = O), 1680 (C = O), 1610, 1600, 774 cm^{-1};

δ_H (60 MHz, $CDCl_3$): 3.97 (3H, s, CO_2Me), 4.20 (2H, s, $COCH_2Cl$), 7.13 (1H, ddd, J 8, 7, 1.5 Hz, 5-H), 7.60 (1H, ddd, J 8, 7, 1.5 Hz, 4-H), 8.10 (1H, dd, J 8, 1.5 Hz, 3-H), 8.75 (1H, dd, J 8, 1.5 Hz, 6-H), 11.93 (1H, br s, NH).

The chloroamide just described (2.0g, 8.8 mmol) and sodium azide (0.86g, 13.2 mmol, 1.5 equiv.) were heated overnight in refluxing 60% aqueous acetone (200 ml). After cooling, the acetone was removed by evaporation, and the resulting suspension was extracted with ether. Drying ($MgSO_4$) and evaporation of the combined ethereal layers gave white crystalline *methyl 2-azidoacetamidobenzoate* (225) (2.20g, 98%);

ν_{max} (nujol): 3260 (NH), 2130 (N_3), 1704 (C = O), 1688 (C = O), 1610, 1595 cm^{-1};

δ_H (90 MHz, $CDCl_3$): 3.98 (3H, s, CO_2Me), 4.14 (2H, s, $COCH_2N_3$), 7.13 (1H, ddd, J 8, 7, 1.5 Hz, 5-H), 7.56 (1H, ddd, J 8, 7, 1.5 Hz, 4-H), 8.03 (1H, dd, J 8, 1.5 Hz, 3-H), 8.67 (1H, dd, J 8, 1.5 Hz, 6-H), 11.63 (1H, br s, NH).

(vii) Attempted condensation of azidoamide (225) with 1-methoxymethylindole-3-carbaldehyde

The azidoamide (225) (1.50g, 6.41 mmol, 4 equiv.) and 1-methoxymethylindole-3-carbaldehyde (0.302g, 1.60 mmol) were dissolved in methanol and added over *ca.* 0.5h to a solution of sodium (0.147g, 6.40 mmol, 4 equiv.) in methanol (5 ml) which had been cooled to -5°C. The mixture was stirred at 0°C for 4h after which time there was no indication of reaction by t.l.c.. The mixture was then allowed to warm to room temperature and stirred for 18h. The t.l.c. still showed no product formation, so the mixture was heated at 50-60°C for 8h. The crude t.l.c. then showed five spots. The mixture was worked up as in the case of the azidoacetate condensations, and the crude brown gum produced was chromatographed on silica gel. Along with 1-methoxymethylindole-3-carbaldehyde (quantitative recovery), four compounds were isolated. The n.m.r. spectra of these showed them to be anthranilate derived materials, and they were not investigated further.

5. Attempts to reduce the 2,3-double bond in the pyrroloindole systems.

(i) With borane-trimethylamine complex.[129]

To a solution of (176d) (0.10g, 0.39 mmol) and borane-trimethylamine complex (0.113g, 1.55 mmol, 4 equiv.) in dioxan (10 ml) was added concentrated hydrochloric acid (10 drops). The mixture initially became green, the colour changing to violet on warming. Refluxing for 0.5h and cooling was followed by addition of 6M hydrochloric acid (20 drops) and further refluxing for 0.25h. The dioxan was then evaporated, and the aqueous suspension was treated with solid sodium bicarbonate, and extracted with ether. The ethereal layer was dried ($MgSO_4$) and evaporated giving a dark semi-solid. Chromatography on a silica gel

p.l.c. plate gave a solid which was crystallized from methanol/nitromethane. Comparison of its spectra with the ethoxycarbonyl compound (176a) strongly suggested that this compound was *methyl 1,8-dihydro-8-methylpyrrolo[2,3-b]indole-2-carboxylate* (228) (0.028g, 32%);

ν_{max} (nujol): 3280 (NH), 1652 (C = O), 1630, 1594 cm^{-1};

δ_H (250 MHz, $CDCl_3/d_6$-DMSO): 3.80 (3H, s, NMe), 3.81 (3H, s, CO_2Me), 7.13 (2H, m, 5-H and 6-H), 7.15 (1H, s, 3-H), 7.39 (1H, m, 4-H or 7-H), 7.66 (1H, m, 7-H or 4-H), 10.81 (1H, br s, NH);

m/z: 228 (M^+, 98%), 196 (100), 168 (96).

(ii) With sodium cyanoborohydride in glacial acetic acid[130]

To a solution of pyrroloindole (180b) (0.10g, 0.37 mmol) in glacial acetic acid (10 ml) was added excess sodium cyanoborohydride (*ca.* 10 equiv.). After stirring at room temperature for 1h, the t.l.c. showed no product formation, and thus the reaction mixture was heated to 60-70°C and stirred at that temperature for 2h. The t.l.c. then showed two spots, a product and unreacted starting material. An additional quantity of sodium cyanoborohydride (*ca.* 5 equiv.) was added and heating continued for a further 2h. At this time, t.l.c. showed complete consumption of starting material, and the solution was then poured into water. Treatment with excess solid sodium bicarbonate, extraction with ether, washing, drying ($MgSO_4$) and evaporation of the ethereal layers gave as an off-white solid *methyl 1,8-dihydro-1,8-dimethylpyrrolo[2,3-b]indole-2-carboxylate* (229) (0.078g, 88%) which gave colourless prisms from methanol, m.p. 133.5-6°C (Found: C, 69.40; H, 5.81; N, 11.52. $C_{14}H_{14}N_2O_2$ requires: C, 69.40; H, 5.82; N, 11.56%);

ν_{max} (nujol): 1690 (C = O), 1620, 1584 cm^{-1};

δ_H (90 MHz, $CDCl_3$): 3.88 (6H, s, 2 × NMe), 4.23 (3H, s, CO_2Me), 7.25 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.30 (1H, s, 3-H), 7.67 (1H, m, 7-H or 4-H);

m/z: 242 (M^+).

(iii) With zinc dust in phosphoric acid[131]

The pyrroloindole (180b) (0.10g, 0.37 mmol) was added as a solid to a suspension of zinc dust (0.072g, 1.10 mmol, 3 equiv.) in 85% phosphoric acid (2 ml) which had previously been warmed to 80°C. The orange-brown solution was stirred at this temperature for 1h, after which time the t.l.c. showed complete consumption of the starting material and formation of a new slower running compound. The mixture was poured into water and treated with solid sodium bicarbonate. Extraction with ethyl acetate, drying of the resultant organic layer ($MgSO_4$) and evaporation, gave a greenish gum from which one compound, a solid, was isolated by silica gel p.l.c.. Comparison of its spectra showed this to be the pyrroloindole (181) (0.011g, 13%).

(iv) Attempted catalytic hydrogenation

The pyrroloindole (176d) (0.10g, 0.39 mmol) was dissolved in methanol (40 ml) and 10% palladium on charcoal (0.01g) was added. The mixture was hydrogenated at 50 atm. for 48h. Subsequently the solution was filtered through Celite, and evaporated, giving a buff solid which was shown by n.m.r. and t.l.c. to be the starting pyrroloindole (176d).

(v) Attempted dissolving metal reduction

The pyrroloindole (180b) (0.10g, 0.37 mmol) was dissolved in THF (5 ml) and added to liquid ammonia (*ca.* 10 ml). Small pieces of sodium were added until the blue colour persisted. Then, solid ammonium chloride was added, giving a yellow solution from which excess ammonia

was allowed to evaporate. Water was added and the whole mixture was extracted with ether. The combined ethereal extracts were dried and evaporated yielding a brown gum. The n.m.r. spectrum of this material showed it to be a complex mixture of unknown nature and it was discarded.

(vi) Reduction of (180b) with Paquette's "cuprous hydride".

To a suspension of cuprous bromide (0.832g, 5.8 mmol, 10.5 equiv.) in anhydrous THF (10 ml) at $0^{o}C$ under an atmosphere of nitrogen, was added Red-Al solution (a 3.5M solution of sodium bis(2-methoxyethoxy) aluminium hydride in toluene, 3.4 ml, 11.9 mmol, 21.6 equiv.). The resulting solution was stirred at $0^{o}C$ for 0.5h and then brought to $-78^{o}C$. Cautious introduction of 2-butanol (1.0 ml, 10.9 mmol, 19.85 equiv.) followed by a solution of pyrroloindole (180b) (0.150g, 0.55 mmol) in THF (5 ml) was then effected. The dark mixture was stirred at $-78^{o}C$ for 2h and then allowed to warm to room temperature. Stirring was continued for a further 4h and then saturated ammonium chloride solution was added. Normal aqueous work-up and ethereal extraction, drying ($MgSO_4$) and evaporation gave a dark gum which by its crude n.m.r. and t.l.c. appeared to consist of three compounds. Column chromatography on silica gel eluting with petrol/ether gave three fractions. The rear band was shown by n.m.r. to consist of rather impure (184) (0.02g, 16%), the middle band was recovered starting material (180b) (0.026g, 17%). The front running material was *1,8-dihydro-1,2-dimethyl-8-methoxymethyl-pyrrolo[2,3-b]indole* (230) (0.022g, 17%) which could be crystallized from petrol giving needles; (Found: M^+ = 228.1263. $C_{14}H_{16}N_2O$ requires: M^+ = 228.1263);

ν_{max} (nujol): 1609m, 1572, 1560, 1518, 1460, 1380, 1110, 1070, 913, 739 cm^{-1};

δ_H (90 MHz, $CDCl_3$): 2.39 (3H, d, *J ca.* 1.0 Hz, 2-Me), 3.27 (3H, s, CH_2OMe), 3.78 (3H, s, NMe), 5.57 (2H, s, CH_2OMe), 6.20 (1H, q, *J ca.* 1.0 Hz, 3-H), 7.16 (2H, m, 5-H and 6-H), 7.35 (1H, m, 4-H or 7-H), 7.59 (1H, m, 7-H or 4-H);

m/z: 228 (M^+, 53%), 197 (22), 183 (100).

6. Attempts to introduce a bridgehead substituent at the 3a-position

(i) Attempted formation of the *N*-Grignard reagents

a) To magnesium turnings (0.05g, 2.08 mmol) was added ether (10 ml) and ethyl bromide (0.225g, 0.154 µl, 2.06 mmol). A small crystal of iodine was carefully introduced, and the mixture was stirred without external heating under an atmosphere of nitrogen until all the magnesium had reacted. Then the pyrroloindole (176a) (0.50g, 2.07 mmol) was added as a solution in THF (*ca.* 15 ml). A deep red colouration developed in the solution upon addition of the pyrroloindole solution, but this was not discharged by addition of excess methyl iodide. The solution was stirred at room temperature for 4h and then refluxed for 4h. After this time the t.l.c. showed only the presence of starting material. Water was added but the red colouration was still not discharged. The mixture was then extracted with ethyl acetate, and the organic layer was dried ($MgSO_4$) and evaporated, giving only starting material.

b) Ethylmagnesium bromide was formed as above from magnesium (0.026g, 1.08 mmol) and ethyl bromide (82 µl, 1.07 mmol), and the pyrroloindole (181) (0.250g, 1.17 mmol) was added as a THF solution. Similar treatment to that described above gave a reddish brown solution which was shown by t.l.c. to contain only starting material, and some highly polar material which did not run off the baseline. Work-up as described above gave a solid shown by n.m.r. to be starting material.

c) Ethylmagnesium bromide was formed from magnesium (0.024g, 1.0 mmol) and ethyl bromide (72 μl, 0.94 mmol). To this Grignard solution the pyrroloindole (176d) (0.250g, 0.97 mmol) was added as a THF solution. Similar treatment to that described above was employed except that instead of methyl iodide, allyl bromide (84 μl, 1.02 mmol) was added. Normal work-up gave a solid which was shown by n.m.r. to be the starting material.

7. Alkylations of (176d) with allylic halides, and rearrangement reactions of some of the resulting products

(i) Attempted rearrangements of model system (182)

a) The pyrroloindole (182) (*ca.* 0.05g) was heated in refluxing *o*-dichlorobenzene for 24h. Removal of the solvent under vacuum gave a gum which was shown by n.m.r. to consist essentially of the starting compound (182).

b) The pyrroloindole (182) (0.245g, 0.91 mmol) was dissolved in spectroscopic grade cyclohexane (200 ml) and the resulting solution was irradiated at 300 nm for 0.5h while a current of nitrogen was bubbled through. After this time t.l.c. showed that no reaction had taken place, and the solution was then irradiated at 254 nm for a further 5h, maintaining the nitrogen current. Evaporation of the solvent left a dark gum which was shown to consist essentially of the starting material (242), by n.m.r. and t.l.c.

c) The pyrroloindole (182) (*ca.* 0.05g) was heated with aluminium chloride (excess) in refluxing benzene for 0.5h, after which time the t.l.c. of the reaction mixture indicated complete conversion to dark highly polar materials, the mixture was therefore discarded.

(ii) Treatment of the *N*-sodium salt of (176d) with allyl bromide.

The pyrroloindole (176d) (0.50g, 1.94 mmol) was added as a solution in DMF (5 ml) to a suspension of sodium hydride (50% suspension in paraffin oil, 0.280g, 5.82 mmol, 3 equiv.) in DMF (5 ml), and allowed to stir for 1h at room temperature. Allyl bromide (252 µl, 2.91 mmol, 1.5 equiv.) was then added, and stirring at room temperature was continued for 1h. The mixture was then poured into water and extracted with ether. The ethereal layers were washed with water, dried ($MgSO_4$) and evaporated, giving a gum which was chromatographed on silica gel, eluting with petrol/ether. Two bands were isolated, the front band was a pale yellow gum which was further purified by short path distillation, this was *methyl 1-allyl-1,8-dihydro-8-methoxymethylpyrrolo [2,3-b]indole-2-carboxylate* (232) (0.41g, 71%), m.p. (picrate) 87-90°C (Found: C, 52.64; H, 3.98; N, 13.25. $C_{23}H_{21}N_5O_{10}$ requires C, 52.37; H, 4.01; N, 13.28%);

ν_{max} (thin film): 1692 (C=O), 1619, 1568 cm^{-1};

λ_{max} (MeOH): 327, 321 sh, 272, 231.5 nm;

δ_H (250 MHz; $CDCl_3$): 3.29 (3H, s, CH_2OMe), 3.84 (3H, s, CO_2Me), 4.79 (1H, d, *J* 16.7 Hz with some fine splitting, *trans* proton of $CH_2CH=CH_2$), 5.13 (1H, d, *J* 10.6 Hz with some fine splitting, *cis* proton of $CH_2CH=CH_2$), 5.40 (2H, m, $CH_2CH=CH_2$), 5.47 (2H, s, CH_2OMe), 6.14 (1H, ddt, *J* 16.7, 10.6, 4.2 Hz, $CH_2CH=CH_2$), 7.22 (2H, m, H-5 and H-6), 7.38 (1H, m, H-4 or H-7), 7.39 (1H, s, 3-H), 7.71 (1H, m, H-7 or H-4);

δ_C (62.9 MHz; $CDCl_3$): 47.56 (86%), 50.73 (56), 55.79 (62), 74.36 (75), 109.20 (98), 109.37 (100), 115.14 (99), 119.43 (95), 120.76 (99), 121.08 (33), 121.46 (25), 122.20 (83), 135.54 (71), 142.58 (38), 143.52 (25), 161.88 (21), only 16 distinct resonances observed;

m/z: 298 (M^+, 100%), 253 (37).

The rear band was the 2H-pyrroloindole (233a) (0.075g, 13%) full data will be quoted in the experimental dealing with the photolysis of (232).

(iii) Attempted thermolytic rearrangement of (232)

The pyrroloindole (232) (*ca.* 0.04g) was refluxed in bromobenzene for 14h, and the solvent evaporated. Only starting material could be detected by n.m.r.. The material was then heated in refluxing decalin for 24h after which time no change could be detected by t.l.c. or n.m.r..

(iv) Photolysis of (232)

The pyrroloindole (232) (0.31g, 1.04 mmol) was dissolved in spectroscopic grade cyclohexane (200 ml), and irradiated for 40 minutes at 300 nm, while a current of nitrogen was bubbled through the solution. After this time, t.l.c. showed almost complete consumption of starting material, and formation of two products. The mixture, after evaporation of the cyclohexane, was chromatographed on silica gel eluting with petrol/ether. Three bands were isolated, the front band was starting pyrroloindole (232) (0.02g, 6%), the middle band was shown by t.l.c., and spectroscopically, to be the cleaved compound (176d) (0.029g, 11%) and the rear band, obtained as a yellowish gum, was *methyl 2-allyl-2,8-dihydro-8-methoxymethyl-2H-pyrrolo[2,3-b]indole-2-carboxylate* (233a)

(0.192g, 62%) which was crystallized from petrol, m.p. 87-9°C (Found: C, 68.50; H, 6.10; N, 9.30. $C_{17}H_{18}N_2O_3$ requires C, 68.44; H, 6.08; N, 9.39%);

ν_{max} (nujol): 1730 (C=O), 1670, 1614, 1576 cm^{-1};

λ_{max} (MeOH): 289.5 (logε 3.39), 277.5 (3.44), 253 (4.38), 248 sh nm (4.34);

δ_H (250 MHz, $CDCl_3$): 2.93 (2H, m, $CH_2CH=CH_2$), 3.38 (3H, s, CH_2OMe), 3.70 (3H, s, CO_2Me), 5.02 (1H, d, *J* 10 Hz with some fine splitting, *cis* proton of $CH_2CH=CH_2$), 5.12 (1H, d, *J* 16.9 Hz with some fine splitting *trans* proton of $CH_2CH=CH_2$), 5.31 (2H, ABq, J_{AB} 11.5 Hz, CH_2OMe), 5.68 (1H, ddt, *J* 16.9, 10, 7.5 Hz, $CH_2CH=CH_2$), 7.08 (2H, m, Ar-H), 7.15 (1H, s, 3-H), 7.35 (1H, m, Ar-H), 7.56 (1H, d, *J* 7.5 Hz with fine splitting, H-4 or H-7);

δ_C (62.9 MHz; $CDCl_3$): 39.66 (88%), 52.42 (65), 56.28 (60), 73.56 (84), 92.95 (29), 110.52 (100), 118.49 (90), 118.60 (22), 121.72 (80), 124.58 (80), 130.35 (85), 132.49 (86), 135.16 (26), 139.22 (89), 151.72 (27), 170.93 (24), 172.27 (20);

m/z: 298 (M^+, 100%), 257 (21), 253 (16), 239 (15), 227 (40), 207 (41).

(v) Treatment of the *N*-sodium salt of (176d) with prenyl bromide

The pyrroloindole (176d) (0.50g, 1.94 mmol) was added as a solution in DMF (5 ml) to a suspension of sodium hydride (50% suspension in paraffin oil, 0.097g, 2.02 mmol, 1.04 equiv.) in DMF (5 ml). After stirring at room temperature under a nitrogen atmosphere for 40 minutes, prenyl bromide (230 µl, 2.33 mmol, 1.2 equiv.) was added and the mixture was stirred at room temperature for a further 2h. Work up was effected as

in the allylation reaction (experiment (ii)), and silica gel chromatography eluting with petrol/ether afforded four fractions. The front band was the *N*-alkylated compound *methyl 1,8-dihydro-8-methoxymethyl-1-(3-methylbut-2-en-1-yl)pyrrolo[2,3-b]indole-2-carboxylate* (235) (0.037g, 6%);

ν_{max} (thin film): 1695 (C = O), 1618, 1565 cm^{-1};

δ_H (250 MHz; $CDCl_3$): 1.70 (3H, d, *J ca.* 1.8 Hz, one of $CH_2CH = CMe_2$), 1.80 (3H, d, *J ca.* 1.2 Hz, one of $CH_2CH = CMe_2$), 3.29 (3H, s, CH_2OMe), 3.84 (3H, s, CO_2Me), 5.27 (1H, m, $CH_2CH = CMe_2$), 5.38 (2H, m, $CH_2CH = CMe_2$), 5.51 (2H, s, CH_2OMe), 7.20 (2H, m, H-5 and H-6), 7.33 (1H, s, 3-H), 7.39 (1H, m, H-4 or H-7), 7.68 (1H, m, H-7 or H-4);

m/z: 326 (M^+, 100%), 258 (66).

The second fastest band consisted of unreacted starting material (176d) (0.064g, 13%), the third fraction was mixed, containing (176d) and (234) in an approximately 50:50 ratio, as estimated by n.m.r. The rear band consisted of pure *methyl 2,8-dihydro-8-methoxymethyl-2-(3-methylbut-2-en-1-yl)-2H-pyrrolo[2,3-b]indole-2-carboxylate* (234) (0.26g, 41%), making a total yield of *ca.* 60% allowing for (234) contained in the mixed fraction. This material was obtained as a yellow gum (Found: M^+ = 326.1626. $C_{19}H_{22}N_2O_3$ requires M^+ = 326.1630);

ν_{max} (thin film): 1730 (C = O), 1666, 1610, 1575 cm^{-1};

λ_{max} (MeOH): 289.5 ($\log\varepsilon$ 3.57), 275.5 (3.67), 252 (4.44), 247 sh nm (4.41);

δ_H (250 MHz; $CDCl_3$): 1.64 (6H, somewhat broadened s, $CH{=}CH = CMe_2$), 2.86 (2H, m, $CH_2CH = CMe_2$), 3.36 (3H, s, CH_2OMe), 3.69 (3H, s, CO_2Me), 5.06 (1H, br t, *J* 7.2 Hz with

δ_H (250 MHz; $CDCl_3$): continued

some fine splitting, $CH_2CH=CMe_2$), 5.30 (2H, ABq, J_{AB} 11.2 Hz, CH_2OMe), 7.08 (2H, m, Ar-H), 7.17 (1H, s, 3-H), 7.33 (1H, m, Ar-H), 7.61 (1H, d, J 7.9 Hz with slight peak broadening, H-4 or H-7);

δ_C (62.9 MHz; $CDCl_3$): 17.80 (77%), 25.66 (94), 34.45 (100), 52.25 (62), 56.09 (89), 73.56 (99), 93.74 (37), 110.47 (89), 118.41 (92), 118.82 (31), 121.61 (100), 124.44 (76), 130.18 (74), 134.75 (31), 134.89 (35), 139.63 (86), 151.72 (34), 171.19 (26), 172.04 (15);

m/z: 326 (M^+, 36%), 295 (7), 258 (100), 227 (23), 226 (36).

(vi) Treatment of the *N*-potassium salt of (176d) with prenyl bromide

The pyrroloindole (176d) (0.245g, 0.95 mmol) was added as a solution in DMF (5 ml) to a suspension of potassium hydride (25% suspension in paraffin oil, 0.167g, 1.04 mmol, 1.1 equiv.) in DMF (7 ml). The experimental procedure described in experiment (v) was followed, and silica gel chromatography of the crude material from the reaction afforded three fractions. The front band consisted of (235) (0.056g, 18%), the second fraction was mixed, (0.019g) and the slowest band consisted of (234) (0.175g, 56%).

(vii) Photolysis of (235)

The pyrroloindole (235) (0.01g, 0.03 mmol) was dissolved in cyclohexane (20 ml) and the resulting solution was irradiated at 254 nm for 15 minutes, after which time complete consumption of (235) was indicated by t.l.c.. The cyclohexane was evaporated and the resulting gum was chromatographed on a silica gel p.l.c. plate. Only one band was

observed, along with a slight baseline, and the material isolated was shown to have an n.m.r. spectrum (250 MHz; $CDCl_3$) identical with (234).

(viii) Treatment of the *N*-sodium salt of (176d) with 3-chloro-2-methylprop-1-ene.

The pyrroloindole (176d) (0.50g, 1.94 mmol) was added as a solution in DMF (10 ml) to a suspension of sodium hydride (50% suspension in paraffin oil, 0.140g, 2.91 mmol, 1.5 equiv.) in DMF (5 ml). After stirring at room temperature under a nitrogen atmosphere for 0.5h, 3-chloro-2-methylprop-1-ene (284 µl, 2.91 mmol, 1.5 equiv.) was added, and the resulting mixture stirred at room temperature for 1h. After this time t.l.c. indicated that no reaction had taken place, and the mixture was thus heated to *ca.* 70°C. After 3h at this temperature the reaction was still not complete, and an excess (568 µl, 5.82 mmol, 3 equiv.) of 3-chloro-2-methylprop-1-ene was added, stirring at 70°C being continued for an additional 3h. Work-up as previously described gave a gum which was shown by t.l.c. to consist of three components, which were separated by silica gel chromatography. The front band, a yellow gum, was *methyl 1,8-dihydro-8-methoxymethyl-1-(2-methylprop-2-en-1-yl)pyrrolo[2,3-b]indole-2-carboxylate* (237) (0.436g, 72%), m.p. (picrate) 78-80°C (Found: C, 53.53; H, 4.24; N, 12.93. $C_{24}H_{23}N_5O_{10}$ requires C, 53.24; H, 4.28; N, 12.93%);

ν_{max} (thin film): 1690 (C=O), 1613, 1564 cm^{-1};

δ_H (250 MHz; $CDCl_3$): 1.86 (3H, br s, $CH_2C(Me)=CH_2$), 3.30 (3H, s, CH_2OMe), 3.83 (3H, s, CO_2Me), 4.20 (1H, br s, one of $CH_2C(Me)=CH_2$), 4.80 (1H, br s, one of $CH_2C(Me)=CH_2$), 5.29 (2H, br s, $CH_2C(Me)=CH_2$), 5.44 (2H, s, CH_2OMe), 7.21 (2H, m, 5-H and 6-H), 7.37 (1H, s, 3-H), 7.38 (1H, m, 4-H or 7-H), 7.71 (1H, m, 7-H or 4-H);

δ_C (62.9 MHz; $CDCl_3$): 19.75 (66%), 50.39 (65), 50.70 (54), 55.74 (60), 74.33 (56), 109.18 (100), 109.22 (85), 109.28 (81), 119.43 (62), 120.70 (60), 121.15 (20), 121.41 (19), 122.17 (68), 142.55 (27), 143.42 (34), 143.61 (18), 161.89 (21), only 17 distinct resonances observed;

m/z: 312 (M^+, 100%), 227 (20), 221 (21), 207 (16).

The middle band was shown to be unreacted starting pyrroloindole (176d) (0.054g, 11%), and the rear band was 2H-pyrroloindole (236) (0.064g, 11%) full data for which will be quoted under the next experiment.

(ix) Photolysis of (237)

The pyrroloindole (237) (0.20g, 0.64 mmol) was dissolved in spectroscopic grade cyclohexane (200 ml) and the resulting solution was irradiated at 300 nm for 40 minutes. Evaporation of the solvent followed by chromatography gave three bands, the first, being unidentified material (0.03g), the second being the cleavage product (176d) (0.025g, 15%) and the third (rear) band being *methyl 2,8-dihydro-8-methoxymethyl-2-(2-methylprop-2-en-1-yl)-2H-pyrrolo[2,3-b]indole-2-carboxylate* (236) (0.099g, 50%) obtained as a yellow gum. (Found: M^+ = 312.1478. $C_{18}H_{20}N_2O_3$ requires M^+ = 312.1474);

ν_{max} (thin film): 1730 (C = O), 1670, 1613, 1576 cm^{-1};

λ_{max} (MeOH): 290, 275, 253, 248 sh nm;

δ_H (250 MHz; $CDCl_3$): 1.75 (3H, s, slightly broadened, $CH_2C(Me) = CH_2$), 2.89 (2H, s, some fine splitting, $CH_2C(Me) = CH_2$), 3.38 (3H, s, CH_2OMe), 3.70 (3H, s, CO_2Me), 4.70 - 4.84 (2H, m, $CH_2C(Me) = CH_2$), 5.30 (2H, ABq, J_{AB} 11 Hz, CH_2OMe), 7.07 (2H, m, Ar-H), 7.18 (1H, s, 3-H), 7.34 (1H, m, Ar-H), 7.56 (1H, d, J 7.4 Hz with some peak broadening, H-4 or H-7);

δ_C (62.9 MHz; $CDCl_3$): 24.12 (62%), 43.35 (88), 52.40 (62), 56.19 (68), 73.60 (79), 93.43 (29), 110.47 (89), 114.90 (81), 118.73 (28), 121.66 (84), 124.49 (100), 130.26 (85), 134.60 (27), 139.61 (76), 140.79 (43), 151.69 (29), 171.15 (17), 171.92 (20);

m/z: 312 (M^+, 100%), 227 (35), 221 (55).

(x) Treatment of the *N*-sodium salt of (176d) with 3-chlorobut-1-ene

The pyrroloindole (176d) (0.50g, 1.94 mmol) was added as a solution in DMF (7 ml) to a suspension of sodium hydride (50% suspension in paraffin oil, 0.098g, 2.04 mmol, 1.05 equiv.) in DMF (5 ml) and stirred at room temperature for 0.75h. After this time 3-chlorobut-1-ene (205 µl, 2.037 mmol, 1.05 equiv.) was added, and the mixture was heated to 70°C, at which temperature it was stirred for 1h. The t.l.c. at this juncture showed very little product formation, and a further quantity of 3-chlorobut-1-ene (586 µl, 5.82 mmol, 3 equiv.) was added. Stirring at 70°C was continued for 3h and the reaction was then worked up as previously described. The crude product contained a considerable quantity of (176d), this could however be separated from the products by washing with petrol, in which it was almost insoluble. In this fashion (176d) (0.26g, 52% recovery) was collected by filtration. The gum which was obtained by evaporation of the petrol washings was chromatographed on silica gel, eluting with petrol/ether. The front band obtained, was an unidentified gum (0.034g) which appeared by n.m.r. to be a mixture, and was discarded. The second and third fractions contained (176d), in the third, apparently mixed with a C-alkylation product (as evidenced by t.l.c.). The rear band appeared as a homogeneous, strongly fluorescent spot on t.l.c., this fluorescence and its R_f value being characteristic of a 2H-pyrroloindole. The n.m.r. (250 MHz; $CDCl_3$) showed this to be in fact, a mixture of three 2H-pyrroloindoles, presumably (240 a, b and

c), showing *inter alia* 2.8 - 3.0 (m, C*H*(Me)CH = CH_2 and CH_2CH = CHMe); *ca.* 3.37 (3x3H, s, CH_2OMe), *ca.* 3.69 (3x3H, s, CO_2Me), 7.08 (m, Ar-H), 7.16 (s, 3-H), 7.35 (m, Ar-H), 7.56 (d, *J* 7.5 Hz, some peak broadening, 4-H or 7-H).

(xi) Treatment of the *N*-sodium salt of (176d) with 3-bromo-3-methylbut-1-yne (241).

The pyrroloindole (176d) (0.50g, 1.94 mmol) was added as a solution in DMF (5 ml) to a suspension of sodium hydride (50% suspension in paraffin oil, 0.098g, 2.04 mmol, 1.05 equiv.) in DMF (5 ml). After stirring for *ca.* 1h, at room temperature under a nitrogen atmosphere, 3-bromo-3-methylbut-1-yne (0.30g, 2.04 mmol, 1.05 equiv.) was added as a solution in DMF (5 ml). The reaction and work-up were carried out as in, for example, experiment (ii). The crude reaction product was washed with petrol and the insoluble unreacted starting material (176d) was filtered off (0.26g, 52% recovery). The gum resulting from evaporation of the petrol washings was chromatographed on silica gel giving five bands which will be described in order of increasing polarity. The first band (0.038g, 6%) was not identified, this material solidified and could be recrystallized from petrol, but it appeared to be a mixture of one major and one minor component by n.m.r. The data (n.m.r.) quoted below refer to the major component.

ν_{max} (nujol): 1715, 1622, 1589, 1578 cm^{-1};

λ_{max} (MeOH): 326, 271, 236 nm;

δ_H (250 MHz; $CDCl_3$): *inter alia* 1.86 and 1.87 (apparently 2x3H, s), 3.19 (3H, s, CH_2OMe), 3.83 (3H, s, CO_2Me), 5.74 (2H, s, CH_2OMe), 7.23 (m, Ar-H). 7.36 (apparently 1H, s), 7.42 (1H, m, Ar-H), 7.69 (1H, s, Ar-H);

m/z: 324 (100%), 309 (10), 293 (16).

The second band (0.024g, 4%) could not be identified. It crystallized from petrol m.p. 79-81°C. (Found: C, 70.61; H, 6.26; N, 8.53. $C_{19}H_{20}N_2O_3$ requires C, 70.35; H, 6.21; N, 8.64%);

ν_{max} (nujol): 1732, 1606 cm^{-1};

λ_{max} (MeOH): 350, 308, 255, 222 nm;

δ_H (250 MHz; $CDCl_3$): 1.76 (3H, d, *J ca.* 1.3 Hz), 1.98 (3H, d, *J ca.* 1.7 Hz), 3.34 (3H, s), 3.98 (3H, s), 5.91 (2H, s), 6.67 (1H, br s), 7.33 (1H, m), 7.56 (1H, m), 7.64 (1H, m), 8.07 (1H, m), 8.18 (1H, d, *J ca.* 0.8 Hz);

m/z: 324 (M^+, 38), 293 (30), 233 (100).

The third band consisted of starting material (176d) (0.058g, 12%).

The fourth band was identified as *methyl 2,8-dihydro-8-methoxymethyl-2-(3,3-dimethylpropyn-3-yl)-2H-pyrrolo[2,3-b]indole-2-carboxylate* (244) (0.013g, 2%), which was obtained as a yellow gum.

ν_{max} (thin film): 3310 (≡C-H), 2120 vw (C≡C), 1740 (C=O), 1670, 1615, 1580 cm^{-1};

λ_{max} (MeOH): 291.5, 278, 254, 248 sh nm;

δ_H (250 MHz; $CDCl_3$): 1.32 (3H, s, one of $C(Me)_2C{\equiv}CH$), 1.57 (3H, s, one of $C(Me)_2C{\equiv}CH$), 2.20 (1H, s, $C(Me)_2C{\equiv}CH$), 3.39 (3H, s, CH_2OMe), 3.72 (3H, s, CO_2Me), 5.31 (2H, ABq, J_{AB} 11.3 Hz, CH_2OMe), 7.07 (2H, m, Ar-H), 7.33 (1H, s, 3-H), 7.35 (1H, m, Ar-H), 7.56 (1H, d with some peak broadening, 4-H or 7-H);

m/z: 324 (M^+, 100%), 277 (46), 258 (65), 257 (54), 227 (62).

The fifth band was tentatively identified as *methyl 2,8-dihydro-8-methoxymethyl-2-(3,3-dimethylpropadien-1-yl)-2H-pyrrolo[2,3-b]indole-2-carboxylate* (245) (0.071g, 11%) obtained as a yellow gum.

ν_{max} (thin film): 1965 vw, 1730 (C = O), 1662, 1608, 1573 cm^{-1};

λ_{max} (MeOH): 293 (logε 3.72), 279 (3.85), 250 (4.51), 247.5 sh nm (4.51);

δ_H (250 MHz; $CDCl_3$): 1.68 (3H, d, *J ca.* 2.2 Hz, one of CH = C = C*Me*$_2$), 1.73 (3H, d, *J ca.* 2.8 Hz, one of CH = C = C*Me*$_2$), 3.38 (3H, s, CH_2OMe), 3.71 (3H, s, CO_2Me), 5.30 (2H, ABq, J_{AB} 11.2 Hz, CH_2OMe), 5.36 (1H, m, C*H* = C = CMe_2), 7.07 (2H, m, Ar-H), 7.20 (1H, s, 3-H), 7.33 (1H, m, Ar-H), 7.55 (1H, d, *J* 7.6 Hz with some peak broadening, 4-H or 7-H);

m/z: 324 (M^+, 100%), 309 (8), 292 (27), 277 (79), 261 (18), 260 (29), 233 (37), 219 (27).

(xii) Reaction of 2H-pyrroloindole (236) with DMAD

The pyrroloindole (236) (0.046g, 0.15 mmol) was heated with DMAD (excess) in toluene (10 ml) at reflux for 2h. Evaporation of the solvent gave a brown gum which was filtered through a thin pad of silica gel, eluting with petrol/ether. The resulting material was obtained as a light brown gum;

λ_{max} (MeOH): 288, 245, 237 sh nm;

δ_H (250 MHz; $CDCl_3$): 1.69 (3H, br s), 3.16 (3H, s), 3.57 (3H, s), 3.68 (3H, s), 3.97 (3H, s), 4.81 (2H, m), 5.40 (2H, ABq, J_{AB} 12 Hz), 6.40 (1H, s), *inter alia.*

(xiii) Thermolysis of 2H-pyrroloindole (233a)

The pyrroloindole (233a) (0.077g, 0.26 mmol) was dissolved in toluene (20 ml) and the resulting solution refluxed in a nitrogen atmosphere for 12h. Evaporation of the solvent gave a gum which appeared by t.l.c. and n.m.r. to consist of two compounds, but these could not be separated

by p.l.c. on silica gel. The mixed bands were thus examined spectroscopically;

λ_{max} (MeOH): 312, 259, 254 sh, 234 nm;

δ_H (250 MHz; $CDCl_3$): 8.91 (br s) and 9.76 (br s) in a ratio of approximately 2:1, *inter alia*.

EXPERIMENTAL FOR CHAPTER FOUR

1. Thermolysis of 2-methylindolyl azidopropenoates

(i) Small scale experiments

The azidopropenoate (264a) (0.05g, 0.16 mmol) was dissolved in the appropriate solvent (10 ml) and the resulting solution refluxed for 0.75 - 4.5 h. The solvent was then evaporated, and the crude residue was analysed by n.m.r. spectroscopy, *cf* Table 5. Full data of products will be quoted under the preparative scale experiments.

(ii) Thermolysis in xylene

The azidopropenoate (264a) (0.50g, 1.6 mmol) was dissolved in xylene (100 ml) and the resulting solution was heated at reflux for 1.5 h. The solvent was then evaporated and the residue chromatographed on silica gel. Three identifiable bands were isolated. The front running band was identified as *ethyl 2-amino-3-(1-methoxymethyl-2-methylindol-3-yl)propenoate* (267a) (0.022g, 5%) obtained as an oil;

ν_{max} (thin film): 3460, 3370 (NH_2), 1700 (C = O) cm^{-1};

δ_H (60 MHz; $CDCl_3$): 1.40 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 2.45 (3H, s, 2-Me), 3.28 (3H, s, CH_2OMe), 4.34 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.43 (2H, s, CH_2OMe), 6.60 (1H, s, $CH=C(NH_2)\varepsilon$), 7.0 - 7.8 (4H, m, 4-H, 5-H, 6-H and 7-H);

m/z: 288 (M^+).

The second band was shown to be 1-methoxymethyl-2-methylindole-3-carbaldehyde (0.059g, 18%), and the third band, isolated as a pale yellow solid was *ethyl 9-methoxymethylpyrido[3,4-b]indole-3-carboxylate* (266a) (0.266g, 59%) which was sublimed to give very pale yellow needles (0.20g, 44%), m.p. 128.5 - 30.5°C from ethanol/petrol. (Found: C 67.67; H, 5.68; N, 9.85. $C_{16}H_{16}N_2O_3$ requires C, 67.59; H, 5.67; N, 9.86%);

ν_{max} (nujol): 1707 (C = O), 1620, 1582, 1558 cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.48 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 3.28 (3H, s, CH_2OMe), 4.50 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.71 (2H, s, CH_2OMe), 7.29 (1H, m, Ar-H), 7.54 (2H, m, Ar-H), 8.10 (1H, d, *J* 8 Hz with some fine splitting, Ar-H), 8.73 (1H, s, 1-H or 4-H), 8.96 (1H, s, 4-H or 1-H);

m/z: 284 (M^+, 36%), 223 (18), 212 (100).

(iii) Thermolysis in de-gassed xylene under nitrogen

Xylene (50 ml) was refluxed under nitrogen for 1.5h to remove dissolved oxygen. The solvent was then allowed to cool, and introduced into a second flask containing the azidopropenoate (264a) (0.25g, 0.8 mmol) by means of a long double-ended hypodermic needle, in order to maintain the whole system in a nitrogen atmosphere. The needle was removed and the resulting solution was brought to reflux and kept at that temperature for 1.5h. The solvent was then evaporated, and the crude n.m.r. spectrum recorded immediately. This showed the presence of two compounds, the β-carboline (266a), and *ethyl 1,2-dihydro-9-methoxymethylpyrido[3,4-b]indole-3-carboxylate* (265);

δ_H (90 MHz, $CDCl_3$): 1.37 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 3.24 (3H, s, CH_2OMe), 4.34 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.0 (2H, s, $C(1)H_2$), 5.38 (2H, s, CH_2OMe), 6.73 (1H, s, 4-H), 7.15 - 7.65 (4H, m, Ar-H).

The ratio of (265) to (266a) was determined to be approximately 55:45. The mixture was chromatographed on silica gel using medium nitrogen pressure. Only β-carboline (266a) (0.191g, 85%) was isolated from the column, the dihydro-β-carboline (265) having been oxidized during chromatography. Sublimation gave the β-carboline as fine off-white needles (0.144g, 64%).

(iv) Thermolysis of the 1-benzyl azidopropenoate (264b)

The azidopropenoate (264b) (0.20g, 0.56 mmol) was dissolved in toluene (80 ml) and the resulting solution heated at reflux overnight. The solvent was then evaporated and the residue chromatographed on silica gel. Fractions were obtained as follows: a front running fraction, tentatively identified as *ethyl 2-amino-3-(1-benzyl-2-methyl-indol-3-yl)propenoate* (267b) (0.011g, 6%);

ν_{max} (thin film): 3480, 3340 (NH_2), 1722 (C = O), 1670, 1618 cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.37 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 2.33 (3H, s, 2-Me), 4.37 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.38 (2H, s, CH_2Ph), 6.73 (1H, s, $CH=C(NH_2)\varepsilon$), 6.9 - 7.4 (9H, m, Ar-H);

m/z: 334 (M^+, 3%), 187 (58), 142 (47), 115 (100), 114 (100), 86 (77).

The middle fractions, were found to consist of unidentifiable material, and the rear band was identified as *ethyl 9-benzylpyrido[3,4-b]indole-3-carboxylate* (266b) (0.14g, 76%) which gave fine yellowish needles (0.106g, 58%) after one recrystallization from ether/petrol, m.p. 120-1°C from aqueous ethanol. (Found: C, 76.20; H, 5.47; N, 8.42. $C_{21}H_{18}N_2O_2$ requires C, 76.34; H, 5.49; N, 8.48%);

ν_{max} (nujol): 1704 (C = O) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.48 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 4.56 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.64 (2H, s, CH_2Ph), 7.10 - 7.70 (8H, m, Ar-H), 8.26 (1H, d, *J* 8 Hz with some fine splitting, Ar-H), 8.92 (2H, s, 1-H and 4-H)*;

m/z: 330 (M^+, 35%), 258 (100), 91 (60).

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*1-H and 4-H are not coincident if the spectrum is recorded in d_6-DMSO, the shifts being δ 8.97 (1H, s) and δ 9.20 (1H, s).

(v) Attempted debenzylation of (266b)

The β-carboline (266b) (0.04g, 0.12 mmol) was added as a solution in THF (5 ml) to liquid ammonia, and sodium metal was added until a permanent blue colour had developed. The resulting solution was quenched with solid ammonium chloride, and the liquid ammonia was allowed to evaporate. The resulting solution was evaporated to dryness and the residue partitioned between water and methylene chloride. Separation, drying ($MgSO_4$) and evaporation of the organic layer gave a small amount of a gummy residue which proved to be complex by n.m.r. and was discarded.

(vi) Deprotection of (266a)

The β-carboline (266a) (0.085g, 0.30 mmol) was heated in 90% formic acid (1.5 ml) and water (0.5 ml) at reflux for 12h. After this time, the whole solution was evaporated to dryness, and the residue chromatographed on silica gel eluting with petrol/ethyl acetate. One band was obtained, which was identified as ethyl pyrido[3,4-b]indole-3-carboxylate[159] (266c) (0.053g, 75%), m.p. 224 - 9.5°C from ethanol;

ν_{max} (nujol): 3255 (NH), 1717 (C = O), 1628 cm^{-1};

δ_H (250 MHz; d_6-DMSO): 1.38 (3H, t, J 7 Hz, $CO_2CH_2CH_3$), 4.37 (2H, q, J 7 Hz, $CO_2CH_2CH_3$), 7.31 (1H, ddd, J 7.8, 6.8, 1.0 Hz, 6-H or 7-H), 7.58 (1H, ddd, J 8.3, 6.8, 1.4 Hz, 7-H or 6-H), 7.66 (1H, d, J 8.3 Hz with some peak broadening, 5-H or 8-H), 8.40 (1H, d, J 7.8 Hz with fine splitting, 8-H or 5-H), 8.91 (1H, s, 1-H or 4-H), 8.96 (1H, d, J 1.3 Hz, 4-H or 1-H), 12.07 (1H, br s, NH);

m/z: 240 (M^+, 27%), 168 (100), 140 (17).

2. Thermolysis of the 2-ethylindolyl azidopropenoate

(i) Initial thermolysis in xylene

The azidopropenoate (268) (0.145g, 0.44 mmol) was dissolved in xylene (29 ml) and the resulting solution was heated at reflux for 20h. The solvent was then evaporated and the residue chromatographed on silica gel. Two bands were obtained, the rear band being the expected *ethyl 9-methoxymethyl-1-methylpyrido[3,4-b]indole-3-carboxylate* (269a) (0.046g, 35%) which was sublimed and then recrystallized from ethanol/petrol, m.p. 105 - 6°C. (Found: C, 68.50; H, 5.97; N, 9.25. $C_{17}H_{18}N_2O_3$ requires C, 68.44; H, 6.08; N, 9.39%);

ν_{max} (nujol): 1704 (C = O) cm^{-1};

δ_H (250 MHz; $CDCl_3$): 1.51 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 3.15 (3H, s, 1-Me), 3.32 (3H, s, CH_2OMe), 4.54 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.87 (2H, s, CH_2OMe), 7.38 (1H, m, Ar-H), 7.64 (2H, m, Ar-H), 8.19 (1H, d, *J* 8 Hz with fine splitting, Ar-H), 8.76 (1H, s, 4-H);

m/z: 298 (M^+), 267, 253, 226.

The front band was identified as *ethyl 6-methoxymethyl-3,4,5,6-tetrahydroazepino[4,5-b]indole-2-carboxylate* (270a) (0.032g, 24%) obtained as a gum;

ν_{max} (thin film): 3380 (NH), 1690 (C = O), 1625 cm^{-1};

δ_H (250 MHz; $CDCl_3$): 1.39 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 3.25 (3H, s, CH_2OMe), 3.29 (2H, t, *J* 5.1 Hz, $C(5)H_2$), 3.48 (2H, t, *J* 5.1 Hz, $C(4)H_2$), 4.33 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.47 (2H, s, CH_2OMe), 6.93 (1H, s, 1-H), 7.21 (2H, m, 8-H and 9-H), 7.38 (1H, m, 7-H or 10-H), 7.73 (1H, m, 10-H or 7-H);

m/z: 300 (M^+, 100%), 269 (15), 255 (43), 181 (53).

(ii) Thermolysis in benzene

The azidopropenoate (268) (0.384g, 1.17 mmol) was dissolved in benzene (80 ml) and the resulting solution was heated at reflux for 2h. Evaporation of the solvent left a brown gummy residue, the crude spectra of which, indicated it to consist essentially of one compound, identified as *ethyl 2-amino-3-(1-methoxymethyl-2-vinylindol-3-yl)propenoate* (271);

ν_{max} (thin film): 3480, 3380 (NH_2), 1705 (C=O), 1635, 1580 cm^{-1};

δ_H (250 MHz; $CDCl_3$): 1.40 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 3.33 (3H, s, CH_2OMe), 3.92 (2H, br s, D_2O exch., NH_2), 4.36 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.51 (2H, s, CH_2OMe), 5.65 (1H, dd, *J* 12, 1.3 Hz, *cis* proton of $CH=CH_2$), 5.72 (1H, dd, *J* 18, 1.3 Hz, *trans* proton of $CH=CH_2$), 6.69 (1H, s, $CH=C(NH_2)\varepsilon$), 6.90 (1H, dd, *J* 18, 12 Hz, $CH=CH_2$), 7.30 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.67 (1H, m, 7-H or 4-H).

The crude enamine (271) was passed down a column of silica gel eluting with petrol/ether. Evaporation of the resulting eluates gave the azepinoindole (270a) (0.186g, 54%).

(iii) Small scale thermolyses of the azidopropenoate (268)

The azidopropenoate (268) (0.05g, 0.15 mmol) was dissolved in the appropriate solvent (10 ml), and the solution refluxed for 1.5 - 24h. The solvent was then evaporated* and the crude residue analysed by n.m.r. spectroscopy, *cf* Table 6.

*Except in the case of DMF thermolyses, when aqueous work-up, ethereal extraction etc. was employed as a means of solvent removal.

(iv) Small scale thermolyses of the enamine (271)

In all cases, the azidopropenoate (268) (0.05g, 0.15 mmol) was heated in refluxing benzene (10 ml) for 2h. The solvent was then evaporated and the residue was re-dissolved in one of the solvents listed in Table 6, and the resulting solution refluxed for 1.5 - 24h. The solvent was then evaporated* and the residue analysed by n.m.r. spectroscopy.

(v) Preparative scale thermolysis in DMF

The azidopropenoate (268) (0.55g, 1.68 mmol) was dissolved in DMF (110 ml) and the resulting solution heated at reflux for 2.5h. After cooling, the solution was poured into water and extracted with ether. Washing the combined ethereal layers with water, drying ($MgSO_4$) and evaporation, gave a brown gum which was chromatographed on silica gel. One product was obtained, the azepinoindole (270a) (0.30g, 60%).

(vi) Preparative scale thermolysis in *o*-dichlorobenzene

The azidopropenoate (268) (0.15g, 0.46 mmol) was dissolved in *o*-dichlorobenzene (30 ml). The resulting solution was heated at reflux for 1h. Evaporation of the solvent gave a brown residue which was purified by silica gel chromatography to give the β-carboline (269a) (0.057g, 43%).

(vii) Ring closure of enamine (271) by silica gel

The enamine (271) prepared as described above from azide (268) (0.05g, 0.15 mmol), was dissolved in ether and stirred at room temperature with silica gel (type 60, 2.0g) overnight. Filtration and evaporation of the suspension gave a gum which was shown to consist of one compound by n.m.r., *viz* the azepinoindole (270a).

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*See footnote on previous page

(viii) Deprotection of (269a)

The β-carboline (269a) (0.037g, 0.12 mmol) was heated in 90% formic acid (2.5 ml) at reflux for 5h. The whole solution was then evaporated and the brown residue chromatographed on silica gel, eluting with petrol/ethyl acetate. One product was obtained, *ethyl 1-methylpyrido[3,4-b]indole-3-carboxylate* (269b) (0.03g, 95%), m.p. 219 - 23°C from aqueous ethanol.

ν_{max} (nujol): 3310 (NH), 1700 (C = O), 1618, 1590 cm^{-1};

δ_H (250 MHz; d_6-DMSO): 1.38 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 2.83 (3H, s, 1-Me), 4.38 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 7.31 (1H, ddd, *J* 8, 6.7, 1.1 Hz, 6-H or 7-H), 7.60 (1H, ddd, *J* 8, 6.7, 1.3 Hz, 7-H or 6-H), 7.66 (1H, d, *J* 8 Hz with some fine splitting, 5-H or 8-H), 8.36 (1H, d, *J* 8 Hz with some peak broadening, 8-H or 5-H), 8.76 (1H, s, 4-H), 12.04 (1H, br s, NH);

m/z: 254 (M^+, 29%), 238 (82), 209 (68), 182 (100).

3. Thermolysis of the 2-*n*-propylindolyl azidopropenoate

(i) Small scale thermolyses of the azidopropenoate (282)

These were carried out in exactly the same manner as was employed for small scale experiments with azide (268), *cf* Table 7. Full data for the products will be quoted under the relevant preparative scale experiments.

(ii) Small scale thermolyses of the enamine (283)

These experiments were carried out in the same manner as the small scale thermolyses of the enamine (271).

(iii) Preparative scale thermolysis of azidopropenoate (282) in benzene

The azidopropenoate (282) (0.10g, 0.29 mmol) was dissolved in benzene (20 ml) and the resulting solution was refluxed for 2h. The solvent was evaporated and the residue was rapidly chromatographed on a column of silica gel. One product was obtained, *ethyl 2-amino-3-(1-methoxymethyl-2-(prop-2-en-3-yl)indol-3-yl)propenoate* (283) (0.06g, 65%) as a gum;

δ_H (250 MHz; $CDCl_3$): 1.40 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 2.01 (3H, dd, *J* 7, 1.7 Hz, CH = CH*Me*), 3.32 (3H, s, CH_2OMe), 3.89 (2H, br s, NH_2), 4.35 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.50 (2H, s, CH_2OMe), 6.22 (1H, dq, *J* 16, 7 Hz, CH = C*H*Me), 6.59 (1H, dq, *J* 16, 1.7 Hz, C*H* = CHMe), 6.68 (1H, s, *CH* = C(NH_2)ε), 7.21 (2H, m, 5-H and 6-H), 7.44 (1H, m, 4-H or 7-H), 7.64 (1H, m, 7-H or 4-H).

(iv) Preparative scale thermolysis in DMF

The azidopropenoate (282) (0.20g, 0.58 mmol) was dissolved in DMF (40 ml) and the solution was heated at reflux for 5h. After cooling, the solution was poured into water, extracted with ether and the combined ethereal extracts washed with water, dried ($MgSO_4$) and evaporated to give a gum which was chromatographed on silica gel. One product was obtained, *ethyl 6-methoxymethyl-4-methyl-3,4,5,6-tetrahydroazepino [4,5-b]indole-2-carboxylate* (284a) (0.094g, 51%) as a gum.

ν_{max} (thin film): 3370 (NH), 1684 (C = O) cm^{-1};

δ_H (250 MHz; $CDCl_3$): 1.39 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 1.44 (3H, d, *J* 6.3 Hz, 4β-Me), 3.06 (1H, dd, *J* 16.8, 8.2 Hz, 5β-H), 3.24 (3H, s, CH_2OMe), 3.26 (1H, dd,

δ_H (250 MHz; $CDCl_3$): continued

J 16.8, 2.2 Hz, 5α-H), 3.44 (1H, ddq, *J* 8.2, 6.3, 2.2 Hz, 4α-H), 4.32 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.44 (2H, s, CH_2OMe), 6.94 (1H, s, 1-H), 7.21 (2H, m, 8-H and 9-H), 7.39 (1H, m, 7-H or 10-H), 7.73 (1H, m, 10-H or 7-H);

Irradiation of the doublet at δ 1.39 resulted in the collapse of the signal at δ 3.44 to a dd, *J* 8.2, 2.2 Hz. Irradiation at δ 3.06 gave an inconclusive and uninformative result.

m/z: 314 (M^+, 100%), 283 (13), 269 (14), 195 (25).

(v) Attempted ring closure of (283) with silica gel

The enamine (283) (0.05g, 0.15 mmol) was dissolved in ether and the solution stirred overnight with silica gel (type H, 3.0g) at room temperature. Filtration and evaporation gave a gum which was determined by n.m.r. spectroscopy to contain (283) and (284a) in a 75:25 ratio.

4. Reactions of the azepinoindoles and enamines

(i) Deprotection of the azepinoindole (270a)

The azepinoindole (270a) (0.063g, 0.21 mmol) was dissolved in ethanol (4 ml) and 5N hydrochloric acid (4 ml), and the resulting solution stood at room temperature for 24h. The solution was neutralized with solid sodium hydrogen carbonate and extracted with ether. The ethereal layer was washed with water, dried ($MgSO_4$) and evaporated, leaving a brown residue. Chromatography on a silica gel p.l.c. plate followed by sublimation and recrystallization from ether/cyclohexane, gave as fine pale yellow needles, *ethyl 3,4,5,6-tetrahydroazepino[4,5-b]indole-2-carboxylate* (270b) (0.035g, 65%), m.p.

152 - 4°C. (Found: C, 70.22; H, 6.29; N, 10.88. $C_{15}H_{16}N_2O_2$ requires C, 70.29; H, 6.29; N, 10.93%);

ν_{max} (nujol): 3380 (NH), 3360 (NH), 1683 (C = O), 1630 cm^{-1};

δ_H (250 MHz; $CDCl_3/D_2O$*): 1.38 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 3.20 (2H, t, *J* 4.4 Hz, C(5)H_2), 3.42 (2H, t, *J* 4.4 Hz, C(4)H_2), 4.32 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 6.96 (1H, s, 1-H), 7.17 (2H, m, 8-H and 9-H), 7.26 (1H, m, 7-H or 10-H), 7.71 (1H, m, 10-H or 7-H);

m/z: 256 (M^+, 100%), 228 (12), 182 (59).

(ii) Deprotection of the azepinoindole (284a)

The azepinoindole (284a) (0.05g, 0.16 mmol) was dissolved in ethanol (4 ml), water (2 ml) and 5N hydrochloric acid (1 ml) and the solution allowed to stand at room temperature for 24h. Work-up and purification as in the previous experiment gave, as pale yellow needles, *ethyl 4-methyl-3,4,5,6-tetrahydroazepino[4,5-b]indole-2-carboxylate* (284b) (0.015g, 35%), m.p. 180-2°C from ether/cyclohexane. (Found: C, 71.37; H, 6.86; N, 10.00. $C_{16}H_{18}N_2O_2$ requires C, 71.09; H, 6.71; N, 10.36%);

ν_{max} (nujol): 3390 (NH), 3360 (NH), 1674 (C = O), cm^{-1};

δ_H (250 MHz; $CDCl_3/D_2O$): 1.40 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 1.41 (3H, d, *J* 7 Hz, 4β-Me), 3.13 (2H, m, 5α and 5β-H), 3.45 (1H, m, 4α-H), 4.32 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 6.95 (1H, s, 1-H), 7.15 (2H, m, 8-H and 9-H), 7.25 (1H, m, 7-H or 10-H),

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*The spectrum recorded without D_2O consists of severely broadened peaks, which could not be reported with any accuracy.

δ_H (250 MHz; $CDCl_3/D_2O$): continued

7.70 (1H, m, 10-H or 7-H);

m/z: 270 (M^+, 100%), 242 (6), 196 (15).

(iii) *N*-acetylation of the enamine (271)[158]

The azidopropenoate (268) (0.10g, 0.3 mmol) was dissolved in benzene (20 ml) and the resulting solution refluxed for 2h. Evaporation of the solvent gave a crude gum which was dissolved in acetic anhydride and pyridine (5 drops), at 0°C. The mixture was allowed to warm to room temperature over 1h, with continual stirring. Water (1 ml) was added and the mixture was allowed to stand at room temperature for 1h, when a further quantity of water (5 ml) was added, and the mixture extracted with chloroform. The organic layer was washed with sodium hydrogen carbonate solution and then with water, dried ($MgSO_4$) and evaporated to give a brown gum. Purification by p.l.c. followed by crystallization from chloroform/cyclohexane gave, as small yellow crystals, *ethyl 2-acetamido-3-(1-methoxymethyl-2-vinylindol-3-yl) propenoate*, m.p. 150 - 60°C dec. (Found: C, 66.76; H, 6.40; N, 8.14. $C_{19}H_{22}N_2O_4$ requires C, 66.65; H, 6.40; N, 8.18%);

ν_{max} (nujol): 3240, 3180 (NH), 1700 (C = O), 1660 (C = O), 1651 sh, 1630 cm^{-1};

δ_H (250 MHz; $CDCl_3$): 1.37 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 1.96 (3H, br s, NHCO*Me*), 3.32 (3H, s, CH_2OMe), 4.35 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.50 (2H, s, CH_2OMe), 5.75 (2H, m, $CH=CH_2$), 6.90 (1H, dd, *J* 18, 11.3 Hz, $CH=CH_2$), 6.93 (1H, br s, $CH=C(NHAc)\varepsilon$), 7.22 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.48 (2H, m, 7-H or 4-H and NH);

m/z: 342 (M^+, 45%), 283 (100), 252 (69).

(iv) *N*-acetylation of the enamine (283)

The enamine (283) (0.06g, 0.19 mmol) was acetylated in acetic anhydride-pyridine as described in the previous experiment. Purification, also as described, gave pale yellow crystals of *ethyl 2-acetamido-3-(1-methoxymethyl-2-(prop-2-en-1-yl)indol-3-yl)propenoate* (0.033g, 49%), m.p. 170-6°C from chloroform/cyclohexane. (Found: C, 67.30; H, 6.82; N, 7.79. $C_{20}H_{24}N_2O_4$ requires C 67.40; H, 6.79; N, 7.86%);

ν_{max} (nujol): 3250, 3180 (NH), 1700 (C=O), 1659 (C=O), 1651 sh, 1620 cm^{-1};

δ_H (250 MHz; $CDCl_3$): 1.37 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 1.95 (3H, br s, NHCO*Me*), 2.02 (3H, dd, *J* 6.7, 1.5 Hz, CH=CH*Me*), 3.32 (3H, s, CH_2OMe), 4.34 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.48 (2H, s, CH_2OMe), 6.23 (1H, dq, *J* 15, 6.7 Hz, CH=C*H*Me), 6.58 (1H, dq, *J* 15, 1.5 Hz, C*H*=CHMe), 6.92 (1H, br s, C*H*=C(NHAc)ε), 7.20 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.43 (1H, m, 7-H or 4-H), 7.47 (1H, br s, NH);

m/z: 356 (M^+), 325, 297, 266, 251.

(v) Attempted borohydride reduction of azepinoindole (270a)

The azepinoindole (270a) (0.05g, 0.17 mmol) was dissolved in ethanol (6 ml) containing glacial acetic acid (0.5 ml), and treated over 2.5h with excess sodium borohydride. Aqueous work-up with sodium hydrogen carbonate solution and ethereal extraction etc., gave a gum which was shown by n.m.r. to consist entirely of unchanged starting material.

(vi) Dehydrogenation of azepinoindole (270a)

The azepinoindole (270a) (0.085g, 0.28 mmol) was dissolved in dichloromethane (10 ml) and the solution cooled to -22°C. *t*-Butyl hypochlorite (38.5 µl, 0.34 mmol, 1.2 equiv.) was added, and the mixture stirred for 1h, during which time it darkened considerably. DBU (50.5 µl, 0.34 mmol, 1.2 equiv.) was then added, and the solution became orange. The solution was warmed to room temperature over 2h and was stirred at that temperature overnight. The organic solution was then washed with water, dried ($MgSO_4$) and evaporated, and the resulting dark gum chromatographed on a silica gel p.l.c. plate. One compound was obtained, as a bright yellow gum, which was identified as, *ethyl 1,6-dihydro-6-methoxymethylazepino[4,5-b]indole-2-carboxylate* (287) (0.015g, 18%). (Found: M^+ = 298.1321; $C_{17}H_{18}N_2O_3$ requires M^+ = 298.1317);

ν_{max} ($CHCl_3$): 1715 (C = O), 1600 cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.34 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 3.27 (3H, s, CH_2OMe), 3.47 (2H, s, $C(1)H_2$), 4.29 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.51 (2H, s, CH_2OMe), 6.90 (1H, d, *J* 8 Hz, 4-H or 5-H), 7.33 (3H, m, 8-H, 9-H and 7-H or 10-H), 7.75 (1H, d, *J* 8 Hz, 5-H or 4-H), 7.81 (1H, m, 10-H or 7-H);

m/z: 298 (100%), 224 (74), 179 (65).

5. Preparation and thermolyses of azidopropenoate (288)[149]

(i) Preparation of 2,6-diethylbenzoic acid

This was carried out by a standard literature method starting with 2,6-diethylbromobenzene[149] (2.593g, 12.17 mmol). The acid was obtained as small white crystals (1.39g, 64%), m.p. 89-91°C from petrol (lit.,[149] 90-2°C).

(ii) Reduction of 2,6-diethylbenzoic acid

The acid (1.03g, 5.79 mmol) was added as a DME solution to a suspension of lithium aluminium hydride (excess) in DME (30 ml) under nitrogen. The resulting mixture was refluxed overnight, after which ethyl acetate was added until no further effervescence was observed. Water was then added and the two-phase mixture filtered through celite. Separation of the layers, drying and evaporation of the organic layer, gave as a pale yellow oil, 2,6-diethylbenzyl alcohol (0.854g, 90%), which was distilled (Kugelrohr) to give a colourless oil, which solidified upon standing at room temperature for 24h, m.p. 67-71°C;

ν_{max} (nujol): 3210 br (OH), 1462, 1005, 1016 cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.30 (6H, t, *J* 9 Hz, 2 x CH_2CH_3), 2.79 (4H, q, *J* 8 Hz, 2 x CH_2CH_3), 2.85 (1H, br s, OH), 4.59 (2H, s, CH_2OH), 6.95 - 7.35 (3H, m, 3-H, 4-H and 5-H).

(iii) Oxidation of 2,6-diethylbenzyl alcohol

The alcohol (0.85g, 5.18 mmol) in acetone (5 ml) was treated with Jones reagent (1M solution in aqueous acetone, 7.8 ml, 1.5 eq.) and the resulting solution stirred at room temperature for 20 minutes. Aqueous work-up and ethereal extraction, washing the organic layer first with sodium thiosulphate solution and then with sodium hydrogen carbonate solution, drying ($MgSO_4$) and evaporation, gave an oil which was shown by n.m.r. to contain some of the starting alcohol. This was thus dissolved in acetone (5 ml) and treated with further Jones reagent (2.6 ml, 0.5 equiv.) and the solution stirred for 1h. The reaction was worked up as before, giving as an oil, *2,6-diethylbenzaldehyde* (0.68g, 81%), m.p. (2,4-dinitrophenylhydrazone) 192.5 - 201°C from methanol/nitromethane. (Found: C, 59.80; H, 5.22; N, 16.47. $C_{17}H_{18}N_4O_4$ requires C, 59.64; H, 5.30; N, 16.37%);

ν_{max} (thin film): 1688 (C = O) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.27 (6H, t, *J* 8 Hz, 2 x CH_2CH_3), 2.99 (4H, q, *J* 8 Hz, 2 x CH_2CH_3), 7.05 - 7.55 (3H, m, 3-H, 4-H and 5-H), 10.53 (1H, s, CHO);

m/z: 162 (M^+, 100%), 133 (71).

(iv) Condensation of 2,6-diethylbenzaldehyde with ethyl azidoacetate

A mixture of the aldehyde (0.50g, 3.09 mmol) and ethyl azidoacetate (1.59g, 12.3 mmol, 4 equiv.) was added to a solution of sodium (0.284g, 12.3 mmol, 4 equiv.) in ethanol (10 ml) at -10°C. The solution was stirred at -10 to -5°C for 6h and then at 3°C overnight. Standard work-up as described in the Chapter 2 experimental section, gave a yellow oil which was shown by n.m.r. to contain unreacted aldehyde as well as the required azide. Repeated chromatography gave a material containing *ca.* 10% of the aldehyde and this material was used for the thermolysis experiments described below. This impure *ethyl 2-azido-3-(2,6-diethylphenyl)propenoate* (288) was obtained as a virtually colourless oil (0.585g, which was estimated to contain *ca.* 0.53g of the azide (288), 63%).

ν_{max} (thin film): 2115 (N_3), 1720 (C = O), 1626 (C = C) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.13 (6H, t, *J* 7 Hz, 2 x CH_2CH_3), 1.36 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 2.45 (4H, q, *J* 7 Hz, 2 x CH_2CH_3), 4.29 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 6.95 - 7.25 (4H, m, 3-H, 4-H, 5-H and $CH = C(N_3)\varepsilon$).

(v) Trial thermolysis of the azide (288) in xylene

A solution of the contaminated azide (288) (0.07g) in xylene (14 ml) was refluxed for 2h. The crude n.m.r. spectrum of the residue after evaporation of the solvent showed the presence (as major product) of

the dihydroisoquinoline (290) δ 6.50 (1H, s, 4-H) *inter alia*. Attempted separation by p.l.c. on silica gel, resulted only in the isolation of a small amount of the isoquinoline (289) and mixed fractions thought to contain (289), (290) and traces of enamine (291).

(vi) Thermolysis in xylene, and subsequent dehydrogenation with iodine

The contaminated azide (288) (0.085g) was dissolved in xylene (16 ml) and the resulting solution heated at reflux for 2h. The solution was cooled, and iodine (*ca.* 1 molar equiv.) was added. After stirring for 5 minutes the solution was washed with aqueous sodium thiosulphate, dried ($MgSO_4$) and evaporated. The residue was chromatographed on a silica gel p.l.c. plate, giving two bands. The rear band was identified as, *ethyl 5-ethyl-1-methylisoquinoline-3-carboxylate* (289) (0.028g, 35%), m.p. (picrate) 132-5°C from ethanol. (Found: C, 53.65; H, 4.22; N, 11.91. $C_{21}H_{20}N_4O_9$ requires C, 53.39; H, 4.27; N, 11.86%);

ν_{max} (thin film): 1718 (C = O) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.41 (3H, t, *J* 8 Hz, 5-CH_2CH_3), 1.51 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 3.06 (3H, s, 1-Me), 3.18 (2H, q, *J* 8 Hz, 5-CH_2CH_3), 4.56 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 7.61 (2H, m, Ar-H), 8.02 (1H, m, Ar-H), 8.61 (1H, s, 4-H);

m/z: 243 (M^+, 10%), 199 (4), 171 (100).

The front band was shown to consist of *ethyl 2-amino-3-(2-ethyl-6-vinylphenyl)propenoate* (291) (0.015g, 19%) as a gum.

ν_{max} (thin film): 3480, 3383 (NH_2), 1710 (C = O) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.18 (3H, t, *J* 8 Hz, 2-CH_2CH_3), 1.40 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 2.62 (2H, q, *J* 8 Hz, 2-CH_2CH_3), 4.33 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.27 (1H, dd, *J* 11, 1.5 Hz, *cis* proton of $CH=CH_2$), 5.72 (1H, dd, *J* 17, 1.5 Hz, *trans* proton of $CH=CH_2$), 6.50 (1H, s, $CH=C(NH_2)\varepsilon$), 6.86 (1H, dd, *J* 17, 11 Hz, $CH=CH_2$), 7.15 - 7.50 (3H, m, 3-H, 4-H and 5-H);

m/z: 247 (M^+ + 2, 23%), 245 (M^+, 27), 216 (18), 174 (100), 157 (34), 145 (50).

(vii) Thermolysis in degassed toluene, and subsequent dehydrogenation

Toluene (*ca.* 20 ml) was degassed by refluxing under nitrogen. Once cool the solvent was added to the contaminated azide (288) (0.089g) by means of a double-ended hypodermic needle. The resulting solution was refluxed for 2h. After evaporation of the solvent, the crude n.m.r. spectrum showed the presence of the enamine (291) and the dihydroisoquinoline (290);

δ_H (90 MHz, $CDCl_3$): *ca.* 1.3 (9H, m, 5-CH_2CH_3, $CO_2CH_2CH_3$ and 1-Me), 2.82 (2H, q, *J* 8 Hz, 5-CH_2CH_3), 4.38 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 6.50 (1H, s, 4-H), 7.0 - 7.30 (3H, m, 6-H, 7-H and 8-H), *inter alia*;

in a *ca.* 25:75 ratio. The crude material was dissolved in toluene and a current of air drawn through for 48h. An appreciable quantity of (290) was still indicated to be present by t.l.c. and n.m.r., and therefore the solution was heated at 90°C with sulphur (0.01g) for 24h and then at reflux for a further 4h. Evaporation of the solvent and p.l.c. resulted in the isolation of two compounds, enamine (291) (0.009g, 13%) and isoquinoline (289) (0.019g, 27%).

(viii) Thermolysis in DMF

The contaminated azide (0.11g) was dissolved in DMF (22 ml) and the resulting solution heated at reflux for 2.5h. The solution was poured into water and extracted with ether. Washing, drying ($MgSO_4$) and evaporation of the combined ethereal extracts gave a gum which was stored at 3°C for 7 days open to the air, and then separated by p.l.c. on silica gel. Three bands were isolated. The front band was a mixture of 2,6-diethylbenzaldehyde and (291) (0.017g total weight, estimated by n.m.r. to contain *ca.* 0.005g of (291), 5%), the rear band contained the expected isoquinoline (289) (0.023g, 26%). The middle band contained a new compound identified as *ethyl 5-ethyl-4-hydroxy-1-methylisoquinoline-3-carboxylate* (292) (0.007g, 7%) obtained as an oil. (Found: M^+ = 259.1202. $C_{15}H_{17}NO_3$ requires M^+ = 259.1208);

δ_H (250 MHz; $(CD_3)_2CO$): 1.32 (3H, t, *J* 8 Hz, 5-CH_2CH_3), 1.45 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 2.80 (3H, s, 1-Me), 3.42 (2H, q, *J* 8 Hz, 5-CH_2CH_3), 4.50 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 7.63 (1H, d, *J* 6 Hz with fine splitting, 6-H or 8-H), 7.75 (1H, dd, *J* 8.5, 6 Hz with fine splitting, 7-H), 8.05 (1H, d, *J* 8.5 Hz with fine splitting, 8-H or 6-H), 12.70 (1H, s, OH);

m/z: 259 (M^+, 65%), 230 (13), 213 (42), 212 (26), 185 (100).

(viii) *N*-Acetylation of the enamine (291)

The enamine (291) (0.015g, 0.06 mmol) was acetylated by treatment with acetic anhydride/pyridine as described (Section 4(iii)) above. Purification by p.l.c. and crystallization from ether/petrol gave white crystals of *ethyl-2-acetamido-3-(2-ethyl-6-vinylphenyl)propenoate*, m.p. 110 - 12°C. (Found: C, 70.87; H, 7.61; N, 4.81. $C_{17}H_{21}NO_3$ requires C, 71.06; H, 7.37; N, 4.87%);

6. Thermolyses of the 2-cyclohexyl and 2-isopropylindolyl azidopropenoates

(i) Thermolysis of azide (293)

a) The azide (293) (0.05g, 0.13 mmol) was dissolved in xylene (10 ml), and the resulting solution heated at reflux for 1.5h. The solvent was evaporated and the crude n.m.r. indicated that complete conversion to enamine (294) had taken place, the data for which will be quoted under a later experiment. The material was heated for a further 15.5h in xylene, the crude n.m.r. being recorded again after a total of 4.5h heating, and finally when the full 17h was complete. These spectra showed only the presence of unchanged enamine (294). The material was thus dissolved in *o*-dichlorobenzene (10 ml) and the solution refluxed for 2h. The only identifiable compound present was the enamine (294), although some decomposition had evidently taken place.

b) The azide (293) (0.05g, 0.13 mmol) was dissolved in DMF (10 ml) and the solution was heated at reflux for 2h. Aqueous work-up, ethereal extraction etc. gave a gum which was shown to be complex by n.m.r. and was discarded.

(ii) Preparation, purification and characterization of enamine (294)

The azide (293) (0.06g, 0.16 mmol) was dissolved in benzene (12 ml) and the resulting solution refluxed for 3h. Evaporation of the solvent and flash chromatography on silica gel gave *ethyl 2-amino-3-(2-(cyclohex-1-en-1-yl)-1-methoxymethylindol-3-yl)propenoate* (294);

δ_H (250 MHz, $CDCl_3$): 1.39 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 1.55 - 1.95 (4H, br m, CH_2-CH_2-C = CH-CH_2-CH_2), 2.15 - 2.40 (4H, br m, CH_2-CH_2-C = CH-CH_2-CH_2), 3.27 (3H, s, CH_2OMe), 3.97 (2H, br s, NH_2), 4.32 (2H, q, *J* 7 Hz,

δ_H (250 MHz, $CDCl_3$): continued

$CO_2CH_2CH_3$), 5.42 (2H, s, CH_2OMe), 5.99 (1H, m, CH_2-CH_2-C = C*H*-CH_2-CH_2), 6.62 (1H, s, C*H* = C(NH_2)ε), 7.23 (2H, m, 5-H and 6-H), 7.47 (1H, m, 4-H or 7-H), 7.67 (1H, m, 7-H or 4-H).

The enamine was acetylated as described previously giving, after chromatography and crystallization from chloroform/petrol, pale yellow crystals of *ethyl 2-acetamido-3-(2-(cyclohex-1-en-1-yl)-1-methoxymethylindol-3-yl)propenoate* (0.028g, 45% from the starting azide (293)), m.p. 140 - 51°C. (Found: C, 69.51; H, 7.14; N, 6.99. $C_{23}H_{28}N_2O_4$ requires C, 69.68; H, 7.12; N, 7.07%);

ν_{max} (nujol): 3240 (NH), 1710 (C = O), 1654 (C = O), 1645 sh, 1632 cm^{-1};

δ_H (250 MHz; $CDCl_3$): 1.36 (3H, t, J 7 Hz, $CO_2CH_2CH_3$), 1.65 - 1.85 (4H, br m, CH_2-CH_2-C = CH-CH_2-CH_2), 1.98 (3H, br s, NHCO*Me*), 2.20 - 2.35 (4H, br m, CH_2-CH_2-C = CH-CH_2-CH_2), 3.29 (3H, s, CH_2OMe), 4.32 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.40 (2H, s, CH_2OMe), 6.02 (1H, m, CH_2-CH_2-C = C*H*-CH_2-CH_2), 6.92 (1H, br s, C*H* = C(NHAc)ε), 7.10 - 7.30 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.47 (1H, m, 7-H or 4-H), 7.52 (1H, br s, NH);

m/z: 396 (M^+, 32%), 365 (8), 350 (15), 337 (100), 305 (37), 291 (39).

(iii) Preparation and *N*-acetylation of the enamine (297).

The azide (296) (0.10g, 0.29 mmol) was dissolved in benzene, and the resulting solution refluxed for 5h. Evaporation of the solvent gave as a gum the crude *ethyl 2-amino-3-(2-isopropenyl-1-methoxymethyl-indol-3-yl)propenoate* (297);

ν_{max} (thin film): 3485, 3380 (NH_2), 1705 (C = O), 1640, 1582 cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.36 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 2.10 (3H, d, *J* 1.5 Hz, CH_3-C = CH_2), 3.27 (3H, s, CH_2OMe), 3.85 (2H, br s, NH_2), 4.34 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.29 (1H, m, one of CH_3-C = CH_2), 5.47 (2H, s, CH_2OMe), 5.62 (1H, m, one of CH_3-C = CH_2), 6.66 (1H, s, CH = C(NH_2)ε), 7.10 - 7.50 (3H, m, 5-H, 6-H and 4-H or 7-H), 7.68 (1H, m, 7-H or 4-H).

The enamine was acylated as described previously, giving, after chromatography and recrystallization from chloroform/petrol, pale yellow crystals of *ethyl 2-acetamido-3-(2-isopropenyl-1-methoxymethyl-indol-3-yl)propenoate* (0.05g, 48% from starting azide (296)), m.p. 130 - 7°C. (Found: C, 67.16; H, 6.78; N, 7.76. $C_{20}H_{24}N_2O_4$ requires C, 67.40; H, 6.79; N, 7.86%);

ν_{max} (nujol): 3238, 3200 sh (NH), 1700 (C = O), 1653, 1650 sh, 1630 cm^{-1};

δ_H (250 MHz; $CDCl_3$): 1.36 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 1.96 (3H, br s, NHCO*Me*), 2.14 (3H, br s, CH_3-C = CH_2), 3.29 (3H, s, CH_2OMe), 4.32 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.28 (1H, br m, one of CH_3-C = CH_2), 5.42 (2H, s, CH_2OMe), 5.65 (1H, br m, one of CH_3-C = CH_2), 6.98 (1H, br s, CH = C(NHAc)ε), 7.10 - 7.55 (5H, m, 4-H, 5-H, 6-H, 7-H and NH);

m/z: 356 (M^+, 28%), 310 (52), 297 (100), 266 (39), 251 (18), 239 (56).

(iv) Thermolysis of azide (296) in xylene

The azide (296) (0.10g, 0.29 mmol) was dissolved in xylene and the solution refluxed for 7h. The solvent was evaporated and the residue was chromatographed on a silica gel p.l.c. plate. One band was

isolated, showing strong pale blue fluorescence under the u.v. lamp. This was shown to be somewhat contaminated, by n.m.r., but further attempts to purify the compound were unsuccessful, and it was never obtained completely pure. The contaminant appeared to be one compound, to which the major component was gradually converting. The major component was identified as *ethyl 1,2-dihydro-1,1-dimethyl-9-methoxymethylpyrido[3,4-b]indole-3-carboxylate* (298);

ν_{max} (thin film): 3380 (NH), 1700 (C = O) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.36 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 1.61 (6H, s, 2 x 1-Me), 3.30 (3H, s, CH_2OMe), 4.33 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.57 (2H, s, CH_2OMe), 6.80 (1H, s, 4-H), 7.1 - 7.8 (4H, m, Ar-H).

The material was stored at *ca.* 3°C in contact with moist air for 70 days after which time it was found to have been completely converted into a new compound, which was purified by p.l.c. and identified as *ethyl 1,1-dimethyl-9-methoxymethyl-4-oxopyrido[3,4-b]indole-3-carboxylate* (299). (Found: M^+ = 328.1421. $C_{18}H_{20}N_2O_4$ requires M^+ = 328.1423).

ν_{max} (thin film): 1736 (C = O), 1658 (C = O), 1635 (C = N) cm^{-1};

δ_H (90 MHz; $CDCl_3$): 1.44 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 1.84 (6H, s, 2 x 1-Me), 3.47 (3H, s, CH_2OMe), 4.49 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.71 (2H, s, CH_2OMe), 7.25 - 7.60 (3H, m, 6-H, 7-H and 5-H or 8-H), 8.29 (1H, m, 8-H or 5-H);

m/z: 328 (M^+, 49%), 297 (18), 255 (11), 229 (100), 214 (47), 184 (99).

(v) Prolonged thermolysis of azide (296) in bromobenzene

The azide (296) (0.05g, 0.15 mmol) was dissolved in bromobenzene (10 ml) and the solution refluxed for 168h under nitrogen. Evaporation of the solvent and chromatography on silica gel gave one band which was spectroscopically identical with β-carboline (269a) (0.005g, 9%). The presence of dihydro-β-carboline (298) in the reaction mixture was monitored by t.l.c., until it had been completely consumed.

7. Thermolysis of the 2-phenylindolyl azidopropenoate (300)

The azidopropenoate (300) (0.02g, 0.05 mmol) was dissolved in xylene (10 ml) and the solution heated at reflux for 1h. Evaporation of the solvent and p.l.c. of the residue, gave after crystallization, yellow prisms of *ethyl 1,8-dihydro-8-methoxymethylbenz[d]azepino[4,5-b]indole-2-carboxylate* (301) (0.01g, 54%), m.p. 144 - 8°C from ethanol/petrol. (Found: C, 72.09; H, 5.68; N, 8.02. $C_{21}H_{20}N_2O_3$ requires C, 72.40; H, 5.79; N, 8.04%);

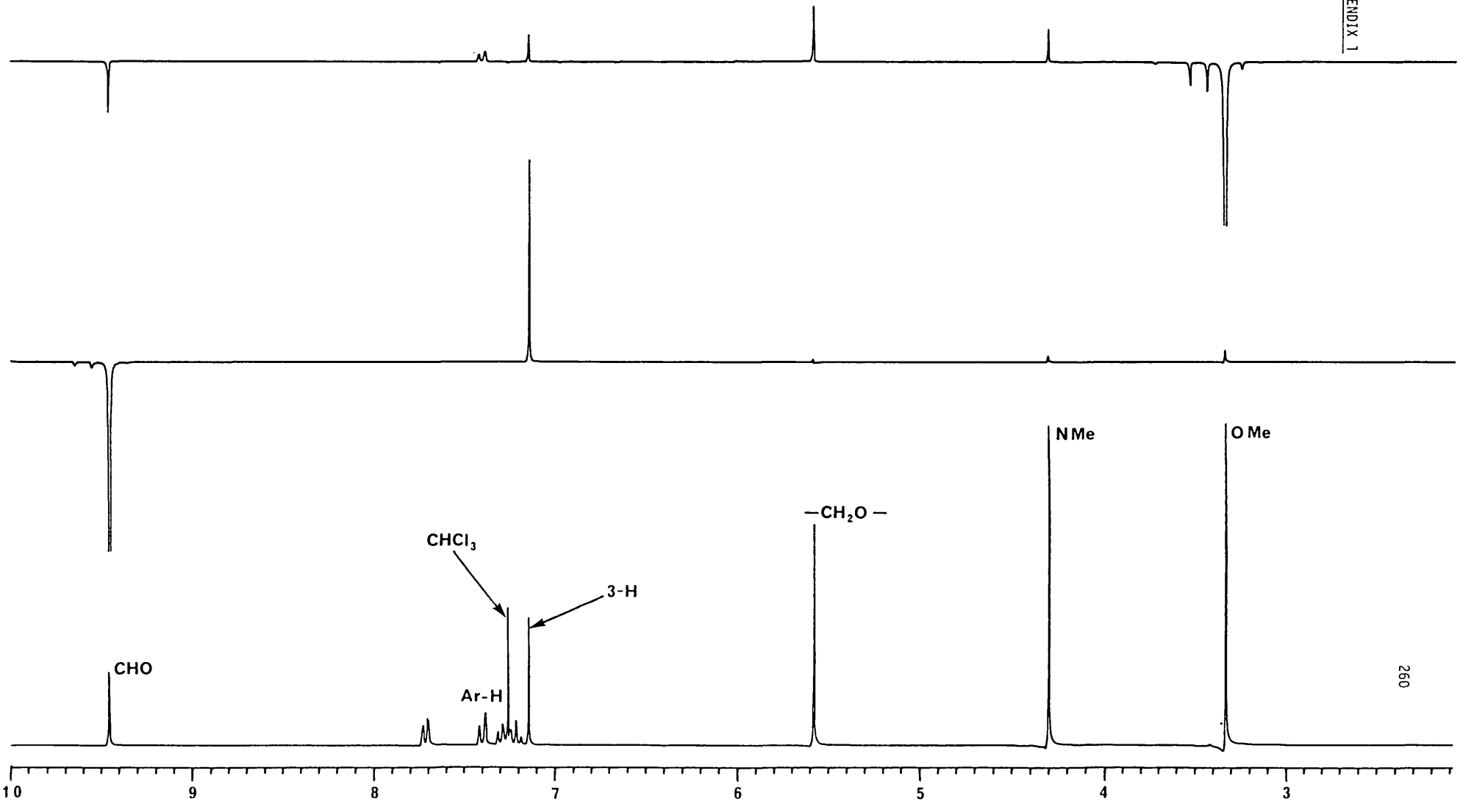
ν_{max} (nujol): 1708 (C = O), 1625 cm^{-1};

δ_H (250 MHz; $(CD_3)_2CO$): 1.31 (3H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 3.46 (3H, s, CH_2OMe), 4.28 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 5.58 (2H, s, CH_2OMe), 7.29 (2H, m, Ar-H), 7.40 - 7.60 (3H, m, Ar-H), 7.70 (1H, m, Ar-H), 7.83 (1H, m, Ar-H), 8.21 (1H, m, Ar-H);

m/z: 348 (M^+, 100%), 303 (98), 229 (82).

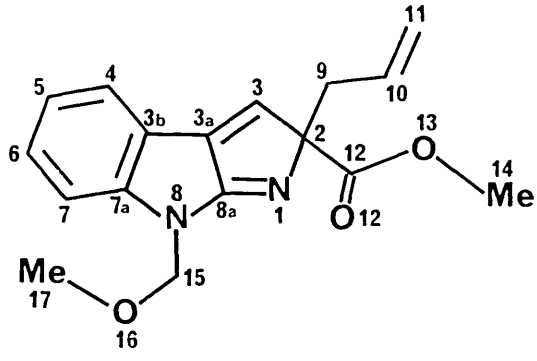
APPENDICES

Figure 1



APPENDIX 2

Bond lengths and angles for compound (233a) as determined by X-ray crystallography.



(i) Bond lengths (Å)

N(1)	- C(2)	1.477(4)	N(1)	- C(8a)	1.280(4)
C(2)	- C(3)	1.523(4)	C(2)	- C(9)	1.539(5)
C(2)	- C(12)	1.510(7)	C(3)	- C(3a)	1.336(5)
C(3a)	- C(3b)	1.447(4)	C(3a)	- C(8a)	1.462(5)
C(3b)	- C(4)	1.384(5)	C(3b)	- C(7a)	1.409(5)
C(4)	- C(5)	1.385(5)	C(5)	- C(6)	1.382(7)
C(6)	- C(7)	1.388(5)	C(7)	- C(7a)	1.380(5)
C(7a)	- N(8)	1.407(4)	N(8)	- C(8a)	1.376(4)
N(8)	- C(15)	1.438(4)	C(9)	- C(10)	1.470(7)
C(10)	- C(11)	1.272(7)	C(12)	- O(12)	1.193(5)
C(12)	- O(13)	1.343(5)	O(13)	- C(14)	1.426(8)
C(15)	- O(16)	1.394(6)	O(16)	- C(17)	1.406(6)

(ii) Bond angles (deg.)

C(2)	- N(1)	- C(8a)	103.6(3)	N(1)	- C(2)	- C(3)	106.4(3)
N(1)	- C(2)	- C(9)	110.0(3)	C(3)	- C(2)	- C(9)	112.9(3)

(ii) Bond angles (deg.) (continued)

N(1) - C(2) - C(12)	110.6(3)	C(3) - C(2) - C(12)	107.6(3)
C(9) - C(2) - C(12)	109.3(3)	C(2) - C(3) - C(3a)	107.6(3)
C(3) - C(3a) - C(3b)	148.9(3)	C(3) - C(3a) - C(8a)	104.8(3)
C(3b) - C(3a) - C(8a)	106.3(3)	C(3a) - C(3b) - C(4)	134.2(3)
C(3a) - C(3b) - C(7a)	106.1(3)	C(4) - C(3b) - C(7a)	119.7(3)
C(3b) - C(4) - C(5)	118.9(4)	C(4) - C(5) - C(6)	120.5(4)
C(5) - C(6) - C(7)	122.1(3)	C(6) - C(7) - C(7a)	117.1(4)
C(3b) - C(7a) - C(7)	121.8(3)	C(3b) - C(7a) - N(8)	110.7(3)
C(7) - C(7a) - N(8)	127.5(3)	C(7a) - N(8) - C(8a)	107.9(3)
C(7a) - N(8) - C(15)	125.7(3)	C(8a) - N(8) - C(15)	125.9(3)
N(1) - C(8a) - C(3a)	117.7(3)	N(1) - C(8a) - N(8)	133.4(3)
C(3a) - C(8a) - N(8)	108.9(3)	C(2) - C(9) - C(10)	111.9(3)
C(9) - C(10) - C(11)	126.8(4)	C(2) - C(12) - O(12)	125.0(4)
C(2) - C(12) - O(13)	112.8(3)	O(12) - C(12) - O(13)	122.0(5)
C(12) - O(13) - C(14)	116.9(3)	N(8) - C(15) - O(16)	113.1(4)
C(15) - O(16) - C(17)	113.8(3)		

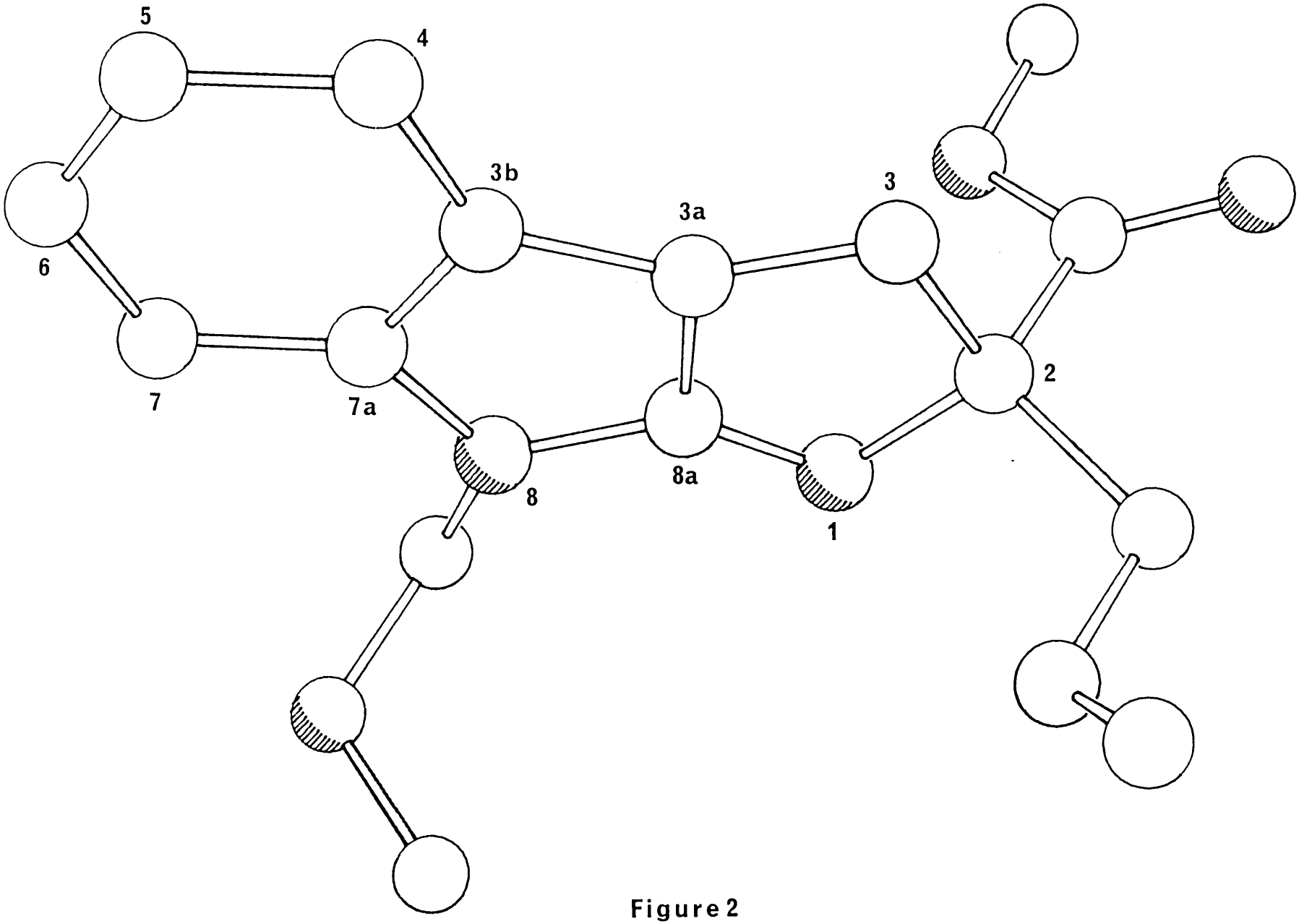
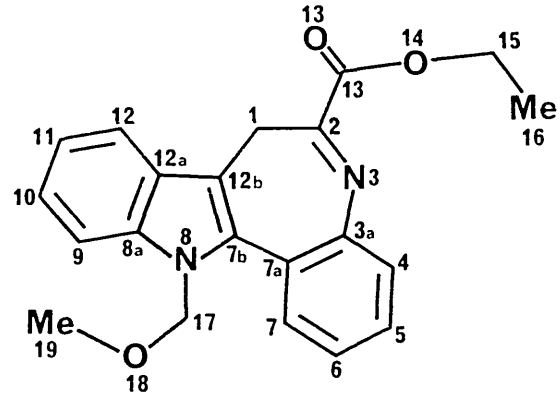


Figure 2

APPENDIX 3

Bond lengths and angles for compound (301) as determined by X-ray crystallography.



(i) Bond lengths (Å)

C(1) - C(2)	1.501(4)	C(1) - C(12b)	1.488(5)
C(2) - N(3)	1.274(3)	C(2) - C(13)	1.497(4)
N(3) - C(3a)	1.404(3)	C(3a) - C(4)	1.398(3)
C(3a) - C(7a)	1.408(4)	C(4) - C(5)	1.360(4)
C(5) - C(6)	1.378(6)	C(6) - C(7)	1.377(4)
C(7) - C(7a)	1.397(3)	C(7a) - C(7b)	1.462(3)
C(7b) - N(8)	1.399(4)	C(7b) - C(12b)	1.364(3)
N(8) - C(8a)	1.382(3)	N(8) - C(17)	1.438(4)
C(8a) - C(9)	1.393(5)	C(8a) - C(12a)	1.407(4)
C(9) - C(10)	1.366(4)	C(10) - C(11)	1.384(6)
C(11) - C(12)	1.376(5)	C(12) - C(12a)	1.396(3)
C(12a) - C(12b)	1.425(4)	C(13) - O(13)	1.186(4)
C(13) - O(14)	1.291(4)	O(14) - C(15)	1.458(5)
C(15) - C(16)	1.267(9)	C(17) - O(18)	1.394(3)
O(18) - C(19)	1.411(5)		

(ii) Bond angles (deg.)

C(2)	- C(1)	- C(12b)	106.3(2)	C(1)	- C(2)	- N(3)	125.1(2)
C(1)	- C(2)	- C(13)	116.7(2)	N(3)	- C(2)	- C(13)	118.2(2)
C(2)	- N(3)	- C(3a)	121.5(2)	N(3)	- C(3a)	- C(4)	115.2(3)
N(3)	- C(3a)	- C(7a)	125.6(2)	C(4)	- C(3a)	- C(7a)	119.0(2)
C(3a)	- C(4)	- C(5)	121.7(3)	C(4)	- C(5)	- C(6)	119.8(3)
C(5)	- C(6)	- C(7)	119.8(3)	C(6)	- C(7)	- C(7a)	121.7(3)
C(3a)	- C(7a)	- C(7)	117.9(2)	C(3a)	- C(7a)	- C(7b)	120.1(2)
C(7)	- C(7a)	- C(7b)	121.9(3)	C(7a)	- C(7b)	- N(8)	126.2(2)
C(7a)	- C(7b)	- C(12b)	124.4(3)	N(8)	- C(7b)	- C(12b)	109.3(2)
C(7b)	- N(8)	- C(8a)	107.6(2)	C(7b)	- N(8)	- C(17)	126.2(2)
C(8a)	- N(8)	- C(17)	125.5(3)	N(8)	- C(8a)	- C(9)	130.4(3)
N(8)	- C(8a)	- C(12a)	108.6(2)	C(9)	- C(8a)	- C(12a)	121.0(2)
C(8a)	- C(9)	- C(10)	117.5(3)	C(9)	- C(10)	- C(11)	122.5(3)
C(10)	- C(11)	- C(12)	120.6(3)	C(11)	- C(12)	- C(12a)	118.7(3)
C(8a)	- C(12a)	- C(12)	119.7(3)	C(8a)	- C(12a)	- C(12b)	106.5(2)
C(12)	- C(12a)	- C(12b)	133.8(3)	C(1)	- C(12b)	- C(7b)	121.7(2)
C(1)	- C(12b)	- C(12a)	130.3(2)	C(7b)	- C(12b)	- C(12a)	107.9(3)
C(2)	- C(13)	- O(13)	121.3(3)	C(2)	- C(13)	- O(14)	115.5(2)
O(13)	- C(13)	- O(14)	123.1(3)	C(13)	- O(14)	- C(15)	117.4(3)
O(14)	- C(15)	- C(16)	115.8(3)	N(8)	- C(17)	- O(18)	115.1(2)
C(17)	- O(18)	- C(19)	114.8(2)				

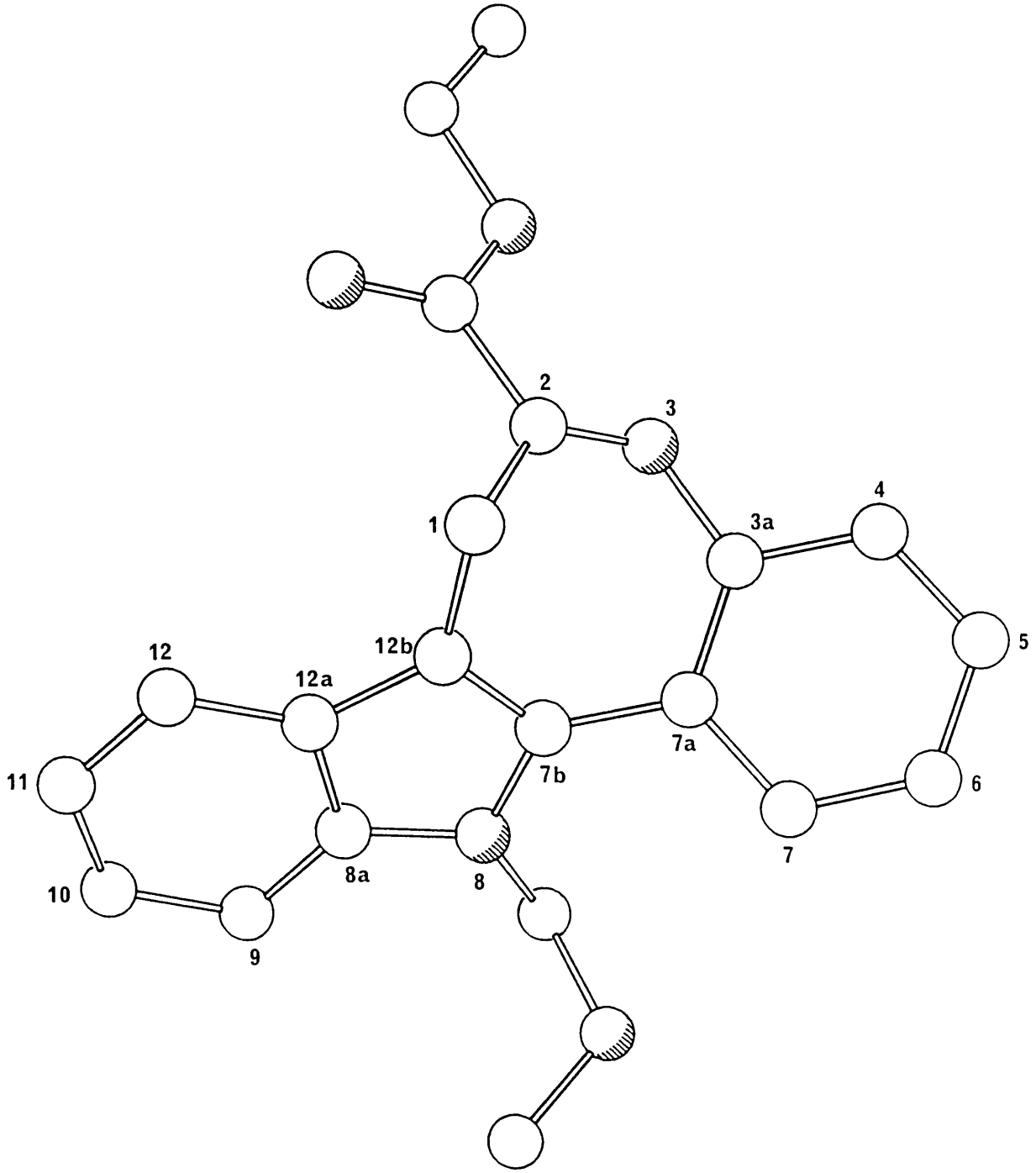


Figure 3

REFERENCES

REFERENCES

1. A.H. Jackson, B. Naidoo, and P. Smith, *Tetrahedron* 1968, 24, 6119.
2. J.W. Huffman, C.B.S. Rao, and T. Kamiya, *J. Org. Chem.* 1967, 32, 697.
3. K. Ishizumi, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* 1967, 15, 863.
4. T. Shioiri, and S. Yamada, *Tetrahedron* 1968, 24, 4159.
5. J. Thesing, and W. Festag, *Experientia* 1959, 15, 127.
6. J.W. Huffman, *J. Am. Chem. Soc.* 1958, 80, 5193.
7. E. Wenkert, and B. Wickberg, *J. Am. Chem. Soc.* 1962, 84, 4914.
8. J. Gutzwiller, G. Pizzolato, and M. Uskoviċ, *J. Am. Chem. Soc.* 1971, 93, 5907.
9. C.A. Scherer, C.A. Dorschel, J.M. Cook, and P.W. Le Quesne, *J. Org. Chem.* 1972, 37, 1083.
10. K.H. Gibson, and J.E. Saxton, *J. Chem. Soc., Chem. Commun.* 1969, 799.
11. J.W. Cook, J.D. London, and P. McCloskey, *J. Chem. Soc.* 1951, 1203.
12. R.A. Abramovitch, and I.D. Spencer, *Adv. Heterocycl. Chem.* 1964, 3, 79.
13. E. Winterfeldt, *Chem. Ber.* 1964, 97, 2463.
14. R. Grigg, H.Q. Nimal Gunaratne, and E. McNaghten, *J. Chem. Soc., Perkin Trans. 1* 1983, 185.
15. D. Soerens, J. Sandrin, F. Ungemach, P. Mokry, S.G. Wu, E. Yamanaka, L. Hutchins, M. Di Pierro, and J.M. Cook, *J. Org. Chem.* 1979, 44, 535.
16. K.M. Biswas, and A.H. Jackson, *J. Chem. Soc., Chem. Commun.* 1983, 85.
17. E. Winterfeldt, and H.J. Altmann, *Angew. Chem., Int. Ed. Engl.* 1968, 7, 466.

18. L.K. Dalton, S. Demerac, and T. Teitei, *Aust. J. Chem.* 1969, 22, 185.

19. Y. Oikawa, and O. Yonemitsu, *J. Chem. Soc., Perkin Trans. 1* 1976, 1479.

20. B.M. Trost, S.A. Godleski, and J.P. Genêt, *J. Am. Chem. Soc.* 1978, 100, 3930.

21. H.-P. Husson, C. Thal, P. Potier, and E. Wenkert, *J. Chem. Soc., Chem. Commun.* 1970, 480.

22. B.A. Dadson, and J. Harley-Mason, *J. Chem. Soc., Chem. Commun.* 1969, 665.

23. D.I.C. Scopes, M.S. Allen, G.J. Hignett, N.D.V. Wilson, M. Harris, and J.A. Joule, *J. Chem. Soc., Perkin Trans. 1* 1977, 2376.

24. D.A. Taylor, and J.A. Joule, *J. Chem. Soc., Chem. Commun.* 1979, 642.

25. R.J. Sundberg, and F.X. Smith, *J. Org. Chem.* 1975, 40, 2613.

26. R.J. Sundberg, and J.D. Bloom, *Tetrahedron Lett.* 1978, 5157.

27. R. Robinson and J.E. Saxton, *J. Chem. Soc.* 1952, 976.

28. R. Robinson, and J.E. Saxton, *J. Chem. Soc.* 1953, 2596.

29. B. Robinson, and G.F. Smith, *J. Chem. Soc.* 1960, 4574.

30. E.E. Van Tamelen, L.J. Dolby, and R.G. Lawton, *Tetrahedron Lett.* 1960, (19), 30.

31. M. Nakagawa, S. Kato, S. Kataoka, and T. Hino, *J. Am. Chem. Soc.* 1979, 101, 3136.

32. K. Inoue, T. Matsuura, and I. Saito, *Bull. Chem. Soc. Jpn.* 1982, 55, 2959.

33. T. Onaka, *Tetrahedron Lett.* 1971, 4391.

34. T.F. Spande, M. Wilchek, and B. Witkop, *J. Am. Chem. Soc.* 1968, 90, 3256.

35. M. Nakagawa, K. Matsuki, and T. Hino, *Tetrahedron Lett.* 1983, 24, 2171.

36. M. Ohno, T.F. Spande, and B. Witkop, *J. Am. Chem. Soc.* 1970, 92, 343.

37. P.D. Davis, and D.C. Neckers, *Tetrahedron Lett.* 1978, 2979.

38. M. Ruccia, N. Vivona, G. Cusmano, M.L. Marino, and F. Piozzi, *Tetrahedron* 1973, 29, 3159.

39. T.L. Gilchrist, and T.G. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1283.

40. R. Bergamasco, Q.N. Porter, and C. Yap, *Aust. J. Chem.* 1978, 31, 1841.

41. D. Beck, and K. Schenker, *Helv. Chim. Acta.* 1968, 51, 264.

42. Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.* 1973, 21, 2770.

43. R.M. Acheson, J.N. Bridson, T.R. Cecil, and A.R. Hands, *J. Chem. Soc., Perkin Trans. 1* 1972, 1569.

44. M.E. Kuehne, D.M. Roland, and R. Hafter, *J. Org. Chem.* 1978, 43, 3705.

45. W. Oppolzer, *Synthesis*, 1978, 793.

46. G. Tacconi, A.G. Invernizzi, and G. Desimioni, *J. Chem. Soc., Perkin Trans. 1* 1976, 1872.

47. G. Tacconi, A. Gamba, F. Marinone, and G. Desimioni, *Tetrahedron* 1971, 27, 561.

48. H. Plieninger, W. Müller, and K. Weinerth, *Chem. Ber.* 1964, 667.

49. E.R. Marinelli, *Tetrahedron Lett.* 1982, 23, 2745.

50. T. Gallagher, and P. Magnus, *Tetrahedron* 1981, 37, 3889.

51. T. Gallagher, and P. Magnus, *J. Am. Chem. Soc.* 1982, 104, 1140.

52. J. Bergman, and R. Carlsson, *Tetrahedron Lett.* 1978, 4051.

53. J. Bergman, and R. Carlsson, *Tetrahedron Lett.* 1977, 4663.

54. W.E. Noland, and J.E. Johnson, *Tetrahedron Lett.* 1962, 589.

55. S. Takano, K. Shishido, M. Sato, and K. Ogaswara, *Heterocycles* 1977, 6, 1699.

56. A.I. Scott, C.-L. Yeh, and D. Greenslade, *J. Chem. Soc., Chem. Commun.* 1978, 947.

57. H.-P. Husson, K. Bannai, R. Freire, B. Mompon, and F.A.M. Reis, *Tetrahedron* 1978, 34, 1363.

58. G.R. Clemo, and J.C. Seaton, *J. Chem. Soc.*, 1954, 2582.

59. R. Helmuth, F. Manske, W.H. Perkin Jr., and R. Robinson, *J. Chem. Soc.*, 1927, 1.

60. W.E. Noland, and M.R. Venkiteswaran, *J. Org. Chem.* 1961, 26, 4263.

61. W.E. Noland, M.R. Venkiteswaran, and C.G. Richards, *J. Org. Chem.* 1961, 26, 4241.

62. M. Sainsbury, *Heterocycles* 1978, 9, 1349.

63. M.G. Beal, W.R. Ashcroft, M.M. Cooper, and J.A. Joule, *J. Chem. Soc., Perkin Trans. 1* 1982, 435.

64. H. Hemetsberger, D. Knittel and H. Weidmann, *Monatsh. Chem.*, 1969, 100, 1599.

65. H. Hemetsberger and D. Knittel, *Monatsh. Chem.*, 1972, 103, 194.

66. T.L. Gilchrist, C.W. Rees and J.A.R. Rodrigues, *J. Chem. Soc., Chem. Commun.*, 1979, 627.

67. D.M.B. Hickey, Ph.D. Thesis, University of London, 1982.

68. S.C. Tsoi, Ph.D. Thesis, University of London,1983.

69. C.F.H. Allen and J. Van Allen, *Org. Synth. Coll.*, 3, 597.

70. C. Jongsma and F. Bickelhaupt, *Rec. Trav. Chim. Pays-Bas*, 1973, 92, 1143.

71. P.N. James and H.R. Snyder, *Org. Synth. Coll.*, 4, 539.

72. A.J. Jackson and A.E. Smith, *J. Chem. Soc.*, 1964, 5510.

73. S. Nakatsuka, M. Miyazaki and T. Goto, *Tetrahedron Lett.*, 1980, 21, 2817.

74. F. Piozzi and M.R. Langella, *Gazz. Chim. Ital.*, 1963, 93, 1382.

75. S. Sugaswara and S. Nakamura, *J. Pharm. Soc. Jpn.*, 1953, 73, 647.

76. V.F. Martynov and G. Ol'man, *Zh. Obshch. Khim.*, 1954, 24, 498.

77. R.E. Lyle and L. Skarlos, *J. Chem. Soc., Chem. Commun.*, 1966, 644.

78. H. Kissman, D. Farnsworth and B. Witkop, *J. Amer. Chem. Soc.*, 1952, 74, 3948.

79. D. Libermann, M. Moyeux, A. Rouaix, J. Maillard, L. Hengl and J. Himbert, *Bull. Soc. Chim. Fr.*, 1953, 957.

80. D.E. Horning and J.M. Muchowski, *Can. J. Chem.*, 1970, 48, 193.

81. H. Hemetsberger, D. Knittel and H. Weidmann, *Monatsh. Chem.*, 1970, 101, 161.

82. F.W. Fowler, *Adv. Heterocycl. Chem.*, 1971, 13, 45; and references therein; G. Smolinsky and C.A. Pryde, in 'Chemistry of the Azido Group', ed. S. Patai, Wiley Interscience, New York, 1971; G. L'Abbe and A. Hassner, *Angew. Chem. Int. Ed. Engl.*, 1971, 10, 98.

83. R. Majima and M. Kotake, *Chem. Ber.*, 1925, 58, 2037.

84. M.N. Preobrazhenskaya, L.A. Savel'eva, K.F. Turchin and N.N. Suvorov, *Dokl. Akad. Nauk. S.S.S.R.*, 1968, 179, 884.

85. M.N. Preobrazhenskaya, L.A. Savel'eva and N.N. Suvorov, *J. Org. Chem. U.S.S.R. (Engl. Transl.)*, 1969, 5, 730.

86. L.A. Savel'eva, M.N. Preobrazhenskaya, N.P. Kostynchenko, and N.N. Suvorov, *J. Org. Chem. U.S.S.R. (Engl. Transl.)*, 1970, 6, 2354.

87. G. Smolinsky and C.A. Pryde, *J. Org. Chem.*, 1968, 33, 2411.

88. W.S. Wadsworth and W.D. Emmons, *J. Amer. Chem. Soc.*, 1961, 83, 1733.

89. T.L. Gilchrist and G.E. Gymer, *Adv. Heterocycl. Chem.*, 1974, 16, 33.

90. F. Piozzi and C. Fuganti, *Ann. Chim. (Rome)*, 1967, 57, 486.

91. C. Shin, Y. Yonezawa, K. Unoki and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, 1979, 52, 1657.

92. J.H. Boyer, W.E. Krueger and R. Modler, *J. Org. Chem.*, 1969, 34, 1987.

93. J. Bergman and J.E. Bäckvall, *Tetrahedron*, 1975, 31, 2063.

94. V. Plavsic, S. Kveder and S. Iskric, *Croat. Chem. Acta.*, 1974, 46, 217.

95. J. Fischer and W. Steglich, *Angew. Chem. Int. Ed. Engl.*, 1979, 18, 167.

96. S. Götze, B. Kubel and W. Steglich, *Chem. Ber.*, 1976, 109, 2331.

97. W. Steglich, P. Gruber, H-U. Heininger and F. Kreidl, *Chem. Ber.*, 1971, 104, 3816.

98. T. Raynham, Undergraduate Research Project, Imperial College, London, 1983.

99. R.J. Sundberg in 'The Chemistry of Indoles', Academic Press, New York, 1970, p.401.

100. A. Treibs and H. Scherer, *Justus Liebigs Ann. Chem.*, 1952, 577, 189.

101. a) F.P. Doyle, M.D. Mehta, G.S. Sach and J.L. Person, *J. Chem. Soc.*, 1958, 4458; R.L. Hinman and S. Theodoropulos, *J. Org. Chem.*, 1963, 28, 3052.

b) R.A. Jones and G.P. Bean in 'The chemistry of pyrroles', Academic Press, London, 1977, p.293.

102. K. Isomura, S. Kobayashi and H. Taniguchi, *Tetrahedron Lett.*, 1968, 3499.

103. K. Isomura, M. Okada and H. Taniguchi, *Tetrahedron Lett.*, 1969, 4073.

104. V.S. Velezheva, V.P. Sevodin, Yu. V. Ereofeev, N.K. Genkina, T.A. Kozik, V.V. Vampilova and N.N. Suvorov, *Chem. Heterocycl. Comp., (Engl. Transl.)*, 1977, 13, 290.

105. N. Shoji, Y. Kondo and T. Takemoto, *Heterocycles*, 1973, 1, 251.

106. J.S. Carlé and C. Christopherson, *J. Amer. Chem. Soc.*, 1979, 101, 4012.

107. Y. Kimura, T. Hamasaki, N. Nakajima and A. Isogai, *Tetrahedron Lett.*, 1982, 23, 225.

108. R. Vlegaar and P.J. Wessels, *J. Chem. Soc., Chem. Commun.*, 1980, 160.

109. M. Nakagawa, H. Okajima and T. Hino, *J. Amer. Chem. Soc.*, 1976, 98, 635.

110. M. Taniguchi and T. Hino, *Tetrahedron*, 1981, 37, 1487.

111. T. Hino, M. Taniguchi, I. Yamamoto, K. Yamaguchi and M. Nakagawa, *Tetrahedron Lett.*, 1981, 22, 2565.

112. A.N. Kost, N.B. Chernyshova, L.G. Yudin and V.I. Terenin, *Chem. Heterocycl. Comp., (Engl. Transl.)*, 1975, 11, 1283.

113. B. Robinson, *Chem. Ind. (London)*, 1965, 87.

114. M. Nakazaki, *Bull. Chem. Soc. Jpn.*, 1959, 32, 588.

115. M. Ikeda, S. Matsugashita, F. Tabusa, H. Ishibashi and Y. Tamura, *J. Chem. Soc., Chem. Commun.*, 1974, 433.

116. M. Ikeda, S. Matsugashita and Y. Tamura, *J. Chem. Soc., Perkin Trans 1*, 1977, 1770.

117. P. Rosenmund and A. Sotiriou, *Angew. Chem.*, 1964, 76, 787.

118. J. Harley-Mason and A.H. Jackson, *J. Chem. Soc.*, 1954, 3651.

119. G. Kollenz, *Monatsh. Chem.*, 1978, 109, 249.

120. J.B.P.A. Wijnberg, H.E. Schoemaker and W.N. Speckamp, *Tetrahedron*, 1978, 34, 179.

121. J.B.P.A. Wijnberg and W.N. Speckamp, *Tetrahedron*, 1978, 34, 2399.

122. R. Smith and T. Livinghouse, *J. Org. Chem.*, 1983, 48, 1555.

123. R.J. De Feo and P.D. Strickler, *J. Org. Chem.*, 1963, 28, 2915.

124. G.M. Coppola, *Synthesis*, 1980, 505.

125. R.V. Stevens, R.M. Cory and S. Rossen, *J. Chem. Soc., Chem. Commun.*, 1975, 742.

126. D.H.R. Barton, I.H. Coates and P.G. Sammes, *J. Chem. Soc., Perkin Trans 1*, 1973, 599.

127. G. Brieger and T.J. Nestric, *Chem. Rev.*, 1974, 74, 567.

128. W. Leimgruber, A.D. Batcho and R.C. Czajkowski, *J. Amer. Chem. Soc.*, 1968, 90, 5641.

129. J.G. Berger, *Synthesis*, 1974, 508.

130. G.W. Gribble and J.W. Hoffman, *Synthesis*, 1977, 859.

131. L.J. Dolby and G.W. Gribble, *J. Heterocycl. Chem.*, 1966, 3, 124.

132. M.E. Osborn, J.F. Pegues and L.A. Paquette, *J. Org. Chem.*, 1980, 45, 167.

133. T. Hoshino, *Justus. Liebigs Ann. Chem.*, 1932, 500, 35.

134. J.M. Patterson, A. Wu, C.S. Kook and W.T. Smith, *J. Org. Chem.*, 1974, 39, 486.

135. S. Inada, K. Nagai, Y. Takayanagi and M. Okazaki, *Bull. Chem. Soc. Jpn.*, 1976, 49, 833.

136. M. Somei and M. Natsume, *Tetrahedron Lett.*, 1973, 2451.

137. M.-P. Seiler, dissertation No. 4574, ETH Zürich (1970), quoted by H.G. Floss, *Tetrahedron*, 1976, 32, 887.

138. B.W. Bycroft and W. Landon, *J. Chem. Soc., Chem. Commun.*, 1970, 168.

139. For a review of Patterson's work in this field and 2H-pyrrole chemistry in general, see: M.P. Sammes and A.R. Katritzky, *Adv. Heterocycl. Chem.*, 1982, 32, 233.

140. J.M. Patterson, J.D. Ferry and M.R. Boyd, *J. Amer. Chem. Soc.*, 1973, 95, 4356.

141. H. Booth, A.W. Johnson, E. Markham and P. Price, *J. Chem. Soc.*, 1959, 1587.

142. R.A. Jones and G.P. Bean, in 'The Chemistry of Pyrroles," Academic Press, London, 1977, p.174.

143. L. Brandsma and H.D. Verkruijsse in 'Synthesis of acetylenes, allenes and cumulenes', Elsevier, Amsterdam, 1981, p.219.

144. D.L. Boger, *Tetrahedron*, 1983, 39, 2869.

145. J.M. Patterson, J.D. Ferry, J.W. de Haan and M.R. Boyd, *J. Amer. Chem. Soc.*, 1975, 97, 360.

146. C. Braestrup, M. Nielsen and C.E. Olsen, *Proc. Natl. Acad. Sci. USA*, 1980, 77, 2288.

147. M. Nielsen and C. Braestrup, *Nature (London)*, 1980, 286, 606.

148. K. Isomura, S. Noguchi, M. Saruwatari, S. Hatano and H. Taniguchi, *Tetrahedron Lett.*, 1980, 21, 3879.

149. R. Reimschneider and B. Diedrich, *Justus Liebigs Ann. Chem.*, 1961, 646, 18.

150. A.N. Kost, V.I. Gorbunov and S.M. Gorbunova, *J. Org. Chem. U.S.S.R. (Engl. Transl.)*, 1976, 12, 1778.

151. M.E. Kuehne, T.H. Matsko, J.C. Bohnert and C.L. Kirkemo, *J. Org. Chem.*, 1979, 44, 1063.

152. M. Julia, J. Bagot and O. Siffert, *Bull. Soc. Chim. Fr.*, 1973, 1424.

153. J.B. Hester, A.H. Tang, H.H. Keasling and W. Veldkamp, *J. Med. Chem.*, 1968, 11, 101.

154. J. Harley-Mason, and A.H. Jackson, *J. Chem. Soc.*, 1955, 374.

155. G. Costa, C. Riche and H.P. Husson, *Tetrahedron*, 1977, 33, 315.

156. R.G. Glushkov, I.M. Zasosova, I.M. Ovcharova, N.P. Solov'eva and Yu. N. Sheinker, *Chem. Heterocycl. Comp., (Engl. Transl.)*, 1979, 15, 780.

157. K. Isomura, H. Taguchi, T. Tanaka and H. Taniguchi, *Chem. Lett.*, 1977, 401.

158. U. Hengartner, D. Valentine, K.K. Johnson, M.E. Larscheid, F. Pigott, F. Scheidl, J.W. Scott, R.C. Sun, J.M. Townsend, and T.H. Williams, *J. Org. Chem.*, 1979, 44, 3741.

159. The authentic sample was prepared by Dr. C.J. Moody by the method of H.R. Snyder, C.H. Hansch, L. Katz, S.M. Parmerter and E.C. Spaeth, *J. Amer. Chem. Soc.*, 1948, 70, 219.