8-HYDROXYISOQUINOLINES

A thesis submitted by DAVID S. MAGRILL

to the University of Glasgow for the

degree of Doctor of Philosophy

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The author wishes to express his gratitude to Dr. N. J. McCorkindale for his assistance and encouragement during the execution of this work and Prof. R. A. Raphael, F.R.S. for his interest in the work.

His thanks are also due to Mr J. M. L. Cameron, B.Sc. and his associates for their fine microanalyses, to Mrs F. Lawrie for certain infra-red measurements, to Mr J. Galt for measuring proton magnetic resonance spectra and finally to the Department of Scientific and Industrial Research for a Research Studentship during the years 1960-63.

SUMMARY

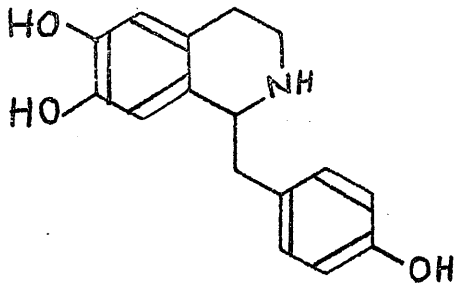
(1) Petaline, an alkaloid from Leontice leontopetalum, Linn., has been shown by synthetic and degradative experiments to be a 2,2-dimethyl-8-hydroxy-7-methoxy-1-(p-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolinium salt and is the first benzylisoquinoline alkaloid reported with this oxygenation pattern.

(2) Several synthetic routes to petaline and to 8-hydroxy-1-(3'-hydroxy-4'-methoxybenzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline derivatives suitable for phenol oxidative coupling to cularine alkaloids have been explored and one of these, involving a modification of the Bischler-Napieralski reaction, appears likely to be successful although it has not yet been completed.

(3) The addition of primary amines to esters and amides of nona-2,7-diyne-1,9-dioic acid has been shown to involve the addition of one mole of amine to each triple bond followed by imine condensation to form compounds related to 1-amino-2-carbethoxy-3-carbethoxymethylenecyclohex-1-ene. Subsequent transamidation and imide ring closure lead to 8-substituted isoquinoline derivatives.

C O N T E N T S

GENERAL INTRODUCTION



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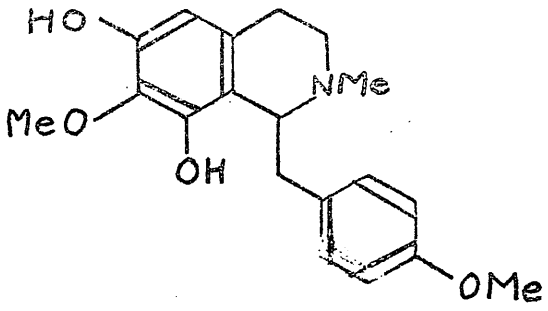

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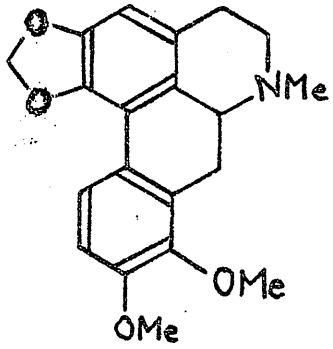

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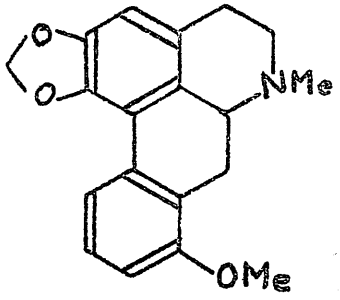

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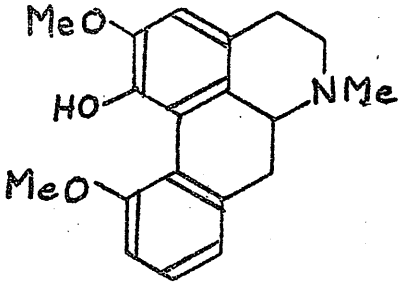

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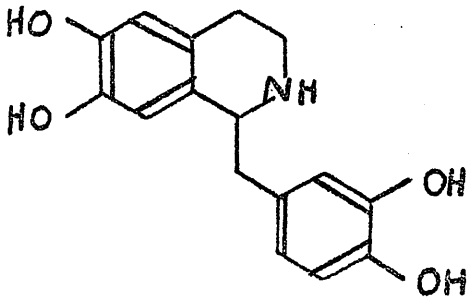

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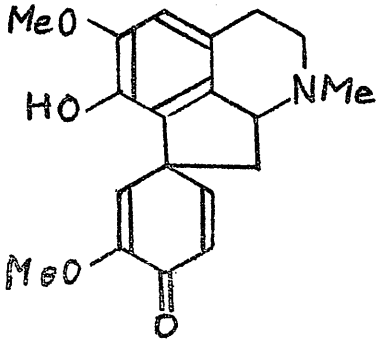

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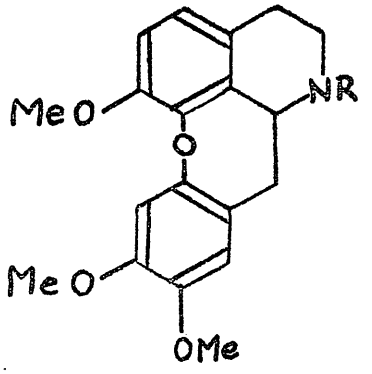

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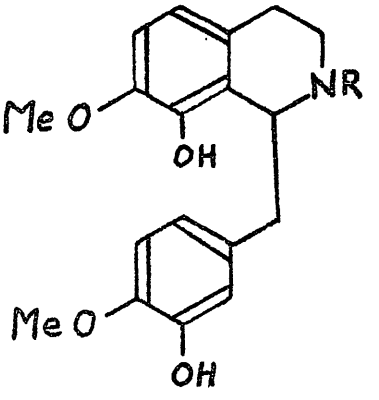

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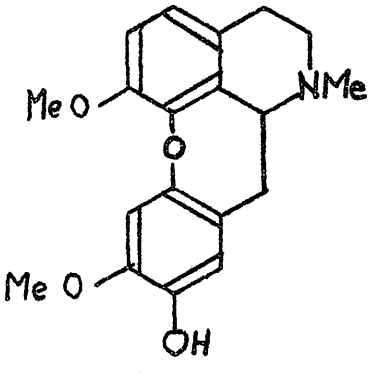

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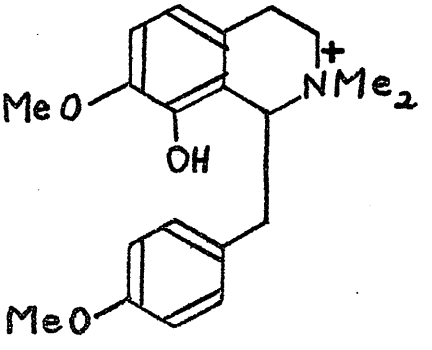

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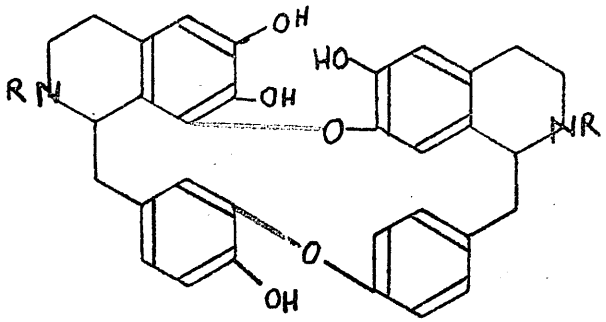
SCHEME I



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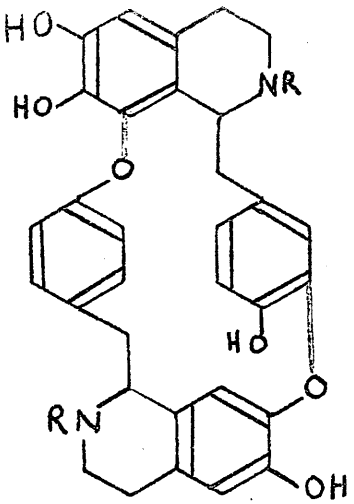
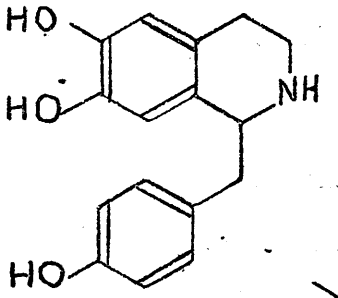


Curine type

Bisbenzylisoquinoline Group



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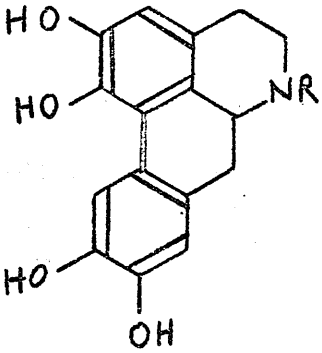

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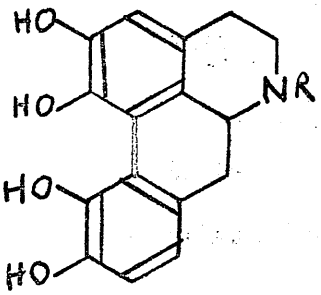
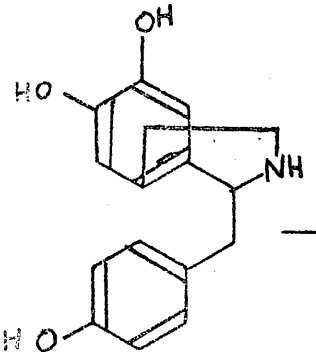
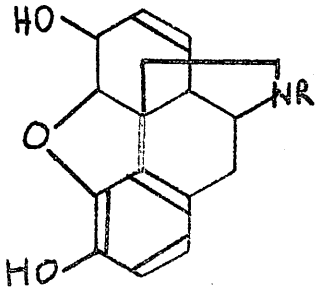


Bulbocapnine type

Aporphine Group





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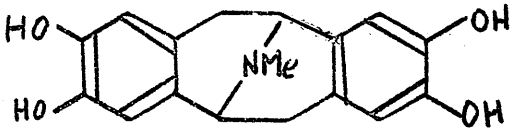
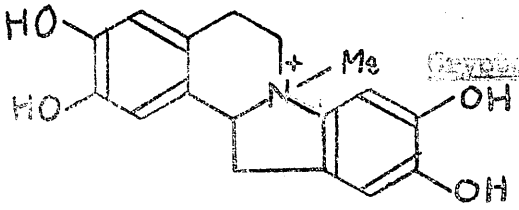


Apomorphine Group



Cryptopleurine Group

GENERAL INTRODUCTION

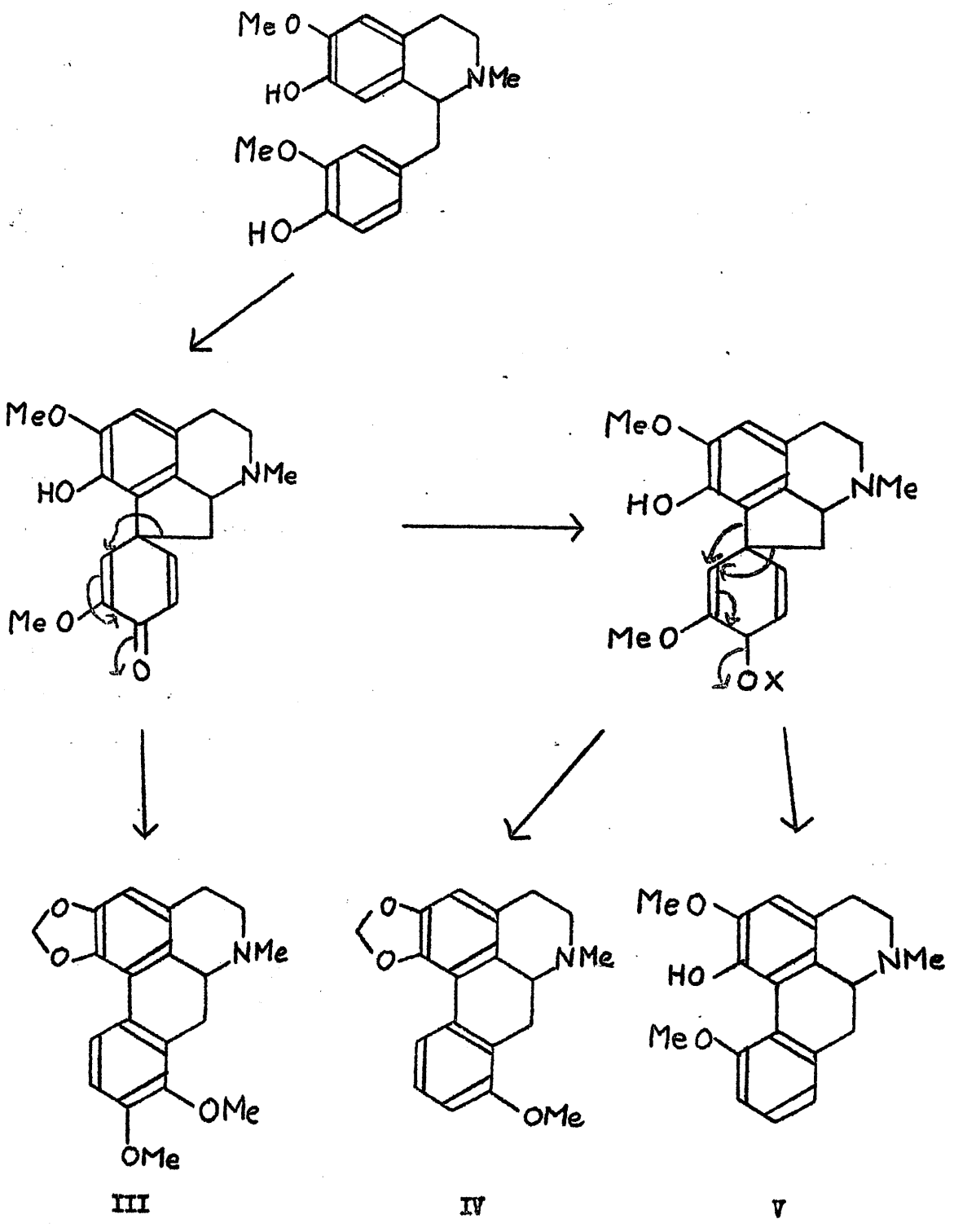
The alkaloids have for many years proved a rich and profitable field for biogenetic speculation (1)(2), although only in rather recent times have the means been available to test the many elegant hypotheses which have been formulated.

A large number of alkaloids, belonging to a variety of groups, are derivable biogenetically from the 1-benzyltetrahydroisoquinoline, I. Thus, as is shown in Scheme I, alkaloids of the bisbenzylisoquinoline, aporphine, morphine, cryptolausine and argemonine types are all derivable from I by sequences involving oxidative condensations (1)(2)(3).

In the majority of cases, the oxygenation pattern of the derived alkaloids reflect this biogenetic route, their hydroxy, methoxy and methylenedioxy groups being sited in positions corresponding to the 6, 7 and 4' positions of I, while further oxygenation often occurs in the 3' - position or, more rarely, in the 8 - position, as for example in corpaverine, II (4).

The aporphine alkaloids crebanine, III, stephanine, IV, and isothebaine, V, were at one time thought to be exceptions to the above rule, having oxygenation patterns which appeared to correspond to the 6, 7, 2', 3', the 6, 7, 2' and the 6, 7, 3' positions respectively of the benzylisoquinoline skeleton. It was suggested (2) that these compounds arise by nuclear hydroxylation of norlaudanosoline, VI, followed by the reduction of one or more hydroxyl groups, although this latter process is without precedent in the biosynthesis of plant products.

SCHEME II



III IV V

However, there is now strong evidence (6)(7) to support an alternative theory, due to Battersby (5) that these aporphine alkaloids are not exceptions but are biosynthesised via I and the dienone, VII, as shown in Scheme II.

Hence the only alkaloids apparently derived from a benzyltetrahydroisoquinoline precursor whose oxygenation pattern fails to correspond to that of I, are the cularine alkaloids of which three are known.

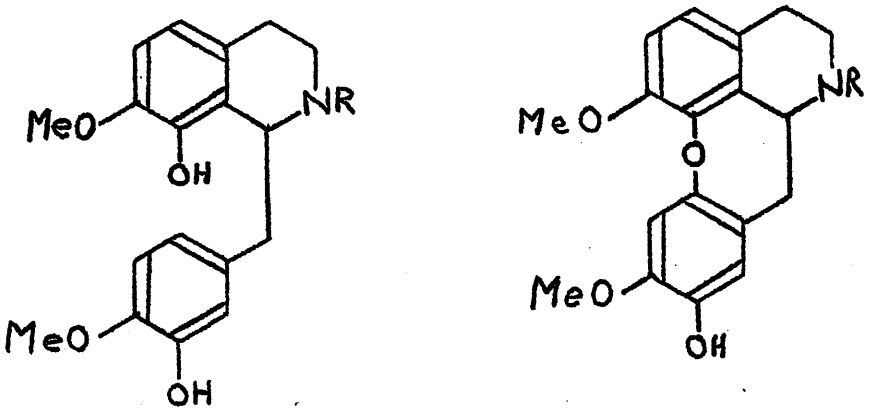
Two of these, cularine and cularimine have been shown both by degradation (8)(9) and synthesis (10)(11) to have the structures VIII (R = Me and H respectively) while the third cularidine, is known (8) to be a des-O-methyl-cularine, but its complete structure remains to be elucidated.

It has been plausibly suggested (8) that these alkaloids are derived biogenetically from a precursor of the type, IX, as shown in Scheme III. This idea predicts that X is a likely structure for cularidine.

Petaline, XI, an alkaloid from Leontice leontopetalum, Linn., whose structural elucidation is now described (Section I), is the first 7, 8 oxygenated benzylisoquinoline alkaloid to be isolated. It lacks, however, the 3' hydroxyl group which would make it a possible precursor to a cularine type of alkaloid.

It is possible that petaline, XI, and the suggested cularine precursor, IX arise by further hydroxylation of a tetrahydro-benzylisoquinoline, e.g. I, followed by reductive removal of one or more

SCHEME III



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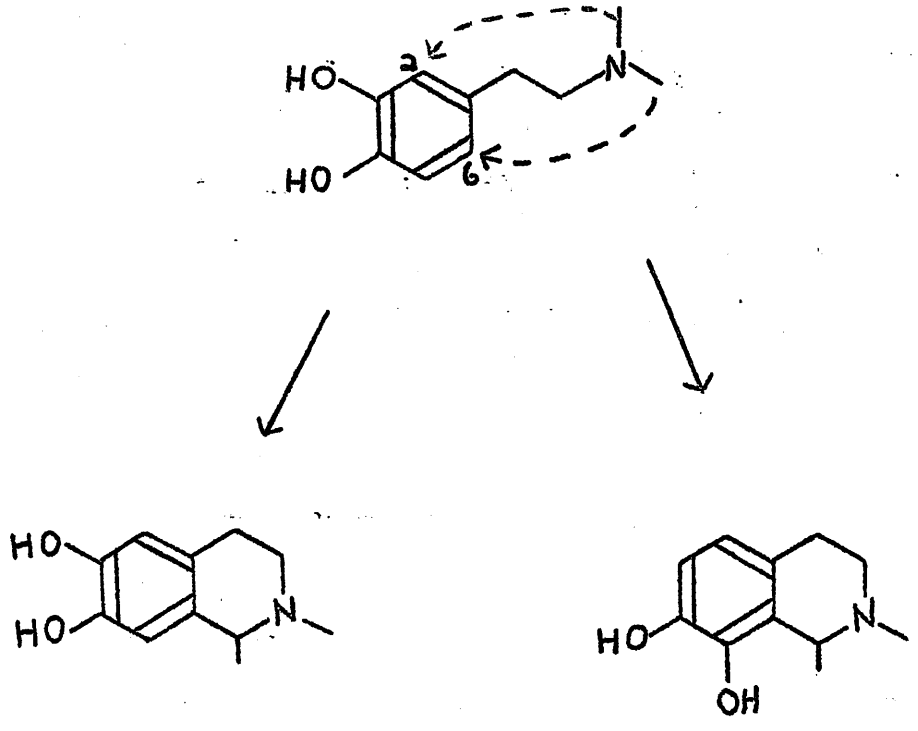


of the original oxygen functions. However, as mentioned earlier, no established precedent exists, in plant biosynthesis, of direct reduction of an aromatic hydroxyl group.

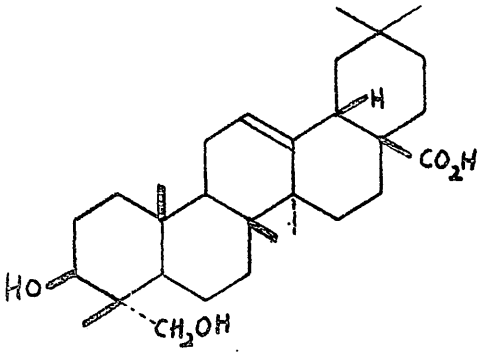
A more attractive theory is that the biogenesis involves the less usual ring closure of a dihydroxyphenylalanine precursor, XII in the position ortho to a phenol (position 2) rather than in the more active para position (position 6) as shown in Scheme IV.

In addition to their interest as possible precursors to the cularine alkaloids, the 7, 8-dioxygenated benzylisoquinolines present a synthetic challenge, since the three most common routes to isoquinolines are not directly applicable. Thus, the Bischler-Napieralski reaction leads exclusively to the 6, 7-dioxygenated system (12), the Pictet-Spengler reaction gives, at best, mixtures of the 6, 7 - and 7, 8-dioxygenated isoquinoline (12) and has the further disadvantage that the required carbonyl component might tend to be intractable (12) while the Pomeranz-Fritsch synthesis is not normally considered to be applicable to the synthesis of 1-substituted isoquinolines (13), although in a synthesis of cularine, Kametani and Fukumoto did report (10) a limited success with this reaction.

8-Hydroxyisoquinoline itself is known, having been prepared by somewhat brutal methods by Robinson (14), and, of course, 6, 7, 8-trioxygenated isoquinolines are readily obtainable from the corresponding trioxygenated phenylethylamines, no question of orientation arising in this case. However, in general very little is known about 8-hydroxyisoquinolines.

This thesis is concerned with the preparation and properties of various 8-hydroxyisoquinolines both synthetic and naturally occurring.

THE STRUCTURE OF PETALINE



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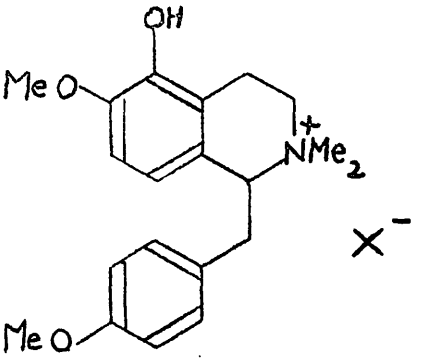

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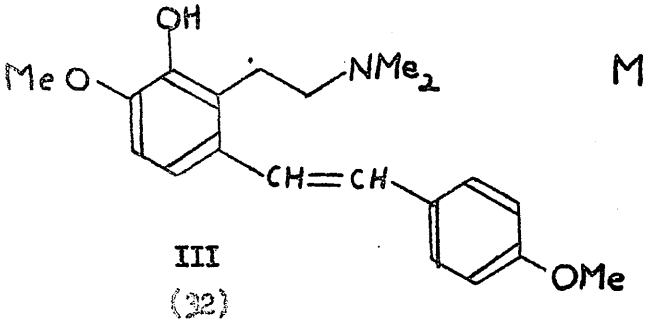

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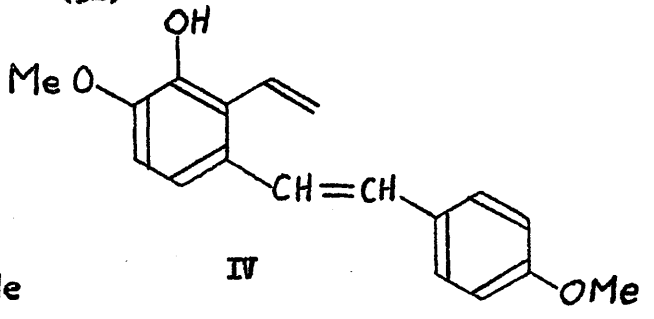

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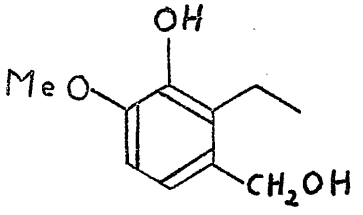

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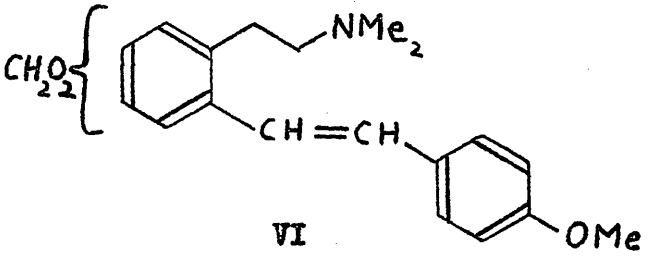

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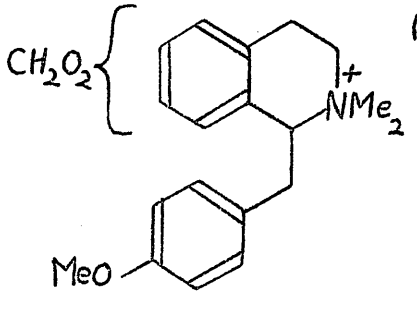

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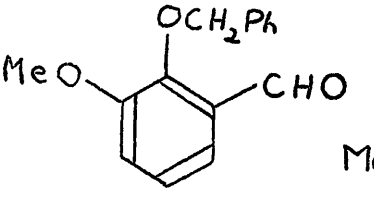

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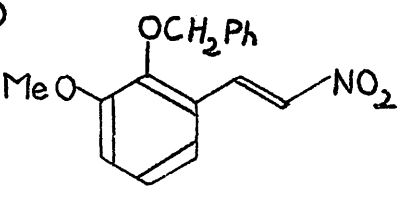

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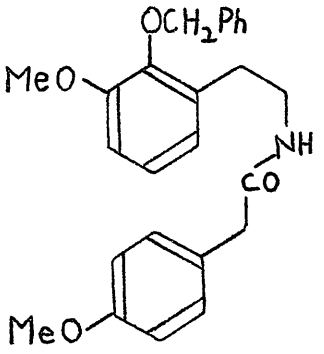

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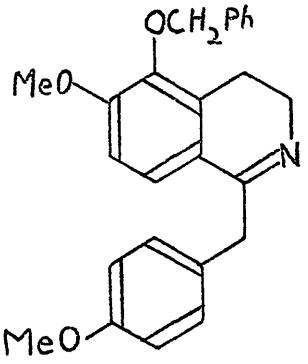

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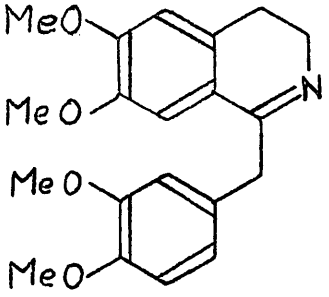

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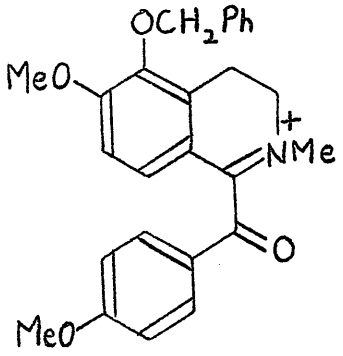

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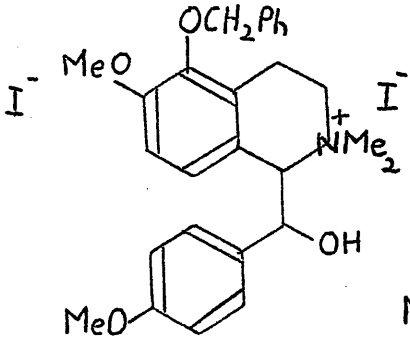

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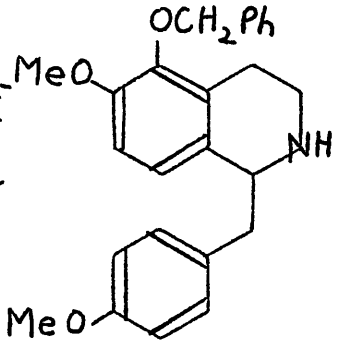

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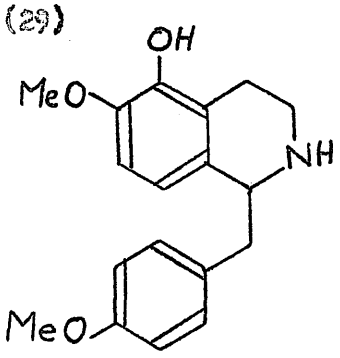

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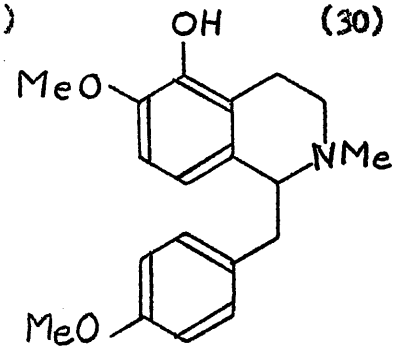

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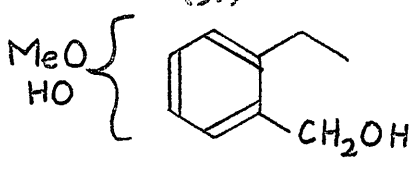

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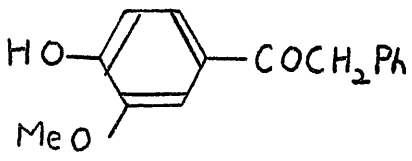

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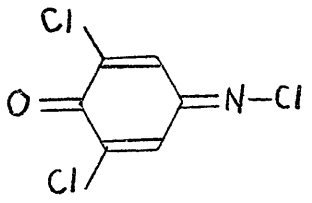

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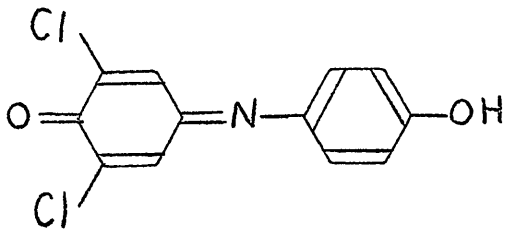

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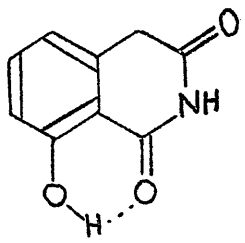

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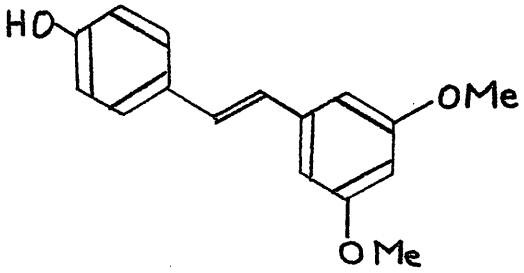

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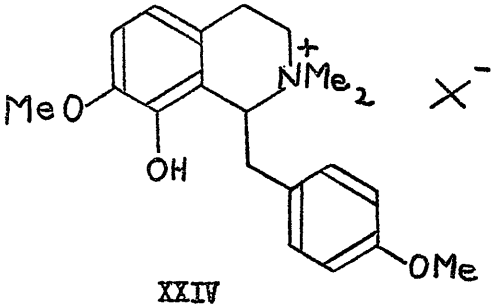

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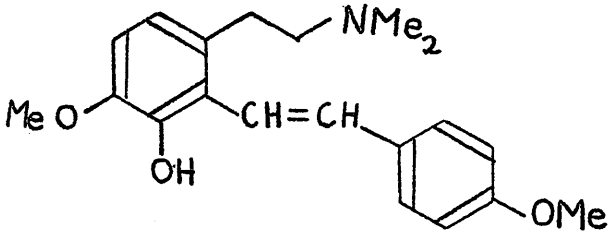

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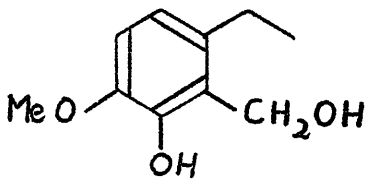

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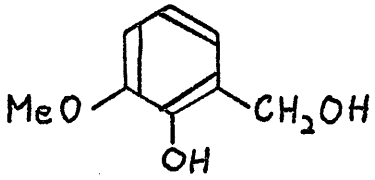

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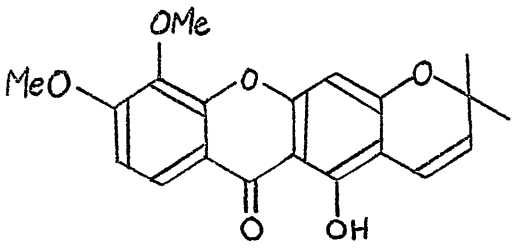

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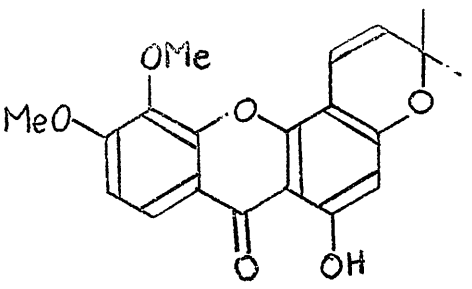

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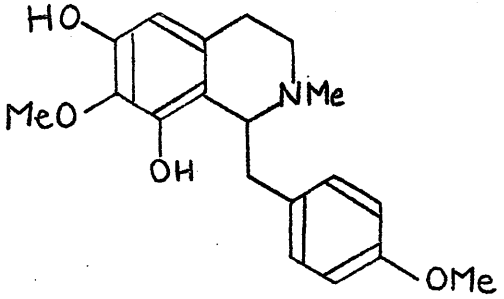

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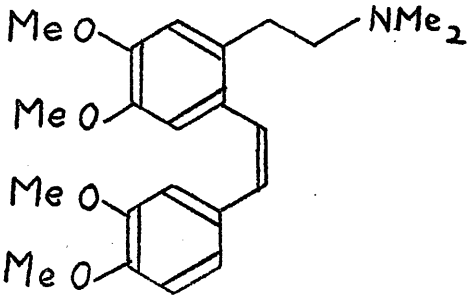

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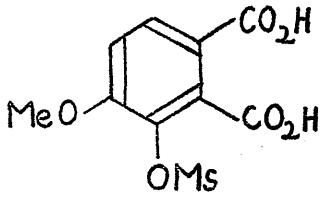

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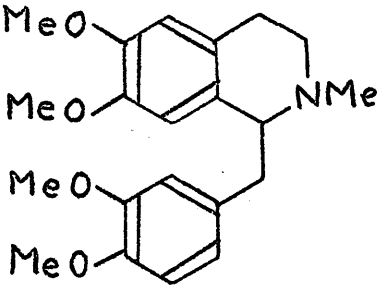

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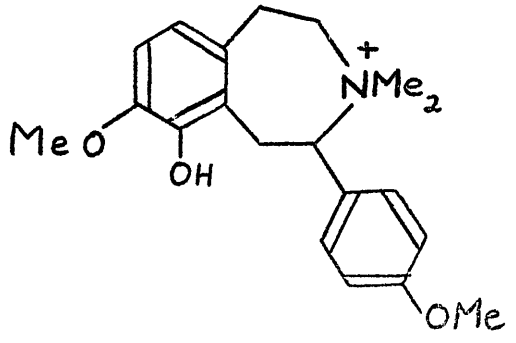


XXXIX

INTRODUCTION

The plant Leontice leontopetalum, Linn., a genus of the Berberidaceae, is a hardy perennial growing to a height of twelve to eighteen inches (1). It occurs widely in Eastern Mediterranean countries, especially in mountainous regions (2). L. leontopetalum and another plant of the same species, L. chrysogonum, have a fairly extensive folk medicinal history, having been, apparently, known to the early Greeks (3) who employed the latter plant as a remedy for snake-bite and sciatica and the former as a treatment for the "bitings of the shrew mouse". L.chrysogonum, introduced into Britain at the end of the sixteenth century (2), was in the seventeenth century applied also in the treatment of ulcers (4). L. leontopetalum has been credited at various times with beneficial results in the treatment of snake-bite(5), overdoses of opium (6) and epilepsy (1). In addition to the medicinal applications mentioned above, the root-tubers of both plants have been employed as a soap substitute.

However, it was the apparent curative effect (1) of L. leontopetalum on epilepsy which stimulated the first chemical investigation (1) of this plant by McShefferty in the 1950's. From a light petroleum extract of the powdered root-tubers were obtained a long-chain paraffin (suspected to be n-nonacosane), ceryl alcohol and a sterol which was considered, on the basis of chemical tests, to be

a 3β-hydroxy-Δ7-stenol [1]. Fatty acids identified in the plant were palmitic, stearic and oleic acids. A fraction was also obtained which exhibited moderate β-glucosidase activity. Extraction of the drug with ethanol afforded a saponin which was designated leontosaponin. Acid hydrolysis of this gave leontosapogenin (which was found to be identical to hederagenin, I), together with four moles of D-glucose and three moles of L-arabinose. Presumably the presence of leontosaponin in the root-tubers accounts for their usefulness as a soap substitute.

After precipitation of the saponin, three alkaloids were obtained from the ethanolic extract of L. leontopetalum [1].

One of these was a saturated ditertiary base, $C_{14}H_{26}N_2$, thought to be identical to leontamine [7][8], an alkaloid isolated from L. ewersmanni, Bge. The frequent occurrence of lupin alkaloids in plants of the Leontice species [9][10][11], combined with the evidence so far available, points to the strong possibility that leontamine is also a quinolizidine alkaloid.

The second alkaloid, isolated [1] in minor amounts (0.018%) was designated "leonticine". It was a chloroform soluble base obtained in colourless needles, m.p. 118.5-119.5°. Leonticine was found to be optically inactive, to have u.v. absorption at 218 mμ (log ε , 4.41); 296 mμ (log ε , 4.41) and to analyse for $C_{20}H_{25}NO_3$. The compound was resistant to catalytic hydrogenation over platinum

oxide but it slowly decolourised acidified potassium permanganate solution.

The third alkaloid was a water-soluble base whose behaviour was typical of a quaternary salt. The alkaloid, which was designated "petaline", was obtained as the reineckate, a pink microcrystalline solid, m.p. 179-181°, which was assigned the formula $C_{20}H_{22}NO_3\,[Cr(SCN)_4.(NH_3)_2]$, later revised by Smith [12] to $C_{20}H_{26}NO_3\,[Cr(SCN)_4.(NH_3)_2]$. Decomposition of the reineckate by the method of Dutcher [13] gave petaline chloride as a yellow deliquescent solid, m.p. 140-143° (d). The base chloride was optically active, $(\alpha)_D^{20}$ + 11.3°, and had λ_{max} 224 mμ (log ε, 4.31); 280 mμ (log ε, 4.06); 328 mμ (log ε, 2.52).

Methoxyl determination showed the presence of two methoxyl groups, the function of the remaining oxygen atom being undetermined.

Treatment of petaline chloride with caustic alkali led only to the production of tars. However, when a solution of the alkaloid in aqueous barium hydroxide was evaporated to dryness under reduced pressure a 30% yield of the base leonticine was obtained. This finding, considered in the light of the alkaline conditions employed during extraction of the plant, led McShefferty [1] to suggest that leonticine is, in fact, an artefact, and this hypothesis has been supported by subsequent investigations [12].

A consideration of the u.v. spectra of petaline derivatives led McShefferty [1] to suggest that the alkaloid belongs to the isoquinoline

Degradations to "dihydropetaline" and to "oxypetaline" were also carried out[1] but these have no direct bearing on the present discussion and are, accordingly, omitted.

group, a theory which was supported by the fact that alkaloids of this type occur prolifically in plants of the genus Berberidaceae (14).

A thorough investigation of the structure of petaline was later undertaken by Smith (12) who confirmed McShefferty's hypothesis (1) that petaline belongs to the isoquinoline group of alkaloids and assigned structures II and III to petaline and leonticine respectively on the evidence described below.

Smith (12) found that petaline, as the chloride or reineckate, could be converted in good yield into leonticine under the exceptionally mild conditions of passage over Amberlite IRA-400 (OH) anion exchange resin. Since petaline has the characteristics of a quaternary base (1) it was thought reasonable to conclude that leonticine, produced from petaline by the action of alkali, is its Hofmann degradation product, and the stoicheiometry of the transformation supports this conclusion.

Under the above conditions leonticine methiodide gave the corresponding methohydroxide which, on refluxing in ethanolic sodium ethoxide solution, readily underwent Hofmann degradation to a nitrogen-free leonticine methine (i.e. petaline bis-methine), $C_{18}H_{18}O_3$, formulated as IV, and trimethylamine which was characterised as the picrate.

Both leonticine and the nitrogen-free degradation product had u.v. absorption which was thought to be compatible with their formulation as cis-stilbenes, showing respectively λ_{max} 216 mμ (log ε, 4.45); 299 mμ (log ε, 4.32) and λ_{max} 209 mμ (log ε, 4.43); 305 mμ (log ε, 4.32), values which were compared to those exhibited by the

cis-methine base of Landamosine which has λ_{max} 215 mμ. (log ε , 4.37); 294 mμ. (log ε , 4.43) (15).

The nitrogen-free degradation product also exhibited absorption at 269 mμ. (log ε , 4.38), ascribed to the styryl double bond.

Further evidence for the stilbene structure of leonticine and its methine came from the results of ozonolysis experiments (12). The nitrogen-free base, on ozonolysis, gave p-methoxybenzaldehyde, identifying one half of the system but the other product could not be isolated. However leonticine methiodide, on ozonolysis, gave, as well as the expected p-methoxybenzaldehyde, a water soluble quaternary salt which was subjected, without characterisation, to Hofmann degradation followed by hydrogenation over Adams' catalyst. The resulting product, formulated by Smith as V, showed no carbonyl absorption in the i.r. but exhibited instead new hydroxyl absorption which indicated the site of the original aldehyde produced by ozonolysis of the stilbene.

Clear cut evidence for the conversion of the dimethylamino-ethyl side-chain of leonticine to the vinyl side-chain of the nitrogen-free methine was found in the n.m.r. spectra. These showed the replacement, in the spectrum of the nitrogen-free product, of the resonance exhibited by leonticine at 7.65 τ (6 protons; singlet), ascribable to the N-methyl groups, and at 7.0-7.6 τ (4 protons; complex), due to the methylene groups, by doublets (each 1 proton) at 4.5 τ (J = 17 c.p.s.) and at 4.9 τ (J = 10 c.p.s.) ascribable to the vinyl protons of a styrene and showing the fine splitting characteristic (16) of such

protons [16][17].

The i.r. spectrum of the nitrogen-free degradation product (KCl disc) showed the expected absorption [18] of a vinyl group at 3086 cm^{-1} and 905 cm^{-1}, these peaks being absent in the spectrum of leonticine.

The evidence so far described established the partial structure, VI, for leonticine and consequently, VII, for petaline.

The remaining atoms were accounted for as follows [12]. The presence of two methoxyl groups in both leonticine and its methine base were indicated by analysis and n.m.r. spectroscopy and the remaining oxygen atom was shown to be present as a phenolic hydroxyl group by the presence of i.r. absorption in both compounds at ca. 3540 cm^{-1} and by positive results in the Gibbs' test [19][20] for a phenol with an unoccupied para position.

The remaining methoxyl and the hydroxyl groups were assigned [12] to the positions shown in structure II since the derived benzyl alcohol was deduced to have structure V on the basis of its positive Gibbs' test and of spectral evidence which will be discussed in detail later.

Ahmed and Lewis [21] tested petaline chloride pharmacologically and showed it to be a more potent convulsant than leptazol (1, 5-pentamethylene tetrazole) although at low dosage levels petaline chloride was found to reduce the convulsant activity of leptazol and to exhibit muscle relaxant activity.

RESULTS AND DISCUSSION

The unique oxygenation pattern of the benzyltetrahydroisoquinoline structure, II, assigned by Smith (12) to petaline was so intriguing that its synthesis was undertaken in order to ascertain its correctness.

The common route to isoquinolines, utilising the Bischler-Napieralski reaction (22) was employed, using benzyl-o-vanillin(23), VIII, as starting material.

This aldehyde was condensed with nitromethane under the influence of acetic acid containing ammonium acetate (cf. p.47), to give 2-benzyloxy-3-methoxy-β-nitrostyrene, IX, whose m.p. was in agreement with published values (24).

The nitrostyrene, IX, was reduced smoothly by lithium aluminium hydride in refluxing ether, to the expected β-phenylethylamine which, without purification, was condensed with homoanisoyl chloride to give N-[2-(2'-benzyloxy-3'-methoxyphenyl) -ethyl] -p-methoxyphenylacetamide, X. Yields and purity of this amide were adversely affected by prolonged reduction. Indeed, there is reason to believe that nitrostyrenes are reduced to phenyl-ethylamines by lithium aluminium hydride in a few minutes (see p. 50).

The base obtained by treatment of the amide, X, with phosphorus oxychloride in refluxing benzene was an oil and unfortunately the corresponding hydrochloride, hydrobromide, picrate, oxalate and methiodide also failed to crystallise. However, evidence that the required dihydroisoquinoline, XI, had been obtained was furnished by its

u.v. spectrum which showed maxima at 278 mμ (in EtOH) and 327 mμ (in EtOH -HCl). The shift on acidification of 49 mμ is typical of an imine (25) and is comparable to that shown by crude dihydropapaverine, XII, which was prepared by the method of Buck, Haworth and Perkin (26) and exhibited u.v. absorption maxima at 305 mμ (in EtOH) and 355 mμ (in EtOH - HCl), the shift on acidification being 50 mμ

Additional evidence was provided by the formation of a crystalline keto-methiodide, XIII, in 17% yield, when a solution of the base in ethanolic methyl iodide was allowed to stand for several days. Reduction of this gave a non-crystalline alcohol which, however, afforded the crystalline methiodide, XIV, whose structure was supported by elementary and mass spectral analysis. (As expected, the parent ion corresponded to the cationic portion of the salt, i.e. $C_{27}H_{32}NO_4^+$, m/e 434).

The keto-methiodide, XIII, evidently arises by oxidation of the expected product, XI. A marked tendency for 1-benzyl-3, 4-dihydroisoquinolines to suffer oxidation to 1-benzoyl-3, 4-dihydro-isoquinolines on exposure to air of a neutral or alkaline solution of the base has been noted before. (22)(26)(27)(28) Acidic solutions, however, appear to be immune to oxidation (26).

An attempt was made to reduce the keto-methiodide, XIII, with lithium aluminium hydride-aluminium chloride complex, a reagent which has been successfully employed in the reduction of allylic and benzylic alcohols and ketones to hydrocarbons (29). However, reduction of the keto-methiodide, XIII, followed by quaternisation of the oily product with

methyl iodide, gave the hydroxy-methiodide, XIV, the reduction in this case having been identical to that produced by sodium borohydride.

The problem of precluding oxidation of the dihydroisoquinoline, XI, was circumvented by the reduction, "in situ", of the 1, 2-double bond with sodium borohydride.

The best conditions were as follows. The cyclisation reaction mixture was extracted with light petroleum and the residual acidic oil was treated with sodium borohydride in methanol. It was found necessary to basify at this stage and treat with more sodium borohydride. Omission of this step, or basification before the first addition of sodium borohydride gave much lower yields. However, the above conditions, combined with the employment of an atmosphere of nitrogen throughout, gave good yields of almost pure 5-benzyloxy-6-methoxy-1-(p-methoxylbenzyl) -1, 2, 3, 4-tetrahydroisoquinoline, XV.

Sodium borohydride is converted to diborane by acid (30) and the above results indicate the possibility that this reduces imines more effectively in an alkaline medium.

The protective benzyl ether of the tetrahydroisoquinoline, XV, was hydrogenolysed over palladium-on-charcoal to give 5-hydroxy-6-methoxy-1-(p-methoxybenzyl)- 1, 2, 3, 4-tetrahydroisoquinoline, XVI.

Methylation of the phenolic base, XVI, by the Eschweiler-Clarke procedure (31) gave only incomplete methylation. A similar problem was solved recently by the use of catalytic reduction in the presence of formaldehyde (32). Under these conditions the secondary base, XVI, was smoothly and quantitatively converted into its N-methyl derivative, XVII,

which was treated directly with methyl iodide in ethanol to yield crystalline 2, 2-dimethyl-5-hydroxy-6-methoxy-1-(p-methoxybenzyl)-1, 2, 3, 4-tetrahydroisoquinolinium iodide, II (x = I).

This quaternary salt, II (x= I), has the structure assigned by Smith [12] to petaline iodide. Comparison of the synthetic material with a sample of the alkaloid was not, however, very conclusive because of the difficulty of comparing a racemate with an optical isomer, because the ionic nature of the compounds rendered i.r. spectra in solution unobtainable, and lastly, but very significantly, because the petaline salts available were not rigorously pure. This last consideration deterred mass spectral comparison of the cations of II and petaline.

However, decisive comparison was made using the most characteristic chemical property of petaline. When the alkaloid is passed through a column of Amberlite IRA-400 (OH) anion exchange resin, the corresponding methine, leonticine, m.p. 123°, is obtained directly and no quaternary hydroxide is isolated [12]. In contrast, the synthetic iodide, II (x = I), was under these conditions smoothly converted to the corresponding quaternary hydroxide which did not appear to be unduly labile. Decomposition of this with refluxing ethanolic sodium ethoxide gave the methine, III, m.p. 172.5°. It was quite evident from comparison of m.p. and of i.r. and n.m.r. spectra* that leonticine and the methine, (designated "pseudoleonticine" hereafter) were not identical and it follows that the assigned structure, II, for petaline is incorrect.

Accordingly, the evidence upon which this assignment was made [12] was examined and a reappraisal was made as follows.

*These spectral data will be discussed later in detail.

The formulation of petaline as a quaternary salt of a benzyltetrahydroisoquinoline is based upon the formation of leonticine, a dimethylamino-stilbene which is evidently the usual Hofmann degradation product of such a system (12). This is now confirmed by the close similarity between the i.r. and n.m.r. spectra of leonticine and pseudoleonticine, III. The 4'-methoxyl group is unambigously located by the isolation of p-methoxybenzaldehyde after ozonolysis of either leonticine methiodide or of the derived nitrogen-free Hofmann degradation product. Since these features of the structure, II, assigned to petaline appear to be unassailable, it follows that the error concerns the orientation of the hydroxyl and methoxyl groups on the isoquinoline nucleus. The biogenetic improbability of the oxygenation pattern of II render this more likely.

The 5, 6 oxygenation pattern was assigned by Smith (12) on three pieces of evidence.

Firstly, leonticine, VI, its methine (corresponding to IV) and the derived benzyl alcohol, XVIII, all show absorption in the i.r. at ca. 3540 cm^{-1}. This was ascribed to the phenolic hydroxyl group and taken to indicate that the group was intra-molecularly hydrogen bonded to the only suitably located electronegative atom - at least in leonticine and its methine - the oxygen atom of the methoxyl group. This was considered to establish the ortho relationship of the two oxygen functions.

This conclusion does not appear to be open to doubt, the quoted frequencies being close to those exhibited by various

o-methoxyphenols prepared in the present work, typical of which is the ketone, XIX, (cf. p. 40) which absorbs at 3548 cm^{-1}. A non-bonded phenolic hydroxyl group would be expected to absorb in the range 3650-3590 cm^{-1}. (33)

Secondly, the positive results of the Gibbs' tests on leonticine, VI, its methine, IV, and the derived benzyl alcohol, XVIII, were taken to show that there was no substitution para to the phenolic hydroxyl group (12).

The Gibbs' test reagent, 2, 6-dichloro-p-benzo-quinone-4-chloroimine, XX, produces with phenols having no para substituent, an indophenol, such as XXI, which is detected by its blue colour (19). However, in its early form the test sometimes gave ambiguous results as indistinct colours were often formed and even the reagent alone, when in solution, rapidly develops a grey colour (20).

Fortunately, this unsatisfactory state of affairs was rectified some years ago by King, King and Manning (20) who put the Gibbs' test on a firm quantitative basis, introducing the use of pyridine as solvent and showing that indophenol formation could then be reliably detected by the presence of a maximum in the range 590-665 mμ (log ϵ, ca. 4.0) in the visible absorption spectrum, whereas substances giving negative results in the Gibbs' test showed only background absorption in the region 500-700 mμ irrespective of the apparent colour of the solution.

In view of the equivocal results sometimes obtained from the Gibbs' test it was decided to repeat the test on leonticine under the

conditions of King, King and Manning [20]. The test solution showed a sharp absorption maximum at 623 mμ (log ε, ca. 4.0), thus confirming Smith's observation [12]. Nevertheless, further caution must be exercised before accepting his conclusions as the rule that phenols with a free para position give a positive result in the Gibbs' test is not without exceptions. Thus, the danger of assigning a structure on the basis of a negative Gibbs' test is illustrated by the compound, XXII, whose test solution exhibits only background absorption in the region 500-700 mμ (cf. p. 92)

The only cases which have so far been reported where a positive Gibbs' test is misleading have a halogen atom or a carboxyl group in the position para to a phenolic hydroxyl group and these, apparently, do not inhibit indophenol formation [20][34].

Perhaps the most relevant Gibbs' test result is that reported for pterostilbene, XXIII, whose test solution, although blue, has no absorption in the region 500-700 mμ [20]

This can be taken as strong evidence that the positive result shown by the stilbene, leonticine, is, indeed, meaningful.

If this evidence is credited, it eliminates the usual 6, 7 oxygenation pattern and reduces the number of possible structures for petaline to two, namely II and XXIV. Since the former compound has now been synthesised and shown to be different from petaline, as described earlier (p. 15), we can now assign the structures XXIV, XXV and XXVI to petaline, leonticine and the derived benzyl alcohol respectively.

Assignment of a structure to a natural product on the basis of a positive Gibbs' test is not without precedent, King, King and Manning having used a positive result in this test to formulate the dimethyl ether of the heartwood constituent, jacareubin, as XXVIII rather than XXIX [20].

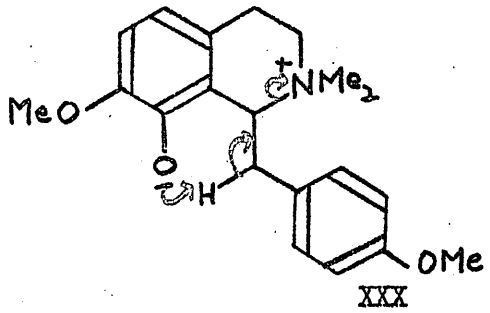
Smith's final item of evidence [12] must therefore be examined critically since it was on these grounds that the wrong structure, II, for petaline was favoured over the correct one, XXIV. The benzyl alcohol, XXVI, derived from leonticine, shows i.r. absorption at 3615 cm^{-1} (ε, 22 in CCl_4) and it was concluded erroneously that this indicated a free hydroxyl group and accordingly showed that the hydroxymethyl group was not situated ortho to the phenolic hydroxyl group.

This conclusion was shown to be fallacious by examination of the i.r. spectrum of o-vanillyl alcohol XXVII (prepared by lithium aluminium hydride reduction of o-vanillin). The absorption at 3615 cm^{-1} (ε, 46) and 3560 cm^{-1} (ε, 182) compared favourably with that observed for the benzyl alcohol derived from leonticine, viz. 3615 cm^{-1} (ε, 22) and 3547 cm^{-1} (ε, 144).

These data cannot be said to favour structure XXVI uniquely but they remove the last objection to the structures XXIV for petaline and XXV for leonticine.

The new structure allows a satisfying explanation to be given of the exceptional ease with which petaline undergoes Hofmann degradation, the chloride or reineckate being converted to the methine, leonticine, by Amberlite IRA-400 (OH) resin, conditions which merely convert other quaternary salts, e.g. leonticine methiodide [12] or pseudopetaline iodide II (x = I), (p. 15), to the corresponding quaternary hydroxide. (No other examples of such a labile quaternary hydroxide appear to have been reported [35]). As indicated in XXX, petaline

carries its own base in the form of the phenolate anion, this being conveniently located for abstracting the hydrogen atom β- to the nitrogen atom via a six-membered cyclic transition state.



XXX

The plausibility of this mechanism and, indeed, its aesthetic appeal, constitute compelling evidence in favour of the structure XXIV for petaline.

It would be predicted on the basis of this mechanism that the alkaloid corpaverine XXXI (36)(37), would also undergo Hofmann degradation under conditions comparable to those employed for petaline although this does not appear to have been put to the test.

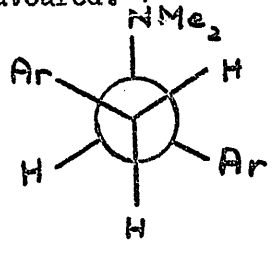
The discussion has hitherto neglected the geometry of the stilbene system of leonticine, XXV.

Smith (12) tentatively formulated leonticine as a cis-stilbene, the suggestion being supported by the rather convincing similarity between the u.v. spectra of leonticine λ_{max} 216 mμ (log ε , 4.45); 299 mμ (log ε , 4.32) and the cis-methine, XXXII, of laudanosine λ_{max} 215 mμ (log ε , 4.37); 294 mμ (log ε , 4.43) (15).

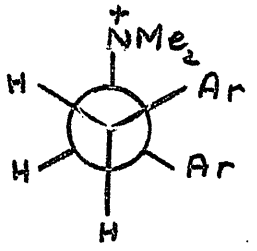
Consideration of the mechanism of the Hofmann degradation reaction, however, leads to the conclusion that the most probable structure of leonticine is the trans-stilbene.

Except in particularly unfavourable cases (which have no bearing on the present discussion), the Hofmann elimination reaction appears to proceed by a concerted trans elimination (E 2) or, occasionally by a two step process (E 1 c b; E 1 elimination in the conjugate base)[35].

The geometrical and steric requirements for reaction by the most probable mechanism (E 2) necessitate the orientation of a benzylisoquinoline to be as shown in XXXIII when viewed along the $C_{(9)}$-$C_{(1)}$ bond. Elimination from the molecule in this conformation can lead only to the trans-stilbene. In order to arrive at the cis-stilbene, elimination must occur from the molecule in the conformation XXXIV, which is far from favoured.



XXXIII



XXXIV

If elimination were to proceed by the E 1 c b mechanism, then the favoured conformation of the intermediate carbanion would for similar reasons also be expected to lead to a trans-stilbene.

The mechanism, XXX, already proposed for the formation of leonticine, XXV, is amenable directly to the above arguments.

Nevertheless, Battersby and Harper have reported [15] the formation, in the degradation of laudanosine, XXXV, of a 9% yield of the cis-methine along with 68% of the trans isomer.

Notwithstanding this surprising finding it is unlikely

TABLE I

U.V. Spectra of Stilbenes

Compound	λ_{max} (mμ)	log ε	Ref.
Leonticine	216 299	4.45 4.32	(2)
Pseudoleonticine	218 257 317	4.20 3.98 4.37	-
Laudanosine cis-methine	215 294	4.37 4.04	(12)
Laudanosine trans-methine	223 333	4.30 4.43	(12)
4-Methyl-trans-stilbene	203 230 298	4.42 4.23 4.50	(41)
4,4'-Dimethyl-trans-stilbene	204 230 301	4.39 4.21 4.51	(41)
2,4,6-Trimethyl-trans-stilbene	201.5 208.5 283	4.47 4.47 4.28	(41)
2,4,6,2',4',6'-Hexamethyl-trans-stilbene	214 263	4.55 4.20	(41)

that leonticine is a cis-stilbene, and, indeed, its i.r. spectrum, measured in carbon disulphide shows strong absorption at 970 cm^{-1}, characteristic of the C-H out-of-plane deformation of a trans double bond (33). Hence leonticine can be confidently formulated as the trans-methine, XXV.

The u.v. spectrum is, in this case, misleading and illustrates the difficulty of identifying chromophones without adequate models. Table I. shows the u.v. spectra of various relevant compounds.

Since leonticine, XXV, and pseudoleonticine, III, differ only in the orientation of substituents, it would, on the surface, appear reasonable to predict that the two isomers should have comparable u.v. spectra (38). As can be seen from Table I, this expectation is not realised, the long-wavelength peak of leonticine occurring at a wavelength 18 mμ shorter than predicted.

Such a shift might be attributed to cis geometry of the stilbene were it not that the more reliable evidence of i.r. absorption has already eliminated this possibility. However the u.v. absorption of leonticine, XXV, can be explained as follows:

Unlike pseudoleonticine, III, leonticine, XXV, carries substituents in both the 2-and the 6-positions - that is, in both positions ortho to the double bond. Steric interaction between these substituents and the vinyl hydrogen atoms is therefore relieved by rotation of the aromatic ring bearing these substituents out of the plane of the double bond. The resulting inhibition of resonance is reflected in a shortening of the long-wavelength u.v. absorption maximum.

Analogous effects have been reported by Suzuki (39), who considered in detail a series of methylated trans-stilbenes. Suzuki found that, while in general, the substitution of a methyl group on an aromatic nucleus of trans-stilbene gave rise to the expected bathochromic shift of the long-wavelength absorption maximum of ca. 3 mμ, substitution on ortho positions caused marked hypsochromic shifts. Thus, while 4, 4'-dimethylstilbene absorbs at 301 mμ, 2, 4, 6-trimethylstilbene absorbs at 283 mμ and the 2, 4, 6, 2', 4', 6'-hexamethyl analogue at 263 mμ.

These differences in the positions of the long-wavelength peaks of the methylated trans-stilbenes are paralleled by differences in the reactivity of the double bond. Thus, Fuson, Denton and Best (40) have shown that the times required to decolourise a solution of 2% aqueous potassium permanganate under standardised conditions are, for trans-stilbene less than a minute, for 2, 4, 6 trimethylstilbene, 4.5 hours and for 2, 4, 6, 2', 4', 6' hexamethylstilbene, 60 hours. This rationalises McShefferty's report (1) that leonticine only slowly decolourises potassium permanganate solution. Doubtless the formerly surprising failure of leonticine to undergo catalytic hydrogenation (1) is also due to steric effects, since the non-planarity of the molecule may prevent its efficient adsorption on the catalyst surface.

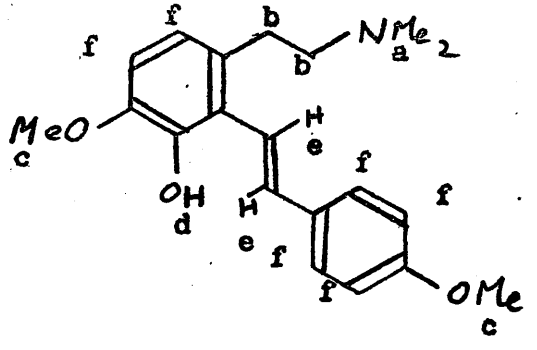
Viewed in this light, these "anomalous" properties of leonticine, XXV, provide further confirmation of the revised structure.

Discussion of the n.m.r. spectra of leonticine, XXV, and pseudoleonticine, III, has been deferred until now so that they may

TABLE II

N.M.R. Spectra of Leonticine and Pseudoleonticine

Compound	Solvent	τ_a	τ_b	τ_c	τ_d	τ_e	τ_f
Leonticine, A	$CDCl_3$	7.69(s)	6.8-7.8(complex)	6.14, 6.18	4.05(b)	3.29(s)	2.4-3.2
Pseudoleonticine, B	$CDCl_3$	7.61(s)	6.8-7.5(complex)	6.13, 6.18	8.72(s)	3.03(s)	2.4-3.4



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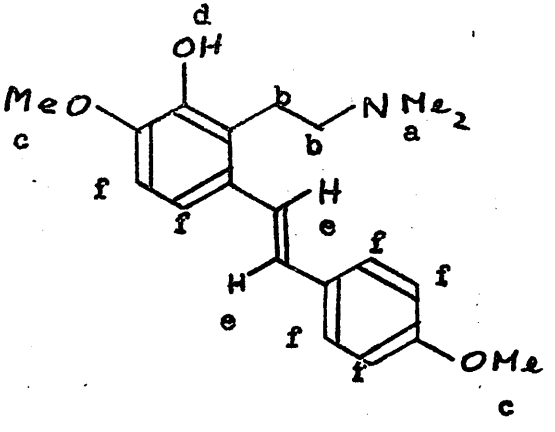


B

be considered in the light of the correct structures.

As can be seen from Table II, the absorptions due to the dimethylamino-ethyl side-chains and the methoxyl groups of both compounds, are almost identical while, as would be expected, the complex aromatic absorptions, although occurring in substantially the same region, are of different form.

The absorption of the vinyl protons of leonticine, however, occurs at 3.29 τ whereas the corresponding protons of pseudoleonticine absorb at 3.03 τ . The vinyl protons of trans-stilbene itself absorb at 2.90 τ and those of cis-stilbene at 3.45 τ .(41) Since substitution ortho to the double bond can only cause increased shielding of the vinyl protons the observation that both leonticine and pseudoleonticine absorb at lower field than cis-stilbene is confirmation of their trans geometry. The value of 3.03 τ for the vinyl protons of pseudoleonticine, III, shows that the shielding by the dimethylamino-ethyl substituent causes an upfield shift of 0.13 τ .

Since the vinyl protons of leonticine are shifted upfield by 0.39 τ relative to stilbene it might be calculated that the ortho hydroxyl group has a shielding effect sufficient to account for 0.26 τ of this shift. However, in view of the previously demonstrated non-planarity of leonticine (see p. 22) this simple quantitative argument is probably invalid and it seems likely that the observed shift is due not only to the two ortho substituents but also to the increased order of the double bond brought about by steric inhibition of resonance.

Apparent anomalies appear when the absorption due to the

phenolic hydroxyl group is considered. The hydroxyl group of leonticine, XXV, absorbs at the unexceptional value [41] of 4.05 τ and the assignment of this peak is confirmed by its disappearance on shaking the solution with deuterium oxide.

On the other hand, pseudoleonticine, III, exhibits no absorption in the neighbourhood of 4 τ which can reasonably be ascribed to the phenolic proton but shows, instead, a sharp singlet (value 1 proton) at 8.72 τ . The exceptionally high τ-value of this absorption makes its assignment to a phenolic proton appear unlikely and this conclusion is reinforced by the observation that it fails to exchange on shaking with deuterium oxide.

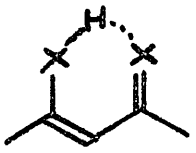
Nevertheless, all other peaks in the spectrum having been assigned to appropriate protons, and the suspected possibility of the peak at 8.72 τ arising from solvent absorption or being a side-band of tetramethylsilane having been tested and rejected, we are obliged to accept the logical conclusion that the phenolic proton of pseudoleonticine, III, absorbs at 8.72 τ and fails to exchange with deuterium under the usual conditions. A possible explanation of this surprising result is as follows.

Hydrogen bonding normally causes the n.m.r. signal of the proton involved to occur at very low field [41] and this phenomenon, in the case of the commonly encountered cyclic hydrogen bonded system whose ring has six members including the hydrogen atom, is presumably due to the tendency for two electronegative atoms (shown as x) to leave the proton relatively denuded of electrons (i.e. deshielded). As can be seen

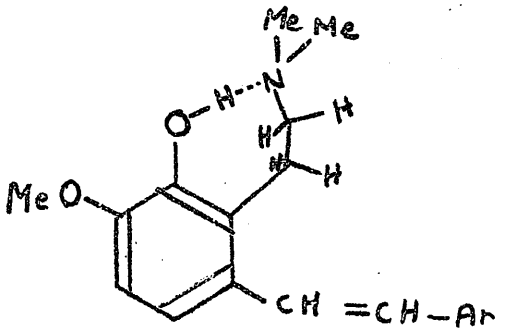
in XXXVI, this is a consequence of the fact that the X-H.....X system is non-linear so that the resultant of the two X ← H electron attracting forces has the effect of increasing the electron density between the two electronegative atoms at the expense of the immediate environment of the proton.

However, inspection of molecular models shows that if pseudoleonticine adopts the seven-membered cyclic hydrogen bonded conformation as depicted in XXXVII, the X-H...X hydrogen bond is linear. Accordingly, the proton lies in the region of maximum electron density, the effect of the nitrogen atom being merely to counteract the electronegativity of the oxygen and thus, by reducing the dipolar character of the O-H bond to cause an upfield shift of the proton signal and render the proton less susceptible to exchange with deuterium oxide.

The geometry requires that one or preferably both of the remaining carbon atoms of the ring should be tetrahedral in order to allow the puckering necessary for the formation of the linear hydrogen bond. These rather rigid steric requirements account for the apparent absence of any other report of this interesting and unusual system.



XXXVI



XXXVII

The significance of the revised structure of petaline is such (vide infra) that it was considered desirable to obtain chemical confirmation of the oxygenation pattern of its isoquinoline nucleus. This was achieved in the following way.

Leonticine was converted to an amorphous mesylate which on oxidation with acidified potassium dichromate gave, as well as the expected anisic acid, 3-methanesulphonoxy-4-methoxyphthalic acid, XXXVIII, which was shown to be identical (i.r. and mixed m.p.) with a sample synthesised as described on p.43 . This result, together with the previously reported synthetic experiments (p.15), fully confirms the structure of petaline as , XXIV.

Petaline is therefore the first reported example (14)(42)(43) of a benzyltetrahydroisoquinoline alkaloid having a 7, 8 oxygenation pattern. The biogenesis of petaline and its bearing on the origin of the cularine alkaloids is discussed elsewhere (p. 2).

While the structure of leonticine has been thoroughly established as XXV, that of petaline has only been inferred to be XXIV, although the biogenetically and chemically less probable structure, XXXIX, cannot be rigidly excluded. However, the cyclic mechanism, XXX, invoked on p.20 to account for the facile Hofmann degradation reaction is not nearly so readily applicable to the latter structure. It is hoped that studies on the alkaloid (which is not at present available) will serve conclusively to eliminate this possibility.

EXPERIMENTAL

2-Benzyloxy-3-methoxy-β-nitrostyrene, IX.

A solution of O-benzyl-o-vanillin, VIII[23], (20 g.), ammonium acetate (4 g.), nitromethane (20 ml.), and glacial acetic acid (40 ml.) was refluxed for 1 hour+ and poured into water. The precipitated solid crystallised from ethanol as yellow needles (15.4 g; 66%), m.p. 72-74°. (Lit.[24] 77°).

N-[2-(2'-Benzyloxy-3'-methoxyphenyl)-ethyl-p-methoxyphenylacetamide, X.

A solution of 2-benzyloxy-3-methoxy-β-nitrostyrene, IX, (1.75 g.) in ether (40 ml.) was added during 15 minutes to a stirred refluxing solution of lithium aluminium hydride (1.6 g.) in ether (200 ml.). Stirring and refluxing were then continued for 1 hour+, the excess of reagent was destroyed by means of ethyl acetate and the complex was decomposed by a minimum volume of water. The ethereal solution was decanted from the inorganic residue which was washed with more ether (2 x 25 ml.) and the combined ether solutions were then extracted with 6N aqueous hydrochloric acid (3 x 50 ml.). The aqueous extracts, after basification with ammonia (0.880) were extracted with ether to give the β-phenylethylamine as an oil (1.25 g.). This oil, without further purification, was dissolved in a mixture of ether (10 ml.) and 0.5N aqueous sodium hydroxide (10 ml.) and stirred with homoanisoyl chloride (1 g.) for 1 hour. The precipitated solid was filtered off and washed successively with dilute aqueous alkali, acid and water. Crystallisation from di-isopropyl ether gave the amide, X, as colourless needles (1.74 g; 78%), m.p. 85-87.5°. (Found: C, 74.15; H, 6.7; N, 3.3. $C_{25}H_{27}NO_4$ requires

+ More prolonged refluxing affected the yields and purity of the product adversely.

C, 74.05; H, 6.7; N, 3.45%).

5-Benzyloxy-6-methoxy-1-(p-methoxybenzyl)-3, 4-dihydroisoquinoline, XI.

A solution of N-[2-(2'-benzyloxy-3'-methoxy-phenyl)-ethyl]-p-methoxyphenylacetamide, X, (0.1 g.) and phosphorus oxychloride (0.75 ml.) in benzene (5 ml.) was refluxed for 30 minutes, cooled and added to light petroleum (b.p. 40-60°) (ca. 30 ml.). After decantation, the residual oil was dissolved in chloroform and the solution washed with dilute aqueous sodium hydroxide. Evaporation of the chloroform gave the 3, 4-dihydroisoquinoline, XI as an oil (ca. 0.1 g.) [λ_{max} (in EtOH) 278 mμ, (in EtOH/HCl) 327 mμ. No C = O absorption in i.r.]. Attempts to purify the base by chromatography or distillation, or to prepare a solid hydrochloride, hydrobromide, oxalate, picrate or methiodide were all unsuccessful.

5-Benzyloxy-6-methoxy-1-(p-methoxybenzyl)-2-methyl- 3, 4-dihydroisoquinolinium iodide, XIII.

The above oily 3, 4-dihydroisoquinoline, XI, (180 mg.) was allowed to stand for 3 days in ethanol (1 ml.) with methyl iodide (1 ml.). At the end of this period the yellow crystals which had formed (18 mg.) were filtered off and the filtrate was evaporated to dryness. The residual oil was taken up in 50% methanol-ether and seeded. After 1 day a further 23 mg. of yellow crystals had separated. (Total yield 41 mg.; 17%). This material crystallised from methanol-ether to give the keto-methiodide, XIII, as yellow needles, m.p. 164-169°. (Found: C, 56.6; H, 4.8. $C_{26}H_{26}INO_4 \cdot \frac{1}{2}H_2O$ requires C, 56.5; H, 4.9%).

5-Benzyloxy-2, 2-dimethyl-1-(3'-hydroxy-4'-methoxybenzyl)-6-methoxy-1, 2, 3,

4-tetrahydroisoquinolinium iodide, XIV.

The above keto-methiodide, XIII, (23 mg.) in methanol (1 ml.) and water (1 drop) was treated with sodium borohydride (45 mg.) in portions during a few minutes. After refluxing for 1 hour the methanol was evaporated and water (5 ml.) was added. Chloroform extraction gave a colourless oil (17 mg.) which did not crystallise and failed to yield a crystalline hydrochloride or picrate. The oil in ethanol (3 ml.) and methyl iodide (0.5 ml.) gave a colourless precipitate after 1.5 hours. Crystallisation of this from methanol-ether gave the tetrahydroisoquinolinium iodide, XIV as fine colourless needles (16 mg; 68%), m.p. 128-138°. Found: C, 57.4; H, 5.7. $C_{27}H_{32}INO_4$ requires C, 57.8; H, 5.7% . Molecular weight (mass spectrometry) 434. $C_{27}H_{32}NO_4$ (cation only) requires 434).

5-Benzyloxy-6-methoxy-1-(p-methoxybenzyl)-1, 2, 3, 4-tetrahydroisoquinoline, XV

A mixture of phosphorous oxychloride (5 ml.) and benzene (10 ml.) was placed in a dropping funnel in one neck of a three-necked flask containing N-[2-(2'-benzyloxy-3'-methoxyphenyl)-ethyl] - p - methoxyphenylacetamide, X, (2 g.). The entire apparatus was flushed with nitrogen for 30 minutes and the phosphorus oxychloride solution was then added to the amide. After refluxing for 30 minutes light petroleum (b.p. 40-60°) (100 ml.) was added to the flask and after 45 minutes the supernatant solvents were decanted. After a further washing with light petroleum, the residual oil (which was strongly acidic) was dissolved in methanol (100 ml.) and water (2 ml.). Sodium borohydride (0.5 g.) was added rapidly in portions and the solution was then basified with 4N

aqueous sodium hydroxide and treated with more sodium borohydride (0.5 g.) in portions. The resulting solution was allowed to stand for 1 hour and the flow of nitrogen, which had been maintained throughout all the above operations, was then discontinued. The solution was evaporated to a small volume and, after water (ca. 25 ml.) had been added, was extracted with ether to give a colourless oil. This was taken up in ether and treated with gaseous hydrogen chloride. The res ulting precipitate crystallised from methanol to give the amine hydrochloride as colourless plates (1.37 g.; 65%), m.p. 200-217°, unimproved by further crystallisation. (Found: C, 70.2; H, 6.5; N, 3.3. $C_{25}H_{28}ClNO_3$ requires C, 70.5; H, 6.6; N, 3.3%). Treatment of this amine hydrochloride with dilute aqueous sodium hydroxide and ether extraction gave the amine, XV which, when pure, crystallised from light petroleum (b.p. 60-80°) as colourless needles, m.p. 82-84°. (Found: C, 76.9; H, 6.8; N, 3.6. $C_{25}H_{27}NO_3$ requires C, 77.1; H, 7.0; N, 3.6%).

5-Hydroxy-6-methoxy-1-(p-methoxybenzyl)-1, 2, 3, 4-tetrahydroisoquinoline, XVI

5-Benzyloxy-6-methoxy-1-(p-methoxybenzyl)-1, 2, 3, 4-tetrahydroisoquinoline hydrochloride (0.87 g.) was suspended in water (25 ml.) containing palladium-on-charcoal (10%; 200 mg.) and hydrogenated at atmospheric temperature and pressure. After a few hours one mole of hydrogen had been absorbed. After removal of the catalyst, the solution was basified with ammonia (0.880) and extracted with chloroform. After evaporation of the solvent, crystallisation of the solid residue from nitromethane gave the phenolic amine, XVI, as colourless needles (333 mg;

50%), m.p. 157-158°. (Found: C, 71.9; H, 7.3. $C_{18}H_{21}NO_3$ requires C, 72.2; H, 7.1%). The picrate crystallised very slowly from methanol as yellow prisms, m.p. 205-215° (Found: C, 54.7; H, 4.7; N, 10.3. $C_{18}H_{21}NO_3.C_6H_3N_3O_7$ requires C, 54.55; H, 4.6; N, 10.6%).

2, 2-Dimethyl-5-hydroxy-6-methoxy-1-(p-methoxylbenzyl)-1, 2, 3, 4-tetrahydroisoquinolinium iodide, II (X = I).

A solution of 5-hydroxy-6-methoxy-1-(p-methoxybenzyl)-1, 2, 3, 4-tetrahydroisoquinoline, XVI, (0.28 g.) in ethanol (25 ml.) and aqueous formaldehyde solution (33%; 4 ml.), containing palladium-on-charcoal (10%; 0.13 g.), was hydrogenated at atmospheric temperature and pressure. After 4 hours one mole of hydrogen had been absorbed. After removal of the catalyst, the solution was evaporated to ca. 5 ml., diluted with water, acidified with dilute aqueous hydrochloric acid and extracted with ether (2 x 20 ml.). The aqueous solution was then basified with ammonia (0.880) and extracted with chloroform to give a pale pink oil (285 mg.). This oil was dissolved in ethanol (10 ml.) and methyl iodide (5 ml.) and allowed to stand overnight. Evaporation of the solvents and crystallisation of the residue from ethanol gave the base methiodide, II (X = I), as colourless hygroscopic needles (300 mg; 69%) m.p. 188-198°. (Found: C, 49.3; H, 6.1; N, 2.9. $C_{20}H_{26}INO_3.2H_2O$ requires C, 48.9; H, 6.15; N, 2.85%).

4, 4'-Dimethoxy-2-(2-dimethylamino-ethyl)-3-hydroxy-trans-stilbene, III.

2, 2-Dimethyl-5-hydroxy-6-methoxy-1-(p-methoxybenzyl)-1, 2, 3, 4-tetrahydroisoquinolinium iodide, II (X = I), (300 mg.) was dissolved in warm ethanol (25 ml.), cooled, and immediately put on to a column of Amberlite IRA-400 (OH) anion exchange resin (6 g.). The material was

slowly eluted with ethanol. On evaporation, the corresponding quaternary hydroxide, II (X = OH) was obtained as an oil. This was refluxed in a 10% solution of ethanolic sodium ethoxide (15 ml.) for 2 hours, under a stream of nitrogen. The cooled solution was diluted with water (15 ml.), acidified with glacial acetic acid and rebasified with ammonia (0.880). Extraction with chloroform gave a pale yellow solid which, on crystallisation from ethanol, afforded the stilbene, III, as colourless plates (92 mg; 44%), m.p. 170-172.5°. (Found: C, 73.2; H, 7.75; N, 4.2. $C_{20}H_{25}NO_3$ requires C, 73.4; H, 7.7; N, 4.3%).

3-Methanesulphonoxy-4-methoxyphthalic acid, XXXVIII.

A solution of leonticine, XXV, (550 mg.) in pyridine (10 ml.) at 0° was treated with methanesulphonyl chloride (2 ml.) in pyridine (2 ml.) during 1 minute and the resulting solution was left in the refrigerator overnight. Ice was then added and, when it had melted, the solution was treated with water (100 ml.) and then saturated aqueous sodium carbonate was added until no more oil separated. The aqueous solution, after standing in the refrigerator overnight, was decanted as far as possible from the rather mobile oil which was then allowed to stand with fresh water overnight. The mesylate was then obtained as an amorphous solid (500 mg.) which failed to crystallise from common organic solvents. [ν_{max} (nujol) 1375 $cm.^{-1}$, 1140 $cm.^{-1}$]. This mesylate (150 mg.) was refluxed for 30 minutes in a solution+ of acidified potassium dichromate (20 ml.), cooled, and treated with gaseous sulphur dioxide until the solution became bright green. Chloroform extraction (3 x 25 ml.) gave a few mgs. of anisic acid (identified by i.r. and mixed m.p. with an

+ Potassium dichromate (24 g.), concentrated sulphuric acid (72 ml.) and water (360 ml.).

authentic sample). The aqueous mother liquor was continuously extracted overnight with chloroform to give 3-methanesulphonoxy-4-methoxyphthalic acid, XXXVIII, (16 mg; 11% based on leonticine), as a colourless powder, m.p. 179-194° identical (i.r. and mixed m.p.) with a sample prepared as described on p.60 .

BIBLIOGRAPHY

(1) J. McShefferty, Ph.D. Thesis, University of Glasgow, 1957.

(2) Loudon, An Encyclopoedia of Plants, Longman, Rees, Orme, Browne and Green, 1829.

(3) Gunther, The Greek Herbal of Dioscorides, Oxford University Press, Oxford, 1934.

(4) Lovell, Compleat Herball, 2nd Ed., Davis, Oxford, 1665.

(5) Low, Die Flora der Juden, Vol. 1, Emil Damask, Vienna and Leipzig, 1929-34.

(6) Lindley, Vegetable Kingdom, Bradbury and Evans, London, 1846.

(7) Orekhov and Konovalova, Arch. Pharm., 1932, 270, 329.

(8) Orekhov and Konovalova, Khim-Farm Prom., 1932, 10, 371.

(9) Yusunov and Sorokina, J. Gen. Chem. (U.S.S.R.), 1949, 19, 1955.

(10) Platanova, Kuzovkov and Massagetov, Zhur. Obshchei. Khim., 1953, 23, 880. J. Gen. Chem. (U.S.S.R.), 1953, 23, 921.

(11) Platanova and Kuzovkov, Zhur. Obshchei. Khim., 1954, 24, 2246.

(12) S. J. Smith, Ph.D. Thesis, University of Glasgow, 1963.

(13) Dutcher, J. Amer. Chem. Soc., 1946, 68, 419.

(14) Henry, The Plant Alkaloids 4th Ed. J. and A. Churchill Ltd., London, 1949.

(15) Battersby and Harper, J., 1962, 3526.

(16) Katritzky, Jones and Bhatnagar, J., 1960, 1950.

(17) Bick, Harley-Mason, Sheppard and Vemengo, J., 1961, 1896.

(18) Bellamy, The Infrared Spectra of Complex Molecules, Methuen, London, 1962, p.34.

(19) Gibbs, J. Biol. Chem., 1927, 72, 649.

(20) King, King and Manning, J., 1957, 563.

(21) Ahmed and Lewis, J. Pharm. Pharmacol., 1960, 12, 163.

(22) Whaley and Govindachari in Organic Reactions, Ed. Adams, Vol. VI, J. Wiley and Sons, New York, 1951.

(23) Merz and Pfaffle, Arch. Pharm., 1955, 288, 96.

(24) Ginsberg, Bull. Soc. chim. France (5), 1950, 17, 510.

(25) Scott, Interpretation of the Ultraviolet Spectra of Natural Products, Pergamox, 1963.

(26) Buck, Haworth and Perkin, J., 1924, 125, 2176.

(27) Lindenmann, Helv. Chim. Acta, 1949, 32, 69.

(28) Kametani and Fukumoto, J , 1963, 4289.

(29) Brewster and Bayer, J. Org. Chem., 1964, 29, 110; ibid, 116.

(30) Gaylord, Reduction with Complex Metal Hydrides, Interscience, London, New York, 1956.

(31) Moore in Organic Reactions, Vol. V, Ed. Adams, J. Wiley and Sons, New York, London, 1949.

(32) Highet, J. Org. Chem., 1964, 29, 471.

(33) Bellamy, The Infrared Spectra of Complex Molecules, Methuen, London, 1954, p.31.

(34) Davidson, Keane and Nolan, Sci. Proc. Roy. Dublin Soc., 1943, 23, 143.

(35) Cope and Trumbull in Organic Reactions, Vol. XI, Ed. Cope, J. Wiley and Sons, London, 1960.

(36) Manske, Can. J. Research, 1938, B16, 81.

(37) Manske, J. Amer. Chem. Soc., 1952, 74, 2864.

(38) Friedel and Orchin, Ultraviolet Spectra of Aromatic Compounds, J. Wiley & Sons, New York, 1951.

(39) Suzuki, Bull Chem. Soc. Japan, 1960, 33, 406.

(40) Fuson, Denton and Best, J. Org. Chem., 1942, 8, 64.

(41) N.M.R. Spectra Catalogue, Varion Associates, 1962, Nos. 304, 305.

(42) Boit, Ergebnisse der Alkaloid-Chemie bis 1960, Akademie-Verlag, Berlin, 1961.

(43) Manske and Holmes, The Alkaloids, Academic Press, New York.

SYNTHETIC APPROACHES TO CULARINE AND PETALINE

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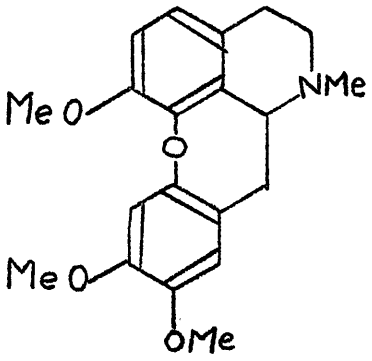

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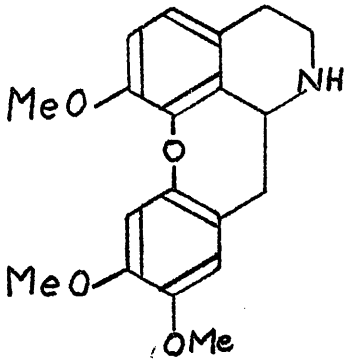

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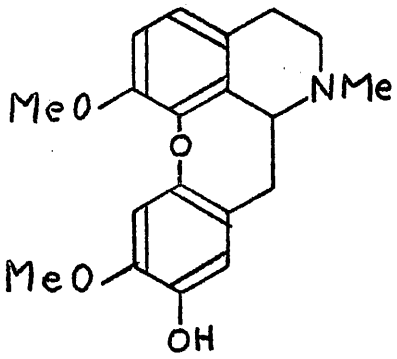

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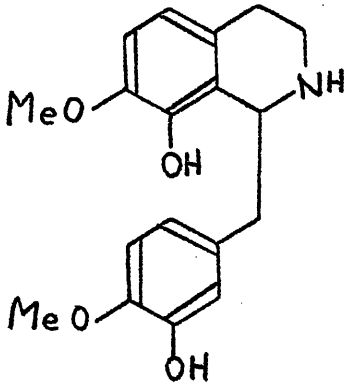

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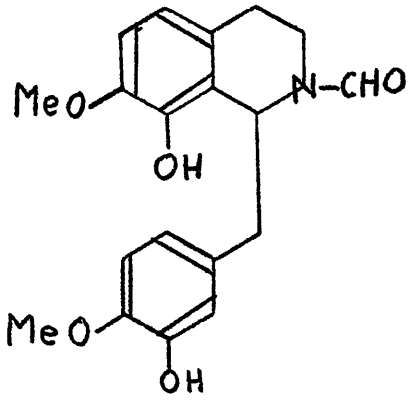

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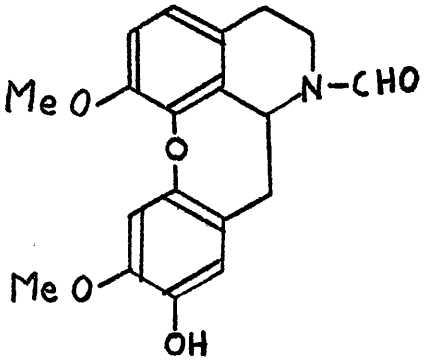
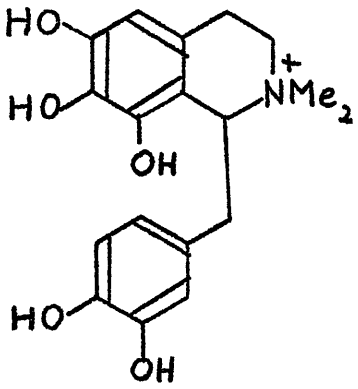


VI



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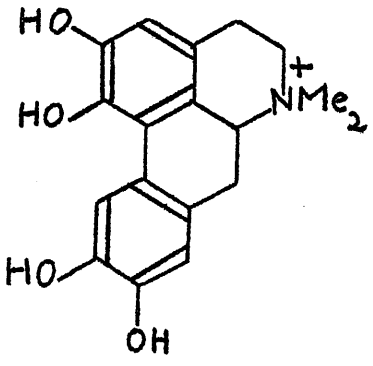

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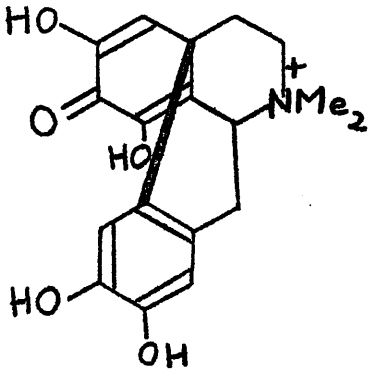

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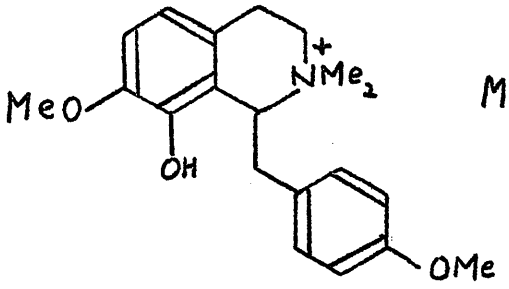

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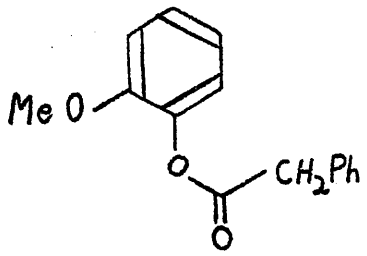

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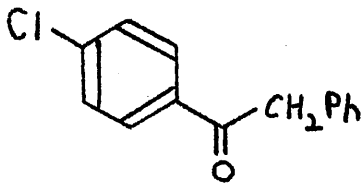

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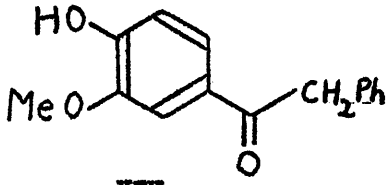

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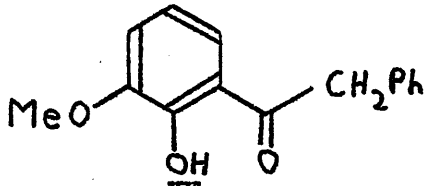

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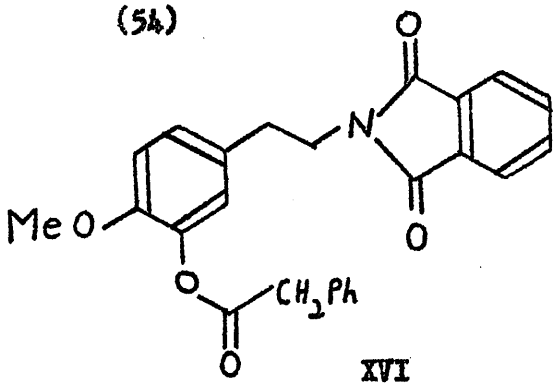

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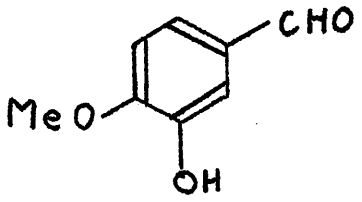

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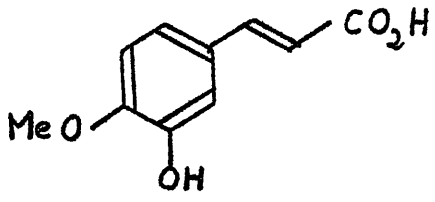

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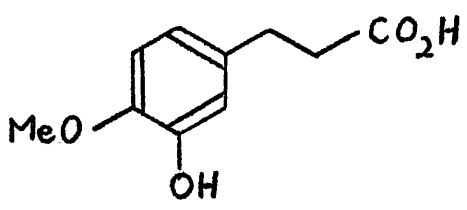

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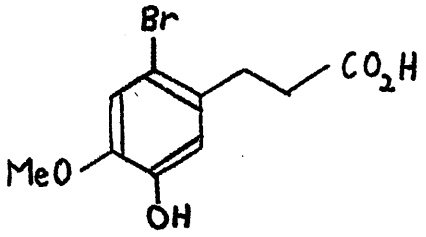

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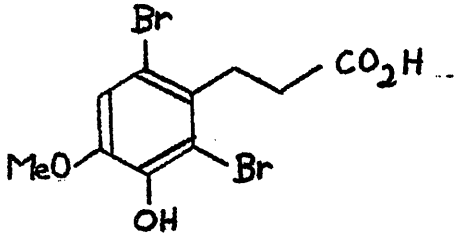

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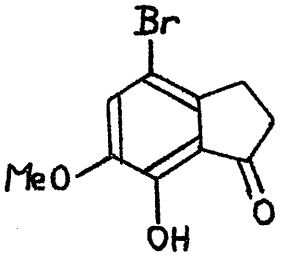

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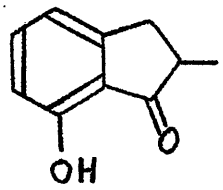

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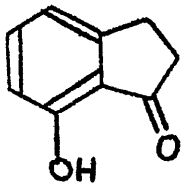

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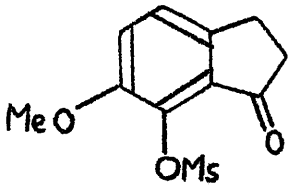

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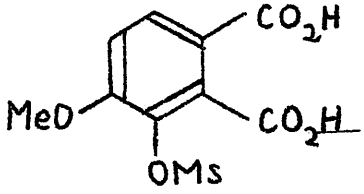

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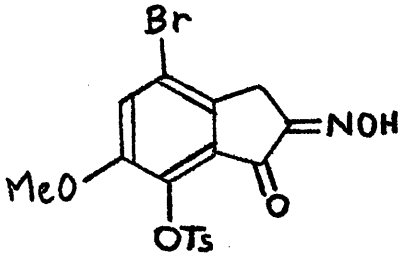

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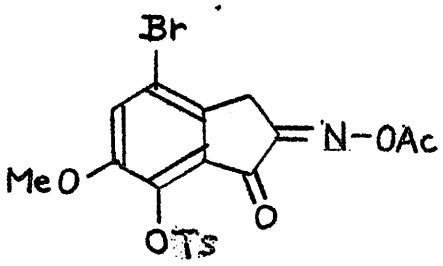

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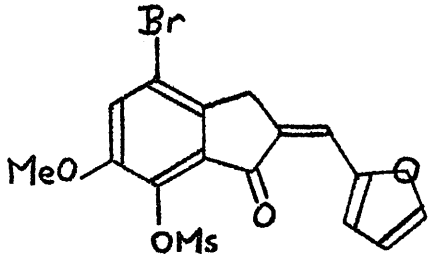

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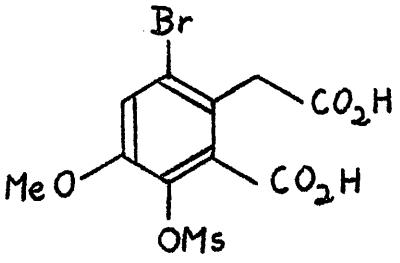

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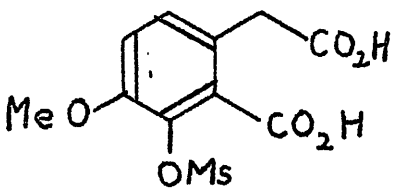

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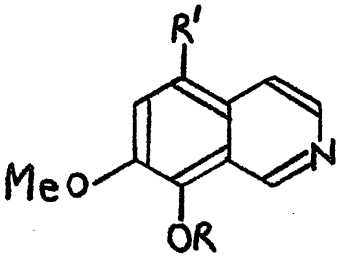

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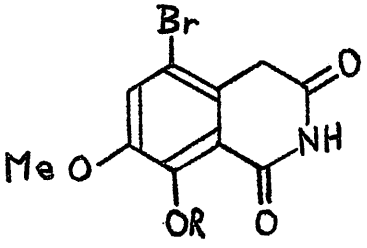

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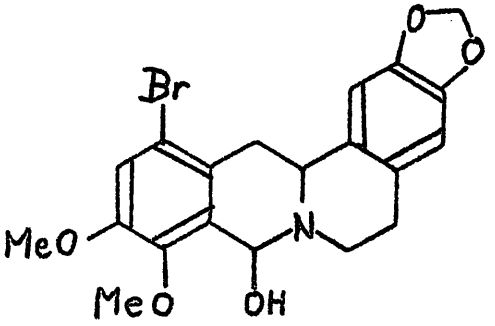

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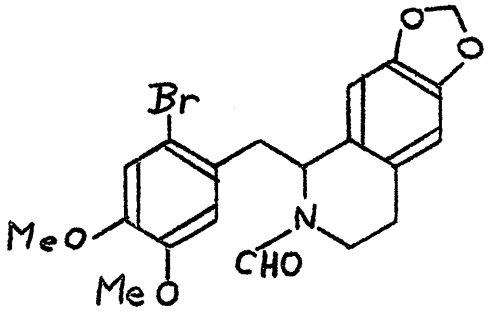

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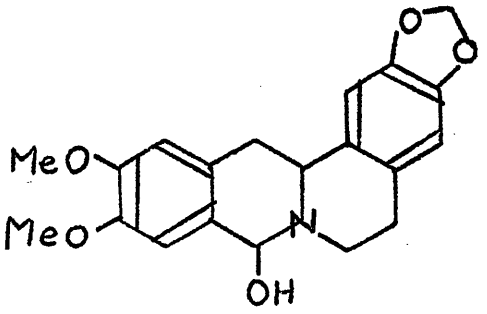

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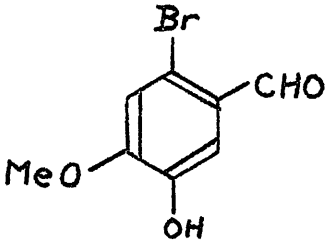

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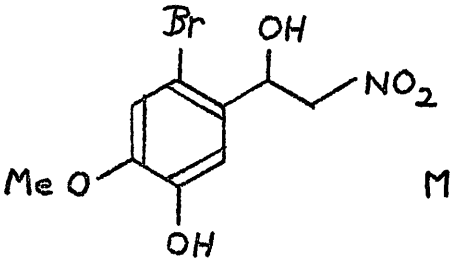

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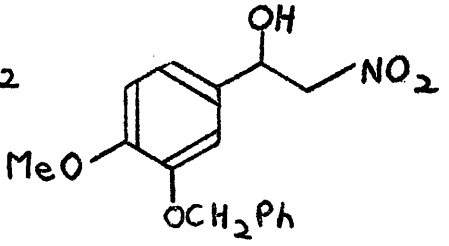

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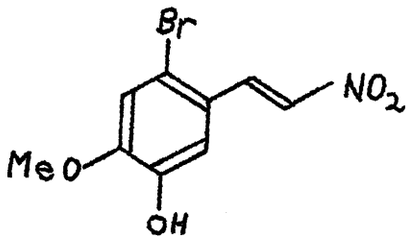

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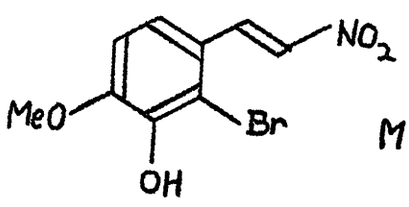

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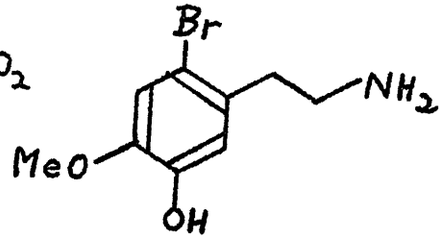

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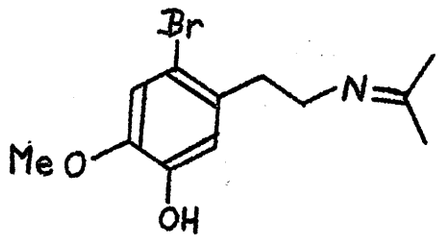

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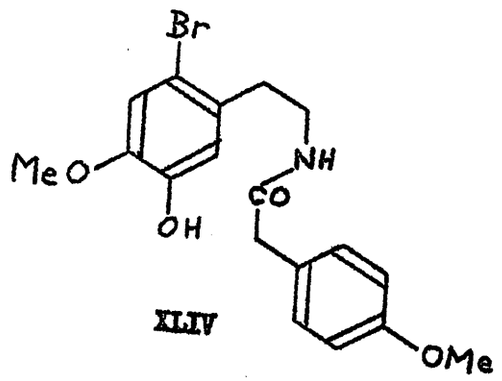

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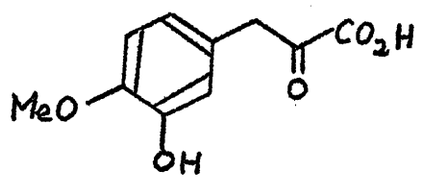

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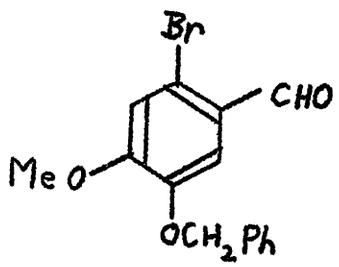

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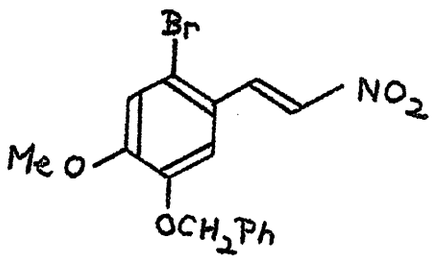

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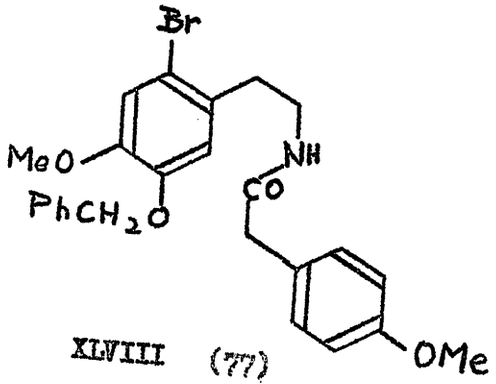

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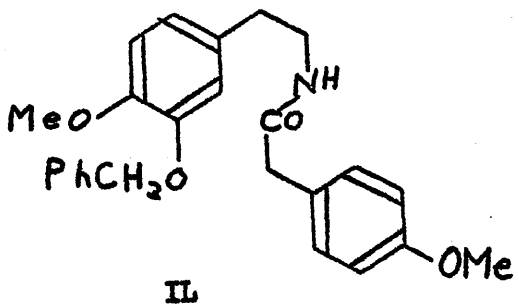

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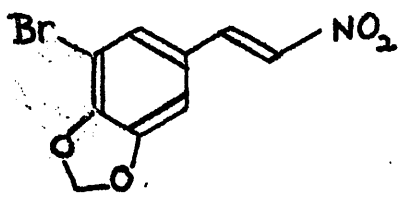

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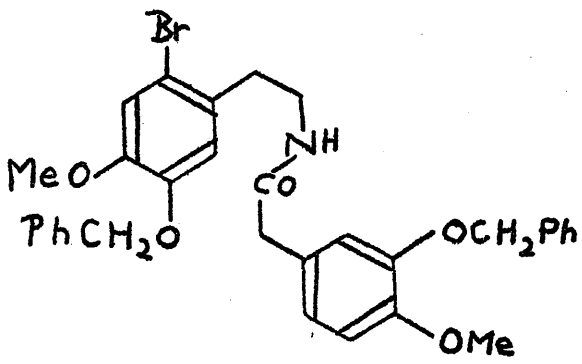

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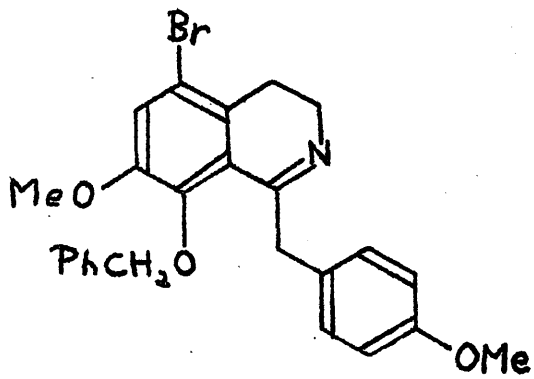

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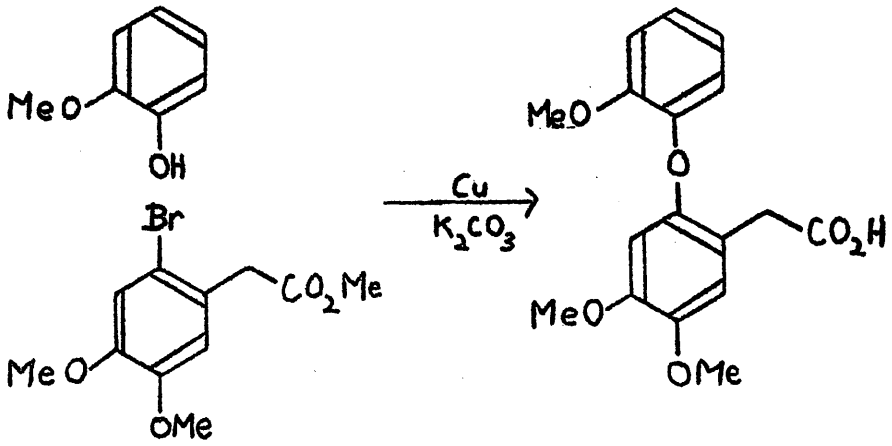
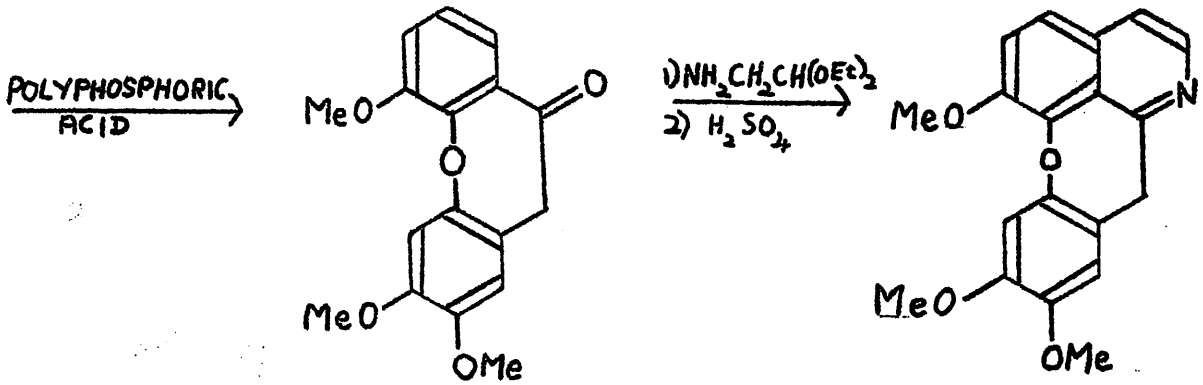
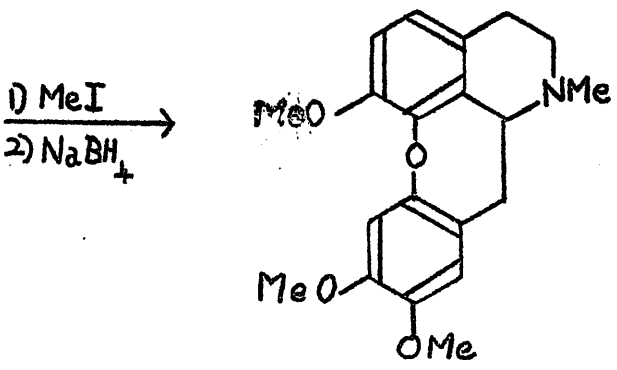
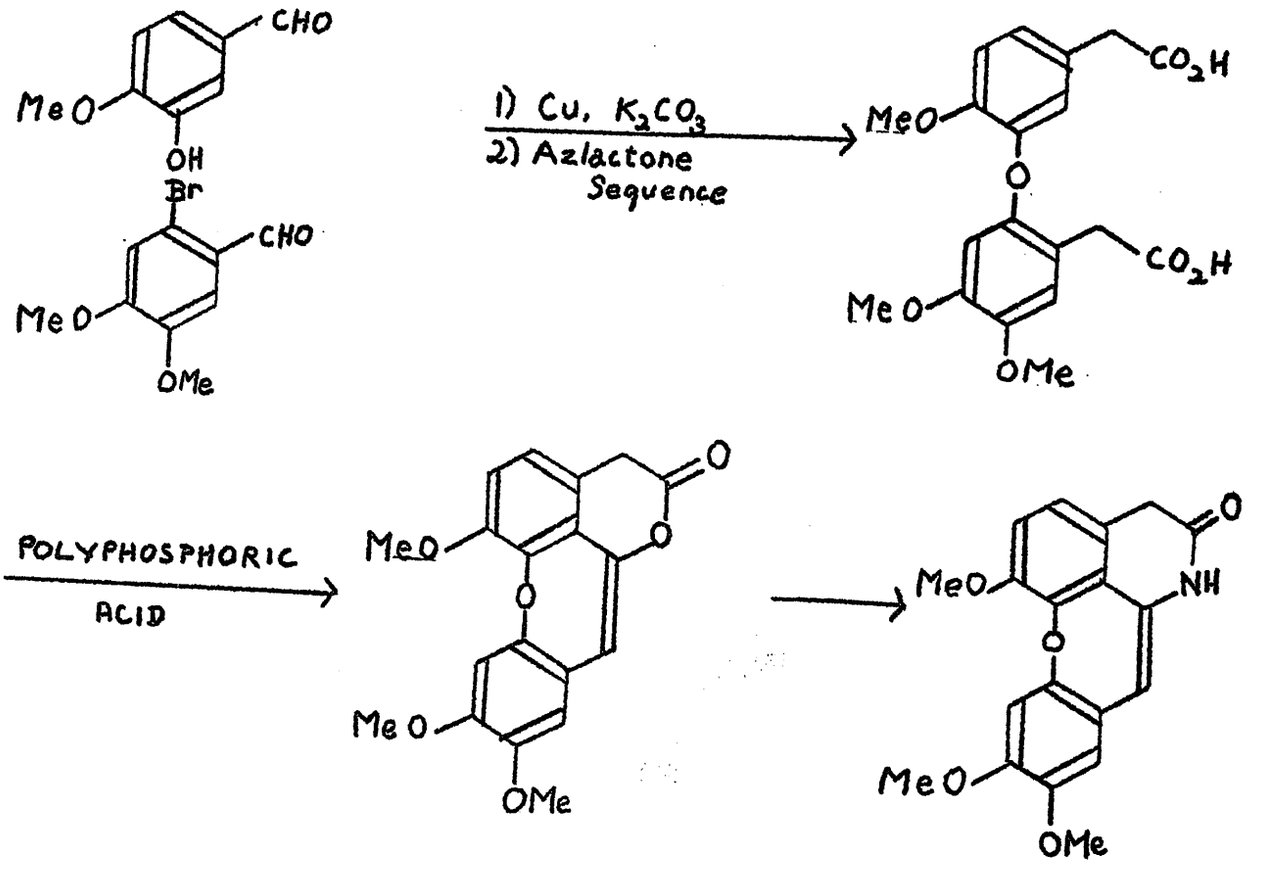






Cularine

SCHEME II[3]



Cularimine

Cularine

INTRODUCTION

The alkaloid, cularine, I,[1] is chiefly remarkable for its unusual ether linkage comprising part of a seven-membered ring. Proposed synthetic routes to the base fall naturally into two classes according to whether this ether linkage is introduced before or after elaboration of the 1-benzylisoquinoline framework.

Two successful syntheses of the former type have recently been reported by Kametani et al.,[2][3] each involving the formation of a diphenyl ether by an Ullmann reaction at an early stage (Schemes I and II).

While these syntheses, particularly the more recent one [3] which also led to cularimine, II[1], effectively confirmed the structures of the alkaloids, it was felt that a synthesis which paralleled the proposed biogenetic route (as outlined in the General Introduction), might be of rather more intrinsic interest and might, in addition, confirm the theory, based on biogenetic grounds, that cularidine, which is known [1] to be a des-O-methyl-cularine, has the structure III.

The initial problem, therefore, was to synthesise a compound related to IV, which, by phenol oxidative coupling and subsequent manipulation, might be convertible into III and thence into cularine, I.

The work of Franck and his collaborators [4] has shown that the difficulties encountered in carrying out phenol oxidative coupling reactions on phenolic bases can be overcome effectively by first quaternising the nitrogen atom.

However if phenol oxidation were applied to a quaternised tetrahydroisoquinoline it might not be possible to convert the resulting

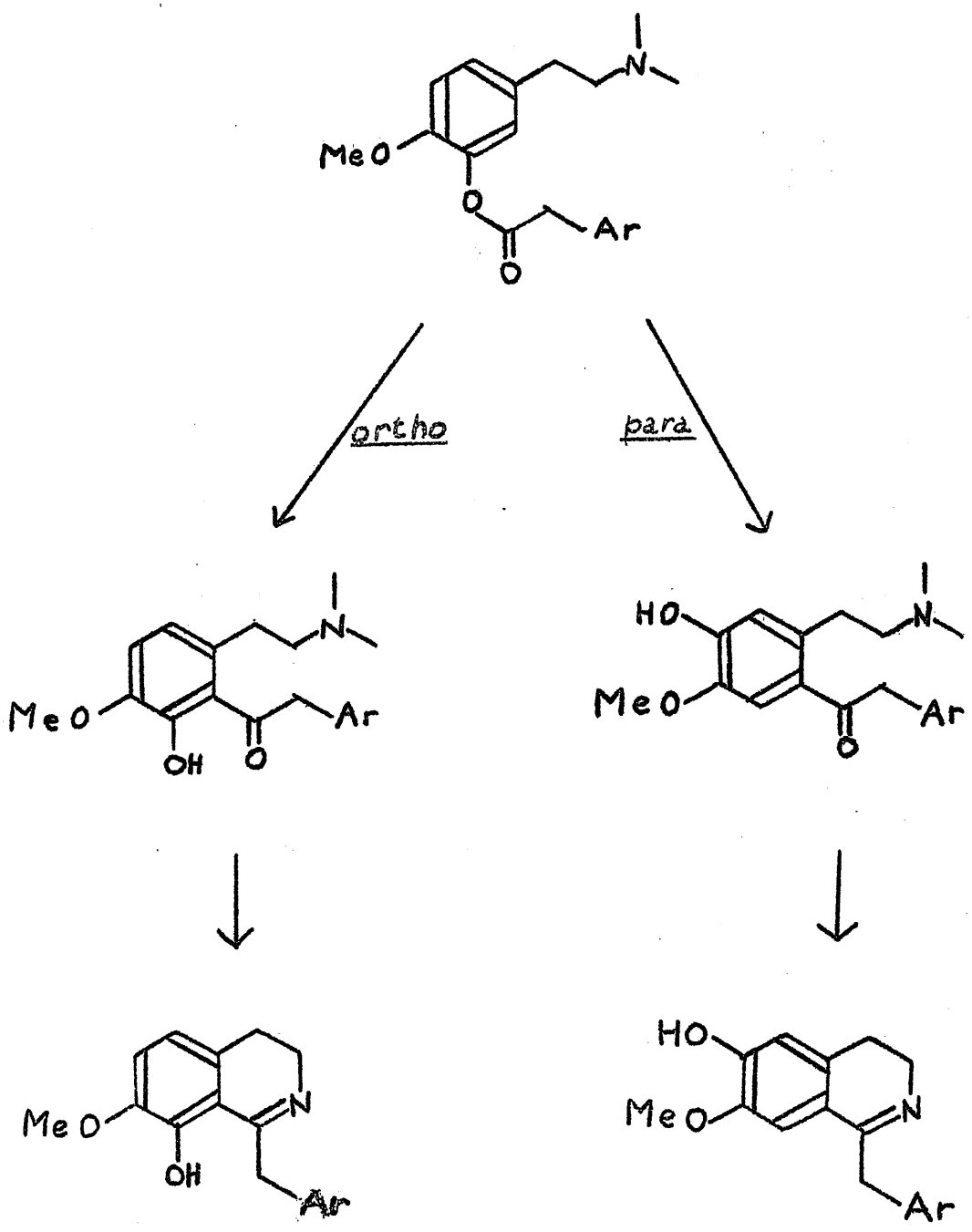
quaternary base to a tertiary amine of the cularine type. However it was hoped that this problem might be overcome by the use of an N-formyl derivative such as V, since the desired product of oxidation of this, viz. VI, ought to be readily convertible into cularine I or cularimine, II.

In an attempt to convert the pentahydroxy-compound, VII into either a cularine-type or morphine-type compound, Franck and Blaschke (4) obtained the aporphine, VIII. It was suggested (4) that this aporphine was produced by a morphine-apomorphine type rearrangement of the intermediate, IX. Should this be the case, the use of a 7-methoxy-isoquinoline, e.g. V, ought to prevent the formation of the dienone system of IX.

Hence, there seem to be reasonable grounds for hope that phenol oxidation of the compound V would lead exclusively to the formation of the required 8-6' ether linkage.

With the elucidation of the structure of petaline as X (described in Section I), this alkaloid became a closely related synthetic objective.

SCHEME III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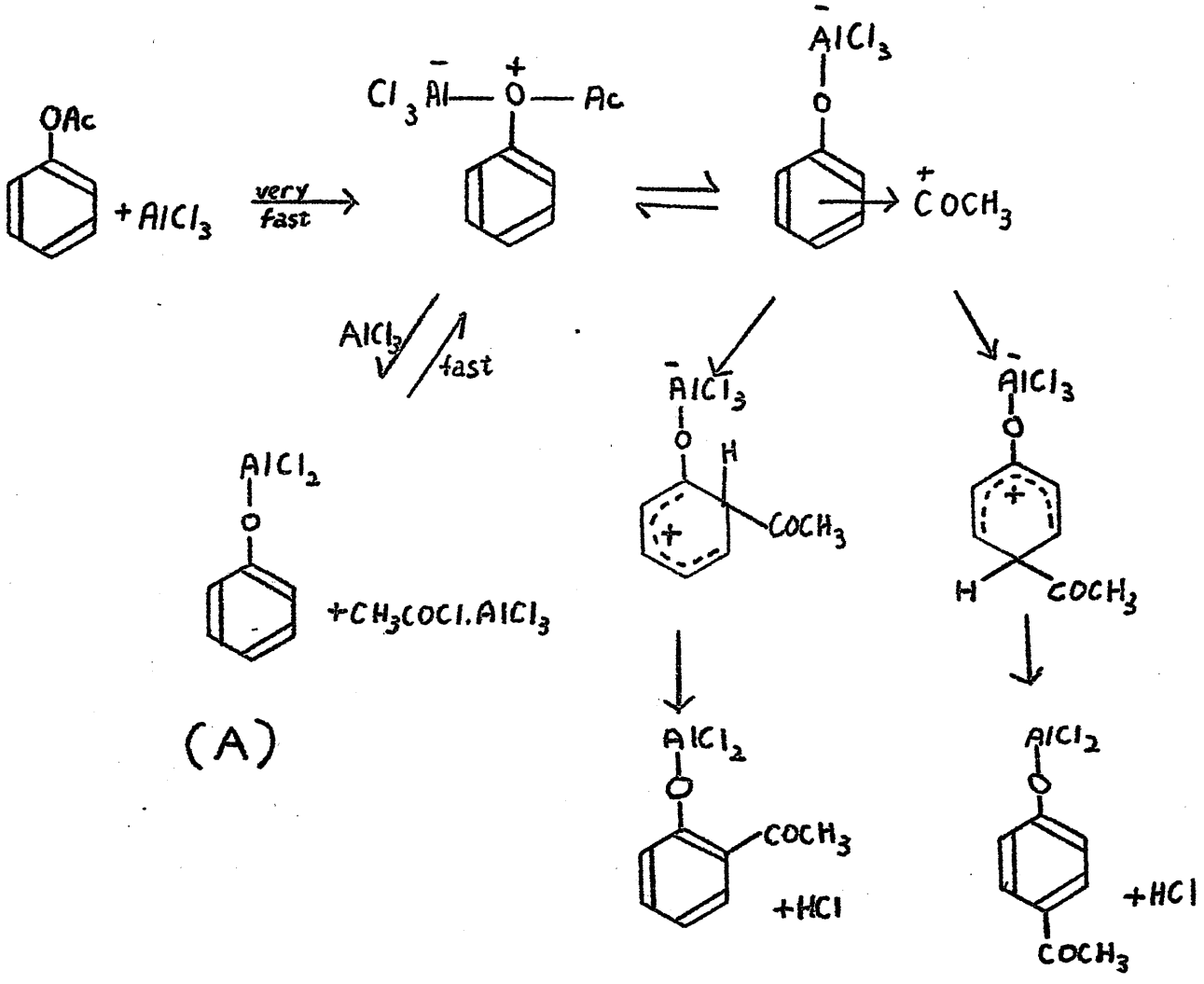
O
Ar
O
ortho
para
MeO
OH
O
Ar
N
HO
MeO
O
Ar
N
MeO
OH
N
Ar
HO
MeO
N
Ar

SCHEME IV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+ AlCl3
very fast
Cl3 Al — O — Ac
AlCl3
O
+ COCH3
AlCl3 fast
AlCl2
O
+CH3COCl.AlCl3
(A)
AlCl3
O
H
COCH3
AlCl3
O
H
COCH3
AlCl2
O
COCH3
+HCl
AlCl2
O
+HCl
COCH3

RESULTS AND DISCUSSION

The first objective in a proposed biogenetic-type synthesis of cularine, I, was a compound related to the diphenol, V.

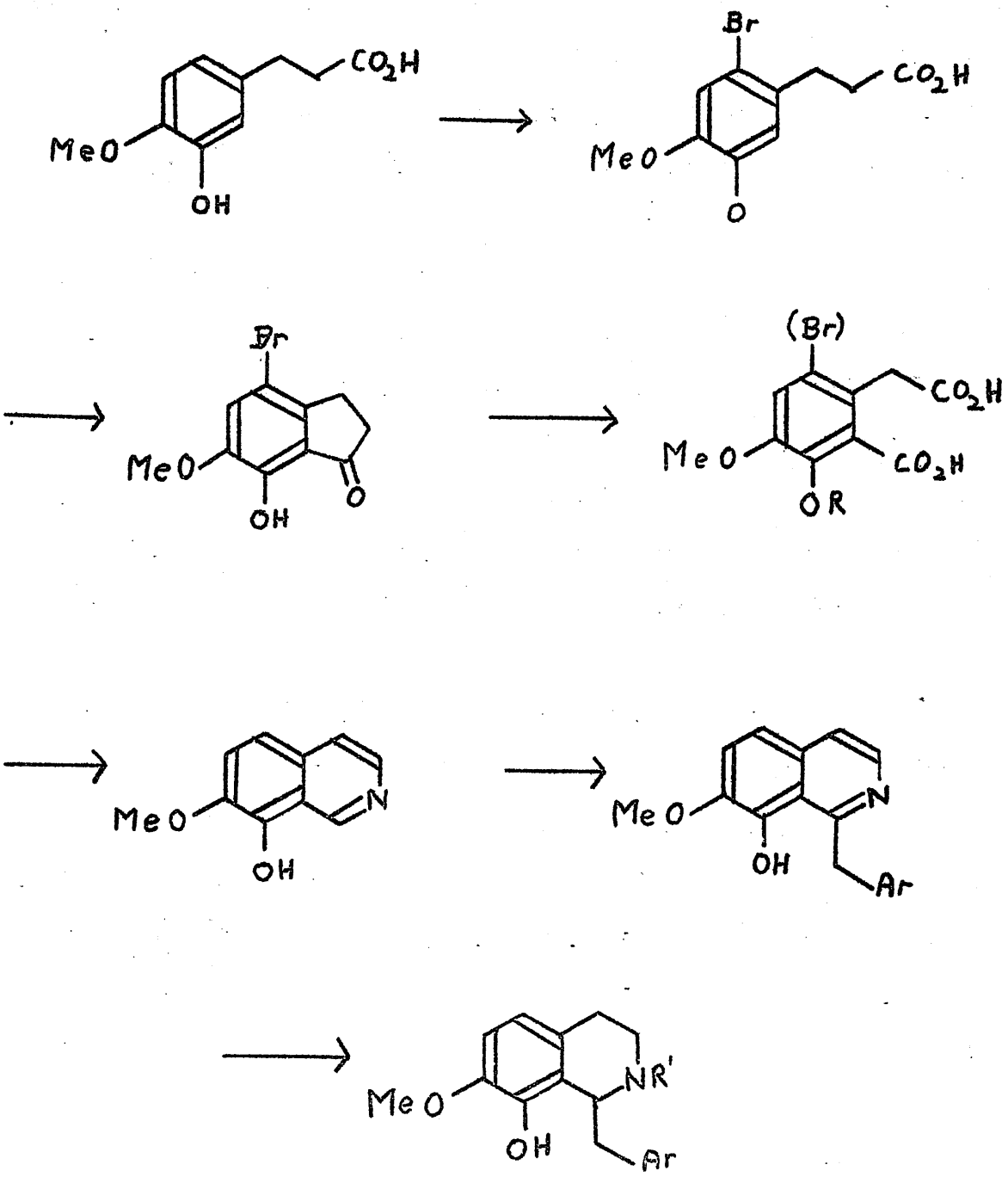
Since, for reasons mentioned in the General Introduction, the conventional isoquinoline syntheses were not directly applicable to this problem, the first route to be investigated was that outlined in Scheme III, involving the Fries rearrangement.(5) As can be seen (Scheme III) acyl migration to the ortho position of the ester, XI would, on subsequent condensation, lead to the desired system, whereas a para rearrangement would give the 6, 7-dioxygenated system which is readily accessible by more usual methods.

It was decided to study the rearrangement reaction, using the readily prepared guaiacol phenylacetate, (6) XII. With aluminium chloride in refluxing chlorobenzene, the only product isolated was 4-chloro-2'-phenylacetophenone, (7) XIII, formed by acylation of the solvent. Several investigators (8)(9) have reported similar acylations effected by esters during the Fries reaction.

In a radio-active tracer study of the mechanism of the Fries reaction of phenyl acetate, Ogata and Tabuchi (10) have recently proposed the mechanism shown in Scheme IV, where the intermediate, A, accounts for the loss of acyl group either by acylation of other species or by evaporation of acyl chloride.

The formation of the product, XIII, was precluded by carrying out the reaction in stannic chloride at 100° in the absence of any other solvent. Under these conditions, para acyl migration occurred

SCHEME V



to give 4-hydroxy-3-methoxy-2'-phenylacetophenone, XIV. This showed i.r. absorption maxima (in carbon tetrachloride) at 3548 cm.$^{-1}$ (OH, bonded only to ortho methoxyl group) and 1673 cm.$^{-1}$ (non-bonded aromatic ketone carbonyl). The product of ortho migration would have been expected to exhibit absorption comparable to that of o-hydroxyacetophenone at 3500-2900 cm.$^{-1}$ (b.w.) and 1639-1613 cm.$^{-1}$.(11)

Attempted rearrangements of guaiacol phenylacetate, XII, under a variety of conditions failed to give any of the required ortho rearrangement product, XV, but in spite of this, experiments were carried out using the closer model compound, 4-methoxy-3-phenylacetoxy-N-phthaloyl-β-phenylathylamine, XVI, prepared from the corresponding phenol (12) and phenylacetyl chloride.

However preliminary attempts to rearrange this ester, XVI, under the high temperature conditions which have been reported (5)(13) to favour ortho Fries rearrangement, failed to produce any phenolic material.

In view of the unpromising nature of these results, this route to 7, 8-dioxygenated isoquinolines was not investigated further.

The second approach to be explored is outlined in Scheme V and was based on the notion that since the 1-position of the isoquinoline nucleus is the most susceptible to nucleophilic substitution, (14) the problems involved in preparing the 1-benzyl-8-hydroxy-7-methoxy-isoquinoline might be tackled stepwise by first preparing the required dioxygenated isoquinoline and subsequently introducing the benzyl group by means of an organo-metallic reagent. (15)(16) The synthesis was undertaken as follows.

Isovanillin, XVII, was smoothly converted to 3-hydroxy-4-methoxycinnamic acid, XVIII, by the action of malonic acid in pyridine containing a little piperidine. Catalylic hydrogenation then gave the corresponding hydrocinnamic acid, XIX. Bromination of the acetate of this in glacial acetic acid gave only complex mixtures of products. However, the unprotected hydrocinnamic acid, XIX, on treatment with one mole of bromine in the same solvent gave exclusively the required 2-bromo-5-hydroxy-4-methoxyhydrocinnamic acid, XX. Cyclisation of this product was expected to lead to an indanone of the required orientation.

The assumption that bromination had occurred para to the phenol rather than ortho, was shown by later work to be correct.

Bromination of the hydrocinnamic acid, XIX, using two moles of bromine, gave exclusively a dibromo derivative, assumed to be XXI.

The above bromination experiments show clearly that two positions of XIX are susceptible to electrophilic substitution but that one is more active than the other. There is much evidence, e.g. the results of Bischler-Napieralski reactions, to suggest that the position para to one of two adjacent, activating oxygen functions is more reactive than a position ortho to one of them.

Attempts to cyclise the hydrocinnamic acid, XX, with polyphosphoric acid met with no success but brief treatment with concentrated sulphuric acid at 100° gave good yields of the required 4-bromo-7-hydroxy-6-methoxyindan-1-one, XXII whose structure, and consequently that of its precursor, XX, was established in the following ways.

TABLE I

7-Hydroxy-2-methylindan-1-one, XXIII.

$\lambda_{max}^{EtOH-HCl}$	316mμ.
$\lambda_{max}^{EtOH-NaOH}$	364mμ.
Shift on ionisation	48mμ.

Indanone, XXII.

λ_{max}^{MeOH}	343mμ.
$\lambda_{max}^{MeOH-KOH}$	384mμ.
Shift on ionisation	41mμ.

The u.v. spectrum of the indanone, XXII, and the shift of the long-wavelength band on basification, compare favourably with those of 7-hydroxy-2-methylindan-1-one, [17] XXIII when due allowance is made for the expected bathochromic shift of XXII due to its extra substitution . (Table I)

The 7-hydroxyindanone, XXIII, has been shown by Conover[17] to have a hydroxyl group which is particularly weakly hydrogen-bonded because of the geometry of the five-membered ring. Presumably as a consequence of this certain chemical properties of the 7-hydroxyindanone, XXIII, as distinct from its 5-hydroxy isomer, are characteristic of the 7-hydroxyindanone system. Thus XXIII gives a deep purple colour with ferric chloride and forms a sodium salt which is insoluble in water and the observation that the indanone XXII behaves similarly is good evidence of its structure.

Finally 7-hydroxyindan-1-one, XXIV, was found to give a yellow-green chelate when an acetone solution is mixed with cupric acetate in acetone. The fact that the hydroxyindanone XXII gives a similar yellow-green solid is further strong evidence for its chelate structure.

Some preliminary experiments were carried out involving debromination at this stage. The bromine atom was hydrogenolysed over palladium-on-charcoal and the resulting oily product was not characterised but immediately converted into a crystalline mesylate, 7-methanesulphonoxy-6-methoxy-indan-1-one, XXV.

Oxidation of this with acidified potassium dichromate (conditions which effect the oxidation of indene to homophthalic acid [18])

gave, not the required homophthalic acid but 3-methanesulphonoxy-4-methoxyphthalic acid, XXVI, which was characterised as its anhydride. This acid, XXVI, however, proved to be a key compound in the elucidation of the structure of petaline as described in Section I (p. 27).

The oxidation of XXV was not, in fact, studied further since the desired homophthalic acid was conveniently obtained from XXII by an alternative route in which debromination was deferred until after oxidation.

Attempts were first of all made to effect the controlled oxidation of the bromo-indanone, XXII, by indirect means. The phenolic group was protected as the tosyl derivative and the corresponding isonitroso compound, XXVII was prepared, albeit in rather poor yield. Attempted Beckmann reaction of this isonitroso compound (cf. ref. (19)) using p-toluenesulphonyl chloride in pyridine or 10% aqueous sodium hydroxide gave complex mixtures while acetic anhydride merely produced the corresponding oxime acetate, XXVIII.

Another "indirect" method attempted was the ozonolysis of the mesylated furfurylidene derivative, XXIX of the bromoindanone, XXII. The fact that neither starting material nor product was obtained after chloroform extraction in the work-up was considered discouraging although subsequent results showed that prolonged liquid-liquid extraction is required to isolate the homophthalic acid.

However, it was found that the homophthalic acid, XXX, was obtainable by direct oxidation of the mesylate of the indanone, XXII, with chromium trioxide in acidic solution, (Jones' reagent), followed by

continuous extraction with chloroform.

Hydrogenolysis of XXX over palladium-on-charcoal gave the bromine-free homophthalic acid, XXXI, which also required to be continuously extracted.

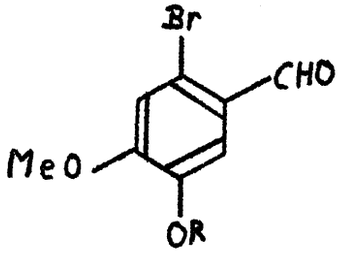
There were two possible approaches to the problem of converting the diacid, XXXI, into an isoquinoline. The first to be attempted involved the reduction of the compound to a diol and conversion of this, perhaps via a dihalide to a tetrahydroisoquinoline, which might then be dehydrogenated to the required isoquinoline, XXXII (R^1 = H).

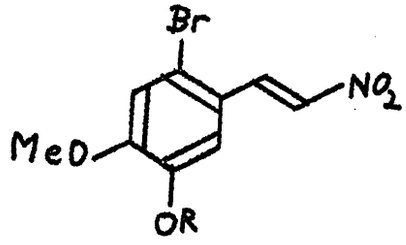
However, reduction of the homophthalic acid, XXXI, or its dimethyl ester (prepared with diazomethane), with lithium aluminium hydride gave only oily products whose i.r. spectra still exhibited carbonyl absorption. This incomplete reduction may have been due to steric factors. A further complication was that the mesyl group would have been removed under the reaction conditions so, possibly, the expected product was, in fact, formed to some extent but was too water soluble to be extracted. Attempted reduction of the brominated homophthalic acid, XXX, gave similar results.

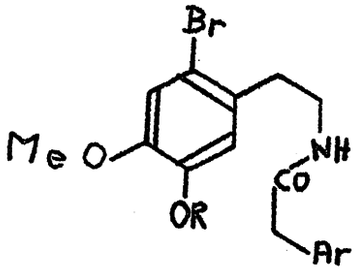
The alternative approach was to convert the homophthalic acid, XXX, into the corresponding homophthalimide, XXXIII, which might then be converted into XXXII (R^1 = Br) by lithium aluminium hydride reduction [20] followed by dehydrogenation or into XXXII (R^1 = H) by hydrogenolysis of the 1, 3-dichloroisoquinoline produced by the action of phosphorous pentachloride [21] on XXXIII.

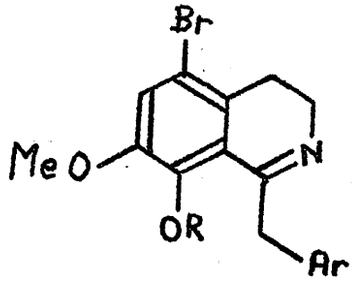
This approach also unexpectedly [21][22][23][24][25]

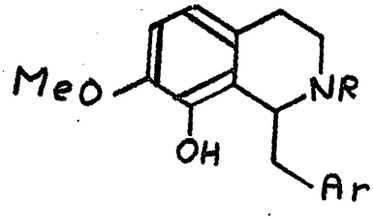
SCHEME VI


Br
CHO
MeO
OR


Br
NO2
MeO
OR


Br
MeO
NH
CO
OR
Ar


Br
MeO
N
OR
Ar


MeO
NR
OH
Ar

failed since the homophthalic acid XXX resisted all attempts to convert it into a homophthalimide. Thus, pyrolysis of the corresponding diammonium or di-methylammonium salts or treatment with boiling phosphorus oxychloride of the corresponding diamide (prepared by the action of phosphorus oxychloride and methylamine) and treatment of the anhydride with liquid ammonia all failed to give any characterisable product. Shortage of material prevented the application of these methods to the halogen-free diacid, XXXI. Possibly the mesyl group was labile under the conditions of the above reactions.

In view of these difficulties, and since the approach described below appeared to show more promise this "indanone" route to isoquinolines was not further investigated.

An entirely different route which was also explored is outlined in Scheme VI. It was intended to try to control the direction of ring closure in a Bischler-Napieralski synthesis [26] by using a bromine substituent to block the more favoured position. There were, however, a number of possible objections to this route.

The first, and most serious of these was that the tendency for ring closure to occur <u>para</u> to an activating oxygen function, rather than <u>ortho</u>, is so marked that the bromine atom might be eliminated in order to allow <u>para</u> ring closure to occur as in the attempted preparation of bromodihydroberberine, XXXIV, from the formamide, XXXV, by Haworth and Perkin [27], which gave only the product, XXXVI. It was hoped, however, that the use of less vigorous conditions than those of Haworth and Perkin (phosphorus oxychloride in refluxing toluene) might obviate this. The

use of a less labile blocking group would have resulted in increased difficulties when its subsequent removal became necessary.

A further drawback to the route indicated in Scheme VI was that during ring closure under Bischler-Napieralski conditions it is necessary to protect the phenolic hydroxyl group and the desired product of ring closure must therefore necessarily have two groups on the peri positions 1 and 8 of its isoquinoline nucleus. It was feared that steric repulsion between these groups would further militate against the desired ring closure.

Notwithstanding the above hazards, it was decided that the route would bear investigation.

The phenol protecting group required at the cyclisation stage must withstand cyclisation conditions, must be easily removed and, if possible, should not be too large. Probably the ideal group for this purpose is the mesyl group although this can only be introduced after the reduction of the nitrostyrene if the preferred reagent, lithium aluminium hydride, is used. +

Since selective O-mesylation of the phenolic phenylethylamine, the reduction product of the nitrostyrene, was considered to be impossible as preferential N-mesylation would be expected, it was decided to defer the protection of the phenol until the final step before cyclisation.

Accordingly, 6-bromoisovanillin, XXXVII, was prepared, along with the unwanted 2-bromo isomer, by a slight modification of the procedure of Henry and Sharp. (29)

+ The procedure of Kametami et al., (28) who recently reduced a tosyloxy-phenylethylamine using Clemmenson reaction conditions might allow the mesyl group to be introduced at an earlier stage.

TABLE II

The i.r. spectra (in Nujol) of the following nitrostyrenes all exhibited sharp maxima at ca. 1620cm.$^{-1}$ and at ca. 1600cm.$^{-1}$.

2-Benzyloxy-3-methoxy-β-nitrostyrene
3-Benzyloxy-4-methoxy-β-nitrostyrene
3-Hydroxy-4-methoxy-β-nitrostyrene
2-Bromo-5-hydroxy-4-methoxy-β-nitrostyrene
2-Bromo-3-hydroxy-4-methoxy-β-nitrostyrene
2-Bromo-5-Benzyloxy-4-methoxy-β-nitrostyrene

TABLE III

2-Bromo-5-hydroxy-4-methoxy-β-nitrostyrene

λ_{max}^{EtOH}	267mμ.	(3.90)
	327mμ.	(3.88)
	375mμ.	(4.03)

2-Bromo-3-hydroxy-4-methoxy-β-nitrostyrene

λ_{max}^{EtOH}	263mμ.	(3.68)
	364mμ.	(4.05)

Attempts to afford temporary protection to the phenolic group of XXXVII by means of a tetrahydropyranyl ether (30) or a methoxymethyl ether, (31) groups which would resist alkaline conditions and reduction with lithium aluminium hydride, but be readily removed by acid, were unsuccessful+ and 6-bromoisovanillin was therefore condensed directly with nitromethane.

Under the usual alkaline conditions the major product of this reaction was the nitro-alcohol, β-(6-bromo-3-hydroxy-4-methoxyphenyl)-β-hydroxynitroethane, XXXVIII. This structure was inferred from elementary analysis, from the absence in the i.r. spectrum (in nujol) of absorption maxima at ca. 1620 $cm.^{-1}$ and 1600 $cm.^{-1}$ characteristic of nitrostyrenes (cf. Table II), and from the u.v. spectrum which, in contrast to nitrostyrenes (cf. Table III) showed no absorption above 300 mμ.

A similar result was reported by Robinson and Sugasawa (32) who, on condensation of O-benzylisovanillin with nitromethane under the influence of methylamine and ammonium acetate, obtained the intermediate nitro-alcohol, XXXIX instead of the expected nitrostyrene.

However, under the experimentally convenient conditions of Govindachari et al., (33) i.e. refluxing 6-bromoisovanillin and nitromethane in glacial acetic acid containing ammonium acetate, the desired nitrostyrene, XL, was obtained in good yield. In the same way 2-bromoisovanillin was readily converted into the corresponding nitrostyrene, XLI.

The nitrostyrene, XL, was reduced with lithium aluminium

+ Hydrogenolysis of a benzyl ether would probably have been accompanied by undesirable debromination.

hydride in refluxing ether and, as had been anticipated no product was obtained on manual extraction with chloroform. However, on continuous extraction with this solvent, an almost quantitative yield was obtained of the β-phenylethylamine, XLII, characterised as the picrate and oxalate. The amine itself was never obtained in a crystalline or pure condition and its subsequent reactions were hindered by its low solubility in non-hydroxylic solvents. Attempts to crystallise it from acetone gave a crystalline condensation product, XLIII.

Unfortunately, attempts under a variety of conditions, to convert the amino-phenol to the amide, XLIV,+ were all unsuccessful. Thus, treatment of the amino-phenol, XLII, with homoanisoyl chloride or with anisoyl diazomethane [cf. ref. (34)], gave intractable mixtures and there was no reaction with homoanisic acid in the presence of dicyclohexylcarbodiimide. Also, oxidative decomposition of homoanisoyl hydrazide in the presence of the amino-phenol [cf. ref. (35)] gave gummy mixtures. The presence of the free phenol was undoubtedly a complicating factor in these reactions.

On the other hand, a free phenol greatly facilitates the Pictet-Spengler isoquinoline ring closure.[26][36][37] However, when the amino-phenol, XLII was treated with formaldehyde or with 3-hydroxy-4-methoxyphenylpyruvic acid, XLV, no basic products were obtained.

These results suggested that it would be desirable to have the phenolic group protected from near the start of the synthesis until after the ring closure had been effected.

In spite of the possible drawback that its bulk might

+ Petaline, X, was by now the immediate synthetic objective.

hinder ring closure in the position ortho to it, it was decided to use a benzyl group which was otherwise very suitable.

Minor difficulties were encountered in the initial preparation of O-benzyl-6-bromoisovanillin, XLVI by the bromination of O-benzylisovanillin, since the hydrobromic acid generated caused partial loss of the benzyl group. This difficulty was readily circumvented by benzylating 6-bromoisovanillin [29] to give the desired aldehyde, XLVI.

Under the usual acidic conditions [33] this aldehyde was smoothly converted into the corresponding nitrostyrene, XLVII, which was then reduced with lithium aluminium hydride. After a neutral work-up, the basic material was precipitated by gaseous hydrogen chloride and, without purification, condensed with homoanisoyl chloride.

Unexpectedly, two amides were obtained from the reaction, the expected product, XLVIII, and the product IL, which must have arisen by reductive removal of the bromine substituent.

Fuller investigation showed that, on reduction of the nitrostyrene, XLVII, for twelve hours in refluxing tetrahydrofuran, only the bromine-free amide, IL, was isolated. Intermediate reflux periods led to the production of mixtures and incomplete reduction occurred when the reaction was carried out at room temperature or with the calculated amount of reagent.

Until very recently, few examples of hydrogenolysis by lithium aluminium hydride had been reported [38][39][40][41] but Karabatsos et al. [42] have now shown this reaction to be more prevalent than had formerly been supposed.

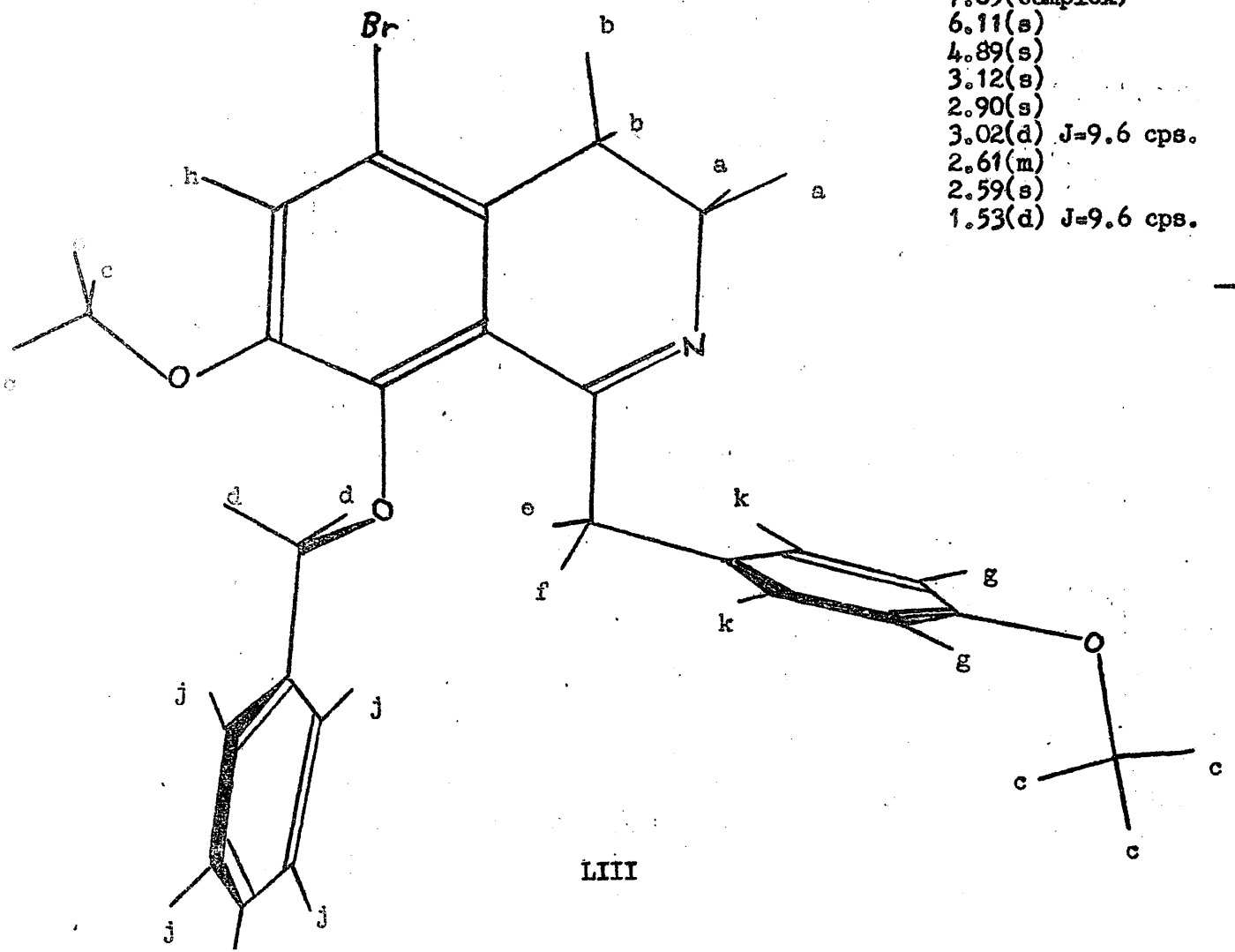
It is noteworthy that, unlike XLVII, the phenolic nitrostyrene, XL, showed no tendency to dehalogenate even on prolonged reduction. However, Erne and Ramirez (43) have reported debromination of the nitrostyrene L.

However very brief reduction of XLVII, which, incidentally, now appears to be all that is generally necessary for nitrostyrenes gave (in rather poor yield) an amine which was readily converted with homoanisoyl chloride and with 3-benzyloxy-4-methoxy-phenylacetyl chloride respectively into the required amides XLVIII and LI.

It was now possible to test the critical reaction of the sequence - the ring closure - and it was felt that to avoid loss of bromine and ring closure in the undesired direction, the mildest possible conditions were indicated. These appeared to entail the use of an excess of phosphorus pentachloride in chloroform at room temperature for several days - a procedure which has been used with telling effect in many syntheses. (26)(32)(44)(45) An advantage of this technique is that the reaction can be followed since the base, as it is generated, forms a crystalline precipitate which is unstable to water and does not appear to have been characterised.

When the amide XLVIII was subjected to the above reaction conditions a precipitate gradually separated over a period of 8 days suggesting that a cyclisation had occurred. On work-up, there was obtained in 50% yield a product m.p. 136.5-138° which analysed for $C_{25}H_{28}BrNO_5$, although the figures would accommodate small variations in the number of

TABLE IV



LIII

Resonance (τ)	Assignment
6.40(complex)	a or b
7.05(complex)	a or b
6.11(s)	c
4.89(s)	d
3.12(s)	e or f
2.90(s)	e or f
3.02(d) J=9.6 cps.	g
2.61(m)	h
2.59(s)	j
1.53(d) J=9.6 cps.	k

hydrogen atoms present. The i.r. spectrum, in nujol, was rather similar to that of the starting material XLVIII, the principal difference being the appearance of a strong peak at 1600 cm.$^{-1}$ The u.v. spectrum exhibited absorption at 290 mμ (log ε, 4.16), 227 mμ (inflection; log ε, 4.17) and 219 mμ (log ε, 4.17), and was unchanged by the addition of acid or base. In fact, the compound could be crystallised unchanged from methanol containing either dilute aqueous hydrochloric acid or dilute aqueous sodium hydroxide.

However, the analytical data of the compound, m.p. 136.5-138° are in accord with its formulation as a dihydrate of the desired dihydroisoquinoline, LII. The anomalous properties of the compound, if it is, indeed, LII, can perhaps be explained by reference to a molecular model which shows clearly that, as expected, severe steric crowding occurs. The model suggests that this is minimised in the conformation shown in LIII, where it can be seen that the anisyl ring is forced into close proximity to the nitrogen atom. Interaction between the aromatic π-electrons and the lone pair electrons of the nitrogen atom (and perhaps also steric factors) may account for the compounds' lack of basic character.

The rather remarkable n.m.r. spectrum of this compound can be interpreted in a manner fully consistent with the structure LIII as indicated in Table IV. The anisyl aromatic protons appears as doublets at 3.02 and 1.53 τ (J = 9.6 c.p.s.) forming an AB system. Here deshielding of two protons (k) by the C = N-grouping could account for the latter doublet. The anisyl methylene protons in LIII (e and f) would

be benzylic, α to the C = N-group and might possibly be further deshielded by the aromatic ring of the benzyl ether. The singlets at the very low values of 3.12 and 2.90 τ are therefore assigned to this methylene group, the protons being regarded as non-equivalent (as can be seen from the model) and therefore absorbing at τ-values which are different but not sufficiently so to allow spin-spin coupling.

These assignments can only be tentative at the moment because of the unique features of the molecule. However, once the benzyl group has been hydrogenolysed, it would be expected that the chemical and spectral properties could be correlated with those of simple isoquinoline derivatives. Unfortunately, supplies of material were insufficient to test this and time did not permit the repetition of the reaction sequence although it is hoped that this may be done in the near future.

If these conclusions are justified, the critical stages in the synthesis of 8-hydroxy isoquinolines like petaline and "protocularine"+ have been overcome.

+ Preliminary attempts to cyclise the amide, LI, gave rise to a product whose chemical and spectral properties were closely analogous to those of the compound m.p. 136.5-138°, although the former product has not yet been obtained quite pure and accordingly has not been characterised.

EXPERIMENTAL

Guaiacol Phenylacetate, XII.

Guaiacol (100 g.) and phenylacetyl chloride (160 g.) were stirred and refluxed overnight in benzene (200 ml.) containing magnesium turnings (23 g.). The product was taken up in ether, washed successively with water (100 ml.), saturated sodium carbonate solution (3 x 100 ml.) and water (3x 100 ml.). Evaporation gave a yellow oil which, on trituration with light petroleum (b.p. 40-60°) afforded almost pure guaiacol phenylacetate, XII, as a yellowish solid (190 g.; 98%). Crystallisation from chloroform-light petroleum (b.p. 60-80°) gave the ester XII as colourless plates, m.p. 40°. (Lit [6] 32°).

Fries Rearrangement of Guaiacol Phenylacetate, XII

(i) 4-Chloro-2'-phenylacetophenone, XIII

A solution of guaiacol phenylacetate, XII, (20 g.) and aluminium chloride (25 g.) in chlorobenzene (100 ml.) was stirred and refluxed under nitrogen for 2 hours and then allowed to stand for 3 days at room temperature. The resulting slurry was added to a mixture of crushed ice (ca. 300 g.) and 6N hydrochloric acid (100 ml.) and stirred until the ice melted. It was then extracted with chloroform (8 x 100 ml.) and the organic solution was washed successively with 2N aqueous sodium hydroxide, and water. Evaporation gave a green oil (9.9 g.) which readily solidified. This material was extracted with boiling light petroleum (b.p. 40-60°) and chromatographed on alumina (Grade H). Elution with 25% benzene - light petroleum (b.p. 40-60°) gave the ketone, XIII, as a colourless solid. Crystallisation from aqueous ethanol gave colourless

prisms, (2.5 g; 13%), m.p. 104-6°. (Lit [16] 105°) (Found: C, 73.1; H, 4.9; Cl, 15.2. Calc. for $C_{14}H_{11}ClO$: C, 72.9; H, 4.8; N, 15.4%). The 2:4-dinitrophenylhydrazone crystallised from benzene -light petroleum (b.p. 40-60°) in orange prisms, m.p. 211°. (Found: C, 58.5; H, 3.8; N, 13.0. $C_{20}H_{15}ClN_4O_4$ requires C, 58.5; H, 3.7; N, 13.6%). No other products were obtained pure from the chloroform extract. However, the aqueous sodium hydroxide extract, on acidification and chloroform extraction gave a brown oil whose i.r. spectrum showed it to be composed principally of guaiacol. This oil was not investigated further.

(ii) 4-Hydroxy-3-methoxy-2'-phenylacetophenone, XIV.

A solution of guaiacol phenylacetate, XII, (10 g.) and anhydrous stannic chloride (11 ml.) was refluxed gently for 30 minutes and allowed to cool. As much as possible was poured into crushed ice (ca. 100 g.) and the viscous residue was extracted with chloroform, this being added to the ice. The organic layer was extracted with dilute aqueous sodium hydroxide (4 x 150 ml.), the combined extracts being subsequently acidified and extracted with chloroform to give a dark brown oil (4.5 g.) Chromatography on silica gel and elution with ether afforded, in the early fractions, the ketone, XIV, which crystallised from benzene-light petroleum (b.p. 60-80°) in colourless needles (2.3 g; 23%) m.p. 110°. (Found: C, 74.65; H, 6.0. $C_{15}H_{14}O_3$ requires C, 74.4; H, 5.8%). ν_{max} (in chloroform) 3548 cm.$^{-1}$ (OH), 1673 cm.$^{-1}$ (C = O). No other products could be obtained from thisfraction.

(iii) Guaiacol and phenylacetic acid were obtained in varying amounts by reaction of guaiacol phenylacetate with the following:

a. aluminium chloride at 140-160° for 10 minutes in the absence of solvent.

b. stannic chloride in s-tetrachloroethane at room temperature for 2 days, or at reflux for 2 hours under nitrogen.

c. stannic chloride in refluxing light petroleum (b.p. 60-80) for 12 hours under nitrogen.

In no case could any other product be obtained.

4-Methoxy-3-phenylacetoxy-N-phthaloyl- β -phenylethylamine, XVI.

3-Hydroxy-4-methoxy-N-phthaloyl- β -phenylethylamine, (12) (2.22 g.), and phenylacetyl chloride (1.5 g.) were refluxed for 24 hours in benzene (25 ml.) containing magnesium turnings (0.106 g.). The cooled solution was then decanted from the residual magnesium, this being washed with ethanol (20 ml.) and the washings added to the decanted solution. After extraction of this with dilute sodium hydroxide, evaporation yielded the ester, XVI, as a yellow oil which solidified slowly on standing and crystallised from benzene-light petroleum (b.p. 60-80°) as colourless needles (2.1 g; 68%) m.p. 125°. (Found: C, 72.2; H, 5.2; N, 3.5. $C_{25}H_{21}NO_5$ requires C, 72.3; H, 5.1; N, 3.4%). λ_{max} (in EtOH) 277 mμ. (log ε , 3.65).

Attempted Fries Rearrangement of 4-methoxy-3-phenylacetoxy-N-phthaloyl- β -phenylethylamine

a. In refluxing chlorobenzene

A solution of 4-methoxy-3-phenylacetoxy-N-phthaloyl- β -phenylethylamine, XVI, (0.76 g.), chlorobenzene (30 ml.), and

anhydrous aluminium chloride (0.50 g.) was refluxed for 30 minutes. The red solution was then cooled and poured with stirring into a mixture of crushed ice (ca. 100 g.) and 6N hydrochloric acid (10 ml.) and allowed to stand for 2 hours. The solution was then extracted with ether (3 x 50 ml.) and the combined ether extracts were extracted with 2N sodium hydroxide solution (4 x 20 ml.). The ethereal extract gave starting material (0.25 g; 33%), identified by its i.r. spectrum. The sodium hydroxide extracts, on acidification and extraction with ether gave only traces of oily material. The use of chloroform in the extractions did not effect any improvement in the yield of phenolic material.

b. In the absence of a solvent

The ester, XVI, (1 g.) and anhydrous aluminium chloride (0.69 g.) were ground together in a mortar and transferred to a flask fitted with a drying tube and heated for 15 minutes at 150°. A reddish-brown slurry formed. When it had cooled it was treated with crushed ice (ca. 10 g.) and 6N hydrochloric acid (15 ml.). The resulting purplish solid crystallised from ethanol (charcoal) in colourless needles (0.30 g; 30%) m.p. 123.5°, shown to be unreacted ester by comparison of i.r. and by mixed melting point. No other products could be obtained from the reaction.

3-Hydroxy-4-methoxy-cinnamic acid, XVIII.

A solution of isovanillin, XVII, (50 g.), malonic acid (77.5 g.), pyridine (300 ml.) and piperidine (5 ml.) was heated for 1 hour on the steam bath and then refluxed for 5 minutes. The cooled solution was poured into water and acidified with 6N hydrochloric acid to yield

the cinnamic acid, XVIII as colourless crystals (55 g; 88%), m.p. 229-232°, sufficiently pure for further reaction. Crystallisation from ethanol gave colourless, optically anisotropic plates, m.p. 233-234°. (Found: C, 61.9; H, 5.2. $C_{10}H_{10}O_4$ requires C, 61.85; H, 5.2%). λ_{max} (in EtOH) 220 mμ (log ε, 4.08), 243 mμ (log ε, 4.03), 295 mμ (log ε, 4.12), 324 mμ (log ε, 4.17).

3-Hydroxy-4-methoxy-hydrocinnamic acid, XIX.

3-Hydroxy-4-methoxy-cinnamic acid, XVIII (52.6 g.) was dissolved in water (200 ml.) containing potassium hydroxide (24 g.) and palladium-on-charcoal (2.2 g.; 10%) and hydrogenated at atmospheric temperature and pressure. After 24 hours 1 mole of hydrogen had been absorbed. After removal of the catalyst, acidification with dilute hydrochloric acid gave the hydrocinnamic acid, XIX as colourless crystals, (51.5 g; 97%), m.p. 146-150°. Crystallisation from benzene gave colourless prisms, m.p. 146-150°. (Found: C, 61.4; H, 5.9. $C_{10}H_{12}O_4$ requires C, 61.2; H, 6.2%).

3-Acetoxy-4-methoxy-hydrocinnamic acid

A solution of 3-hydroxy-4-methoxy-hydrocinnamic acid, XIX, (2.5 g.) and fused sodium acetate (1.6 g.) in acetic anhydride (25 ml.) was refluxed for 1 hour and poured into water (ca. 60 ml.). The acetate crystallised in colourless plates (2.35 g.) or standing. Extraction with ether gave a further 0.5 g., (total yield of crude ester, m.p. 126-30°, 2.85 g; 94%). Crystallisation from benzene gave colourless plates, m.p. 129-132.5°. (Found: C, 61.0; H, 6.8; $C_{12}H_{14}O_5$ requires C, 60.5; H, 5.9%).

2-Bromo-5-hydroxy-4-methoxy-hydrocinnamic acid, XX.

A stirred solution of 3-hydroxy-4-methoxy-hydrocinnamic acid, XIX, (5 g.) in glacial acetic acid (100 ml.) at room temperature was treated with a solution of bromine (1.55 ml.) in glacial acetic acid (25 ml.), added dropwise during 20 minutes.+ Stirring was continued overnight and the solvent was evaporated under reduced pressure to give a quantitative yield of the bromo-acid, XX, as a colourless solid, sufficiently pure for further reaction. Crystallisation from benzene gave colourless needles, m.p. 142-144°. (Found: C, 43.8; H, 4.4. $C_{10}H_{11}BrO_4$ requires C, 43.6; H, 4.0%).

The ethyl ester, prepared by brief boiling of the acid in ethanol containing a trace of mineral acid, crystallised from light petroleum (b.p. 80-100°) as colourless needles, m.p. 58-62°. (Found: C, 47.2; H, 5.3. $C_{12}H_{15}BrO_4$ requires C, 47.4; H, 5.0%).

2, 6-Dibromo-3-hydroxy-4-methoxy-hydrocinnamic acid, XXI.

A solution of bromine (3.6 g; 2 equivs.) in glacial acetic acid (10 ml.) was added dropwise during 5 minutes to a stirred solution of 3-hydroxy-4-methoxy-hydrocinnamic acid, XIX, (2 g.) in glacial acetic acid (40 ml.) at room temperature. Stirring was continued overnight and the precipitated product was filtered off. Crystallisation from ethanol gave the dibromo-acid, XXI, as colourless needles (2.6 g; 69%) m.p. 211-212 . (Found: C, 33.3; H, 3.0. $C_{10}H_{10}Br_2O_4$ requires C, 33.9; H, 2.8%).

4-Bromo-7-hydroxy-6-methoxy-indan-1-one, XXII.

A mixture of 2-bromo-5-hydroxy-4-methoxy-hydrocinnamic acid, XX, (11.8 g.) in concentrated sulphuric acid (100 ml.), was heated

+ Rapid addition of bromine solution caused the formation of significant quantities of 2:6-dibromo-3-hydroxy-4-methoxy-hydrocinnamic acid.

on the steam-bath for 10 minutes under an atmosphere of nitrogen. The hot solution was immediately poured on to crushed ice (ca. 500 g.). When the ice had melted the resulting solution was extracted with chloroform, the extracts being washed thoroughly with saturated aqueous sodium bicarbonate. Evaporation of the chloroform gave the indanone, XXII, as a colourless solid (8.3 g; 70%), sufficiently pure for further reaction. Crystallisation from ethanol gave colourless prisms, m.p. 132-133°. (Found: C, 46.7; H, 3.8. $C_{10}H_9BrO_3$ requires C, 46.7; H, 3.5%). λ_{max} (in MeOH) 226 mμ. (log ε, 4.23), 262 mμ. (log ε, 3.79), 343 mμ. (log ε, 3.45). λ_{max} (in MeOH/KOH) 241 mμ. (log ε, 4.27) ca. 267 mμ. (inflexion) 384 mμ. (log ε, 3.68). The indanone gave a blue colouration with ethanolic ferric chloride and formed an orange 2, 4-dinitrophenylhydrazone. Its sodium, lithium and potassium salts were sparingly soluble in water.

7-Methanesulphonoxy-6-methoxy-indan-1-one, XXV.

A solution of 4 bromo-7-hydroxy-6-methoxy-indan-1-one, XXII, (5 g.) in methanol (150 ml.) containing palladium-on-charcoal (10%; 0.6 g.) was hydrogenated at atmospheric temperature and pressure for several hours, one mole of hydrogen being consumed. After removal of the catalyst, evaporation gave an oil which, without further purification, was dissolved in pyridine (25 ml.). To the resulting solution, cooled in ice, was added dropwise an ice-cold solution of methanesulphonyl chloride (2.5 ml.) in pyridine (2.5 ml.). The solution was allowed to stand overnight at 0°, then poured into water. The precipitate crystallised from methanol (charcoal) to give the indanone, XXV, as stout, colourless

prisms (2.4 g; 48%) m.p. 126.5-127.5°. (Found: C, 51.9; H, 4.95. $C_{11}H_{12}O_5S$ requires C, 51.6; H, 4.7%).

3-Methanesulphonoxy-4-methoxyphthalic acid, XXVI, and anhydride.

A solution of 7-methanesulphonoxy-6-methoxy-indan-1-one, XXV, (0.2 g.) in potassium dichromate solution+ (15 ml.) was refluxed for 20 minutes and allowed to cool. After saturation with gaseous sulphur dioxide, chloroform extraction (2 x 15 ml.) was found to give only traces of material. The mother liquors were continuously extracted overnight to give the phthalic acid XXVI as a colourless solid (74 mg; 34%) m.p. 180-194° which failed to crystallise from common organic solvents. Sublimation at 160°/0.02 mm. gave the anhydride as a colourless powder, m.p. 170°. (Found: C, 42.6; H, 3.1. $C_{10}H_8O_7S$ requires C, 44.0; H, 2.8%).

4-Bromo-6-methoxy-7-(p-toluenesulphonoxy)-indan-1-one.

A solution of 4-bromo-7-hydroxy-6-methoxy-indan-1-one, XXII, (1 g.) and p-toluenesulphonyl chloride (1 g.) in pyridine (10 ml.) was allowed to stand at room temperature for 36 hours and then poured into water. Crystallisation of the precipitate from ethanol afforded the tosylate as colourless needles (1.25 g; 75%), m.p. 191-194°. (Found: C, 49.7; H, 3.9. $C_{17}H_{15}BrO_5S$ requires C, 49.7; H, 3.65%).

4-Bromo-2-hydroxylimino-6-methoxy-1-oxo-7-(p-toluenesulphonoxy)-indane, XXVII

A mixture of 4-bromo-methoxy-7-(p-toluenesulphonoxy)-indan-1-one (0.5 g.), iso-amyl nitrite (1 g.), benzene (15 ml.), and concentrated hydrochloric acid (0.3 g.) was refluxed for 45 minutes and allowed to cool. the resulting precipitate on crystallisation from aqueous pyridine gave the

+ Potassium dichromate (24 g.), concentrated sulphuric acid (72 ml.) and water (360 ml.).

iso-nitroso derivative, XXVII, as pale yellow needles (0.28 g; 51%) m.p. 217-232° (d) with darkening at ca. 120°. (Found: C, 46.2; H, 3.4; N, 3.5. $C_{17}H_{14}BrNO_6S$ requires C, 46.3; H, 3.2; N, 3.2%).

2-Acetoxylimino-4-bromo-6-methoxy-1-oxo-7-(p-toluenesulphonoxy)-indane, XXVIII.

A solution of 4-bromo-2-hydroxylimino-6-methoxy-1-oxo-7-(p-toluenesulphonoxy)-indane, XXVII, (0.1 g.) in acetic anhydride (10 ml.) was allowed to stand at room temperature for 2 days then poured into water. The precipitate, on repeated crystallisation from chloroform-light petroleum (b.p. 40-60°) gave the acetoxylimino-compound XXVIII as colourless prisms (16 mg; 12%), m.p. 216-24° (d), with darkening from 120°. (Found: C, 40.0; H, 3.2; N, 2.9. $C_{19}H_{16}BrNO_7S.CHCl_3$ requires C, 40.0; H, 2.8; N, 2.3%). ν_{max} (Nujol) 1770 cm^{-1} (ester C = O), 1717 cm^{-1} (ketonic C = O). No acidic material could be isolated from the reaction.

Further attempt to cleave 4-bromo-2-hydroxylimino-6-methoxy-1-oxo-7-(p-toluenesulphonoxy)-indane, XXVII

A mixture of 4-bromo-2-hydroxylimino-6-methoxy-1-oxo-7-(p-toluenesulphonoxy)-indane, XXVII, (0.2 g.) and p-toluenesulphonyl chloride (0.2 g.) in pyridine (5 ml.) was heated on the steam-bath for 15 minutes then poured into water. A small amount of precipitate was shown by t.l.c. to contain at least six components and was not further investigated. Chloroform extraction of the acidified mother liquors failed to yield any materials. Similar results were obtained when the pyridine was replaced by a 10% aqueous solution of sodium hydroxide.

4-Bromo-2-furfurylidene-7-hydroxy-6-methoxy-indan-1-one

A slurry of 4-bromo-7-hydroxy-6-methoxy-indan-1-one XXII (6 g.) in ethanol (50 ml.), was added to a stirred, refluxing solution of sodium hydroxide (3 g.) in ethanol (100 ml.).+ A solution of furfuraldehyde (5 ml.) in ethanol (10 ml.) was added and stirring and refluxing were continued for 15 minutes. The cooled solution was acidified with dilute aqueous hydrochloric acid and the resulting precipitate crystallised from ethanol to give the furfurylidene derivative as yellow, feathery needles (6.6 g, 84%), m.p. 187-189°. A further 1.1 g. (14%) of less pure material was obtained from the mother liquors after some hours. (Found: C, 53.6; H, 3.6. $C_{15}H_{11}BrO_4$ requires C, 53.8; H, 3.3%).

4-Bromo-2-furfurylidene-7-methanesulphonoxy-6-methoxy-indan-1-one, XXIX

Ice cold solutions of 4-bromo-2-furfurylidene-7-hydroxy-6-methoxy-indan-1-one (1 g.) in pyridine (10 ml.) and methane sulphonyl chloride (1 ml.) in pyridine (2 ml.) were mixed and the resulting solution was allowed to stand overnight and then poured into water. The mesylate, XXIX, crystallised from glacial acetic acid as yellow needles (1.12 g; 91%), m.p. 232-235.5°. (Found: C, ; H, . $C_{16}H_{13}BrO_6S$ requires C, 46.5; H, 3.15%).

7-Benzyloxy-4-bromo-6-methoxy-indan-1-one

A mixture of 4-bromo-7-hydroxy-6-methoxy-indan-1-one (1 g.), benzyl chloride (2 ml.), potassium carbonate (1 g.) and absolute ethanol (50 ml.) was refluxed overnight, cooled, filtered and diluted with chloroform (50 ml.). The solution was shaken with 4N sodium hydroxide solution (50 ml.) and the resulting precipitate was treated with hot,

+ Failure to add the indanone as described resulted in precipitation of the sodium salt and inhibition of the reaction.

dilute, aqueous hydrochloric acid to give starting material (0.3 g; 30%), identified by its i.r. spectrum. The organic layer of the filtrate, on evaporation of the solvent, gave a pale yellow oil which solidified on trituration with light petroleum (b.p. 40-60°). Crystallisation from light petroleum (b.p. 100-120°) furnished the benzyl ether as small, colourless prisms (0.51 g; 38%), m.p. 84-85°. (Found: C, 58.9; H, 4.5. $C_{17}H_{15}BrO_3$ requires C, 58.8; H, 4.3%).

4-Bromo-7-methanesulphonoxy-6-methoxy-indan-1-one

Ice-cold solutions of 4-bromo-7-hydroxy-6-methoxy-indan-1-one, XXII, (2 g.) in pyridine (20 ml.) and methanesulphonyl chloride (2 ml.) in pyridine (4 ml.) were mixed and the resulting solution was kept in the refrigerator overnight and then poured into water. Crystallisation of the precipitate from ethanol gave the mesylate as almost colourless prisms (2.3 g.; 88%), m.p. 161-162°. (Found: C, 39.15; H, 3.6. $C_{11}H_{11}BrO_5S$ requires C, 39.4; H, 3.3%).

6-Bromo-2-carboxy-3-methanesulphonoxy-4-methoxy-phenylacetic acid, XXX

A refluxing solution of 4-bromo-7-methanesulphonoxy-6-methoxy-indan-1-one (0.3 g.) in glacial acetic acid (7.5 ml.) and 6N aqueous sulphuric acid (7.5 ml.) was treated dropwise during ca. 2 minutes with Jones' reagent+ (3.5 ml.) and refluxing was continued for a further 7 minutes. The solution was allowed to cool during ca. 30 minutes, then gaseous sulphur dioxide was passed through it until it had turned green. Continuous extraction with chloroform for 24 hours, followed by trituration of the resulting oily solid with chloroform, then light petroleum (b.p. 40-60°) gave the bromo-homophthalic acid, XXX, as a colourless powder

+ Jones reagent: Chromium trioxide (267 g.) dissolved in concentrated sulphuric acid (230 ml.) and made up to 1 litre with water.

(0.18 g.; 53%), sufficiently pure for further reaction. Crystallisation from glacial acetic acid-light petroleum (b.p. 40-60°) gave colourless needles, m.p. 195-200°. (Found: C, 34.5; H, 2.95. $C_{11}H_{11}BrO_8S$ requires C, 34.6; H, 2.9%).

2-Carboxy-3-methanesulphonoxy-4-methoxy-phenylacetic acid, XXXI.

6-Bromo-2-carboxy-3-methanesulphonoxy-methoxyphenylacetic acid, XXX, (0.1 g.) was dissolved in a solution of sodium hydroxide (0.4 g.) in water (15 ml.), containing palladium-on-charcoal (0.05 g; 10%), and hydrogenated at atmospheric temperature and pressure. One mole of hydrogen was absorbed in a few minutes. After removal of the catalyst and acidification with dilute aqueous hydrochloric acid, the solution was extracted with chloroform (2 x 10 ml.). Evaporation of the chloroform gave only traces of oily material. Continuous extraction of the mother liquor with chloroform for 2 days gave an oily solid. Trituration with light petroleum (b.p. 40-60°) and crystallisation from ethyl acetate-light petroleum (b.p. 40-60°) gave the homophthalic acid, XXXI, as colourless prisms, (54 mg; 67%), m.p. 177-85°. (Found: C, 43.6; H, 4.3. $C_{11}H_{12}O_8S$ requires C, 43.4; H, 4.0%).

Attempts to reduce 2-carboxy-3-methanesulphonoxy-4-methoxy-phenylacetic acid, XXXI

(i) Treatment of 2-carboxy-3-methanesulphonoxy-4-methoxy-phenylacetic acid, XXXI, with lithium aluminium hydride in refluxing tetrahydrofuran-ether for 1 hour gave an oily product which could not be crystallised. Its i.r. spectrum was somewhat indefinite but showed strong carbonyl absorption. Similar results were obtained using only

tetrahydrofuran as solvent. (Similar results were obtained in the reduction of 6-bromo-2-carboxy-3-methanesulphonoxy-4-methoxy-phenylacetic acid, XXX.)

(ii) Treatment of the crude diester of the above acid XXXI (prepared in quantitative yield by the addition of diazomethane solution to a solution of the acid in methanol-ether), with lithium aluminium hydride in cold or refluxing tetrahydrofuran or ether for periods varying from 1 hour to 2 days gave results similar to those described in (i).

Attempts to convert 6-bromo-2-carboxy-3-methanesulphonoxy-4-methoxy-phenylacetic acid, XXX, into a homophthalimide.

(i) 6-Bromo-2-carboxy-3-methanesulphonoxy-4-methoxy-phenylacetic acid XXX was converted to the corresponding anhydride by refluxing the acid (100 mg.) in acetic anhydride (10 ml.) for 1 hour and then pouring into water. Chloroform extraction gave the anhydride as an oily solid (75 mg; 78%) which crystallised from ethyl acetate-light petroleum (b.p. 60-80°) as a colourless powder, m.p. 170-183°, with weeping from 160°. Both further crystallisation and sublimation failed to improve the melting point. [ν_{max} (Nujol) 1750 cm^{-1}; 1800 cm^{-1} (anhydride, six-membered ring)]. The crude anhydride (50 mg.) was treated with liquid ammonia (ca 5 ml.) and the ammonia allowed to evaporate to give a grey glass whose i.r. spectrum suggested it to be a mixture of ammonium salts [ν_{max} (Nujol) 2860 cm^{-1} (s)], amides, [ν_{max}, 1640 cm^{-1} (conjugated amide C = O), 1650 cm^{-1} (unconjugated amide C = O)] and imide [ν_{max} 1710 cm^{-1} (w)]. Without purification this material was allowed to stand overnight in pyridine (5 ml.) and thionyl chloride (1.5 ml.) and then poured into water. Chloroform extraction failed to

give any product. Treatment of the above anhydride with ethanolic methylamine at room temperature gave only an intractable gum.

(ii) Upon stirring a mixture of 6-bromo-2-carboxy-3-methanesulphonoxy-4-methoxyphenylacetic acid, XXX, (100 mg.) and phosphorus pentachloride (200 mg.) in ether (35 ml.) for 2 hours at room temperature, adding ethanolic methylamine (10 ml; 33%), stirring for a further hour and adding water (30 ml.), chloroform extraction gave an oil, which on trituration with petrol solidified to give the corres ponding di-secondary amide as colourless needles (30 mg; 27%), m.p. 240-6° (with weeping from 235°). (Found: N, 7.2. $C_{13}H_{17}BrN_2O_6S$ requires N, 6.9%). ν_{max} 1650 cm^{-1}, 1545 cm^{-1} (secondary acyclic amide), 3250 cm^{-1} (N-H bonded), 3350 cm^{-1} (w.) (N-H free). Treatment of this diamide with refluxing phosphorus oxychloride for 30 minutes, followed by pouring on to crushed ice and extraction with chloroform failed to yield any product.

(iii) 6-Bromo-2-carboxy-3-methanesulphonoxy-4-methoxyphenylacetic acid XXX was converted into its di-ammonium salt by dissolving it in liquid ammonia and allowing the excess of ammonia to evaporate, and into its di-methylammonium salt by refluxing the acid (100 mg.) in ethanol (5 ml.) containing ethanolic methylamine solution (0.5 ml; 33%) for 1 hour and evaporating the solution. The di-ammonium salt gave a glass (90%) on being heated at 100° overnight or at 140° for 1 hour. This glass failed to crystallise from common organic solvents, would not sublime and could not be eluted on silica plates. Its i.r. spectrum was rather indefinite. The di-methylammonium salt behaved in an analogous manner.

2-Bromoisovanillin and 6-Bromoisovanillin, XXXVII.

A solution of bromine (10.7 g.) in glacial acetic acid (15 ml.) was added during 30 minutes to a stirred solution of isovanillin, XVII, (10 g.) in glacial acetic acid (15 ml.) at room temperature. Stirring was continued for several hours after which the precipitated product was filtered off (ca. 4.5 g.), m.p. ca. 190-210°. Concentration of the filtrate gave a further crop (ca. 6.5 g.) m.p. 160-180°. Evaporation of the filtrate gave a pale brown solid residue (ca. 3.5 g.), m.p. 75-85°. Fractional crystallisation of the first crop from ethanol and the lower melting crops from aqueous ethanol gave approximately equal amounts of 2-bromoisovanillin as colourless needles, m.p. 211-212° and 6-bromoisovanillin, XXXVIII, as a monohydrate which formed colourless needles, m.p. 112-114°. The conversion of isovanillin is quantitative. The above procedure is essentially that described by Henry and Sharp [29] differing from the method of these authors only in that stirring is employed. It was found that chromatography was less successful in separating the isomers than Henry and Sharp's original fractional crystallisation technique.

Attempted preparation of 2-bromo-4-methoxy-5-tetrahydropyranyloxy-β-nitrostyrene

Treatment of 6-bromo-isovanillin XXXVIII with an excess of redistilled dihydropyran and a drop of concentrated hydrochloric acid in ether or benzene for 12 hours at room temperature gave only starting material on work-up. However the protected phenolic aldehyde was obtained as follows: A mixture of 6-bromo-isovanillin XXXVIII (1.89 g.),

dihydropyran, (15 ml.) and concentrated hydrochloric acid (2 drops) was shaken at room temperature for 2 days. The product was taken up in ether and washed well with 2N aqueous sodium hydroxide and then water. Evaporation gave the crude tetrahydropyranyl derivative as a pale yellow oil (0.5 g; 19%), α_D^{20}, 1.5112. The alkaline washings, on acidification and chloroform extraction gave unchanged 6-bromoisovanillin, XXXVIII, (1.29 g; 68%), identified by its i.r. spectrum.

The tetrahydropyranyl derivative (0.5 g.) without purification was dissolved in ethanol (20 ml.) and nitramethane (0.9 ml.) added. The resulting solution, stirred and cooled in a freezing mixture, was treated dropwise with a solution of potassium hydroxide (0.21 g.) in ethanol (20 ml.) during 30 minutes and stirring was continued for a further 30 minutes. The solution was then diluted with water (25 ml.) and ether extraction afforded a yellow oil which charred on attempted short-path distillation and could not be induced to crystallise. Its i.r. spectrum (Nujol) lacked the characteristically sharp absorption at ca. 1600 cm^{-1} and ca. 1620 cm^{-1} shown by all nitrostyrenes prepared in these studies.

2-Bromo-5-hydroxy-4-methoxy- β -nitrostyrene, XL.

A solution of 6-bromo-isovanillin XXXVIII (1.6 g.), nitromethane (2 ml.) and ammonium acetate (1 g.) in glacial acetic acid (25 ml.) was refluxed for 2 hours, cooled and poured into water (50 ml.) The precipitate, on crystallisation from methanol, gave the nitrostyrene, XL, as yellow needles (1.4 g; 74%), m.p. 160-3° (with sublimation from ca. 140°). On exposure to air for a few minutes the crystals developed an orange-red colour. Crystallisation from benzene gave yellow prisms,

m.p. 160-162°. λ_{max} (in EtOH) 267 mμ. (log ε, 3.90), 327 mμ. (log ε, 3.88), 375 mμ. (log ε, 4.03). (Found: C, 39.7; H, 3.2; N, 4.9. $C_9H_8BrNO_4$ requires C, 39.45; H, 2.9; N, 5.1%). The i.r. spectra of the needles and prisms were different in Nujol but identical in chloroform. The u.v. spectra were identical and a mixed melting point was undepressed.

β-(2-Bromo-5-hydroxy-4-methoxyphenyl)-β-hydroxynitroethane, XXXVIII.

A solution of potassium hydroxide (0.25 g.) in ethanol (20 ml.) was added dropwise during 35 minutes to a stirred solution of 6-bromoisovanillin XXXVIII (0.475 g.) and nitromethane (0.8 ml.) in ethanol (20 ml.) at 0°. The solution was then acidified with dilute hydrochloric acid and the ethanol was evaporated under reduced pressure. A solid (75 mg; 9%) separated out and was identified as 2-bromo-5-hydroxy-4-methoxy-β-nitrostyrene XL by comparison of its i.r. spectrum with that of a sample prepared as above. Ether extraction of the aqueous mother liquors gave a yellow oil which, on crystallisation from benzene-light petroleum (b.p. 40-60°) afforded the hydroxy-nitro compound XXXVIIIas pale yellow needles (0.29 g; 48%), m.p. 105-112°, raised by further crystallisation to 114.5-115.5°. λ_{max} (in EtOH) 287 mμ. (log ε, 3.57), (unaltered by addition of acid). ν_{max} (Nujol) ca. 3300 cm.$^{-1}$ (m.) (OH), ca. 1600 cm.$^{-1}$ (v.w.) (aromatic C = C). (Found: C, 37.15; H, 3.7; N, 4.6. $C_9H_{12}BrNO_5$ requires C, 37.0; H, 3.5; N 4.8%).

2-Bromo-3-hydroxy-4-methoxy-β-nitrostyrene, XLI.

2-Bromo-3-hydroxy-4-methoxy-β-nitrostyrene was prepared from 2-bromo-isovanillin in a manner analogous to that described above for

the 6-bromo-compound. The nitrostyrene XLI was obtained as yellow needles from methanol (84%), m.p. 186-188°. (Found: C, 39.25; H, 2.9; N, 5.2. $C_9H_8BrNO_4$ requires C, 39.45; H, 2.9; N, 5.1%). λ_{max} (in EtOH) 263 mμ. (log ε, 3.86), 364 mμ. (log ε, 4.05).

2-Bromo-5-hydroxy-4-methoxy-β-phenylethylamine XLII.

2-Bromo-5-hydroxy-4-methoxy-β-nitrostyrene, XL, (1 g.) was continuously extracted overnight from a Soxhlet thimble into a stirred solution of lithium aluminium hydride (0.9 g.) in refluxing ether (250 ml.). When the solution had cooled, the excess of reagent was decomposed by the cautious addition of ethyl acetate. The complex was decomposed with water (100 ml.) and the resulting emulsion was separated into two layers by vigorous stirring with Rochelle salt. The organic layer was separated, but on evaporation it gave only traces of material. The aqueous layer was continuously extracted overnight with chloroform to yield the amine, XLII as a brownish solid. (0.96 g; ca. 100%), λ_{max} (in EtOH) 288 mμ. (log ε, 3.44); (in EtOH/KOH) 296 mμ. (log ε, 3.48). This solid was difficultly soluble in water but readily soluble in dilute aqueous acid or alkali. All attempts to crystallise the amine were unsuccessful. The picrate crystallised from ethanol as yellow prisms, m.p. 181-185° (with softening at 175°). (Found: C, 37.8; H, 3.3; N, 11.7. $C_9H_{12}BrNO_2.C_6H_3N_3O_7$ requires C, 37.9; H, 3.2; N, 11.8%). The oxalate, prepared by dropwise addition of the amine, in ethanol, to a stirred solution of oxalic acid (1 mole) in ethanol, sublimed at 200°/0.01 mm. as a colourless powder, m.p. 209-215° (d). (Found: C, 39.7; H, 4.3; N, 4.4. $C_9H_{12}BrNO_2.C_2H_2O_4$ requires C, 39.3; H, 4.2; N, 4.2%).

The acetone imine derivative, XLIII prepared by cooling a hot solution of the amine in acetone, crystallised from acetone as colourless, feathery needles, m.p. 155°. (Found: C, 50.5; H, 5.4. $C_{12}H_{16}BrNO_2$ requires C, 50.05; H, 5.6%).

Attempts to prepare N-[2-(6-bromo-3-hydroxy-4-methoxyphenyl)-ethyl]-p-methoxyphenylacetamide, XLIV.

(i) A solution of 6-bromo-3-hydroxy-4-methoxy-β-phenylethylamine XLII (0.74 g.) and homoanisoyl chloride (0.6 g.) in tetrahydrofuran (30 ml.), was refluxed for 3 hours and poured into water and extracted with chloroform, the extracts being washed thoroughly with dilute aqueous hydrochloric acid and saturated aqueous sodium bicarbonate, to give an oil (0.97 g.) which was shown (t.l.c.) to consist of at least four significant components. The oil was taken up in chloroform and extracted with dilute aqueous extracts, followed by chloroform extraction gave 20 mg. of material, consisting of at least two major components (t.l.c.). As the bulk of the material did not have the expected properties of the desired phenolic amide it was not further investigated.

(ii) Silver oxide (0.15 g.) was added in portions to a solution of the above phenylethylamine XLII (0.4 g.) and 1-diazo-p-methoxy-acetophenone [46] (0.25 g.) in dioxan (20 ml.), kept at 65-70°, during 1 hour. After heating at this temperature for a further 4 hours the solution was filtered through Celite 535, diluted with water and extracted with chloroform, the extracts being washed with dilute aqueous hydrochloric acid and saturated aqueous sodium bicarbonate, to give an oil which was shown by t.l.c. to contain significant amounts of at least seven compounds.

Chromatography on silica gel yielded, as the only product which could be obtained pure from the column, 2-chloro-p-methoxy-acetophenone, as colourless prisms from light-petroleum (b.p. 60-80°), (50 mg.), m.p. 98.5-100°. (Found: C, 58.6; H, 4.75. $C_9H_9ClO_2$ requires C, 58.5; H, 4.9%). This material was presumably present as an impurity in the diazoketone. Similar results were obtained using diethylene glycol dimethyl ether as solvent.

(iii) No products were obtained on allowing the above phenylethylamine XLII (50 mg.) and homoanisic acid (34 mg.) to stand overnight at 0° in tetrahydrofuran (10 ml.), containing dicyclohexylcarbodiimide (44 mg.) and triethylamine (50 mg.)

(iv) A solution of the above amino-phenol XLII (123 mg.), homoanisoyl hydrazide (prepared from methyl homoanisate by refluxing in methanol with a small excess of hydrazine hydrate for 1 hour, evaporation and crystallisation from methanol-ether. Obtained as colourless plates, m.p. 132 °) (90 mg.), and triethylamine (255 mg.) in dimethyl-acetamide (4 ml.) was treated with one of iodine (254 mg.) in the same solvent (1 ml.). After shaking for 1 minute at room temperature (effervescence and decolourisation) and excess of aqueous sodium thiosulphate solution was added, followed by water (20 ml.) and the solution was acidified with dilute hydrochloric acid. Chloroform extraction followed by evaporation gave a solution in dimethyl-acetamide. An oil (ca. 150 mg.) was precipitated by addition of a large volume of light petroleum (b.p. 40-60°). This oil had a rather indefinite i.r. spectrum and t.l.c. showed it to be composed of at least three compounds which could not be separated

by chromatography on silica gel. Similar results were obtained using tetrahydrofuran as solvent.

Reaction of formaldehyde with 6-bromo-3-hydroxy-4-methoxy-β-phenylethylamine. XLII

6-Bromo-3-hydroxy-4-methoxy-β-phenylethylamine, (0.89 g.) and formaldehyde (2.2 ml; 36% aqueous solution) were heated in 2N hydrochloric acid (12 ml.) on a steam-bath for 1 hour and allowed to stand overnight in the refrigerator. Some black solid (ca. 10 mg.) was filtered off and discarded. On neutralisation with saturated aqueous sodium bicarbonate a dark brown amorphous precipitate (ca. 250 mg.) was obtained. Additional quantities of this material (ca. 100 mg.) were obtained from the mother liquors, firstly on standing and then after continuous extraction with chloroform. Attempts to crystallise this material from common organic solvents were unsuccessful although it did separate from dimethyl sulphoxide-ethanol. Ethanolic ferric chloride gave a colouration and a Belstein test for halogen was positive. The i.r. spectrum (Nujol) was very indefinite but was not identical to that of the starting material. The same product (45 mg.) was obtained by heating the amine oxalate (0.25 g.) and formaldehyde (1 ml; 36% aqueous solution) in 2N hydrochloric acid (6 ml.) for 15 minutes on the steam-bath. In view of the difficulty experienced in trying to purify this material, an attempt was made to characterise it as the acetate. A solution of the material (45 mg.) in pyridine (5 ml.) and acetic anhydride (5 ml.) was allowed to stand for 2 days and then poured into water. Extraction with chloroform gave a brown glass which could not be crystallised. The i.r.

spectrum of this material had a new absorption band at 1760 cm^{-1} (phenolic ester) and showed only very little OH stretching absorption.

Reaction of 6-bromo-3-hydroxy-4-methoxy- β -phenylethylamine with 3-hydroxy-4-methoxyphenylpyruric acid.

(i) On refluxing a solution of 6-bromo-3-hydroxy-4-methoxy- β -phenylethylamine with an equivalent amount of 3-hydroxy-4-methoxy-phenylpyruric acid in 3N hydrochloric acid for 2 days under a stream of nitrogen unreacted starting material was recovered in high yield.

(ii) A solution of the amine (0.17 g.) and the keto-acid (0.23 g.) in toluene (40 ml.) was heated on the steam bath for 3 hours. Addition of light petroleum (b.p. 60-80°) to the cooled solution gave a brown amorphous solid (0.20 g.). This failed to crystallise from common organic solvents although it was readily soluble in hot ethanol or toluene. It was recovered unchanged after treatment with dry hydrogen chloride in toluene and was soluble in dilute aqueous acid or alkali. Attempts to prepare a picrate in ethanol or benzene were unsuccessful. In view of the difficulty experienced in purifying this material, and since its properties did not corres pond with those expected of the desired base it was not further investigated.

(iii) A mixture of the amine (as its oxalate) (0.32 g.), the keto-acid (0.45 g.), phosphoric acid (20 ml.), and formic acid (30 ml.) was stirred at room temperature overnight. After addition of water (100 ml.) and neutralisation with saturated aqueous sodium bicarbonate, extraction with chloroform gave some of the above amorphous product as an oily solid (ca. 50 mg.) identified by its i.r. spectrum. Continuous

extraction of the mother liquors with chloroform gave unreacted 6-bromo-3-hydroxy-4-methoxy-β-phenylethylamine (0.12 g; 50%) after 12 hours, and after several days, an intractable brown gum (0.12 g.) which was not further investigated.

Bromination of O-benzyl-isovanillin

a. In glacial acetic acid

A stirred, ice-cooled solution of O-benzyl-isovanillin (5 g.) in glacial acetic acid (10 ml.) was treated dropwise with a solution of bromine (2.7 ml.) in glacial acetic acid (5 ml.) and the resulting solution was allowed to stand overnight. The precipitated product (4.5 g.) melted over a wide range (149-174°) despite repeated crystallisation from chloroform-light petroleum (b.p. 40-60°). A sample was chromatographed on alumina (Grade III) using 10% chloroform-benzene as elutrient. The first fraction gave a colourless solid, (ca. 10% of sample) which on crystallisation from ethanol afforded colourless needles, m.p. 209-11°, identified as 2-bromo-isovanillin by comparison of its i.r. spectrum with that of an authentic sample. (29) No other pure product was obtained from the column.

b. In carbon tetrachloride

O-Benzyl-isovanillin was shaken with bromine in a solution of carbon tetrachloride at room temperature overnight. Starting material was recovered in high yield.

5-Benzyloxy-2-bromo-4-methoxybenzaldehyde, XLVI.

A mixture of 6-bromoisovanillin, XXXVIII, (40 g.), potassium carbonate (20 g.), benzyl chloride (100 ml.) and absolute

ethanol (1 litre) was refluxed for 6 hours, cooled, filtered and evaporated to ca. 300 ml. On cooling a yellow precipitate was formed which, on crystallisation from methanol (charcoal) gave the benzyl ether, XLVI, as colourless, optically anisotropic needles (35 g.; 64%), m.p. 142-145°. (Found: C, 56.1; H, 4.4. $C_{15}H_{13}BrO_3$ requires C, 56.0; H, 4.1%).

5-Benzyloxy-2-bromo-4-methoxy-β-nitrostyrene, XLVII.

5-Benzyloxy-2-bromo-4-methoxy-β-nitrostyrene, XLVII, was prepared from the corresponding aldehyde, XLVI, in a manner analogous to that previously described (p.68) for 2-bromo-5-hydroxy-4-methoxy-β-nitrostyrene, XL. The nitrostyrene, XLVII, crystallised from glacial acetic acid as matted yellow needles (78%) m.p. 164-175°, unimproved by further crystallisation. (Found: C, 53.8; H, 4.5. $C_{16}H_{14}BrNO_4$ requires C, 52.8; H, 3.8%).

Reduction of 5-benzyloxy-2-bromo-4-methoxy-β-nitrostyrene, XLVII.

(i) N-[2-(5'-Benzyloxy-4'-methoxyphenyl)-ethyl]-p-methoxyphenylacetamide, IL.

A solution of 5-benzyloxy-2-bromo-4-methoxy-β-nitrostyrene, XLVII, (2.85 g.) in tetrahydrofuran (60 ml.) was added during 30 minutes to a stirred, refluxing solution of lithium aluminium hydride (2.5 g.) in tetrahydrofuran (250 ml.). Stirring and refluxing were continued overnight. The reaction was worked-up using ethyl acetate, water and Rochelle salt and the tetrahydrofuran solution decanted from the inorganic residue which was washed with ether (2 x 50 ml.), the washings being added to the tetrahydrofuran solution. The organic solution was extracted with 6N hydrochloric acid solution (3 x 50 ml.) and the aqueous

extracts, on basification with 4N aqueous sodium hydroxide and extraction with ether gave an oil (1.2 g.). This oil, in ether (20 ml.) and 0.2N aqueous sodium hydroxide (50 ml.), was treated with homoanisoyl chloride (0.6 g.) and the resulting mixture was stirred for 1 hour, filtered and the precipitate washed in turn with dilute alkali and acid. Crystallisation from ethanol gave the halogen-free amide, IL, as colourless needles (0.38 g; 12%), double m.p. 113-5°; 122-3°. (Found: C, 73.75; H, 6.5; N, 3.6. $C_{25}H_{27}NO_4$ requires C, 74.05; H, 6.7; N, 3.45%).

(ii) N- [2-(5'-Benzyloxy-2'-bromo-4'-methoxyphenyl)-ethyl]-p-methoxyphenylacetamide, XLVIII.

A solution of 5-benzyloxy-2-bromo-4-methoxy-β-nitrostyrene, XLVII, (2.7 g.) in dry tetrahydrofuran (90 ml.) was added in ca. 2.5 minutes to a stirred solution of lithium aluminium hydride)1.7 g.) in ether (125 ml.) at room temperature. The addition caused vigorous refluxing which was maintained by heating for a further 4 minutes. The heating was then removed and, after a further 9 minutes' stirring the excess of lithium aluminium hydride was decomposed by addition of ethyl acetate as rapidly as was safely possible. The complex was decomposed by addition of a minimum volume of water and the organic solution was decanted from the inorganic residue, which was washed with ether (2 x 50 ml.), the washings being added to the decanted solution. The combined organic solution was dried ($MgSO_4$), and evaporated, and the resulting oil was taken up in dry ether and treated with gaseous hydrogen chloride. The precipitated hydrochloride (2.2 g.), dissolved in a mixture of ether (40 ml.) 1N aqueous sodium hydroxide (100 ml.) was

treated with homoanisoyl chloride (1.25 g.) and the resulting mixture was stirred at room temperature for 2 hours. The precipitated solid was washed with dilute alkali and acid successively. Several crystallisations from ethanol gave the amide, XLVIII, as colourless needles (1.4 g; 36%), m.p. 152-3.5°. (Found: C, 61.8; H, 5.7; N, 2.7. $C_{25}H_{26}BrNO_4$ requires C, 62.05; H, 5.4; N, 2.8%).

(iii) N-[2-(5'-Benzyloxy-2'-bromo-4'-methoxyphenyl)-ethyl]-3"-benzyloxy-4"-methoxyphenylacetamide, LII.

This was prepared in a manner analogous to that described in (ii) for N-[2-(5'-benzyloxy-2'-bromo-4'-methoxyphenyl)-ethyl]-p-methoxyphenylacetamide, replacing the homoanisoyl chloride by an equivalent amount of 3-benzyloxy-4-methoxy-phenylacetyl chloride. The amide, LII crystallised from ethanol as colourless plates (25%), m.p. 155-7.5°. (Found: C, 64.8; H, 5.3; N, 2.5. $C_{32}H_{32}BrNO_5$ requires C, 65.1; H, 5.5; N, 2.4%).

Cyclisation of N-[2-(5'-benzyloxy-2'-bromo-4'-methoxyphenyl)-ethyl]-p-methoxyphenylacetamide, XLVIII.

Phosphorus pentachloride (166 mg.) was added to a solution of N-[2-(5'-benzyloxy-2'-bromo-4'-methoxyphenyl)-ethyl]-p-methoxyphenylacetamide, XLVIII (83 mg.) in chloroform+ (0.8 ml.). The mixture was allowed to stand for 4 days at room temperature after which more phosphorus pentachloride (92 mg.) was added. After standing for a further 4 days precipitation appeared to be complete and the solution was evaporated to dryness at $< 40°$. The residue was cautiously treated with methanol to decompose the excess of reagent and then dissolved in

+ Freshly dried by passing over blue silica gel.

hot methanol. On addition of dilute aqueous hydrochloric acid and cooling a precipitate was obtained which crystallised from aqueous methanol as colourless needles (25 mg; 30%) m.p. 136.5-138°. (Found: C, 60.2; H, 5.2; Br, 15.8; N, 3.1. $C_{25}H_{24}BrNO_3.2H_2O$ requires C, 59.9; H, 5.6; Br, 15.9; N, 2.8%). λ_{max} (in methanol) 290 m.μ (log ε, 4.16), 227 m.μ (inflection; log ε, 4.17), 219 m.μ (log ε, 4.22).

BIBLIOGRAPHY

(1) Manske, J. Amer. Chem. Soc., 1950, 72, 55.

(2) Kametani and Fukumoto, J., 1963, 4289; Chem. and Ind., 1963, 291.

(3) Kametani, Fukumoto and Masuko, J. Pharm. Soc. Japan, 1963, 83, 1052.

(4) Franck, Angew. Chem. internate. edit., 1964, 3, 192.

(5) Blatt, in Organic Reactions, Vol. I, Ed. Adams, J. Wiley & Sons. Inc., New York, London, 1942.

(6) Anselmi, Boll. chim. farm., 1954, 93, 247; C.A., 1954, 48, 12308g.

(7) P.G. Stevens, J. Amer. Chem. Soc., 1939, 61, 1714.

(8) Ogata, Kometani and Oda, Bull. Inst. Phys. Chem. Res (Tokyo) 1943, 22, 828; C.A., 1949, 43, 7924 c.

(9) Marey, Baddar and Awad, Nature, 1953, 172, 1187.

(10) Ogata and Tabuchi, Tetrahedron, 1964, 20, 1661.

(11) Bellamy, The Infra-red Spectra of Complex Molecules, Methuen, London 1954.

(12) Crowder, Glover, Grundon and Kaempfen, J., 1963, 4578.

(13) Rosemund & Schnurr, Annalen, 1928, 460, 56.

(14) Gensler, in Heterocyclic Compounds, Vol. 4, Ed, Elderfield, Chapman and Hall, London, 1952, p. 409.

(15) Bergstrom and McAllister, J. Amer. Chem. Soc., 1930, 52, 2845.

(16) Bergmann & Rosenthal, J. Prakt. Chem., (2), 1932, 135, 267.

(17) Conover, in Symposium on Antibiotics and Mould Metabolites, The Chemical Society, London, 1956.

(18) Cooney and Whitmore, J. Amer. Chem. Soc., 1944, 66, 1239.

(19) Chakraverti, J. Ind. Chem. Soc., 1943, 382.

(20) Gaylord, Reduction with Complex Metal Hydrides, Interscience, London, 1956, p. 672.

(21) Gabriel, Ber., 1886, 19, 1653, 2354; 1887, 20, 2499.

(22) Haworth and Pink, J., 1925, 127, 368.

(23) Peters, Ber., 1907, 40, 240.

(24) Harriman, Shelton, Van Campon and Warren, J. Amer. Chem. Soc., 1945 67, 1481.

(25) Meyer and Vittenet, Annalen, (10), 1932, 17, 271.

(26) Whaley and Govindachari, in Organic Reactions, Vol. VI, Ed. Adams, Chapman and Hall, London, 1951.

(27) Haworth and Perkin, J., 1925, 127, 1448.

(28) Kametani, Takano and Karibe, J. Pharm. Soc. Japan, 1963, 83, 1035.

(29) Henry and Sharp, J., 1930, 2285.

(30) Parkam and Anderson, J. Amer. Chem. Soc., 1948, 70, 4187.

(31) Pauly and Wascher, Ber., 1923, 56, 609.

(32) Robinson and Sugasawa, J., 1931, 3163.

(33) Govindachari, Rajadurai, Ramadas and Viswanathan, Chem. Ber., 1960, 93, 360.

(34) Eistert, Angew. Chem., 1941, 54, 124.

(35) Wolman, Gallop, Patrchornik and Berger, J. Amer. Chem. Soc., 1962, 84, 1889.

(36) Schoff and Bayerle, Annalen, 1934, 513, 190.

(37) Schut, Chem. and Ind., 1960, 1246.

(38) Johnson, Blizzard and Carhart, J. Amer. Chem. Soc., 1948, 70, 2661.

(39) Trevoy and Brown, J. Amer. Chem. Soc., 1949, 71, 1675.

(40) Alsop, Burdon and Tatlow, J., 1962, 1801.

(41) Corbett and Holt, J., 1963, 2385.

(42) Karabatsos, Shone and Scheppele, Tetrahedron Letters, 1964, 31, 2113.

(43) Erne and Ramirez, Hely. chim. Acta, 1950, 33, 912.

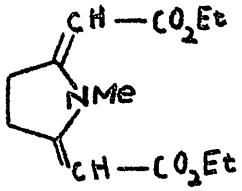
(44) Gulland and Haworth, J., 1933, 581.

(45) Robinson and Sugasawa, J., 1933, 280.

(46) Bachmann and Struve in Organic Reactions Vol I. Ed. Adams, Wiley, London, 1942.

NOVEL HETEROCYCLIC COMPOUNDS FROM DIETHYL NONA-2, 7-DIYNE-1, 9-DIOATE

Numbers in red refer to the location of preparations



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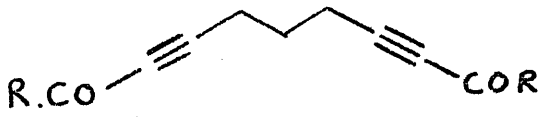

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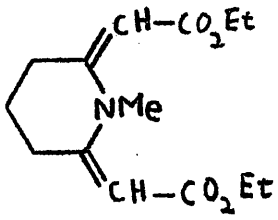

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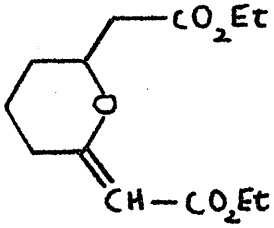

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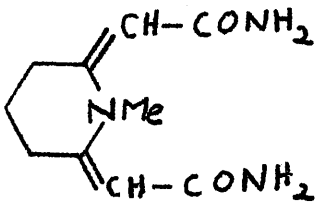

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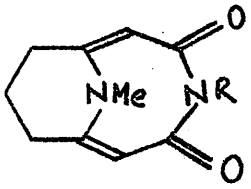

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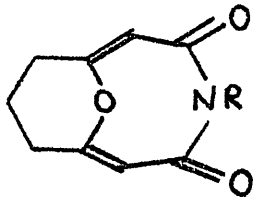

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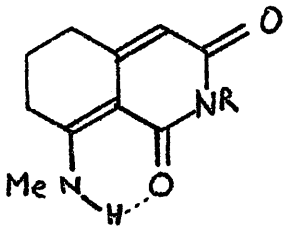

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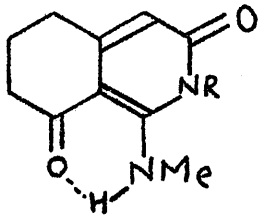

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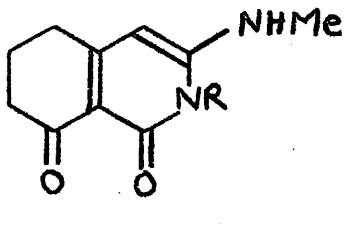

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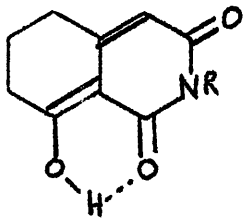

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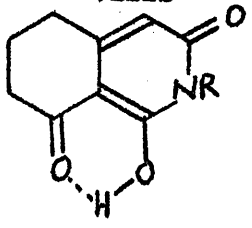

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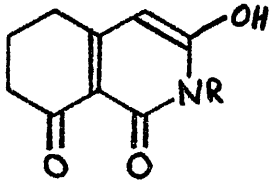

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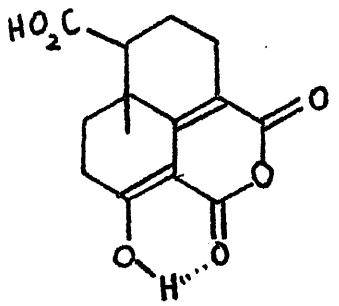

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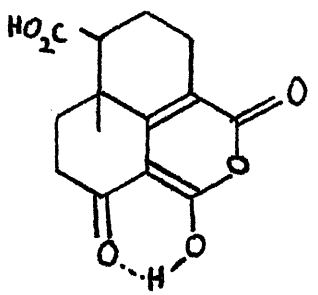

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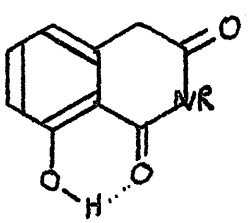

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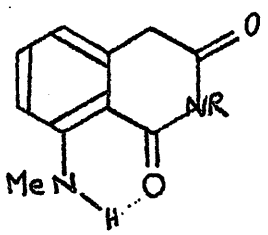

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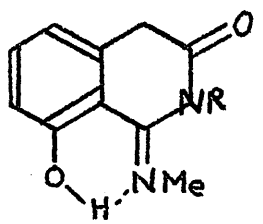

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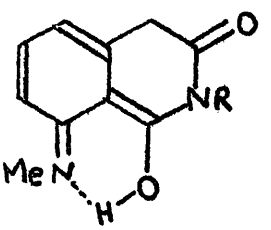

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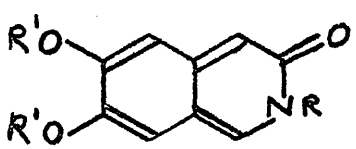

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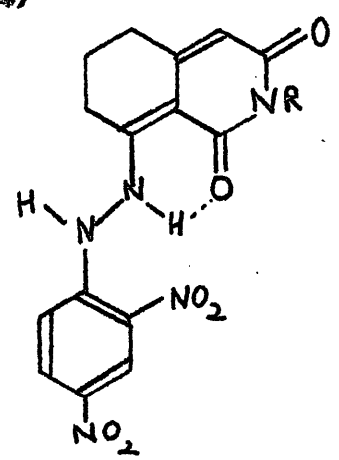

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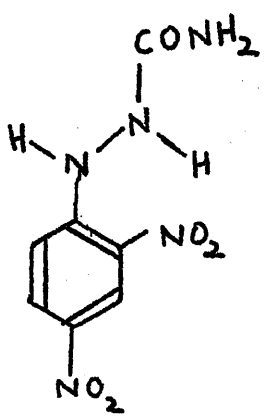
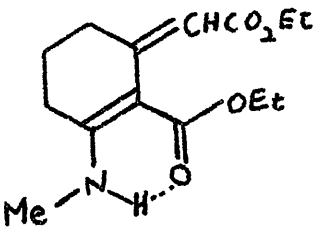


XXII



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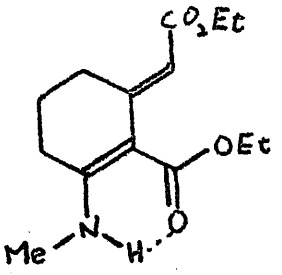
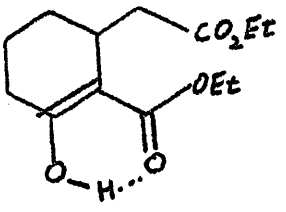


XXIIIa



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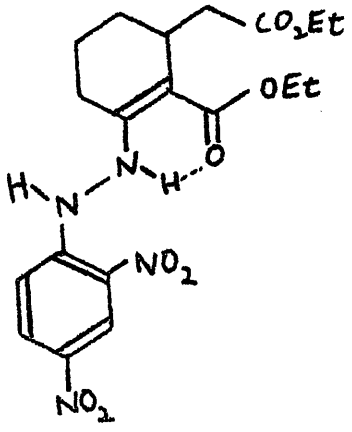

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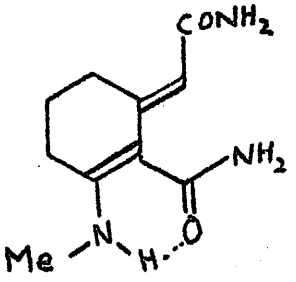

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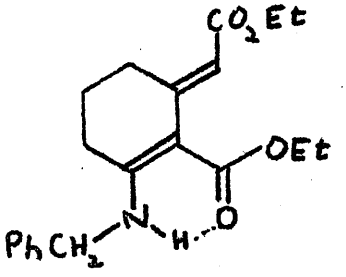

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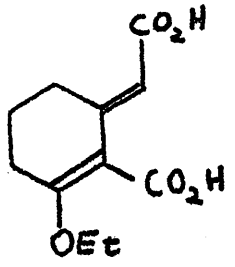
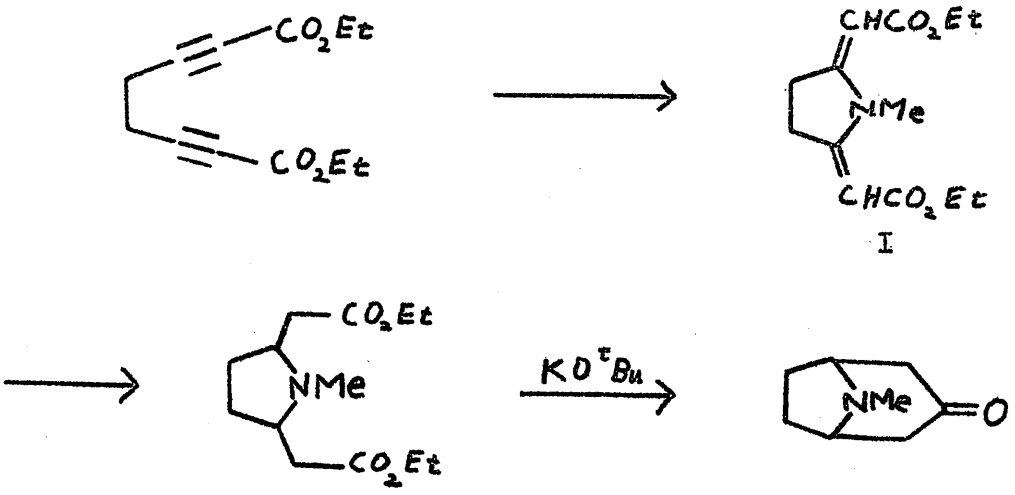


XXVIII

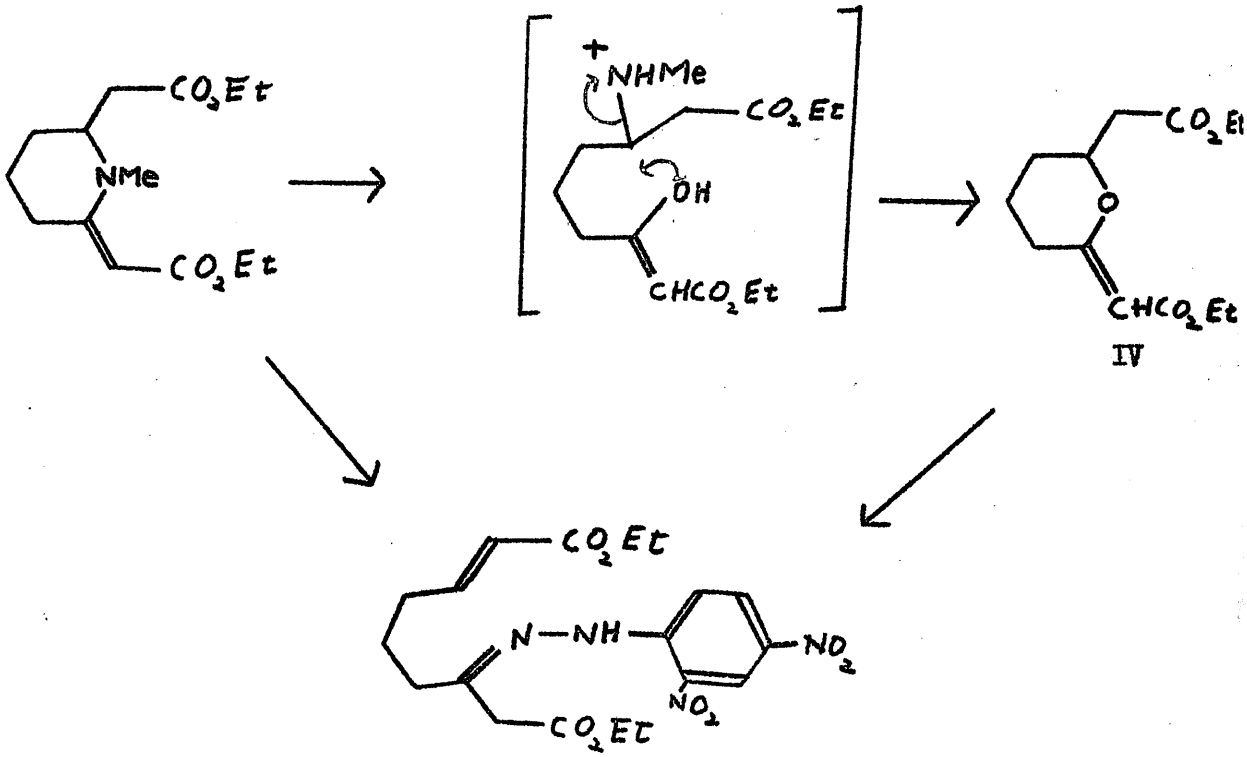
$HO_2C-(CH=CH)_2-CH=C(OEt)-CO_2H$

XXIX

SCHEME I



SCHEME II



INTRODUCTION

In 1959, the addition of one mole of methylamine across two activated acetylenic bonds simultaneously was exploited [1][2] in a synthesis of tropinone via the pyrollidine diester, I, as indicated in Scheme I. However, application of this method to the homologous ester, diethyl nona-2, 7-diyne-1, 9-dioate, II (R = OEt) proved to be less successful.

Although an oily product, E, whose analysis was consistent with the desired piperidine, III, could be obtained by the action of hot ethanolic methylamine, only one double bond of this could be reduced even after prolonged hydrogenation in ethanol, while, in acetic acid, catalytic hydrogenation gave a product formulated as the pyran, IV. Both reduction products afforded the same derivatives with Brady's reagent. [1][2] The mechanisms which were proposed [2] to account for these transformations are shown in Scheme II. An analogous product, F, formulated as V, was produced in the same way from the diamide, II ($R = NH_2$). [1]

Treatment of the dimethyl ester II (R = OEt) with cold aqueous ammonia or methylamine gave the corresponding diamides, II ($R = NH_2$ and NHMe respectively). [1] With hot aqueous methylamine however, the dimethyl or diethyl ester II (R = OMe or OEt) gave a compound, A, m.p. 160-162.5°, which was chiefly remarkable for its high wavelength u.v. absorption at 348 mμ (log ε, 4.51); 284 mμ (log ε, 3.32); 240 mμ (log ε, 3.91). This compound contained nitrogen and absorbed one mole of hydrogen (assuming a molecular weight of ca. 230). No molecular formula was assigned to it. [1]

TABLE I

Starting Material	Reagent	Product	Melting Point
A, $C_{11}H_{14}N_2O_2$	Sodium ethoxide	C, $C_{10}H_{11}NO_3$	95.5-96.5°
B, $C_{10}H_{12}N_2O_2$	Sodium ethoxide	D, $C_9H_9NO_3$	262-264°
D, $C_9H_9NO_3$	Methylamine	B, $C_{10}H_{12}N_2O_2$	277-279°
B, $C_{10}H_{12}N_2O_2$	Hydrazine	$C_9H_{11}N_3O_2$	dec. > 290°
C, $C_{10}H_{11}NO_3$	p-Bromobenzenesulphonylhydrazide	$C_{16}H_{16}BrNO_4S$	262°
C	p-Bromobenzoylhydrazide	$C_{17}H_{15}BrN_3O_3$	needles, 266-9° prisms, 280-5°
C	2,4-Dinitrophenylhydrazine	$C_{16}H_{15}N_5O_6$	261.5-262° (d)
D, $C_9H_9NO_3$	2,4-Dinitrophenylhydrazine	$C_{15}H_{13}N_5O_6$	260-263° (d)

A compound, B, m.p. 277-279° (d), whose properties (i.r., u.v., response to microhydrogenation) were closely analogous to those of the compound, A, was obtained by the action of hot aqueous methylamine on the diamide, II (R = NH_2). (1)

Later, these compounds, A and B, were assigned the respective molecular formulae $C_{11}H_{14}N_2O_2$ and $C_{10}H_{12}N_2O_2$. (3)

It was found (3) that A could also be produced by the action of hot aqueous methylamine on E, (alleged to be III) an observation which appeared to be paralleled by the formation of a little of the compound, B, with F. (1)

A and B, when treated with refluxing sodium ethoxide solution, yielded respectively the acidic compounds C, $C_{10}H_{11}NO_3$ and D, $C_9H_9NO_3$. (3)

The compounds A, B, C, and D, were found (3) to undergo facile reactions when treated with various primary amines, the stoicheiometry of each transformation corresponding to the replacement of methylamine (in A and B) or water (in C and D) by the amine. The results of these transformations are recorded in Table I.

In the following discussion of the structures and chemistry of A, B, C and D, reaction of methylamine with nona-2, 7-diyne-1, 9-dioic esters and amide is shown to take an unusual course.

SCHEME III

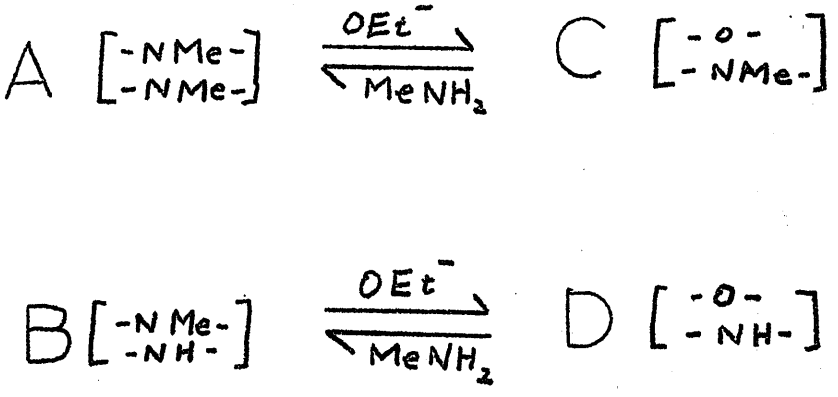


TABLE II

N.M.R. SPECTRA OF A, B, C, AND D.

COMPOUND	SOLVENT	τ_a	τ_b and τ_c	τ_d	τ_e	τ_f	τ_g
A (R=Me;X=NMe)	$CDCl_3$	4.35*	7.36,7.43*	8.07**	6.90**	6.68(s)	-2.1(b)
B (R=H; X=NMe)	CF_3CO_2H	3.68*	6.99*	7.79**	6.53**	===	===
C (R=Me;X=O)	$CDCl_3$	4.16*	7.37*	7.99**	-	6.68(s)	+++
D (R=H; X=O)	CF_3CO_2H	3.57*	6.98,7.08*	7.74**	-	===	===

* Broad singlet. (Peak appears to be split into a triplet (J<1c.p.s.) by protons 'b'.

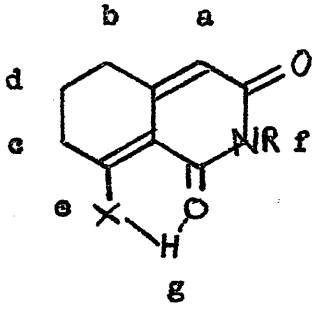
* Superimposed triplets (J=ca.6c.p.s.).

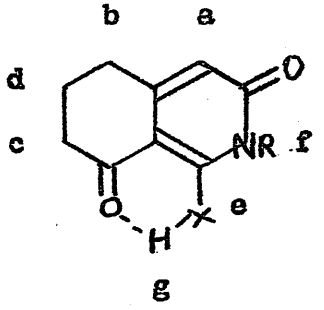
** Multiplet.

** Doublet (J=5.4c.p.s.).

=== Not sought.

+++ Not found > -10τ.





RESULTS AND DISCUSSION

In considering structures for compounds A, B, C and D, it soon became apparent that these compounds are closely related. Firstly, the interconvertibility of A and B with C and D respectively indicates that an - NMe - function in the former compounds corresponds to an -O- function in the latter pair. Secondly, the fact that B is derived from the di-primary amide, II, (R = NH_2) (1) while A is possibly formed via the di-secondary amide II (R = NHMe) suggests that A and C might be N-methyl analogues of B and D. This conclusion is fully borne out by analytical data and by n.m.r., i.r. and u.v. spectra (vide infra). These relationships are summarised in Scheme III.

An important observation (3) is that A can be derived by the action of methylamine in hot aqueous medium on compound E, * and since this had been formulated as III a possible structure assignment for A and B was as the bicyclo-imides, VI (R = Me and H respectively) with the derived "acids" C and D being formulated as VII (R = Me and H respectively), having been formed as in Scheme I. The bridgehead double bonds of these structures do not contravene Bredt's rule since they are in an eight-membered ring and models do not show undue strain in the molecules. However, these structures were clearly excluded by the n.m.r. spectra of all four compounds, Table II, which each exhibited the resonance of only one vinyl proton. In addition A and B exhibited doublets (J = 5.4 c.p.s.) at 6.90 τ (deuterochloroform) and 6.53 τ (trifluoroacetic acid) respectively, absent in C and D, betraying the presence in A and B of an -NHMe grouping (4) which is presumably replaced by -OH in C and D.

* A similar relationship probably also exists between B and F (cf. p.84).

TABLE III

I.R. SPECTRA OF A, B, C, AND D.

Carbonyl Absorption in Nujol.

Compound	$\nu_{C=O}$
A	1655cm.$^{-1}$
B	1655cm.$^{-1}$
C	1660cm.$^{-1}$
D	1660cm.$^{-1}$

In Solution.

Compound	Solvent	$\nu_{C=O}$	$\nu_{OH \text{ or } NH}$
A	$CHCl_3$	1650cm.$^{-1}$	3225cm.$^{-1}$
C	CCl_4	1687cm.$^{-1}$	2900-3050cm.$^{-1}$

The spectra of all four compounds showed absorption at ca. 7.4 τ and ca. 8.0 τ (deuterochloroform) and at ca. 7.0 τ and ca. 7.7 τ (trifluoroacetic acid) consistent with its assignment to an $A_2B_2C_2$ system, where A and C are almost equivalent.

The i.r. spectra of the compounds A, B, C and D all show strong carbonyl absorption (cf. Table III) and their u.v. spectra (Table IV) show evidence of an extensively conjugated system. These data can be accommodated by the structures VIII a, b, or c for A and B (with R = Me or H respectively) and IX a, b or c (with R = Me or H respectively) for C and D.

The structures VIII represent vinylogous amides and IX the corresponding vinylogous acids so that the principal features of the chemistry of all four compounds, A, B, C and D are explicable on the basis of these formulations.

The broad signal at -2.1 τ (Table II) in the n.m.r. spectrum of A can be attributed to the N-H proton, its low field position suggesting that it is participating in hydrogen bonding. The corresponding hydrogen bonded O-H expected in C could not be found above -10 τ.+ This rather surprising result is presumably due to the involvement of the proton in a rapid tautomeric shift between the two oxygen atoms to which it is bonded. The rate of exchange must be sufficiently fast to prevent the detection of a signal corresponding to either extreme position, yet not fast enough to allow the spectrometer to "see" the proton in only one intermediate position [5]. Accordingly this result may be taken as evidence for a chelated system.

+ Since the spectra of B and D were obtained only in trifluoroacetic acid their low field protons were not sought.

TABLE IV

U.V. SPECTRA OF A, B, C, AND D AND RELATED COMPOUNDS

Compound	λ_{max}^{EtOH} (mμ)	log ε	$\lambda_{max}^{EtOH-NaOH}$	log ε	$\lambda_{max}^{on\ reacid}$	log ε
A	350 286 236	4.38 3.23 3.72	350 281 257	4.42 3.48 3.70	350 286 236	4.38 3.23 3.72
B	349 284 235	4.44 3.32 3.79	352 282 257	4.39 3.61 3.88	349 284 235	4.44 3.32 3.79
C	320 240	4.26 3.89	329 280 211	4.25 3.64 3.33	320 240	4.26 3.89
D	319 233	4.20 3.89	334 278	4.37 3.57	319 233	4.20 3.89
C methyl ester	287 224 204	4.14 4.01 3.91	365 (inf) 335 284 224	3.61 4.21 3.63 4.25	320 240	4.11 3.76
Decevinic acid[6], X.	325	4.25				

The stability conferred by this chelate system seems to be indicated by the great tendency shown by the rather unstable methyl ester of C to hydrolyse back to C. Thus the u.v. spectrum (Table IV) underwent a change on treatment of the solution with a drop of dilute aqueous sodium hydroxide, and, on immediate reacidification became identical to that of the acid, C.

The sensitivity to hydrolysis of the ester explains an anomaly in the formulation of C and D as the vinylogous acids corresponding to the vinylogous amides A and B - that treatment of the amides with sodium ethoxide ought to give the corresponding esters. If formed, these might be hydrolysed in the work-up. An alternative explanation that the acids are produced by $B_{AL}2$ hydrolysis of the esters, may well be complementary to this.

Further evidence of the chelate system is furnished by the i.r. spectra (Table III), by the formation by C and D of stable, insoluble, green complexes on treatment with cupric acetate in acetone, and by the production of deep red-purple colourations by all four compounds when treated with ethanolic ferric chloride.

The demonstration of hydrogen bonding in A, B, C and D allows structures VIII C and IX C to be eliminated.

While the two remaining possibilities for both C and D, viz. IX a and IX b are, in fact, tautomeric, the corresponding pair of structures for A and B, viz. VIII a and VIII b are structural isomers and so ought to be fairly readily distinguishable - at least in principle.

Unfortunately, the u.v. spectra (Table IV) of the

TABLE V

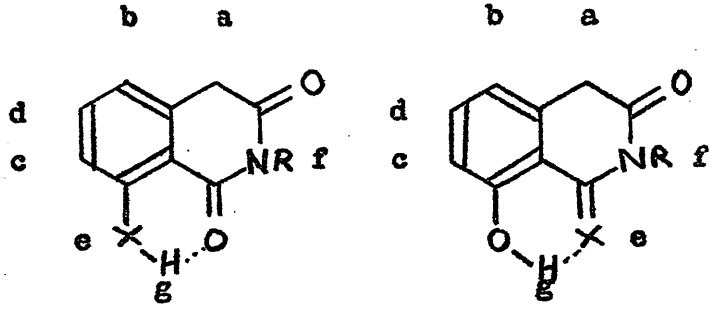
N.M.R. SPECTRA OF DEHYDRO-A, DEHYDRO-B, DEHYDRO-C AND DEHYDRO-D.

Compound	Solvent	τ_a	τ_b and c	τ_d	τ_e	τ_f	τ_g
Dehydro-A (R=Me;X=NMe)	$CDCl_3$	6.06(s)	3.43, 3.62+	2.64*	7.06(s)	6.70(s)	2.30(b)
Dehydro-B (R=H;X=NMe)	CF_3CO_2H	5.69(s)	2.15(complex)		6.59(s)	++	++
Dehydro-C (R=Me;X=O)	$CDCl_3$	5.98(s)	3.10, 3.26+	2.55*	-	6.66(s)	-1.75(s)
Dehydro-D (R=H;X=O)	CF_3CO_2H	5.58(s)	2.80, 2.90+	2.20*	-	++	++

\+ Indistinct doublets (J=ca. 8c.p.s.)

* Quartet (J=7.8c.p.s.)

++ Not sought



compounds A, B, C and D do not allow a distinction to be drawn between the rather different chormophoric systems of series "a" and "b" + because of the absence of reliable model compounds.

The most relevant published spectrum (6) is that of decevinic acid, X b, which absorbs at 325 mμ (log ε, 4.25) compared to values of 320 mμ (log ε, 4.26) and 319 mμ (log ε, 4.20) for C and D respectively - a reasonably close correspondence in view of the small variations which may be expected in comparing an anhydride with its imide counterpart. However, it must be pointed out that there is no published reason why decevinic acid should not exist as the tautomer, X a.

In order to confirm the correctness of the carbon skeleton derived for the compounds A, B, C and D and, if possible, to assign them to the appropriate series, attempts were made to dehydrogenate them to aromatic compounds. It was found that, on treatment with 10% palladium-on-charcoal for periods ranging from two minutes to one hour, all four compounds lost two hydrogen atoms to give the corresponding dehydro-derivatives.

Dehydro-C and dehydro-D, irrespective of the series to which the parent compounds, C and D, belong, should have the structures XI (R = Me and H respectively), a prediction which is borne out by the n.m.r. spectra (Table V). Particularly significant in these spectra is the appearance of peaks corresponding to the aromatic protons at 2.5 - 3.5 τ (deuterochloroform) or 2.2 - 3.0 τ (trifluoroacetic acid) and of a methylene singlet at 5.98 τ (deuterochloroform) or 5.58 τ (trifluoroacetic acid). The presence of the hydrogen bonded hydroxyl group is demonstrated

+ While it must be borne in mind that the tautomeric form of C and D has no bearing on the structures of A and B (i.e. IX a may be derived from VIII b, etc.), it will be convenient for future purposes to refer to the compounds as belonging to series "a" or "b" according as A and B may be represented by VIII a or VIII b.

by the appearance in the spectrum of de-hydro-C, of a sharp singlet at -1.75 τ. The corresponding peak in dehydro-D is presumably obscured by the solvent, trifluoroacetic acid.

Both dehydro-C and dehydro-D behave like phenols, being insoluble in saturated aqueous sodium bicarbonate but soluble in dilute sodium hydroxide from which they are reprecipitated by acid.

These data, together with further evidence which is presented below, can be taken to substantiate firmly the structures (but not the tautomeric forms) of C and D as IX (R = Me and H respectively) and consequently, also to establish the carbon skeleton of A and B.

The bases dehydro-A and dehydro-B can be assigned the structures XII a or XII b. Their n.m.r. spectra (Table V) show resonance due to aromatic and methylene protons comparable to that observed for dehydro-C and dehydro-D. However the N-methyl group of both bases occurs as a sharp singlet at 7.06 τ (deuterochloroform) or 6.59 τ (trifluoroacetic acid).

The absence of spin-spin coupling of this methyl group suggests that the compounds belong to series "b". However, Dudek [7] has pointed out that while the occurrence of a methyl doublet is excellent evidence for a hydrogen atom on the methyl-bearing nitrogen atom, the absence of coupling does not lead with any certainty to the converse conclusion. This is because when the energy barrier for hydrogen exchange between oxygen and nitrogen becomes sufficiently low, exchange becomes rapid and, accordingly, irrespective of the length of time spent by the proton on any one site, spin-spin coupling is eliminated. Hence

TABLE VI

Calculation of values for the Aromatic Protons of XIIa (R=Me)

	ortho	meta	para
Found for XI (R=Me)	3.26 or 3.18	2.55	3.10 or 3.26
Subtract effect for -OH	-0.37	-0.37	-0.37
Add effect for -NHMe	+0.80	+0.30	+0.57
∴ Calculated for XIIa (R=Me)	3.69 or 3.53	2.48	3.30 or 3.46
Observed for dehydro-A	3.62	2.64	3.43

if the compounds belong to series "a", the lack of spin-spin coupling may be attributable to rapid tautomerism between the two forms XII a and XIII .

While the n.m.r. spectra of dehydro-A and dehydro-C were measured in deuterochloroform, solubility considerations dictated the use of trifluoroacetic acid as a solvent for their analogues unmethylated on the heterocyclic nitrogen atom, dehydro-B and dehydro-D. Nevertheless the τ-values of the aromatic protons of the phenols dehydro-C and dehydro-D are comparable when allowance is made for the shift expected due to change of solvent. (8) As expected, the proton on H_6 occurs as a quartet, being spin-coupled to two ortho protons while the protons on H_5 and H_7 occur as doublets at rather higher field.

The fact that the aromatic protons of the base, dehydro-A, appear at higher fields than those of the phenol dehydro-C, now assigned the structure XI (R = Me) is well in accord with structure XII a for the former compound. As shown in Table VI, values calculated for the aromatic protons of structure XII a (R = Me) relative to those found experimentally for XI (R = Me) using published values (9) for the changes in chemical shifts of aromatic protons due to the addition of various substituents, correspond well with those found for dehydro-A.*

The same relationship does not apply to the spectra of the unmethylated analogues, dehydro-B and dehydro-D, measured in trifluoroacetic acid, since protonation of the base, dehydro-B, by the solvent, causes a large downfield shift of the signals due to the aromatic protons which accodingly absorb as an ill-defined multiplet centred at 2.15 τ.

* Unfortunately the data are not available to allow the same treatment to be applied to structure XII b.

Finally the N-H (or O-H) peak of dehydro-A absorbs in a broad peak centred at 2.30 τ. Its chemical shift shows it to be hydrogen bonded but not very strongly.

While the n.m.r. spectra of the four dehydrogenation products are in good agreement with structures for A and B belonging to series "a" they cannot be held completely to rule out series "b". The same is true of other spectral evidence discussed in later pages and it was only upon the following chemical evidence that the correct structure assignments could be made.

Both bases, dehydro-A and dehydro-B are soluble in dilute aqueous alkali or acid but not in water. While their basic nature is readily understood on either formulation XII a or XII b their acidic nature is explicable as being due to either the well-known acidity of the homophthalimide nucleus [10] (if series "a") or their phenolic nature (if series "b").

Since, if the dehydro-bases belonged to series "b" they were expected to behave as phenols, these compounds were tested with ethanolic ferric chloride (which readily produces a green colouration with the phenols dehydro-C and dehydro-D). However the test solutions of the dehydro-bases only slowly developed a brown colour, presumably due to oxidation.

The Gibbs' test [11][12] for a phenol with a free <u>para</u> position gave similar results. As expected the test solution of dehydro-C exhibited a visible absorption maximum at 690 mμ, characteristic of the indophenol produced in a positive Gibbs' test, whereas the test solution

TABLE VII

U.V. SPECTRA OF DEHYDRO COMPOUNDS UNDER GIBBS' TEST CONDITIONS

Compound	λ_{max} pyridine	relative optical density	λ_{max} (in 30% pyridine-borate buffer(pH9.2)	
			Initially	After 30 minutes
Dehydro-A	375	-	394	354
Dehydro-B	378	-	391 313	351
Dehydro-C	411 317	1 5	392 310	332
Dehydro-D	390 317	1 5	391 307	335

TABLE VIII

U.V. SPECTRA OF DEHYDRO COMPOUNDS

Compound	λ_{max}^{EtOH} (mμ)	log ε	$\lambda_{max}^{EtOH-NaOH}$	log ε	$\lambda_{max}^{EtOH-HCl}$*	log ε
Dehydro-A	375	3.77	396	3.91	295+	2.94
	260	3.95	313	3.96	283	3.08
	242	4.01	287	4.13	248	3.88
	222	4.05	250	4.20	235+	3.80
			226	4.18	210	4.01
Dehydro-B	378	3.71	404	3.83	294+	3.04
	261	3.89	313	3.90	284	3.18
	243	3.92	289	4.03	247	3.89
	223	3.90	251	4.03	235	3.84
			229	4.00	217	3.76
Dehydro-C	316	3.58	392	3.73		
	257	3.88	309	4.14		
	222+	3.95	299	4.09		
	214	4.01	264	3.99		
			234	4.13		
Dehydro-D	318	3.58	391	3.82		
	253	3.93	306	4.22		
	220+	4.11	296+	4.16		
	212	4.21	264+	4.04		
			227+	4.32		
			221	4.33		
N-ethyl-homophthalimide	285	3.10	390	3.35		
			305	4.10		

\+ Inflection

* Measured in 50% aqueous ethanolic hydrochloric acid (3N).
In the presence of smaller concentrations of acid, intermediate spectra were obtained.

of dehydro-A exhibited only background absoprtion in the region 500-700 m.μ. +

Since the failure to detect the presence of a phenolic group in the bases, dehydro-A and dehydro-B, made their assignment to series "a" seem possible, confirmation of this was sought and obtained in the formation from dehydro-A of a solid, yellow N-nitroso derivative, diagnostic of a secondary amine.

The above evidence reinforced by one other compelling argument (see p. 97) allowed the compounds A and B to be assigned to series "a".

An interpretation follows of the remaining spectral evidence of the dehydrogenation products in terms of the derived structures, XII a (R = Me and H respectively) for dehydro-A and dehydro-B, and XI (R = Me and H respectively) for the phenols, dehydro-C and dehydro-D.

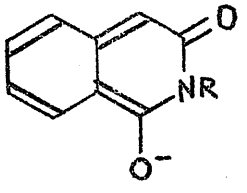
The long wavelength peaks of the u.v. spectra of the bases, dehydro-A and dehydro-B are higher by ca. 60 m.μ. than those of the phenols dehydro-C and dehydro-D (cf. Table VIII). However, the bathochromic shifts on basification of the phenols are much greater (ca. 75 m.μ.) than those of the bases (ca. 24 m.μ.) and so all four compounds, in basic colution, have very similar u.v. spectra.

In the published u.v. spectrum of N-ethylhomophthalimide (13)

+ The results of Gibbs' tests on not only dehydro-B, but also dehydro-D, were negative, indicating apparently that the free N-H of an imide system invalidates this test. Comparison of the u.v. spectra (Table VII) of the four dehydro compounds in pyridine and in 30% pyridine-borate buffer (pH 9.2) shows that there are no significant differences between the corresponding N-methyl and N-H derivatives, before addition of reagent.

(Table VIII) the peak observed at ca. 285 mμ, in neutral solution, changes in alkali to maxima at 390 mμ and 305 mμ, bearing a marked similarity to the spectra of dehydro-C and dehydro-D in alkali. The implication from this that the phenol groupings in the last two compounds do not have any significant influence on the chromophore is strongly supported by the following observations.

The spectrum of N-ethylhomophthalimide in alkali is itself notably similar to those of the neutral form of the 3-isoquinolones XIV (R = H or Me, R' = Me or 2R' = $-CH_2-$) (14) and bears no resemblance to those of 1-isoquinolones. This suggests that the chromophore of the homophthalimide in base is due mainly to the form XV assuming that the effect of the enolate anion on the basic 3-isoquinolone chromophore is comparable with that of two ether functions in XIV



XV

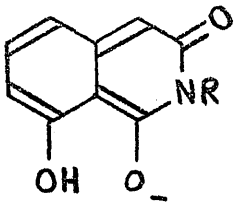
It is therefore possible that the hydroxyl group of the 8-hydroxyhomophthalimides, XI, would not significantly affect the chromophore since further ionisation of the ionised form, XVI, would tend to be suppressed by the adjacent negative charge and tautomerism

TABLE IX

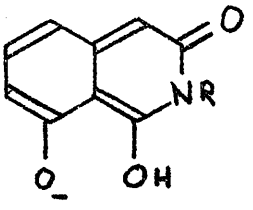
I.R. Spectra (in Nujol) of the Dehydro-Compounds

Compound	ν max ($cm.^{-1}$)	
	C=O (position 3)	C=O (position 1)
Dehydro-A	1695	1660
Dehydro-B	1695	1660
Dehydro-C	1700	1640
Dehydro-D	1700	1660

between XVI and XVII would not greatly disturb the chormophore.



XVI



XVII

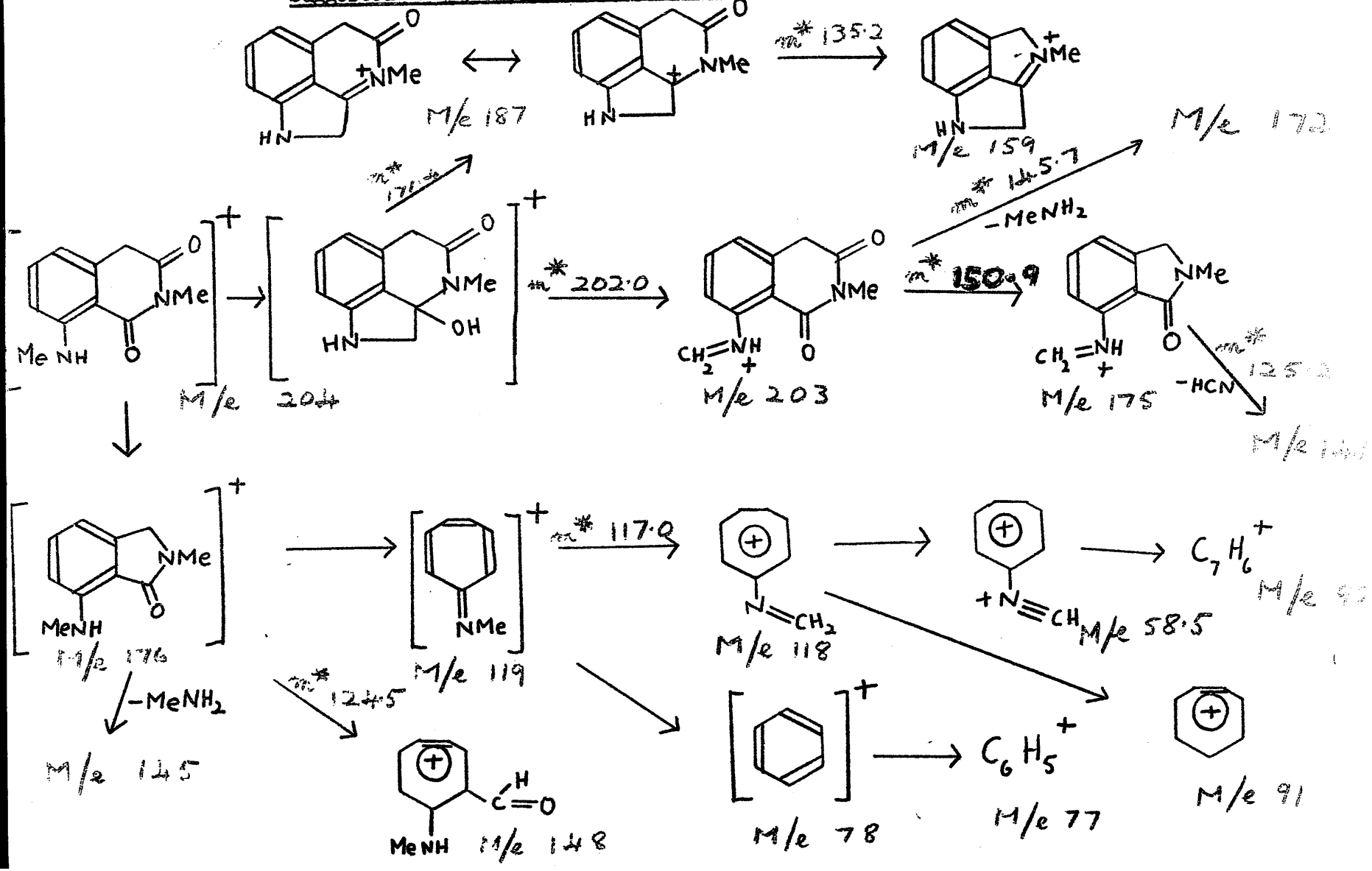
If this argument is valid, then substitution of an -NHMe group for the -OH group in XVI should not materially alter its u.v. The fact that the four dehydro-compounds all have very similar u.v. spectra in base seems to support this interpretation.

The phenolic and methylamino groups do, however, contribute to the chormophore in neutral solution. Thus the phenols, dehydro-C and dehydro-D absorb at 316 and 318 mμ respectively and the bases dehydro-A and dehydro-B at 375 and 378 mμ respectively, compared with 285 mμ for the parent N-ethylhomophthalimide. (13) That these increments may be due to delocalisation of the lone pair of the 8-substituent group is reflected, in the case of the bases, by the reversion of the spectra in acid (where the lone pair is now involved in salt formation) to near that of N-ethylhomophthalimide (cf. Table VIII).

The i.r. spectra (Table IX) of the four dehydro-compounds, in Nujol, show the expected (15) absorption at ca. 1700 cm^{-1}, due to the carbonyl group in position 3. The other carbonyl group occurs at rather

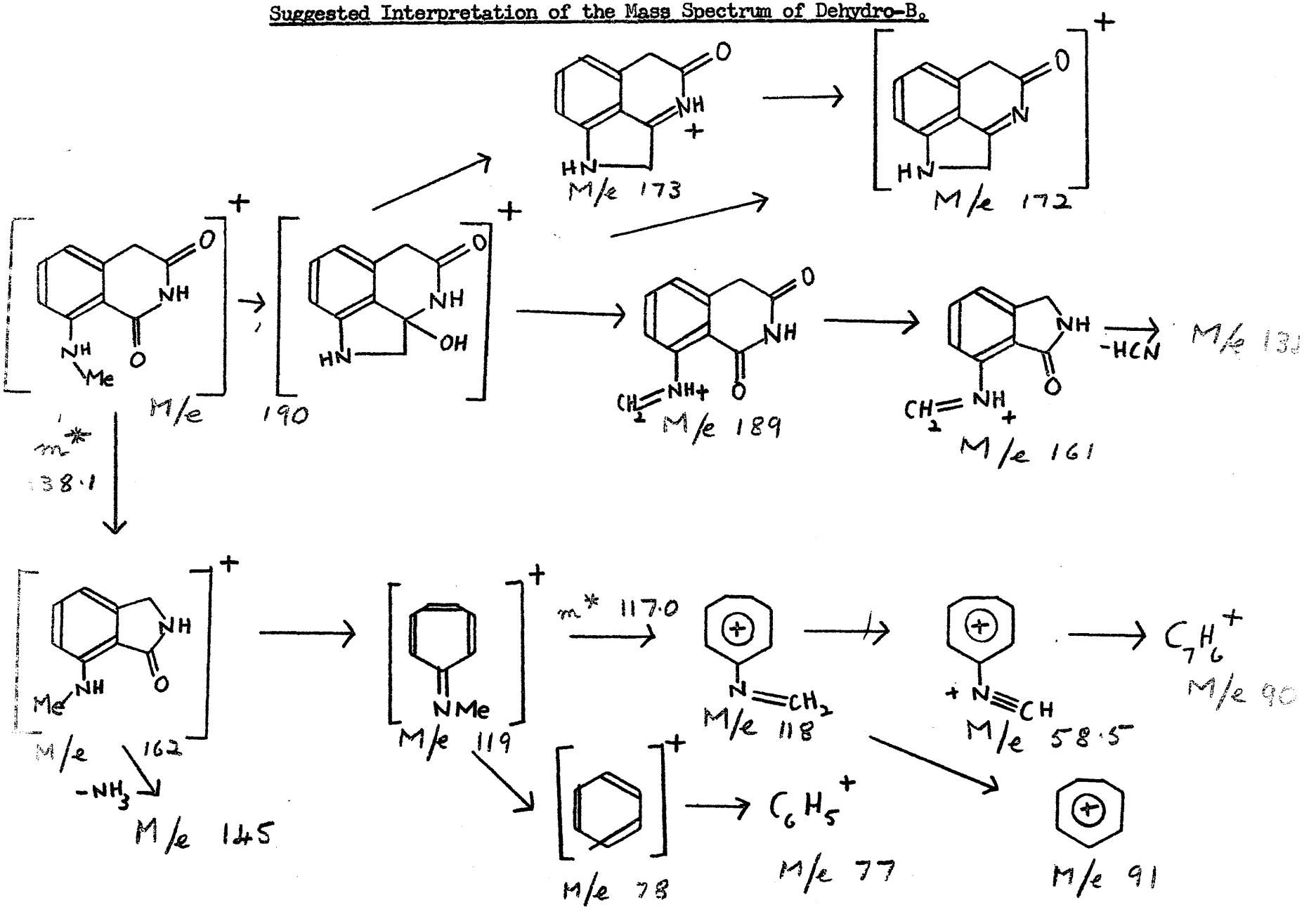
SCHEME IV

Suggested Interpretation of the Mass Spectrum of Dehydro-A.



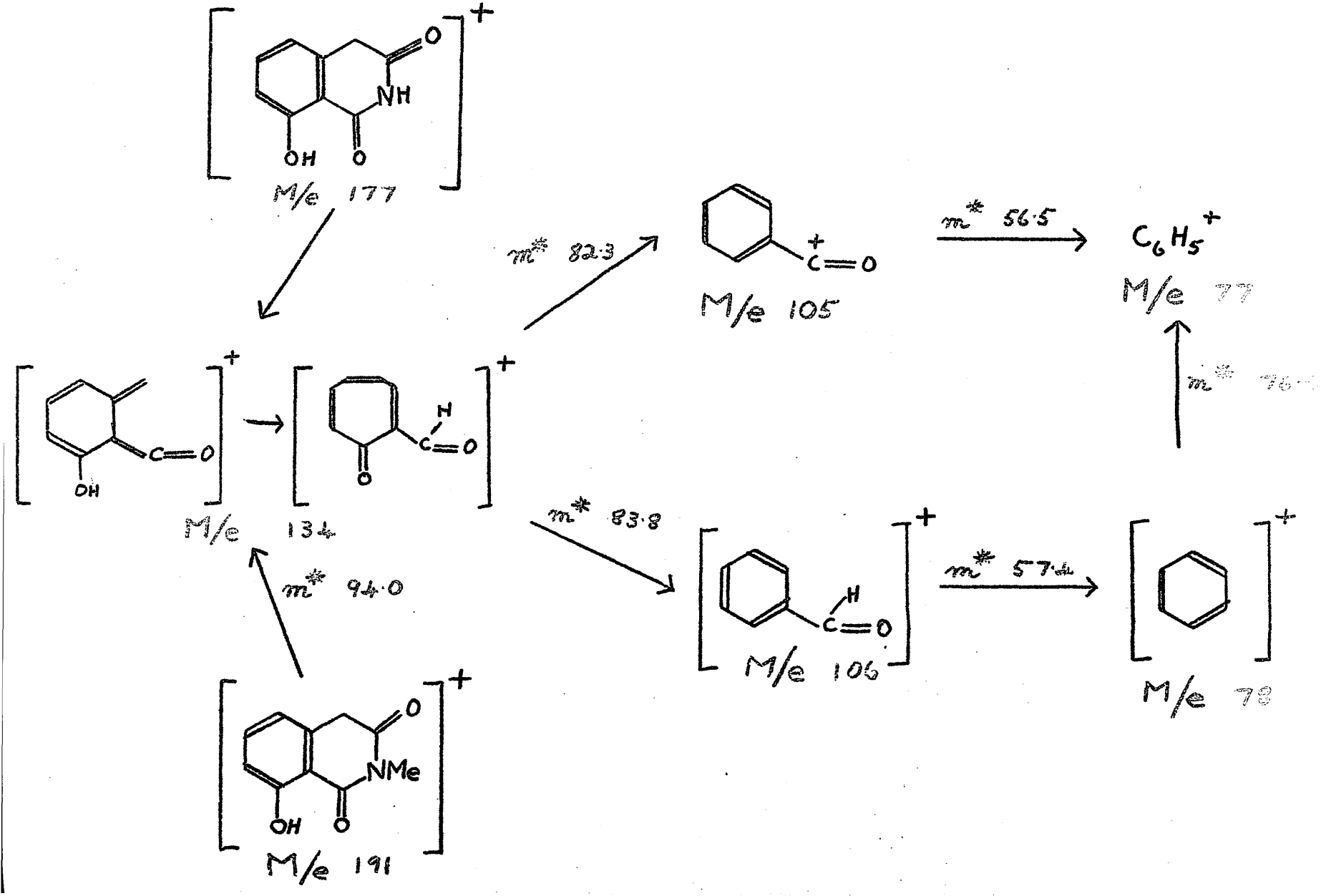
SCHEME V

Suggested Interpretation of the Mass Spectrum of Dehydro-B.



SCHEME VI

Suggested Interpretation of the Mass Spectra of Dehydro-C and Dehydro-D.



SCHEME VII

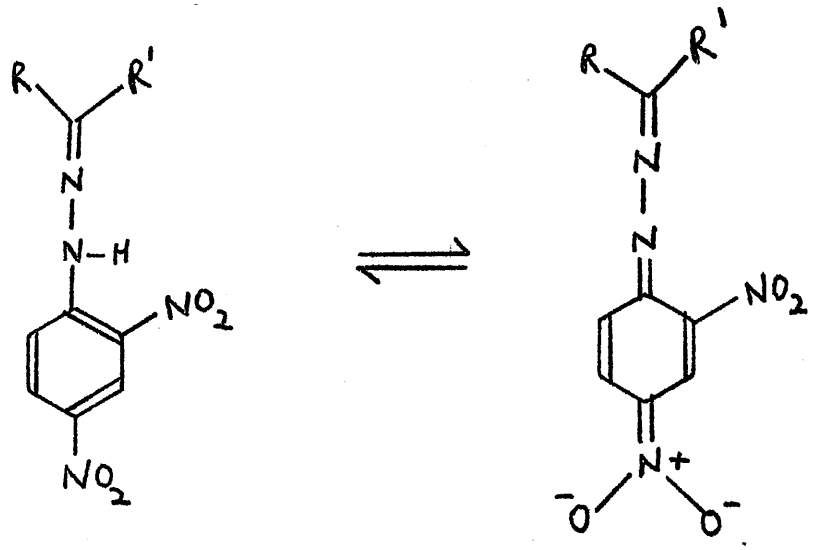


TABLE V

Mass spectrum of Dehydro-A.*

M/e	% Abund.	M/e	% Abund.	M/e	% Abund.
205	12.3	146	6.5	90	14.8
204	100.0	145	7.8	89	12.9
203	29.3	131	7.7	78	5.0
187	8.3	119	28.6	77	12.9
176	12.3	118	41.8	76	5.2
175	14.2	117	7.5	65	6.1
172	8.0	116	77.6	63	8.0
159	8.1	104	12.0	58.5	6.8
148	6.8	92	7.0	57	5.9
147	6.7	91	17.5	51	10.2

* Only ions of abundance < 5% included

Metastable Ions

M/e	Transition
202.0	204 to 203
171.4	204 to 187
151.8	204 to 176
150.9	203 to 175
145.7	203 to 172
135.2	187 to 159
125.2	175 to 148
124.5	176 to 148
117.0	119 to 118

TABLE XI

Mass Spectrum of Dehydro-B*

M/e	% Abce.	M/e	% Abce.	M/e	% Abce	M/e	% Abce
191	12.4	145	17.4	92	10.2	64	10.7
190	100.0	134	8.3	91	20.6	63	11.3
189	27.9	133	5.1	90	16.0	62	5.1
173	9.2	119	21.3	89	17.4	55.5	9.5
163	7.3	118	31.5	81	5.9	56	9.6
172	12.0	117	14.1	78	7.1	55	7.5
161	14.6	116	10.5	77	17.3	52	7.0
148	6.1	105	5.9	76	7.8	51	14.2
		104	14.1	65	10.9		

Metastable Ions

M/e	Transition
138.1	190 to 162
117.0	119 to 118

TABLE XII

Mass Spectrum of Dehydro-C*

M/e	% Abce.	M/e	% Abce
192	7.4	105	14.6
191	83.1	78	19.4
173	7.0	77	12.4
135	8.3	52	8.7
134	100.0	51	15.6
106	24.6		

Metastable Ions

M/e	Transition
94.0	191 to 134
83.8	134 to 106
82.3	134 to 105

TABLE XIII

Mass Spectrum of Dehydro-D*

M/e	% Abce.	M/e	% Abce.	M/e	% Abce
178	5.4	91	6.8	62	13.4
177	38.4	79	12.9	55	5.8
149	8.4	78	70.2	53	11.9
135	7.1	77	57.0	52	44.5
134	46.1	76	28.0	51	100.0
121	13.6	75	12.9		
106	42.9	74	10.6		
105	48.3	67	5.0		
104	13.1	66	9.8		
103	6.8	65	17.0		
93	13.6	64	9.8		
92	6.0	63	30.5		

Metastable Ions

M/e	Transition
83.8	134 to 106
76.0	78 to 77
57.4	106 to 78
56.5	105 to 77

* Only ions of abundance > 5% included

TABLE XIV

U.V. Spectra and Acidity of 2,4-Dinitrophenylhydrazones and Related Compounds

	pK_a (aq. dioxan)	Solvent	λ^{HA}_{max} (mμ)	log ε	$\lambda^{A^-}_{max}$ (mμ)	log ε
XVIII (R=Me)	6.6±0.2	EtOH-HCl	370	4.28	-	-
		EtOH-NaOH	-	-	525	4.30
		pyridine	-	-	536	-
XVIII (R=H)	6.6±0.2	EtOH-HCl	370	4.29	-	-
		EtOH-NaOH	-	-	524	4.30
		pyridine	-	-	536	-
D.N.P. of benzaldehyde[18]	10.90±0.19	aqueous dioxan	387	4.48	473	4.52
D.N.P. of acetophenone[18]	11.16±0.05	aqueous dioxan	385	4.42	468	4.40
D.N.P. of p-nitrobenzaldehyde[18]	10.42±0.19	aqueous dioxan	404	4.52	545	4.61
D.N.P. of p-nitroacetophenone[18]	10.58±0.22	aqueous dioxan	394	4.49	553	4.53
2,4-Dinitrophenyl-semicarbazide, XXII	10.5 pK 6.6	MeOH	331	4.15	-	-
		aqueous dioxan	331	4.15	-	-
		aqueous dioxan-NaOH	-	-	452	4.23
		pyridine	-	-	452	-

lower values (ca. 1660 cm^{-1}) than in homophthalimide itself (1684 cm^{-1})[15] presumably because of hydrogen bonding.

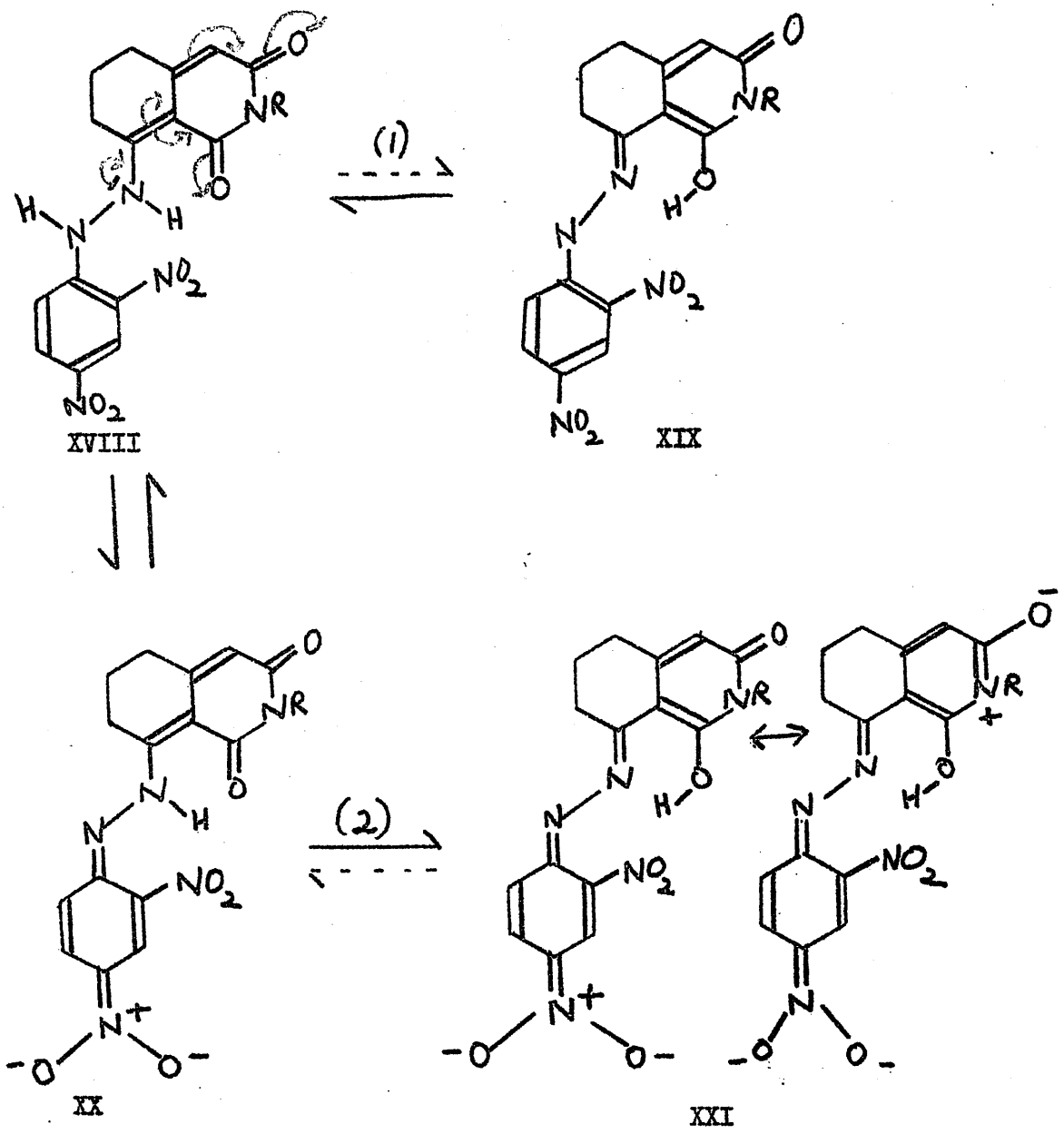
The mass spectra (Tables X - XIII) of the four dehydro-compounds, show certain similarities to one another and can be interpreted as in Schemes IV - VI on the basis of the structures XII and XI. (cf. refs [16] and [17]).

Before the true nature of compounds C and D was known, these were tested with 2, 4-dinitrophenylhydrazine [3]. Under the usual condition of hydrazone formation, orange compounds were obtained which may now be formulated as the vinylogous 2, 4-dinitrophenylhydrazides, XVIII (R = Me and H respectively). These compounds showed a remarkable tendency to turn purple under very mildly basic conditions. Their pyridine solutions were bright purple and even methanolic solutions tended to be dark-coloured. [3]

2, 4-Dinitrophenylhydrazones are weakly acidic, according to the equilibrium shown in Scheme VII. The pKa of this dissociation usually lies in the region 11-12. [18] The visible absorption maxima of a variety of compounds in neutral solution occur at 380-400 $m\mu$, while the corresponding anions absorb at 460-490 $m\mu$ [18]+ The u.v. spectra (Table XIV) of the derivatives obtained from C and D have maxima in neutral solution at 370 $m\mu$, a wavelength rather lower than would be anticipated for 2, 4-dinitrophenylhydrazones. However, in basic solution, these 2, 4-dinitrophenylhydrazides absorb at the unusually high wavelengths of 525 $m\mu$ and 524 $m\mu$ respectively. Furthermore these compounds are much stronger acids than normal 2, 4-dinitrophenylhydrazones having pKa

+ The 2, 4-dinitrophenylhydrzones of p-nitrobenzaldehyde and p-nitroacetophenone, however, absorb at 545 $m\mu$ and 553 $m\mu$ respectively. [18]

SCHEME VIII



values, measured spectroscopically (cf. ref. [18]), of 6.6 ± 0.2.

The above data indicate the probability that the vinylogous hydrazides are converted by alkali into the basic forms of highly conjugated 2, 4-dinitrophenylhydrazones. It is significant that during pK measurement there was no indication of the presence of any intermediate form corresponding to the unionised 2, 4-dinitrophenylhydrazone.

The above findings can be rationalised as shown in Scheme VIII. While a mechanism exists [reaction (1)] for the tautomeric conversion of the arylhydrazides XVIII (R = Me and H) into the hydrazone form XIX, there is no driving force for this reaction to occur. That a ketamine form is more stable than the corresponding enol-imine form is well established and if further evidence were required, there is the analogy of compounds A and B, VIIIa (R = Me and H respectively). Hence the formation of the 2, 4-dinitrophenylhydrazones, XIX, is not observed.

The acidity of 2, 4-dinitrophenylhydrazones is probably due mainly to the withdrawal of electrons from the N-H bond by the dinitrophenyl ring. The adjacent azomethine group is electron releasing and, if anything, discourages ionisation. However, the compounds, XVIII (R = Me and H), are more acidic since, in addition to the electron withdrawal by the dinitrophenyl ring the acidic N-H is further activated by the mesomerically transmitted effect of two carbonyl groups (red arrows in Scheme VIII).

The arguments cited above against reaction (1) do not necessarily apply to reaction (2) since it may be supposed that the loss

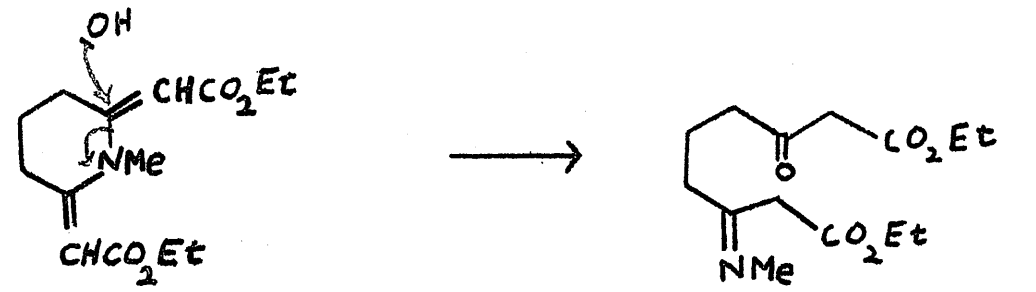
of stability involved in changing the anion, XX, from the ketamine to enol-imine form will be more than offset by the gain in stability resulting from increased conjugation. Hence reaction (2) may be considered to occur immediately after ionisation so that only XXI, the anionic form of a 2, 4-dinitrophenylhydrazone, is detected.

An analogy for this behaviour is found in 2, 4-dinitrophenylsemicarbazide, XXII, which was reported [19] to be soluble in hot water with a change in colour and to give rise to a "dark black colour" in aqueous base. This compound (prepared from 2, 4-dinitrochlorobenzene in a manner analogous to that described [19]) had u.v. absorption, in aqueous dioxan or methanol, at 331 mμ (log ε, 4.15) and, in pyridine or aqueous alkali, at 452 mμ (log ε, 4.23) (Table XIV). These results indicate that the semicarbazide derivative, XXII, is a weaker acid than the 2, 4-dinitrophenylhydrazide derivatives prepared from C and D (since the latter compounds are partially ionised even in methanol) but, as predicted, it is a stronger acid than are 2, 4-dinitrophenylhydrazones (which fail to ionise in pyridine). The greater acidity of the derivatives of C and D is presumably ascribable to their additional carbonyl group.

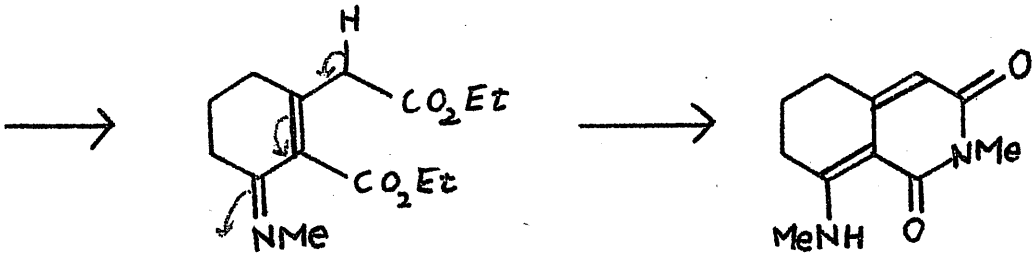
The anions, XXI (R = Me and H) absorb light at a very high wavelength, 525 mμ. Comparable extended chromophores are found in the anionic forms of the dinitrophenylhydrazones of p-nitrobenzaldehyde (545 mμ) and p-nitroacetophenone (553 mμ).

Compelling evidence of the correctness of the formulation of A and B as VIIIa (R = Me and H respectively) appeared as a result of considering the mechanism of their formation.

SCHEME IX



III

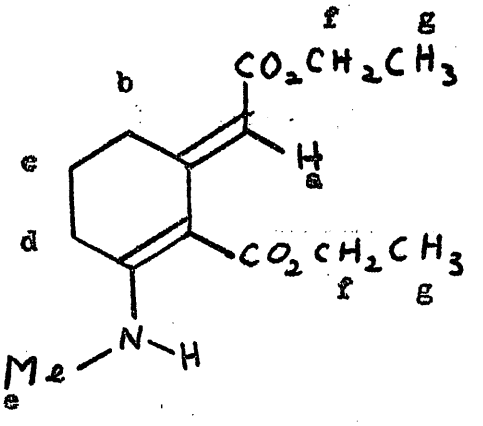


VIIIa (R=Me)

TABLE XV

N.M.R. Spectrum of E. XXIIIa.

Resonance (τ)	Assignment
3.87(s)	a
ca. 6.9(complex)	b
8.25(complex)	c
7.60(complex)	d
7.05(d) J=5.4cps.	e
5.90(q) J=6.6cps.	f
8.67 and 8.76 (superimposed triplets) J=6.6cps.	g



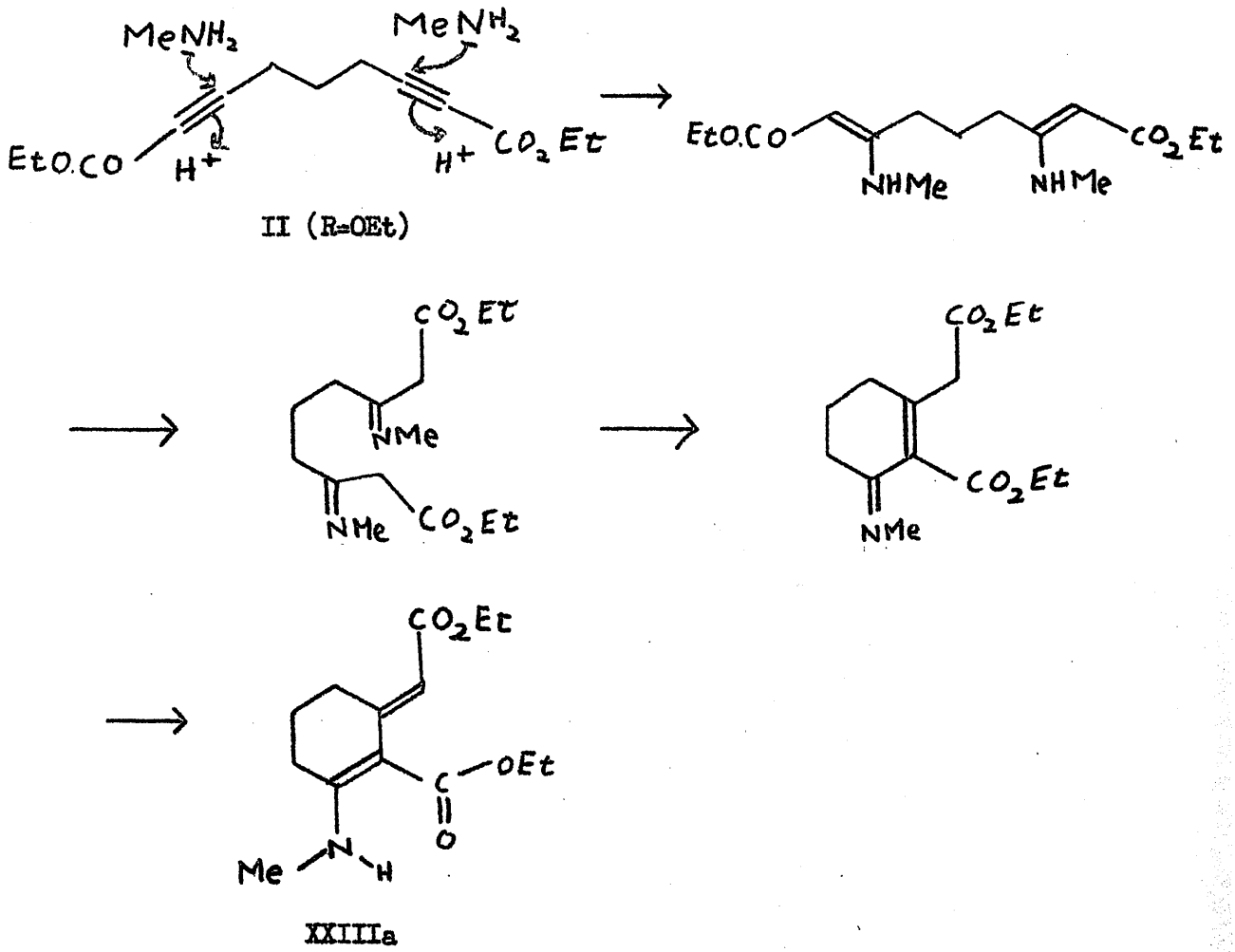
Since it was shown [3] that compound A, VIIIa (R = Me) is obtained from compound E, (which had been formulated [1][2] as III) it was reasonable first to consider whether E was an intermediate in the formation of A from the nonadiynedioate, II (R = OEt). A mechanism, involving opening of the piperidine ring of III and reclosure in a different sense (Scheme IX) can be envisaged for this transformation.

However, in view of the anomalous behaviour [1][2] of E (cf. Introduction) it was tempting to suppose that it might have been misformulated and that its correct structure is XXIII, a structure which not only explains its ready transformation into A, but also accounts for its failure to absorb more than one mole of hydrogen. (Compounds A and B also absorb only one mole, [1] the vinylogous amide system being, apparently, resistant to hydrogenation).

The product of hydrogenation in acetic acid [1][2] can now be understood to be the acid analogue, XXIV, and the common "2, 4-dinitrophenylhydrazone" [1][2] can be reformulated as the vinylogous hydrazide, XV. Finally, the u.v. absorption at 322 mμ (log ε, 4.32) is now readily understood to be due to a chromophoric system similar in most respects to that of A and B.

Decisive evidence of the correctness of this theory came from the n.m.r. spectrum of E (Table XV) which exhibited a methyl doublet at 7.05 τ (J = 5.4 c.p.s.) and a single, unsplit vinyl proton at 3.86 τ. The occurrence of the resonance of one of the methylene groups as a multiplet at ca. 6.9 τ compared to the value observed for A at ca. 7.4 τ (cf. Table II) indicates that the former group is deshielded by the

SCHEME X



II (R=OEt)

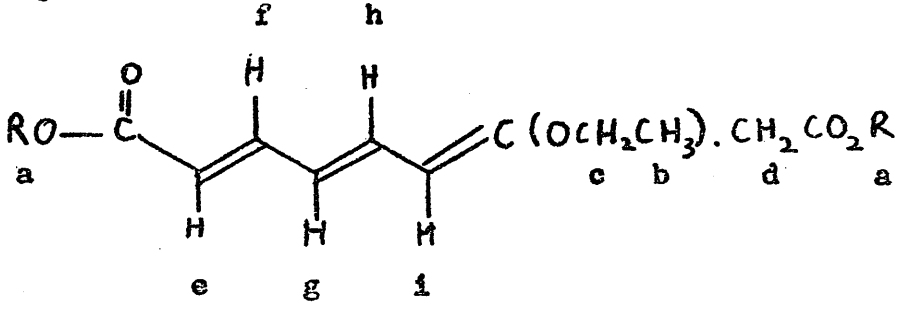
XXIIIa

TABLE XVI

N.M.R. Spectra of G, XXIX, and its Dimethyl Ester

Compound	Solvent	τ_a	τ_b	τ_c	τ_d	τ_e to τ_i
G (R=H)	$(CD_3)_2SO$	-	8.76(t) J=6.6cps.	6.13(q) J=6.6cps.	6.63(s)	2.50-4.60*
Estar (R=Me)*	$CDCl_3$	6.25(s)	8.68(t) J=6.8cps.	6.11(q) J=6.8cps.	6.62(s)	2.30-4.60+

* Spectrum measured on Perkin-Elmer 40M/c Spectrometer.
\+ Vide infra.



\+ Olefinic Protons (of ester)

Proton	τ-values		
e	4.2	J_{EF}	15.2 cps.
f	2.61	J_{EF}	15.2 cps.
		J_{FG}	10.8 cps.
g	3.53	J_{FG}	10.8 cps.
		J_{GH}	10.8 cps.
h	3.53	J_{GH}	10.8 cps.
		J_{HI}	10.8 cps.
i	4.49	J_{HI}	10.8 cps.

—— Large coupling constant implies trans geometry

—— Chemical shift implies trans geometry (cf. ref (9) p.237)

carbethoxyl group and so indicates that the double bond geometry of E is as shown in XXIIIa, [cf. refs. (20) and (21)].+

A possible mode of formation of E, XXIIIa, involves the addition of one mole of methylamine to each triple bond of the nonadiynedioate, II (R = OEt), followed by imine condensation, as shown in Scheme X.

Further reaction of E occurs only with aqueous methylamine, the readier protonation in this medium presumably facilitating transamidation or imide ring closure.++

In view of the above mechanism, it was of interest to investigate whether caustic alkali would effect a similar transformation of the nonadiynedioate, II (R = OEt). Brief treatment with hot aqueous ethanolic sodium hydroxide gave homophthalic acid and a pale yellow crystalline compound, G, each in ca. 20% yield. (3)

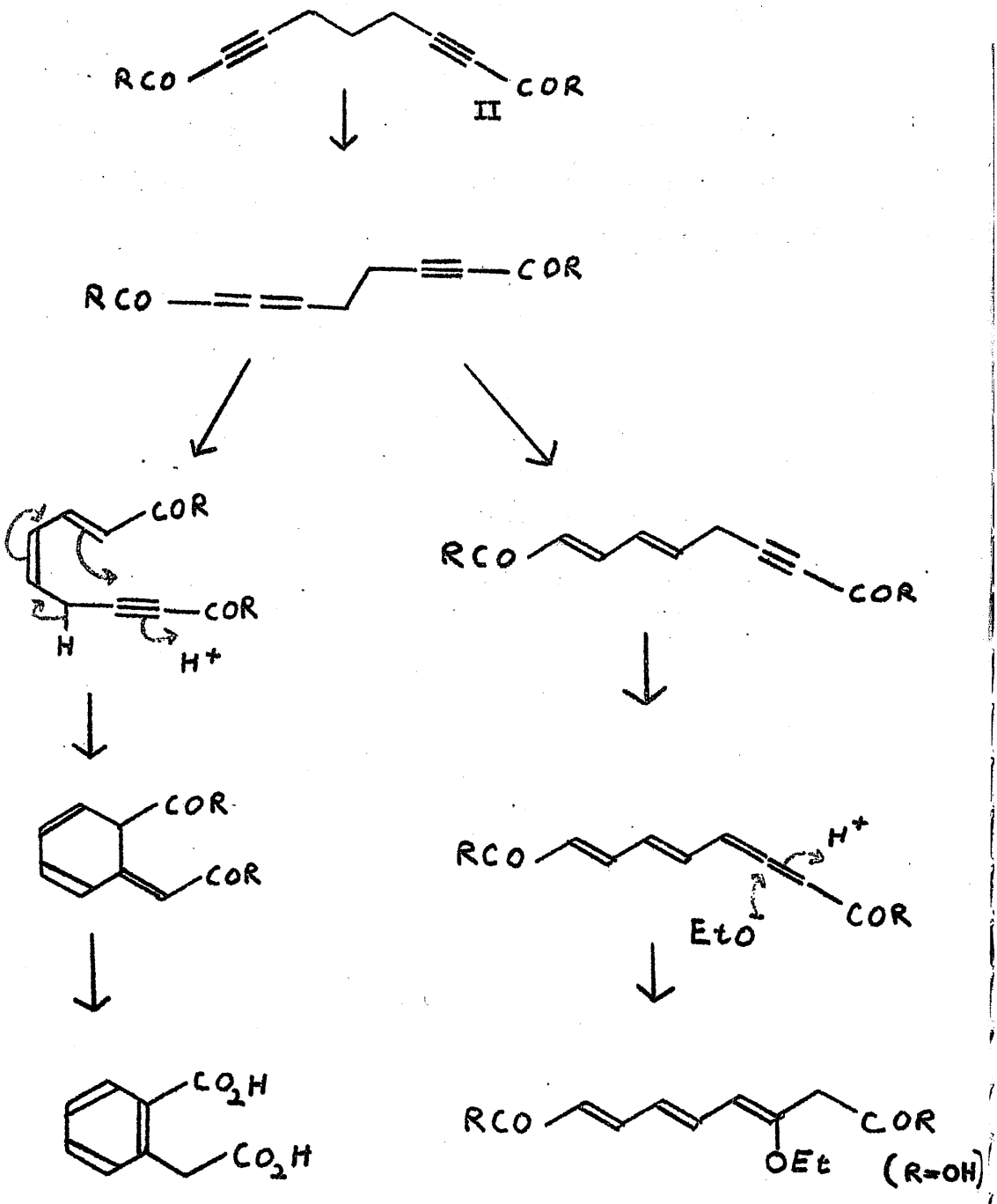
Microanalysis of G was consistent with the structure, XXVIII, and in accord with thisstructure, G formed a dimethyl ester with diazomethane, was unaffected by further treatment with alkali, but was decomposed by treatment with acid. Moreover, it absorbed in the u.v. at 328 m.μ. (log ε , 4.47) (cf. compound E, XXIIIa, absorbing at 322 m.μ.).

However, the structure of G was revised to XXIX on the following grounds. On microhydrogenation, at least two moles of hydrogen were absorbed. The n.m.r. spectra of G and of its dimethyl ester were in accord with the revised structures as indicated in Table XVI. The decisive features are the complex olefin resonances (value 5 protons) and

+ Although n.m.r. spectra have not yet been obtained there seems to be little doubt that F (previously formulated(1) as V) is, in fact XXVI. The N-benzyl analogue (1) of E also requires to be reformulated as XXVII.

++Possibly reversible hydration of the exocyclic double bond permits alteration of its geometry prior to cyclisation.

SCHEME XI



Homophthalic acid

XXIX

the singlet (value 2 protons) at 6.62τ due to a methylene group having no protons on the adjacent carbon atoms. The interpretation shown in Table XVI of the olefinic resonance suggests the partial double bond geometry indicated.

The u.v. absorption to be expected for the diacid, XXIX, can be calculated by adding to 294 mμ. (the value reported [22] for octa - 2, 4, 6-trienoic acid) the increment due to the ethoxyl group. In the β or δ position, this contributes ca. 30 mμ. to a conjugated dienone [33] and this figure gives a calculated value for the diaicid, XXIX, of 324 mμ., in good agreement with the observed value of 328 mμ.

A possible explanation (outlined in Scheme XI) of the formation of G and of homophthalic acid is that, under the influence of strong base, one acetylenic group rearranges, via an allene to either a cis-diene leading to homophthalic acid, or a trans-diene leading to the diacid, G, XXIX.

However, in the presence of inorganic bases at controlled pH, addition of water to the acetylenic linkages follows the same course as does methylamine. Thus, a small yield of D, IX (R = H), was obtained when the diamide, II (R = NH_2) was refluxed in aqueous borate buffer solution (pH 9.2).

Accordingly it appears that under mildly basic conditions, nucleophiles add individually to both triple bonds of esters and amides of nona-2, 7-diyne-1, 9-dioic acid, II (R = OH), and that the resulting product readily undergoes intramolecular condensation to give products related to compound E.

EXPERIMENTAL

All m.p.'s are uncorrected.

I.r. spectra were obtained on a Unicam SP 200 or a Unicam SP 100 spectrophotometer. U.v. spectra were measured on a Perkin-Elmer 137 UV or a Unicam SP 800 spectrophotometer. N.m.r. spectra were measured on a Perkin-Elmer, 60 M.c. spectrometer. Mass spectra were measured on an A.E.I. M.S.9 mass spectrometer.

Copper Complexes These were prepared by adding a saturated solution of cupric acetate in acetone to an acetone solution of the compound to be tested.

pK Measurement This was carried out by the procedure of Jones and Mueller.[18]

1, 2, 3, 5, 6, 7-Hexahydro-2-methyl-8-methylamino-1, 3-dioxisoquinoline, VIIIa (R = Me)+

a.[1][3] Diethyl nona-2, 7-diyne-1, 9-dioate, II (R = OEt) (4.3 g.) was refluxed with 25% aqueous methylamine (25 ml.) and ethanol (40 ml.) for 2 hours. Evaporation and crystallisation of the residue from benzene gave the 2-methyl-8-methylamino compound, VIIIa (R = Me) as prisms (2.5 g.; 67%) m.p. 161-162.5°. (Found: C, 64.1; H, 617; N, 13.9. $C_{11}H_{14}N_2O_2$ requires C, 64.1; H, 6.8; N, 13.6%).

b.[3] Compound E, XXIIIa prepared as described previously[1][2] (where it is formulated as IV) (1 g.) was refluxed for 2 hours with aqueous alcoholic methylamine as in a. The 2-methyl-8-methylamino-compound VIIIa (R = Me) obtained in this way (0.38 g.; 44%) was identical with a sample prepared as in a.

1, 2, 3, 5, 6, 7-Hexahydro-8-methylamino-1, 3-dioxoisoquinoline, VIIIa (R = H) [1][3]+

+ A few experiments (preparations of compounds A, B, C, D and G) are as described previously[1][3] but are included for the sake of completeness.

The acetylenic diamide II (R = NH_2) (9.9 g.) was refluxed for 15 minutes with 25% aqueous methylamine (200 ml.) and methanol (150 ml.). The methylamino-compound VIIIa (R = H) which separated on concentration of the solution, crystallised from methanol in small cubes (5.9 g.); 64%), m.p. 227-279°. (Found: C, 62.8; H, 6.5; N, 14.5. $C_{10}H_{12}N_2O_2$ requires C, 62.5; H, 6.2; N, 14.6%).

1, 2, 3, 5, 6, 7-Hexahydro-8-hydroxy-2-methyl-1, 3-dioxoisoquinoline, IX (R = Me) (3)+

The above 2-methyl-8-methylamino compound, VIIIa (R = Me), (0.54 g.) was refluxed for several hours with a solution prepared from sodium (0.4 g.) in ethanol (30 ml.). After evaporating to dryness the residue was dissolved in water and acidified with dilute aqueous hydrochloric acid. The precipitate was crystallised from light petroleum (b.p. 60-80°) to give the 8-hydroxy-2-methyl compound, IX (R = Me), as colourless plates (0.35 g.; 69%), m.p. 95.5-96.5°. (Found: C, 62.1; H, 5.8; N, 7.5. $C_{10}H_{11}NO_3$ requires C, 62.2; H, 5.7; N, 7.3%).

1, 2, 3, 5, 6, 7-Hexahydro-8-hydroxy-1, 3-dioxoisoquinoline, IX (R = H)

a. (3)+ This was prepared from the 8-methylamino compound, VIIIa (R = H) in a manner analogous to that described above for the 8-hydroxy-2-methyl compound, IX (R = Me). The 8-hydroxy compound crystallised from ethanol as colourless needles (83%), m.p. 262-264°. (Found: C, 60.5; H, 5.3; N, 7.7. $C_9H_9NO_3$ requires C, 60.3; H, 5.1; N, 7.8%).

b. The acetylenic diamide, II (R = NH_2), (109 mg.) was refluxed for 1.5 hours in aqueous borate buffer solution (pH 9.2) (10 ml.). Chloroform extraction of the cooled solution gave only traces of oil. The

mother liquor was acidified and re-extracted with chloroform to yield the 8-hydroxy compound, IX (R = H), as a colourless solid (7 mg.; 8%), identical (i.r. and mixed m.p.) to material prepared as in a. above.

8-methoxy-2-methyl-1, 3-dioxoisoquinoline

1, 2, 3, 5, 6, 7-Hexahydro-8-methoxy-2-methyl-1, 3-dioxoisoquinoline.

1, 2, 3, 5, 6, 7-Hexahydro-8-hydroxy-2-methyl-1, 3-dioxoisoquinoline, IX (R = Me), (200 mg.) in ether (20 ml.) was allowed to stand for 20 minutes at room temperature in the presence of diazomethane. Evaporation gave an oil which was dissolved in chloroform and extracted with saturated aqueous sodium bicarbonate. Evaporation of the oil gave a solid which on crystallisation from light petroleum (b.p. 60-80°) gave the vinylogous ester as colourless needles (ca. 60 mg.; 28%), m.p. 96-104°. (Found: C, 63.1; H, 6.7. $C_{11}H_{13}NO_3$ requires C, 63.8; H, 6.3%).

Dehydrogenations

Dehydrogenations were carried out by refluxing the compound in a metal bath with 20% by weight of palladium-on-charcoal (10%) in diphenyl ether (1 ml. for 100 mg. material), for varying periods. After refluxing and cooling for ca. 1 minute the reaction mixture was poured into a large excess of light petroleum (b.p. 40-60°). After 1 hour the solid was filtered off and the product extracted from the accompanying catalyst by a suitable solvent.

1, 2, 3, 4-Tetrahydro-8-hydroxy-2-methyl-1, 3-dioxoisoquinoline XI (R = Me)

Prepared from 1, 2, 3, 5, 6, 7-hexahydro-8-hydroxy-2-methyl-1, 3-dioxoisoquinoline, IX (R = Me) by dehydrogenation during 15 minutes. The product was extracted from the catalyst by chloroform and crystallised from methanol to give the hydroxy-homophthalimide, XI (R = Me)

as long, pale yellow needles (56%), m.p. 140-141°. (Found: C, 62.8; H, 4.5; N, 7.5. $C_{10}H_9NO_3$ requires C, 62.8; H, 4.7; N, 7.3%).

1, 2, 3, 4-Tetrahydro-8-hydroxy-1, 3-dioxoisoquinoline XI (R = H)

Prepared from 1, 2, 3, 5, 6, 7-hexahydro-8-hydroxy-1, 3-dioxoisoquinoline, IX (R = H) by dehydrogenation during 1 hour. The product was extracted with hot ethanol which, on cooling, deposited the hydroxy-homophthalimide XI, (R = H), as pale brown needles (74%), m.p. 195-215° (d). (Found: C, 61.2; H, 3.8; N, 8.0. $C_9H_7NO_3$ requires C, 61.0; H, 4.0; N 7.9%).

1, 2, 3, 4-Tetrahydro-2-methyl-8-methylamino-1, 3-dioxoisoquinoline, XIIa (R = Me)

Prepared from 1, 2, 3, 5, 6, 7-hexahydro-2-methyl-8-methylamino-1, 3-dioxoisoquinoline, VIIIa (R = Me), by dehydrogenation for 2 minutes. Extraction with chloroform and crystallisation from ethanol gave the methylamino-homophthalimide XIIa (R = Me), as orange needles (56%), m.p. 156.5-158.5°. (Found: C, 64.5; H, 5.9; N, 13.8. $C_{11}H_{12}N_2O_2$ requires C, 64.7; H, 5.9; N, 13.7%).

1, 2, 3, 4-Tetrahydro-8-methylamino-1, 3-dioxoisoquinoline, XIIa (R = H)

Prepared from 1, 2, 3, 5, 6, 7-hexahydro-8-methylamino-1, 3-dioxoisoquinoline, VIIIa (R = H) by dehydrogenation for 15 minutes. The product was extracted with hot ethanol and, after evaporation, the residue was sublimed at 160-180°/0.1 mm. to give the methylamino-homophthalimide, XIIa (R = H) as an orange powder (ca. 50%), m.p. 214-220° (d). (Found: C, 63.4; H, 5.3; N, 14.6. $C_{10}H_{10}N_2O_2$ requires C, 63.15; H, 5.3, N, 14.7%).

Treatment of 1, 2, 3, 4-tetrahydro-8-methylamino-1, 3-dioxoisoquinoline, XII (R = H) with (1) acid, and (2) base.

(i) On refluxing the above compound XIIa (R = H) for 1.5 hours in equal volumes of 6N aqueous hydrochloric acid and ethanol only tars were obtained.

(ii) Similar results were obtained on refluxing for 2 hours in a solution of sodium (0.15 g.) in methanol (5 ml.).

Attempts to reduce 1, 2, 3, 4-tetrahydro-2-methyl-8-methylamino-1, 3-dioxoisoquinoline XIIa (R = Me).

(i) Hydrogenation of the above compound XIIa (R = Me) in methanolic solution over palladium-on-charcoal caused no significant uptake of hydrogen after 4 hours. The compound was also resistant to sodium borohydride in aqueous methanol at room temperature.

(ii) Reduction of the above compound, XIIa (R = Me) with lithum aluminium hydride in tetrahydrofuran at room temperature gave, on working up under neutral conditions, a brown oil which was shown (t.l.c.) to have at least 6 components. It was not further investigated.

3-Ethoxynona-3, 5, 7-triene-1, 9-dioic acid, XXIX (3)

Diethyl nona-2, 7-diyne-1, 9-dioate, II (R = OEt), (10 g.) was refluxed for 30 minutes with ethanol (50 ml.) and 4N aqueous sodium hydroxide (50 ml.). The solution was then evaporated under reduced pressure to ca. 50 ml., cooled and carefully acidified. The precipitate crystallised from ethanol to give the trienoic acid, XXIX, as yellow needles, m.p. 198-202°. (Found: C, 58.25; H, 6.5. $C_{11}H_{14}O_5$ requires C, 58.4; H, 6.2%). λ_{max} (in EtOH) 327 mμ. (log ε , 4.69) disappearing

irreversibly on addition of acid. Extraction of the mother liquor from the above reaction with chloroform gave homophthalic acid, identical (i.r. and mixed m.p.) with an authentic sample. The dimethyl ester of the trienoic acid XXIX (prepared in methanol-ether with an excess of diazomethane, melted at 91-91.5°. (Found: C, 60.6; H, 7.0; M.W. (mass spectrometry), 254. $C_{13}H_{18}O_5$ requires C, 61.4; H, 7.1%; M.W., 254). λ_{max} (in EtOH) 333 m.μ. (log ε , 4.10).

BIBLIOGRAPHY

(1) D. I. Wilkinson, Ph.D. Thesis, Queen's University of Belfast, 1957.

(2) Parker, Raphael and Wilkinson, J., 1959, 2433.

(3) Experiments carried out by Dr. N. J. McCorkindale.

(4) N.M.R. Spectra Catalogue, Varian Associations, California, Vol. 2, 1963, No. 652.

(5) Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, Pergamon, London, 1959.

(6) Barton, Jeger, Prelog and Woodward, Experientia, 1954, 10, 81.

(7) Dudek, J. Amer. Chem. Soc., 1963, 85, 694.

(8) Chem. Pharm. Bull., 1963, 243.

(9) Stothers in Technique of Organic Chemistry, Ed. Weissberger, Vol. XI, Interscience, London, 1963, p.209.

(10) Gensler in Heterocyclic Compounds, Ed. Elderfield, Vol. IV, Wiley, London, 1952.

(11) King, King and Manning, J., 1957, 563.

(12) Gibbs, J. Biol. Chem., 1927, 72, 649.

(13) Buu-Hoi, Bull. Soc. chim. France, (5), 1945, 12, 313.

(14) McCorkindale and McCulloch, unpublished results.

(15) Bluhm, Spectrochim. Acta, 1958, 13, 93.

(16) Budzikiewicz, Djerassi and Williams, Interpretation of Mass Spectra of Organic Compounds, Holden-Day, Inc., San Fransisco, 1964.

(17) Willhalm, Thomas and Gautschi, Tetrahedron, 1964, 20, 1185.

(18) Jones and Mueller, J. Org. Chem., 1962, 27, 2356.

(19) Kapil and Joshi, J. Indian Chem. Soc., 1959, 36, 505.

(20) Jackman and Wiley, J., 1960, 2886.

(21) Barker, Foster, Lamb and Jackman, Tetrahedron, 1962, 18, 177.

(22) Weedon and Woods, J., 1951, 2687.

(23) Scott, Interpretation of the Ultra-Violet Spectra of Natural Products, Pergamon Press, London, 1964, p. 58.