STUDIES ON

HYDROXYISOQUINOLINES

A thesis submitted by ARCHIBALD W. McCULLOCH

to the University of Glasgow for the

degree of Doctor of Philosophy

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TO MY MOTHER

The author wishes to thank Dr. N. J. McCorkindale for his supervision and interest during the preparation of this work.

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He is also indebted to Mr. J. M. L. Cameron, B.Sc. and his staff for microanalyses, to Mrs F. Lawrie for certain infrared measurements, to Mr J. Gall for measuring nuclear magnetic resonance spectra, and to Miss J. Alexander for conducting bioassays. Finally he would also like to thank his laboratory colleagues for many helpful discussions.

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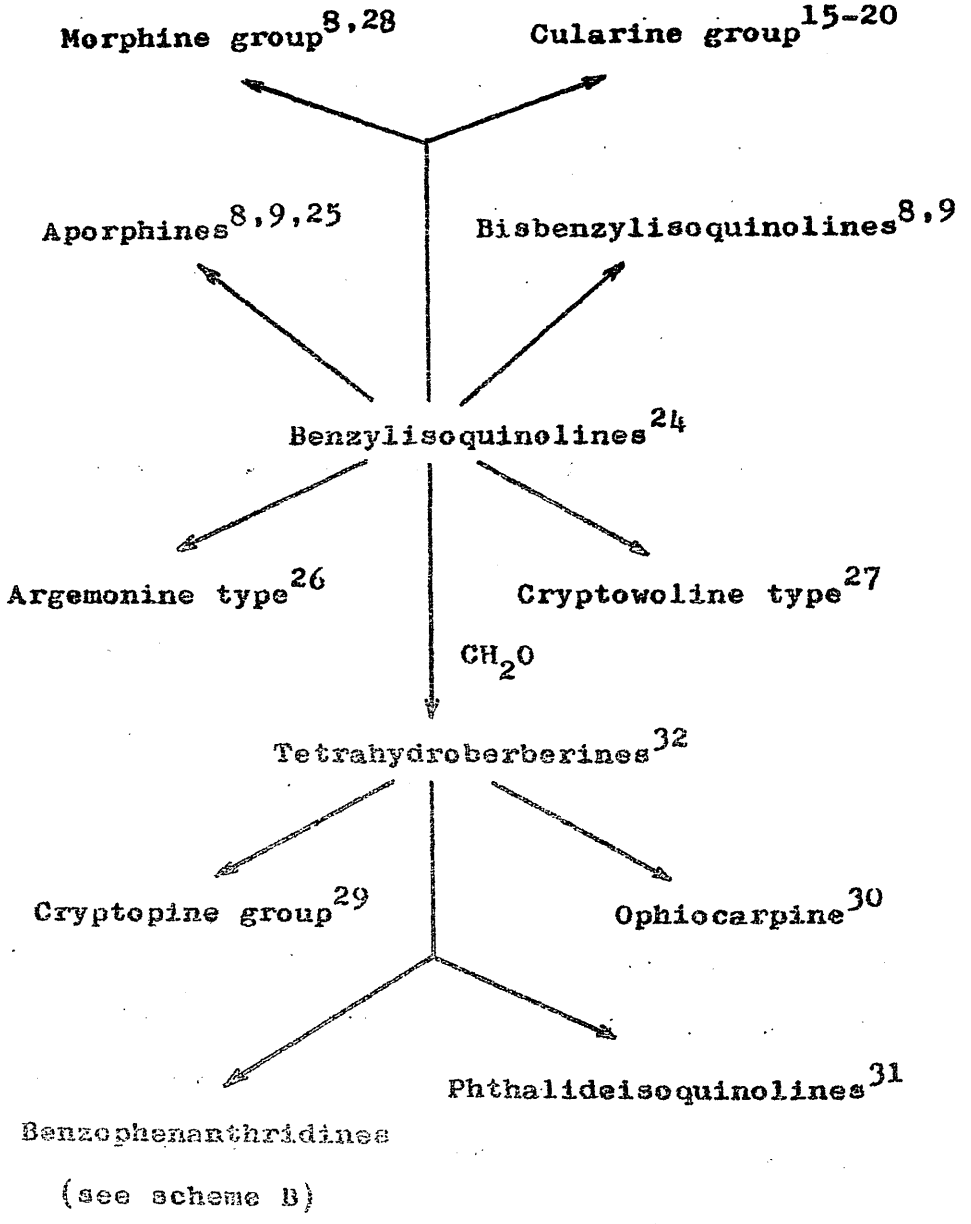
GENERAL

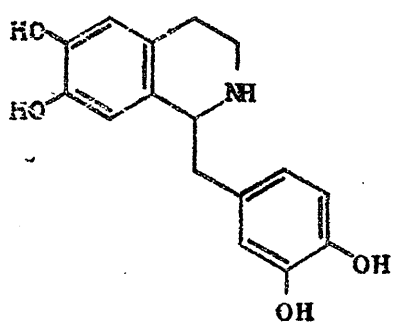
INTRODUCTION

Scheme A.


Morphine group[8,28]
Cularine group[15-20]
Aporphines[8,9,25]
Bisbenzylisoquinolines[8,9]
Benzylisoquinolines[24]
Argemonine type[26]
Cryptowoline type[27]
CH_2O
Tetrahydroberberines[32]
Cryptopine group[29]
Ophiocarpine[30]
Phthalideisoquinolines[31]
Benzophenanthridines
(see scheme B)

GENERAL INTRODUCTION

The diversity and widespread occurrence of the alkaloids have rendered them the subject of much biogenetic speculation.[1-4] The advent of radioactive tracer techniques has in recent years made possible the development of many theories concerning the biogenetic origin of these molecules.[4,5] With the results of many such investigations it became clear that a very large number of alkaloids belonging to a variety of structural types are derivable from a 1-benzyltetrahydroisoquinoline[4-7] such as norlaudanosoline (1),

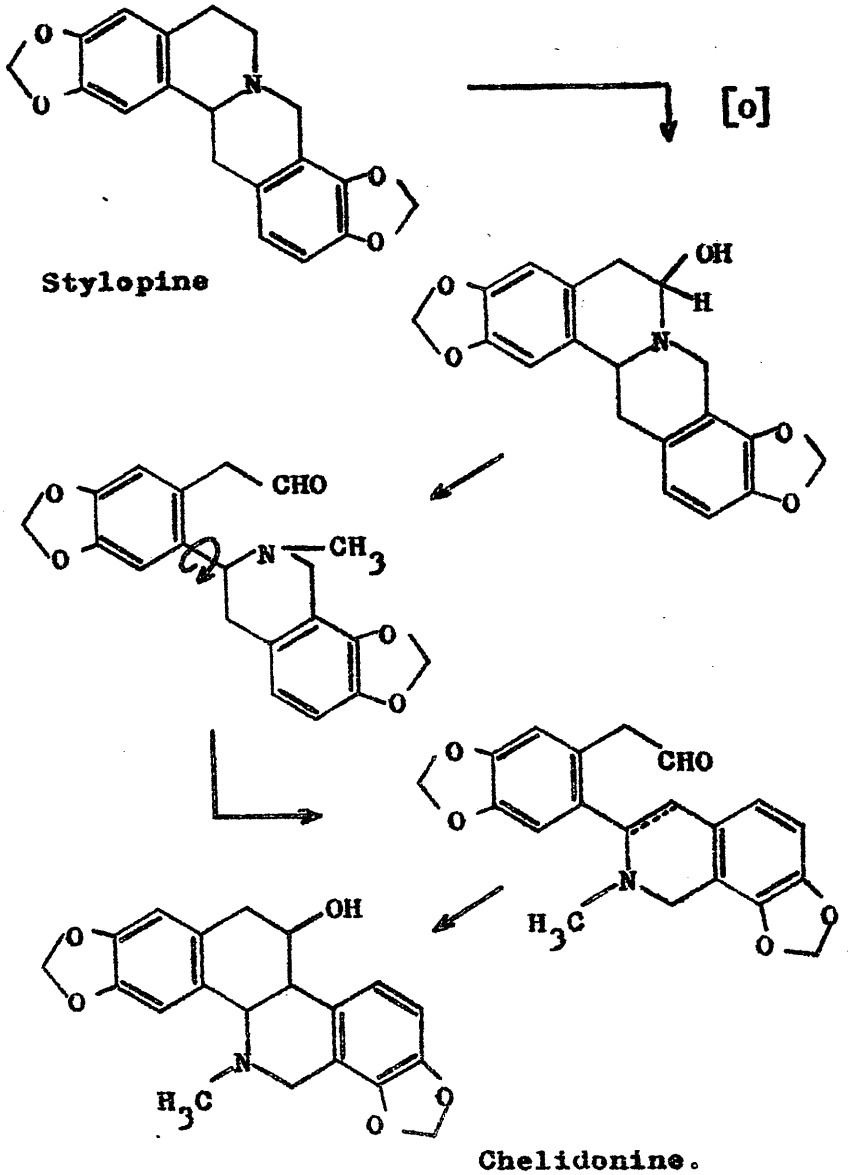


(1)

mainly by oxidative coupling processes[1,2,8-10] with additional modifications by secondary reactions such as O- or N-methylation. The common biogenetic origin of many alkaloids is summarised in Scheme A.

In particular the benzophenanthridine alkaloids have been shown to be derivable from tetrahydroberberines[11-13] by way of N-methylation, ring-fission, and

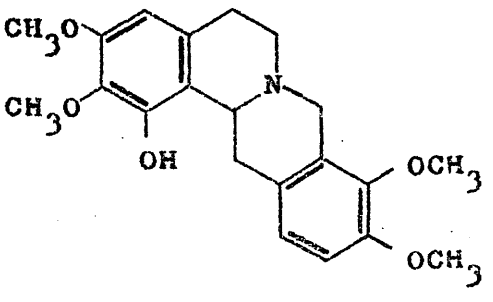
Scheme B. 11-14



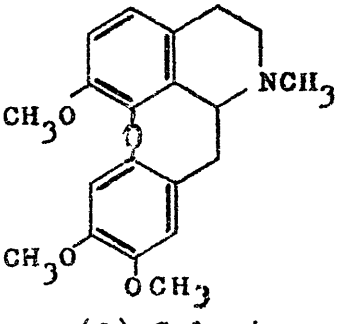
recyclisation, as depicted in Scheme B. An alternative hypothesis concerning the origin of these compounds, proposed by Manske[14], involving condensation of two moles of 3,4-dihydroxyphenylacetaldehyde, has been shown by tracer experiments[13] to be no longer tenable.

The common origin of many different alkaloids is indicated by their possession of hydroxyl, methoxyl, or methylenedioxy substituents located at positions corresponding to positions 6,7, and 4' of the benzylisoquinoline precursor. In many cases further oxygenation is present at position 3', and in a few cases at position 8, as in capaurine (2).

The only exceptions to this rule are the alkaloids of the cularine group which are found only in the genera Dicentra and Corydalis.[15,16] Four of these compounds are now known. These are cularine (3)[17], cularimine (4)[17], cularicine (5)[18], and cularidine[19], which is a des O-methyl cularine. The structures of



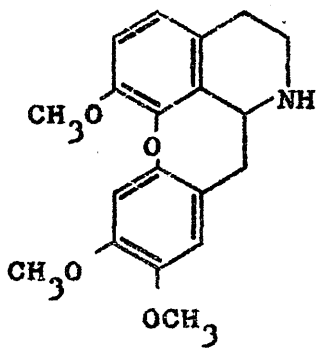
(2) Capaurine



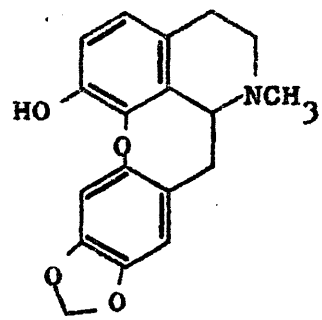
(3) Cularine

the first two alkaloids have been elucidated by means

of degradation[17,19] and synthesis.[20] These alkaloids are characterised by their highly unusual 7,8-dioxygenation.

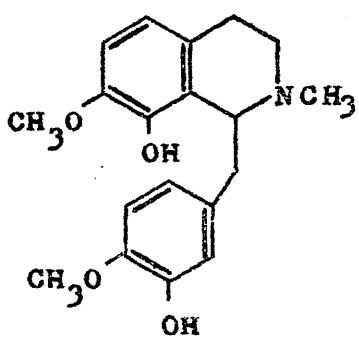


(4) Cularimine



(5) Cularicine

One possible derivation is by radical oxidation and O-alkylation of either of the diphenols (6) or (7),



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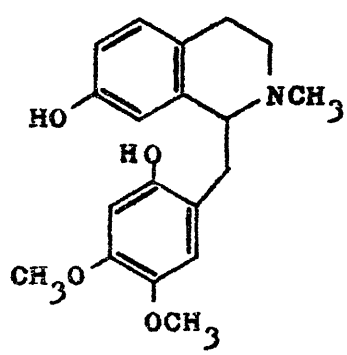
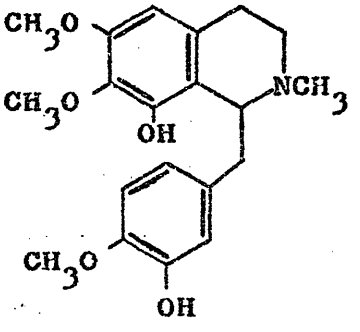


(7)

although an alternative origin, which Bentley has suggested as more likely,[15] would be the trioxygenated base (8), with subsequent reductive removal of the additional oxygen substituent. An interesting observation is the occurrence of the trioxygenated alkaloid capaurine (2) in certain Corydalis species. However, removal of oxy substituents from an isoquinoline nucleus has no analogies in nature. At one time it was thought to occur

in the benzyl portion of certain aporphines[3], but in these cases an alternative biosynthetic scheme has been suggested,[21] for which strong evidence now exists.[22]



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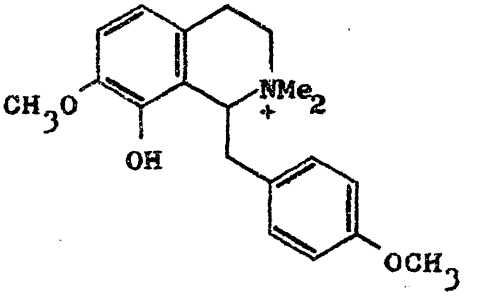

(9) Petaline

The second part of this thesis describes synthetic approaches to the alkaloid petaline whose structure has been shown[23] to be (9), making it the first 7,8-dioxygenated benzylisoquinoline to be isolated. The 3'-hydroxy substituent of the hypothetical cularine precursor (6) is absent in this compound.

As described in the first section of this thesis the potential uses of 3-isoquinolones for the synthesis of various alkaloidal systems (in particular tetrahydroberberines and benzophenanthridines) are here explored, and the groundwork for employing this type of intermediate provided by development of an efficient method of synthesis and a better understanding of their properties.

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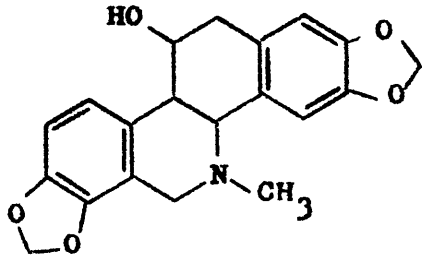
PART 1

PREPARATION AND PROPERTIES

OF 3-ISOQUINOLONES



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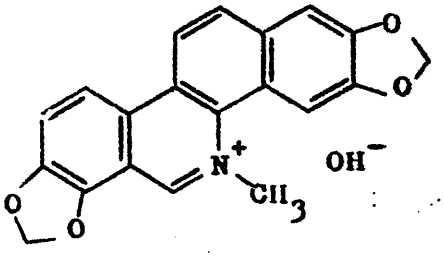

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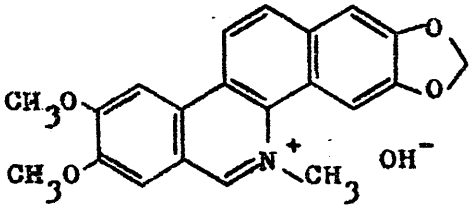

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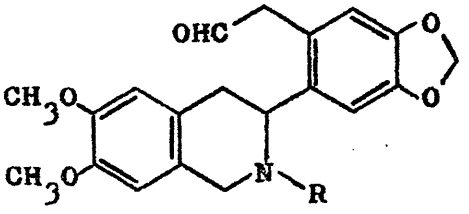

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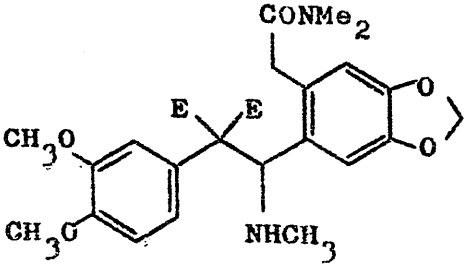
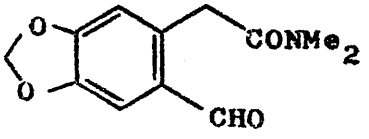


(5) E = COOEt



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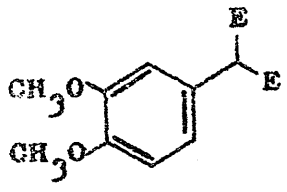

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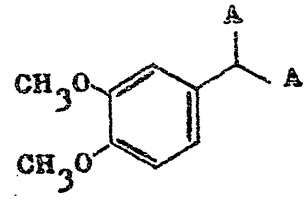

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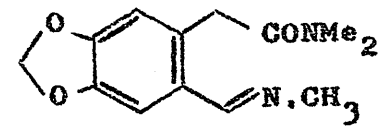

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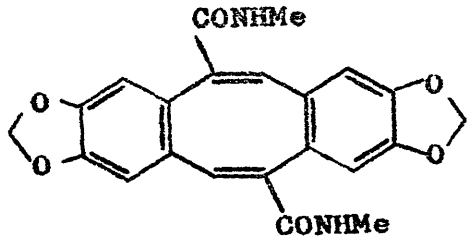

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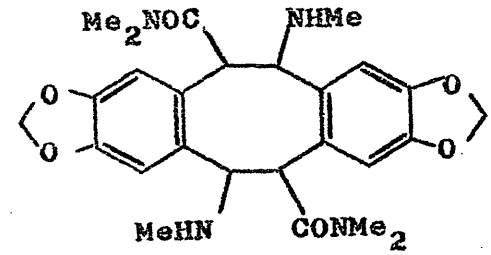

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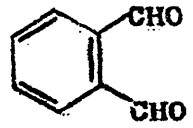

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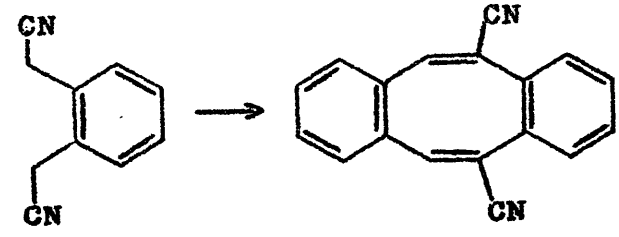

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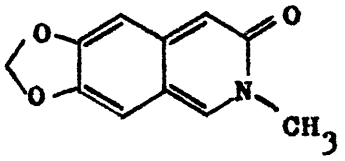

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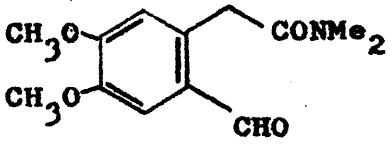

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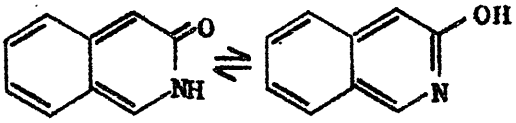

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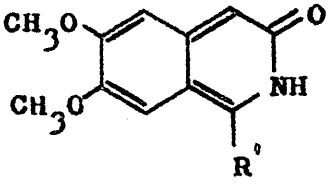
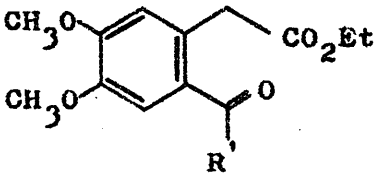


(18)

a, $R^{'} = CH_3$

b, $R^{'} = Ph$

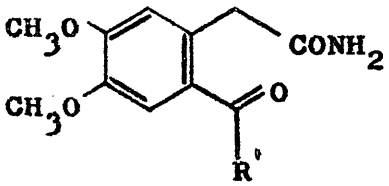


(19)

a, $R^{'} = CH_3$

b, $R^{'} = Ph$

c, $R^{'} = Bz$



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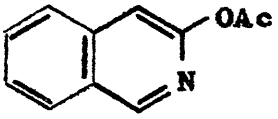
b, $R^{'} = Ph$



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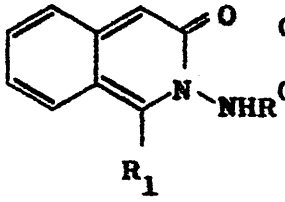
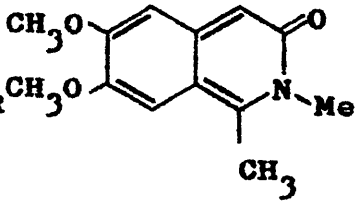
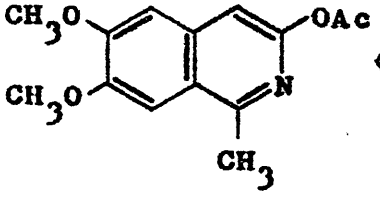
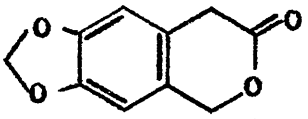


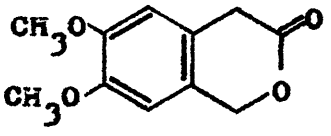


(22) (23)

a, R_1 = H or Me
R^1 = H
b, R_1 = H or Me
R^1 = Ph







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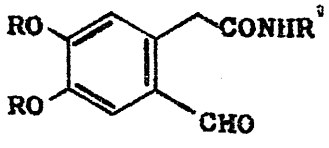

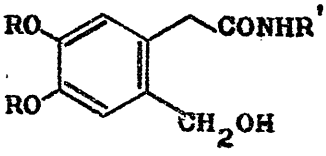

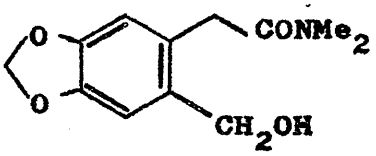

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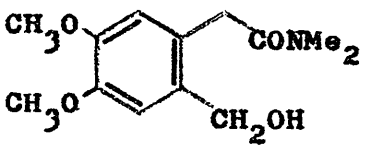

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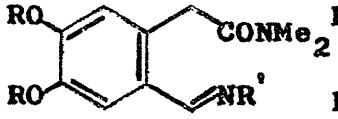

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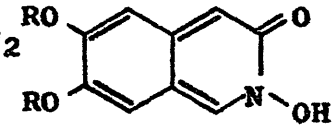

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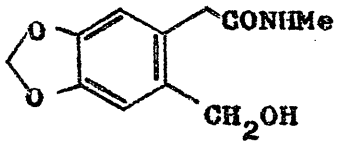

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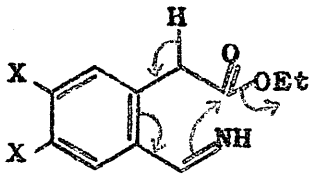

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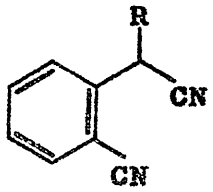

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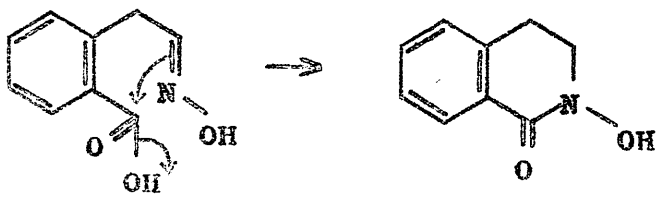

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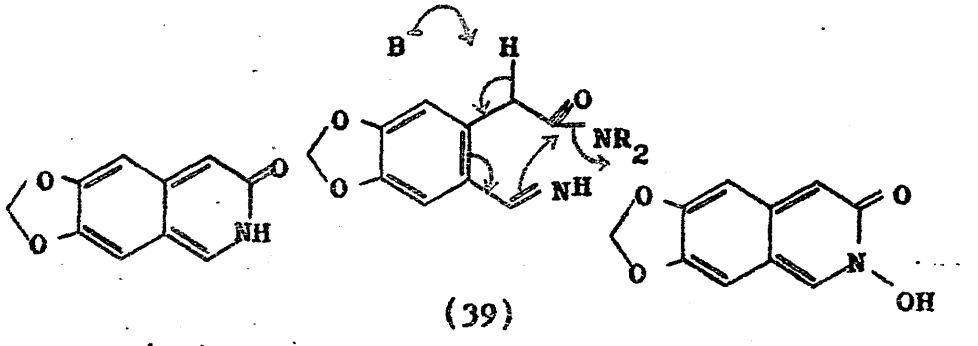

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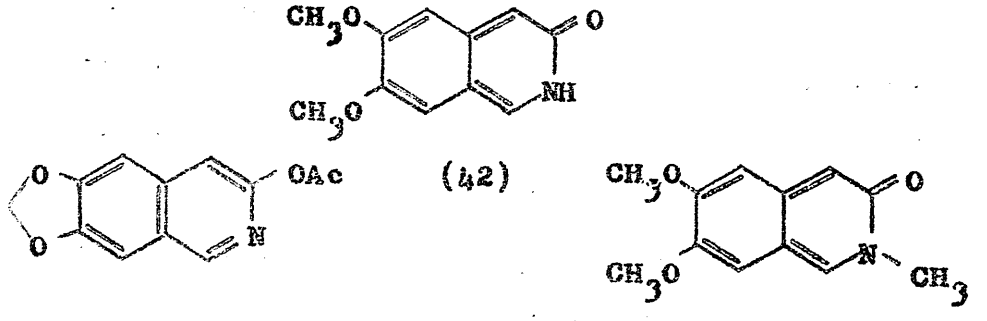

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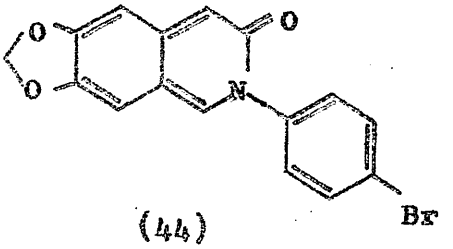

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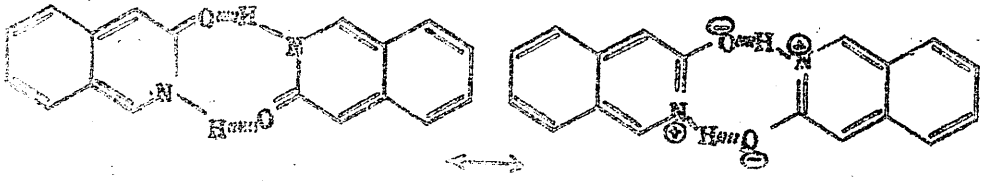

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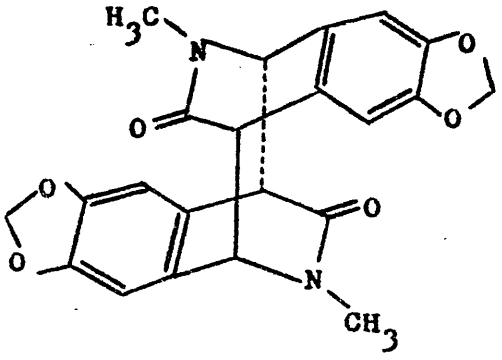

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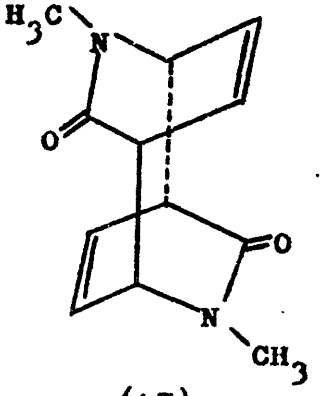

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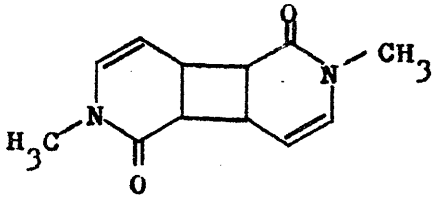

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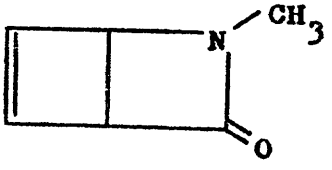

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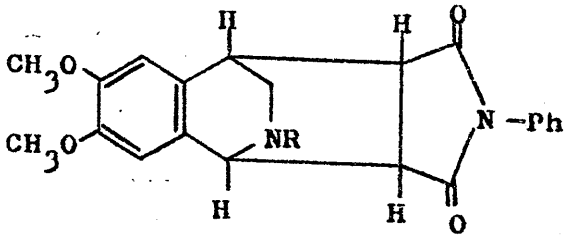

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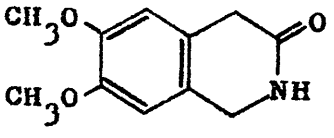

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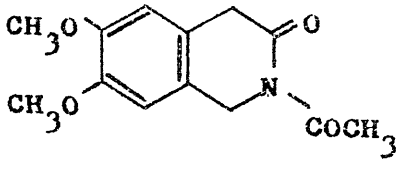

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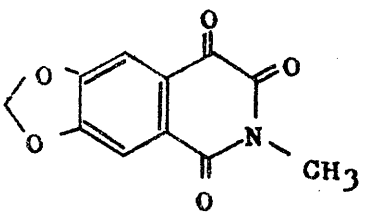

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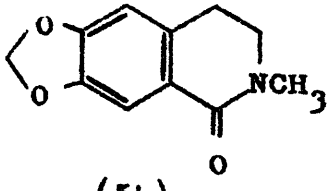

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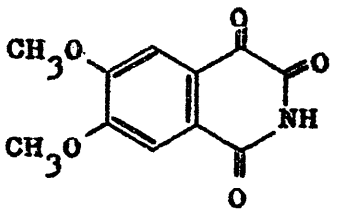

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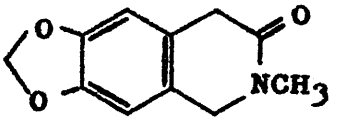

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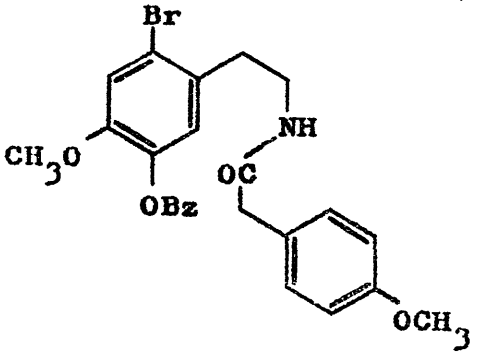

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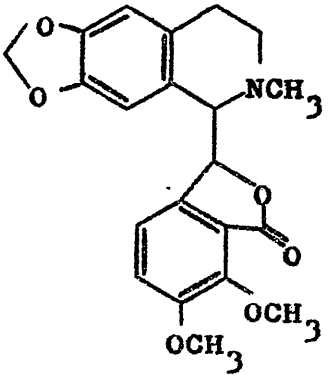

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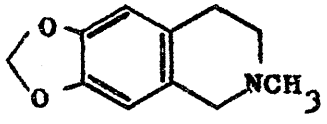

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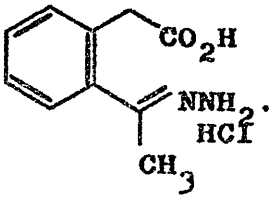

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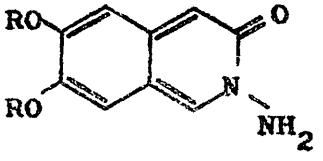

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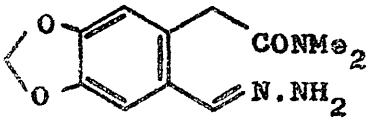

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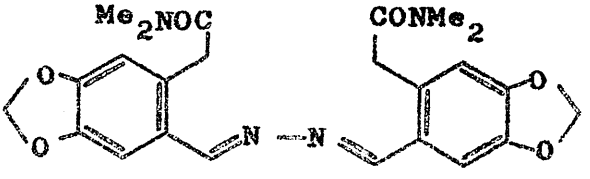

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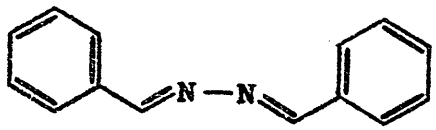

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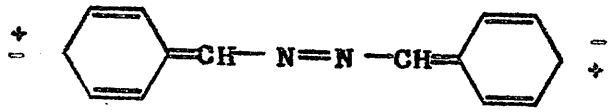

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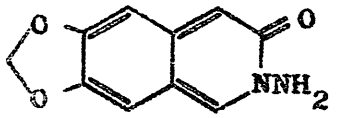

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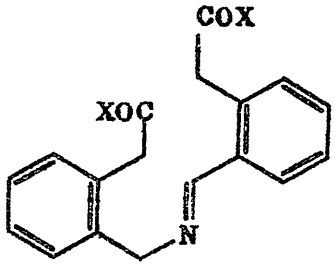

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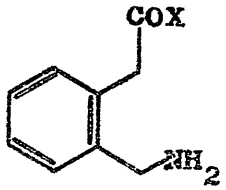

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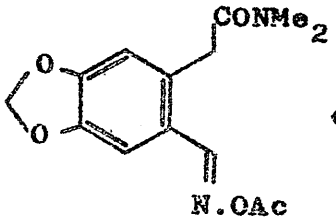

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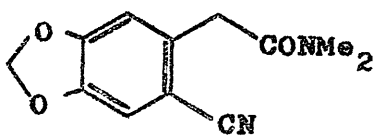

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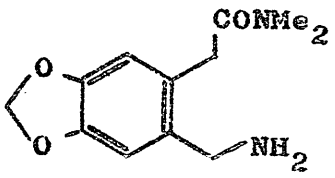

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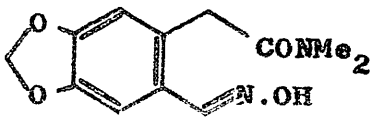

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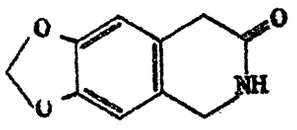

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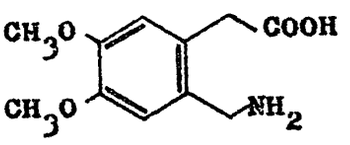

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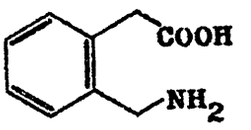

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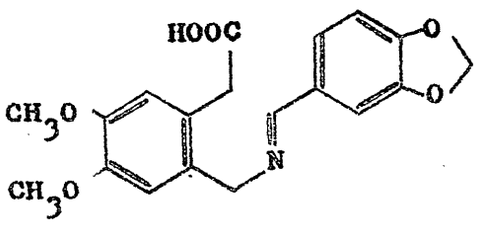

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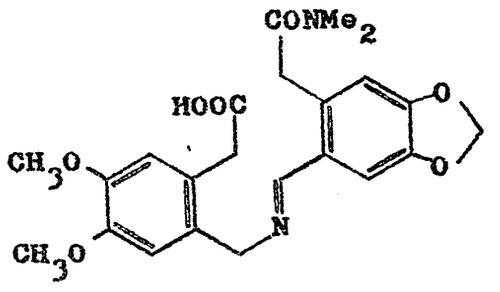

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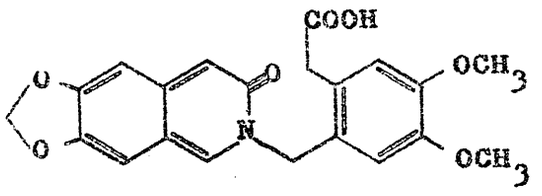

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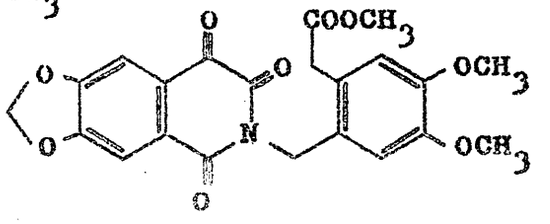

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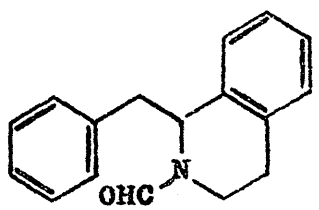

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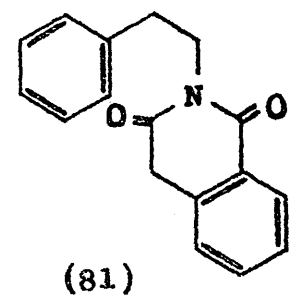

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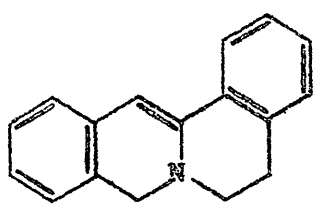

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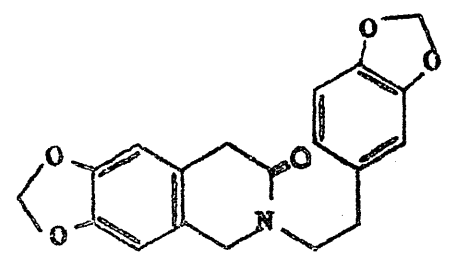

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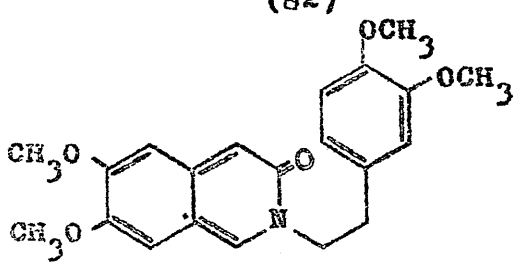

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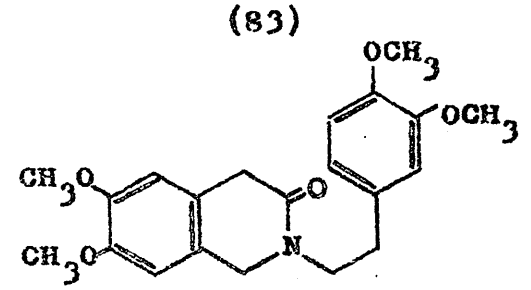

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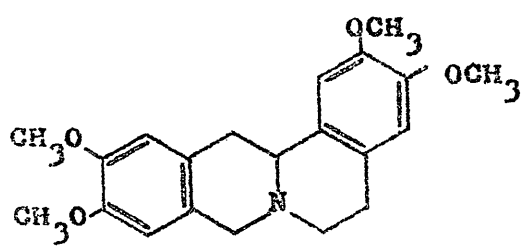
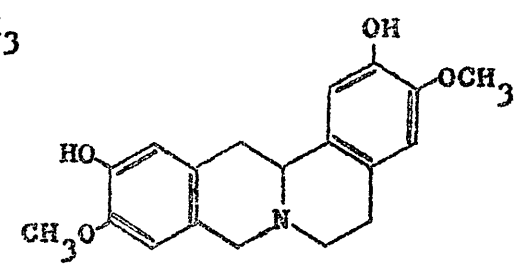
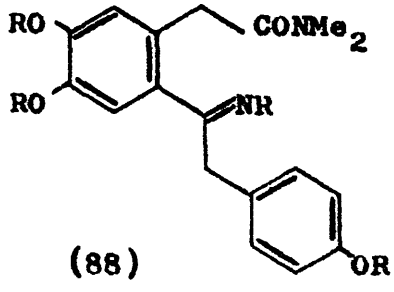


(86)

Norcoralydine.



(87) Corexímine



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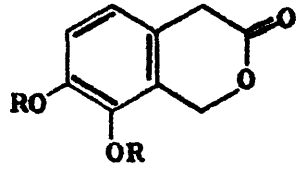

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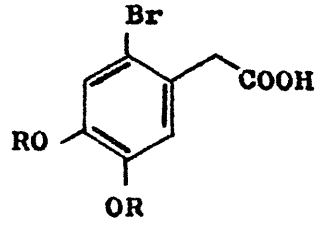

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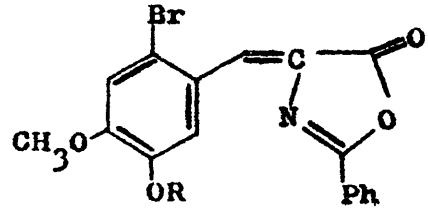
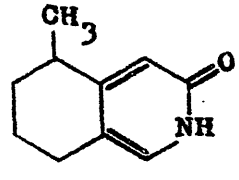


(91) a, R=H
b, R=Bz



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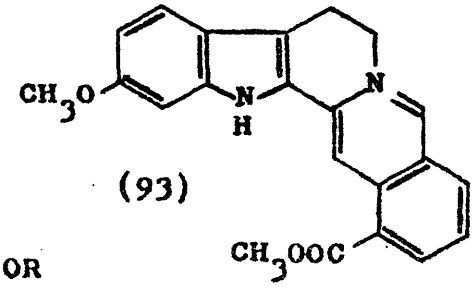

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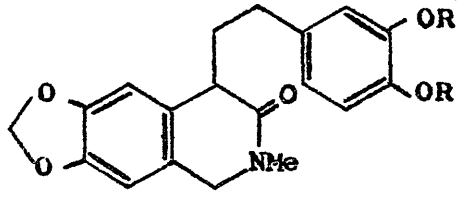

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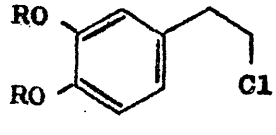

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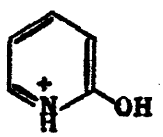

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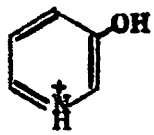

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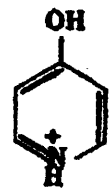
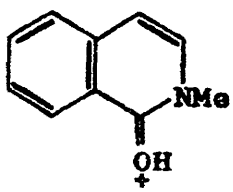


(98c)



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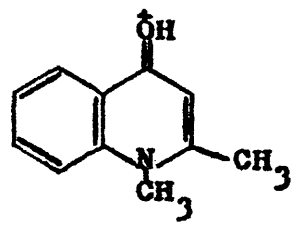
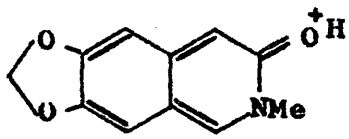


(100)



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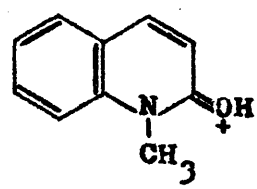

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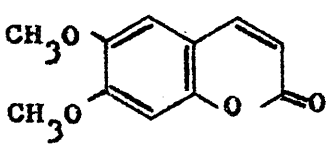

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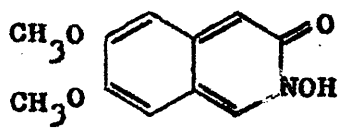

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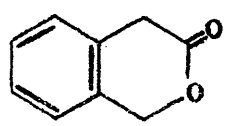


(105)

1. INTRODUCTION

Syntheses of alkaloids belonging to the benzophenanthridine group, such as chelidonine (1), sanguinarine (2), and nitidine (3) have been strictly limited[1-8], the most convenient procedure being through a phenyltetralone[2,8].

In an earlier investigation[9] the possibility of a biogenetic type synthesis via a suitably substituted 3-arylisoquinoline derivative of the type (4) was explored, an attempt being made to prepare the amine (5) by a Mannich reaction between the aldehyde (6), diethyl-3,4-dimethoxyphenylmalonate (7), and methylamine (cf. refs. 10,11). Two products were isolated from this reaction, neither of which was the desired amine (5). One was the corresponding phenylmalonamide (8), prepared independently by reaction of the diester with methylamine. The second product was a high melting bright yellow compound, shown to be formed during the work-up procedure which involved successive treatments with acid and base of the intermediate imine (9), which was isolated and characterised[9].

Preliminary information (microanalysis, amide absorption, molecular weight measurements) suggested a dimeric structure such as dibenzocyclooctatetraene (10).

the mode of formation of which would resemble that of the compound (11) (by condensation of o-phthalaldehyde (12) and the dinitrile (13))[12], but which would also invoke a secondary transamidation process, possibly via the condensed intermediate (14).

However, when a mixture of the aldehydes (6) and (16) was treated with ammonia good yields of the respective products expected from each (see later) were obtained, no third "mixed" product being detected, suggesting that the reaction is intramolecular. Further spectral and chemical evidence (ensuing discussion) eliminated the dimeric structure and led unequivocally to the monomeric isoquinoline structure (15).

Hydroxyisoquinolines and particularly 3-hydroxy-isoquinolines form a class of relatively simple hydroxylated N-heteroaromatic compounds whose chemical properties and tautomerism[13] have been comparatively neglected. One of the chief obstacles to detailed studies of the 3-hydroxyisoquinolines has been their relative inaccessibility. Since the development of the present work indicated that a general and facile synthesis of 3-hydroxyisoquinolines was now available, an investigation of their properties and synthetic potential was undertaken.

2. HISTORICAL

Early studies on halo- and hydroxy- isoquinolines were made at the end of the nineteenth century by Gabriel and his co-workers, who obtained 1-chloro-3-hydroxyisoquinoline by partial reaction of homophthalimide with phosphorous oxychloride[14]. It was not until 1951, however, that a compound, thought to be 3-isoquinolinol (17), was isolated in trace amount, as a by-product in the preparation of 3-fluoroisoquinoline.

The first established synthesis of 3- isoquinolinols was reported by Bentley, Dawson, and Spring[16], who prepared compounds (18a,b) in 60% yield by reaction of the corresponding ortho-acyl phenylacetate (19a,b) with ammonia (a reaction analogous to an earlier synthesis of 3-methylisocarbostyril[17]). The 1-methyl derivative was formed by the action of aqueous ammonia, but ethanolic ammonia at 130-140° was required for formation of the 1-aryl-3-isoquinolinol. These workers visualised a mechanism involving the corresponding amides (20a,b) as intermediates. All attempts to isolate the amides were, however, unsuccessful. It was concluded that these hydroxyisoquinolines were probably phenolic in nature although the study of their chemistry was limited to

reactions with ferric chloride (violet colour) and benzenediazonium chloride (bright red azo derivative), and the formation of a picrate, hydrochloride, and O-acetate.

A different approach was used in the preparation of 3-hydroxyisoquinoline itself, which was first achieved in 18% yield by diazotisation of 3-aminoisoquinoline[18]. The sodium salt was also prepared as was the acetate (21), which was formed directly when the diazotisation was carried out using glacial acetic acid and isoamyl nitrite. On the basis of an i.r. absorption ca. 3410 cm^{-1} and a positive ferric chloride test it was concluded that 3-isoquinolinol possesses a phenolic hydroxyl group.

This synthesis of 3-hydroxyisoquinoline was improved (53-65% yield) by Baumgarten, Murdock, and Dirks[19] using a modified diazotisation technique. From an evaluation of pK data they found that 3-isoquinolinol is a weaker acid than 3-hydroxyquinoline, being only slightly stronger than phenol: its basic character was found to be akin to that of 4-quinolone. They concluded from their ionisation data that there was an appreciable contribution from the amide tautomeric form, a hypothesis supported by i.r. and u.v. spectral evidence.

A further development of the Bentley method of synthesis was the acid-catalysed cyclisation of O-acetyl

and O-formyl phenylacetic acid hydrazones[20] to give the N-amino 3-hydroxyisoquinolines (22a,b).

An apparently unconnected synthesis of 3-hydroxyisoquinoline N-oxides recorded recently[21], by nitrosation of 2-indanones under alkaline conditions, may have common mechanistic features to the Bentley route (see section 3). 3-Hydroxyisoquinoline N-oxide itself has since been prepared by hydrolysis of the 3-chloro compound.[22]

Since the completion of much of this work, the preparation in 55% yield of an N-alkylated 3-hydroxyisoquinoline has been described, again using the synthetic method of Bentley *et al*. Some i.r. and u.v. data are presented[23] both for this compound (23) and for the acetate (24), first prepared by the former workers.

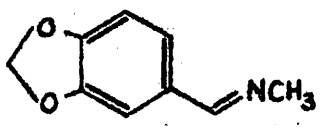
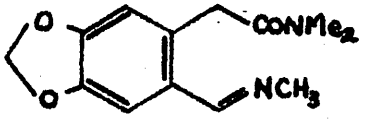
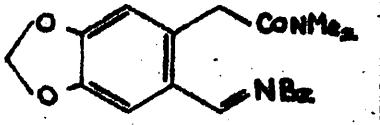
In the present work, the improved yield and generality of the synthetic method has allowed the following more comprehensive investigation of the 3-isoquinolone system. (Both from such evidence as provided in the above studies and from the current work to be described, these compounds seem to exist predominantly in the lactam form and will therefore be referred to hereafter as 3-isoquinolones.)

3. PREPARATION AND CHEMICAL PROPERTIES.

All the compounds prepared in the present study of the properties and synthetic potential of the 3-isoquinolone system are derived from the lactones (25) and (26) (ν_{CO} 1735-1740cm^{-1}). These were prepared by a slight modification of the method used by Stevens[24] for the synthesis of the former compound, whereby the crude mixture of benzoic and homo acids obtained by hydrolysis and oxidative decomposition of the azlactones of piperonal or veratraldehyde[25] was directly chloromethylated, the benzoic acid being removed by subsequent washing with saturated aqueous sodium bicarbonate. In the case of the second lactone final purification proved difficult and it was found that chloromethylation of commercially available 3,4-dimethoxyphenylacetic acid gave a purer product and was more convenient.

A compound of the type (27) was originally required for a proposed synthesis of 3-arylisoquinolines (see introduction). While various amines effected ring-opening of the lactones (25,26) to give the corresponding amide-alcohol (28), it was found that no aldehydes could be isolated from oxidation of primary or secondary amides. However the tertiary amides (29) and (30), obtained in good yield by refluxing the lactones with

TABLE 3. ULTRAVIOLET ABSORPTIONS OF IMINES.

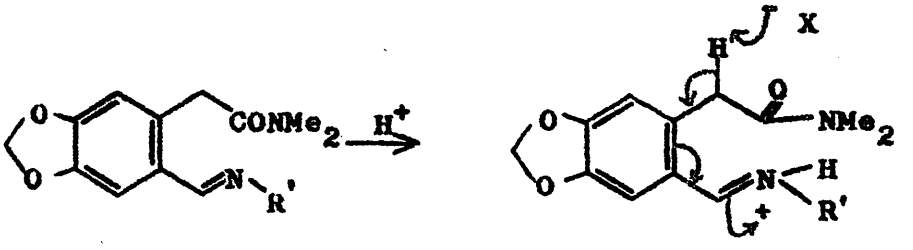
					
NEUTRAL	ACID	NEUTRAL	ACID	NEUTRAL	ACID
mμ (log ε)	mμ (log ε)	mμ (log ε)	mμ (log ε)	mμ (log ε)	mμ (log ε)
225 (4.35)	246.5 (4.11)	230 (4.28)	246 (4.58)	233 (4.18)	251 (4.02)
268 (4.02)	346 (4.18)	274 (3.95)	353 (4.25)	278 (3.78)	360 (3.92)
306.5 (3.97)	297.5 (3.92)	311 (3.85)	305 (4.16)	313 (3.65)	308 (3.65)
Shift : 78 mμ		Shift : 79 mμ		Shift : 82 mμ	

alcoholic dimethylamine, could be smoothly oxidised to the corresponding aldehydes by shaking in chloroform with manganese dioxide.[26] That the required aldehydes (6,16) had indeed been formed was indicated by i.r. absorptions at 2760 cm^{-1} and 1690 cm^{-1} (CHO) and at 1645 cm^{-1} (amide C=O), and by the similarity of the u.v. spectra to those of piperonal and veratraldehyde.

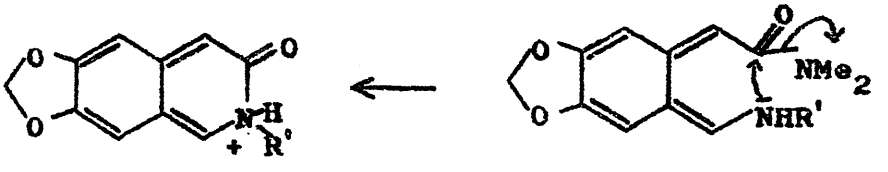
The present synthetic route to 3-isoquinolones makes use of the fact that, with hot acid, imino derivatives of type (31) readily undergo cyclisation, the products being precipitated as their hydrochlorides. The required imines were obtained in high yield by refluxing the aldehydes with alcoholic solutions of primary amines, and showed the properties expected of such compounds (tendency to hydrolyse[27], reversible red shift of ca. 80 mμ in the u.v. on acidification[28] - see Table 3). Oximes and hydrazones were prepared by standard methods.

The rapidity with which cyclisation occurs probably depends on the basicity of the nitrogen atom in the imino grouping since it was found to vary from ca. 60 seconds (31, R' = methyl, benzyl, or hydroxyl) to 20-30 minutes (31, R' = amino or p-bromophenyl). Although it was possible to prepare the N-hydroxy compounds (32) in one step by reaction of the aldehydes (6,16) with hydroxylamine hydrochloride, this type of reaction did

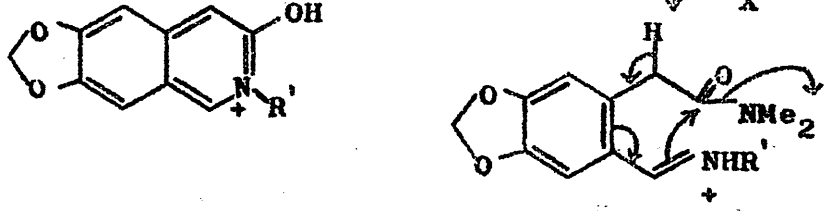
Scheme I



Type A



OR, better:-

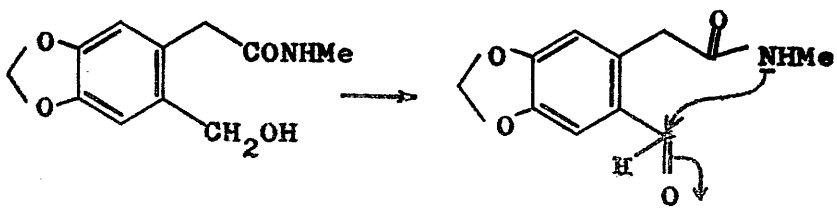


not seem to be generally applicable since the aldehyde (6) failed to react with alcoholic ethylamine hydrochloride.

The free isoquinolones were obtained from their hydrochlorides by basification with ammonium hydroxide and subsequent extraction with chloroform. As with all previously known 3-isoquinolones these compounds are high-melting bright yellow solids, exhibiting a very intense blue fluorescence in solution.

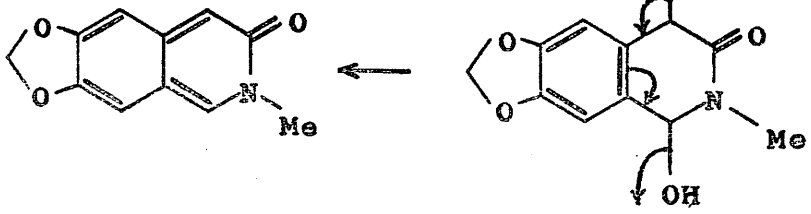
The mechanism of this cyclisation, which represents a modification of the method used by Bentley, Dawson, and Spring[16], presumably involves attack on the arylacetamide carbonyl group and the liberation of dimethylamine in the manner shown (type A) in Scheme I, the ease of reaction depending on the fact that the dimethylamino moiety is an excellent leaving group, a further driving force being the highly conjugated nature of the product. The comparable synthesis[16] of the isoquinolones (18a,b) by Bentley et al, starting from the keto-esters (19a,b), may operate by the alternative mechanism suggested by these workers, ring closure involving attack of the arylacetamide nitrogen in the proposed intermediates (20a,b) upon the ketonic carbonyl group (type B). In support of this the alcohol (33)

Scheme II



(33)

Type B.



(38)

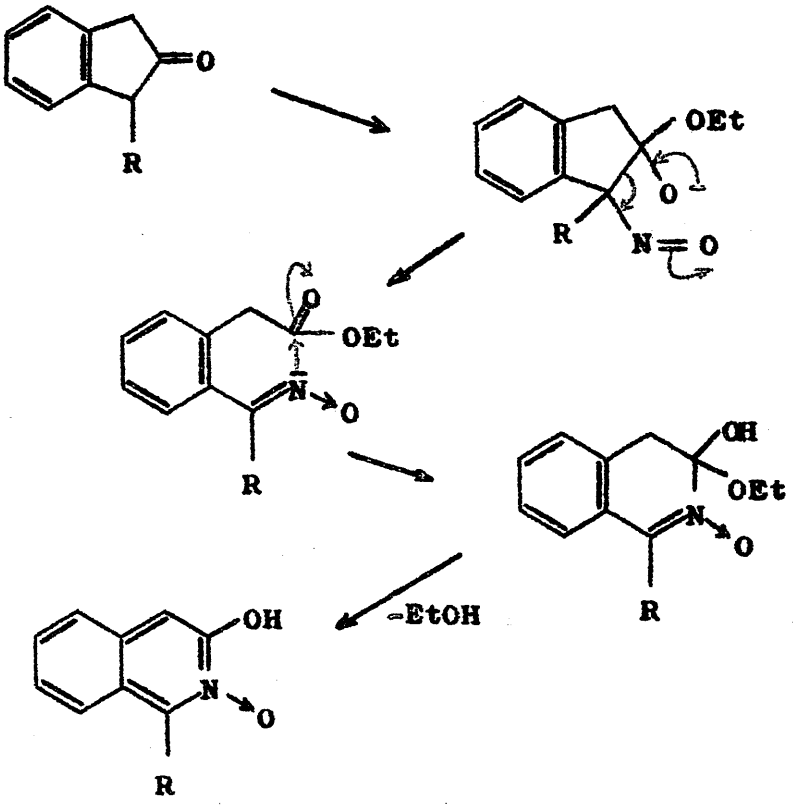
undergoes oxidative cyclisation to yield the N-methyl 3-isoquinolone (15), presumably by the type B mechanism depicted in Scheme II, and involving 1,4 elimination of water (see later). However it is also possible that their reaction may involve type A attack on the arylacetic ester carbonyl group in an intermediate (34).

The ring-closure step in the production of N-hydroxy-3-isoquinolones from indanones[21] may also be interpreted analogously in terms of type A nucleophilic attack on the arylacetic ester carbonyl, either by the nitrogen lone pair (Scheme IIIa) or in a concerted mechanism (Scheme IIIb) by a pair of electrons.

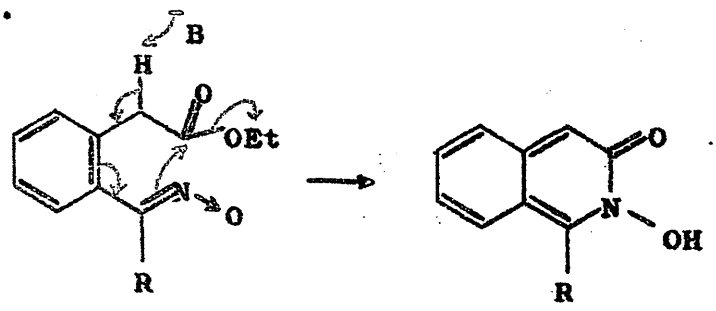
The production of 1-halo-3-aminoisoquinolines by acid-catalysed cyclisation of dinitriles of the type (35)[29] seems to provide a clear example of a type A mechanism as does the more closely analogous thermal cyclisation of the oxime (36) to the N-hydroxy dihydroisocarbostyril (37)[30].

The dimethoxy analogues of most of the methylenedioxy 3-isoquinolones discussed below were obtained by parallel routes. These showed a close correspondence in properties to the methylenedioxy series of compounds, but in many cases were less

Scheme III a.



Scheme III b.



attractive for study since they showed greater susceptibility to air oxidation.

2-Methyl-6,7-methylenedioxy-3-isoquinolone (15) was obtained from methanol as bright yellow prisms m.p.253°, or from water as a dihydrate, m.p. 238°. Full spectral data for all the three-isoquinolones studied are tabulated and discussed later in connection with the tautomerism of these compounds, but the following spectral data confirmed the 3-isoquinolone structure. The product showed strong absorption in the amide carbonyl region in chloroform at 1663 cm^{-1} and 1652 cm^{-1}. The u.v. spectrum in ethanol exhibited a very strong maximum at 248 mμ (log ε 4·76), and a visible absorption at 399 mμ (log ε 3·63), a pattern reported to be characteristic of compounds with a potential o-quinonoid structure[19]. The u.v. spectrum is similar to that recorded[19] for 3-isoquinolone itself. Moreover, the n.m.r. spectrum was in full accord with the proposed structure (see section 4).

The corresponding N-unsubstituted isoquinolone (38) was readily prepared in almost quantitative yield by overnight treatment of an ethanolic solution of the aldehyde (6) with excess ammonium hydroxide (s.g. 0·88) at room temperature. It is

interesting to note that this cyclisation occurs under basic conditions, the reaction being initiated presumably by abstraction of a proton from the benzylic methylene of the intermediate imine (39). (c.f. Scheme IIIb). It was found that the optimal reaction time was ten hours, the yield after two hours in one experiment being only 33%. The isoquinolone could not be crystallised because of insolubility in both aqueous and organic solvents, but was purified by sublimation at 180°, being obtained as bright yellow prisms, m.p. 285°. The analytical figures and mass spectrum confirm the molecular formula $C_{10}H_7O_3N$. The compound formed a hydrochloride but it was not possible to obtain satisfactory analyses for this derivative as it tended to liberate HCl on drying. This facile loss of HCl, coupled with the observation that the N-methylisoquinolone (15) can be extracted from its hydrochloride with chloroform indicate the fairly weakly basic character of these compounds.

Comparable behaviour of the secondary and tertiary lactams was also shown in their rapid decolorisation of cold aqueous permanganate and their resistance to acid or base hydrolysis. The secondary compound (38) gave a deep red coloration with

ferric chloride, but this cannot be taken as evidence of phenolic character, as a similar reaction was also given by the corresponding N-methyl isoquinolone (15).

A similar ferric chloride colour reaction was given by the N-hydroxyisoquinolone (40). In addition this compound formed a bright red nickel complex and blue-green copper complex on contact with the corresponding metals, reactions characteristic of hydroxamic acids.

One highly characteristic property of the unsubstituted isoquinolone (38) was the ready formation of colourless hydrated alkali metal salts (lithium, sodium, and potassium) merely on crystallisation from dilute aqueous solutions of the corresponding hydroxides. These salts exhibited strong i.r. maxima ca. 1600 cm^{-1}, with only very weak absorption in the carbonyl region. This behaviour is closely analogous to that of 2-pyridone[31,32].

The fact that the secondary lactam (38) was not attacked at all by excess diazomethane is suggestive of the absence of significant phenolic character. On the other hand, reaction of the sodium salt with excess refluxing methyl iodide produced in five hours a 77% yield of the N-methyl

derivative (15). Methylation on the nitrogen atom indicates only that the anion can react through the N-negative mesomer. However, evidence that the secondary lactam (38) can react through its enolic tautomer is provided by its reaction with acetic anhydride. This gave a colourless product of lower m.p. (136°). A molecular formula consistent with its being a monoacetate was indicated by analyses and molecular weight. To obtain the latter recourse was made to the isothermal distillation method which gave a mean value of 249 (theoretical 231) since the compound apparently underwent facile degradation in the heated inlet of the mass spectrometer to give the parent lactam (molecular weight 189).

This product was assigned the acetoxyisoquinoline structure (41), rather than an N-acetyl isomer, on the following evidence. The i.r. (KCl disc) showed bands at 1758, 1746, and 1238 cm^{-1}, assigned to the phenolic acetate grouping, and a strong band at 1601 cm^{-1} not observed in the spectra of the isoquinolones and taken as evidence of an isoquinoline system. The u.v. maxima at 235, 265, 278, 287, 317, and 329 mμ are also in accord with the acetoxyisoquinoline structure, being quite

similar to those reported[33] for isoquinoline itself - maxima at 260, 267, 271, 308, and 320 mμ. Finally the n.m.r. spectrum of this compound (see section 4) was compatible only with this structure. In particular the proton adjacent to nitrogen resonated at 1·26τ and the acetate methyl at 7·66τ. The latter signal is in accord with an O-acetate structure[34] rather than an N-acetate. The product of an acetylation reaction has been recently assigned[23] the O-acetyl structure (24) mainly on the basis of an i.r. absorption at 1760 cm^{-1}.

The acetate (41) was slowly hydrolysed in the cold in water, dilute base, or 95% ethanol, but was converted rapidly to the isoquinolone hydrochloride on treatment with cold dilute hydrochloric acid. This is in contrast[18] to the ready hydrolysis by water of 2-acetoxypyridine and 2-acetoxyquinoline[35,36].

A characteristic feature of the secondary lactams (38) and (42) was the appearance of broad NH absorption centred at 2600 cm^{-1} in their solid state spectra, indicative of strong hydrogen-bonding.[37] The fact that the N-methyl compounds (15) and (43) are comparatively much more soluble in common organic solvents can probably be attributed to the

existence of very strong intermolecular hydrogen-bonding in the NH compounds. The solubilities of various N-heteroaromatic compounds and their hydroxy derivatives have been interpreted in these terms by Albert[38]. In fact 6,7-methylenedioxy-3-isoquinolone was only sparingly soluble in organic solvents. However, it was found that the dimethoxy compounds as a series were more soluble than their methylene-dioxy counterparts, 6,7-dimethoxy-3-isoquinolone (42) being sufficiently soluble in chloroform to allow solution studies to be made in this solvent.

Although the parent molecular ion for the latter compound was recorded at m/e 205, confirming the expected molecular formula, measurements in chloro-form (isothermal distillation method) over a series of concentrations gave apparent molecular weights in the range 362-401 (higher values corresponding to higher concentrations), indicating that in this solvent the compound exists mainly as a dimer. Since similar measurements on the N-arylisoquinolone (44) and the acetoxyisoquinoline (41) indicated monomeric structures for these compounds in chloroform solution, it seems reasonable to assume that the dimeric form of the isoquinolone (42) is of the type (45), having two units linked through two strong intermolecular

hydrogen bonds in an eight-membered ring. This is similar to the dimers of 2-pyridone[39] and carbostyril[37] which have been likened to carboxylic acid dimers in strength on the basis of their complex and broad NH absorption between 3300 and 2400 cm^{-1}, persisting even in dilute solutions, and for which comparable resonance stabilised structures[40] have been suggested. The dimeric hydrogen bonding in isocarbostyril is reported to be somewhat weaker.[37]

A covalently bonded dimeric structure (46) can be proposed for the product obtained by irradiation of the tertiary lactam (15) with u.v. light or on exposure to sunlight. This was a colourless crystalline solid with no true m.p. below 335°. Characterisation was not possible owing to the insolubility of the product in common organic solvents. An n.m.r. spectrum in trifluoroacetic acid showed broad signals at 3.00τ (2), 3.90τ (2), 4.90-5.00τ (2), and 7.17τ (3), the relative intensities being given in parentheses. The material possessed strong amide carbonyl absorption at 1660 cm^{-1}. The evidence is not inconsistent with the photodimer structure (46), analogous to the 1,4-photodimer (47) of N-methyl 2-pyridone, originally assigned[41] the structure (48), but later revised on i.r., u.v., and n.m.r. evidence[42,43] and recently confirmed by X-ray invest-

igation[44]. Recently Corey et al[45] have irradiated N-methyl 2-pyridone in ether and have obtained the monomeric photo-pyridone (49) as a colourless liquid. The physical state of the compound derived from N-methyl 6,7-methylenedioxy 3-isoquinolone and its n.m.r. signals suggest that the 1,4 type of dimer may have been obtained. The high-field N-methyl signal is consistent with the expected shielding effect of an overlapping aromatic ring (especially in trifluoroacetic acid). The colourless infusible solid obtained by exposure of 1-methyl-2-amino-3-isoquinolone (22a) to sunlight[20] may have a similar structure. 1,4-Photoaddition is particularly plausible since one of the characteristic properties of the 3-isoquinolone system is 1,4-addition, as evidenced by the recently reported[23] facile Diels Alder addition of N-phenyl maleic imide to give high-melting adducts of type (50).

A further example of 1,4-addition is catalytic reduction which could be carried out most conveniently using Adams' catalyst in aqueous ethanol. The structures of these dihydro derivatives follow from spectral data to be discussed elsewhere.

The dimethoxydihydroisoquinolone (51) showed no signs of strong intermolecular hydrogen bonding in the i.r. (ν_{NH} 3402 cm^{-1}) and molecular weight measurements

in chloroform solution indicated a monomeric structure for this compound. Resonance stabilisation of the type postulated for the parent 3-isoquinolone (42) is no longer possible.

In contrast to the unsubstituted 3-isoquinolone (42) which on reaction with acetic anhydride gave an O-acetyl derivative, similar reaction of the dihydro derivative (51) yielded a monoacetate, shown by spectral data to be an N-acetyl derivative (τ7.41, ν_{CO} 1712, 1703 cm^{-1}). The signal of the methylene adjacent to the nitrogen atom (5.10τ) is shifted downfield (with respect to the same group in the parent lactam (51)) by 0.4τ, which is appreciably greater than the downfield shift (0.15τ) observed for the second methylene (6.30τ), indicative of an N-acetyl structure (52) with deshielding by the acetyl carbonyl. This acetate was not readily hydrolysed by warm water, but was converted rapidly to the parent compound (51) on treatment with dilute sodium hydroxide.

Further evidence of the olefinic character of the 3-isoquinolones is provided by their susceptibility to oxidation. The course of this oxidation was elucidated as a result of studying the attempted oxidation of the secondary amide-alcohol (33) to the corresponding aldehyde with manganese dioxide. This gave as main

product a bright yellow solid, m.p. 226°, analysis and parent molecular ion (m/e 233) of which indicated the molecular formula $C_{11}H_7O_5N$. The i.r. spectrum ($\nu_{max.}$ 1730, 1701, 1681 cm^{-1}) was in accord with the presence of imide and ketone functions (it formed a bright orange 2,4-dinitrophenylhydrazone). Its n.m.r. spectrum in deuterochloroform comprised one-proton singlets at 2.30τ and 2.44τ, a two-proton singlet at 3.76τ, and a three-proton singlet at 6.55τ. These data are in accord with the isoquinoline 1,3,4-trione structure (53). The unusual low-field positions of the aromatic protons can be accounted for by strong deshielding caused by the peri carbonyl groups[46], diminished somewhat by the shielding effect[47] of the methylenedioxy substituent (see section 7).

It was found that after a shorter period of oxidation with manganese dioxide, a second product, identified as the N-methyl-3-isoquinolone (15) could be isolated. This is probably an intermediate in the oxidation to the trione since it is itself readily oxidised to the trione under similar conditions (or by air, especially in the presence of light). It may be noted that 2-pyridone and N-methyl isocarbostyril were unaffected by these conditions, as was oxyhydrastinine (54).

The corresponding dimethoxy isoquinolinetrione (55)

was obtained from the isoquinclone (42) in much lower yield, owing to the highly sensitive nature of the latter. A compound of this structure has been isolated by other workers[48] from degradation of alkaloids and the synthetic compound corresponded closely in m.p. (267-270°) to that reported for the degradation product.

It has been reported that oxidation of isoquinolines[48-50] and isoquinolones[51,52] with chromic acid gives isoquinolinetrione derivatives and that N-methyl phthalimides are produced by oxidation of these[53] with potassium permanganate[50] or molecular oxygen,[51] but it was unexpected that the "mild" oxidising agent manganese dioxide would so readily convert 3-isoquinolones to this type of compound.

It had been noted that the colourless N-methyl-dihydroisoquinolone (56) tended to turn yellow on standing. It seemed possible that this might be due to the formation of the yellow trione (53). In fact treatment of this compound with manganese dioxide afforded pure trione in 12% yield. Small amounts of the N-methyl isoquinolone (15) were also formed and, since the methylene groups of the amide (57) were totally unaffected by manganese dioxide under the above conditions, the isoquinolone would seem to be a plausible intermediate in the oxidation. Formation of the isoquinolone

could occur via oxidation at the methylene adjacent to the nitrogen atom, followed by 1,4-elimination of water.

It seemed possible that the oxidation of a dihydroisoquinolone might be controlled to produce the isoquinolone if alkaline conditions were used which would precipitate the sodium salt. A preliminary experiment showed that alkaline hypochlorite in fact did convert the dihydroisoquinolone (51) to a sodium salt from which was recovered not the expected dimethoxyisoquinolone (42), but a yellow solid, m.p. 300°, which appeared from i.r., u.v., and basicity to be a secondary 6,7-dimethoxy 3-isoquinolone. However the fact that all u.v. maxima were shifted to the red (variously by 3 to 16 mμ) suggested that chlorination had also occurred. This compound was not studied further.

It would seem that the facile isoquinolone synthesis described earlier could be easily extended to produce tetrahydroisoquinoline derivatives, and it was therefore of interest to study the reduction of these compounds. Their catalytic reduction has already been discussed.

The methylenedioxy N-methyl 3-isoquinolone (15) readily underwent reduction with zinc and hydrochloric acid, also giving the dihydro derivative (56). More

surprisingly the trione (53) also afforded this compound in good yield under the same conditions. The detection of the isoquinolone (15) in the last reaction suggested that this might be an intermediate in this reduction.

Reduction to the tetrahydroisoquinolines could now be completed by reduction of these dihydroisoquinolones with lithium aluminium hydride[54] in tetrahydrofuran. The product derived in this way from the methylenedioxy dihydroisoquinolone (56) was shown to be hydrohydrastinine (58) by its i.r. (no $\nu_{C=O}$), its n.m.r. spectrum (see section 7), and finally by comparison with a sample prepared via lithium aluminium hydride reduction of oxyhydrastinine (54) (a degradation product[55,56] of hydrastine (59)).

It was later found that the isoquinolone (15) itself could be smoothly reduced to hydrohydrastinine using lithium aluminium hydride at room temperature overnight. The presence of a small amount of the dihydro derivative (56) in the crude reaction product suggested its possible intermediacy. In this connection it is interesting to note that reduction of the isoquinolone (15) to the dihydro compound could be effected in fair yield using sodium borohydride, a rather surprising result and one which suggests reaction through the

zwitterionic form of the isoquinolone (cf. reduction of papaverine methiodide[57]). On the other hand, attempted reduction of the dimethoxyisoquinolone (42) with lithium aluminium hydride in tetrahydrofuran at reflux or room temperature produced only tarry material, again underlining the highly sensitive nature of these dimethoxy derivatives.

One property common to all of the 3-isoquinolones studied was a marked resistance to hydrolysis by hot acid or base. The alleged facile acid hydrolysis[20] of 1-methyl-2-amino-3-isoquinolone (22a) to give the o-acetyl phenylacetic acid hydrazone hydrochloride (60) is at variance with this. However, this reaction involved the addition of one mole each of water and hydrochloric acid, and it seems probable that the product was simply a monohydrated hydrochloride. In support of this interpretation the dimethoxy N-amino 3-isoquinolone (61) was found to form a stable monohydrated hydrochloride which retained a typical 3-isoquinolone u.v. spectrum.

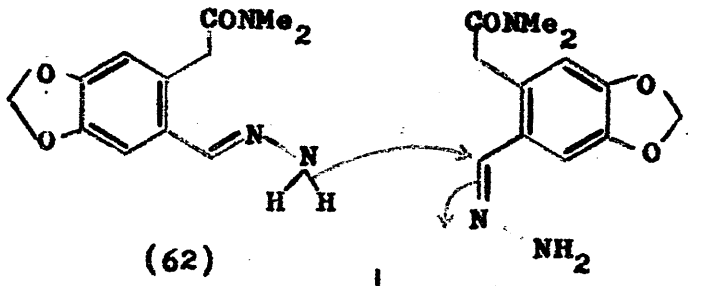
Although it was possible to prepare the corresponding methylenedioxy N-amino 3-isoquinolone in 94% yield from the hydrazone (62), fairly strong heating was required to effect cyclisation and the hydrazone itself proved unusually sensitive.

The product obtained by reaction of the aldehyde (6) with excess hydrazine hydrate at room temperature was an almost colourless solid, m.p. 145°, resolidifying to yellow-orange needles, m.p. 259°. It was found that on repeated crystallisation from boiling ethanol or on preparative t.l.c., this was converted irreversibly to a yellow solid, m.p. 258°. It was soon evident that the properties of this were at variance with those of the N-amino isoquinolone.

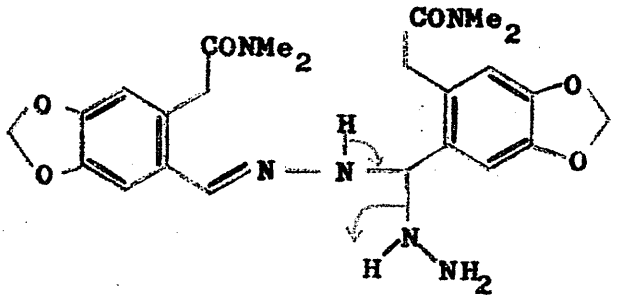
Although its instability under the usual conditions of purification did not allow good analytical data to be obtained, the colourless solid, m.p. 145°, was deduced to be the hydrazone (62) on the basis of physical data. The presence of NH protons was indicated by i.r. ($\nu_{max.}$ 3470, 3260 cm^{-1}) and n.m.r. (4.5τ), and the u.v. spectrum was reasonably similar to that of the corresponding oxime.

Attempted purification of the compound, m.p. 258°, by sublimation resulted in some decomposition, the i.r. spectrum of the sublimate suggesting some formation of nitrile. However, after crystallisation from chloroform-light petroleum analyses were obtained corresponding to the azine structure (63). The i.r. showed no absorption between 3500 and 3000 cm^{-1} and the u.v. spectrum, with a strong maximum at 353 mμ,

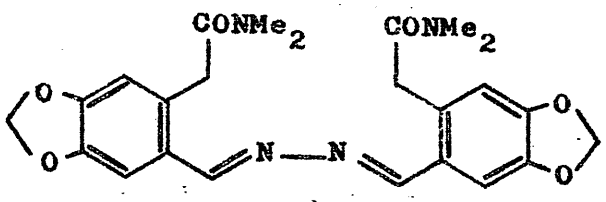
Scheme IV



(62)



$-N_2H_4$



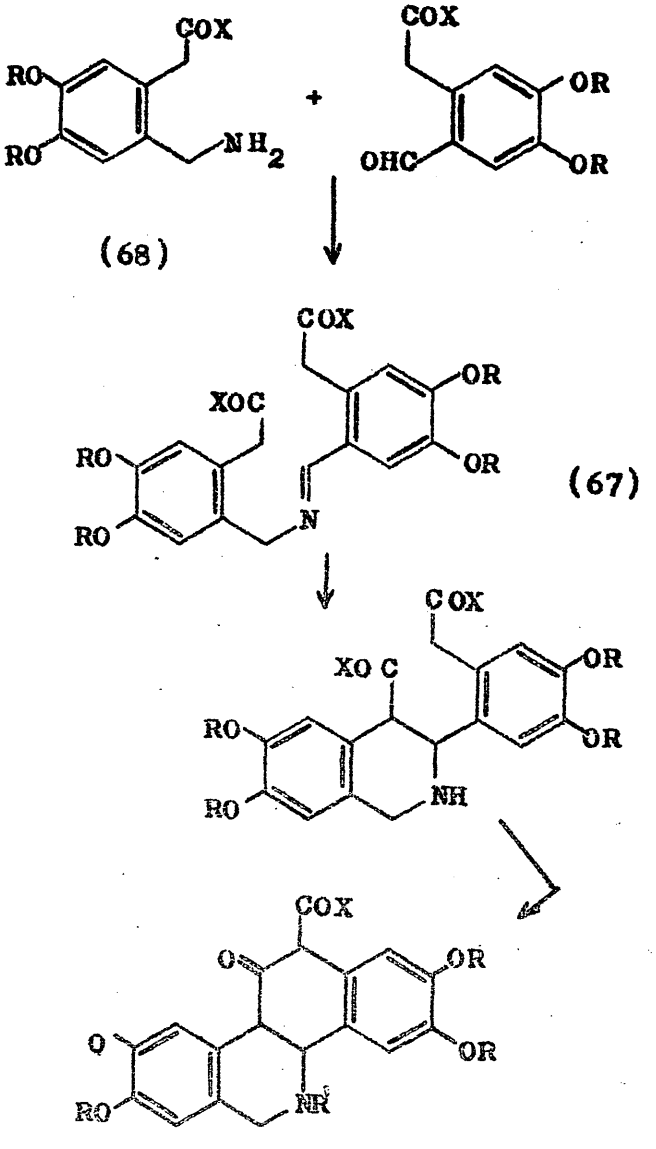
(63)

is in accordance[58,59] with a benzalazine structure. Benzalazine itself (64) possesses a maximum at 304 mμ which has been interpreted in terms of resonance involving the entire molecule as in (65). Normally the azine has been found to absorb 52-58 mμ farther towards the red than the parent aldehyde.[58] The difference observed in this case is rather less (37mμ), but this may be due to disturbance of conjugation caused by the presence of large ortho substituents. The azine structure was also confirmed by n.m.r. spectroscopy (see section 7).

Chemical confirmation of the azine structure (63) was provided firstly by its reaction with hot acid. This gave the aldehyde (6) (72% recovery) together with the N-amino-3-isoquinolone (66) (in 92% yield), the latter evidently by hydrolysis followed by cyclisation. Secondly, the azine could be prepared in 70% yield by reaction of the aldehyde (6) with exactly half-molar quantities of hydrazine.[20] The formation of the azine (63) from the hydrazone (62) can be rationalised in terms of the mechanism depicted in Scheme IV, involving nucleophilic attack at the imine carbon (analogous to attack at a carbonyl), followed by loss of hydrazine at the "aldol" stage.

One possible synthetic approach to the benzophen-

Scheme V


COX
RO
RO
NH2
+
COX
OR
OHC
OR
(68)
COX
XOC
OR
RO
OR
RO
N
(67)
COX
XO C
OR
RO
OR
RO
NH
COX
O
OR
O
OR
RO
NR

anthridine alkaloids, from a 3-arylisoquinoline as depicted in Scheme V, would involve intramolecular cyclisation of an imino derivative** of type (67), the latter being prepared from a suitably substituted benzylamine (68). However, the preparation of benzylamines of this type presents some difficulty.

It seemed possible that catalytic reduction of the oxime acetate (69) or nitrile (70) might provide the benzylamine (71). However, reduction of the mixture of these compounds obtained by the action of acetic anhydride on the oxime (72) gave instead a low yield of a pale yellow solid, together with much tarry material. This solid was shown to be the dihydroisoquinolone (73) by its analyses and spectra (i.r., u.v., and mass) and by comparison of its properties with those of an authentic sample prepared by catalytic reduction of the isoquinolone (38). Formation of this compound may involve cyclisation of the intermediate imine (39) followed by reduction of the resulting isoquinolone. Direct cyclisation of the benzylamine

** This type of reaction has analogies in the condensations of Schiff bases with phenylacetic acid derivatives, catalysed in the case of the free acid by sodamide[10], and in the case of an ester by aluminium chloride.[11]

(71) is also possible. An obvious alternative to catalytic reduction would be reduction by a metal hydride but it was feared that the amide function of the oxime (72) would be attacked by lithium aluminium hydride, and this compound was unaffected by treatment with borohydride. Attempted preparation of the benzylamine (71) by reductive amination of the aldehyde (6) using borohydride in the presence of ammonium acetate[60] was unsuccessful, the only product being the corresponding alcohol (29).

An alternative approach via ring cleavage of a dihydroisoquinolone was studied. The dihydroisoquinolone (51) was found to be totally unaffected by refluxing alcoholic dimethylamine. Hydrolytic opening of the lactam ring[61] could however be effected by hot base or, more conveniently, by hot acid, the product being the corresponding salt of the amino-acid (74). The lactam (51) could be recovered by sublimation from the amino-acid hydrochloride, an observation in accord with the previously reported[62] thermal cyclisation of the amino-acid (75).

The amino-acid hydrochloride was converted in high yield to its methyl ester by normal means. The spectral and analytical data are consistent with the expected structure, but the free amino-ester could not be

isolated as it underwent spontaneous cyclisation to the lactam (51) under basic or neutral conditions. The facility of this cyclisation meant that the amino-ester was not such a potentially useful intermediate as had been hoped, since it was not possible to condense it with carbonyl compounds under neutral or basic conditions.

The amino-acid (74), however, which could be obtained in zwitterionic form under exactly neutral conditions, could be condensed with carbonyl compounds under basic conditions, the products being isolated as the carboxylic acid sodium salts. In this way the imino-acids (76) and (77) were prepared from piperonal and the aldehyde (6). These products had i.r. absorptions in keeping with carboxylate anions ($\nu_{max.}$ 1600, 1380 cm^{-1}) and the presence of an imine function in both was shown by the reversible red shift (ca. 80 mμ) in their u.v. spectra on protonation[28], and by the facility with which the latter (77) underwent hydrolysis (during attempted intramolecular cyclisation with tosyl chloride in pyridine or attempted esterification via the silver salt) to afford the parent aldehyde (6) and lactam (51).

Under acidic conditions the imino-acid (77) was as expected converted into the 3-isoquinolone (78). The latter and its methyl ester, which could be formed

directly from the imino acid sodium salt under Fischer-Speier conditions, were characterised by their u.v. and n.m.r. spectra. This ester was found to be very susceptible to aerial oxidation, the product, which was also formed by oxidation with manganese dioxide, being the corresponding isoquinolinetrione (79). This compound had a distinctive n.m.r. spectrum consisting of no fewer than nine singlets (see section 7). It seems likely that under basic conditions (e.g. use of sodamide[10]) cyclisation of an imine of this type could be achieved, but unfortunately time did not permit further study of this problem.

Although compounds of type (80) and (81) have been successfully cyclised under Bischler-Napieralski conditions[63] to yield protoberberine bases of type (82), Stevens was unsuccessful in his attempts[64] to cyclise the 1,4-dihydro-3-isoquinolone (83). It seemed a worthwhile project to reinvestigate this cyclisation since a dihydroisoquinolone of this type would be readily obtainable by the synthetic method described above. Accordingly the aldehyde (16) was condensed with 3,4-dimethoxyphenylethylamine and the resulting imine (acid shift of 80mμ[28]) treated with warm dilute hydrochloric acid. The isoquinolone (84) (characteristic u.v. absorptions) was liberated from the

precipitated hydrochloride and, without purification, catalytically reduced. The product was a pale yellow solid possessing spectral properties consistent with structure (85). This lactam was virtually unaffected by prolonged treatment with phosphorous pentoxide in boiling benzene.[cf.64] However, treatment with phosphorous oxychloride afforded a solid product, decomposing slowly above 250°, which exhibited no acid or base shift in a highly complex u.v. This was reduced with methanolic borohydride, the product being a yellow gum. Preparative t.l.c. yielded an almost colourless gummy solid which apparently oxidised rapidly in air, becoming yellow. Repeated p.l.c. did not yield a purer sample. The product had only very weak absorption in the carbonyl region ($\nu_{max.}$ 1640 cm^{-1}), but had strong $\nu_{max.}$ at 1600 cm^{-1} and 1525 cm^{-1}. Its u.v. maxima, unaltered by acid or base, were at 226 and 285 mμ. Evidence that cyclisation had occurred was provided by the n.m.r. spectrum of the reduced product, which showed four distinct one-proton singlets (3.19, 3.26, 3.31, and 3.35τ) in the aromatic region. In addition to the methoxyl signal at 6.12τ a complex pattern of methylene resonances was observed between 5.5τ and 7.4τ. There was a strong signal at 5.25τ,

attributable to the hygroscopic nature of the product. These spectral data are in accord with the tetrahydroberberine structure (86). This compound, norcoralydine, has previously been prepared by methylation of the alkaloid coreximine (87), and is reported to have m.p. 157°.[65] Confirmation of structure awaits a mass spectrum.

Although lack of time has precluded a detailed study of the synthetic potential of the 3-isoquinolones some possible applications can be considered. Perhaps the main value in the facile cyclisation is to be found in the ease with which N-alkylated compounds are apparently reduced in good yield with lithium aluminium hydride to the corresponding tetrahydroisoquinolines. Thus one logical extension which comes to mind is in the synthesis of 1-benzyl tetrahydroisoquinolines from a ketimine (88), an additional advantage being that concomitant N-methylation is possible. Bentley *et al*[16] were unable to form a 3-isoquinolone from their benzyl keto-ester (19c), but it may be that the present cyclisation would occur more readily since a better leaving group is involved.

A further modification, in the synthesis of 7,8-dioxygenated isoquinoline derivatives, would require initial synthesis of a 7,8-dioxy lactone (89), presumably via chloromethylation of a brominated phenylacetic

acid (90). However, initial attempts to form a homo-acid of this type through hydrolysis and decomposition of the azlactones (91 a,b) resulted only in the production of much tarry material.

The use of the 5,6,7,8-tetrahydro-3-isoquinolone (92) in the synthesis of the alkaloid alstoniline (93) has recently been reported.[66] It is possible to envisage further application of 3-isoquinolones in alkaloid synthesis. The formation of the protoberberine skeleton has already been discussed (see above). Alkylation of dihydro-3-isoquinolones at C_4 has been reported.[67] If alkylation of the dihydroisoquinolone (56) could be successfully accomplished with the alkyl halide (94) we would have an amido derivative (95), ideal for Bischler-Napieralski cyclisation to the relatively inaccessible benzophenanthridine skeleton, the original aim in this work. In addition it may yet be possible to take advantage of the hydrolytic ring-cleavage of the dihydroisoquinolones and to achieve cyclisation of an imino derivative of the type (77).

The resemblance of the 3-isoquinolone system to the 2-pyridones which have found application in poly-functional catalysis,[68] suggests that these compounds may also be useful in this respect.

4. TAUTOMERISM AND SPECTRAL PROPERTIES

Introduction

Prototropic tautomerism of the type found in hydroxy derivatives of N-heteroaromatic compounds[69-71] is a very widespread phenomenon and is an important factor in the chemistry of many natural products such as alkaloids and nucleic acids. Katritzky and Lagowski[71] have summarised the methods (chemical and physical) available for studying this phenomenon.

There are inherent dangers in conclusions based on evidence from chemical reactions, since the more reactive tautomer may be present only in trace amounts at equilibrium. The conclusion that 2-pyridone exists as 2-hydroxypyridine[72] since its reaction with diazomethane yields 2-methoxypyridine is an example of an erroneous conclusion based on chemical evidence. The application of physical methods[73,74] to the study of prototropic tautomerism has proved much more informative. These include X-ray crystallography, infrared and ultraviolet spectroscopy, basicity measurements, and, more recently, proton magnetic resonance spectroscopy.

As a result of early applications of these various physical methods it was concluded[69] that α- and γ-

Table 4-1. Amide/enol ratios.[76]

Compound	Amide/Enol
2-hydroxypyridine	340
4-hydroxypyridine	2200
2-hydroxyquinoline	3000
4-hydroxyquinoline[cf.106]	24000
1-hydroxyisoquinoline	18000
5-hydroxyacridine	10,000,000

hydroxy derivatives of N-heteroaromatic compounds (e.g. pyridine) are in equilibrium with only small amounts of the enol (which will however always be available for its typical reactions), and exist predominantly in the amide form, the latter being stabilised by resonance with the zwitterion, confirmed in the case of 4-pyridone by dipole moment measurements.[75,76] The amide:enol ratios for a number of such compounds have been estimated by Albert and Phillips[76] and are listed in Table 4-1. The α- and γ-hydroxy derivatives generally are found to be exceptionally weak, both as acids and bases, in accord with their lactam structures. In contrast, the β-hydroxy derivatives were found to exist mainly in the enolic form, with a very considerable contribution from the isomeric zwitterionic form.[77,78]

In recent years much confirmatory evidence[70] has been obtained especially by Mason who has published data on a whole series of hydroxy N-heteroaromatics.[77-79] From a study of their ultraviolet spectra[78] Mason estimated amide:enol ratios and found that these increased with conjugation between the oxygen and nitrogen atoms, and with the addition of fused benzene rings, but decreased with aza substitution, with a rise in temperature and with a fall in the dielectric

constant of the solvent. Substantial physical evidence has shown that 2- and 4-hydroxypyridine exist as lactams[37,39,80-85] as do 2- and 4-hydroxyquinoline[82,86-90] and 1-hydroxyisoquinoline.[88]

A brief study of the tautomerism of 3-hydroxyisoquinoline has been made by Baumgarten, Murdock, and Dirks[19], who concluded that the predominant contribution is from the o-quinonoid lactam form. In the following pages the spectral properties of the 3-isoquinolones discussed above are shown to be in accord with cyclic amido structures.

Infrared spectra.

Infrared[91,92] studies on α- and γ-hydroxy derivatives of N-heteroaromatics (pyridones, quinolones, and isocarbostyrils) have shown that the most prominent feature of their spectra is strong absorption in the carbonyl region at positions consistent with their possessing lactam structures.[30,79,82-3,85,90,93-97] The fact that the infrared spectra (Tables 4-2,3) of all the 6,7-dioxygenated 3-isoquinolones studied in the present work show strong absorption in the region 1630-1670 cm^{-1} is strong evidence that these compounds also have lactam structures. The structural similarity between the 3-isoquinolones and 2-pyridones is underlined by comparison of their spectra (Table 4-2).

In particular peaks which have been assigned in the pyridones to ring-stretching modes, a band at ca. 1550 cm^{-1} in tertiary lactams, and peaks at 1325 and 1110 cm^{-1} in N-hydroxy 2-pyridone, all find parallels in the corresponding isoquinolones.

The extremely broad absorption between 2300 and 2800 cm^{-1} in the spectra of the unsubstituted isoquinolones (38) and (42) has been accounted for (see p.22) in terms of strong dimeric intermolecular hydrogen bonding.[37] The spectra of the isoquinolones are strikingly different in general from those of the corresponding 1,4-dihydro derivatives and in particular the latter show non-bonded NH absorption (see Tables 4-5,6). However the intramolecular hydrogen bonding of the N-hydroxy-isoquinolone (cf. refs. 85 and 114) seems also to be present in its dihydro derivative.

Each of the unsubstituted isoquinolones (38,42) shows a weak but broad absorption ca. 2015 cm^{-1} which might be taken as evidence of zwitterionic contribution, although a similar assignment for 3-hydroxypyridine[98] has been contested.[79] The dimethoxyisoquinolone (42) also has a weak absorption at 3400 cm^{-1}, much the same as that reported previously for 3-isoquinolone by Boyer and Wolford[18] and later attributed to the presence of moisture by Baumgarten *et al.*[19] Weak bands of this

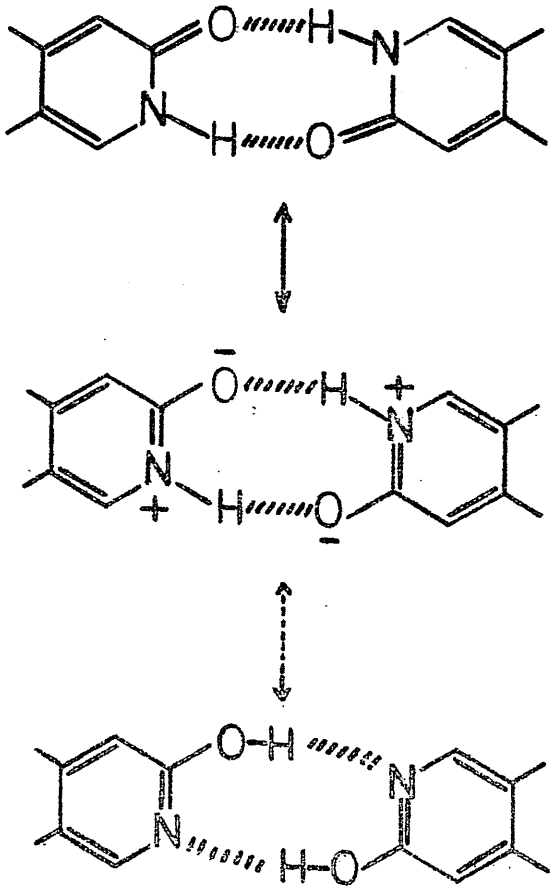
nature (3420-3400 cm^{-1}) have been observed in the spectra of several compounds in the present series, including the N-methyl derivative (15). It therefore seems very probable that they can indeed be attributed to the presence of moisture.

The poor solubility of the 3-isoquinolones in organic solvents imposed a limit on the generality of solution studies.[cf.85] The absorptions which could be recorded are detailed in Table 4-4. These are not appreciably different from those measured in the solid state, the solvent change also having very little effect (cf. ref.99), factors suggesting similar tautomeric structures. In contrast to the 3-isoquinolones which exhibit two barely resolved maxima in the carbonyl region N-methyl isocarbostyril shows two well-separated symmetrical peaks (Table 4-4).

Previously reported data (Table 4-2) for 3-isoquinolone itself[19] and for the more closely analogous dimethoxyisoquinolone (23)[23] are fully consistent with those obtained in the present work. In particular the possession of strong carbonyl absorption furnishes quite compelling evidence in favour of the o-quinonoid 3-isoquinolone structure and is further substantiated by close analogies with the 2-pyridones.

Ultraviolet spectra

Ultraviolet spectroscopy has been the most widely-used and perhaps most valuable of all the techniques available for studying prototropic tautomerism.[105] Comparison of the spectrum of a hydroxy N-heteroaromatic compound with those of its O- and N-alkylated derivatives, which must possess fixed structures, indicates the tautomeric composition or at least reveals which tautomer predominates. Despite certain limitations[71] this technique has been successfully applied to a variety of compounds.[33,78,81,88-9,106-109] The ultraviolet spectra of the 3-isoquinolones (Table 4-7) show a remarkable consistency, very similar spectra being recorded, irrespective of the substituent on the nitrogen atom. All exhibit a very strong maximum in the region 247-252 mμ (log ε 4.7-4.8) and a further weaker band at 390-414 mμ. There are also at least two weaker absorptions at 300-310 mμ and 314-322 mμ. The fact that all of these derivatives show virtually identical spectra is highly suggestive of their possessing similar lactam structures. The appearance of a weak absorption ca. 350 mμ (shoulder) in the spectra of the three unsubstituted compounds studied, absent in the N-substituted compounds, may be attributed to a contribution from the "mesomeric" enolic form of the

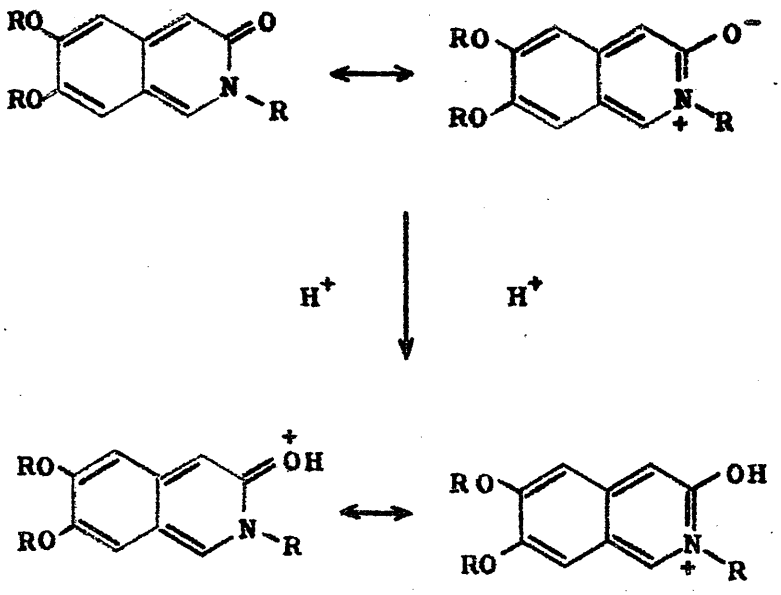


dimer (96). O-Alkyl derivatives were not obtained, but the O-acetates exhibited completely different spectra (Table 4-8), more in keeping with a true isoquinoline structure.[33]

The ultraviolet absorptions of 3-isoquinolone itself have been compared to those of certain other potentially o-quinonoid systems,[19] all of which are characterised by an intense maximum near 230 mμ and a second weaker band in the vicinity of 400 mμ.

A second technique which has been applied to the estimation of tautomeric composition is based on the fact that enolic compounds (e.g. 3-hydroxypyridine and 3-hydroxyquinoline) exhibit distinct bathochromic shifts in both acid and base in contrast with those with lactam structures (e.g. 2-pyridone, 2-quinolone, and 1-isoquinolone) which are virtually unchanged.[88] On acidification the principal absorption band of the 3-isoquinolones is essentially unaffected, in accord with a common lactam structure, but the longer wavelength bands are altered (Table 4-9). The visible absorption of the neutral molecule is absent in the colourless hydrochloride, having been shifted to 355-370 mμ, a shift consistent with O-protonation and destruction of the o-quinonoid system (see later). The minor bands at 305 and 315 mμ suffer an appreciable

Scheme VI



increase in intensity. This may represent evidence of some zwitterionic contribution in neutral medium. It is clearly not evidence of an enolic contribution as the same degree of intensification is recorded in both the unsubstituted and N-alkylated compounds (Table 4-10). The intensity increase can be accounted for in two possible ways. Either the 305 and 315 mμ bands in the neutral molecule are evidence of some zwitterionic contribution, protonation destroying the negative charge on oxygen, or else these bands are characteristic of the amide mesomer, with protonation occurring at the carbonyl function (see Scheme VI). This intensity increase does however provide some evidence in favour of the site of protonation in these molecules being the amido oxygen atom. (see section 5).

The spectra of the N-substituted isoquinolones in basic medium (Table 4-9) are virtually superposable on those of the neutral compounds. The unsubstituted isoquinolones, however, exhibit in addition to the main absorption maximum ca. 250 mμ, a broad band centred near 370 mμ, consistent with the formation of a mesomeric anion,[cf.82] as is the i.r. spectrum of the sodium salt ($\nu_{max.}$ 1600 cm^{-1}).

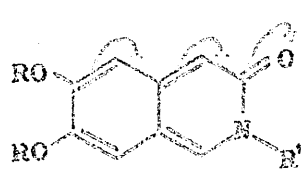
The application of the two ultraviolet techniques

(comparison with alkylated derivatives and acid-base shifts) have therefore produced evidence which strongly suggests an o-quinonoid lactam structure, shared by all of the 3-isoquinolones.

Nuclear magnetic resonance spectra

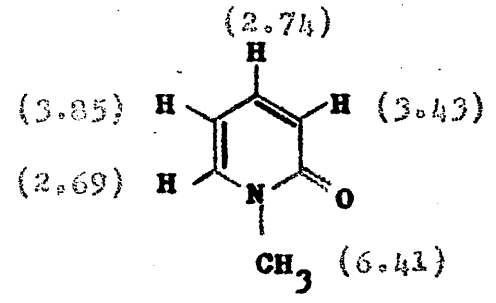
It is also possible to investigate prototropic tautomerism by means of nuclear magnetic resonance spectroscopy,[111] in much the same way as the ultraviolet technique has been used, by a comparison of the positions of the ring protons in the tautomeric compounds and in their alkylated derivatives. The proton magnetic resonance spectra of the 3-isoquinolones are highly characteristic and provide some indications of their tautomeric composition.

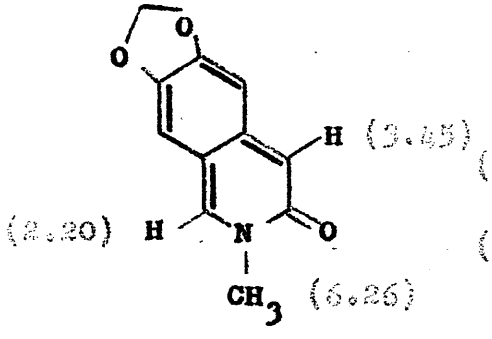
The n.m.r. spectra of the 3-isoquinolones in dimethyl sulphoxide (Table 4-11) show four singlets for the aromatic protons. If we assume that the predominant direction of electron movement in 3-isoquinolones, as indicated by their properties (acetylation, sodium salt formation, protonation) is as shown below (97)

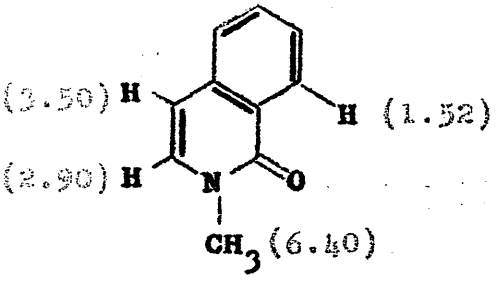


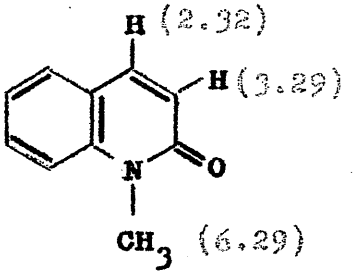
(97)

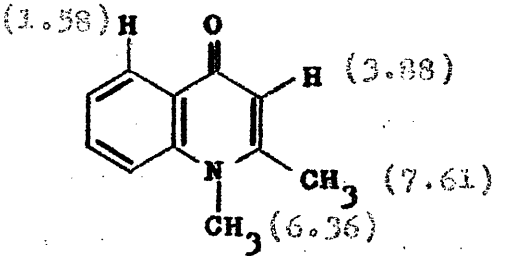
Scheme VII (cf. ref. 112)

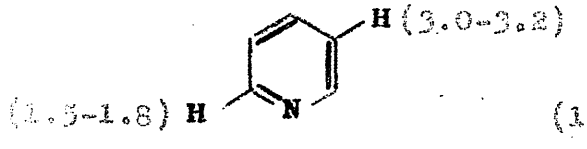


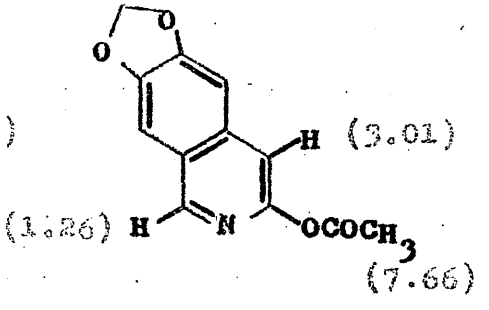












then we can predict that protons at positions 4,5 and 7 will have τ values lying at higher field than those at positions 1,6 and 8. As regards H_1, we have also to take into account the positive pole on nitrogen, which will tend to deshield this proton. A low-field signal is characteristic of a proton adjacent to a nitrogen atom in a hetero ring. (cf. value of 1.5τ in pyridine[47]). By analogy with the signal observed for the proton α to the carbonyl group of 2-pyridones[112,113] we may assign the highest of these signals to H_4. On this basis the signals for 2-methyl-6,7-methylenedioxy-3-isoquinolone appearing at 1.56, 3.07, 3.22, and 3.51 τ can be assigned to H_1, H_8, H_5, and H_4 respectively.

In Scheme VII the n.m.r. spectral characteristics of N-methylated 2-quinolone and 1- and 3-isoquinolones are compared to those reported[112] for several pyridone derivatives. It is clear that a close structural relationship exists. The n.m.r. data obtained for a number of hetero lactams are tabulated in Table 4-13.

The n.m.r. absorption signals of the two 3-acetoxy-isoquinolines in deuterochloroform are given in Table 4-12. Comparison of these data with those for typical pyridinoid models[112] (Scheme VII) suggests that these acetates represent a truly aromatic model for the 3-isoquinolones. From a comparison of the spectra of

the dimethoxyisoquinolone (42) and its O-acetate, in deuterochloroform (Table 4-12), it can be seen that the positions of the ring protons in the former are appreciably higher (especially H_4, α to the potential carbonyl group), indicating that the isoquinolone must exist predominantly in non-aromatic form, presumably as the mesomeric o-quinonoid lactam. Recently[112] the aromaticity of 2-pyridone, relative to benzene, has been estimated to be 36%, on the basis of n.m.r. data. The close analogies between the spectra of the isoquinolones and model pyridones suggest that similar structural types are involved.

In spectra recorded in dimethyl sulphoxide (Table 4-11) the aromatic protons of the unsubstituted isoquinolone (38) come into resonance at somewhat lower field than those of the N-substituted compounds, suggesting a greater degree of aromatic character in the former, which can possibly be attributed to the stabilisation of the zwitterion (or enol) in the intermolecularly hydrogen bonded dimer (cf. 96). A similar stabilisation by hydrogen bonding may operate intramolecularly in the N-hydroxy compound (40) ($\nu_{max.}$ 2250-2850 cm^{-1}, cf. refs. 85, 114), which has its aromatic proton resonances at lower field than the N-alkylated or N-amino derivatives.

The unsubstituted isoquinolones exhibit in both dimethyl sulphoxide and deuterochloroform a singlet corresponding to H_1. This means that the tautomeric exchange is so rapid as to prevent observation of coupling between the NH proton and H_1.

Comparison of the spectra of the isoquinolones which were measured in both deuterochloroform and dimethyl sulphoxide shows that in the latter solvent the τ values of the aromatic protons are rather lower. This applies in particular to H_1. The relatively high H_1 resonance (ca. 2.2τ) in the lactams in deuterochloroform tends to rule out a major zwitterionic contribution in this solvent. In a more powerful ionising solvent such as dimethyl sulphoxide we would expect a greater contribution from the zwitterion, which would lead to an increased net positive charge on the nitrogen atom, which in turn would be reflected by a deshielding of H_1. The observed shift for H_1 is therefore evidence of an increased zwitterionic (aromatic) contribution in the more polar solvent. In keeping with this the signals for H_5 and H_8 are also shifted downfield (by 0.2-0.3τ). On the other hand the N-methyl protons and H_4 in the lactam (15) if anything appear at higher field in dimethyl sulphoxide than in chloroform, the respective deshielding effects of a more positive

nitrogen and increased aromaticity possibly being counteracted by diminished deshielding by C=O and by increased shielding by $C-O^{-}$.

The chemical and physical evidence here presented indicates that in the tautomeric 3-isoquinolones the predominant tautomer is, as expected, the o-quinonoid cyclic amide, which is stabilised by resonance with the zwitterion. In order to accurately depict these compounds and to explain their properties it is however necessary to consider all three forms as shown below.

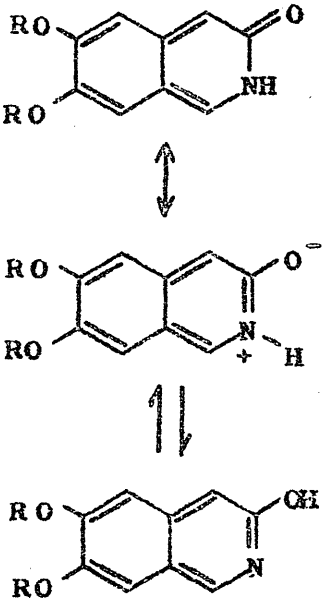


TABLE 4-2. IR OF 3-ISOQUINOLONES AND 2-PYRIDONES.

	Methylenedioxyisoquinolones			Pyridones [82,85]		
	N-H	N-CH_3	N-OH	N-H	N-CH_3	N-OH
NH or OH	2600 b.	--	2600 b.	2980	--	2400 b.
Amide	1644	1662 1648 1566	1647* b.	1670 1656	1665 1545	1655
Ring-stretching	1606 1487 1455	1618 1489 1446	1617 1478 1449	1619 1472 1444	1590 1500 1415	1570 1500 1446
N-O	--	--	1322 1132	--	--	1325 1110
β C-H	1156	1161	1161	1156	1154	1182
Methylenedioxy [151]	1260 1040 947	1253 1020 934	1255 1021 947	--	--	--

* Similar carbonyl frequencies have been reported for N-hydroxy quinolones [100-104] and for N-hydroxy isocarbostyril.[30]

TABLE 4-3. IR SPECTRA OF 3-ISOQUINOLONES (KCl DISCS)

Assignment	6,7-Methylenedioxy-3-isoquinolones			3-isoquinolones	
	N-Bz	N-Ar	$N-NH_2$	3-isoquinolone	Cpd. (23)
NH/OH Region	--	--	3293 3168 3072 3034	2540 b.	3000- 2100 b.
Amide	1661 1655 1566	1663 1655 1563, 1554	1659 1541	1651	1645
Ring-stretching	1621 1500 1491 1448	1620 1488 1450	1614 1488 1454	($CHCl_3$ Soln.) 3370 1649 1637	
β-C-H	1165	1163	1162		
$-OCH_2-O-$	1261 1026 940	1260 1041 952	1252 1037 950		

TABLE 4-4. SOLUTION SPECTRA OF ISOQUINOLONES

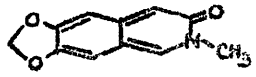
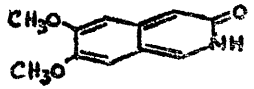
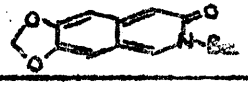
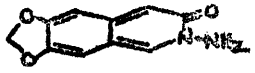
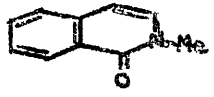
COMPOUND	SOLVENT	ABSORPTIONS (cm^{-1})			
	$CHCl_3$	1663	1652	1619.5	1559
	$CHBr_3$	1661	1650	1618	1556
	$CHCl_3$			1653	1637
	$CHBr_3$	3535	3368	1650	1635.5
	$CHBr_3$	1660 sh.	1651	1619	1559
	$CHBr_3$	1662	1652	1610	1546 b.
	$CHCl_3$	1647	1625	1602	1596
	$CHBr_3$	1645	1623.5	1600.5	1593.5

TABLE 4-5. IR SPECTRA (KCl) OF DIHYDRO 3-ISOQUINOLONES

Assignment	6,7-Methylenedioxy			6,7-Dimethoxy	
	N-Me	N-H	N-NH_2	N-H	N-OH
NH or OH	--	3320 3196 3050	3326 3280 3248 3208 3058	3190	3125 3200- 2800 b.
Amide	1650 b.	1682 sh. 1663	1644 1623	1688 1658	1650 sh. 1635
Ring-stretching modes	1500 1480	1502 1489 1469	1506 1489	1519 1472 1464	1523 1482 1462
Methylenedioxy[151]	1029 938	1038 941	1036 930	--	--
Methoxyl[151]	--	--	--	1249 992 852	1249 996 852
Other prominent bands	1401 1313 1238 1228	1405 1340 1236 1228	1401 1332 1230 s. 1004	1400 1326 1236 1224	1406 1330 1231 1226

Table 4-6. I.R. Spectra ($CHCl_3$ solution) of 1,4-dihydro-3-isoquinolones.

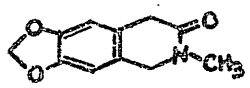
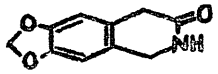
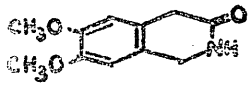
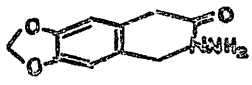
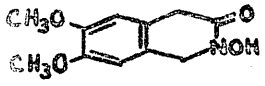
Compound	NH/OH region	C=O region
	--	1646.5 (ε 733)
	3424 (ε 100)	1685 sh. 1673.5 (ε 866)
 in $CHBr_3$	3402, 3205 cf. ref 40	1672.5 1658 1612.5 1517.5
	not measured	1644.5 (ε 604), 1615
	3310 br.	1633 (ε 632)

TABLE 4-7 (1). ULTRAVIOLET ABSORPTIONS OF 3-ISOQUINOLONES (in EtOH)

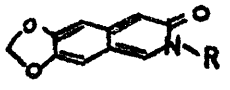
	mμ (log ε)	mμ (log ε)	mμ (log ε)	mμ (log ε)	mμ (log ε)	mμ (log ε)
R=H	246.5 (4.70)	288 (3.55)	301 (3.53)	313 (3.57)	354 (3.35)	396 (3.54)
R=CH_3	248 (4.76)	290 (3.43)	305.5(3.51)	315.5 (3.55)		399 (3.63)
R=Bz	252 (4.84)	293 (3.54)	307 (3.70)	318.5 (3.72)		401 (3.72)
R=OH	246.5 (4.78)	290 (3.61)	303 (3.75)	314.5 (3.76)		393 (3.62)
R=NH_2	250 (4.81)	293 (3.50)	307 (3.71)	318.5 (3.73)		400 (3.71)
R=p.BrC_6H_4	252 (4.78)		310 (3.83)	321 (3.86)		408 (3.65)

TABLE 4-7 (ii). ULTRAVIOLET ABSORPTIONS OF 3-ISOQUINOLONES (in EtOH)

	mμ (log ε)	mμ (log ε)	mμ (log ε)	mμ (log ε)	mμ (log ε)	mμ (log ε)
R=H	252 (4.66)	287 (3.46)	301 (3.46)	314 (3.46)	354 (3.12)	398 (3.57)
R=CH_3	251.5 (4.80)	288 (3.38)	303 (3.54)	314 (3.56)		394 (3.46)
R=OH	251 (4.64)		305 (3.69)	314 (3.69)		390 (3.48)
R=NH_2 hydrochloride	251.5 (4.82)		308 (3.84)	316 (3.86)	371 (3.44)	402 (3.29)
Hypochlorite Oxid'n. Product	255	293	308	322	357	414

Table 4-8. U.V. absorptions of 3-acetoxyisoquinolines.

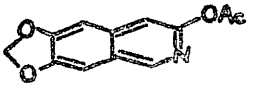
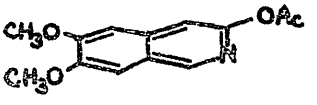
			
mμ	(logε)	mμ	(log ε)
235	(4.46)	239	(4.64)
265	(3.66)	268	(3.67)
278	(3.65)	280	(3.62)
287	(3.62)	291	(3.57)
317	(3.51)	315	(3.45)
329	(3.53)	327	(3.46)

TABLE 4-9. UV ABSORPTIONS OF 3-ISOQUINOLONES IN ACID AND BASIC MEDIA

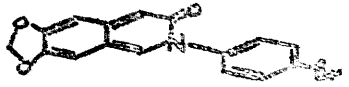
FORMULA	MEDIUM	mμ	mμ	mμ	mμ	mμ
	Acid	243		306	314	363
	Base	247				372
	Acid	245		307	315	364
	Base	248	290	305	317	399
	Acid	245		305	313	365
	Base	247.5		305	317	394
	Acid	248		307	318	362
	Base	250		307	318	398
	Acid	253		314	323	366
	Base	250		313	323	412
	Acid	249		306	313	364
	Base	250	277			372

TABLE 4-10. UV OF 3-ISOQUINOLONES: INTENSITY INCREASES ON PROTONATION

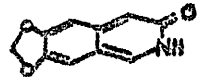
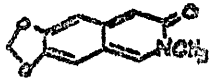
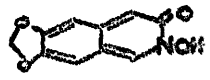
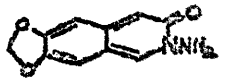
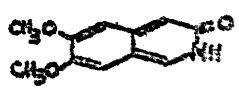
COMPOUND	MEDIUM	mμ (log ε)	mμ (log ε)	mμ (log ε)
	N	248.5 (4.71)	305 (3.54)	317 (3.59)
	A	246 (4.71)	307 (3.87)	316 (3.94)
	N	248 (4.76)	305.5 (3.51)	317.5 (3.55)
	A	245 (4.68)	307 (3.90)	315 (3.95)
	N	246.5 (4.78)	303 (3.75)	314.5 (3.76)
	A	244.5 (4.75)	305 (3.90)	314 (3.95)
	N	250 (4.81)	307 (3.81)	318.5 (3.83)
	A		310 (3.98)	317 (4.02)
	N	252 (4.66)	301 (3.46)	314 (3.47)
	A	249 (4.52)	306 (3.50)	313 (3.54)
	N	251 (4.64)	305 (3.69)	314 (3.69)
	A	249 (4.66)	306 (3.87)	315 (3.91)

Table 4-11. τ-Values of 3-isoquinolones in DMSO.

Cpd.	H_1	N-R	H_4	H_5	Ether	H_8
6,7-Methylenedioxy derivatives						
N-H	1.51	-	3.29	2.99	3.91	2.78
N-Me	1.56	6.37	3.51	3.22	3.91	3.07
N-Bz	1.55	2.67 4.70	3.52	3.27	3.96	3.12
N-OH	1.32	4.16	3.39	3.17	3.94	3.02
$N-NH_2$	1.53	2.9 -3.8	3.52	3.24	3.95	2.99
6,7-Dimethoxy derivative						
N-H	1.43	-	3.25	2.96	6.10 6.14	2.75

TABLE 4-12. NMR OF 3-ISOQUINOLONES AND DERIVATIVES IN $CDCl_3$

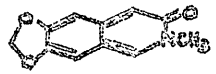
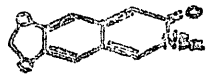
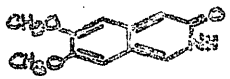
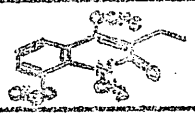
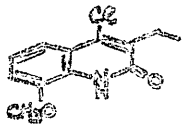
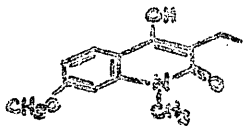
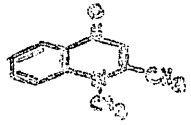
COMPOUND	H_1	N-R	H_4	H_5	Ethers	H_8	OAc
	2.20	6.26	3.45	3.40	4.04	3.40	--
	2.26	4.66 2.66	3.48	3.47	4.08	3.34	--
	1.75	--	3.27	3.24	6.01 6.05	3.14	--
	1.26	--	3.01	2.87	3.96	2.78	7.66
	1.15	--	2.98	2.85	6.02	2.72	7.65

TABLE 4-13. NMR SPECTRA OF LACTAMS IN $CDCl_3$

COMPOUND	SIGNALS (δ) FOR GROUPS ATTACHED AT POSITIONS							
	1	2	3	4	5	6	7	8
	6.29	--	3.29 d, J=9.6	2.32 d, J=9.6	2.5-2.8			
	6.30	--	7.28 q 8.79 t	6.07	3.04-3.25			6.07
	0.43 b	--	7.09 q 8.80 t	--	2.44 J_1=7.8 J_2=1.8	2.74 J_1=7.8	3.03 J_1=7.8 J_2=1.8	6.03
	6.03 or 6.11	--	7.09 q 8.83 t	--	2.24 J_1=6 J_2=2.4	2.87 J_1=6	6.03 or 6.11	2.93 J_2=2.4
	--	6.40	2.90 d, J=7.5	3.50 d, J=7.5	2.41 (m)			1.52 J_1=8.4 J_2=2.5
	6.36	7.61	3.88	--	1.58 J_1=9 J_2=2	2.2-2.8		

5. PROTONATION

Introduction

The problem of the site of protonation in amides has been the subject of much controversy over the last two decades.[115-117] From theoretical considerations it is to be expected that the cations of the hydroxy-pyridines will be pyridinoid (i.e. 98 a,b,c), the O-protonated cations of the 2- and 4-isomers being capable of stabilisation by resonance whereas the N-protonated forms are not. The main challenge to this hypothesis has come from the work of Spinner who, following an investigation into the Raman and infrared spectra of the hydrochlorides, concluded[118] that in fact protonation occurred on nitrogen in 2- and 4-pyridone. Recent isotopic work however has shown that Spinner's assignments were probably incorrect.[119] Cook has identified bands characteristic of the protonated carbonyl groups[120,121] in the spectra of salts formed by strong acids and various carbonyl compounds including pyrones,[122,123] 2- and 4-pyridones,[124-127] and 2-quinolones.[126,127]

Crystallographic studies[128] have also indicated that coordination to the metal in amide complexes occurs through the carbonyl oxygen. Cook has also demonstrated

that N-acyl derivatives of tertiary amines, which are formally equivalent to the postulated N-protonated amide salts, are highly unstable and possess very characteristic carbonyl absorption ca. 1800 cm^{-1}, absent in the amide salts.[129]

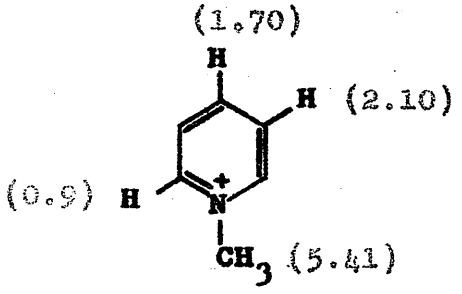
The application of the nuclear magnetic resonance technique[130] has produced a large amount of data all of which favours protonation on oxygen, assignments being made mainly on the basis of splitting effects. Compounds which have been studied in this way include 2-pyridones,[131] 4-pyridones,[132-134] and more recently simple molecules such as dimethylformamide.[135] By means of low temperature measurements in fluorosulphuric acid it has been possible to capture the actual proton signal in the salts of a number of amides, providing further conclusive evidence that the site of protonation is oxygen.[136]

Results

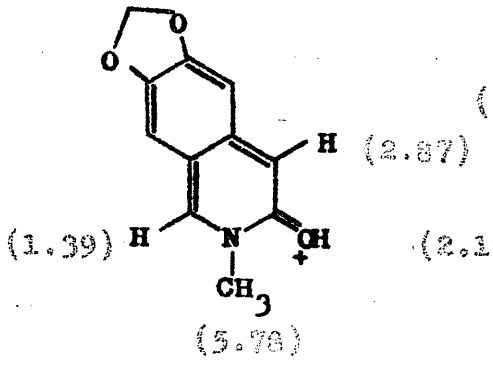
We can therefore predict from the foregoing that the 3-isoquinolone system will be protonated at the carbonyl function. Some support for this was obtained from their ultraviolet spectra (see section 4).

Table 5-1 records the n.m.r. spectra of the 3-isoquinolones in trifluoroacetic acid. The latter is a

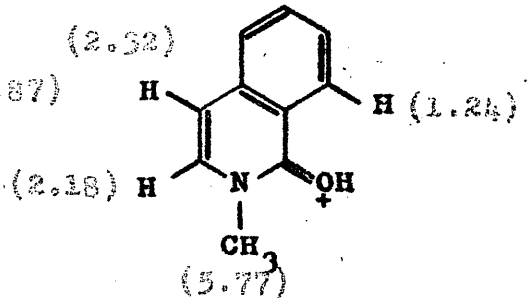
Scheme VIII



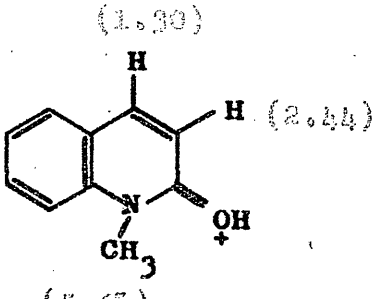
(cf. ref.112)



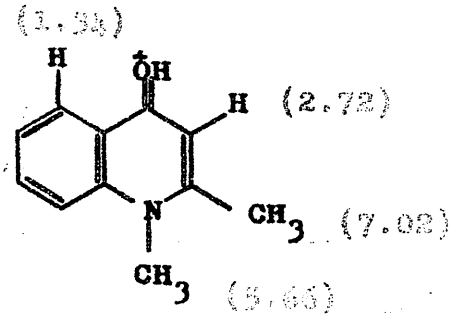
(101)



(99)



(102)



(100)

particularly convenient solvent[137,138] as all of the compounds were soluble, apparently without decomposition, and, since it is a strong acid, it can be assumed that the system will be protonated.[139,140]

The N-substituted 3-isoquinolones all exhibit a distinct singlet for H_1 in trifluoroacetic acid, evidence of the absence of a proton on the nitrogen atom of their cations. The spectra of the unsubstituted compounds in trifluoroacetic acid, however, possess a low-field doublet (J=6c/s.), evidence of the existence of only a single proton on nitrogen coupling with H_1, further proof of O-protonation, since in the N-protonated form the H_1 signal would appear as a multiplet.

An outstanding feature of the spectra of N-methyl-1-isoquinolone and of N-methyl-2-methyl 4-quinolone in trifluoroacetic acid (Scheme VIII) is the low-field signal observed for H_8 (1.24τ) and H_5 (1.34τ) respectively. Deshielding of these protons can be readily interpreted only on the basis of retention of appreciable carbonyl character in these cations, as in (99) and (100). Furthermore, comparison of the data here obtained (Table 5-2) and those obtained for pyridone cations by Katritzky[131] with those reported for pyridinium salts[112] (cf. Scheme VIII) indicate that

these cations cannot be accurately depicted, as they usually are, as hydroxypyridinium salts. The [illegible] of the signals suggest that the mesomeric "protonated carbonyl" forms must be considered to make a very significant contribution. (cf. i.r. studies by Cook).

The cations of N-methyl 6,7-methylenedioxy-3-isoquinolone and of N-methyl 2-quinolone can then be considered to have the mesomeric structures (101) and (102) with considerable double bond character retained in the carbonyl function, similarities between their structures and those of the 4-quinolone and isocarbostyril cations being indicated by the close correspondence of their N-methyl resonances. The latter are again considerably higher than would be expected by analogy with the pyridinium salts.[112] (cf. Scheme VIII)

It had been hoped that the shift of the N-methyl signal[cf.141] on moving from deuterochloroform to trifluoroacetic acid might provide a new method of distinguishing between 2- and 4-quinolones.[97] However, this shift was not sufficiently diagnostic to be used for this purpose.

Thus the evidence is consistent with protonation on oxygen in the 3-isoquinolones, the cation existing predominantly as the mesomeric form shown below, although

an accurate representation would also involve a contribution from the N-protonated tautomer.

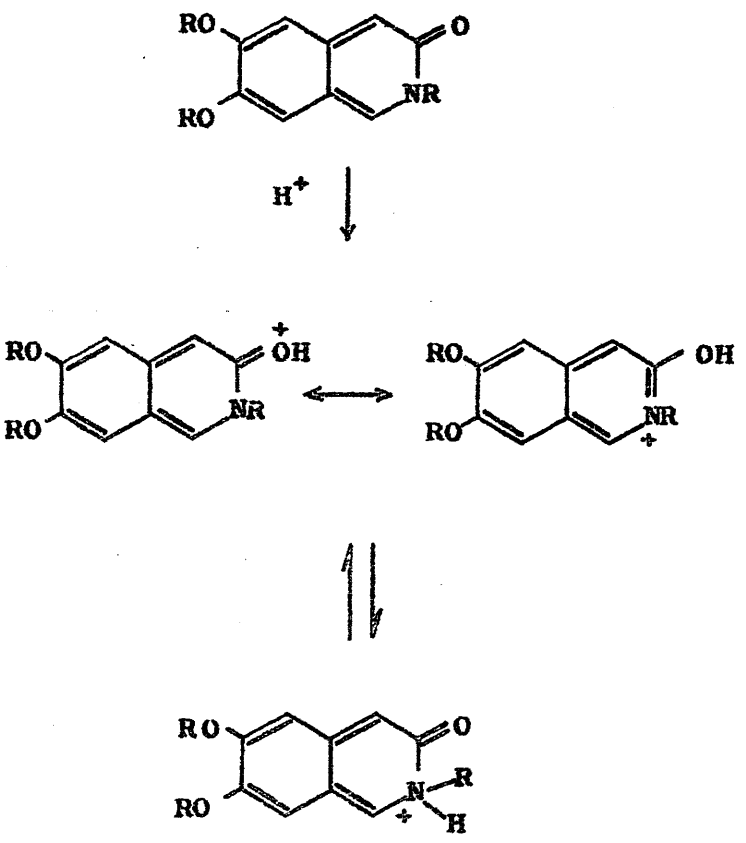
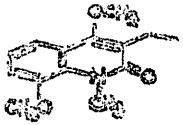
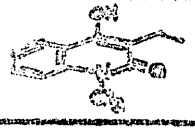
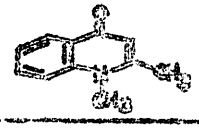


Table 5-1. N.M.R. Spectra of 3-isoquinclones in trifluoroacetic acid.

N-R	H_1	N-R	H_4	O-R	H_5 and H_8
6,7-methylenedioxy compounds					
N-CH_3	1.39	5.78	2.87	3.79	2.55,2.77
N-H	1.24	---	2.72	3.68	2.47,2.60
N-OH	1.07	---	2.75	3.70	2.39,2.68
N-Bz	1.29	2.46 4.24	2.78	3.73	2.46,2.73
N-NH_2	1.04	---	2.74	3.67	2.40,2.67
N-pBr.C_6H_4	1.29	2.05 2.51	2.69	3.64	2.35,2.69
6,7-Dimethoxy compounds					
N-H	1.08	---	2.60	5.73 5.77	2.38,2.42
N-CH_3	1.19	5.69	2.69	5.77 5.80	2.36,2.56
N-OH	0.96	---	2.65	5.80 5.83	2.30,2.55
N-NH_2	0.84	---	2.59	5.75 5.78	2.23,2.48

TABLE 5-2. NMR SPECTRA OF LACTAMS IN TRIFLUOROACETIC ACID

COMPOUND	SIGNALS (δ) FOR GROUPS ATTACHED AT POSITIONS							
	1	2	3	4	5	6	7	8
	5.65	--	2.44 d, J=9.6	1.30 d, J=9.6	1.88 (m)			
	5.72 5.75 or 5.87	--	6.93 q 8.64 t	5.72 5.75 or 5.87	1.71 d, J=9	2.4-2.7		5.72 5.75 or 5.87
	--	--	6.80 q 8.64 t	--	1.9-2.7			5.79
	5.87 or 5.54	--	6.97 q 8.67 t	--	1.9-2.6		5.54 or 5.87	1.9 -2.6
		5.77	2.18 d, J=7.2	2.52 d, J=7.2	1.86 (m)			1.24 (m)
	5.66	7.02	2.72	--	1.34 (m)	1.7 - 2.3		

6. MASS SPECTRA

The cracking patterns of 3-isoquinolones do not appear to have been studied but these follow well-established pathways. From a comparison of the spectra of the unsubstituted (38) and N-methylated (15) 6,7-methylenedioxy 3-isoquinolones it is possible to suggest a common breakdown pathway, which is outlined in Scheme 6-1. In the spectra of both compounds the parent molecular ion is also the base peak and abundant doubly-charged ions are observed at m/e 94.5 and m/e 101.5 respectively, underlining the stability of the 6,7-methylenedioxy 3-isoquinolone system. The initial, and most characteristic, loss is of 28 mass units, which can be readily explained in terms of extrusion of carbon monoxide, as in the coumarins.[142,143] This fragmentation will produce an isoindole structure, which will be susceptible to further breakdown at the ether function, which is apparently cleaved as formaldehyde. Loss of the nitrogen atom apparently occurs only in the final stages of the breakdown process. In the N-methyl compound ions are observed (m/e 160, 130, and 102) corresponding to the loss of the methyl group at various stages of the breakdown. These represent, however, secondary processes, and in the main fragmentation

pathway (m/e 175,145, and 117) the nitrogen again seems to be retained until the final stages, possibly being eliminated after loss of methyl (m/e 102) as hydrogen cyanide (m/e 75).

In the unsubstituted dimethoxyisoquinolone (42), as in 6,7-dimethoxycoumarin (103)[143] there is a loss of 28 (CO) from the parent. The ortho dimethoxy function apparently then breaks down by loss of two methyl groups and two moles of carbon monoxide either alternately or successively. The first process, by analogy with o-dimethoxybenzene,[144] seems the more probable and in fact the most abundant ions in the spectrum (m/e 177, 162, 134, 119, and 91) correspond to those expected for this type of cracking pattern (Scheme 6-2). An additional complicating process in this molecule is the potential loss of formaldehyde, which is known to occur from aromatic methoxyls.[144] Such a loss would explain the reasonably abundant ions at m/e 147, 132, and 104.

The N-hydroxy dimethoxyisoquinolone (104), the enolic tautomer of which is an N-oxide, has its parent molecular ion at m/e 221 and is characterised by a $(P-16)^{+}$ ion of 44%.[145] It has been shown[145] that a loss of 16 mass units is typical of such N-oxides. The mass spectrum of this compound was recorded using a direct insertion probe as a previous attempt to record that of

the methylenedioxy hydroxamic acid (40) using a heated inlet system had resulted in initial loss of oxygen, the spectrum recorded being that of the unsubstituted lactam (38).

Although an initial loss of 28 is also observed in the spectra of dihydrocoumarins,[142] it is not observed in those of both unsubstituted dihydroisoquinolones (51,73). In these compounds the initial loss is of 43, presumably as CONH, possibly in a retro Diels-Alder cleavage as in Scheme 6-3. Similar cleavage in the N-methyl dihydrisoquinolone (56) would explain its facile loss of 57 mass units, corresponding to CH_3-N=C=O. A similar fission was observed in the spectrum of the isoquinolinetrione (53) which, after an initial loss of carbon monoxide, also loses 57 mass units.

The dimethoxy lactone (26) provided an interesting contrast to that of the dihydroisoquinolone (51). The former showed the expected parent molecular ion at m/e 208, but the base peak was at m/e 166. This facile fission presumably involves loss of ketene (42) from the parent (see Scheme 6-4). A similar loss of 42 (12%) has been observed[142] from dihydrocoumarin (105). There is also some loss of carbon dioxide (36%) from the lactone function of (26), expected by analogy with the dihydro-isoquinolones.

Finally the percentage abundances of the $(P-43)^+$ ions in the methylenedioxy and dimethoxy dihydroisoquinolones (90% and 58% of the parent (base) peaks respectively) suggest that the methylenedioxy aromatic system is relatively more stable than that with two o-methoxyls.

Mass spectrum of 6,7-methylenedioxy-3-isoquinolone.

m/e	% abund.	m/e	% abund.	m/e	% abund.
190	15	104	12	74	12
189	100	103	34	63	8
162	11	94.5	7	62	8
161	78	80.5	7	53	8
160	13	80	17	52	7
133	7	77	10	51	10
131	8	76	27	50	20
105	12	75	19		

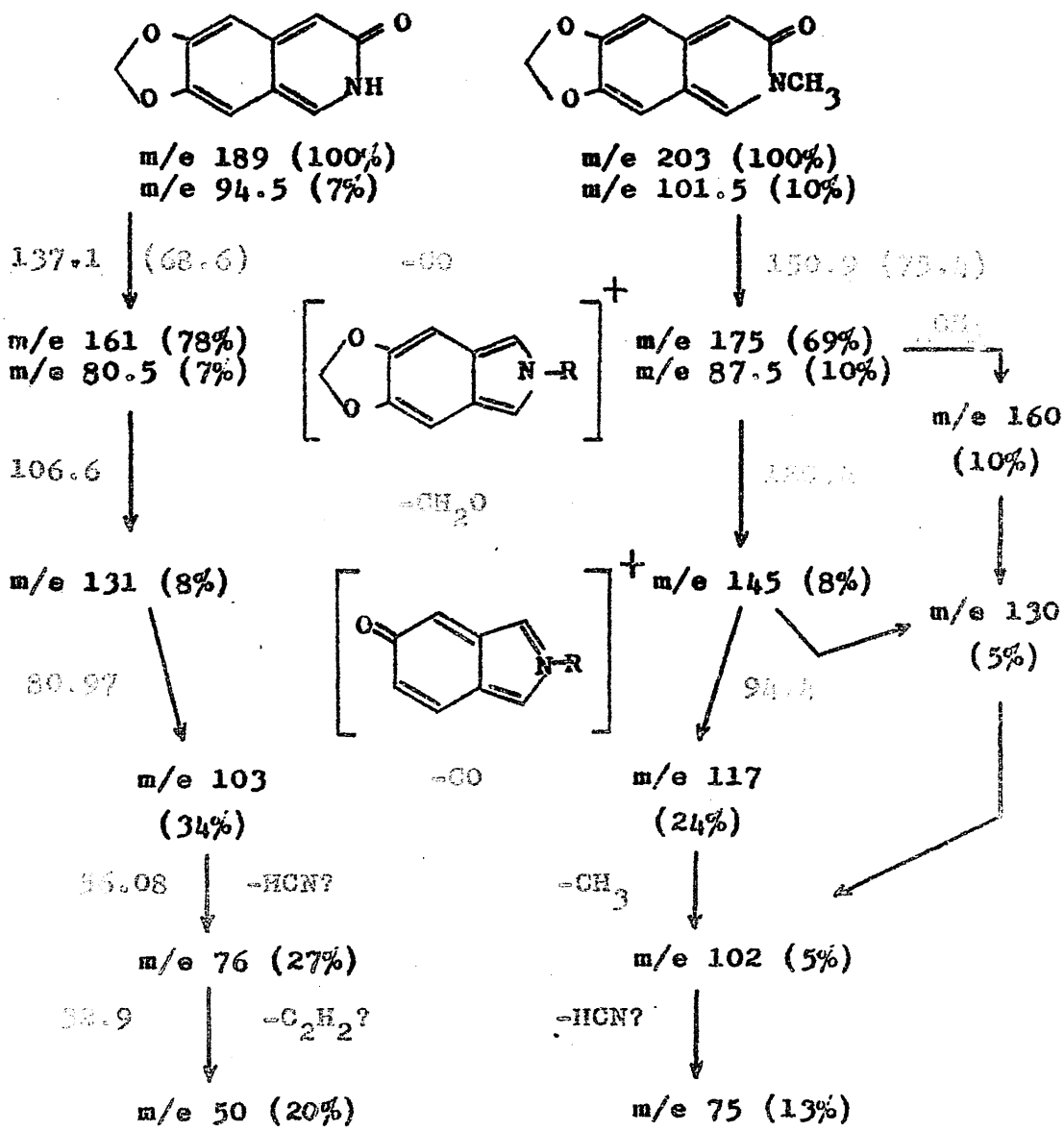
Transition	metastable	Transition	metastable
189 to 161	137.1	76 to 50	32.9
161 to 131	106.6	133 to 103	79.6
131 to 103	80.97	161 to 160	159.0
103 to 76	56.08	94.5to 80.5	68.6

Mass spectrum of N-methyl-6,7-methylenedioxy-3-isoquinolone.

m/e	% abund.	m/e	% abund.	m/e	% abund.
204	5	133	8	89	11
203	100	130	5	87.5	10
189	6	119	10	87	18
176	13	118	11	76	10
175	69	117	24	75	13
174	13	116	8	74	8
160	10	102	5	63	10
146	6	101.5	10	50	11
145	8	90	10		

Transition	metastable
203 to 175	150.9
175 to 145	120.4
145 to 117	94.41
101.5to 87.5	75.4

Scheme 6-1.



Metastables are shown in red.

Mass spectrum of 6,7-dimethoxy-3-isoquinolone.

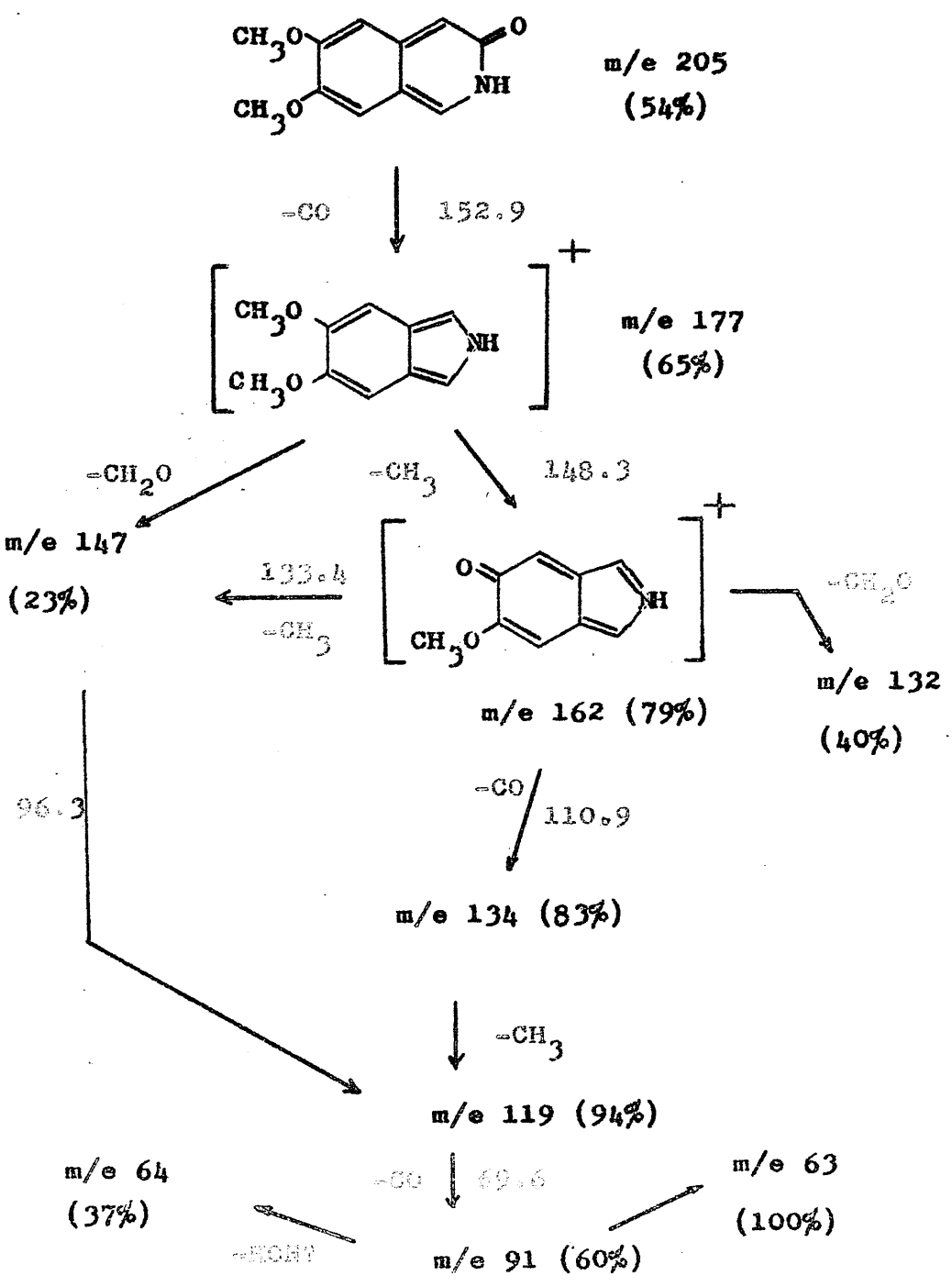
m/e	% abund.	m/e	% abund.
205	54	89	27
191	21	77	31
177	65	76	35
162	79	75	31
160	19	74	23
147	23	64	37
134	83	63	100
132	40	62	38
119	94	53	23
115	25	52	15
104	38	51	27
103	21	50	42
91	60		

Transition	metastable
205 to 177	152.9
177 to 162	148.3
162 to 147	133.4
162 to 134	110.9
147 to 119	96.3
119 to 91	69.6

Mass spectrum of N-hydroxy-6,7-dimethoxy-3-isoquinolone.

m/e	% abund.	m/e	% abund.
222	13	161	7
221	100	160	8
206	17	149	5
205	44	148	5
204	9	147	6
193	5	134	10
190	8	133	10
178	6	119	11
177	17	132	9
176	57	110.5	6
162	11	63	19

Scheme 6-2.


m/e 205
(54%)
-CO
152.9
m/e 177
(65%)
-CH2O
-CH3
148.3
m/e 147
(23%)
133.4
-CH3
m/e 162 (79%)
-CH2O
m/e 132
(40%)
96.3
-CO
110.9
m/e 134 (83%)
-CH3
m/e 119 (94%)
m/e 64
(37%)
-CO
69.6
m/e 63
(100%)
-HCN?
m/e 91 (60%)

Mass spectra of 1,4-dihydro-3-isoquinolones.

(a) 6,7-Dimethoxy (51)

m/e	% abund.	m/e	% abund.
208	13	164	58
207	100	149	16
206	29	134	7
205	14	121	25
190	8	104	6
188	5	103	6
178	15	91	9
176	24	82	10
165	10	77	13

Transition	metastable
207 to 178	153.1
207 to 176	149.6
207 to 164	129.8
178 to 149	124.7
164 to 149	135.4
149 to 121	98.3

(b) 6,7-methylenedioxy (73).

m/e	% abund.	m/e	% abund.
192	13	147	43
191	100	105	16
190	28	104	15
189	16	103	11
162	27	91	22
161	24	90	13
149	24	89	23
148	90	77	26

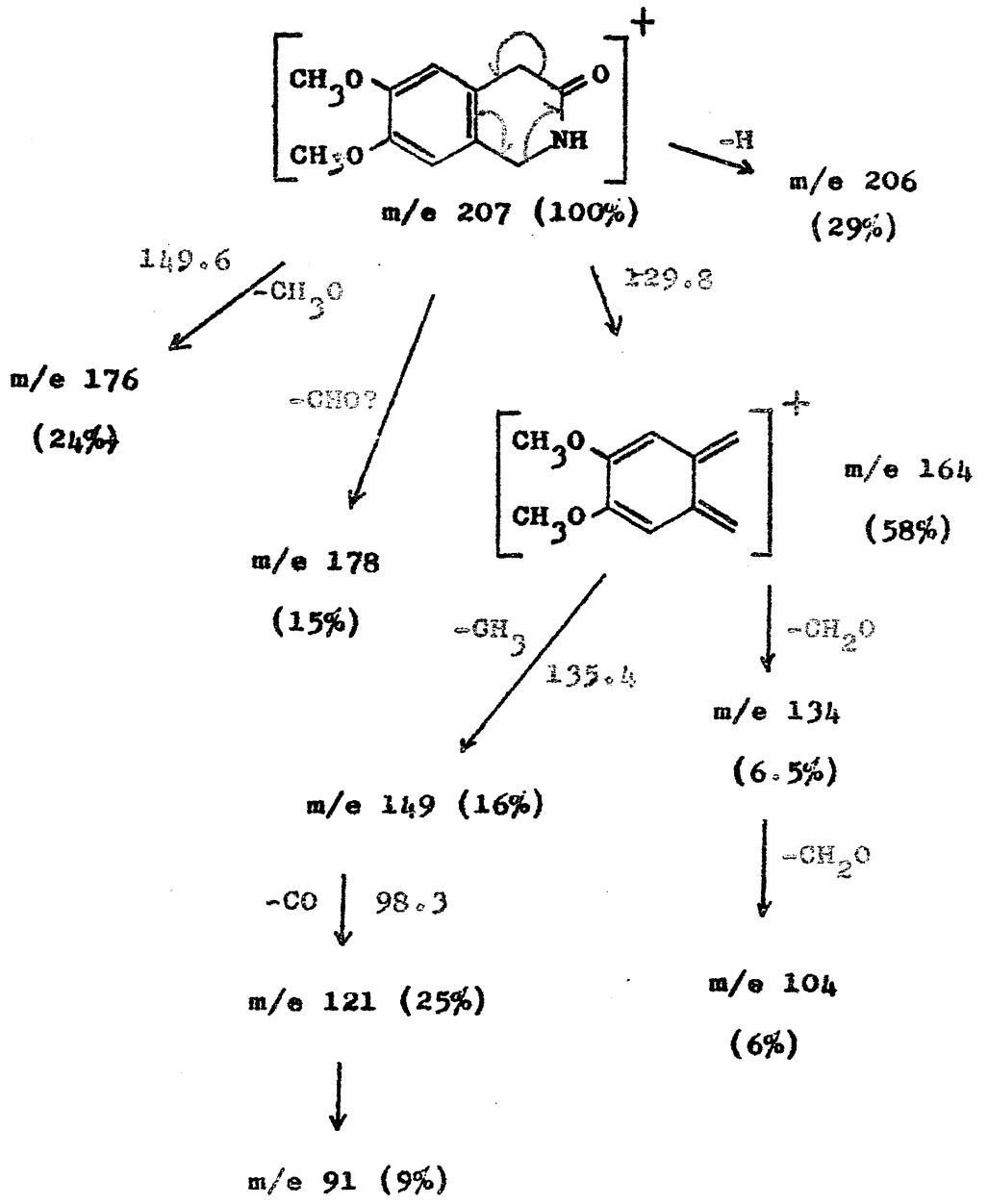
no metastables observed.

(c) N-methyl-6,7-methylenedioxy (56).

m/e	% abund.
205	81
176	19
162	10
149	100

Transition of 205 to 162 - m^* at 106.9

Scheme 6-3.



Metastable ions are shown in red.

Mass spectrum of the dimethoxy lactone (26).

m/e	% abund.	m/e	% abund.
208	51	123	38
167	12	121	22
166	100	108	15
165	11	105	12
164	36	96	47
151	41	94	50
149	9	77	24

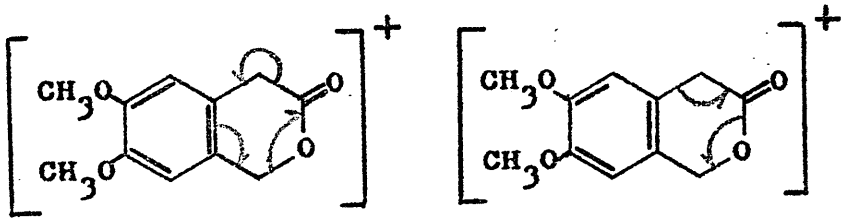
Transition	metastable
208 to 164	129.3
164 to 149	135.4
166 to 151	137.4
166 to 165	164.0
151 to 123	100.2
149 to 121	98.3
123 to 108	94.8
121 to 94	73.0

Mass spectrum of the isoquinolinetrione (53).

m/e	% abund.
233	43
205	64
177	8
176	7
161	47
148	100
120	66

Transition of 233 to 205 is confirmed by a metastable ion at m/e 180.4.

Scheme 6-4.



m/e 208 (51%)

129.3 ↓ $-CO_2$; $-CH_2CO$ ↓

m/e 164 (36%) ; m/e 166 (100%)

135.4 ↓ $-CH_3$; 137.4 ↙ $-CH_3$; 164.0 ↘

m/e 149 (9%) ; m/e 151 (41%) ; m/e 165 (11%)

98.3 ↓ $-CO$; $-CO$ ↓ 100.2

m/e 121 (22%) ; m/e 123 (38%)

73.0 ↓ ; 94.8 ↙ $-CH_3$; ↘

m/e 94 (50%) ; m/e 108 (15%) ; m/e 96 (47%)

Metastable ions are shown in red.

7. LONG-RANGE EFFECTS IN N.M.R. SPECTRA

(a) Deshielding effects of carbonyl groups

Prominent features of the n.m.r. spectra of the isoquinolinetrione derivatives (Table 7-1) are the low-field signals for the aromatic protons. These protons are subject to the strong deshielding influence of peri carbonyl groups,[46] reduced to a certain extent by the shielding effect of alkoxy substituents.[47] An excellent model compound to illustrate this effect is oxyhydrastinine (54) in which the aromatic protons (Table 7-2) are well separated. The position of H_5 in this compound is determined mainly by the shielding effect of the ether grouping (3.38τ), whereas H_8 is affected also by the deshielding effect of the lactam carbonyl and consequently is at significantly lower field - viz. 2.44τ. The aromatic protons in hydrohydrastinine (58), in which only the shielding effect of the ether operates, come into resonance at notably higher field (3.43, 3.52τ).

The deshielding effect of the ortho carbonyl groupings appears to extend to the methylenedioxy protons, the signal for these appearing in the spectra of the triones at a rather lower field than is characteristic of this group. This effect, which is probably due to electron withdrawal from the aromatic ring, is greatly diminished

in the absence of a second ortho carbonyl function, a more typical methylenedioxy resonance (4.01τ) being recorded for oxyhydrastinine, only slightly lower than that (4.14τ) for hydrohydrastinine. The methoxyl signals in the trione (55) are apparently also deshielded, although an additional small downfield shift, attributable to the effect of trifluoroacetic acid as solvent,[137] has to be considered, as can be seen by comparison of the τ-values for the protons of the trione (53), recorded in both deuterochloroform and trifluoroacetic acid.

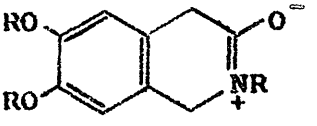
The N-methyl protons in the isoquinolinetrione (53), which are subject to a double deshielding caused by the two adjacent carbonyl groups, appear at 6.55τ, while those in 1,4-dihydro-N-methyl-3-isoquinolone (56) and in oxyhydrastinine (54), which are subject only to the deshielding influence of a single carbonyl, appear at 6.90τ and 6.87τ respectively.

Deshielding of aromatic protons by peri carbonyl groups was also observed in the spectra (see section 4) of N-methyl 1-isoquinolone (H_8, 1.52τ)[cf.146] and N-methyl 2-methyl-4-quinolone (H_5, 1.58τ). The effect has been used in structural elucidation, particularly in the alkaloid field[46,147-148] a recent application[34] resulting in the revision from an O-acetyl to an

N-acetyl structure of the acyl derivative of phthalazone.

(b) Long-range coupling

An interesting feature of the spectra (Table 7-2) of the dihydroisoquinolones (51 and 56) is the apparent long-range coupling (J=1.8c/s.) of the methylene protons. In the case of the N-methylated lactam (56) both methylene signals are slightly broadened (to triplets). In the unsubstituted lactam (51) the methylene adjacent to nitrogen, already a doublet (J=3c/s.) is further broadened almost to a quartet, and the second methylene almost to a triplet. This weak coupling may be through the mesomeric forms of the lactams as shown below.[cf.149]



The absence of such coupling in the N-acetyl derivative (52) is then readily explicable in terms of electron withdrawal from the nitrogen atom, decreasing the tendency for zwitterion formation. The absence of any coupling of this type in the lactone (26) is in keeping with diminished 2,3-double bond character relative to the lactams.

(c) Deshielding by imino functions and allylic coupling

The n.m.r. spectra of three imino derivatives of the type (31) are summarised in Table 7-3. In each spectrum there is a low-field signal assignable to the imino proton. Deshielding of the ortho aromatic proton by the carbon-nitrogen double bond is evident, the second aromatic proton in each compound appearing (as in many of the compounds studied - see also Table 7-2) at a value ca. 3.3τ, consistent with shielding by an ether substituent. The deshielding influence of an imine function appears to be similar to that of a carbonyl group.

In the N-methyl imine "allylic" coupling of the imino proton with the N-methyl protons is indicated by the one-proton quartet (J=ca.2c/s.) at 1.57τ and the three-proton doublet at 6.52τ.

TABLE 7-1. N.M.R. SPECTRA OF ISOQUINOLINE TRIONES

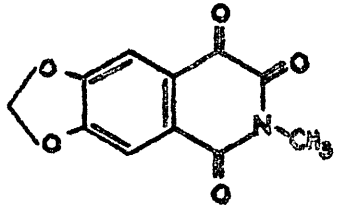
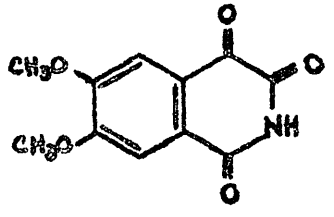
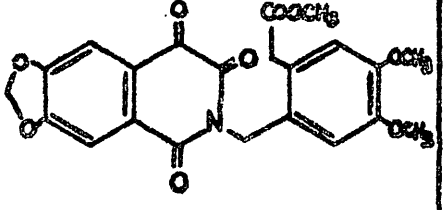
COMPOUND	SOLVENT	N-R	H_5	H_8	R^1-O	OTHERS
	$CDCl_3$	6.55	2.30 or 2.44	2.30 or 2.44	3.76	--
	CF_3CO_2H	6.41	2.15 or 2.30	2.15 or 2.30	3.70	--
	CF_3CO_2H	--	2.00 or 2.07	2.00 or 2.07	5.76 + 5.79	--
	$CDCl_3$	4.77	2.28 or 2.43	2.28 or 2.43	3.74	2.91 1H 3.24 1H 6.02 2H 6.14 6H 6.33 3H

Table 7-2.

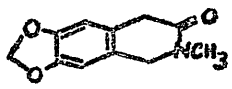
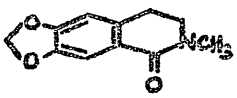
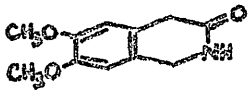
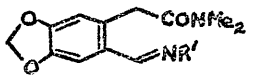
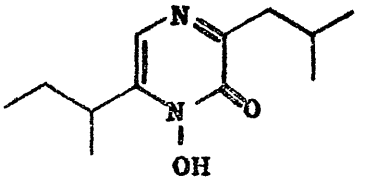
Compound	H_1	N-R	H_3	H_4	H_5	R'O	H_8
	5.58	6.90	-	6.47	3.35	4.03	3.35
	-	6.87	6.46	7.05	3.38	4.01	2.44
	6.54	7.59	7.26 or 7.31	7.26 or 7.31	3.43 or 3.52	4.14	3.43 or 3.52
	5.50	2.33	-	6.45	3.30	6.11	3.30
	5.10	7.41	-	6.30	3.14 or 3.23	6.11	3.14 or 3.23
	4.72	-	-	6.35	3.18 or 3.23	6.10	3.18 or 3.23

Table 7-3. N.M.R. Spectra of imino derivatives.

	R'	-CH=	Aromatic Protons		CH_2	$-CH_2-$	NMe
methyl imine	6.52	1.57	2.66	3.28	4.02	6.07	6.94 7.01
hydrazone	4.50	2.04	2.74	3.31	4.02	6.02	6.97 7.00
azine	--	1.28	2.50	3.25	4.00	6.08	6.93 7.00
aldehyde	--	0.00	2.68	3.19	3.93	5.94	6.87 7.02

8. BIOLOGICAL ACTIVITY

The mould product aspergillic acid (106) has been found to have a pronounced antibacterial action, which



(106)

has been attributed to its hydroxamic acid grouping.[cf.100] Supporting evidence has resulted from studies of a variety of cyclic hydroxamic acids,[100,150] all of which have been found to be active in this way.

In the light of these results it was decided to bioassay the two N-hydroxy 3-isoquinolones. These compounds have been found to inhibit growth of B.subtilis, E.coli, and S.aureus to approximately the same extent (see Table 8-1). The significant absence of such antibiotic activity in the reduced hydroxamic acid, and in the unsubstituted and N-amino isoquinolones (Table 8-2) suggests that in fact the activity of these compounds may be due to their ability to enolise to their N-oxide tautomer. In this connection quinoline N-oxide did also show a weak inhibition.

The inhibition caused by the hydroxamic acids was, however, only temporary, growth of the bacteria resulting

Table 8-1. Activities of N-hydroxy-3-isoquinolones

Bacterium	Mean inhibition (mm.)	
	Methylenedioxy	Dimethoxy
B.subtilis	12.5, 15.8	11.9, 15.8
E.coli	9.6, 15.8	10.0
S.aureus	10.8, 15.0	11.6

Table 8-2. Activities against B.subtilis.

Compound	Inhibition
6,7-dimethoxy-3-isoquinolone	negligible
N-amino-6,7-methylenedioxy-3-isoquinolone	0
N-(p-bromophenyl)-6,7-methylenedioxy-3-isoquinolone	10.8
N-methyl-6,7-methylenedioxyisoquinolinetrione	14.2
1,4-dihydro-N-hydroxy-3-isoquinolone, 6,7-dimethoxy	negligible
quinoline N-oxide	11.3

in two apparent zones of inhibition (cf. Table 8-1). One possible explanation would be oxidative destruction of the system (these compounds are highly susceptible to oxidation, especially in solution) which could lead to loss of activity. The fact that the inhibition which was found to be caused by the trione (53) was not time-dependent in this manner is in keeping with the relative stability of this compound to oxidation.

Note

Bacteriostatic activities of methanolic or aqueous solutions of tested materials (concentration 1mg./ml.) were normally measured after 24 hours growth at 30° on Bouillon's agar. Solutions were inserted into precut discs (diameter 9.2mm.) and the zone of inhibition measured in the usual way (total diameter).

Table 8-3. Inhibition of B.subtilis with time.

N-hydroxy-3-isoquinolone	Inhibition mm.		
	6 hrs.	22 hrs.	28 hrs.
6,7-methylenedioxy	18.1	13.7	12.8
6,7-dimethoxy	17.9	14.6	13.3

9. EXPERIMENTAL

Melting-points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared (i.r.) spectra in Nujol were measured on a Perkin-Elmer 137 IR or Unicam SP 200 spectrophotometer. Precise infrared measurements (KCl discs and solution spectra) were made on a Unicam SP 100 instrument. Ultraviolet (u.v.) spectra were recorded in 95% ethanol unless otherwise stated and were measured using a Perkin-Elmer 137 UV or Unicam SP 800 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R 10 60 Mc. spectrometer, using tetramethylsilane as internal standard. Mass spectra were obtained with an A.E.I. MS 9 double-focussing mass spectrometer. Molecular weight measurements were made in chloroform solution using a Mechrolab 301 A vapour pressure osmometer. Analytical thin-layer chromatography (t.l.c.) was carried out using Merck Kieselgel G in 0.25mm. layers, using mainly iodine vapour for detection. For preparative thin-layer chromatography (p.l.c.) 0.6mm. layers were used. Hydrogenations were performed at atmospheric temperature and pressure. All chloroform extracts were dried over anhydrous magnesium sulphate and evaporation of solvents carried out by means of a rotary film

evaporator. The term petroleum-ether refers to petroleum-ether (b.p. 60-80°) unless otherwise stated. The following abbreviations are used in reporting n.m.r. spectra : s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet, H, proton.

2-Hydroxymethyl-4,5-methylenedioxyphenylacetic acid lactone

Hydrolysis and oxidative decomposition of piperonal azlactone (200g.), according to the method of Snyder, Buck, and Ide[25], afforded a mixture of benzoic and homopiperonylic acids. The crude mixture was dissolved in glacial acetic acid (500ml.) and a mixture of concentrated (36N) hydrochloric acid (150ml.) and 40% formaldehyde (150ml.) added. The solution was heated on the steam-bath for one hour, then poured into cold water (500ml.). The aqueous solution was extracted with chloroform and the extract thoroughly washed successively with saturated sodium bicarbonate solution and water. The product obtained by evaporation of solvent was a sticky brown solid, easily soluble in chloroform and sparingly soluble in ethanol. Decolorisation with animal charcoal followed by crystallisation from ethanol gave the lactone as a sand-coloured solid (33g., 25%), m.p. 125-130°. Filtration of a 50% chloroform-methanol solution through Woelm grade I

alumina proved to be the most efficient method of removal of tars. Successive crystallisations from ethanol gave an almost colourless solid, m.p. 132-135°. (lit. 137°)

$\nu_{max.}$(Nujol) : 1735 cm^{-1}.

$\lambda_{max.}$: 240mμ (log ε 3.49), 292mμ (log ε 3.64).

4,5-Dimethoxy-2-hydroxymethylphenylacetic acid lactone.

(a) Veratraldehyde azlactone (200g.) was hydrolysed and decomposed according to the method of Snyder et al[25] to yield a mixture of benzoic and homoveratric acids which was chloromethylated using the same conditions as were employed in the preparation of 2-hydroxymethyl-4,5-methylenedioxyphenylacetic acid lactone. The crude product was a viscous red-brown gum, which solidified on standing overnight at 0°. Trituration with warm ethanol gave the lactone as a putty-coloured solid (44.52g., 33%), m.p. 103-106°. Decolorisation with animal charcoal and repeated crystallisation , first from ethanol as needles, m.p. 109.5-110°, and then from benzene-petroleum ether gave colourless leaflets, m.p. 110-111.5°.

$\nu_{max.}$(Nujol) : 1740 cm^{-1}.

$\lambda_{max.}$: 234 mμ (log ε 3.75), 286 mμ (log ε 3.48).

τ values ($CDCl_3$) : 3.18 (1H,s), 3.23 (1H,s), 4.72 (2H,s), 6.10 (6H,s), 6.35 (2H,s).

Found: C, 63.49; H, 6.01

$C_{11}H_{12}O_4$ requires: C, 63.46; H, 5.77%.

(b) Chloromethylation of 3,4-dimethoxyphenylacetic acid (100g.) using the conditions of Stevens[24], gave the lactone as a pale yellow crystalline solid (75.64g., 72%).

N-Methyl-2-hydroxymethyl-4,5-methylenedioxyphenylacetamide.

2-Hydroxymethyl-4,5-methylenedioxyphenylacetic acid lactone (6.22g.) and 33% ethanolic methylamine (135ml.) were refluxed for six hours. Colourless needles separated from the solution on standing overnight. Crystallisation from ethanol gave the alcohol as colourless needles (5.26g., 73%), subliming above 165°, with m.p. 172-173°.

$\nu_{max.}$ (Nujol) : 3280, 3100, 1635, 1590 cm^{-1}.

$\lambda_{max.}$: 241 mμ (log ε 3.63), 290 mμ (log ε 3.54).

Found: C, 59.12; H, 5.71; N, 6.48

$C_{11}H_{13}O_4N$ requires: C, 59.19; H, 5.83; N, 6.28%.

N,N-Dimethyl-2-hydroxymethyl-4,5-methylenedioxyphenyl-acetamide.

2-Hydroxymethyl-4,5-methylenedioxyphenylacetic acid lactone (14.82g.) was refluxed gently with 33% ethanolic dimethylamine (300ml.) for three hours. Evaporation of solvent gave the alcohol (17.94g., 98%), which crystallised from benzene-petroleum ether in colourless needles, m.p. 98-99°.

$\nu_{max.}$ (Nujol) : 3450, 1630 cm^{-1}.

$\lambda_{max.}$: 244 mμ (log ε 3.67), 294 mμ (log ε 3.61).

Found: C, 60.99; H, 6.25; N, 5.92

$C_{12}H_{15}O_4N$ requires: C, 60.75; H, 6.37; N, 5.90%.

N,N-Dimethyl-4,5-dimethoxy-2-hydroxymethylphenylacetamide.

4,5-Dimethoxy-2-hydroxymethylphenylacetic acid lactone (10g.), derived by direct chloromethylation of homoveratric acid, was refluxed with 33% ethanolic dimethylamine (200ml. for 3½ hours. Evaporation gave the alcohol as a pale yellow crystalline solid (11.95g., 98%), m.p. 120-125°, possessing no lactone carbonyl absorption. Successive crystallisations from benzene-petroleumether gave colourless prisms, m.p. 127-128°.

$\nu_{max.}$ (Nujol) : 3325, 1620 cm^{-1}.

$\lambda_{max.}$: 216 mμ (log ε 4.03), 235 mμ (log ε 3.96), 284 mμ (log ε 3.46).

Molecular weight (isothermal distillation): 267 (calc. 25

Found: C, 61.93; H, 7.61; N, 5.72

$C_{13}H_{19}O_4N$ requires: C, 61.66; H, 7.51; N, 5.53%.

The yield of alcohol depended on the purity of the lacto used. With crystallised lactone yields were in the order of 85% : when the crude lactone was used the alcohol was contaminated by tars, reducing the yield after purification to ca. 65%.

N,N-Dimethyl-2-formyl-4,5-methylenedioxyphenylacetamide.

N,N-Dimethyl-2-hydroxymethyl-4,5-methylenedioxyphenylacetamide (10.77g.) was dissolved in chloroform (250ml.) and the solution shaken with powdered manganese dioxide (100g.) for 60 hours at room temperature. The solution was filtered (glass paper) and the residue washed several times with hot chloroform. Evaporation of solvent gave the aldehyde as a pale yellow solid (9.48 g., 89%), m.p. 128-131°.

$\nu_{max.}$ (Nujol) : 2760, 1690, 1645, 1610 cm^{-1}.

$\lambda_{max.}$: 236 mμ (log ε 4.39), 281 mμ (log ε 3.73), 316 mμ (log ε 3.78).

The aldehyde was characterised as its semicarbazone, m.p. 226° (from 40% aqueous ethanol).

$\lambda_{max.}$: 219 mμ (log ε 4.45), 292 mμ (log ε 4.31), 322 mμ (log ε 4.27), no change on acidification.

Found: C, 53.38; H, 5.31; N, 19.26

$C_{13}H_{16}O_4N_4$ requires: C, 53.42; H, 5.52; N, 19.17%.

Similar results were achieved using methylene chloride as a solvent for the oxidation, but much poorer yields were recorded when the reaction was carried out in tetrahydrofuran, results suggesting some oxidative attack on the solvent. The aldehyde was recovered unchanged after refluxing with dimethylamine or triethylamine. It was also unaffected by warm alcoholic ethylamine hydrochloride

N,N-Dimethyl-4,5-dimethoxy-2-formylphenylacetamide.

N,N-Dimethyl-4,5-dimethoxy-2-hydroxymethylphenylacetamide (11.78g.) was shaken with manganese dioxide (100g.) in chloroform (200ml.) for 48 hours. Filtration (glass paper) and evaporation of solvent gave the aldehyde as a pale yellow solid (10.57g., 90%), m.p. 110-113°. Decolorisation with animal charcoal and crystallisation from petroleum ether gave colourless needles, m.p. 112.5-113.5°.

$\nu_{max.}$ (Nujol) : 1685, 1640, 1610, 1575, 1525 cm^{-1}.

$\lambda_{max.}$: 236 mμ (log ε 4.36), 283 mμ (log ε 4.00), 315 mμ (log ε 3.81).

Found: C, 62.16; H, 6.63; N, 5.42

$C_{13}H_{17}O_4N$ requires: C, 62.15; H, 6.77; N, 5.58%.

The same yield was obtained using methylene chloride as solvent.

N,N-Dimethyl-4,5-methylenedioxy-2-methyliminomethyl-phenylacetamide.

N,N-Dimethyl-2-formyl-4,5-methylenedioxyphenylacetamide (6.77g.) was refluxed with 33% ethanolic methylamine (135 ml.) for ninety minutes. The imine was obtained on evaporation as a pale brown solid (7.09g., 99%), m.p. 120-126°. Crystallisation from benzene-petroleum ether afforded very pale yellow needles, m.p. 127-128.5°.

$\nu_{max.}$ (Nujol) : 1635 cm^{-1}, no absorption ca. 1700cm^{-1}.

$\lambda_{max.}$ (EtOH) ; 230 mμ (log ε 4.28), 274 mμ (log ε 3.95), 311 mμ (log ε 3.85); (acid): 246 mμ (log ε 4.58), 305 mμ (log ε 4.16), 353 mμ (log ε 4.25); (base): 237, 269, 313 mμ., acid shift = +79 mμ.

τ values ($CDCl_3$) : 1.57 (1H,q, J=2c/s.), 2.66 (1H,s), 3.28 (1H,s), 4.02 (2H,s), 6.07 (2H,s), 6.52 (3H,d, J=2c/s.) 6.94 (3H,s), 7.01 (3H,s).

Found: C, 63.05; H, 6.75; N, 11.24

$C_{13}H_{16}O_3N_2$ requires: C, 62.89; H, 6.50; N, 11.28%.

Although thermally stable this compound was partially hydrolysed by treatment with animal charcoal in hot ethanol

N,N-Dimethyl-2-benzyliminomethyl-4,5-methylenedioxy-phenylacetamide.

N,N-Dimethyl-2-formyl-4,5-methylenedioxyphenylacetamide (264mg.) and benzylamine (118mg.) were refluxed in ethanol (20ml.) for three hours. Evaporation gave a yellow gum which crystallised on standing. The resultant yellow solid was washed with cold ether, leaving the imine as an almost colourless solid (300mg., 82%), m.p. 78-83°. Crystallisation from benzene-petroleum ether provided very pale yellow plates, m.p. 86-87.5°.

$\nu_{max.}$ (Nujol) : 1640 cm^{-1}.

$\lambda_{max.}$ (EtOH) : 233 mμ (log ε 4.18), 278 mμ (log ε 3.78), 313 mμ (log ε 3.65); (acid) : 251 mμ (log ε 4.02), 308 mμ

(log ε 3.65), 360 mμ (log ε 3.92); (base) : 232, 278, 313 mμ, acid shift = +82 mμ.

Found: C, 70.63; H, 6.02; N, 8.40

$C_{19}H_{20}O_3N_2$ requires: C, 70.37; H, 6.17; N, 8.64%.

N,N-Dimethyl-2-(p-bromophenyl)-iminomethyl-4,5-methylenedioxyphenylacetamide.

N,N-Dimethyl-2-formyl-4,5-methylenedioxyphenylacetamide (560mg.) and p-bromoaniline (400mg.) were refluxed in ethanol (40ml.) for three hours. Evaporation of solvent gave the p-bromoanil derivative as a light brown solid (920mg., 100%). Colourless fluffy needles, m.p. 141-142.5°, were obtained by crystallisation from ethanol.

$\nu_{max.}$ (Nujol) : 1645, 1620, 1580 cm^{-1}.

$\lambda_{max.}$ (EtOH) : 237 mμ (log ε 4.30), 290 mμ (log ε 4.00), 337 mμ (log ε 4.17); (acid) ; 227 mμ (log ε 4.23), 236 mμ (log ε 4.22), 285 mμ (log ε 3.69), 318 mμ (log ε 3.62); (base) : 237, 285, 313 mμ.

Found: C, 55.83; H, 4.32; N, 7.14; Br, 20.32

$C_{18}H_{17}O_3N_2Br$ requires: C, 55.55; H, 4.37; N, 7.20; Br, 20.57%.

N,N-Dimethyl-2-hydroxyiminomethyl-4,5-methylenedioxyphenylacetamide.

The oxime of N,N-dimethyl-2-formyl-4,5-methylenedioxyphenylacetamide was prepared in 92% yield by the standard

method using equivalent amounts of hydroxylamine hydrochloride and sodium acetate trihydrate. (Three hours at room temperature). Crystallisation from ethanol gave colourless plates (slow crystallisation gave needles) which melted at 173.5-174.5° and immediately recrystallised as yellow needles, m.p. 257-264°, decomp.

$\nu_{max.}$ (Nujol) : 3250, 1620 cm^{-1}.

$\lambda_{max.}$: 212 mμ (log ε 4.35), 228 mμ, infl. (log ε 4.19), 273 mμ (log ε 3.99), 309 mμ (log ε 3.75).

Molecular weight (isothermal distillation): 270 (calc. 250)

Found: C, 57.72; H, 5.65; N, 11.01

$C_{12}H_{14}O_4N_2$ requires: C, 57.60; H, 5.60; N, 11.20%

The oxime acetate was prepared by heating the oxime with excess acetic anhydride on the steam-bath for five minutes and pouring the resultant solution on to crushed ice. The precipitated colourless solid was crystallised from benzene-petroleum ether as colourless needles, m.p. 148-163°, dependent on the rate of heating. A single compound was indicated by t.l.c.

$\nu_{max.}$ (Nujol) : 1760, 1640, 1600 cm^{-1}, no absorption between 3000 and 3600 cm^{-1}.

Found: C, 57.92; H, 5.80; N, 9.84

$C_{14}H_{16}O_5N_2$ requires: C, 57.53; H, 5.48; N, 9.59%.

N,N-Dimethyl-2-oximinomethyl-4,5-dimethoxyphenylacetamide.

The oxime of N,N-dimethyl-4,5-dimethoxy-2-formylphenylacetamide was prepared by the standard method (see above), in 95% yield. Crystallisation from ethanol gave colourless needles, m.p.175-178°, decomp.

$\nu_{max.}$ (Nujol) : 3250, 1640 cm^{-1}.

$\lambda_{max.}$: 217 mμ (log ε 4.27), 229 mμ (log ε 4.31), 272 mμ (log ε 4.06), 304 mμ (log ε 3.67).

Found: C, 58.51; H, 6.49; N, 10.60

$C_{13}H_{18}O_4N_2$ requires: C, 58.64; H, 6.77; N, 10.53%.

The oxime reacted with hot acetic anhydride to give a mixture with $\nu_{max.}$ at 2200, 1770, 1640, 1600, 1575, and 1525 cm^{-1}. This was not investigated further.

2-Methyl-6,7-methylenedioxy-3(2H)-isoquinolone.

The imine, obtained by the reaction of N,N-dimethyl-2-formyl-4,5-methylenedioxyphenylacetamide (8.0g.) with ethanolic methylamine, was dissolved in hot 6N hydrochloric acid (200ml.). After heating for about 60 seconds the isoquinolone hydrochloride precipitated. It was filtered, washed with cold 6N hydrochloric, and dried at room temperature to give a pale yellow solid (7.64g., 94%). Crystallisation from 6N hydrochloric acid gave colourless needles, m.p. 195-200°, resubliming with m.p. 235-240°.

$\nu_{max.}$ (Nujol) : 3320, 2600, 2500, 2300, 1900, 1645, 1615, 1560 cm^{-1}.

τ values (DMSO) : 0.92 (1H,s), 2.58 (1H,s), 2.68 (2H,s), 3.73 (2H,s), 6.04 (3H,s).

Found: C, 54.79; H, 4.60; N, 5.86

$C_{11}H_9O_3N.HCl$ requires: C, 55.12; H, 4.21; N, 5.84%.

The hydrochloride, derived by acid treatment of the imine (7.06g.) was basified with ammonium hydroxide (s.g. 0.88). The precipitated solid and basic solution were thoroughly extracted with chloroform. Evaporation gave the isoquinolone as a bright yellow solid (5.78g.,100%). An alternative procedure used was to shake the hydrochloride (7.64g.) with ammonia (200ml.) and to filter the insoluble hydrate. On drying at 100° overnight the isoquinolone was obtained as a bright yellow powder (6.0g., 92%); overall yield from the aldehyde : 87%.

The isoquinolone was obtained with m.p. 243-247°, raised to 251-253° by crystallisation from methanol.

$\nu_{max.}$ (KCl) : 1662, 1648, 1618, 1566, 1446, 1161, 1020 cm^{-1}.

$\nu_{max.}$ ($CHBr_3$) : 1661, 1650, 1618, 1556 cm^{-1}.

$\nu_{max.}$ ($CHCl_3$) : 1663, 1652, 1619.5, 1559 cm^{-1}.

$\lambda_{max.}$ (EtOH) : 248 mμ (log ε 4.76), 290 mμ infl. (log ε 3.43), 305.5 mμ (log ε 3.51), 317.5 mμ (log ε 3.55), 399 mμ (log ε 3.63); (acid): 245 mμ (log ε 4.67), 307 mμ infl. (log ε 3.90), 315 mμ (log ε 4.00), 364 mμ (log ε 3.70); (base): 248, 290, 305, 317, 399 mμ.

τ values : ($CDCl_3$): 2.20 (1H,s), 3.40 (2H,s), 3.45 (1H,s), 4.04 (2H,s), 6.26 (3H,s); (DMSO): 1.56 (1H,s), 3.07 (1H, s), 3.22 (1H,s), 3.51 (1H,s), 3.91 (2H,s), 6.37 (3H,s); (CF_3CO_2H): 1.38 (1H,s), 2.54 (1H,s), 2.76 (1H,s), 2.87 (1H,s), 3.78 (2H,s), 5.77 (3H,s).

Parent molecular ion at m/e 203.

Found: C, 64.94; H, 4.31; N, 7.06

$C_{11}H_9O_3N$ requires: C, 65.02; H, 4.46; N, 6.89%.

The isoquinolone formed a dihydrate of m.p. 232-238°.

$\nu_{max.}$ (Nujol) : 3250 (broad), 1665, 1620, 1540 cm^{-1}.

Found: C,54.95; H, 5.43; N, 5.87

$C_{11}H_9O_3N.2H_2O$ requires: C,55.23; H, 5.48; N, 5.86%.

The isoquinolone decolourised cold aqueous permanganate. An alcoholic solution gave an immediate deep red coloration with methanolic ferric chloride. A bright red colour was also produced by reaction with nitrous acid at 0°. Attempts to hydrolyse the lactam with concentrated hydrochloric acid, concentrated sulphuric acid, or 10% sodium hydroxide yielded only slightly decomposed starting material. The compound was recovered unchanged from liquid ammonia, and from refluxing alcoholic hydrazine hydrate. In addition there was no reaction with ethereal diazomethane after standing at room temperature for three days.

6,7-Dimethoxy-2-methyl-3(2H)-isoquinolone.

N,N-Dimethyl-4,5-dimethoxy-2-formylphenylacetamide (1.00g.) was refluxed on the steam-bath with 33% ethanolic methylamine (50ml.) for two hours. Evaporation of the solvent gave a highly fluorescent orange gum with $\nu_{max.}$ at 1640 and 1600 cm^{-1}, but none ca. 1700cm^{-1}. Its $\lambda_{max.}$ were at 228, 238, 274, and 308 mμ, shifted on acidification to 220, 247, 312, and 354 mμ. The observed reversible acid shift (+80 mμ) is characteristic of an imine.[28] All attempts to obtain the imine in crystalline state were unsuccessful.

The methyl imine formed in the above reaction was warmed with 6N hydrochloric acid (30ml.). It dissolved initially but after about one minute the isoquinolone hydrochloride precipitated from the hot acid solution as a pale yellow solid (935mg., 81%). Basification and chloroform extraction of the filtrate yielded only gummy material which appeared from its spectral characteristics to be mainly aldehyde. The crude hydrochloride was crystallised from 6N hydrochloric acid as pale yellow fluffy needles, which turned yellow on heating and sublimed to needles ca. 190° (elimination of HCl?), with m.p. 226-233°, decomp. The solid was dried overnight at 65°.

$\nu_{max.}$ (Nujol) : 3400 (broad), 1950, 1640, 1620, 1570, 1540 cm^{-1}.

$\lambda_{max.}$ (EtOH) : 251.5 mμ (log ε 4.80), 288 mμ (log ε 3.38),

303 mμ (log ε 3.54), 314 mμ (log ε 3.56), 394 mμ (log ε 3.46); (acid): 249, 306 infl., 314 mμ (log ε 3.84), 364 mμ; (base): as in ethanol.

τ values (CF_3CO_2H): 1.20 (1H,s), 2.37 (1H,s), 2.58 (1H,s), 2.70 (1H,s), 5.70 (3H,s), 5.77 (3H,s), 5.81 (3H,s).

Found: C, 49.33; H, 5.98; N, 4.89

$C_{12}H_{13}O_3N.HCl.H_2O$ requires: C, 49.41; H, 6.18; N, 4.80

$C_{12}H_{13}O_3N.2HCl$ requires: C, 49.34; H, 5.14; N, 4.80%.

A sample of the hydrochloride was dissolved in ammonium hydroxide and the basic solution extracted with chloroform. Evaporation of solvent gave a bright yellow solid which rapidly darkened and became moist on exposure to air, eventually turning a blood-red colour at the surface. Attempted purification by direct sublimation or by sublimation from the hydrochloride was unsuccessful, the latter yielding a yellow solid, m.p. 204-221°, decomp., with a tendency to form a glass and to undergo aerial oxidation.

2-Benzyl-6,7-methylenedioxy-3(2H)-isoquinolone.

The benzyl imine, prepared by reaction of N,N-dimethyl-2-formyl-4,5-methylenedioxyphenylacetamide (820mg.) with benzylamine (370mg.) was treated, without purification, with warm 6N hydrochloric acid (50ml.). The isoquinolone hydrochloride crystallised almost immediately as a colourless solid. Its solution in 4N sodium hydroxide was extracted with chloroform to give the isoquinolone as a

sticky yellow-brown solid. Trituration with cold ethanol gave a dry yellow-orange solid (900mg., 92%). Crystallisation from ethanol gave bright yellow needles, m.p.210-213°.

$\nu_{max.}$ (KCl): 1661, 1655, 1621, 1566, 1448, 1261, 1165, 1026 cm^{-1}; ($CHBr_3$): 1660, 1651, 1619, 1559, cm^{-1}.

$\lambda_{max.}$ (EtOH) : 252 mμ (log ε 4.84), 293 mμ (log ε 3.54), 307 mμ (log ε 3.70), 318.5 mμ (log ε 3.72), 401 mμ (log ε 3.72); (acid): 248, 308 infl., 319, 365 mμ; (base): 252, 293, 306.5, 319, 399 mμ.

τ values: ($CDCl_3$): 2.26 (1H,s), 2.66 (5H,s), 3.34 (1H,s), 3.48 (2H,s), 4.08 (2H,s), 4.66 (2H,s); (DMSO): 1.55 (1H, s), 2.67 (5H,s), 3.12 (1H,s), 3.27 (1H,s), 3.52 (1H,s), 3.95 (2H,s), 4.70 (2H,s); (CF_3CO_2H): 1.29 (1H,s), 2.46 (1H+5H,s), 2.73 (1H,s), 2.78 (1H,s), 3.73 (2H,s), 4.24 (2H,s).

Found: C, 73.38; H, 4.79; N, 5.23

$C_{17}H_{13}O_3N$ requires: C, 73.13; H, 4.66; N, 5.02%.

2-(p-Bromophenyl)-6,7-methylenedioxy-3(2H)-isoquinolone.

The p-bromoanil (585mg.) from N,N-dimethyl-2-formyl-4,5-methylenedioxyphenylacetamide was heated on the steam-bath with a solution of 6N hydrochloric acid (15ml.) in water (10ml.) for ten minutes. The isoquinolone hydrochloride crystallised from the hot acid solution as pale yellow needles (160mg., 28%). Further material (255mg., 44%) was obtained by heating for a further 25 minutes.

The hydrochloride (140mg.) was dissolved in ammonium hydroxide (s.g. 0.88) and the basic solution extracted with chloroform until colourless. Evaporation gave the isoquinolone as a bright yellow solid (125mg.), exhibiting a strong green fluorescence in solution. Two sublimations at 244° and 0.01mm. gave a bright yellow solid which sublimed with some decomposition ca. 250° to bright yellow needles, m.p. 310-315°: decomp.

$\nu_{max.}$ (KCl): 1663, 1655, 1620, 1590, 1563, 1554, 1488, 1450, 1260, 1163, 1041 cm^{-1}.

$\lambda_{max.}$ (EtOH) : 252 mμ (log ε 4.78), 310 mμ (log ε 3.83), 321 mμ (log ε 3.86), 408 mμ (log ε 3.65); (acid): 253, 314 infl., 323, 366 mμ ; (base): 250,313, 323, 412 mμ.

τ values (CF_3CO_2H): 1.30 (1H,s), 2.05 (2H,d, J=9c/s.), 2.35 (1H,s), 2.51 (2H,d, J=9c/s.), 2.63 (1H,s), 2.69 (1H,s), 3.64 (2H,s).

Molecular weight (isothermal distillation): 364 (calc.344).

Found: C, 55.94; H, 3.22; N, 3.98

$C_{16}H_{10}O_3NBr$ requires: C, 55.83; H, 2.91; N, 4.07%.

2-Hydroxy-6,7-methylenedioxy-3(2H)-isoquinolone.

(a) N,N-Dimethyl-2-formyl-4,5-methylenedioxyphenylacetamide (320mg.) was dissolved in warm ethanol (5ml.) and the solution treated with hydroxylamine hydrochloride (400mg.) in ethanol (4ml.). After warming on the steam-bath for one minute a crystalline solid separated. On

cooling, the isoquinolone hydrochloride was obtained as a light brown solid (235mg., 71%), subliming above 210° to yellow needles, m.p. 277-279°.

τ values (DMSO) : 1.08 (1H,s), 2.83 (1H,s), 2.94 (1H,s), 3.04 (1H,s), 3.84 (2H,s).

Crystallisation from a very small volume of dilute ammonium hydroxide and washing with cold water gave yellow needles, m.p. 282-285°, purified by sublimation at 190° and 0.01mm. as a pale yellow solid, m.p. 285-286°. The compound appears to be thermochromic, being bright yellow when hot.

$\nu_{max.}$ (KCl): 1647 (broad), 1617, 1554 sh., 1527 sh., 1510, 1161, 1021 cm^{-1}.

$\lambda_{max.}$ (EtOH): 246.5 mμ (log ε 4.78), 290 mμ (log ε 3.61), 303 mμ (log ε 3.75), 314.5 mμ (log ε 3.76), 393 mμ (log ε 3.62); (acid): 245, 305 infl., 313, 365 mμ ; (base): 247, 305, 317, 373 infl., 394 mμ.

τ values: (DMSO): 1.32 (1H,s), 3.02 (1H,s), 3.17 (1H,s), 3.39 (1H,s), 3.94 (2H,s), 4.16 (OH?) ; (CF_3CO_2H): 1.07 (1H,s), 2.39 (1H,s), 2.68 (1H,s), 2.75 (1H,s), 3.70 (2H,s).

Found : C, 58.69; H, 3.84; N, 7.04

$C_{10}H_7O_4N$ requires: C, 58.53; H, 3.41; N, 6.83%.

(b) Treatment of alcoholic solutions of either the oxime or oxime acetate from N,N-dimethyl-2-formyl-4,5-methylenedioxyphenylacetamide with a few drops of dilute

hydrochloric acid caused rapid precipitation of the isoquinolone hydrochloride as pale green needles, identified by m.p. (274-279°) and infrared spectra.

Attempts to hydrolyse the isoquinolone with 10% sodium hydroxide or concentrated (36N) hydrochloric acid were unsuccessful. The isoquinolone gave a blood-red coloration with ferric chloride and also formed a bright red nickel complex.

6,7-Dimethoxy-2-hydroxy-3(2H)-isoquinolone.

(a) The oxime (285mg.) of N,N-dimethyl-4,5-dimethoxy-2-formylphenylacetamide was dissolved in warm ethanol (12ml.) and 6N hydrochloric acid (6ml.) added. A pale green colour developed initially, but changed to pale orange after standing overnight at room temperature. The solution was extracted with chloroform. Evaporation gave a pale pink solid (225mg., 95%, assuming uncharged isoquinolone). A sample was crystallised from 6N hydrochloric acid as colourless needles, which were dried overnight at 70-75°, giving a pale yellow solid, subliming above 165°, with m.p. 216.5-221°, decomp.

Found:	C, 54.76; H, 4.80; N, 5.64
$C_{11}H_{11}O_4N.HCl$ requires:	C, 51.26; H, 4.66; N, 5.44
$C_{11}H_{11}O_4N$ requires:	C, 59.73; H, 4.98; N, 6.33
40% loss of HCl req'd:	C, 54.65; H, 4.79; N, 5.80%.

The N-hydroxyisoquinolone was obtained as a bright yellow solid, subliming above 190°, with m.p. 218-222.5°, decomp., by sublimation from the analytical sample of the hydrochloride at 140-200° and 0.1mm.

$\nu_{max.}$ (Nujol): 1655, 1635, 1580, 1550, 1525, 1510 cm^{-1}.

$\lambda_{max.}$ (EtOH) : 251 mμ (log ε 4.64), 305 mμ (log ε 3.69), 314 mμ (log ε 3.69), 390 mμ (log ε 3.48) ; (acid): 249, 306 infl., 315, 364 mμ ; (base): 252, 305, 316.5, 389 mμ.

τ values (CF_3CO_2H) : 0.96 (1H,s), 2.30 (1H,s), 2.55 (1H, s), 2.65 (1H,s), 5.80 (3H,s), 5.83 (3H,s).

Parent molecular ion at m/e 221.

Found: C, 59.48; H, 4.94

$C_{11}H_{11}O_4N$ requires: C, 59.73; H, 4.98%.

(b) N,N-Dimethyl-4,5-dimethoxy-2-formylphenylacetamide (880mg.) was dissolved in warm ethanol (30ml.). To this solution was added a solution of hydroxylamine hydrochloride (1.25g.) in 50% aqueous ethanol (40ml.). The mixture was warmed gently, allowed to stand at room temperature for four hours, and then extracted with chloroform. Evaporation of solvents gave the isoquinolone as a yellow solid (722mg., 93%), m.p. 210-220°, decomp., subliming rapidly to needles and turning bright yellow above 190°.

The isoquinolone formed a bright red nickel complex. It was also susceptible to aerial oxidation, the surface

of the material darkening fairly rapidly on exposure to the atmosphere.

2-Amino-6,7-methylenedioxy-3(2H)-isoquinolone.

The crude hydrazone, formed by reaction of N,N-dimethyl-2-formyl-4,5-methylenedioxyphenylacetamide (1.32g.) and excess ethanolic hydrazine hydrate in ten minutes, was heated on the steam-bath with 6N hydrochloric acid. Initially the solid turned a bright orange colour. The orange solid was heated with excess hydrochloric acid on the steam-bath for fifteen mins., during which time it gradually dissolved to give a pale green solution. This was cooled and basified with 4N sodium hydroxide. A bright yellow solid precipitated at this point. The solid and solution were extracted with chloroform. Evaporation of solvent gave the isoquinolone as a bright yellow solid (1.08g., 94%), m.p. 220-242°, decomp. Crystallisation from ethanol gave orange-yellow needles, m.p. 222-234°, decomp.

$\nu_{max.}$ (KCl) : 1659, 1614, 1541, 1454, 1252, 1162, 1037 cm^{-1}., ($CHBr_3$) : 1662, 1652, 1610, 1546 cm^{-1}.

$\lambda_{max.}$ (EtOH) : 250 mμ (log ε 4.81), 293 mμ, infl. (log ε 3.50), 307 mμ (log ε 3.71), 318.5 mμ (log ε 3.73), 400 mμ (log ε 3.71); (acid): 248, 307 infl., 318, 357, 367 mμ; (base): 250, 307, 318, 398 mμ.

τ values (DMSO) : 1.53 (1H,s), 2.99 (1H,s), 3.24 (1H,s),

3.52 (1H,s), 3.95 (2H,s); (CF_3CO_2H) : 1.04 (1H,s), 2.40 (1H,s), 2.67 (1H,s), 2.74 (1H,s), 3.67 (2H,s).

Found: C, 59.00; H, 3.98; N, 13.33

$C_{10}H_8O_3N_2$ requires: C, 58.82; H, 3.92; N, 13.73%.

The compound is only sparingly soluble and compares in most of its properties to 2-hydroxy-6,7-methylenedioxy-3(2H)-isoquinolone.

2-Amino-6,7-dimethoxy-3(2H)-isoquinolone.

Similarly, the crude hydrazone obtained from N,N-dimethyl-4,5-dimethoxy-2-formylphenylacetamide (1.43g.) was heated with 6N hydrochloric acid (50ml.) on the steam-bath for ca. 30 minutes. On cooling to 0° colourless needles (1.30g., 89%, assuming a monohydrochloride, 78% assuming a dihydrochloride) crystallised from the solution. Successive crystallisations from 6N hydrochloric acid afforded pale yellow needles, m.p. 197-207°, decomp. These were dried overnight at 55°. The hydrochloride was found to be hygroscopic.

$\nu_{max.}$ (Nujol) : 3400, 3200, 2540, 1880 (broad), 1640, 1625, 1575 cm^{-1}.

$\lambda_{max.}$ (EtOH) : 251.5 mμ (log ε 4.82), 308 mμ (log ε 3.84), 316 mμ (log ε 3.86), 371 mμ (log ε 3.44), 402 mμ (log ε 3.29); (acid) : 249, 317, 364 mμ; (base): 252, 307, 317, 395 mμ.

τ values: (DMSO): 0.97 (1H,s), 2.60 (2H,s), 2.72 (1H,s), 6.05 (3H,s), 6.13 (3H,s); (CF_3CO_2H): 0.84 (1H,s), 2.23 (1H,s), 2.48 (1H,s), 2.59 (1H,s), 5.75 (3H,s), 5.78 (3H,s).

Found: C, 47.93; H, 5.67; N, 10.15

$C_{11}H_{12}O_3N_2.HCl.H_2O$ requires: C, 48.08; H, 5.46; N, 10.20%.

The isoquinolone was obtained from its hydrochloride by basification (ammonium hydroxide) and extraction with chloroform. It was found to be very susceptible to aerial oxidation and readily decomposed. It did not crystallise from common organic solvents and could not be sublimed.

$\nu_{max.}$ (Nujol): 3300, 3220, 1670, 1650, 1540 cm^{-1}.

6,7-Methylenedioxy-3(2H)-isoquinolone.

N,N-Dimethyl-2-formyl-4,5-methylenedioxyphenylacetamide (1.45g.) was dissolved in warm ethanol (10ml.) and 0.88 ammonium hydroxide (70ml.) added. The mixture was allowed to stand overnight at room temperature. The precipitate was filtered and dried to give the isoquinolone as a bright yellow solid (1.13g., 97%). The optimum reaction time was ten hours: the yield after two hours was only 33%. The reaction was also carried out in the absence of ethanol, but the yield was unaltered. The bright yellow solid was sublimed at 180-185° and 0.05mm. as bright yellow prisms, m.p. 284-285°.

$\nu_{max.}$ (KCl): 1644, 1606, 1466, 1455, 1156, 1040 cm^{-1}.

$\lambda_{max.}$ (EtOH): 246.5 mμ (log ε 4.70), 288 mμ infl. (log ε 3.55), 301 mμ (log ε 3.53), 313 mμ (log ε 3.57), 354 mμ (log ε 3.35), 396 mμ (log ε 3.54); (acid): 243, 306, 314, 357, 368 mμ; (base): 247, 372 mμ.

τ values: (DMSO): 1.50 (1H,s), 2.78 (1H,s), 2.99 (1H,s), 3.29 (1H,s), 3.91 (2H,s); (CF_3CO_2H): 1.24 (1H,d, J=6c/s.), 2.47 (1H,s), 2.60 (1H,s), 2.72 (1H,s), 3.68 (2H,s).

Parent molecular ion at m/e 189.

Found: C, 63.80; H, 3.85; N, 7.61

$C_{10}H_7O_3N$ requires: C, 63.49; H, 3.70; N, 7.41%.

Evaporation of trifluoroacetic acid from the n.m.r. sample gave a colourless solid, m.p. 168-172°, but resolidifying as bright yellow prisms which decomposed slowly above 250° and rapidly above 270°.

The isoquinolone was found to be highly insoluble, especially in organic solvents. It formed a colourless hydrated hydrochloride (needles), which on drying at 50-60° turned pale yellow, with m.p. 270-272°.

τ values (DMSO): 0.65 (NH?), 1.17 (1H,s), 2.54 (1H,s), 2.68 (1H,s), 2.70 (1H,s), 3.75 (2H,s).

Found: (i) C, 54.28; H, 4.06; N, 6.41

(ii) C, 53.89; H, 4.20

$C_{10}H_7O_3N.HCl$ requires: C, 53.23; H, 3.55; N, 6.21%.

After drying at 60° for 72 hours the hydrochloride eliminated HCl completely and the lactam was recovered

as a bright yellow solid, m.p. 285°.

The isoquinolone formed a sodium salt on crystallisation from dilute sodium hydroxide. This crystallised as pale yellow plates, m.p. not less than 360°, and gave a yellow flame test.

$\nu_{max.}$ (Nujol): 1640 (weak), 1600 (strong) cm^{-1}.

Found, assuming residue to be sodium carbonate:

C, 53.26; H, 4.45; N, 6.86; Na, 10.38%

$C_{10}H_6O_3NNa.H_2O$ requires:

C, 52.41; H, 3.49; N, 6.11; Na, 10.04%.

A sample was reconverted to the hydrochloride by crystallisation from 6N hydrochloric acid as colourless needles, having an i.r. spectrum identical to that of the material described previously. The sodium salt is only sparingly soluble in water. The isoquinolone also formed lithium and potassium salts in similar manner, the latter being much more soluble.

The isoquinolone was recovered unchanged after standing for three days at room temperature with excess diazomethane in ether. As with the N-methyl compound it gave bright red colours with ferric chloride and with nitrous acid at 0°, and decolourised cold aqueous permanganate. Attempted hydrolysis with 10% sodium hydroxide or concentrated sulphuric acid yielded only the corresponding salts.

6,7-Dimethoxy-3(2H)-isoquinolone.

N,N-Dimethyl-4,5-dimethoxy-2-formylphenylacetamide 6,7-Dimethoxy-3(2H)-isoquinolone. (1.53g.) was dissolved in warm ethanol (30ml.) and 0.88 ammonium hydroxide (50ml.) added. The mixture was allowed to stand overnight at room temperature and was then repeatedly extracted with cold chloroform. Evaporation of solvent gave a pale yellow fluorescent solid (1.21g. 97%), m.p. 235-245°, decomp. A sample was sublimed at 175-180° and 0.02mm. as bright yellow prisms, m.p. 236-245°, decomp.

$\nu_{max.}$ (KCl): 1656, 1638, 1614, 1580, 1560 cm^{-1}; ($CHBr_3$): 1650, 1635 cm^{-1}; ($CHCl_3$): 1653, 1637 cm^{-1}.

$\lambda_{max.}$ (EtOH): 252 mμ (log ε 4.66), 287 mμ infl. (log ε 3.46), 301 mμ (log ε 3.46), 314 mμ (log ε 3.46), 398 mμ (log ε 3.57); (acid): 249 mμ (log ε 4.52), 306 mμ (log ε 3.49), 313 mμ (log ε 3.54), 364 mμ (log ε 3.62); (base): 250, 277 infl., 372 mμ.

τ values: ($CDCl_3$): 1.75 (1H,s), 3.14 (1H,s), 3.24 (1H,s), 3.27 (1H,s), 6.01 (3H,s), 6.05 (3H,s); (DMSO): 1.43 (1H,s), 2.75 (1H,s), 2.96 (1H,s), 3.25 (1H,s), 6.10 (3H,s), 6.14 (3H,s); (CF_3CO_2H): 1.08 (1H,d, J=6c/s.), 2.37 (1H,s), 2.41 (1H,s), 2.59 (1H,s), 5.72 (3H,s), 5.76 (3H,s).

Parent molecular ion at m/e 205.

Molecular weight (isothermal distillation): 362, 377,

373, 368, 385, 401. (Calc., 205).

Found: C, 64.65; H, 5.68; N, 7.05

$C_{11}H_{11}O_3N$ requires: C, 64.39; H, 5.37; N, 6.83%.

Since the isoquinolone is susceptible to oxidation, chloroform solutions gradually turning red, it was necessary in its preparation to limit the reaction time to about ten hours.

Like the corresponding methylenedioxy compound the isoquinolone formed a hydrochloride and a sodium salt ($\nu_{max.}$ 1600 cm^{-1}). The material recovered from the n.m.r. sample by evaporation of trifluoroacetic acid was a colourless solid, m.p. 185°, decomp., subliming to needles, m.p. 212-218°, decomp.

$\nu_{max.}$ (Nujol): 2700, 2050, 1690, 1640, 1200, 1180, 1160, 1140 cm^{-1}.

The isoquinolone gave no reaction with diazomethane. Attempted reduction with lithium aluminium hydride in refluxing tetrahydrofuran gave only tars, as did reaction with refluxing phosphorous oxychloride. Overnight reduction with lithium aluminium hydride at room temperature gave a pink gum which formed a semi-solid hydrochloride. The latter rapidly decomposed to a tar.

3-Acetoxy-6,7-methylenedioxyisoquinoline.

6,7-Methylenedioxy-3(2H)-isoquinolone was refluxed

for four hours with excess acetic anhydride. The initial bright yellow colour rapidly faded to give an almost colourless solution. Evaporation under reduced pressure gave a quantitative yield of pale brown needles, m.p. 133-135°. Crystallisation from ethyl acetate-petroleum ether (charcoal) gave the acetate as colourless leaflets, m.p. 134-136°.

$\nu_{max.}$ (KCl): 1758 sh., 1746, 1601, 1238, 1208, 1143, 1032 cm^{-1}; ($CHCl_3$): 1767, 1752 sh., 1602 cm^{-1}.

$\lambda_{max.}$ 235 mμ (log ε 4.46), 265 mμ (log ε 3.66), 278 mμ (log ε 3.65), 287 mμ infl. (log ε 3.62), 317 mμ (log ε 3.51), 329 mμ (log ε 3.53).

On standing at room temperature the solution gradually exhibited a return to the chromophore of the parent isoquinolone and the characteristic blue fluorescence of the latter. e.g. after 2½ hours: 235 mμ (log ε 4.52), 392 mμ (log ε 2.98); after 8½ hours: 392 mμ (log ε 3.28); after 22 hours: 392 mμ (log ε 3.40).

τ values ($CDCl_3$): 1.26 (1H,s), 2.78 (1H,s), 2.87 (1H,s), 3.01 (log ε 1H,s), 3.96 (2H,s), 7.66 (3H,s).

Highest molecular ion at m/e 189.

Molecular weight (isothermal distillation): 249. (calc., 231).

Found: C, 62.59; H, 3.94; N, 6.05

$C_{12}H_9O_4N$ requires: C, 62.34; H, 3.92; N, 6.06%.

The acetate was hydrolysed only slowly on shaking at room temperature with water or dilute aqueous base, but was converted rapidly to the isoquinolone hydrochloride on treatment with dilute hydrochloric acid. The formation of the acetate was shown by t.l.c. to occur on treatment of the isoquinolone sodium salt with acetyl chloride.

3-Acetoxy-6,7-dimethoxyisoquinoline.

6,7-Dimethoxy-3(2H)-isoquinolone reacted with hot acetic anhydride to give the corresponding acetate as a light brown solid, Crystallisation from petroleum ether gave an almost colourless crystalline solid, m.p. 96-98.5°.

$\nu_{max.}$ (Nujol): 1760 cm^{-1}.

$\lambda_{max.}$: 239 mμ (log ε 4.64), 268 mμ (log ε 3.67), 280 mμ (log ε 3.62), 291 mμ (log ε 3.57), 315 mμ (log ε 3.45), 327 mμ (log ε 3.46). After standing at room temperature for 24 hours the maxima were positioned at 243, 313, 328, and 392 mμ.

τ values ($CDCl_3$): 1.15 (1H,s), 2.72 (1H,s), 2.83 (1H, s), 2.98 (1H,s), 6.02 (6H,s), 7.65 (3H,s).

The acetate was hydrolysed by 10% potassium hydroxide at 100° for 1 hour, the potassium salt crystallising from the cooled reaction mixture, the isoquinolone being recovered by acidification,

rebasification (NH_4OH) and extraction ($CHCl_3$).

Methylation of 6,7-methylenedioxy-3(2H)-isoquinolone.

The isoquinolone sodium salt (350mg.) was refluxed vigorously with redistilled methyl iodide (35ml.) for five hours. The solution was then evaporated to dryness, yielding a dry yellow powder. The residue was thoroughly extracted with hot chloroform. Evaporation of solvent gave a bright yellow powdery solid (240mg., 77%). A sample of the product was sublimed at 165° and 0.07mm. as a bright yellow solid, with an infrared spectrum (in Nujol) identical to that of N-methyl-6,7-methylenedioxy-3(2H)-isoquinolone. A mixed m.p. with a sample of the latter prepared from the methyl imine gave m.p. 242-250°, both subliming as bright yellow prisms. Further proof of their identity was provided by t.l.c. (10% methanol/chloroform). The ultraviolet absorptions of the alkylation product in neutral and basic media were superposable (250, 291, 306.5, 318, and 400 mμ). The intense fluorescence and increased solubility in chloroform of the product were also characteristic of the N-methyl derivative.

Reaction of N,N-dimethyl-4,5-dimethoxy-2-formylphenylacetamide and N,N-dimethyl-2-formyl-4,5-methylenedioxyphenylacetamide with ammonia.

A mixture of the above two aldehydes (600mg. of each) was dissolved in warm ethanol (15ml.) and the solution treated with excess (35ml.) ammonium hydroxide (s.g.0.88). On standing overnight 6,7-methylenedioxy-3(2H)-isoquinolone (290mg., 60%) was precipitated and identified by t.l.c., i.r., and m.p. Chloroform extraction of the filtrate gave predominantly 6,7-dimethoxy-3(2H)-isoquinolone (330mg., 67%), identified by t.l.c. and i.r. In neither fraction was it possible to detect (t.l.c.) a third product.

Irradiation of 2-methyl-6,7-methylenedioxy-3(2H)-isoquinolone.

(a) A solution of the isoquinolone (230mg.) in ethanol (75ml.) was irradiated for 48 hours using a Hanovia mercury vapour lamp as source of ultraviolet radiation. The solution was concentrated and the insoluble colourless crystalline solid (47mg.) filtered. Evaporation of the filtrate yielded only intractable gummy material. The solid product was only very sparingly soluble in ethanol (it precipitated from the refluxing reaction solution). It had no true m.p. below 335°, but slowly decomposed at high temperature.

$\nu_{max.}$ (Nujol): 1660 cm^{-1}.

$\lambda_{max.}$: 211, 251 infl., 297 mμ, no shift in acid.

τ values (CF_3CO_2H): 3.00 (2H,s), 3.90 (2H,s), 4.90-5.00 (2H, broad), 7.17 (3H,s).

The material recovered by evaporation of the trifluoro-

acetic acid from the n.m.r. sample showed strong i.r. absorptions at 1890, 1770, 1590, 1220, and 1160 cm^{-1}.

(b) A solution of the isoquinolone hydrate (80mg.) in ethanol (20ml.) was allowed to stand for three days in a position subjected to reasonably strong sunlight. The precipitated colourless solid was filtered and shown to have the same infrared spectrum as the product isolated above (a).

1,4-Dihydro-2-methyl-6,7-methylenedioxy-3(2H)-isoquinolone.

2-Methyl-6,7-methylenedioxy-3(2H)-isoquinolone (3.01g.) was dissolved in 25% aqueous ethanol (150ml.) and hydrogenated over Adams' catalyst (400mg.) for four hours. The catalyst was removed by filtration through glass paper. Evaporation of solvent from the filtrate then yielded a pale yellow gum which gradually crystallised as a pale cream-coloured solid (3.25g.). Repeated crystallisation from water gave the dihydro derivative as very pale green, almost colourless needles, subliming above 115°, with m.p. 136-137°.

$\nu_{max.}$ (KCl): 1650, 1500, 1480, 1313, 1238, 1228, 1029 cm^{-1}.

$\nu_{max.}$ ($CHCl_3$): 1646.5 cm^{-1}.

$\lambda_{max.}$: 210 mμ (log ε 3.93), 236 mμ (log ε 3.32), 291 mμ (log ε 3.56).

τ values ($CDCl_3$): 3.35 (2H,s), 4.03 (2H,s), 5.58 (2H,t, J=1.8c/s.), 6.47 (2H,t, J=1.8c/s.), 6.90 (3H,s).

Found: C, 64.68; H, 5.38; N, 6.90

$C_{11}H_{11}O_3N$ requires: C, 64.39; H, 5.37; N, 6.83%.

The hydrogenation was carried out less efficiently using 10% palladium on charcoal as catalyst and aqueous acetic acid as solvent. Any great increase in the ratio of water to ethanol caused precipitation, and only partial reduction was effected.

2-Amino-1,4-dihydro-6,7-methylenedioxy-3(2H)-isoquinolone.

2-Amino-6,7-methylenedioxy-3(2H)-isoquinolone (500mg.) in aqueous ethanol (90ml.) was hydrogenated over Adams' catalyst (60mg.) for three hours. The solution was filtered through celite and the almost colourless aqueous alcoholic solution concentrated to low volume (10ml.), when an almost colourless solid crystallised out (335mg.) Evaporation of the remaining solvent gave a sticky pink solid (130mg.). The crude product sublimed ca. 140°, with m.p. 162-182°, decomp. A sample was sublimed at 160-175° and 0.02mm. as a pale green crystalline solid, subliming with some decomposition to needles above 165°, with m.p. 182-186°, decomp., with some softening from 178°.

$\nu_{max.}$ (KCl): 3326, 3208, 1644, 1623, 1616 sh., 1506, 1489, 1332, 1230, 1036 cm^{-1}; ($CHCl_3$): 1644.5, 1615 cm^{-1}.

$\lambda_{max.}$: 242 mμ infl. (log ε 3.61), 292.5 mμ (log ε 3.60).

Found: C, 58.35; H, 4.67; N, 13.40

$C_{10}H_{10}O_3N_2$ requires: C, 58.25; H, 4.85; N, 13.59%.

1,4-Dihydro-6,7-dimethoxy-2-hydroxy-3(2H)-isoquinolone.

6,7-Dimethoxy-2-hydroxy-3(2H)-isoquinolone (600mg.) was dissolved in 50% aqueous ethanol (100ml.) and hydrogenated over Adams' catalyst (75mg.) for 2½ hours. The solution was filtered free of catalyst (celite) and the solvents evaporated to give the crude dihydro derivative as a light brown solid (520mg., 86%), m.p. 175-190°, decomp. A sample was sublimed at 140-170° and 0.05mm. and then crystallised from ethanol as very pale green needles, softening at 181°, with m.p. 185-197°, decomp.

$\nu_{max.}$ (KCl): 3125 (broad), 1650 sh., 1635, 1615, 1523, 1374, 1330, 1263, 1249, 1231, 1226, 1115, 1111 cm^{-1}.

$\nu_{max.}$ ($CHCl_3$): 3310 (broad), 1633 cm^{-1}.

$\lambda_{max.}$: 221.5 mμ (log ε 4.17), 284 mμ (log ε 3.87), no shift in acid.

Found: C, 59.12; H, 5.70; N, 6.30

$C_{11}H_{13}O_4N$ requires: C, 59.20; H, 5.83; N, 6.28%.

Hydrogenations using aqueous acetic acid as solvent did not proceed smoothly and gave rise to amorphous products of very wide melting range. Filtration through celite appeared to cause partial decomposition of the material.

1,4-Dihydro-6,7-dimethoxy-3(2H)-isoquinolone.

6,7-Dimethoxy-3(2H)-isoquinolone (2.07g.) was dissolved

in 15% aqueous ethanol (120ml.) and hydrogenated over Adams' catalyst (200mg.) for 5½ hours. Filtration (glass paper), concentration, and extraction with chloroform, gave the dihydroisoquinolone as an almost colourless solid (1.98g., 95%). Use of 10% palladium on charcoal as catalyst or aqueous acetic acid as solvent resulted in only partial reduction. The progress of reaction could be followed by the disappearance of the characteristic fluorescence of the starting material. Crystallisation of the crude product from ethanol gave yellow-green leaflets, subliming to prisms above 180°, with m.p.201-203°, decomp. Purification of a sample by p.l.c., followed by sublimation at 180-195° and 0.2mm. gave a pale green crystalline solid, subliming above 170°, with m.p.201-204°, decomp.

$\nu_{max.}$ (KCl): 3190, 1688, 1658, 1610, 1519, 1249 cm^{-1}.

$\nu_{max.}$ ($CHCl_3$): 3402, 3205, 1672.5, 1658, 1612.5, 1517.5 cm^{-1}.

$\lambda_{max.}$: 230 mμ (log ε 3.38), 285 mμ (log ε 3.56), no acid or base shift.

τ values ($CDCl_3$): 2.33 (1H, broad), 3.30 (2H,s), 5.50 (2H,q, J_1 = 5c/s, J_2 = 1.8c/s.), 6.11 (6H,s), 6.45 (2H, t, J_2 = 1.8c/s.).

Parent molecular ion at 207 m/e.

Molecular weight (isothermal distillation): 237, 212, 207, 225. (Calc. 207).

Found: C, 63.69; H, 6.01; N, 6.80

$C_{11}H_{13}O_3N$ requires: C, 63.77; H, 6.28; N, 6.76%.

Attempts to prepare this compound by chloromethylation of 3,4-dimethoxyphenylacetamide resulted only in formation of 4,5-dimethoxy-2-hydroxymethylphenylacetic acid lactone.

1,4-Dihydro-6,7-dimethoxy-3(2H)-isoquinolone was recovered unchanged after refluxing for six hours with excess 33% alcoholic dimethylamine.

2-Acetyl-1,4-dihydro-6,7-dimethoxy-3(2H)-isoquinolone.

1,4-Dihydro-6,7-dimethoxy-3(2H)-isoquinolone (100mg.) was heated on the steam-bath with acetic anhydride (5ml.) for two hours. The material dissolved almost at once to give a colourless solution. A pale yellow colour developed as heating was continued. The excess reagent was destroyed by methanol. Evaporation gave a yellow crystalline solid (117mg.) which crystallised from ethanol (charcoal) in colourless prisms, subliming to needles above 125°, with m.p. 137-139°.

$\nu_{max.}$: (KCl) : 1697 (broad), 1613, 1522, 1232, 1001 cm^{-1}.

$\nu_{max.}$ ($CHCl_3$): 1712, 1703, 1614 cm^{-1}.

$\lambda_{max.}$: 236 mμ (log ε 3.59), 286 mμ (log ε 3.57).

τ values ($CDCl_3$): 3.14 (1H,s), 3.23 (1H,s), 5.10 (2H,s), 6.11 (6H,s), 6.30 (2H,s), 7.41 (3H,s).

Found: C, 62.79; H, 6.07; N, 5.33

$C_{13}H_{15}O_4N$ requires: C, 62.65; H, 6.02; N, 5.62%.

The acetate was not readily hydrolysed by warm water, but was rapidly hydrolysed to the parent lactam by dilute sodium hydroxide.

2-Methyl-6,7-methylenedioxyisoquinoline-1,3,4-trione.

(a) By oxidation of N-methyl-2-hydroxymethyl-4,5-methylenedioxyphenylacetamide.

(1) The alcohol (180mg.) was dissolved in slightly aqueous acetone (20ml.) and the solution shaken for 48 hours with manganese dioxide (2g.). Filtration and evaporation gave a bright yellow solid, which sublimed above 190° to needles, m.p. 216-220°. A sample was sublimed at 160-180° and 0.03mm. as a bright yellow solid, m.p. 225-226.5°.

$\nu_{max.}$ (KCl): 1725.5, 1692, 1675, 1627, 1614, 1593, 1502, 1424, 1351, 1332, 1323, 1073, 1023 cm^{-1}., ($CHCl_3$): 1730 (w), 1701 (m), 1681 (s), 1616, 1605, 1596 cm^{-1}.

$\lambda_{max.}$: 227 mμ infl. (log ε 3.84), 267 mμ (log ε 4.40), 337 mμ infl. (log ε 3.21), 374 mμ (log ε 3.37)., no shift in acid.

τ values ($CDCl_3$): 2.30 (1H,s), 2.44 (1H,s), 3.76 (2H,s), 6.55 (3H,s); (CF_3CO_2H): 2.15 (1H,s), 2.30 (1H,s), 3.70 (2H,s), 6.41 (3H,s).

Parent molecular ion at 233m/e.

Found: C, 56.87; H, 3.28; N, 6.13

$C_{11}H_7O_5N$ requires: C, 56.65; H, 3.00; N, 6.01%.

A solution of the trione in methanol was mixed with a methanolic solution of 2,4-dinitrophenylhydrazine. On warming the mixture a very bright orange precipitate formed. This had no true m.p. below 350°, but slowly decomposed above 330°. It failed to crystallise from the common organic solvents.

$\lambda_{max.}$ (dioxane): 224 mμ (log ε 4.24), 254 mμ (log ε 4.20), 285 mμ infl. (log ε 4.05), 330 mμ (log ε 3.84), 384 mμ infl. (log ε 3.46), 442mμ (log ε 4.25).

(ii) The alcohol (1.19g.) was dissolved in pyridine (40ml.) and the solution shaken for 30 hours with manganese dioxide (12g.). The reaction mixture was filtered through celite and the residues washed well with hot chloroform. The organic solution was extracted with 6N hydrochloric acid, then washed with water and dried. Evaporation gave a bright yellow solid (750mg.), with m.p. 125-190°. Treatment of an ethanolic solution of this material with dilute ammonium hydroxide or dilute sodium hydroxide at room temperature for several hours, followed by dilution with water and chloroform extraction gave relatively pure 2-methyl-6,7-methylenedioxy-3 (2H)-isoquinolone (180mg.), identified by t.l.c. and

conversion to the hydrochloride. T.L.C. indicated that the main oxidation product was the same as that in reaction (i) above, and also showed that the N-methyl 3-isoquinolone was present in both crude products.

A repeat reaction was followed by means of t.l.c., aliquots being withdrawn at regular intervals.
% alcohol gradually decreased: none left after 18 hours.
% isoquinolone gradually increased: present after 1 hour.
% trione gradually increased: only in the later stages of the reaction, being present in appreciable amount only after 6 hours.

(b) By oxidation of 2-methyl-6,7-methylenedioxy-3(2H)-isoquinolone.

(i) The isoquinolone (50mg.) was dissolved in chloroform (10ml.) and shaken with manganese dioxide (1g.) for six hours. The normal work-up gave a yellow solid which was submitted to p.l.c. (10% methanol-chloroform). Extraction of the least polar fraction (visible yellow colour) gave a bright yellow solid (20mg., 35%), subliming to needles above 180°, with m.p. 222-224°, and shown to be identical to the isoquinoline trione isolated in (a) above by i.r. and t.l.c. T.L.C. confirmed the presence of a trace of the trione after only fifteen seconds. The characteristic fluorescence of the isoquinolone was almost completely quenched after three minutes.

2-Pyridone and N-methyl 1-isoquinolone were unaffected by manganese dioxide under similar conditions.

(ii) The effect on the isoquinolone of air and of light with or without the addition of manganese dioxide was studied by placing samples (1-2mg.) dissolved in chloroform (0.5ml.) in a series of ignition tubes and allowing to stand at room temperature for 72 hours under the conditions indicated in the table below.

Conditions			Reaction products (t.l.c.)	
AIR	LIGHT	MnO_2	Isoquinolone	Trione
-	-	-	main component	none
-	+	-	main component	small amount
+	-	-	main component	trace
+	+	-	none	main component
+	-	+	approx. 50%	approx. 50%
+	+	+	none	approx. 100%

These results show that the oxidation process occurred to the greatest extent in the presence of manganese dioxide, was catalysed to a considerable extent by light, but was retarded in the absence of oxygen.

(c) By oxidation of 1,4-dihydro-2-methyl-6,7-methylenedioxy-3(2H)-isoquinolone.

Oxidation of the dihydroisoquinolone (230mg.) by shaking a solution in chloroform (20ml.) with manganese

dioxide (2g.) for 13 hours gave, after p.l.c. (10% methanol-chloroform), 6,7-methylenedioxyisoquinoline-1,3,4-trione (31mg., 12%), together with a fraction (123mg.) comprising mainly starting material, but containing about 10% trione. Small amounts of the parent isoquinolone were also present.

The trione was also formed by aerial oxidation of the dihydroisoquinolone in chloroform solution or in the solid state.

6,7-Dimethoxyisoquinoline-1,3,4-trione.[48]

6,7-Dimethoxy-3(2H)-isoquinolone (260mg.), crystallised from water as bright yellow needles, was dissolved in chloroform (40ml.) and shaken with manganese dioxide at room temperature for 7½ hours. Filtration and evaporation gave a dark green gummy residue. Preparative t.l.c. (10% methanol-chloroform) showed the presence of at least 22 components, but allowed the isolation of a discrete yellow band with R_f ca. 0.8. This yielded a bright yellow solid (19mg., 6.4%), m.p. 250-258°, decomp. Attempted purification by sublimation at 220° and 0.02mm. gave a yellow solid, m.p. 228-249°, decomp. The compound was purified by p.l.c. and was obtained as a bright yellow solid, subliming to needles above 190°, with m.p. 267-70°, decomp. This is in accord with the reported m.p. (subliming to needles ca. 200°, with m.p. 269-275°,dec.),

$\nu_{max.}$ (Nujol): 3250, 3100, 1720, 1700, 1685, 1575, 1520 cm^{-1}.

$\lambda_{max.}$: 207 infl., 233, 264, 337, 370 mμ, no change on acidification.

τ values (CF_3CO_2H): 2.00 (1H,s), 2.07 (1H,s), 5.76 (3H,s), 5.79 (3H,s).

Reaction of sodium hypochlorite with 1,4-dihydro-6,7-dimethoxy-3(2H)-isoquinolone.

The dihydroisoquinolone (80mg.) was treated with freshly-prepared 1N sodium hypochlorite (5ml.). After shaking at room temperature for 20 hours the mixture was heated on the steam-bath for 25 minutes. Light green plates (54mg.) crystallised on cooling. These had i.r. absorptions at 3350 (broad), 1640 (weak), and 1600 cm^{-1} (strong), and left a heavy deposit on burning (yellow flame). On acidification with dilute hydrochloric acid a pale yellow solid was obtained. This had i.r. maxima at 3550, 3400, 2700 (broad), 2100, and 1640 cm^{-1}, and turned bright yellow on heating above 180°, subliming to prisms, m.p. 292-295°, decomp. On basification with ammonium hydroxide, followed by chloroform extraction and evaporation, a bright yellow solid was obtained, m.p. ca. 300° (subliming completely at 295°). $\nu_{max.}$ (Nujol): 1640 cm^{-1}. An ethanolic solution exhibited a strong blue-green fluorescence.

$\lambda_{max.}$ (EtOH): 255, 293, 308, 322, 257 infl., 414 mμ; (acid): 253, 310 infl., 321, 373 mμ; (base): 252, 283, 294 infl., 383 mμ.

1,4-Dihydro-2-methyl-6,7-methylenedioxy-3(2H)-isoquinolone.

(a) From 2-methyl-6,7-methylenedioxyisoquinoline-1,3,4-trione.

The trione (30mg.) was suspended in 6N hydrochloric acid (15ml.) and zinc powder (300mg.) added. The mixture was heated on the steam-bath until colourless (ca. 10 minutes) and was then allowed to stand at room temperature for a further 90 minutes. The acid solution was filtered and basified with ammonoum hydroxide. Chloroform extraction of the basic solution afforded a gum which solidified to give a cream-coloured solid (25mg.). This was shown by t.l.c. to be a mixture of two compounds, the major product being the dihydroisoquinolone, previously prepared by catalytic reduction of 2-methyl-6,7-methylenedioxy-3(2H)-isoquinolone. The second, minor component was the isoquinolone itself. No trione survived this treatment. A sample of the dihydroisoquinolone (15mg.,57%) (characterised by i.r., u.v., and t.l.c.) was isolated by p.l.c. (10% methanol-chloroform) as a colourless solid, m.p. 131-135°.

(b) From 2-methyl-6,7-methylenedioxy-3(2H)-isoquinolone.

(i) The isoquinolone (100mg.) was suspended in 6N hydrochloric acid (20ml.) and the mixture heated on the steam-bath with zinc powder (1g.) for one hour, eventually yielding a colourless solution. The solution was cooled, filtered from residual metal, and the filtrate basified with ammonium hydroxide . Chloroform extraction of the basic solution yielded a yellow-green gum (90mg.) which solidified. Preparative t.l.c. of the solid material afforded a non-fluorescent non-polar fraction which yielded the dihydroisoquinolone as a cream-coloured solid (67mg., 66%), subliming to needles above 110°, with m.p. 134-136°, characterised by i.r., u.v., and t.l.c.

(ii) A solution of the isoquinolone (100mg.) in methanol (15ml.) was treated with sodium borohydride (250mg.) at room temperature for 30 minutes, then warmed for 15 minutes. The mixture was poured into water and extracted with chloroform to afford a bright yellow solid (96mg.), shown by t.l.c. to be ca. 20% dihydroisoquinolone.

This yellow solid was redissolved in methanol (15ml.) and the solution refluxed with sodium borohydride (300mg.) for 30 minutes, until almost colourless. The work-up as above, followed by p.l.c. (10% methanol/chloroform) gave the dihydroisoquinolone as

a colourless solid (60mg., 59%), identified by m.p. (133-137°), i.r., and n.m.r.

2-Methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline. (Hydrohydrastinine).

(a) From 1,4-dihydro-6,7-methylenedioxy-3(2H)-isoquinolone.

A solution of the lactam (550mg.) in sodium-dried tetrahydrofuran (60ml.) was added to a stirred suspension of lithium aluminium hydride (1.5g.) in anhydrous ether (100ml.). The mixture was refluxed under nitrogen for 15 hours, cooled, dry tetrahydrofuran (90ml.) added, and reflux then continued for a further 4 hours. After cooling, the excess reagent was destroyed by the cautious addition of ethyl acetate and the complex decomposed with water. The organic layer was decanted and dried. Evaporation gave a pale yellow oil (501mg.), which had no carbonyl and no strong NH or OH absorptions and was shown by t.l.c. to contain one major component and no starting material. The product was isolated by p.l.c. (10% methanol/chloroform) as colourless needles (425mg., 83%), m.p. 57-61°. It was shown to be identical to a sample of hydrohydrastinine prepared in (b) below, by means of t.l.c., i.r., m.p., and identity of the

i.r. spectra of the colourless hydrochlorides prepared from each.

τ values ($CDCl_3$) of the base: 3.43 (1H,s), 3.52 (1H, s), 4.14 (2H,s), 6.54 (2H,s), 7.26 (2H,t), 7.31 (2H,t), 7.59 (3H,s).

(b) From 3,4-dihydro-2-methyl-6,7-methylenedioxy-1(2H)-isoquinolone. (Oxyhydrastinine).

A solution of oxyhydrastinine (340mg.) in dry tetrahydrofuran (25ml.) was added to a suspension of lithium aluminium hydride (1g.) in dry ether (50ml.) and the mixture refluxed under nitrogen for 18 hours. The work up as in (a) above gave hydrohydrastinine as a pale yellow oil (315mg.). Preparative t.l.c. afforded colourless needles (270mg., 85%), m.p. 56-60° (lit. 60-61°).

(c) From 2-methyl-6,7-methylenedioxy-3(2H)-isoquinolone.

To a suspension of lithium aluminium hydride (1g.) in anhydrous ether (100ml.) was added a solution of the isoquinolone (150mg.) in sodium-dried tetrahydrofuran (60ml.). The mixture was stirred under nitrogen at room temperature for 12 hours. Work-up as in (a) above gave a yellow oil (115mg.), with i.r. very similar to that of hydrohydrastinine, except for a weak carbonyl absorption ($\nu_{max.}$ 1660cm^{-1}) in the amide

region. Hydrohydrastinine (89mg., 63%) was isolated by p.l.c. and its identity confirmed by t.l.c. and by conversion to the hydrochloride (i.r.). A small amount (8mg.) of 1,4-dihydro-2-methyl-6,7-methylenedioxy-3(2H)-isoquinolone was also isolated by p.l.c.

Preparation of the hydrazone of N,N-dimethyl-2-formyl-4,5-methylenedioxyphenylacetamide.

The aldehyde (360mg.) was dissolved in warm ethanol (15ml.) and 100% hydrazine hydrate (5ml.) added. The mixture was allowed to stand at room temperature for one hour and water (15ml.) added. The mixture was extracted with chloroform until the aqueous layer gave no colouration with dilute hydrochloric acid. On evaporation the hydrazone was obtained as an almost colourless solid, which crystallised from ethanol at low temperature as pale yellow needles (303mg., 79%), m.p. 143.5-145°, resolidifying as yellow-orange needles, m.p. 254-259°, decomp. The hydrazone is easily soluble in cold chloroform and in warm ethanol.

$\nu_{max.}$ (Nujol): 3470, 3260, 1655 sh., 1630, 1580 cm^{-1}.

$\lambda_{max.}$ (EtOH): 217 mμ (log ε 4.37), 284 mμ (log ε 4.15), 314 mμ (log ε 3.98); (acid): 206 mμ (log ε 4.32), 239 mμ (log ε 4.24), 284 mμ (log ε 3.78), 316 mμ (log ε 3.94), 354 mμ (log ε 3.87); (base): 213, 237 infl., 284, 317 mμ.

τ values ($CDCl_3$): 2.04 (1H,s), 2.74 (1H,s), 3.31 (1H,s), 4.02 (2H,s), 4.50 (2H, broad), 6.20 (2H,s), 6.97 (3H,s), 7.00 (3H,s).

Preparation of the azine of N,N-dimethyl-2-formyl-4,5-methylenedioxyphenylacetamide.

(a) The above hydrazone was rapidly and quantitatively converted to the azine on repeated crystallisation from hot ethanol or on p.l.c., the product being obtained as a pale yellow solid, m.p. 252-258°, decomp., only sparingly soluble in chloroform and ethanol. Crystallisation from chloroform-petroleum ether (b.p. 40-60°) gave bright yellow prisms, m.p. 249-253°, dec. $\nu_{max.}$ (Nujol): 1630, 1595 cm^{-1}., no strong absorption between 3500 and 3000cm^{-1}.

$\lambda_{max.}$ (EtOH): 206 mμ (log ε 4.51), 220 mμ infl. (log ε 4.41), 246 mμ (log ε 4.48), 307 mμ infl. (log ε 4.05), 352 mμ (log ε 4.41); (acid): 206 mμ (log ε 4.53), 237 mμ (log ε 4.56), 283 mμ (log ε 4.00), 318 mμ (log ε 4.13), 353 mμ (log ε 4.04), 414 mμ (log ε 3.62); (base): 211, 237, 248 infl., 283, 318 mμ.

τ values ($CDCl_3$): 1.28 (2H,s), 2.50 (2H,s), 3.25 (2H,s), 4.00 (4H,s), 6.08 (4H,s), 6.93 (6H,s), 7.00 (6H,s).

Found: C, 61.49; H, 5.81; N, 12.15

$C_{24}H_{26}O_6N_4$ requires : C, 61.79; H, 5.62; N, 12.01%.

Attempted purification of the azine by sublimation

gave a small amoint of a bright yellow solid with i.r. maxima at 2700, 2240 (CN), 1645, and 1610 cm^{-1}. This was not investigated further.

(b) A solution of N,N-dimethyl-2-formyl-4,5-methylene-dioxyphenylacetamide (235mg.) in ethanol (15ml.) was treated with an alcoholic solution of sodium acetate trihydrate (136mg.) and hydrazine dihydrochloride (55mg) which had been filtered free of sodium chloride, and the mixture refluxed for 10 minutes. On cooling the azine separated as a yellow crystalline solid (163mg., 70%), m.p. 252-257°, decomp., shown to be identical to the material prepared in (a) above by i.r. and u.v.

Action of 6N-hydrochloric acid on the azine (63).

The azine (52mg.) was heated on the steam-bath with 6N hydrochloric acid (10ml.). The initial bright orange solid gradually dissolved (2-3 mins.) to give an orange solution which turned pale yellow. No material separated on cooling to 0°. The acid solution was thoroughly extracted with chloroform to give a bright yellow gummy solid (23mg.). A colourless solid (19mg., 72%), m.p. 128-131.5°, was isolated by p.l.c. (10% methanol/chloroform) and shown to be identical to N,N-dimethyl-2-formyl-4,5-methylenedioxyphenylacetamide by i.r., u.v., and t.l.c. The aqueous layer was basified

with 0.88 ammonium hydroxide and extracted with chloroform. The product was in this case a yellow solid (21mg., 92%), shown to be 2-amino-6,7-methylenedioxy-3(2H)-isoquinolone by i.r., u.v., and t.l.c.

1,4-Dihydro-6,7-methylenedioxy-3(2H)-isoquinolone.

(a) N,N-Dimethyl-2-formyl-4,5-methylenedioxyphenylacetamide (400mg.) was dissolved in warm acetic anhydride (20ml.) and the solution heated on the steam-bath for 15 minutes. Evaporation of the anhydride under reduced pressure gave sticky yellow crystals, which were washed with petroleum ether to give a pale brown solid (400mg.). T.L.C. of the solid indicated two components.

$\nu_{max.}$ (Nujol): 2240 (CN), 1750 (C=O ester), 1645 cm^{-1} (C=O amide).

The above solid (390mg.) was dissolved in ethanol (70ml.) and hydrogenated over Adams' catalyst (90mg.) for $3\frac{1}{2}$ hours. The catalyst was removed by filtration through celite, the solution concentrated to low volume, and water added. The aqueous solution was extracted with chloroform to yield a sticky red-brown solid. Slow evaporation at room temperature of a chloroform solution of the crude product yielded mainly tars and also a pale yellow crystalline solid (70mg.). Repeated crystallisation from ethanol gave very pale green

needles, softening at 217°, with m.p. 218.5-224°, decomp.

$\nu_{max.}$ (KCl): 3320 (w), 3196 (s), 3050 (s), 1682 sh., 1663, 1502 cm^{-1}.

$\nu_{max.}$ ($CHCl_3$): 3424, 1685 sh., 1673.5 cm^{-1}.

$\lambda_{max.}$: 210 mμ (log ε 3.92), 235 mμ infl. (log ε 3.49), 291 mμ (log ε 3.61).

Parent molecular ion at m/e 191.

Found: C, 62.56; H, 4.80; N, 7.50

$C_{10}H_9O_3N$ requires: C, 62.84; H, 4.71; N, 7.33%.

(b) 6,7-Methylenedioxy-3(2H)-isoquinolone (100mg.) was dissolved in glacial acetic acid (50ml.) and hydrogenated over Adams' catalyst (50mg.) for 3 hours. The acid solution was decanted from the catalyst and water (50ml.) added. The solution was extracted with chloroform and the extract washed thoroughly with saturated sodium bicarbonate solution, then water. Evaporation gave the dihydro derivative as a colourless solid (70mg., 69%), shown by i.r. and t.l.c. to be identical to the product obtained by catalytic reduction of the oxime acetate above (a). Crystallisation from ethanol gave pale yellow-green needles, softening at 217°, with m.p. 219-224°.

Attempted preparation of N,N-dimethyl-2-aminomethyl-4,5-methylenedioxyphenylacetamide.

(a) To a mixture of ammonium acetate (555mg.) in water (5ml.) and N,N-dimethyl-2-formyl-4,5-methylenedioxyphenylacetamide (250mg.) in methanol (5ml.) at 0° was added sodium borohydride (335mg.) in small portions during a 10-minute period. The mixture was allowed to stand at room temperature for one hour. Water (10ml.) was added and the solution extracted with chloroform to yield a colourless gum which solidified giving a colourless solid (230mg., 91%), identified as N,N-dimethyl-2-hydroxymethyl-4,5-methylenedioxyphenylacetamide by i.r. and t.l.c.

Development of faint blue fluorescence in the reaction medium was also noted (isoquinolone formation?).

(b) The oxime of N,N-dimethyl-2-formyl-4,5-methylenedioxyphenylacetamide was recovered unchanged after treatment with methanolic sodium borohydride at room temperature.

2-Aminomethyl-4,5-dimethoxyphenylacetic acid hydrochloride.

(a) 1,4-Dihydro-6,7-dimethoxy-3(2H)-isoquinolone (1.51g.) was heated on the steam-bath for 2½ hours with 6N hydrochloric acid (50ml.). Evaporation of the acid under reduced pressure gave a light brown

hygroscopic solid which was washed with chloroform to give the amino-acid hydrochloride as a colourless solid (1.42g., 75%), m.p. 175-183°. Crystallisation from methanol-ether gave colourless leaflets, m.p. 168-176°, dependent on the rate of heating.

$\nu_{max.}$ (Nujol): 3250, 2700, 2600, 1700, 1618, 1585 cm^{-1}.

τ values (CF_3CO_2H): 2.69 (1H,s), 2.92 (1H,s), 5.44 (2H, broad), 5.98 (8H, broad s).

Found: C, 50.51; H, 6.15; N, 5.62

$C_{11}H_{15}O_4N.HCl$ requires: C, 50.49; H, 6.12; N, 5.36%.

The amino-acid hydrochloride is insoluble in cold chloroform and readily soluble in cold water.

Treatment of a methanolic solution of the amino-acid hydrochloride (115mg.) with an exactly molar quantity of sodium hydroxide yielded the zwitterion, contaminated by sodium chloride, as an insoluble colourless crystalline solid (91mg.). The same material was obtained by treatment with one mole of sodium acetate trihydrate.

$\nu_{max.}$ (Nujol): 3150, 2100 (NH^+), 1600, 1375 cm^{-1} (COO^-).

(b) The dihydroisoquinolone (50mg.) was heated on the steam-bath for two hours with 10% sodium hydroxide (10ml.). The solid gradually dissolved to give an almost colourless solution. The mixture was then poured into water and acidified with 6N hydrochloric acid.

Chloroform extraction of the acid solution yielded no material. The acid solution was evaporated to dryness and the inorganic residue extracted with hot chloroform. Evaporation gave a light brown solid (34mg., 55%), m.p. 175-185°, decomp., with identical i.r. spectrum to that of the compound prepared in (a) above.

Sublimation at 130-190° and 0.05mm. gave a light yellow-green solid, shown by i.r., t.l.c., and m.p. (198-201°) to be 1,4-dihydro-6,7-dimethoxy-3(2H)-isoquinolone.

Methyl-2-Aminomethyl-4,5-dimethoxyphenylacetate hydrochloride.

A solution of 2-aminomethyl-4,5-dimethoxyphenylacetic acid hydrochloride (465mg.) in methanol (50ml.) was saturated with gaseous hydrogen chloride and allowed to stand overnight. Evaporation gave the amino-ester hydrochloride as a colourless solid (450 mg.). Crystallisation from methanol-ether gave colourless needles (396mg., 81%), m.p. 164.5-173°, relatively soluble in cold chloroform.

$\nu_{max.}$ (Nujol): 2740, 2655, 1720, 1615, 1600 cm^{-1}.

$\lambda_{max.}$: 238.5 mμ (log ε 3.75), 283 mμ (log ε 3.41).

τ values (CF_3CO_2H): 2.67 (1H, broad), 2.94 (2H,s), 5.45 (2H, broad), 5.99 (6H,s), 6.07 (2H,s).

Found: C, 52.06; H, 6.31; N, 5.12

$C_{12}H_{17}O_4N.HCl$ requires: C, 52.28; H, 6.53; N, 5.08%.

The amino-ester hydrochloride dissolved with effervescence in sodium bicarbonate solution. Extraction of the resultant aqueous solution with chloroform gave a colourless solid with the characteristics of the dihydroisoquinolone (e.g. blue-black staining of t.l.c. spot in iodine vapour). Alternatively, washing of a chloroform solution with bicarbonate or treatment with an exactly equivalent amount of sodium acetate trihydrate caused cyclisation to the lactam, identified by i.r. and t.l.c.

Reaction of 2-aminomethyl-4,5-dimethoxyphenylacetic acid hydrochloride with 3,4-methylenedioxybenzaldehyde.

The amino-acid hydrochloride (155mg.) was dissolved in methanol (5ml.) and a solution of sodium hydroxide (48mg. = 2moles) in methanol (3ml.) added. A solution of piperonal (89mg.) in methanol (3ml.) was added and the mixture refluxed for 2½ hours. Evaporation gave a gum which crystallised. This was filtered and washed with chloroform to give the sodium salt of the imino-acid (180mg.), contaminated by sodium chloride.

$\nu_{max.}$ (Nujol): 1640, 1595, 1585, 1520, 1500, 1380 cm^{-1}.

$\lambda_{max.}$ (EtOH): 208 mμ (log ε 4.32), 227 mμ (log ε 4.18),

269 mμ (log ε 3.86), 291 mμ infl. (log ε 3.72), 307 mμ (log ε 3.81); (acid): 235, 281, 288, 306, and 3.49 mμ (log ε 3.97); (base): 230, 271, 288, 308 mμ. Reversible acid shift = +80mμ.

Reaction of 2-aminomethyl-4,5-dimethoxyphenylacetic acid hydrochloride with N,N-dimethyl-2-formyl-4,5-methylenedioxyphenylacetamide.

The amino-acid hydrochloride (310mg.) and the aldehyde (280mg.) were refluxed in methanol (25ml.) containing sodium hydroxide (100mg. = 2moles) for two hrs. Evaporation gave a pale brown solid which was washed with chloroform to yield the sodium salt of the imino-acid (contaminated by sodium chloride) as a colourless solid (521mg.).

$\nu_{max.}$ (Nujol): 1640, 1580, 1520, 1380 cm^{-1}.

$\lambda_{max.}$ (EtOH): 233 mμ (log ε 4.24), 277 mμ (log ε 3.94), 311 mμ (log ε 3.79); (acid): 219 mμ (log ε 4.11), 241 mμ (log ε 4.17), 290 mμ (log ε 3.75), 303 mμ (log ε 3.79), 357 mμ (log ε 3.95); (base): 217, 232, 277, 311 mμ. Reversible acid shift = + 80 mμ.

Overnight treatment of the crude sodium salt (103mg.) with p-toluenesulphonyl chloride (104mg., 2.4 moles) in pyridine (2ml.) at room temperature, followed by an aqueous work-up (ice, chloroform extraction) yielded

two products which were separated by p.l.c. and identified by i.r. and t.l.c. as N,N-dimethyl-2-formyl-4,5-methylenedioxyphenylacetamide (27mg.) and 1,4-dihydro-6,7-dimethoxy-3(2H)-isoquinolone (24mg.). Similarly, attempts to esterify via the silver salt were unsuccessful, the same two hydrolysis products being obtained.

2-(2-Carboxymethyl-4,5-dimethoxybenzyl)-6,7-methylenedioxy-3(2H)-isoquinolone.

The sodium salt (155mg.) of the imino-acid (77) was dissolved in warm 6N hydrochloric acid (3ml.) and the mixture allowed to stand. After a few minutes there was heavy precipitation of the isoquinolone hydrochloride as a colourless crystalline solid (107mg.), m.p. 257-262°, decomp.

$\nu_{max.}$ (Nujol): 3340, 1710, 1640, 1620, 1525 cm^{-1}.

$\lambda_{max.}$ (EtOH): 250 mμ (log ε 4.79), 277 mμ infl. (log ε 3.86), 288 mμ (log ε 3.73), 305.5 mμ (log ε 3.72), 317.5 mμ (log ε 3.77), 381 mμ (log ε 3.46), 398 mμ (log ε 3.53); (acid): 247, 291 infl., 307 infl., 317, 358 mμ; (base): 250, 278 infl., 288 infl., 305, 317, 400 mμ.

τ values (CF_3CO_2H): 1.36 (1H,s), 2.30 (1H,s), 2.73 (3H,s), 2.82 (1H,s), 3.68 (2H,s), 4.11 (2H,s), 5.90-5.97 (8H).

It was not found possible to recover the neutral compound by basification and extraction (due to salt formation) nor was it possible to sublime the compound from its hydrochloride. Basification produced the characteristic bright yellow colour and fluorescence of the 3-isoquinolone system. Careful reacidification caused precipitation of a bright yellow solid, m.p. 250-257°, decomp. As yet this has not been characterised.

2-(2-Carboxymethyl-4,5-dimethoxybenzyl)-6,7-methylenedioxy-3(2H)-isoquinolone. 2-(2-Carboxymethyl-4,5-dimethoxybenzyl)-6,7-methylenedioxyisoquinoline-1,3,4-trione.

The sodium salt (100mg.) of the imino-acid (77) was dissolved in methanol (10ml.) and the solution saturated with gaseous hydrogen chloride. The bright yellow solution was filtered from the precipitated sodium chloride and allowed to stand overnight. Evaporation gave the ester hydrochloride as an orange crystalline solid (92mg.), m.p. 102-106°.

$\nu_{max.}$ (Nujol): 3400, 3200, 2400, 1730, 1640, 1600 cm^{-1}.

$\lambda_{max.}$ (EtOH): 250.5 mμ (log ε 4.54), 278 mμ (log ε 3.72), 289 mμ (log ε 3.61), 305.5 mμ (log ε 3.57), 318 mμ (log ε 3.60), 401 mμ (log ε 3.41); (acid): 247.5, 290, 306, 317, 362 mμ.

This compound was also formed by esterification of 2-(2-carboxymethyl-4,5-dimethoxybenzyl)-6,7-methylenedioxy-3(2H)-isoquinolone under normal Fischer-Speier conditions.

The ester hydrochloride was dissolved in sodium bicarbonate solution and the basic solution extracted with chloroform. Evaporation afforded a bright yellow gummy solid (90mg.), t.l.c. (10% methanol-chloroform) of which indicated that the major component was a non-polar compound (R_f 0.9). That this was the corresponding isoquinoline 1,3,4-trione was shown by comparison (i.r., t.l.c.) with a sample prepared by oxidation of the above gummy solid with manganese dioxide. The product after p.l.c. was a bright yellow solid, m.p. 198-204°, decomp.

$\nu_{max.}$ (Nujol): 1725, 1685, 1665, 1615, 1595, 1525, 1505 cm^{-1}.

$\lambda_{max.}$: 216 mμ (log ε 4.21), 233 mμ (log ε 4.16), 267.5 mμ (log ε 4.24), 290 mμ infl. (log ε 3.74), 333 mμ (log ε 3.40), 370 mμ infl.; (base): 225, 288.5, 304 mμ.

τ values ($CDCl_3$): 2.28 (1H,s), 2.43 (1H,s), 2.91 (1H,s), 3.24 (1H,s), 3.74 (2H,s), 4.77 (2H,s), 6.02 (2H,s), 6.14 (6H,s), 6.33 (3H,s).

1,4-Dihydro-6,7-dimethoxy-2-(3,4-dimethoxyphenylethyl)-3(2H)-isoquinolone.

N,N-Dimethyl-4,5-dimethoxy-2-formylphenylacetamide (1.81g.) and homoveratrylamine (1.35g.) were refluxed in ethanol (50ml.) for two hours. Evaporation of solvent gave an orange gum which showed strong green fluorescence.

$\lambda_{max.}$ (neutral and basic): 232, 276, 305 mμ; (acid): 236, 287 infl., 312, 355 mμ. Acid shift = +79 mμ.

This gum was treated with hot 6N hydrochloric acid (40ml.). A heavy pale yellow precipitate formed very rapidly. A suspension of this in water was basified with ammonia and the resultant bright yellow solid and highly fluorescent yellow-green solution extracted with chloroform until the aqueous phase was colourless. The organic solution was evaporated to yield an orange-red oil, having the u.v. maxima expected of 2-(3,4-dimethoxyphenylethyl)-6,7-dimethoxy-3(2H)-isoquinolone.

$\lambda_{max.}$ (neutral and basic): 253.5, 286, 303.5, 315, 399 mμ.

$\lambda_{max.}$ (acid): 252, 286, 308, 316, 362 mμ.

The isoquinolone,,without purification, was dissolved in ethanol (140ml.) and hydrogenated over Adams' catalyst (350mg.) for 6½ hours. Filtration and evaporation gave the dihydroisoquinolone as a yellow oil which crystallised on trituration with petroleum ether

as a pale yellow solid, m.p. 110-114°. (2.18g., overall yield from aldehyde, 82%).

$\nu_{max.}$ (Nujol): 1650 cm^{-1}.

$\lambda_{max.}$: 230 mμ (log ε 4.21), 280 mμ (log ε 3.91),

τ values ($CDCl_3$): 3.22 (2H,s), 3.28 (1H,s), 3.35 (1H,s), 3.47 (1H,s), 5.79 (2H, t, J=1.8 c/s.), 6.16 (12H,s), 6.26 (2H,t), 6.48 (2H, t, J=1.8 c/s.), 7.14 (2H,t).

An almost quantitative recovery of the dihydroisoquinolone was made after treatment with phosphorous pentoxide on pumice in refluxing benzene for 18 hours.

A similar reaction sequence using N,N-dimethyl-2-formyl-4,5-methylenedioxyphenylacetamide (705mg.) yielded the hydrochloride of 2-(3,4-dimethoxyphenylethyl)-6,7-methylenedioxy-3(2H)-isoquinolone as a pale yellow solid (1.06g.). The free isoquinolone was liberated from the salt in the usual manner and was identified by its u.v. maxima.

$\lambda_{max.}$ (EtOH): 250 mμ (log ε 4.75), 304 mμ (log ε 3.64), 316 mμ (log ε 3.66), 398 mμ (log ε 3.62); (acid): 246.5, 278, 286, 306 infl., 358, 368 mμ.

Cyclisation of 1,4-dihydro-6,7-dimethoxy-2-(3,4-dimethoxyphenylethyl)-3(2H)-isoquinolone. Preparation of norcoralydine.

The lactam (520mg.) was refluxed for four hours with

phosphorous oxychloride (12ml.), then stirred overnight at room temperature (all operations under nitrogen). The cooled reaction mixture was dropped into ice and stirred until homogeneous. The yellow solid product was filtered. (503mg.), dec. > 250°.

$\nu_{max.}$ (Nujol): 1610 cm^{-1}.

$\lambda_{max.}$ (relative optical densities): 210 mμ (0.73), 231 mμ (0.66), 241 mμ (0.64), 255 mμ (0.56), 265 mμ (0.60), 288 mμ (1.00), 310 mμ (0.70), 341 mμ (0.53), 375 mμ (0.35); no shift in acid or base.

The above cyclisation product (100mg.) was dissolved in methanol (15ml.) and treated with sodium borohydride (200mg.) at room temperature for 15 minutes. The mixture was refluxed for a further 30 minutes (under nitrogen), then poured into water. Chloroform extraction yielded a yellow oil, p.l.c. (5% methanol-chloroform) of which afforded the tetrahydroberberine as a pale yellow semi-solid (97mg.) of R_f ca. 0.80, m.p. 135-142° (lit. 157°), insufficiently volatile for mass spectral mol. wt. determination using a heated inlet system.

$\nu_{max.}$ (Nujol): 1610, 1520 cm^{-1}.

$\lambda_{max.}$ (rel. opt. density): 226 mμ (1.00), 283 mμ (0.53), 286 mμ (0.53). Signal at 5.25τ (H_2O?).

τ values ($CDCl_3$): 3.18 (1H,s), 3.27 (1H,s), 3.31 (1H,s), 3.35 (1H,s), 6.12 (12H, s), 5.5-6.0, 6.1-7.4 (complex).

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PART 2

THE SYNTHESIS OF

HYDROXYLEONTICINE

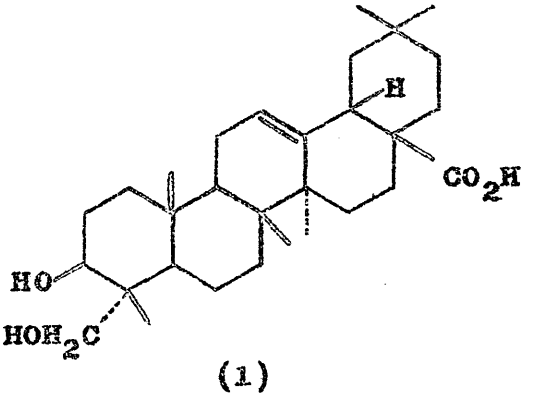
INTRODUCTION

Leontice leontopetalum, Linn is a hardy perennial herb, found chiefly in mountainous regions throughout Eastern Mediterranean countries.[1,2] In central Lebanon it is widespread as a weed in wheatfields.[1] The plant grows to a height of twelve to eighteen inches and possesses large root tubers.[1,3] It has gained some local notoriety in the Lebanon on account of the apparent curative effect of an extract from these tubers in the treatment of epilepsy. Although highly toxic some degree of success has seemingly been recorded.[cf.4]

This plant and a second species of the genus Leontice (a member of the family Berberidaceae), namely L.chrysogonum, were used by the ancient Greeks as medicines,[5] the latter as a snake-bite remedy and in the treatment of sciatica. L.chrysogonum was introduced into Britain in the late sixteenth century[3] and in the seventeenth found additional medicinal use in the treatment of ulcers.[6] The powdered roots of the plant have also been used as a soap substitute.[6] The root tubers of L.leontopetalum have found application as a soap substitute,[7-10] a snake-bite antidote,[8] in the treatment of overdoses of opiates[7] and "bitings of the shrew mouse",[5] and as a native remedy for

epilepsy.[1,8,11]

It was this last activity which prompted the first chemical investigation of the plant in 1955 by McShefferty, in an endeavour to identify the constituents responsible for the curative action of the drug.[4] From a light petroleum extract of the powdered root tubers were isolated a long-chain alkane (probably n-nonacosane), ceryl alcohol, and a 3β-hydroxy-Δ^7-sterol, together with palmitic, stearic, oleic, and linoleic acids. An ethanol extract afforded a saponin ("leontosaponin") which on acid hydrolysis yielded hederagenin (1), four moles of D-glucose and three moles of L-arabinose. Leontosaponin is presumably responsible for the usefulness of the root tubers as a soap substitute.[7-10]



(1)

The chief interest in the constituents of the plant, however, was its alkaloid content. McShefferty was able to isolate three compounds, thought to be alkaloids. One of these, a saturated ditertiary base, possessed

identical properties to leontamine,[12,13] an alkaloid previously isolated from L.ewersmanni Bge., and thought to be a quinolizidine alkaloid on the basis of the available chemical evidence and the frequent occurrence of lupin alkaloids in plants of the Leontice genus.[14-16] The second alkaloid, designated "petaline", was a water-soluble base, the properties of which were in accord with those expected of a quaternary salt. The third, a tertiary base, was given the name "leonticine". On the basis of ultraviolet spectral correlations McShefferty suggested that petaline was an isoquinoline alkaloid, and in addition the conversion of petaline into leonticine under relatively mild basic conditions led him to indicate that the latter might well be an artefact, produced during the extraction procedure.

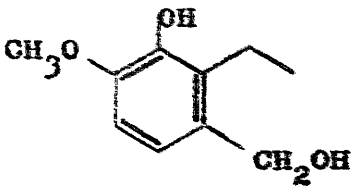
The structural elucidation of petaline and leonticine was carried out initially by Smith[17] and later by Magrill.[18] Smith reported that passage of petaline chloride or reineckate over Amberlite IRA-400 (OH) anion exchange resin caused conversion to leonticine in good yield, suggesting that leonticine is in fact the Hofmann degradation product of petaline. That petaline methine (leonticine) contains two methoxyl groups was confirmed by microanalysis and by its n.m.r. spectrum. Evidence[18] of the presence of a phenolic hydroxyl were

an i.r. maximum at 3540 cm^{-1} (a position consistent with that of a phenol weakly intramolecularly hydrogen-bonded to an ortho methoxyl group), a signal at 4.05τ, destroyed upon deuteration, a deep purple coloration with methanolic ferric chloride, and the formation of a sparingly soluble sodium salt.

The presence of a dimethylaminoethyl side-chain was demonstrated[17] by means of the conversion of leonticine methohydroxide under Hofmann elimination conditions (refluxing alcoholic sodium ethoxide) into trimethylamine, characterised as its picrate, and a styrene, the structure of which was deduced with the aid of a parent molecular ion at m/e 282 and the appearance of a u.v. absorption at 269 mμ, superimposed on the stilbene chromophore. Two doublet signals, each integrating for a single proton, at 4.5τ (J=17c/s.) and 4.9τ (J=10 c/s.), both further split into a doublet (J=ca. 1.6c/s.), in the n.m.r. spectrum of the styrene acetate characterised the vinyl protons of the diolefin.

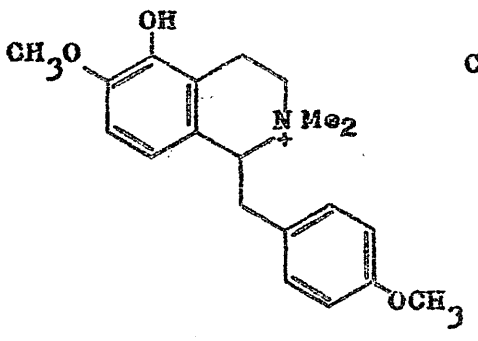
That the position para to the phenol group in petaline methine was unsubstituted was indicated by a positive Gibbs' test.[19] Ozonolysis of the methiodide[17] produced p-methoxybenzaldehyde (also formed by ozonolysis of leonticine itself) and a water-soluble quaternary salt which was immediately subjected to Hofmann

degradation and the styrene product catalytically reduced. Smith observed that the i.r. spectrum of the reduction product showed two OH stretching bands at 3615 cm^{-1} (ε 22) and 3547 cm^{-1} (ε 112), which he assigned to the benzylic and phenolic hydroxyls of (2). He

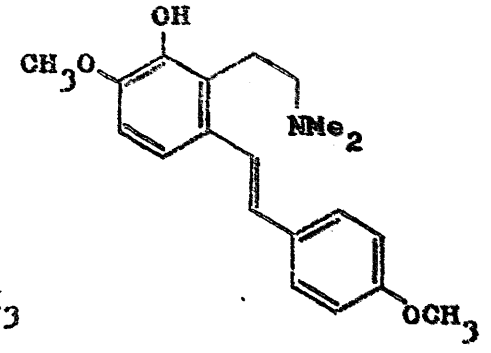


(2)

argued that the benzylic hydroxyl group is not intramolecularly bonded as one would expect it to be in a position ortho to a phenolic hydroxyl or methoxyl. On the basis of much of the above evidence Smith assigned the structures (3) and (4) to petaline and its methine respectively.



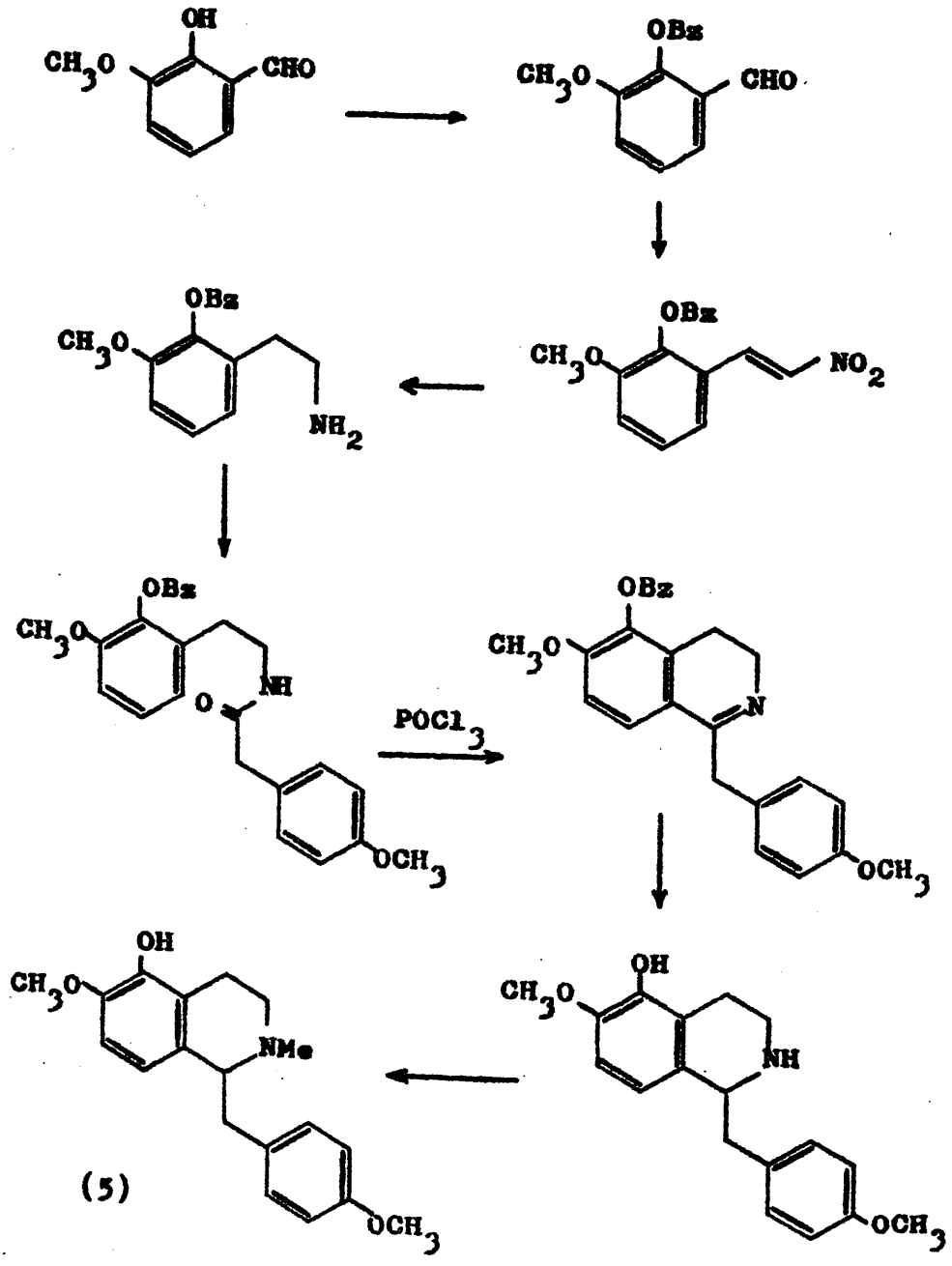
(3)



(4)

Since such an oxygenation pattern is biogenetically

Scheme 1

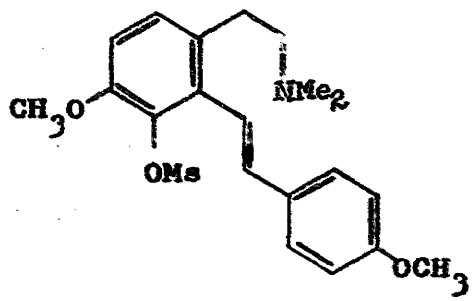

OH
CH3O
CHO
OBz
CH3O
CHO
OBz
CH3O
NO2
OBz
CH3O
NH2
OBz
CH3O
NH
O
OCH3
POCl3
OBz
CH3O
N
OCH3
OH
CH3O
NMe
OCH3
OH
CH3O
NH
OCH3

(5)

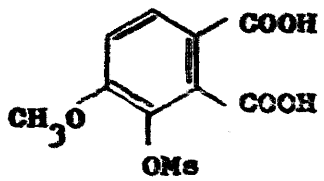
unique Magrill undertook the synthesis of these structures.[18] The synthetic route depicted in Scheme 1 afforded the tetrahydroisoquinoline (5). Quaternisation with methyl iodide and passage of an alcoholic solution of the product over an Amberlite ion exchange resin resulted in formation of a quaternary hydroxide, successful Hofmann elimination of which was only accomplished by use of fairly vigorous conditions (refluxing alcoholic sodium ethoxide). The product was different from leonticine (in particular in its u.v. maxima) and was designated pseudoleonticine. However the similarity of the i.r. and n.m.r. spectra of the two stilbenes confirmed the formulation of petaline as a quaternary salt of a benzylisoquinoline.

Magrill thus concluded that the oxygenation pattern, instead of being 5,6 must be 7,8. He repeated the Gibbs' test on a quantitative basis and confirmed the absence of a substituent para to the phenol. Additional evidence for the absence of a para substituent was provided by the oxidation of the O-mesyl derivative (6) which yielded p-methoxybenzoic acid and 3-mesyl-4-methoxyphthalic acid (7), the latter being characterised as its anhydride. It was further shown that the hydroxyl frequencies in the ethyl vanillyl alcohol (8) had been misinterpreted, as o-vanillyl alcohol (9) shows very

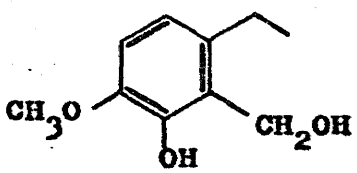
similar hydroxyl absorptions, namely at 3615 cm^{-1} (ε 46) and 3560 cm^{-1} (ε 182).



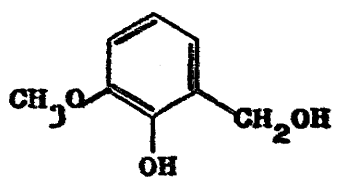
(6)



(7)

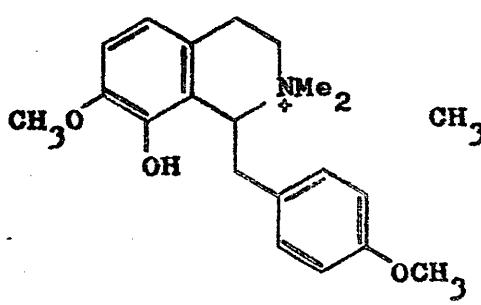


(8)

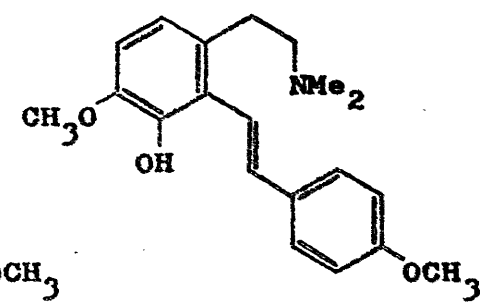


(9)

Thus petaline and its methine were reassigned structures (10) and (11) respectively.[18] The 8-hydroxy



(10)



(11)

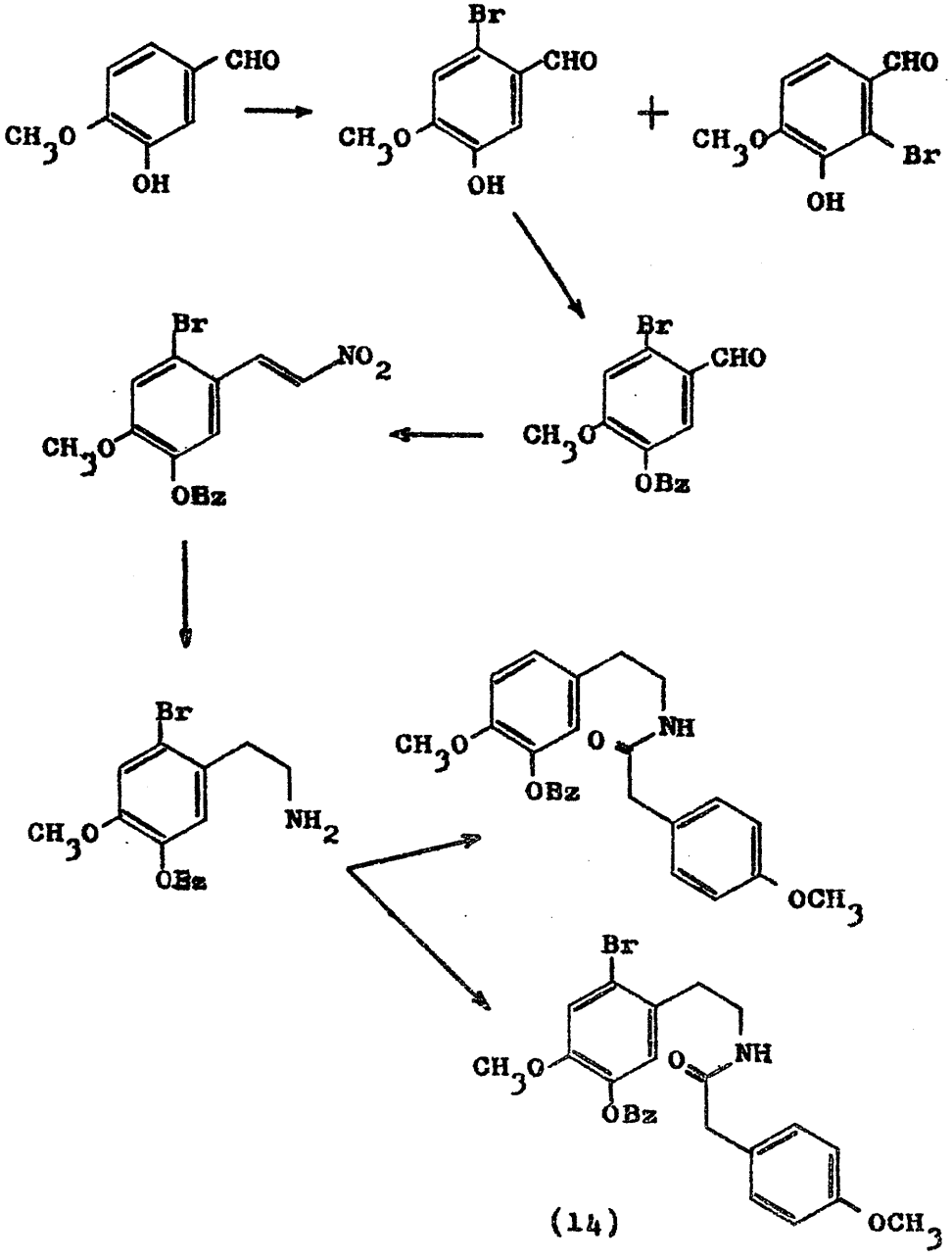
subatituent explains the position of the long wavelength band of petaline methine at 299 mμ, on the grounds of

steric inhibition of resonance.[20] The cis-stilbene structure tentatively assigned[17] to leonticine on the basis of the very close similarity between the u.v. spectra of this compound and of cis laudanosine methine [21] was also questioned[18] on the grounds that mechanistic considerations would favour a trans stereochemistry in the Hofmann product.

The synthesis of isoquinoline derivatives possessing oxygen substituents at positions 7 and 8 presents a special problem. The conventional methods of isoquinoline synthesis are not generally considered to be directly applicable. The Bischler-Napieralski reaction[22] is reputed to lead exclusively to the 6,7-dioxygenated system, the Pictet-Spengler method[23] gives at best mixtures of 6,7 and 7,8-dioxygenated isoquinolines, and the Pomeranz-Fritsch synthesis[24] is usually considered to be inapplicable to the preparation of isoquinolines substituted in position 1, although the modification recently reported[25] by Bobbitt et al may prove useful in this respect.

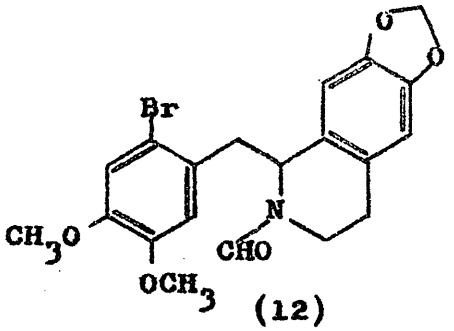
After several synthetic routes had proved unsuccessful, Magrill decided in spite of anticipated difficulties to attempt a synthesis employing the Bischler-Napieralski reaction. Two important factors have to be considered in this reaction. Firstly it is necessary

Scheme 2

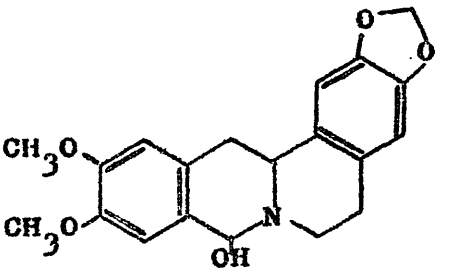

CHO
CH_3O
OH
Br
CHO
CH_3O
OH
+
CHO
CH_3O
Br
OH
Br
CHO
CH_3O
OBz
Br
NO_2
CH_3O
OBz
Br
NH_2
CH_3O
OBz
CH_3O
O
NH
OBz
OCH_3
Br
CH_3O
O
NH
OBz
OCH_3

(14)

to protect the phenolic hydroxyl during the ring-closure and, since the desired product has substituents in the peri positions 1 and 8 of the nucleus, steric factors may be operative. Secondly, cyclisation conditions would have to be carefully selected since a reported[26] attempt to cyclise the brominated amide (12) had resulted in exclusive formation of the bromine-free product (13), emphasising the driving force for electrophilic attack para to an activating group (although a case of concomitant ortho cyclisation has recently been reported.[27])

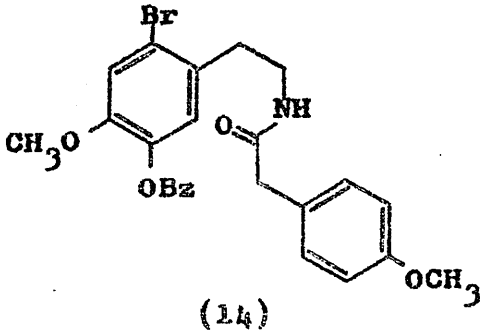


(12)



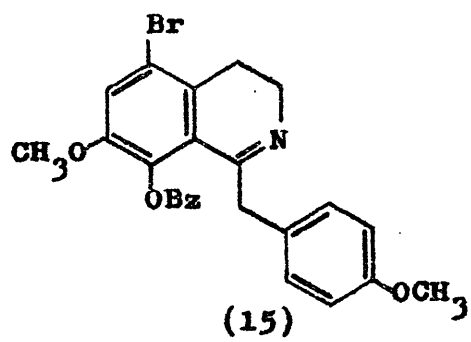
(13)

Magrill used the synthetic plan outlined in Scheme 2. Reaction of the brominated amide (14) with phosphorous pentachloride in chloroform over an extended period- these mild Bischler-Napieralski conditions being used [28]



(14)

in the hope of avoiding dehalogenation and ring-closure at the undesired position- yielded a product of m.p. 138°. Its i.r. spectrum was similar to that of the amide (14) and its u.v. spectrum unchanged on the addition of acid or base. However the compound analysed for a dihydrate of the desired dihydroisoquinoline (15) and the n.m.r. spectrum was interpreted in such a way as to be consistent with this structure. This assumed that the properties of the compound were anomalous (strong deshielding of two of the anisyl ring protons and lack of basic character), but could be



(15)

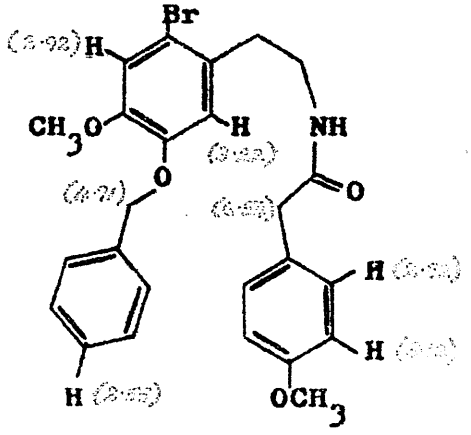
explained in terms of interaction between the nitrogen atom and the anisyl ring, resulting from steric repulsion between the peri substituents (benzyloxy and anisyl groups). In addition the two one-proton singlets at 3.12τ and 2.90τ were assigned to the two non-equivalent protons of the benzylic methylene group, absorbing at τ values which were not sufficiently separated to allow spin-spin coupling.

RESULTS AND DISCUSSION

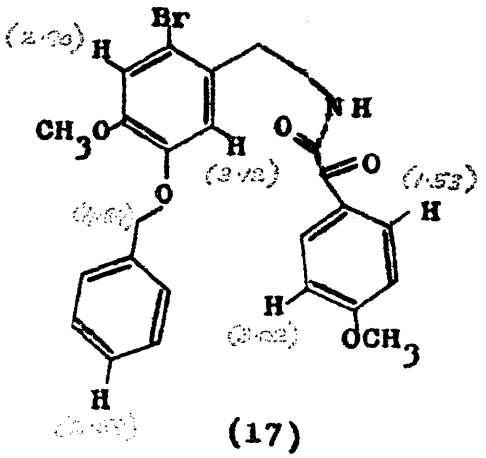
With a view to further investigating and subsequently taking advantage of the above cyclisation the synthesis of the bromo-amide (14) was repeated as in Scheme 2 with a slight modification in the initial step. The bromination of isovanillin was carried out by Magrill[18] using a slight modification of the procedure of Henry and Sharp[29] and resulted in formation of approximately equal quantities of the 2- and 6-bromo isomers. The improved technique employed in the present work in which the main product (63%) was the desired 6-bromo isomer, was essentially that used by Hazlet and Brotherton.[30] Proof of purity of the 6-isomer was established by its n.m.r. spectrum in trifluoroacetic acid which indicated two uncoupled aromatic protons (2.37τ and 2.72τ). Formation of the benzyl ether and condensation to the nitrostyrene (Scheme 2) were carried out using the methods employed by Magrill[18], similar yields being recorded.

In the preparation of the amide (14) considerable difficulty was found in that dehalogenation of the aromatic nucleus appeared to be more prevalent than was supposed. Magrill had observed that when intermediate reflux periods were used in the nitrostyrene

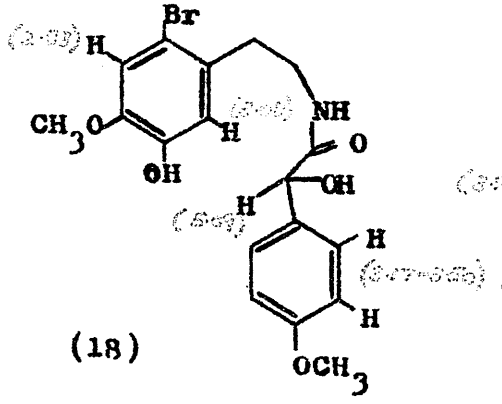
Table 1 N.M.R. Spectra of amides. (in $CDCl_3$)



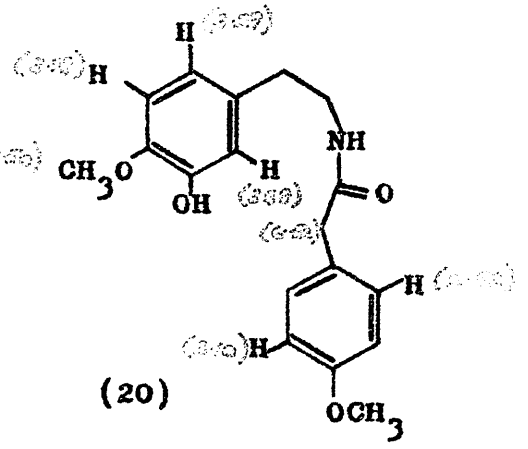
(14)



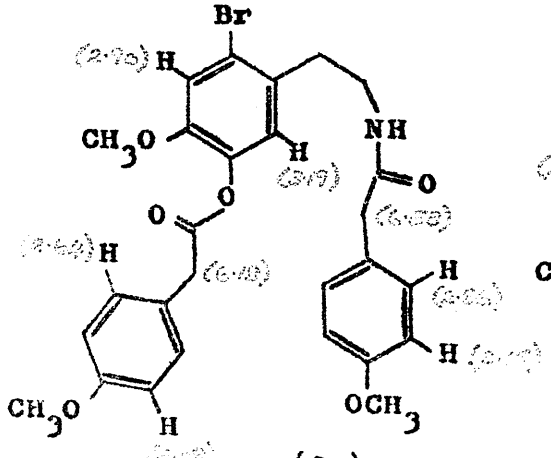
(17)



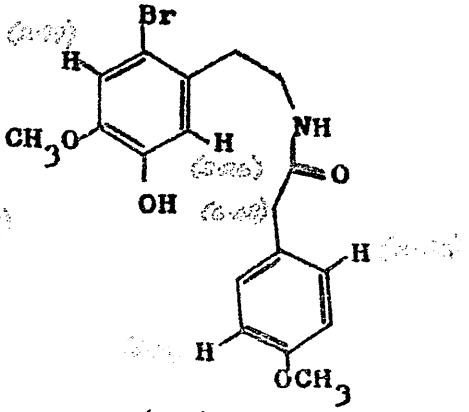
(18)



(20)



(24)

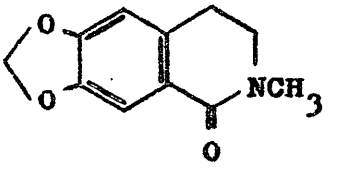


(22)

reduction a mixture of the two amides was eventually obtained (Scheme 2). It was found that even reduction at room temperature with lithium aluminium hydride, the excess of reagent being destroyed immediately upon completion of the addition of the substrate, led to considerable debromination. Fractional crystallisation of the amide mixture from ethanol afforded only a 20-27% yield of the desired brominated amide (14). Several examples of hydrogenolysis of aromatic halogens by lithium aluminium hydride[31] have been reported. Thus it might be advantageous to use an alternative method of reduction of the nitrostyrene, such as electrolytic reduction[32] or using zinc amalgam[33,34] (cf. the successful reduction of a nitrostyrene having both aromatic bromo and benzyloxy substituents[33].).

The n.m.r. spectrum (in $CDCl_3$) of the bromo-amide (14) is an interesting model for compounds to be discussed later (Table 1). The aromatic protons of the anisyl ring appear as a typical AB system (J=9c/s.) at 2.82τ and 3.12τ, the remaining aromatic protons as singlets (para protons) at 2.92τ and 3.22τ. The methylene protons of the phenylethylamine portion appear at 7.19τ (triplet) and 6.55τ (multiplet), positions similar to those for the correspondingly-sited protons in oxyhydrastinine (16) (7.05τ and 6.46τ).

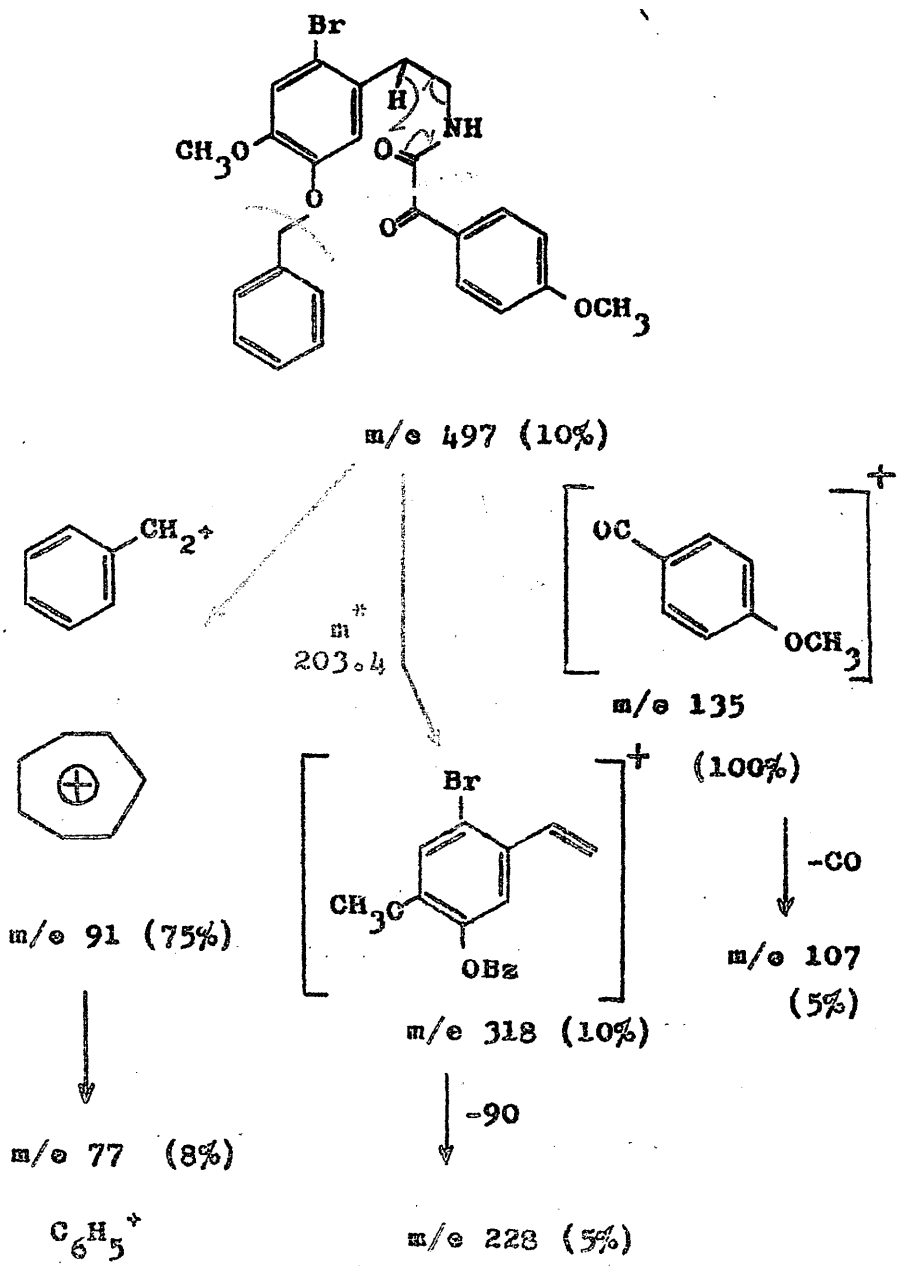
Repetition of the reaction of the amide (14) with phosphorous pentachloride afforded the same product as was obtained previously,[18] but it soon became clear that the spectral properties of this product were not



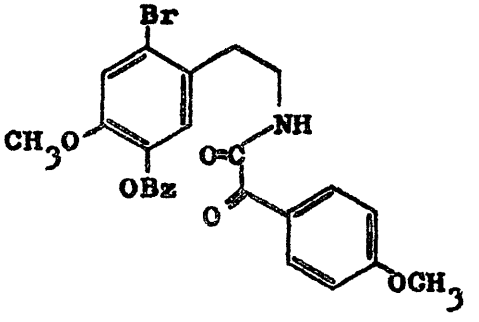
(16)

in accord with the dihydroisoquinoline structure (15) assigned to it. In particular, the parent molecular ion was at m/e 497, that expected being m/e 465. The base peak of the mass spectrum was at m/e 135, a fact which, coupled with the obvious deshielding of two aromatic protons (1.53τ), indicated that the p-methoxybenzoyl grouping is present in the molecule. The presence of a ketonic function was further indicated by a colour reaction with 2,4-dinitrophenylhydrazine and the appearance in the i.r. spectrum (in chloroform) of a carbonyl absorption at 1685 cm^{-1}. That the amide function had been retained was shown by i.r. maxima at 3418 cm^{-1} (NH) and at 1661 cm^{-1} (C=O). Final confirmation of the α-keto amide structure (17) was furnished by its n.m.r. spectrum (Table 1), which can be reinterpreted as follows. The AB system of the anisyl

Scheme 3 **Mass spectrum of α-keto amide (17).**



ring protons can be readily accommodated since two are deshielded (1.53τ) by the ortho carbonyl group, and two are subject only to the shielding (3.02τ) by the methoxyl substituent. The remaining aromatic protons resonate



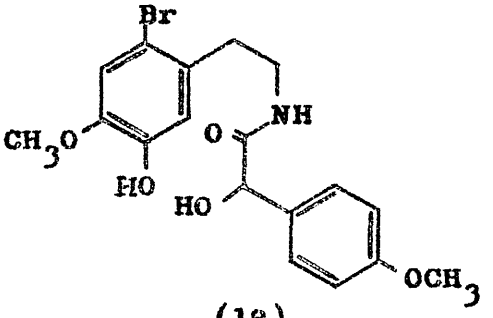
(17)

at 2.90τ (a position apparently characteristic of a proton sited between bromo and methoxyl substituents), and at 3.12τ. The absence of the methylene singlet of the starting amide at ca. 6.5τ is final proof of oxidation at this centre. The cracking pattern of the α-keto amide is characterised by a facile McLafferty rearrangement (cleavage β to the amide carbonyl group with transfer of a γ hydrogen), resulting in elimination of p-methoxyphenylpyruvamide and formation of an ion of m/e 318 (see Scheme 3).

Although oxidation at the benzylic methylene of benzylisoquinolines is a well-known occurrence (see later), this appears to be the first example of oxidation occurring at this position prior to cyclisation. A possible mechanism for benzylic oxidation in this

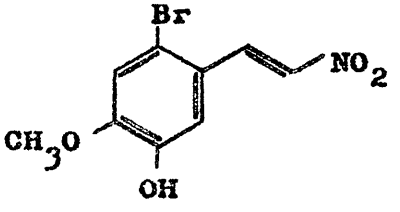
instance would be via free radical chlorination at this position. The chloroform used as reaction solvent was dried by passage through blue silica gel, a process which will also result in its destabilisation, hence making a free radical reaction not unlikely. That this centre is not normally highly susceptible to oxidation was shown by the fact that the amide (14) was recovered totally unchanged after treatment with manganese dioxide.

In the course of elucidating its structure catalytic reduction of the α-keto amide (17) was carried out under a variety of conditions. This yielded two main p.l.c. fractions, the more polar of which afforded a colourless solid, m.p. 110°. The bromine-containing parent molecular ion of this product was at m/e 409 and the base peak at m/e 137 ($CH_3O.C_6H_4.CHOH$). The spectrum was further characterised by a McLafferty rearrangement, which produced an ion at m/e 228. Accordingly the structure proposed for this product is the benzyl alcohol (18). Supporting evidence was



(18)

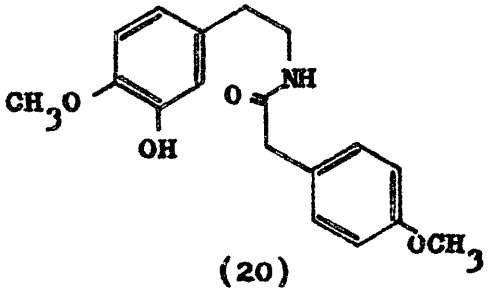
provided by its n.m.r. spectrum (Table 1). That the benzoyl carbonyl group had been reduced was indicated by loss of the low-field aromatic signal characteristic of the carbonyl-deshielded protons. A one-proton singlet at 5.09τ can be assigned to the methine proton located under the hydroxyl group. The retention of the aromatic halogen, even after hydrogenolysis at a pressure of four atmospheres, is rather surprising, but may be due to the presence of the free phenolic group. (cf. stability of bromine to lithium aluminium hydride in the phenolic nitrostyrene (19)[18]).



(19)

No characterisable product could be isolated from the less polar fraction.

The phenolic amide (20), shown by t.l.c. to be

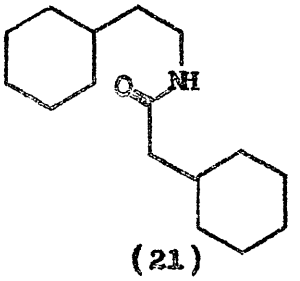


(20)

absent in both fractions from the above reduction, was prepared by hydrogenolysis (10% palladium on charcoal catalyst) of the benzyloxy amide (14). The product ($\nu_{NH/OH}$ 3437, 3322 cm^{-1}, $\nu_{C=O}$ 1643 cm^{-1}) was characterised by a mass spectral parent ion at m/e 315 and also by an ion at m/e 150, resulting from fission of p-methoxyphenylacetamide. Evidence of loss of bromine was provided by its n.m.r. spectrum (Table 1) in which the signals for the anisyl protons appeared at 2.82τ and 3.10τ, and for the remaining aromatic protons at 3.29τ (2H) and 3.38τ (1H).

An earlier attempted reduction of the bromo-amide (14), using Adams' catalyst in ethanol, afforded a colourless solid, the analytical data of which indicated an unexpectedly high carbon and hydrogen content, and only 5.5% oxygen. The i.r. spectrum of this product was consistent with a typically aliphatic material, having strong absorptions at 2928, 2854, and 1442 cm^{-1}, and retention of the amide function was shown by peaks at 3313, 3092, 1641, and 1554 cm^{-1}. The aliphatic nature of the product was confirmed by its u.v. spectrum, which exhibited only end-absorption, and by its n.m.r. spectrum which was characterised by a broad band at 4.40τ (NH), a multiplet at 6.7τ ($-NH-CH_2-$), and a broad signal between 7.9τ and 9.0τ for the remaining protons. The

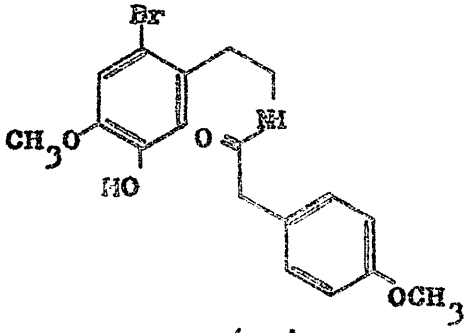
saturated structure (21) was confirmed by the parent molecular ion at m/e 251. Reductive cleavage of aromatic hydroxyl and methoxyl substituents is not an unknown phenomenon,[35] in this instance reaction possibly being



(21)

due to the use of an abnormally active sample of catalyst.

One of the original synthetic routes to petaline attempted by Magrill[18] involved the bromo phenolic amide (22). However its synthesis by condensation of the amine (23) with homoanisoyl chloride was unsuccessful.



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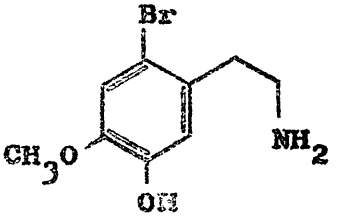
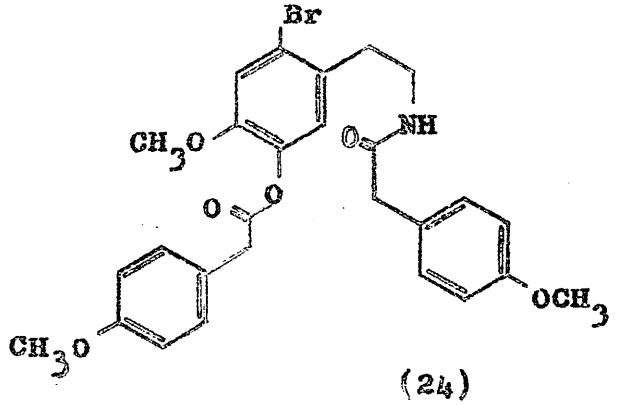


(23)

It has now been shown that reaction of the phenolic amine (23) with an excess of homoanisoyl chloride under similar conditions to those used in the preparation of the amide (14), yields the amido-ester (24). The structure

of this product was elucidated with the aid of its i.r. absorptions at 3348, 1659 cm^{-1} (amide) and at 1752, 1244 cm^{-1} (ester), and by its n.m.r. spectrum (Table 1) which exhibits two AB systems, the four doublets being centred at 2.64, 2.86, 3.08, and 3.15τ, each with a coupling constant of 9c/s. There were in addition two



(24)

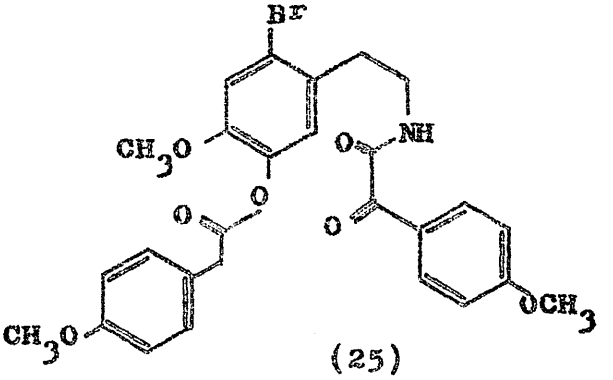
methylene singlets at 6.58τ (α to amide) and 6.18τ (α to ester).

Although the ester (24) was not readily attacked by dilute acid, the desired bromo phenolic amide (22) could now be prepared in high yield by base hydrolysis. The structure of this product was readily ascertained by examination of its n.m.r. spectrum (Table 1). Consistent i.r. data ($\nu_{NH/OH}$ 3360, 3300 cm^{-1}, $\nu_{C=O}$ 1645 cm^{-1}) were also recorded.

Treatment of the bromo phenolic amide (22) with phosphorous pentachloride in dry chloroform using the same conditions as led to formation of the α-keto amide

(17) did not in this case cause oxidation, an almost quantitative recovery of starting material being made. This result provides some support for the hypothesis of free radical chlorination, as the presence of a free phenolic function capable of "mopping-up" radicals may prevent such a reaction taking place in this case.

Similar reaction of the amido-ester (24) with phosphorous pentachloride, however, produced two carbonyl compounds, the less polar as the major product, the more polar in only trace amount. Retention of the amide and ester functions in the major product was signified by the absorptions at 3400, 1755, and 1665 cm^{-1}, and a new carbonyl absorption at 1675 cm^{-1} was also present. This compound was not analysed, but there is a strong likelihood that it possesses structure (25),



(25)

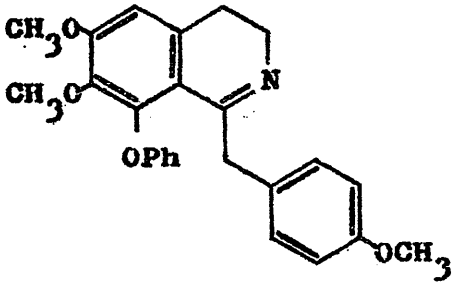
on the basis of its n.m.r. spectrum which exhibits a two-proton doublet (J=9.6c/s.) centred at 1.53τ, the remaining aromatic protons appearing as an 8-proton

complex between 2.5τ and 3.2τ. The remaining signals were consistent with oxidation only at the benzylic methylene adjacent to the amide grouping. The minor carbonyl component had $\nu_{max.}$ at 3400 cm^{-1} and 1655 cm^{-1} (amide), and probably has the phenolic structure, arising by hydrolysis during the work-up.

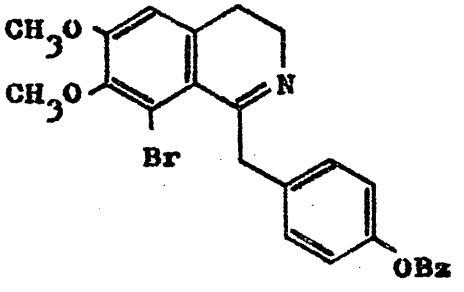
In deciding upon alternative conditions for ring-closure, the various factors affecting this Bischler-Napieralski reaction were reviewed. This reaction involves electrophilic attack on the aromatic nucleus,[36] the facility with which this occurs being dependent on the electron density at the point of attack.[22] Thus the direction of ring-closure is controlled by the substituents. In general an oxy or other electron-releasing substituent greatly facilitates cyclisation in the para position but if anything has a retarding effect if cyclisation is required in the meta position. (Forcing conditions are required to effect cyclisation of acyl p-methoxyphenylethylamines.[37]) The presence of a meta bromine atom will at best have no effect and may well cause retardation, although the synthesis of 5-bromoisoquinoline has been achieved under rather forcing conditions.[37]

It is not generally considered feasible to employ a

phenolic compound in the Bischler-Napieralski reaction (unlike the Pictet-Spengler cyclisation[23]), such a grouping normally being protected either as a benzyl ether[38] or as an ester.[39] In the bromo amide (14) the ortho benzyloxy grouping will provide some activation for electrophilic attack, but would result in the formation of a molecule with two bulky groups positioned peri to each other. This however need not prevent cyclisation as shown by the preparation of the 8-phenoxy derivative (26);[40] and the 8-bromo compound (27).[41]

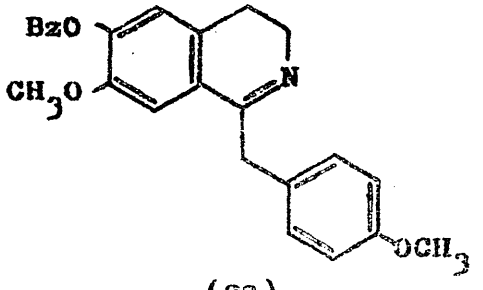


(26)



(27)

The main difficulty in dealing with the bromo amide (14) is that under forcing conditions debromination might occur, the product being the undesired 6,7-dioxygenated dihydroisoquinoline (28).



(28)

A thorough investigation into possible methods of ring-closure in the three available amides (14), (22), and (24) was carried out. The results of a series of fifty experiments are summarised in the experimental section.

After initial attempts using phosphorous oxychloride had failed, recourse was made to more specialised methods. A modification of the Bischler-Napieralski reaction which has been used with telling effect[42] consists of cyclisation of the intermediate imino-chloride with the aid of a Friedel Crafts catalyst. The crystalline solid deposited in the early stages of reaction of the benzyloxy amide (14) with phosphorous pentachloride may have been the corresponding imino halide. It was found that initial treatment of the benzyloxy amide (14) with phosphorous pentachloride or phosphorous oxychloride, followed by reaction with aluminium chloride or stannic chloride gave a low yield of basic material. This was found to be very variable when phosphorous oxychloride was used, and in some cases no basic material could be isolated. Two other compounds were isolated from the stannic chloride reaction. These were the starting amide (14) and the bromo-phenolic amide (22), derived by cleavage of its ether group. In fact debenzylation was achieved in 69% yield by means

of stannic chloride in benzene at room temperature for 24 hours. In contrast the ester grouping of the amide (24) was essentially non-labile under acidic conditions.

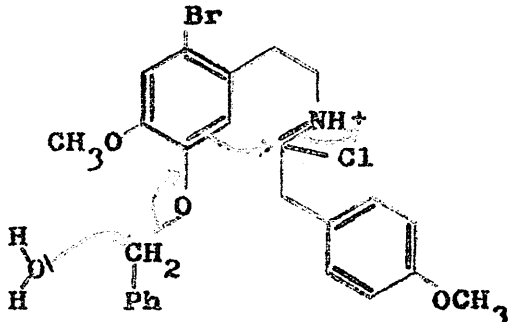
Reaction of the bromo amide (14) with phosphorous pentoxide on pumice gave only a small amount of basic material, although a further somewhat intractable basic fraction could be recovered from the pumice residues by washing with base and chloroform extraction.

All these basic fractions contained two main components, as detected by t.l.c. The yellow colour of the crude material in each case was destroyed by acidification which also caused a small but variable shift to the red in u.v. (270-290mμ), suggestive of a 3,4-dihydroisoquinoline component.[43]

The readiness with which debenzylation occurred and the presence of the bromo phenolic amide (22) in the product from several experiments involving the benzyloxy compound (14) suggested that the cyclisation product might be phenolic and that cyclisation was effected only owing to the presence of a highly activating ortho substituent. However no basic material was isolated from any reactions employing the phenolic amide (22).

It was found that the addition of a controlled amount of water to a mixture of the benzyloxy amide (14) and phosphorous oxychloride in benzene, gave a more

satisfactory yield of basic products. A plausible explanation is that the presence of water will aid acid-catalysed fission of the benzyl ether, promoting concomitant ortho cyclisation (29).



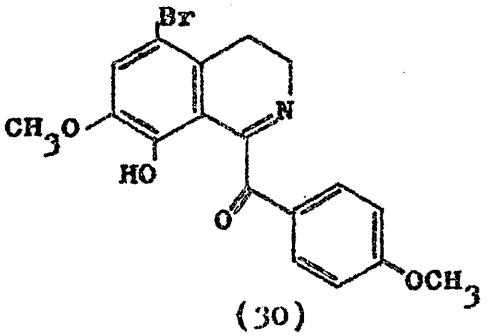
(29)

Analysis of the basic fraction from this cyclisation by t.l.c. indicated two major components, one highly polar (R_f 0.10) and bright yellow, the other a less polar (R_f 0.40) orange material. Attempted preparative t.l.c. afforded two well-separated bands, but during extraction of these with chloroform and evaporation of the solvent the component of R_f 0.10 was irreversibly converted to that of R_f 0.40, identity being established by t.l.c. and u.v.

On repeated p.l.c. a bright orange-red solid, R_f 0.40, m.p. 180°, was obtained. The acid shift in its u.v. spectrum (280 mμ to 299 mμ) suggested that cyclisation had occurred and the retention of the bromine atom, confirmed by the mass spectrum, showed that this must have occurred in the desired ortho position. Conclusive

evidence that this red solid was an oxidation product, as suggested by its mode of formation, was provided by its n.m.r. (deshielded aromatic low-field doublet at 2.02τ), i.r. ($\nu_{max.}$ 1670 cm^{-1}), and mass spectrum (base peak at m/e 135), which showed that a 1-benzoyl substituent was present. The presence of two methoxyl groups in the product was confirmed by n.m.r., as was the loss of the benzyl group. Further evidence of its phenolic character was provided by i.r. ($\nu_{max.}$ 3523 cm^{-1}, ε 124). The aromatic region of the n.m.r. showed in addition to the expected AB quartet (2.02τ and 3.07τ) a one-proton singlet at 2.95τ, further evidence that cyclisation had occurred.

Finally comparison of the molecular weight expected of the 1-benzoyl derivative (30) with that observed (m/e 403) indicated a further difference of 14 mass units,

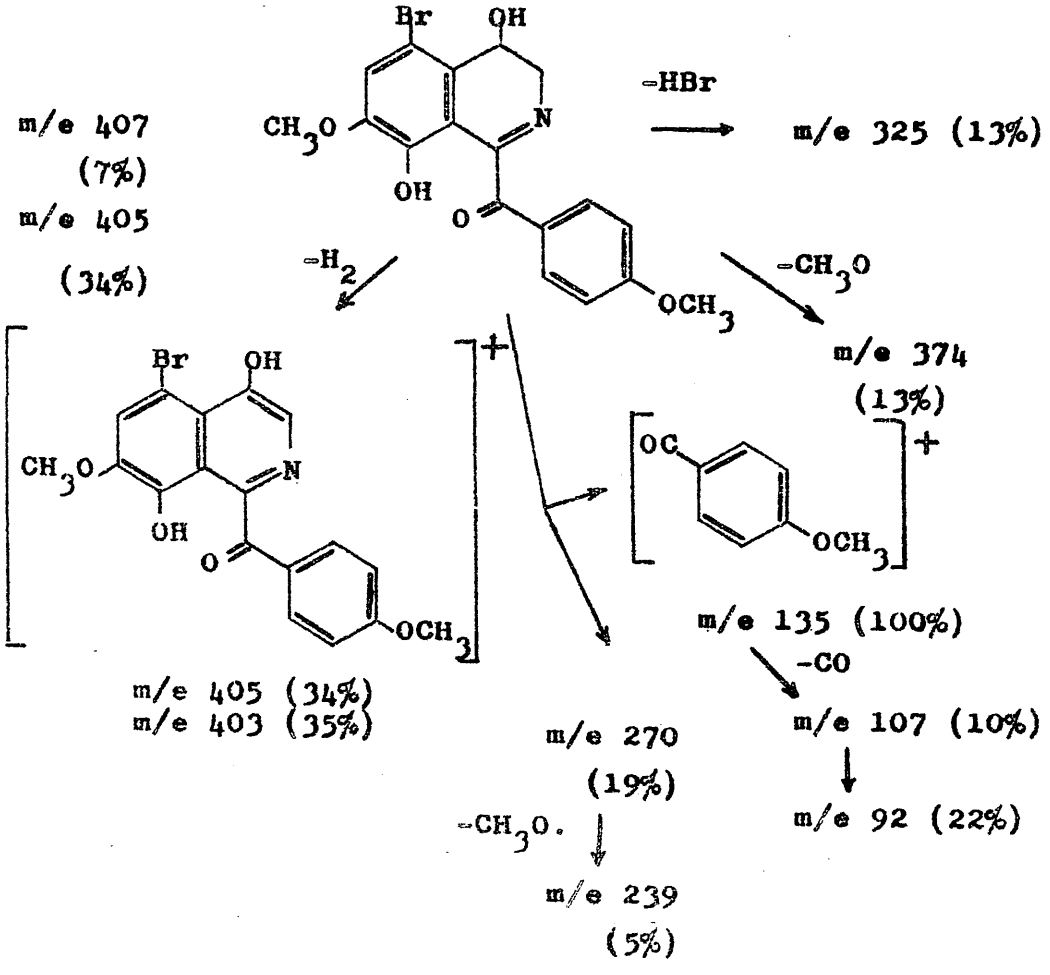


(30)

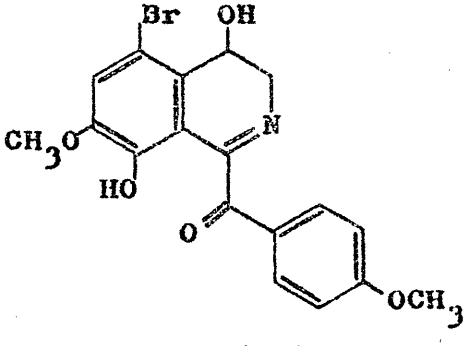
which can be most readily explained in terms of further oxidation (replacement of CH_2 by C=O). However the

Scheme 4 Mass spectrum of cyclisation product (31).

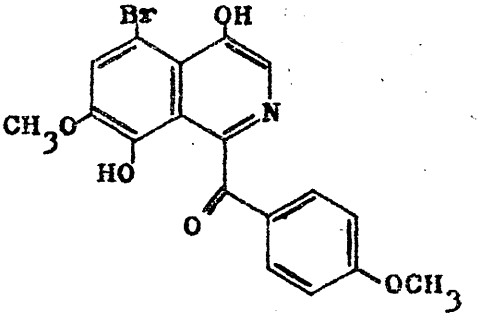
m/e	% abund.	m/e	% abund.	m/e	% abund.
407	7	325	13	146	5
405	34	296	6	136	13
403	35	272	14	135	100
390	3	271	8	107	10
388	4	270	19	92	22
386	3	269	9	77	25
377	4	241	5	76	7
376	10	239	5	64	12
375	6	192	10	63	11
374	13				



n.m.r. spectrum showed an ABX system, with a two-proton multiplet between 6.8τ and 7.8τ. The spectral information available indicated that the point of oxidation was probably the remaining benzylic carbon atom and the structure which can be most readily accommodated is that of the alcohol (31) ($\nu_{max.}$ 3608 cm^{-1}, ε 22). A 4-oxo-isoquinoline structure (32) can be discounted on the basis of the absence of a low-field aromatic signal expected from the proton α to the ring nitrogen.



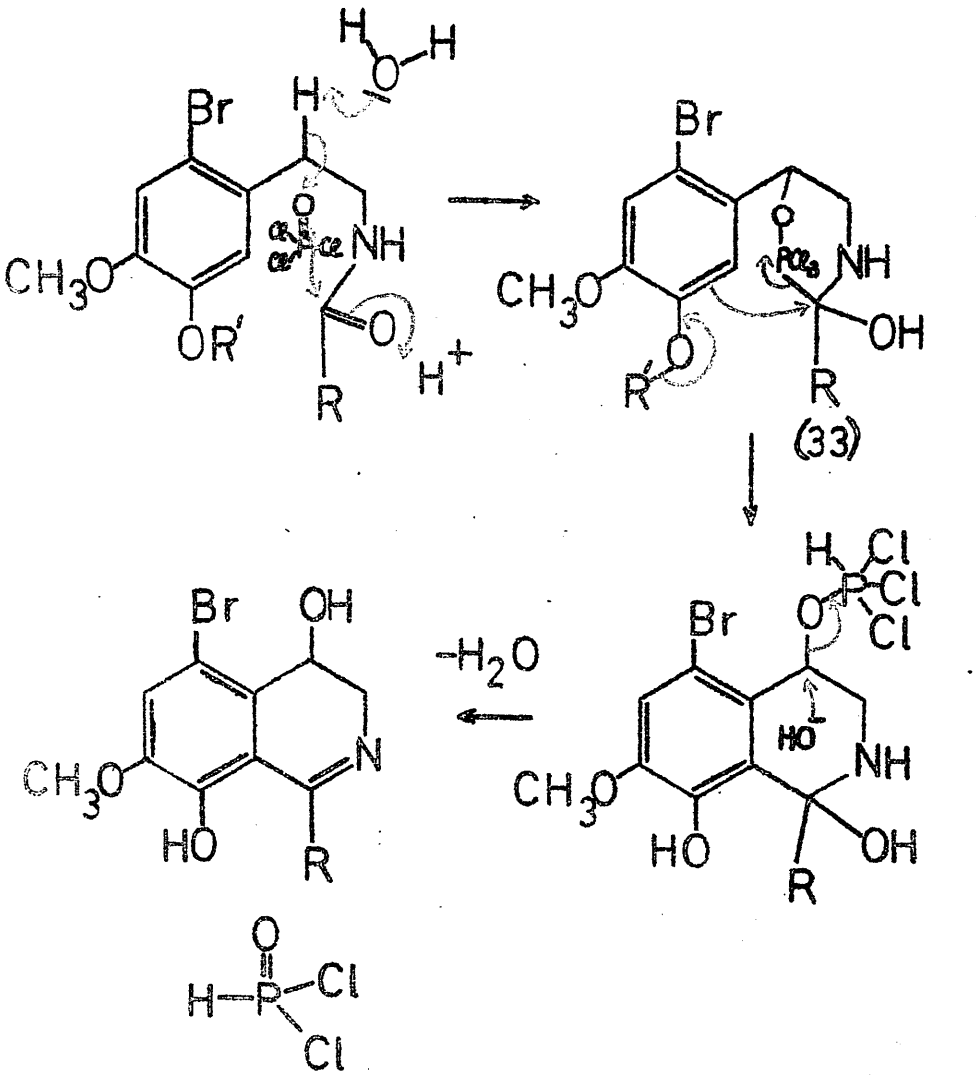
(31)



(32)

Although the highest molecular ion was at m/e 403, evidence that the true molecular weight was in fact 405 was provided by the following mass spectral characteristics (see Scheme 4). Firstly the base peak at m/e 135, arising by fission of the p-methoxy benzoyl group, can be correlated with the reasonably abundant (19%) bromine-containing ion at m/e 270 only on the basis of a parent of m/e 405. Secondly, the peak at m/e 374 can be better explained in terms of loss of 31 (CH_3O) from a parent of m/e 405 than as loss of 29 from a parent of m/e 403,

Scheme 5. **Mechanism of formation of 4-hydroxyisoquinoline derivative.**



especially as a loss of 31 is apparently observed in a transition of m/e 270 to m/e 239. Thirdly, the ion arising by debromination appears at m/e 325. Now loss of bromine from a parent of m/e 403 would produce an ion at m/e 324: however, loss of hydrogen bromide from a parent of m/e 405 would yield this ion (m/e 325). Loss of two mass units from the parent can be readily accommodated, since this is merely an aromatisation step.

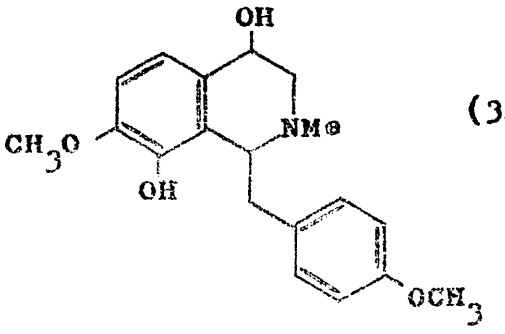
The mechanism by which this compound is produced is not immediately obvious. While oxidation at the acyclic methylene group of 1-benzyl 3,4-dihydroisoquinolines is well known to occur very readily[44-47] (especially under basic conditions,[44] and even on an alumina column[45]) oxidation at C_4 is without precedent. The completeness of the oxidation at this point and the fact that oxidation at the acyclic methylene group has been shown to be a secondary process, only occurring during work-up, suggest that this oxidation occurs as an integral part of the cyclisation reaction. It is possible to envisage oxidation by means of phosphorous oxychloride, giving a highly reactive intermediate such as (33) in Scheme 5. This mechanism is to be further investigated.

Although the isolated cyclisation product did not possess the expected properties it was thought that reductive removal of the unwanted oxygen might be

achieved in the later stages of the synthetic scheme.

The crude cyclisation product, without purification (in order to minimise aerial oxidation), was immediately reduced with methanolic sodium borohydride to yield a green oil which possessed the expected u.v. absorptions of a tetrahydroisoquinoline and a highly complex n.m.r. spectrum, which did not exhibit any low-field signals for carbonyl-deshielded protons. This crude material was now hydrogenolysed over 10% palladium in ethanol and then submitted to reductive methylation with formaldehyde (cf. ref.48). It was found possible to combine these two steps in a single reduction. That N-methylation had been achieved was shown by n.m.r. (3H,7.67τ). The methylene protons of the benzyl substituent (7.18τ) were coupled with the methine proton at C_1 (5.94τ). This implies that the major part of the cyclisation product was not in fact oxidised at the acyclic methylene, as borohydride is known[46] only to reduce carbonyl groups of this type to the corresponding alcohols.

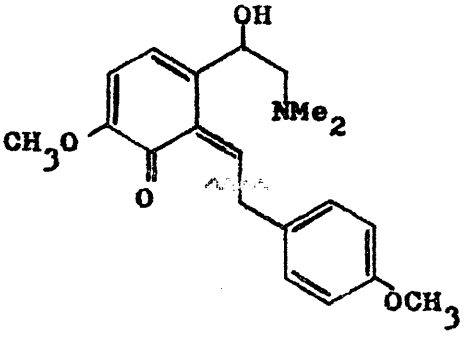
The N-methyl tetrahydroisoquinoline (34) was now



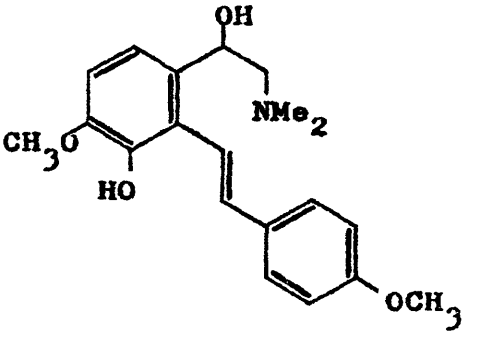
(34)

quaternised with methyl iodide. The quaternary salt was found to undergo Hofmann elimination under exactly analogous conditions to those used for petaline iodide (see later), the product being a yellow gum. This product was very similar to leonticine, being slightly more polar. Like the latter it exhibited pale blue fluorescence and gave a deep purple coloration with ferric chloride. In addition both stained a characteristic bright blue colour on t.l.c. development with ceric ammonium nitrate. Its u.v. spectrum was virtually identical to that of leonticine under all conditions of pH. The i.r. spectrum showed strong absorption at 1610 cm^{-1}. The aromatic, olefinic, methoxyl, and N-methyl protons in the n.m.r. spectrum appeared at almost exactly the same positions as in leonticine. The very close similarity in the olefinic and aromatic region confirms the 7,8-dioxygenation pattern assigned to petaline and leonticine. The methylene resonances of leonticine and of pseudoleonticine (4) were not present in the stilbene derived from the current synthesis, although a signal (ca. two protons) was spread over the 6.2-7.5τ region. Comparison of the mass spectral parent ion (m/e 341) with that of leonticine (m/e 327) still showed a difference of 14 mass units, again suggesting an oxygenated analogue.

In the mass spectra of both leonticine and the synthetic product an ion of m/e 121 was present. This could be explained by cleavage of the p-methoxybenzyl moiety, as in (35). The spectral characteristics of the stilbene are not inconsistent with the hydroxyleonticine structure (36). The parent molecular ion can be explained in terms of oxidation of the sample prior to measurement.



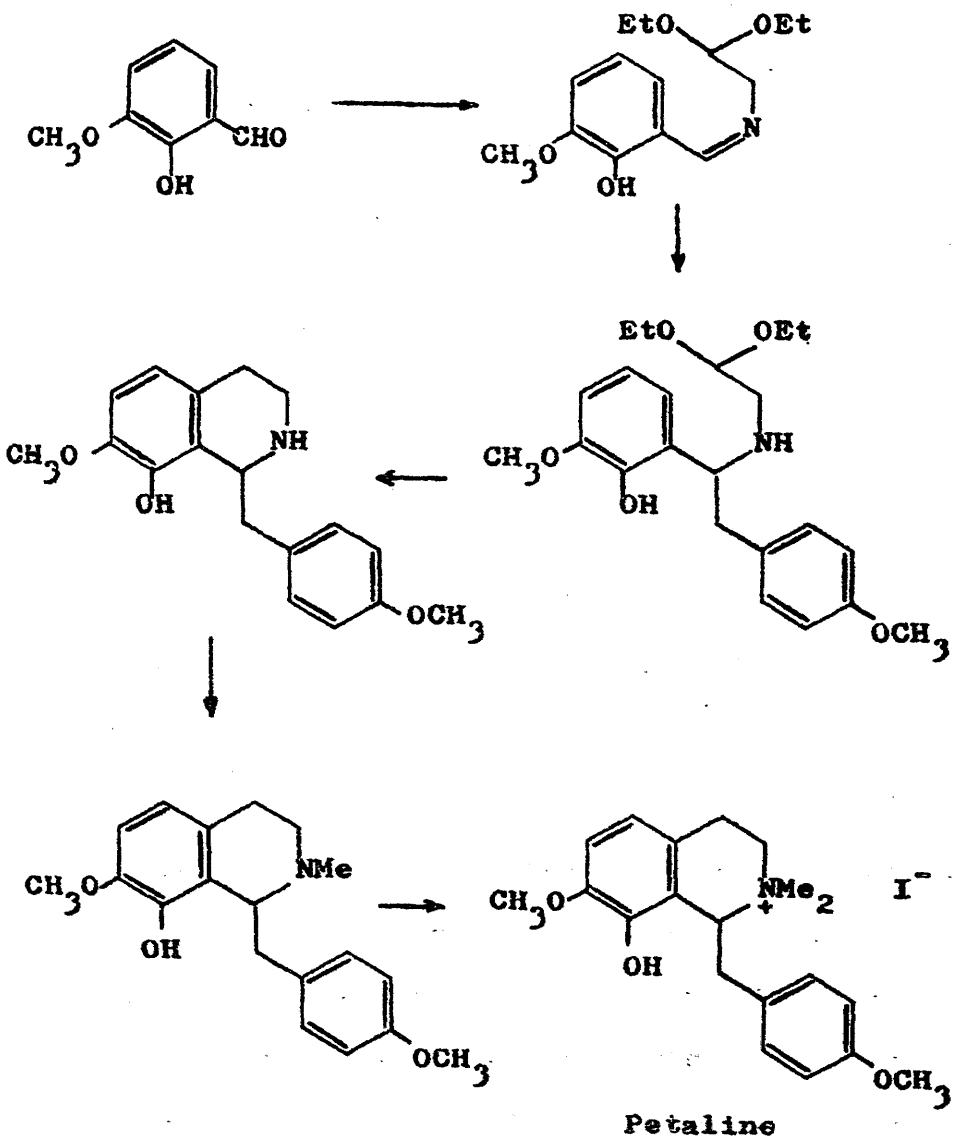
(35)



(36)

Several unsuccessful attempts were made to remove the unwanted benzylic hydroxyl group. These included hydrogenolysis over 10% palladium in glacial acetic acid, at room temperature or at 70°, reduction with zinc and sulphuric acid, hydrogenolysis via the tosylate, or by hydrogenolysis in concentrated hydrochloric acid or acetic acid with added perchloric acid. (The last two methods yielded an even more polar product, cursory examination of which indicated possible cleavage of the methoxyl groups).

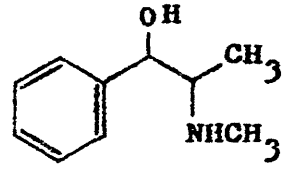
Scheme 6 **Synthetic route to petaline**[25]



Petaline

Hydroxyleonticine (36) bears a marked resemblance to ephedrine (37). Reference to the deoxygenation of the latter alkaloid[49] suggests a possible mode of removal of the hydroxy substituent would be via reduction of a halo derivative and this has to be investigated further.

A compound of identical R_f and similar staining characters to hydroxyleonticine has been obtained from



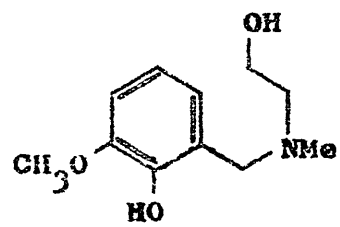
Ephedrine

(37)

leonticine when a chloroform solution of the latter was allowed to stand exposed to the atmosphere. However, unlike hydroxyleonticine, this product showed no fluorescence (on plates). This compound could for example, be a peroxy derivative.

The recently reported modification of the Pomeranz-Fritsch reaction developed by Bobbitt[25] and employed in the synthesis of 7-methoxy-8-hydroxyisoquinolines suggested an alternative route to petaline. The synthetic scheme shown in Scheme 6 was investigated. The Schiff base, derived by reaction of o-vanillin and amino-acetal, was subjected to Grignard reaction[cf.50]

with p-methoxybenzyl magnesium chloride. The reaction mixture was hydrolysed by 6N hydrochloric acid and allowed to stand overnight in the acid solution, which was then catalytically reduced over 10% palladium on C. The basic product was then reductively methylated. The major product at this stage was shown by t.l.c. to be the N-methylated amino-phenol (38), prepared independently by reaction of o-vanillin and ethanolamine followed by reduction and methylation.

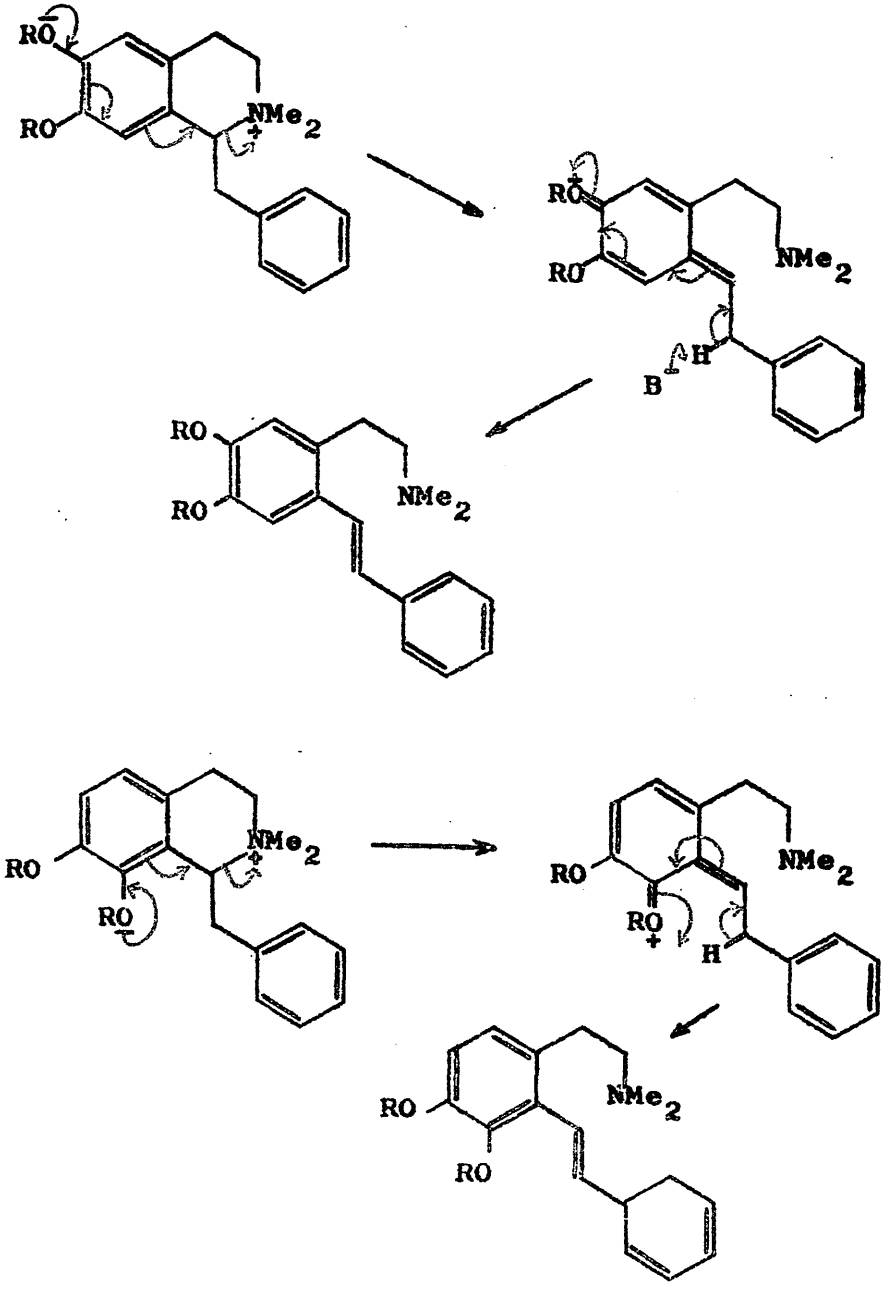


(38)

The crude mixture of methylation products was allowed to react with methyl iodide overnight and the product submitted to the usual Hofmann elimination conditions (see later). From the variety of products were detected two pale blue fluorescent materials, both of which had the characteristic bright blue staining (with ceric ammonium nitrate) and u.v. spectral characteristics of 7,8-dioxygenated stilbenes. One of these had the R_f of leonticine and the other the R_f of hydroxyleonticine. It is conceivable that the latter could arise as an intermediate in the cyclisation process. These two

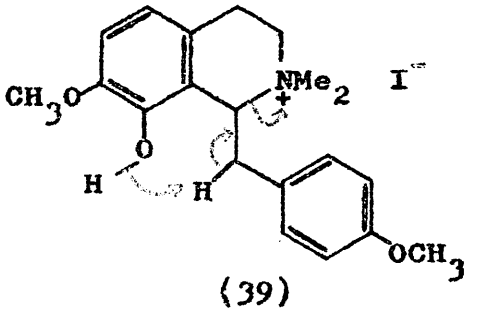
components were isolated in only trace amount (probably due to failure at the Grignard stage) and insufficient material was produced for full identification. However since the full experimental details of the Bobbitt modification have now been published[25], it may be possible to improve this synthetic method.

Scheme 7 **Participation in the Hofmann elimination.**



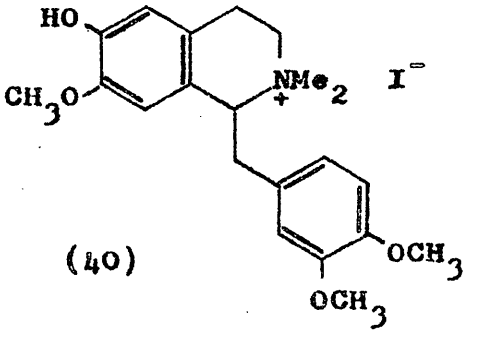
THE HOFMANN DEGRADATION OF PETALINE AND OTHER OXYGENATED BENZYLISOQUINOLINES

Smith has reported[17] that the Hofmann elimination of petaline to leonticine occurs on passage of a solution of the chloride or reineckate through Amberlite IRA 400 (OH) anion exchange resin. These mild conditions were taken as evidence of participation by the phenolic function as in (39).[18a] Warnhoff[51] has suggested that



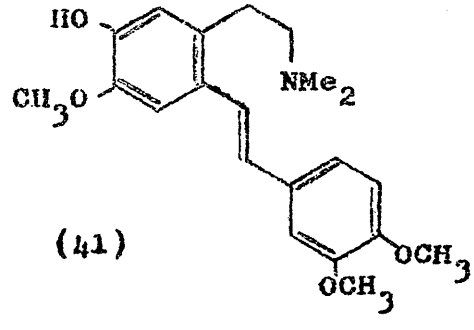
(39)

an alternative mechanism of participation may operate as shown in Scheme 7. In order to investigate this point a similar reaction was carried out on pseudolaudanine methiodide (40), the required base being



(40)

prepared by borohydride reduction of the phenolic zwitterion obtained by the action of mild base on papaverine methiodide.[52] Catalytic reduction or chemical reduction employing tin and hydrochloric acid did not produce a reasonable yield of the desired base. It was found that when an alcoholic solution of pseudolaudanine methiodide was cycled through a column of the ion exchange resin and evaporated to dryness the product possessed a typical stilbenoid u.v. spectrum.[18] The u.v. absorptions of the solution from the column, however, did not have such a pattern, but instead possessed maxima characteristic of the quaternary hydroxide. Only on heating this solution did elimination occur to give pseudolaudanine methine (41).

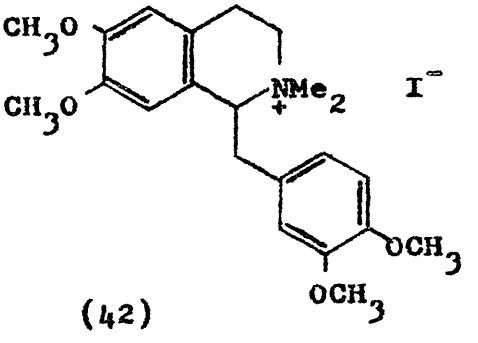


(41)

On reinvestigation of the petaline/leonticine conversion it was found that a similar situation existed. Passage through the resin does not in fact cause elimination. This occurs only on evaporation to dryness under reduced pressure or on warming a concentrated

alcoholic solution of the quaternary hydroxide.

Since these results indicated a similar degree of lability in the quaternary hydroxides, which may be a function of their 6- or 8-hydroxy substituents, the Hofmann elimination of laudanosine methiodide (42) was studied. Under similar conditions the latter was converted by the resin into the quaternary hydroxide, which on evaporation to dryness under reduced pressure yielded a mixture of two products (t.l.c.), the u.v. spectrum



(42)

of which indicated the cis and trans stilbenes. The elimination appears to occur with ease equal to that with which those of petaline hydroxide or pseudo-laudanine methchydroxide occur.

Some light was shed on the mechanism by a reinvestigation of the Hofmann elimination of pseudopetaline iodide (3). As reported previously[18,18a] the latter was converted to a quaternary hydroxide by the ion exchange resin. This hydroxide was, however, not heat-labile and did not eliminate on evaporation under

Table 2. U.V. Absorptions of alcoholic solutions directly eluted from ion exchange resin.

$\lambda_{max.}$ (relative optical densities).							
Pseudolaudanine methohydroxide							
226	(2.29)	260	(1.04)	282	(1.0)	305	(0.49)
Petaline hydroxide							
230	(2.27)	260	(1.14)	278 285	(1.0) (1.0)	300	(0.83)
Pseudopetaline hydroxide							
231	(2.35)	259	(0.96)	278 284	(0.95) (1.0)	300	(0.83)
Laudanosine methohydroxide							
214	(2.35)	235	(2.50)	282	(1.0)		
O-methyl pseudopetaline hydroxide							
(i) directly from column:							
235	(1.68)	262	(0.81)	278 284	(1.0) (1.0)	300	(0.56)
(ii) on evaporation to dryness:							
229	(1.77)	279 285	(0.90) (1.00)	302	(0.96)	328	(0.78)

reduced pressure or on gentle warming on the steam-bath. Successful conversion to the stilbene was achieved by Magrill[18] only on refluxing with alcoholic, sodium ethoxide.

Treatment of a sample of petaline iodide with excess diazomethane, followed by attempted Hofmann elimination of the product (passage through resin and evaporation to dryness) produced material with a u.v. spectrum ($\lambda_{max.}$ at 325 mμ and increased intensity ca. 300 mμ), which suggested partial conversion to a stilbene.

A study of the above results (see Table 2) suggests that facile decomposition of the quaternary hydroxide will occur whenever there is an electron-releasing substituent in the 6- or 8-position (Scheme 7), unless in the case of a methoxyl group there is a free phenolic function ortho to it, which can prevent electron release by hydrogen bonding.

EXPERIMENTAL

Bromination of isovanillin. (cf. ref. 30)

Isovanillin (10.09g.) was dissolved in chloroform (70ml.) and a solution of bromine (10.99g.) in chloroform (25ml.) added dropwise under nitrogen to the stirred refluxing solution during a 20 minute period. Heating was discontinued when the addition was complete and the mixture stirred for a further hour under nitrogen, then allowed to stand overnight. The precipitate was collected, washed with cold water and dried to give a colourless solid (3.82g., 25%), shown by m.p. (ca. 185-202°) and i.r. to be predominantly the unwanted 2-bromo isomer. The filtrate was evaporated to dryness and the sticky colourless residue thoroughly washed with cold water and dried to yield a colourless crystalline solid (11.43g.) shown by i.r. to be essentially pure 6-bromoisovanillin monohydrate. Crystallisation of this fraction from 1:1 aqueous methanol, followed by drying at 50°, gave colourless needles (9.64g., 63%), m.p. 113.5-117°. Identification by i.r. spectral comparison with those of authentic samples proved to be the most reliable indication of purity of the isomers.

τ values for 6-bromoisovanillin (CF_3CO_2H): 0.13 (1H,s), 2.37 (1H,s), 2.72 (1H,s), 5.91 (3H,s).

When the bromination was carried out on a larger scale the addition of the halogen had to be carefully regulated in order to control the copious evolution of the gaseous hydrogen bromide generated. Purification on the larger scale was effected by fractional crystallisation from aqueous methanol.

5-Benzyloxy-2-bromo-4-methoxybenzaldehyde.[18]

6-Bromoisovanillin (43.85g.) was dissolved in absolute ethanol (1 litre). To this solution was added anhydrous potassium carbonate (22g.) and benzyl chloride (100ml.). The mixture was refluxed for 6½ hours, cooled, filtered, and concentrated to ca. 100ml. After standing overnight at 0°, the benzylated compound was obtained as a cream-coloured crystalline solid (35.69g., 63%), m.p. 143-144.5° (lit. 142-145°).
$\nu_{max.}$(Nujol): 1680 cm^{-1}.

5-Benzyloxy-2-bromo-4-methoxy-β-nitrostyrene.[18]

A mixture of 5-benzyloxy-2-bromo-4-methoxybenzaldehyde (35.5g.), ammonium acetate (19g.) and nitromethane (50ml.) in glacial acetic acid (400ml.) was refluxed for 3 hours, then cooled. The precipitate was collected and dried over KOH to give the nitrostyrene as a bright yellow solid (32.51g., 78%), m.p. 151-167°, identity

with an authentic sample being established by i.r. $\nu_{max.}$ (Nujol): 1620, 1590 cm^{-1}.

N-[2-(5-Benzyloxy-2-bromo-4-methoxyphenyl)-ethyl]-p-methoxyphenylacetamide.[18]

A solution of 5-benzyloxy-2-bromo-4-methoxy-β-nitrostyrene (22.12g.) in sodium-dried tetrahydrofuran (300ml.) was added during 15 minutes to a stirred suspension of lithium aluminium hydride (9g.) in anhydrous ether (500ml.). The excess reagent was immediately destroyed with ethyl acetate and the complex decomposed with water. The overall reaction time was 30 minutes. The organic solution was decanted from the inorganic residue which was washed with ether (2x50ml.), the washings being combined with the decanted solution. Evaporation gave a viscous red oil which was dissolved in dry ether and treated with gaseous hydrogen chloride. The hydrochloride was precipitated as an orange gum. This was dissolved with difficulty in a mixture of ether (250ml.) and 4N sodium hydroxide (200ml.) in water (450ml.). The resultant two-phase system was treated with an excess of crude homoanisoyl chloride (ca. 20g.) and the mixture stirred at room temperature for two hours. The precipitated cream-coloured solid (20.25g.) was collected and washed successively with dilute alkali,

acid, and water. Fractional crystallisation from ethanol afforded colourless needles (6.36g.,21.6%), shown to be the desired brominated amide (14) by m.p., 149.5-151.5° (lit. 152-153.5°) and i.r.
τ values ($CDCl_3$): 2.55 (5H,s), 2.82 (2H,d, J=9c/s.), 2.92 (1H,s), 3.12 (2H,d, J=9c/s.), 3.22 (1H,s), 4.40 (1H,broad), 4.91 (2H,s), 6.12 (3H,s), 6.20 (3H,s), 6.54 (2H,s), 6.55 (2H,m), 7.19 (2H,t).

Crystallisation from benzene of the residual semi-solid obtained by concentration of the mother liquors, yielded a colourless solid (3.07g.), identified by m.p., 123-127° (lit.[18] 122-123°), and i.r. as the bromine-free amide. The remainder of the material was an intractable red-brown gum. Over a series of experiments the best yield of pure brominated amide was only 26.8%.

5-Benzyloxy-2-bromo-4-methoxy-β-phenylethylamine.

In one experiment reduction of 5-benzyloxy-2-bromo-4-methoxy-β-nitrostyrene (6.57g.) yielded the amine as a semi-solid mass (6.56g.), from which part was obtained as a colourless solid (1.01g.), sparingly soluble in ether and moderately soluble in cold chloroform. The latter product was crystallised from benzene as colourless crystals, m.p. 134-5-137°.

$\nu_{max.}$ (Nujol): 2250, 1640 (w), 1385, 1260, 1220, 1170,

1025 cm^{-1}.

$\lambda_{max.}$: 237 mμ (log ε 3.79), 285 mμ (log ε 3.47).

τ values ($CDCl_3$): 2.60 (5H,s), 2.93 (1H,s), 3.13 (1H,s), 3.25 (2H, broad), 4.86 (2H,s), 6.13 (3H,s), 7.05 (2H,m), 8.03 (2H,m).

Found: C, 56.32; H, 6.38; N, 3.53

$C_{16}H_{18}O_2NBr$ requires: C, 57.15; H, 5.39; N, 4.17%.

Addition of hydrochloric acid to a concentrated aqueous solution caused precipitation of a colourless solid. Treatment of a sample with homoanisoyl chloride in a medium containing ether and aqueous sodium hydroxide caused conversion to the brominated amide, identified by i.r.

N-[2-(5-Benzyloxy-2-bromo-4-methoxyphenyl)-ethyl]-p-methoxyphenylpyruvamide.

N-[2-(5-Benzyloxy-2-bromo-4-methoxyphenyl)-ethyl]-p-methoxyphenylacetamide (1.91g.) was dissolved in chloroform (30ml.) which had been dried by recycling through a column of blue silica gel several times. Solid phosphorous pentachloride (4.34g.) was added and the mixture stirred at room temperature under nitrogen. After stirring for ca. 20 minutes the clear golden-yellow solution became turbid and over the next 10 minutes fairly heavy precipitation took place. Stirring was

continued under nitrogen for 15 hours, then in a sealed system for a further 30 hours, when most of the precipitated solid had redissolved and the solution was greenish in colour. The solvent was evaporated at room temperature to give a brown gummy residue. The excess reagent was destroyed by cautious treatment with methanol. The addition of water caused precipitation of an oil which solidified on the addition of methanol and warming. The solid (730mg.) was filtered and the filtrate treated with water, causing precipitation of a second crop of colourless solid (410mg.). Two further crops of solid material (178mg., 72mg.) were obtained by successive treatments of the filtrate with water. That the first two fractions were essentially pure product was indicated by t.l.c. (100% chloroform) which also showed that the latter two were quite heavily contaminated by starting material. The α-keto amide (red spot with D.N.P. spray) was obtained by crystallisation of the first two fractions from ethyl acetate/petroleum ether as colourless needles (760mg., 39%), subliming above 135° to needles, m.p. 141.5-143°. (lit.[18] 136.5-138°).

$\nu_{max.}$ ($CHCl_3$): 3418 cm^{-1} (ε 93), 1685 cm^{-1} (ε 357), 1661 cm^{-1} (ε 614), 1598 cm^{-1} (ε 857), 1571 cm^{-1} (ε 194).

$\lambda_{max.}$: 215 mμ (log ε 4.39), 230 mμ (log ε 4.23), 291 mμ (log ε 4.18).

τ values ($CDCl_3$): 1.53 (2H,d, J=9.6c/s.), 2.59 (5H,s), 2.61 (1H,m), 2.90 (1H,s), 3.02 (2H,d, J=9.6c/s.), 3.12 (1H,s), 4.89 (2H,s), 6.11 (6H,s), 6.36 (2H,m), 7.05 (2H,t).

Parent molecular ion at m/e 497. Base peak at m/e 135.

Found:

(i) from ethyl acetate/petroleum ether:

C, 60.77; H, 5.46; N, 2.80

(ii) after drying at 100° for 72 hours:

C, 60.59; H, 4.87

(iii) from aqueous methanol:[18]

C, 60.24; H, 5.2; N, 3.1; Br, 15.8

$C_{25}H_{24}O_5NBr$ requires: C, 60.24; H, 4.82; N, 2.81; Br, 16.03%

N-[2-(5-benzyloxy-2-bromo-4-methoxyphenyl)-ethyl]-p-methoxyphenylacetamide was unaffected by manganese dioxide in chloroform at room temperature even after shaking for 17 hours. The total absence of the α-keto amide was confirmed by t.l.c.

Catalytic reduction of N-[2-(5-benzyloxy-2-bromo-4-methoxyphenyl)-ethyl]-p-methoxyphenylpyruvamide.

(a) The α-keto amide (385mg.) was dissolved in ethanol (110ml.) and the solution hydrogenated over 10% Pd on C (310mg.) for 2 hours. The solution was filtered and evaporated to yield a brown oil (340mg.), with a strong

aromatic odour (toluene?), shown by t.l.c. to contain the same mixture of products as was obtained in (b) below.

(b) The α-keto amide (620mg.) in ethanol (150ml.) was reduced over Adams' catalyst (175mg.) at a pressure of 4 atmospheres (55-60lbs./sq.in.) for 5 hours. The product was a colourless gum, shown by t.l.c. (10% methanol-chloroform) to contain the same mixture of products as was obtained in (a) above, but in a different ratio (see below). Preparative t.l.c. allowed the separation of two main bands of R_f 0.4-0.55 and R_f 0.65-0.80.

conditions	more polar	:	less polar
normal pressure	5	:	2
4 atmospheres	3	:	5

(i) More polar product: This was initially a colourless gum, but repeated p.l.c. afforded a colourless solid (90mg.), m.p. 109-112°. (no reaction with 2,4-dinitrophenylhydrazine).

$\nu_{max.}$ (KCl): 3495, 3350, 1654, 1609, 1584, 1574, 1536, 1509 cm^{-1}.

$\lambda_{max.}$ 231.5 mμ (log ε 3.90), 277 mμ infl. (log ε 3.55), 282 mμ (log ε 3.64), 289 mμ infl. (log ε 3.63).

τ values ($CDCl_3$): 2.83 (1H,s), 3.08 (1H,s), 3.17-3.50 (4H, complex), 6.17 (3H,s), 6.22 (3H,s), 6.58 (2H,m), 7.38 (2H,t)., 5.09 (1H,s).

Parent molecular ion at m/e 409. Base peak at m/e 137. The compound was not analysed, but the spectral information listed above indicates that it is N-[2-(2-bromo-5-hydroxy-4-methoxyphenyl)-ethyl]-α-hydroxy-p-methoxyphenylacetamide. (18)

(ii) Less polar fraction: This was separated from non-polar ketonic material (42mg.) and was isolated as a colourless gum (160mg.). This was shown by t.l.c. to consist of two materials of very similar polarity. Repeated p.l.c. yielded a colourless gum (70mg.) (no reaction with 2,4-dinitrophenylhydrazine).

$\nu_{max.}$ (Nujol): 3400, 1650 cm^{-1}.

$\lambda_{max.}$: 229, 277, 281.5 mμ.

τ values ($CDCl_3$): 2.69 (2H, d, J=9.6c/s.), 3.10 (2H,d, J=9.6c/s.), 3.22 (2H, broad), 4.25 (1H, broad), 6.12 (3H,s), 6.60 (2H,m), 6.70 (2H,s), 7.28 (2H,t).

No parent molecular ion could be recorded, the mass spectrum suggesting the possibility of self-intermolecular reaction. This product was not investigated further.

N-[2-(5-Hydroxy-4-methoxyphenyl)-ethyl]-p-methoxyphenylacetamide.

N-[2-(5-Benzyloxy-2-bromo-4-methoxyphenyl)-ethyl]-p-methoxyphenylacetamide (525mg.) was suspended in

ethanol (150ml.) and hydrogenated over 10% palladium on charcoal (180mg.) for one hour. The product was soluble and the solution gradually clarified during the reduction. Uptake ceased after about 10 minutes. Filtration (glass paper) and evaporation yielded a brown gum which was purified by p.l.c. (10% methanol-chloroform) to give the phenolic amide as a colourless crystalline solid (225mg., 71%), which crystallised from ethyl acetate-petroleum ether in colourless needles, m.p. 118.5-121°.

$\nu_{max.}$ (KCl): 3437, 3322, 1643, 1615, 1552, 1516 cm^{-1}.

$\lambda_{max.}$ (EtOH): 228.5 mμ (log ε 4.25), 278 mμ (log ε 3.75), 282.5 mμ (log ε 3.74); (basic): 222.5 mμ (log ε 4.30), 247 mμ (log ε 4.02), 284.5 mμ (log ε 3.80), 295 mμ (log ε 3.80).

τ values ($CDCl_3$): 2.82 (2H,d, J=9c/s.), 3.10 (2H,d, J=9c/s.), 3.29 (2H, broad s), 3.38 (1H,s), 4.50 (1H, broad), 6.12 (3H,s), 6.18 (3H,s), 6.52 (2H,s), 6.54 (2H,m), 7.38 (2H,t).

Parent molecular ion at m/e 315.

Found: C, 68.44; H, 6.55; N, 4.74

$C_{18}H_{21}O_4N$ requires: C, 68.58; H, 6.67; N, 4.44%.

N-(2-Cyclohexylethyl)-cyclohexylacetamide.

N-[2-(5-Benzyloxy-2-bromo-4-methoxyphenyl)-ethyl]-p-methoxyphenylacetamide (370mg.) was suspended in

ethanol (125ml.) and hydrogenated over Adams' catalyst (160mg.) for 3½ hours. The total uptake, inclusive of that of the catalyst, was 300ml. Filtration and evaporation gave a colourless gum which was submitted to p.l.c. (10% methanol-chloroform) from which the major band, of R_f ca. 0.8, yielded a sticky colourless solid (97mg.), m.p. 78.5-91°. Repeated p.l.c. gave a distinct band of R_f 0.67-0.85, which afforded the aliphatic amide as a colourless solid (66mg., 34%), readily soluble in cold chloroform or methanol and moderately soluble in petroleum ether. Crystallisation from aqueous methanol gave colourless needles, m.p. 95-98°.

$\nu_{max.}$ (KCl): 3313, 3092, 2928, 2854, 1641, 1554, 1442 cm^{-1}

$\lambda_{max.}$: only end-absorption.

τ values ($CDCl_3$): 4.40 (broad), 6.7 (m), 7.90-9.00 (multiple broad signal).

Parent molecular ion at m/e 251.

Found: C, 76.96; H, 12.39; N, 5.21

$C_{16}H_{29}ON$ requires: C, 76.44; H, 11.63; N, 5.57%.

N-[2-(2-Bromo-4-methoxy-5-O-p-methoxyphenylacetyl)-phenylethyl]-p-methoxyphenylacetamide. Amido-ester (24).

2-Bromo-5-hydroxy-4-methoxyphenylethylamine (1.34g.) was dissolved in a mixture of 1N sodium hydroxide (35ml.) and ether (10ml.). To the stirred mixture was added a

solution of homoanisoyl chloride (2.18g.) in ether (6ml.). There was almost immediate precipitation of a light brown solid. After stirring for 90 minutes the product was filtered and washed with water to give a light tan-coloured solid (1.97g.). Crystallisation from ethyl acetate-petroleum ether gave the amido-ester as colourless needles (1.31g.,44%), m.p. 144-146.5°.

$\nu_{max.}$ (KCl): 3348, 1752, 1659, 1613, 1590, 1543, 1515, 1504, 1244, 1144, 1129 cm^{-1}.

$\lambda_{max.}$ (EtOH): 234.5 mμ (log ε 3.99), 277 mμ (log ε 3.74), 282 mμ (log ε 3.73); (base): 235, 250, 276.5, 283.5, 303 mμ.

τ values ($CDCl_3$): 2.64 (2H,d, J=9c/s.), 2.86 (2H,d,J=9c/s. 2.90 (1H,s), 3.08 (2H,d, J=9c/s.), 3.15 (2H,d, J=9c/s.), 3.19 (1H,s), 4.30 (1H, broad), 6.18 (2H,s), 6.22 (3H,s), 6.24 (3H,s), 6.27 (3H,s), 6.58 (2H,s), 6.57 (2H,m), 7.22 (2H,t).

Found: C, 59.77; H, 5.01; N, 2.87

$C_{27}H_{28}O_6NBr$ requires: C, 59.77; H, 5.17; N, 2.58%.

The amido-ester was unaffected by dilute hydrochloric acid at room temperature.

N-[2-(2-Bromo-5-hydroxy-4-methoxyphenyl)-ethyl]-p-methoxyphenylacetamide. Bromo phenolic amide (22).

The above amido-ester (165mg.) was suspended in

methanol (6ml.) and 4N sodium hydroxide (6ml.). The mixture was warmed on the steam-bath for a few minutes, when the solid dissolved to give a pale yellow solution. This was allowed to cool and was then acidified with dilute hydrochloric acid and thoroughly extracted with chloroform. The extract was washed twice with saturated sodium bicarbonate, once with water, then dried. Evaporation gave a gum which was submitted to p.l.c. (10% methanol-chloroform). The main fraction, R_f 0.60, yielded the bromo phenolic amide as a colourless gum (111mg.), shown to be free of starting material by t.l.c. This solidified on trituration with chloroform. Crystallisation from ethyl acetate-petroleum ether gave small stout needles (75mg., 62%), m.p. 124.5-125.5°.

$\nu_{max.}$ (Nujol): 3360, 3300, 1645 cm^{-1}.

$\lambda_{max.}$: 230 mμ (log ε 3.76), 278 mμ (log ε 3.28), 284 mμ (log ε 3.32), 294 mμ (log ε 3.03).

τ values ($CDCl_3$): 2.80 (2H,d, J=9c/s.), 2.99 (1H,s), 3.10 (2H,d, J=9c/s.), 3.26 (1H,s), 3.66 (1H, broad s), 4.40 (1H, broad), 6.13 (3H,s), 6.18 (3H,s), 6.48 (2H,s), 6.53 (2H,m), 7.22 (2H,t).

Found: C, 54.55; H, 5.32; N, 3.94

$C_{18}H_{20}O_4NBr$ requires: C, 54.83; H, 5.08; N, 3.55%.

Reaction of the amido-ester (24) with phosphorous pentachloride.

A solution of the amido-ester (70mg.) in dry chloroform (5ml.) was treated with phosphorous pentachloride (110mg.). The mixture was stirred under nitrogen at room temperature for 72 hours. The solvent was evaporated and the residue treated with aqueous methanol, the products then being extracted with chloroform. Preparative t.l.c. (100% chloroform) of the products yielded three fractions. Fraction A, R_f 0.72-0.84, yielded a non-ketonic (D.N.P.) colourless gum (10mg.): fraction B, R_f 0.56-0.72, gave a ketonic colourless gum (30mg.): fraction C, R_f 0.44-0.56, afforded more ketonic gum (8mg.). Fractions B and C were shown by t.l.c. to contain the same two carbonyl components and were combined and repurified by p.l.c. (10% methanol-chloroform). The least polar material was detected by D.N.P. development. Extraction afforded a colourless wax (29mg.).

$\nu_{max.}$ (Nujol): 3400, 2850, 1755, 1675, 1665, 1600 cm^{-1}.

$\lambda_{max.}$ (neutral): 228, 279, 284, 288, 297 mμ; (basic): 225, 252, 278, 285, 297 mμ.

τ values ($CDCl_3$): 1.53 (2H,d, J=9.6c/s.), 2.5-3.2 (8H, complex), 6.0-6.30 (11H, $3xOCH_3$ and ester methylene), 6.50 (2H,m), 7.04 (2H,t).

The minor carbonyl component had $\nu_{max.}$ (Nujol) at 3400 (broad), 1655, and 1600 cm^{-1}.

Debenzylation of N-[2-(5-benzyloxy-2-bromo-4-methoxyphenyl)-ethyl]-p-methoxyphenylacetamide.

The benzyloxy amide (100mg.) was dissolved in a mixture of sodium-dried benzene (6ml.) and dry chloroform (1.5ml.). Stannic chloride (1ml.) was added to the solution and the mixture allowed to stand, with occasional shaking, for 24 hours. (After only 10 minutes a crystalline solid had separated). The mixture was poured into cold water and the aqueous solution extracted with chloroform. The gummy product was purified by p.l.c. (10% methanol-chloroform). A band of R_f 0.25-0.50 yielded a colourless wax which solidified on trituration with chloroform to give the bromo phenolic amide (22) as a colourless solid (56mg., 69%), identified by i.r. and t.l.c. A second fraction, R_f 0.55-0.65, afforded essentially pure benzyloxy amide (12mg.), identified by i.r. and t.l.c.

Attempted Bischler-Napieralski Cyclisations.

Cyclisations of the bromo amide (14), amido-ester (24), and bromo phenolic amide (22) were attempted under the conditions indicated in the following tables, the normal work-up being as follows.

On completion of the reaction (all carried out under nitrogen) the mixture was poured on to crushed ice, a

small amount of acid being added. The organic layer was separated and the aqueous layer extracted for neutral and acidic materials. The aqueous layer was then basified with ammonium hydroxide and extracted with chloroform to afford the basic fraction. In experiments employing phosphorous pentoxide on pumice further basic material was obtained by washing of the pumice residues with ammonium hydroxide and subsequent extraction with chloroform.

Attempted cyclisations of the bromo amide (14).

Reagents	Conditions	Neutral and Acid products	Basic * products
$POCl_3$ in chloroform	2 hours at reflux, ovnt. R.T.	Starting material (76% recovery)	None
PCl_5 in chloroform followed by $AlCl_3$	2 hours at R.T. 30 mins at R.T.	Not investigated	5.6%
PCl_5 in chloroform followed by $SnCl_4$	1 hour at R.T. 30 mins at R.T.	Starting material (46% recovery); Bromo phenolic amide (24.5%)	7.2%

Reagents	Conditions	Neutral and Acid products	Basic* products
PCl_5 in chloroform followed by P_2O_5	45 mins at R.T. 60 mins. at R.T.	Starting material (85% recovery)	None
P_2O_5 on pumice, with $POCl_3$ in benzene	Overnight reflux	Starting material and bromo-phenolic amide.	(i) 5.5% (ii) from pumice 39%.
$POCl_3$ in chloroform followed by $AlCl_3$	60 mins. at reflux 90 mins. at reflux	Not investigated	22.7%** or none
$POCl_3$ in chloroform followed by $SnCl_4$	50 mins. at reflux 30 mins. at reflux	Not investigated	9.6%** or none

* Yields of basic material are quoted as a percentage of the weight of starting material used.

** Highly variable results.

Attempted cyclisations of the amido-ester (24).

Attempted cyclisations of the amido-ester (24).

Reagents	Conditions	Neutral and Acid products	Basic products
$POCl_3$ in benzene	3 hours at reflux	Starting material and bromo-phenolic amide	None
PCl_5 in chloroform followed by $SnCl_4$	30 mins at R.T. 90 mins at R.T.	Starting material and bromo-phenolic amide	None
P_2O_5 on pumice in benzene	11 hours at reflux	Starting material (70% recovery), trace of bromo-phenolic amide	12%

Attempted cyclisations of the bromo phenolic amide (22).

PCl_5 in chloroform	5 days at R.T.	Starting material (88% recovery)	None
PCl_5 in chloroform followed by $SnCl_4$	30 mins at R.T. 60 mins at R.T.	Starting material (89% recovery)	None

Cyclisation of N-[2-(5-benzyloxy-2-bromo-4-methoxy-phenylethyl]-p-methoxyphenylacetamide.

The bromo amide (2.20g.) was dissolved in a mixture of dry benzene (20ml.) and dry freshly-distilled phosphorous oxychloride (25ml.) and the pale green solution heated under nitrogen for one hour. After cooling (15 mins.), water (0.1ml.) was added and reflux then continued for a further 60 mins. The dark red-brown mixture was allowed to cool slowly over 20 mins. and then poured into a large excess (350ml.) of petroleum ether (b.p. 40-60°). After standing for some time the solvent was decanted, the residue washed with petroleum ether, and taken up in chloroform. The solution was washed twice with ammonium hydroxide (50%), once with water, dried, and evaporated to yield a red gum (1.88g.). T.L.C. (1% methanol-chloroform) indicated two main components- one bright yellow and very polar (R_f 0.1), the other pale orange and less polar (R_f 0.4). These components had been observed previously in basic fractions from several attempted cyclisations. A sample (150mg.) of the cyclisation product was submitted to p.l.c. (10% MeOH/$CHCl_3$), which afforded two main bands. The less polar band (R_f 0.7) yielded an orange gum (30mg.): the more polar, bright yellow band (R_f 0.5) was extracted with chloroform to yield a bright yellow

solution. However on standing, even in the dark, this solution rapidly faded to pale orange and evaporation gave an orange gum (60mg.), shown by u.v. and t.l.c. to be identical to that obtained by extraction of the band of R_f 0.7. Repeated p.l.c. afforded an orange-red solid (47mg.), m.p. 177-180°, the spectral properties of which suggested that it was 5-bromo-4,8-dihydroxy-7-methoxy-1-p-methoxybenzoyl-3,4-dihydroisoquinoline.

$\nu_{max.}$ (KCl): 3500-2300 cm^{-1} (broad), 1673, 1599, 1575, 1536, 1510 cm^{-1}.

$\nu_{max.}$ ($CHCl_3$): 3523 cm^{-1} (ε 124), 3608 cm^{-1} (ε 22), 1670 cm^{-1} (ε 259), 1599, 1575 cm^{-1}

$\lambda_{max.}$ (EtOH): 224.5 mμ (log ε 4.38), 280 mμ (log ε 4.20), 333 mμ (log ε 3.47), 456 mμ (log ε 2.71); (acid-bright yellow solution): 226 mμ (log ε 4.25), 299 mμ (log ε 4.18), 414 mμ (log ε 3.43).

τ values ($CDCl_3$): 2.02 (2H,d, J=9c/s.), 2.95 (1H,s), 3.07 (2H,d, J=9c/s.), 6.14 (3H,s), 6.21 (3H,s), 6.8-7.8 (2H, m, ABX).

Highest molecular ion at m/e 403. ($C_{18}H_{16}O_5NBr$ requires 405). Base peak at m/e 135.

<u>4,8-Dihydroxy-7-methoxy-1-p-methoxybenzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline.</u>

The above crude red oil (1.72g.) was dissolved in

methanol (100ml.) and filtered free of insoluble solid material (103mg.), shown to be unreacted bromo amide (14) by i.r. and t.l.c. The filtrate was treated with 6N hydrochloric acid (5ml.) and sodium borohydride (2.5g.) added in small portions with stirring under nitrogen during 30 mins. Stirring was continued for two hours. The solution was diluted with an equal volume of water, acidified with concentrated hydrochloric acid (ice-cooling), then rebasified with ammonium hydroxide. Chloroform extraction afforded a green oil (ca.1.6g.), t.l.c. (5% MeOH/$CHCl_3$) of which indicated one major product, of R_f 0.35. A sample (200mg.) was purified by p.l.c. (10% MeOH/$CHCl_3$) to yield the 4-hydroxy-5-bromo-tetrahydroisoquinoline as a pale yellow gum (119mg.)

$\lambda_{max.}$ (rel. opt. density): 232 mμ (1.87), 279 mμ (0.93), 284 mμ (1.0), 293 mμ infl. (0.90).

τ values ($CDCl_3$): 2.88 (2H,d, J=9c/s.), 3.20 (2H,d, J=9c/s.), 2.99 (1H,s), 2.63 (1H, broad), 6.14 (3H,s), 6.24 (3H,s), highly complex spectrum in region 5-8τ.

The above green oil (ca. 1.4g.) was dissolved in ethanol (120ml.) and hydrogenated over 10% palladium on charcoal (480mg.) for 5½ hours. Filtration and evaporation yielded the bromine-free 4-hydroxytetrahydroisoquinoline as a light brown glass (1.29g.).

This was dissolved in a mixture of ethanol (100ml.) and 33% aqueous formaldehyde (20ml.) and the mixture shaken in an atmosphere of hydrogen over 10% Pd/C (450mg.) for 3½ hours. The solution was filtered, diluted with an equal volume of water, and acidified. The acid solution was extracted with ether. The aq. solution was then basified with ammonium hydroxide and extracted with chloroform. Evaporation gave an orange semi-solid (1.22g.), shown by t.l.c. (10% MeOH/$CHCl_3$) to have the same main component (R_f 0.68) as that obtained if the above two steps were combined in one catalytic reduction. The product was contaminated by formaldehyde. A sample (100mg.) was purified by p.l.c. (10% MeOH/$CHCl_3$) giving the N-methyl 4-hydroxytetrahydroisoquinoline as a pale yellow oil (34mg.).

$\lambda_{max.}$ (rel. opt. density): 233 mμ (2.70), 278 mμ (1.0), 283 mμ (1.0).

τ values ($CDCl_3$): 2.8-3.5 (6H, complex), 4.6 (1H, br.), 5.90 (1H,t, J=5c/s.), 6.14 (3H,s), 6.23 (3H,s), 7.09 (2H,d, J=5c/s.), 7.67 (3H,s), 7.5-7.9 (complex).

<u>Hofmann elimination of N,N-dimethyl-4,8-dihydroxy-7-methoxy-1-p-methoxybenzyl-1,2,3,4-tetrahydroisoquinolinium iodide.</u>

The above methylation product (270mg.) was dissolved

in a mixture of ethanol (6ml.) and methyl iodide (6ml.) and allowed to stand at room temperature. After two hours the precipitated colourless needles (120mg.) were filtered and shown by the absence of the appropriate i.r. and u.v. absorptions to be a non-aromatic by-product, probably derived from formaldehyde. The filtrate after standing overnight was evaporated to yield a yellow gum.

$\lambda_{max.}$ (rel. opt. density): 230 mμ (2.81), 278 mμ (0.94), 283 mμ (1.0).

An alcoholic solution of this product was passed down a column of Amberlite 400 IRA (OH) anion exchange resin (see later). The u.v. absorptions of the solution directly from the column were as follows:

$\lambda_{max.}$ (rel. opt. density): 228 mμ (3.03), 257 mμ (1.55), 278 mμ (1.10), 283 mμ (1.00), 300 mμ (0.85).

On evaporation to dryness a red gum (150mg.) of unpleasant odour was obtained:

$\lambda_{max.}$ (rel. opt. density): 223 mμ (1.57), 295 mμ (1.0).

P.L.C. (10% MeOH/$CHCl_3$) afforded hydroxyleonticine as a pale yellow gum (33mg.).

$\nu_{max.}$ (Nujol): 1680 cm^{-1} (very weak), 1610 cm^{-1} (strong).

$\lambda_{max.}$: 219 mμ (log ε 4.41), 300 mμ (log ε 4.28).

$\lambda_{max.}$ (base): 222 mμ (2.13), 255 mμ (1.20), 298 mμ (1.00), 356 mμ (0.50).

τ values ($CDCl_3$): 2.40-3.30 (8H, complex, virtually superposable on the same region in the spectrum of leonticine), 4.00 (1H, broad), 6.10 (3H,s), 6.17 (3H,s), 7.58 (3H,s), 6.4-7.4 (2H, m).
Highest molecular ion at m/e 341. ($C_{20}H_{25}O_4N$ requires 343).

Attempted synthesis of petaline and leonticine by a modified Pomeranz-Fritsch reaction.[25]

p-Methoxybenzyl chloride was obtained as an almost colourless oil (b.p. 80°, 0.25 mm.) by borohydride reduction of anisaldehyde followed by saturation of a benzene-petroleum ether solution of the alcohol with gaseous hydrogen chloride at 0°. Reaction of o-vanillin (10.19g.) and aminoacetal (10.15g., 15% excess) on the steam-bath for two hours gave the Schiff base as a yellow-orange oil (16.64g., 92%,), b.p. 166° at 0.25 mm.

To the Grignard reagent prepared from magnesium turnings (1.2g.) and p-methoxybenzyl chloride (7g.) in dry ether (40ml.) was added a solution of the above Schiff base (2.82g.). The mixture was refluxed under nitrogen for 2½ hours. The cooled suspension was added cautiously to a mixture of 6N hydrochloric acid (100ml.) and crushed ice (20ml.). The yellow acid layer was allowed to stand overnight and was then hydrogenated

over 10% Pd on C (625mg.) for 5 hours. Filtration gave an almost colourless solution which was extracted with ether. The acid solution was then basified with ammonia and the pale pink solution extracted with chloroform to give a brown oil (500mg.). This was dissolved in a mixture of ethanol (100ml.) and 33% aqueous formaldehyde (25ml.) and hydrogenated over 10% Pd on C (50mg.) for 5 hours. The solution was filtered, concentrated to ca. 40ml., and then diluted with water (40ml.) and acidified with 6N hydrochloric acid (15ml.). The acid solution was extracted with ether, then basified with ammonia. Extraction with chloroform afforded an orange semi-solid material (950mg.), heavily contaminated with formaldehyde. One product, identified by t.l.c. and staining characteristics was N-methyl-N-(2-hydroxy-3-methoxyphenylmethyl)-ethanolamine, prepared by methylation of the borohydride-reduced product from the condensation of o-vanillin and ethanolamine.
τ values ($CDCl_3$): 3.10-3.50 (3H, complex), 5.34 (2H,s), 6.18 (2H,s), 6.28 (2H,t), 7.37 (2H, t), 7.71 (3H,s).

The above crude methylation product was dissolved in ethanol (25ml.) and methyl iodide (25ml.) and the mixture allowed to stand overnight. The mixture was filtered from the precipitated colourless needles (see earlier) and evaporated to give a yellow gum. This

was dissolved in ethanol and passed down an Amberlite anion exchange resin. Evaporation gave a red oil (304mg.). T.L.C. indicated inter al two pale blue fluorescent materials with similar staining characteristics to leonticine. Initial p.l.c. (10% MeOH/$CHCl_3$) afforded an enriched fraction (80mg.). Repeated p.l.c. yielded only traces of the two compounds. The first had identical R_f (ca. 0.30) to leonticine and in addition had u.v. maxima at 223 (1.38), 285mμ (0.86), and 305 mμ (0.70), shifted in base to 223 mμ (1.66), 247 mμ (1.25), 294 mμ (1.02), and 350 mμ infl, (0.27). (Optical density readings in parentheses). The second component had the R_f (0.25) of hydroxyleonticine and had corresponding u.v. absorptions at 224 mμ (1.62), and 290 mμ (1.52), shifted in base to 224 mμ (1.74), 255 mμ (1.37), 289 mμ (1.30) and 350 mμ infl. (0.50).

Insufficient material was obtained in this experiment to fully characterise these components and obtain confirmation of the synthesis of leonticine and hydroxyleonticine, but this has to be carried out shortly.

1-(3,4-Dimethoxybenzyl)-2,2-dimethyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline.

N-Methyl-1-(3,4-dimethoxybenzyl)-6-hydroxy-7-methoxy-isoquinoline betaine was prepared from papaverine

methiodide as described in the literature.[52] Its attempted conversion to pseudolaudanine by catalytic reduction over Adams' catalyst or by reduction with tin and hydrochloric acid was only partially successful.

The above betaine (660mg.) was dissolved in methanol (40ml.) and sodium borohydride (1.5g.) added in small portions at 0° over 20 mins. The colourless mixture was refluxed for 45 mins., and then treated in the cold with more borohydride (0.2g.) until again colourless. Water was added and the solution acidified. Extraction with chloroform gave the base hydrochloride as a colourless glass. This was dissolved in water and carefully basified with ammonia. The precipitated colourless solid (490mg.) was collected and washed with water to afford pseudolaudanine, m.p. 111-114°.

$\lambda_{max.}$: 283 mμ (log ε 3.81).

τ values ($CDCl_3$): 3.2-3.5 (4H, complex), 3.99 (1H,s), 4.40 (1H, broad), 6.15 (3H,s), 6.22 (3H,s), 6.44 (3H,s), 6.5-7.4 (6H, complex), 7.47 (3H,s).

Hofmann degradations.

Regeneration of a column of Amberlite IRA 400 (OH) anion exchange resin (resin:substrate = 20:1) was carried out by initial washing with 10% aqueous sodium

hydroxide, followed by thorough washing with distilled water. The freshly prepared column was thoroughly washed with ethanol immediately before use. In each case a solution of the quaternary salt in ethanol was cycled six times through the column. Ultraviolet spectra are tabulated in the discussion.

(a) Pseudolaudanine methiodide.

Passage of the methiodide, prepared by overnight treatment of pseudolaudanine (200mg.) with methyl iodide (10ml.) in ethanol (10ml.), through the ion exchange resin and evaporation yielded a slightly gummy solid product (167mg.). Crystallisation from ethyl acetate-petroleum ether yielded the stilbene as almost colourless needles (128mg., 63%), m.p. 166-169°, raised to 169-170.5° by repeated crystallisation.

$\nu_{max.}$ (Nujol): 1600 cm^{-1}.

$\lambda_{max.}$: 219 mμ (log ε 4.38), 243 mμ infl. (log ε 4.23), 299 mμ (log ε 4.29), 335 mμ (log ε 4.47).

Found: C, 70.74; H, 7.61; N, 3.99

$C_{21}H_{27}O_4N$ requires: C, 70.58; H, 7.56; N, 3.92%.

The solution obtained directly from the column had the u.v. absorptions (233, 258, 282, and 303 mμ) of the quaternary hydroxide, but the stilbene (226, 291, and 334 mμ) was obtained on evaporation to dryness or on refluxing for 60 seconds, or on standing at room

temperature (almost total decomposition to stilbene in 10 days).

(b) Petaline reineckate.

The reineckate (20mg.) in ethanol (10ml.) was passed through the ion exchange resin. The solution directly from the column had the u.v. spectrum (228, 261, 278, 285, and 302 mμ) of the hydroxide, but on evaporation to dryness a pale yellow gum was obtained, shown by u.v. (218.5, 293 mμ) and t.l.c. to be leonticine. The quaternary hydroxide was unaffected by standing at room temperature for 24 hours or on low-temperature evaporation to dryness, but was rapidly decomposed to the methine on heating a concentrated alcoholic solution.

(c) Laudanosine methiodide.

The methiodide, prepared from laudanosine (800mg.), was eluted through the resin in the usual way. The solution directly from the column had the u.v. maxima (214, 235, and 282 mμ) of the quaternary hydroxide. Evaporation to dryness under reduced pressure afforded a pale yellow oil (747mg.) which crystallised and was shown by u.v. (207 mμ, 222.5 mμ, 296 mμ (log ε 4.15), 309 mμ infl. (log ε 4.17), 330 mμ (log ε 4.23)) and t.l.c. to be a mixture of cis and trans stilbenes. Attempted separation by p.l.c. (10% MeOH/$CHCl_3$) was unsuccessful, but results indicated that the ratio of

cis to *trans* methine was rather greater than that previously reported.[21]

The quaternary hydroxide was readily decomposed on evaporation or on refluxing an alcoholic solution.

(d) Pseudopetaline iodide.

The iodide (16mg.) in ethanol (8ml.) was treated in the above manner to yield on evaporation a pale yellow oil with the u.v. absorptions (230, 260, 278, 284, 301 mμ) of the quaternary hydroxide. Elimination did not occur even on fairly strong heating under reduced pressure.

(e) O-Methyl pseudopetaline iodide.

Pseudopetaline iodide (18mg.) was dissolved in methanol (4ml.) and the solution treated overnight with excess diazomethane at room temperature. Evaporation gave a yellow glass. This was submitted to the usual elimination conditions. The product obtained on evaporation did exhibit u.v. absorption (228.5, 279, 285, 302, 325 mμ) consistent with some stilbene formation. T.L.C. (10% $MeOH/CHCl_3$) showed two close-running materials (R_f 0.4-0.5) in accord with a mixture of *cis* and *trans* olefins. The solution directly from the column had the u.v. maxima (215, 226, 262, 278, 283, 300 mμ) of a quaternary hydroxide.

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