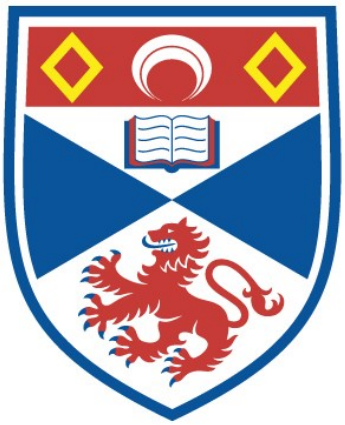
SYNTHESIS OF SUBSTANCES RELATED TO RUBREMETINIUM SALTS

David Thackray

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



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SYNTHESIS OF SUBSTANCES RELATED TO RUBREMETINIUM SALTS

being a thesis presented by David Thackray, B.Sc.

to the University of St. Andrews,

in application for the Degree of

Doctor of Philosophy

ms 2177

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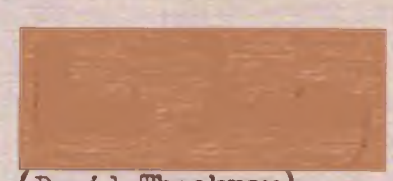
DECLARATION

I hereby declare that the following thesis is a record of experiments carried out by me, that the thesis was composed by me, and that it has not been previously presented for a higher degree. The experiments were carried out in the Chemical Research Laboratory of the University of St. Andrews, under the direction of H. T. Openshaw, M.A., D. Phil.



(David Thackray)

27th February, 1961.

CERTIFICATE

I certify that David Thackray, B. Sc., has spent thirteen terms at research work under my direction, that he has fulfilled the conditions of Ordinance No. 16 (St. Andrews), and that he is qualified to submit the accompanying thesis in application for the degree of Ph. D.

(H. T. Openshaw, M. A., D. Phil)

Director of Research.

20th March 1961.

UNIVERSITY CAREER AND RESEARCH EXPERIENCE

The author entered Manchester University in October, 1949. He passed out of this University in June, 1952 with the degree of B. Sc. (Honours 2 (ii)), and in September, 1952 began research at the University of St. Andrews. At the end of his second year of research, the author was awarded a St. Andrews University Post-Graduate Scholarship. The experimental part of the research was completed in December, 1955.

PUBLICATIONS

Part of the research is mentioned in :

Openshaw, Chemical Society Special Publication No.3, 1955, p.32.

ACKNOWLEDGEMENTS

Many thanks are due to Professor J. Read for his kindly interest and encouragement. The author is indebted to his supervisor, Dr. H. T. Openshaw, and to Mr. D. M. G. Lloyd, for their valuable criticisms and helpful suggestions.

The author is very grateful to the University Authorities for generous finanical assistance. Finally, the author wishes to thank his father, without whose great generosity the research could not have begun.

PART I

INTRODUCTION

The intensely orange-red rubremetinium salts with which this thesis is concerned are oxidation products of the alkaloid emetine. Emetine is the principal alkaloid of "ipecacuanha" or "ipecac," which is the dried root of a shrub. This shrub, which is a forest shrub, is found in various parts of the world (see below). It is low and straggling, having a short green stem with few leaves; it bears white flowers and purple berries. (1).

Emetine is obtained commercially from two varieties of the shrub. The first variety, Cephaelis Ipecacuanha A. Rich, is indigenous to Brazil and Bolivia and is also cultivated in India and Malaya. The second variety, Cephaelis Acuminata Karsten, is cultivated in Columbia and Venezuela. (2). In a typical extraction process (1), the dried root and rhizome of the shrub are extracted with alcohol, which is then concentrated. The concentrate is diluted with water, and shaken with an ether to remove fat, resin etc. It is then basified with ammonia, which liberates the alkaloids. The alkaloids are extracted with ether; the ethereal solution is washed with dilute alkali, which removes the cephaeline, then with dilute acid, which extracts the emetine as a crude aqueous salt. The crude emetine is purified by recrystallisation of the hydrobromide or hydriodide. Pure emetine is usually described as a white, amorphous solid, m.p. 74° (3), but it has recently been obtained

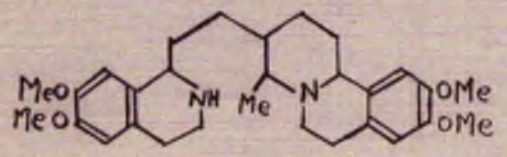
crystalline, m.p. 104-5° (86).

Emetine gives the shrub certain therapeutic properties. The shrub is known in Brazil as "ipecacuanha", meaning "the little way-side plant which causes vomiting". (4). As early as the six-teenth century, ipecacuanha root was used medicinally in Brazil. About the middle of the seventeenth century it was introduced into Europe, where it was used as an expectorant and emetic, and, in the eighteenth century, to cure amoebic dysentery. (2). In 1817, Pelletier and Magendie (5) prepared from ipecauanha root a crude, alkaloidal extract which they named "emetine". In 1894, Paul and Cownley (6) applied this name to the principal alkaloid of the extract, which they had isolated in a pure form. In 1912, Rogers (7) showed that pure emetine can cure amoebic dysentery.

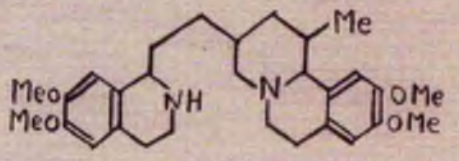
Emetine has a number of uses (2,4). It may be used as an expectorant and emetic; for this it is administered orally in doses of 10-20 mg. It finds its main use, however, in the treatment of amoebic dysentery: it is effective when other drugs fail e.g. in curing amoebic abcesses, and amoebic hepatitis. For dysentery, it is administered subcutaneously or intramuscularly, as it then has little emetic action; the dosage is 60-100 mg. Prolonged treatment causes toxic effects such as damage to the heart. Excretion of the drug is erratic, so it may accumulate; the toxic dose for man by

accumulation is 1.1-1.8 g.

The therapeutic value of emetine added impetus to work carried out on the elucidation of its molecular structure. In this field, the first significant advance was made in 1913, by Carr and Pyman (3). These workers performed exhaustive analyses on emetine and some of its salts, and thus established its molecular formula: $C_{29}H_{40}O_4N_2$. Further experimental evidence was provided by degradative experiments (e.g. 8,9,10) and spectral studies (11). In 1925, Robinson (12) suggested on biogenetic grounds the structure I. This was modified in 1927 to II by Brindley and Pyman (12), in order to provide a logical explanation of the formation and properties of the rubremetinium salts. Formula II was in satisfactory agreement with most of the evidence available at the time. It thus became generally accepted, and remained virtually unchallenged for many years. Not until 1949 was it finally established, by Späth, Pailer and Porschinski (13) and by Battersby, Openshaw and Wood (14), that the correct structural formula for emetine is III.



I



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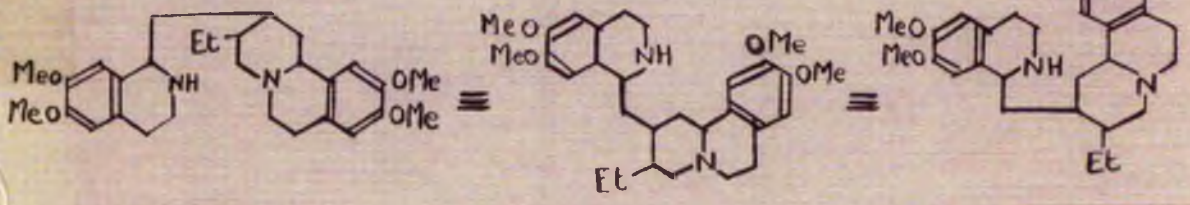


III

The problem of the structure of emetine, which had engaged the attention of many chemists over a long period of time, was thus eventually solved. In the process, however, other problems had arisen: the structures of some of the degradation products of emetine were still in doubt, in particular, the structure of the rubremetinium salts.

In 1952, the evidence available was still insufficient to decide between various structures proposed for the rubremetinium salts. The author has therefore attempted togather further evidence. The evidence available in the literature is discussed in Part II, and the author's work in Parts III and IV, of this thesis.

The substances which the present author has termed rubremetinium salts have more than one name in the literature. Karrer uses the name "dehydroemetin." Pyman, who discovered the salts, at first used "rubremetine." It was later found, however, that the salts are quaternary, so Pyman applied to the quaternary ion the name "rubremetinium." This name will be used throughout the present thesis.

PART II

THE CHEMISTRY OF RUBREMETINIUM SALTS

As stated in the introduction, the rubremetinium salts were first obtained in degradation experiments on emetine.

The oxidation of emetine with vigorous oxidising agents causes breakdown of the molecule into smaller fragments. Certain mild acidic oxidising agents however, do not break the carbon skeleton: they dehydrogenate it in a stepwise fashion, the ultimate product being a rubremetinium salt.

Several dehydrogenating agents of the above type have been used. These include: aqueous ferric chloride (3), iodine in alcohol (16, 9), bromine in chloroform (16, 17) and mercuric acetate in dilute acetic acid (15). All of these reagents convert emetine to a rubremetinium salt. (The last reagent is convenient, and gives the highest yield (45%), and is thus the preferred reagent for the conversion). With these reagents, two intermediate dehydrogenation products have also been isolated: O-methylpsychotrine and tetradehydroemetine. Palladium can also be employed to dehydrogenate emetine. The reaction then follows a different course, giving emetamine (XII, see p.14) (87).

A rubremetinium salt was first prepared in 1914 by Carr and Pyman (3), by heating emetine hydrochloride with an excess of aqueous ferric chloride. The aqueous solution was extracted with chloroform, and the extract was evaporated, giving a black resin.

The resin was extracted with water, and the extract crystallised from water, giving rubremetinium chloride in a yield of 35%.

O-methylpsychotrine was first found as a constituent of ipecacuanha in 1917 by Pyman (16). Its molecule contained two hydrogen atoms less than that of emetine. It was readily oxidised to rubremetinium salts, and Pyman showed it to be an intermediate in the dehydrogenation of emetine. When emetine was treated with iodine in alcohol (16), in the proportion of eight atoms of iodine per molecule of emetine, the only product isolated was the rubremetinium salt. When only two atomic proportions of iodine were used, however, it was possible to isolate a 5% yield of O-methylpsychotrine.

Tetradehydroemetine was obtained in 1949 by Battersby and Openshaw (15), by treating emetine with mercuric acetate in dilute acetic acid. With excess of this reagent, the main product was once again a rubremetinium salt, but a small yield of a new base was obtained as its hydrogen oxalate. Analysis and hydrogenation indicated that it had been formed from emetine by removing four hydrogen atoms; it was therefore named tetradehydroemetine. When only four atomic proportions of mercuric acetate were used, the yield of rubremetinium salt was greatly reduced, and the yield of tetradehydroemetine was increased to 27%. In 1951, Hazlett and McEwen (18) reported the isolation of a 28% yield of a more stable, isomeric base; they named this isotetradehydroemetine.

It is now appropriate to consider the relationship of the dehydrogenation products (D) to emetine (E), and to one another. This will be done with the help of (i) the molecular formulae (F) indicated by analysis (3, 16, 15; emetine: 3); (ii) the results of attempts to dehydrogenate the products further, and (iii) the results of attempts to hydrogenate them.

(i) D:	Rubremetinium Chloride	O-Methylpsychotine	Tetradehydroemetine
F_D:	$C_{29}H_{33}O_4N_2Cl$	$C_{29}H_{38}O_4N_2$	$C_{29}H_{36}O_4N_2$
F_E:	$C_{29}H_{40}O_4N_2$	$C_{29}H_{40}O_4N_2$	$C_{29}H_{40}O_4N_2$
F_D-F_E:	-8H +HCl	-2H	-4H

(ii) When rubremetinium salts are treated with the above-mentioned dehydrogenating agents, there is little tendency to further reaction; under similar conditions, however, O-methylpsychotrine (16, 19) and tetradehydroemetine (15) are each converted to a rubremetinium salt.

(iii) From the hydrogenation of rubremetinium salts (described later) no one has ever isolated emetine or any of its stereoisomers. The hydrogenation of O-methylpsychotrine, however, gives emetine and isoemetine (16, 20); and the hydrogenation of tetradehydroemetine has given emetine and two new stereoisomers on one occasion (18), and isoemetine (78%) on another occasion. The evidence (i), (ii) and (iii) leads to the following conclusions:

(a) The dehydrogenation of emetine yields O-methylpsychotrine, tetradehydroemetine, and rubremetinium salts by the elimination of

2, 4 and 8 atoms of hydrogen respectively.

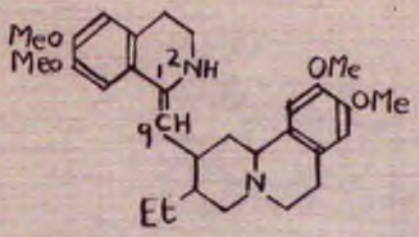
(b) O-Methylpsychotrine and tetradehydroemetine are intermediates in the formation of rubremetinium salts.

(c) The skeleton of the emetine molecule, basically unaltered in the formation of O-methylpsychotrine and tetradehydroemetine, suffers a more fundamental change in the transformation to a rubremetinium salt.

Since O-methylpsychotrine and tetradehydroemetine are intermediates in the formation of rubremetinium salts, a study of the structures of these intermediates affords a natural approach for investigating the structure of the salts.

As suggested by the above evidence, O-methylpsychotrine is probably formed from emetine III by converting a single bond to a double bond. The double bond was allocated by Pyman (16) to the 1: 9-position, as in structure IV. Pyman chose this position rather than the 1: 2-position, because he was able to prepare an N-acyl derivative. Openshaw and Wood (23), however, noted that most of the above-mentioned dehydrogenating agents are able to convert a tetrahydroisoquinoline into a 3: 4-dihydroisoquinoline. They also noted the work of Bills and Noller (21) which had shown that, in many 1-substituted, 3:4-dihydroisoquinolines, the double bond prefers the 1:2-to the 1:9-position. Openshaw and Wood therefore studied the absorption spectrum of O-methylpsychotrine. The spectrum contained maxima corresponding to those of a 3:4-dihydroisoquinoline system, and to those of a tetrahydroisoquinoline.

This suggests that in O-methylpsychotrine the double bond does prefer the 1:2-position, and that the structure of O-methylpsychotrine is V. Formation of the N-acyl derivative probably involves tautomerisation to the structural type IV.



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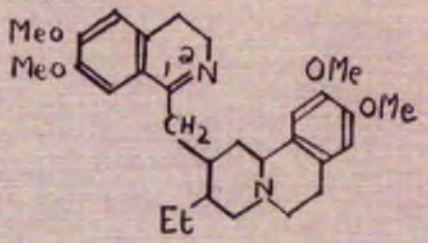
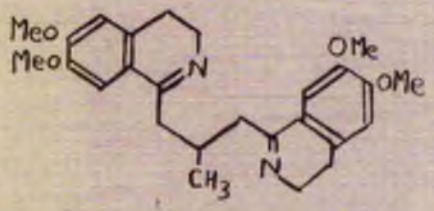


V

Tetradehydroemetine is presumably formed from O-methylpsychotrine by introducing a further double bond. Openshaw and Wood (23) compared the absorption spectrum of the hydrogen oxalate of tetradehydroemetine with the absorption spectrum of the hydrogen oxalate of the base VI. The two spectra were closely similar, which suggests that tetradehydroemetine has the structure VII. This conclusion is, however, challenged by some results of Hazlett and McEwen (18). When these authors prepared tetradehydroemetine, they also isolated an isomeric base having virtually identical ultra-violet absorption. They named this isotetradehydroemetine. Hydrogenation of tetradehydroemetine yielded emetine, isoemetine and two new stereoisomers of emetine, whilst hydrogenation of isotetradehydroemetine yielded emetine only. The formation of the two isomeric dehydrogenation products cannot be accommodated by structure VII. Openshaw (23) stated that the results are most

easily interpreted by formulating the bases as cis-trans isomers of the structure VIII. He has also commented, however, that several attempts to repeat Hazlett and McEwens' preparation of isotetradehydroemetine have been unsuccessful. It is to be concluded that the structure of tetradehydroemetine is still in doubt. The work done on tetradehydroemetine, therefore, does not yield much information regarding the structure of the rubremetinium salts.



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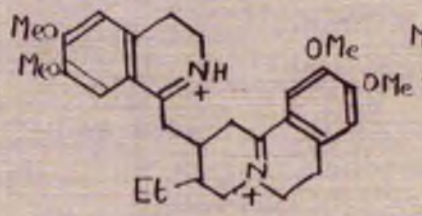

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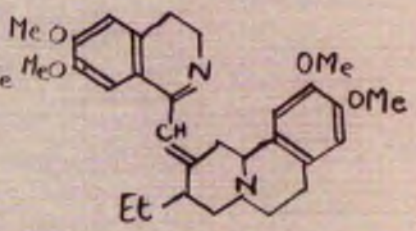


VIII

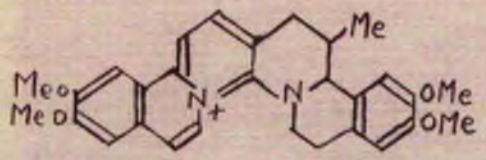
Some fundamental properties of rubremetinium salts will now be considered briefly. Rubremetinium chloride, bromide or iodide are readily precipitated from a cold, aqueous solution of the chloride, by adding concentrated solutions of hydrochloric acid, potassium bromide or potassium iodide respectively (3). This shows that, in all the rubremetinium salts produced by all the various dehydrogenating agents, it is the same organic cation that we are studying: the rubremetinium ion. Rubremetinium salts are intensely orange-red; they possess a well-defined ultra-violet absorption spectrum. They are optically active. The rubremetinium ion cannot be made from N-methylemetine (12), or emetamine (12, 20).

As we have seen (p.7), the ion is formed from the emetine molecule by the elimination of eight hydrogen atoms. No other atoms are eliminated: the ion contains two nitrogen atoms; yet, significantly, one of these is practically non-basic. (3). That the other nitrogen atom is quaternary has been shown (15) by potentiometric titration with 0.Cl normal sodium hydroxide. The alkaline solution showed no fall in pH on standing, which indicated that no appreciable amount of pseudo-base had been formed. When (15) an aqueous solution of rubremetinium chloride was treated with silver oxide, the resulting solution was deep red, halogen-free and strongly alkaline. A sample of this alkaline solution was treated with hydrochloric acid, and the rubremetinium chloride was regenerated. When another sample of the solution was evaporated, two solid products were obtained. One solid was a bright, orange-red and was microcrystalline. It dissolved in water to give an alkaline solution, which, on treatment with hydrochloric acid, again regenerated rubremetinium chloride. This solid was probably the quaternary hydroxide. The other solid was orange-yellow, amorphous, and insoluble in water but soluble in ether. It was probably a pseudo-base or anhydro-base.

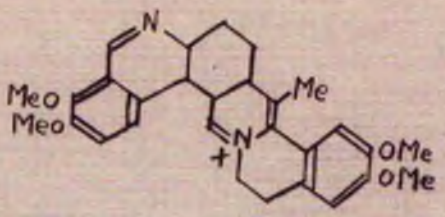
Most of the above properties of rubremetinium salts were described soon after the salts had been discovered. As time passed, further experimental evidence accumulated, and a succession of structural formulae were suggested for emetine, and for the rubremetinium ion. In 1949, the structure of emetine was elucidated;

but the structure of the rubremetinium ion remained in doubt, and further structures were proposed. The various structural formulae proposed for the rubremetinium ion will now be considered.

In the introduction (p.3) we noted that, in 1925, Robinson (12) suggested structure I for emetine. Now the rubremetinium ion behaves as if one of the nitrogen atoms were non-basic (3), and Brindley and Pyman (12) considered that structure I for emetine was incompatible with this. In 1927, therefore, Brindley and Pyman (12) suggested that emetine should be represented by II, and the rubremetinium ion by IX. Formula II differs from I only in the position of the C-methyl group. Owing to this difference, however, the conversion of emetine to the rubremetinium ion can be represented as involving a cyclisation. The structure IX contains an amidine type of grouping, and might indeed be expected to behave as a monoacidic base. (Amidines are characteristically monoacidic, the cation being stabilised by resonance). Pyman's structure II for emetine thus accounted for the behaviour of the nitrogen atoms of the rubremetinium ion; it was consistent with the fact that N-methylemetine will not yield a rubremetinium - like salt, and it was also in agreement with Robinson's biogenetic theories. Pyman's structures for emetine and the rubremetinium ion (II and IX) thus had much to commend them, and they were favourably received.



IX



X

In the same year (1927), Staub (17) pointed out that Pyman's structure IX contains two hydrogen atoms less than the number indicated by analysis. Staub advanced alternative structures for emetine, and for the rubremetinium ion: X. He represented emetine, however, as a derivative of dihydrobenzene. There was little evidence to support this, and his structures never came into general favour. His objection to IX remained; but it seemed unimportant, as the analysis of rubremetinium salts (p. 30) is subject to considerable error. Staubs' objection did not therefore interfere with the general acceptance of Pymans' structure IX.

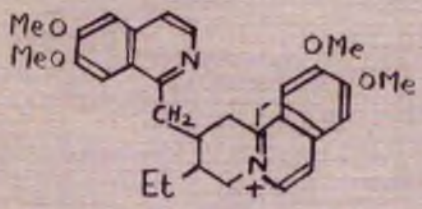
Pymans' structures for emetine and the rubremetinium ion remained generally accepted until 1948. During the intervening period of time there were no significant additions to the chemistry of these substances.

In 1948, Karrer (20) found that rubremetinium bromide can be reduced by zinc and acid, to give a crystalline, optically active product: $C_{29}H_{36}O_4N_2$. The reduction can be represented by:

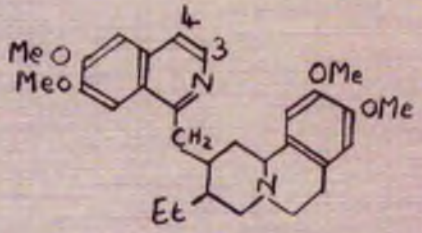
$$C_{29}H_{33}O_4N_2Br + 4H \longrightarrow C_{29}H_{36}O_4N_2 + HBr.$$

The product was thus named tetrahydrodehydroemetine. This product resisted catalytic hydrogenation. Karrer considered that this resistance could not be explained in terms of the structures proposed by Pyman (IX) or Staub (X) for the rubremetinium ion; Karrer proposed an alternative partial structure.

Shortly afterwards, it was shown (13,14) that emetine has the structure III. This is incompatible with the structures suggested for the rubremetinium ion by Pyman (IX), and Staub (X), and hence disposes of them. Karrer's partial structure of the ion now assumes the form XI. This structure contains an isoquinolinium ring, which, by analogy with known cases, should be preferentially reducible to a tetrahydrogenated structure XII.



XI



XII

Karrer's structure XI for the rubremetinium ion thus accounts well enough for the formation of tetrahydrodehydroemetine. It is unsatisfactory, however, in some other respects:

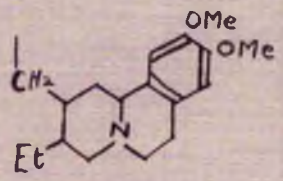
(i) It is likely that a substance of the structure XI would be reducible to emetine (III), or a stereoisomer. No such reduction of a rubremetinium salt has been observed.

(ii) Karrer's structure XI does not account for the colour of the

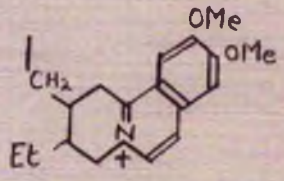
rubremetinium ion.

(iii) It does not account for the lack of basicity of one of the nitrogen atoms.

(iv) (23) When emetine was shown to have the structure III, it followed from work of Brindley and Pyman that the structure of emetamine (a minor alkaloid) is XII. This has recently been confirmed by Battersby (28). When Karrer proposed this same structure for tetrahydrodehydroemetine, he assumed that the two substances must be stereoisomers. If the formulae of emetine (III) and emetamine (XII) are compared, it can be seen that both contain the grouping XIII. If the rubremetinium ion has Karrer's structure XI, the oxidation of emetine to this ion must involve conversion of grouping XIII to XIV. Now emetamine contains the same grouping XIII, hence oxidation by the same reagents would be expected to effect an analogous conversion: emetamine should also be oxidisable to the rubremetinium ion. In fact, although oxidation of emetamine does give a red quaternary ion (a "rubremetaminium" cation) this ion is not identical with the rubremetinium ion (12, 20).

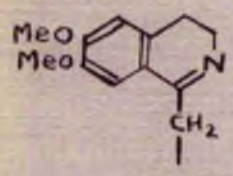


XIII

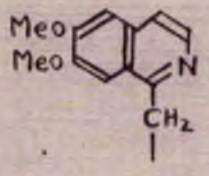


XIV

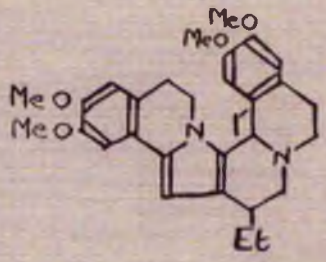
(v) If the formulae of O-methylpsychotrine (V, p. 9) and 3 : 4-dihydro-6 : 7-dimethoxy-1-methylisoquinoline are compared, it can be seen that both contain the grouping XV. If the rubremetinium ion has Karrer's structure XI, the oxidation of O-methylpsychotrine to this ion, with mercuric acetate, must involve conversion of grouping XV to XVI. The above isoquinoline contains the same grouping XV, so treatment of it with mercuric acetate would be expected to effect an analogous conversion. In fact however, 3:4-dihydro-6:7-dimethoxy-1-methylisoquinoline is not dehydrogenated by the mercuric acetate reagent (23).



XV



XVI



XVII

(vi) Battersby and Openshaw (23) carried out a catalytic hydrogenation of rubremetinium chloride. The hydrogenation was conducted in ethanol. It was found to proceed more readily in the presence of sodium acetate, which was taken as an indication that the quaternary nitrogen is involved. Two isomeric products were isolated; they were named α- and β-dihydrorubremetines. (XVII; see next paragraph, (vi)). The reaction required 1.0 moles of hydrogen. This was absorbed readily, then absorption ceased rather abruptly. The absorption of only 1.0 moles of hydrogen is not readily accounted for

in terms of Karrer's structure XI.

The points (i)-(vi) listed above suggest that Karrer's formula XI for the rubremetinium ion is incorrect.

In 1949, Battersby, Openshaw and Wood (24) advanced another structure for the rubremetinium ion: XVIII. It can be seen that the above criticisms (i)-(vi), levelled against Karrer's structure XI, do not apply to Openshaw's structure:

(i) Openshaw's structure XVIII contains an additional ring not present in emetine (III). It is not to be expected, therefore, that it would be reducible to emetine or a stereoisomer.

(ii) Openshaw's structure represents the ion as having a cyanine dye type of structure: a resonating system of double bonds permits the two nitrogen atoms to share a single positive charge.

The extensive resonance would account for the colour of the ion.

(iii) The structure would behave as a monoacidic base.

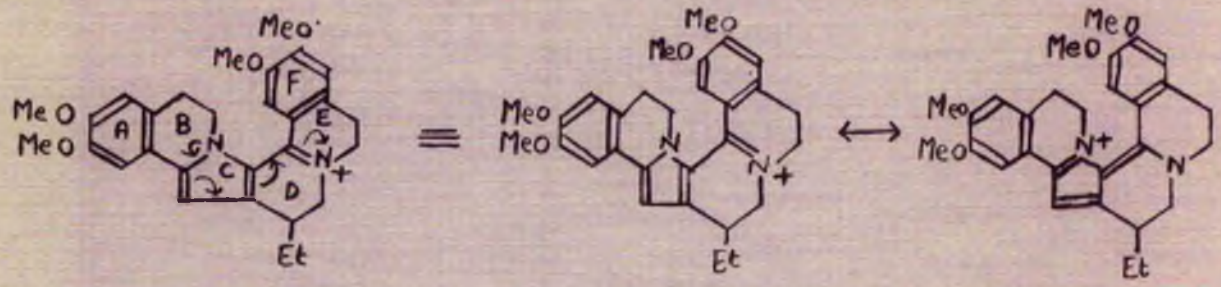
(iv) Emetamine (XII) possesses a double bond in the 3:4-position, which is not present in Openshaw's structure for the rubremetinium ion. Dehydrogenation of emetamine, therefore, would not be expected to give Openshaw's structure; but it might give an analogous structure, with a double bond in the 3:4-position.

(v) Openshaw's structure is consistent with the fact that 3:4-dihydro-6:7-dimethoxy-1-methylisoquinoline is not dehydrogenated by mercuric acetate.

(vi) It accounts for the fact that when the rubremetinium ion is

hydrogenated catalytically, two (α and β) dihydrorubremetines are formed. These were assigned the structure XVII, the two isomers differing in their configuration at $C_{1'}$.

Openshaw's structure is also consistent with the fact that N-methylemetine does not yield a rubremetinium-like ion.



XVIII

Openshaw's structure XVIII for the rubremetinium ion differs from all the previous ones in that it contains a pyrrole ring. Positive evidence for the presence of this ring was obtained (23) by repeating Karrer's reduction of rubremetinium bromide with zinc and acid. The crude product gave a red pine-shaving reaction, and a blue-green colouration with Ehrlich's reagent. Both of these colour reactions are typical of pyrroles.

Openshaw had not as yet explained how his structure for the rubremetinium ion could account for the formation of tetrahydrodehydroemetine. It will be seen, however, that he later gave an adequate explanation.

Openshaw's structure XVIII drew criticisms, and reports of further experiments, from some other workers in the field: Karrer,

and Hazlett and McEwen.

In 1950, Karrer (22) found that rubremetinium bromide could be reduced by lithium aluminium hydride to an unstable crystalline compound. From its analysis, and from the known reduction of simple isoquinolinium salts to 1:2dihydrocompounds. this compound was named ortho-dihydrorubremetine. Ortho-dihydrorubremetine could be reduced further by hydrogen in the presence of platinum. After one molar proportion of hydrogen had been absorbed, two products were isolated: tetrahydrodehydroemetine, and another, alleged to be an isomer: "isotetrahydrodehydroemetine." Karrer drew an analogy between his reduction of rubremetinium bromide and known reductions of isoquinolinium salts. He contended that his results confirmed the presence of a fully aromatic isoquinolinium ring in the rubremetinium ion, and that they invalidated Openshaw's structure XVIII. He also criticised this structure on the grounds that it contains two dihydropyridine rings; these, he argued, would be highly susceptible to further dehydrogenation.

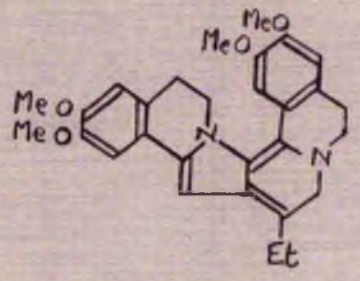
In 1951, Hazlett and McEwen (18) heated rubremetinium chloride with alcoholic sodium hydroxide. They obtained an unstable crystalline base which they named dehydrohalorubremetine. This substance could not be converted back to rubremetinium chloride by hydrochloric acid. On catalytic hydrogenation, the substance gave a mixture, from which they isolated an optically inactive, crystalline compound which they named tetrahydrodehydrohalorubremetine. These reactions, stated

Hazlett and McEwen, could not be accounted for by Openshaw's structure for the rubremetinium ion. They also argued that, if his structure were correct, tetrahydrodehydroemetine would contain a pyrroline ring; and pyrroline rings are readily hydrogenated, whereas (20) tetrahydrodehydroemetine is resistant to hydrogenation.

In 1952, Openshaw and Wood (23) replied to Karrer's criticisms. They suggested that he had misinterpreted his own results. The lithium aluminium hydride reduction of Karrer's structure XI would introduce a new asymmetric centre (at $C_{1'}$) and give two stereoisomeric products. Karrer had isolated only one product. The subsequent reduction would not create further asymmetry, yet from it Karrer had isolated two products. Openshaw and Wood further noted a pronounced resemblance between Karrer's "isotetrahydrodehydroemetine" and their α-dihydrorubremetine, in both melting point and laevorotation. They also noted that Karrer's own analysis result corresponded more closely to a dihydrorubremetine. In view of these facts, they suggested that Karrer's "isotetrahydrodehydroemetine" was, in fact α-dihydrorubremetine. In fact, this was later confirmed by Hazlett and McEwen (25), (who, however, agreed with Karrer in formulating the compound as a tetrahydro derivative). Karrer thus isolated only one isomer of tetrahydrodehydroemetine, and his results do not in any way favour his structure XI for the rubremetinium ion. As regards Openshaw's own structure XVIII, it was pointed out that the dihydro-pyridine rings are fused to other aromatic rings, and

form part of a resonating structure: they would not be expected to behave like isolated dihydropyridine rings. Ring D is fused to a pyrrole ring. Ring E, fused to a benzene ring, is part of a 3:4-dihydroisoquinoline system; it would certainly be expected to be stable to halogens (26) and mercuric acetate (23).

In the same paper (23), Openshaw and Wood also replied to the criticisms of Hazlett and McEwen. Openshaw and Wood suggested that dehydrohalorubremetine was probably XIX. As Hazlett and McEwen had admitted, the "tetrahydrodehydrohalorubremetine" had been prepared from a crude material Openshaw and Wood doubted whether the name was appropriate, and considered it more likely that the product was a racemic dehydrorubremetine. Openshaw and Wood did not yet suggest a structure for tetrahydrodehydroemetine, but, as will be seen later, it is not necessary to assume that this substance contains a pyrroline ring, as was stated by Hazlett and McEwen.



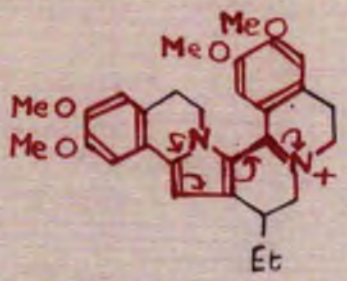
XIX

Much progress had now been made in elucidating the structure of the rubremetinium ion. In 1949, the number of structures possible

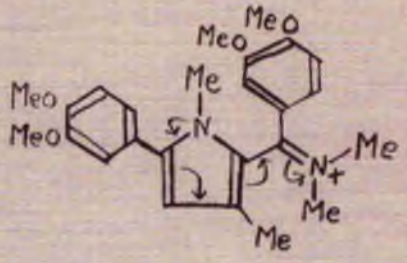
had been greatly reduced by the elucidation of the emetine structure. Of the structures so far suggested for the ion, only those of Karrer, XI and Openshaw, XVIII remained. Of these two, it seemed that XVIII gave much the better explanation of the experimental evidence. At this point the present author began research. It was decided that he should try to confirm that the ion has the structure XVIII.

For confirming that the rubremetinium ion has the structure XVIII, synthetic methods seemed more promising than degradative methods. In XVIII, the controversial feature is the pyrrole ring. It therefore seemed that the synthesis of XVIII from a simple pyrrole, and a comparison of the product with the rubremetinium ion, would provide the desired confirmatory evidence. A survey of the methods available indicated that such a synthesis of XVIII would be rather formidable. It was decided, however, that the idea might be used in a modified form. A substance with the structure XVIII would have a well-defined light absorption in the ultra-violet and visible regions of the spectrum. This would be mainly due to the parts of the ion marked (in XX) in red, which thus constitute its chromophoric system. By eliminating parts of the carbon skeleton of XX, it can be reduced to a simpler structure such as XXI. This contains the same chromophoric system as XX, but, since it is simpler, its synthesis would be expected to be easier. If such a simpler substance were synthesised, and if its absorption spectrum were found to be closely similar to that of the rubremetinium ion. it

would strongly suggest that the two chromophoric systems were identical: it would thus establish the structure of the rubremetinium ion almost as satisfactorily as by the total synthesis. It was decided that the above method should be adopted for the attempt to test the correctness of the structure XVIII.



XX

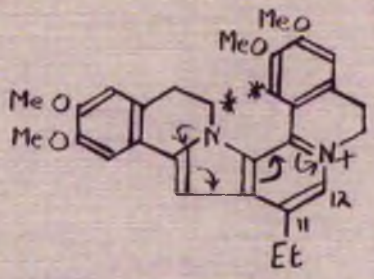


XXI

While the author's work progressed, other workers made further significant contributions to the chemistry of the rubremetinium salts. These will now be described.

In 1953, Woodward proposed yet another structure, XXII, for the rubremetinium ion. Woodward's structure (published by Tietz and McEwen (25)) was a modification of Openshaw's structure XVIII. The modification was, perhaps, suggested because Openshaw's structure had not yet provided a satisfactory explanation for the formation of tetrahydrodehydroemetine. Woodward's structure XXII differs from XVIII in having an additional double bond at C_{11}-C_{12}. This requires rubremetinium salts to have the molecular formula: $C_{29}H_{31}O_4N_2X$, which, however, is still compatible with the analytical evidence. With the introduction of the double bond, C_{11} has lost its asymmetry;

yet the rubremetinium salts are optically active. For this reason, the structure XXII had been rejected by Openshaw. Woodward, however, attributed the optical activity to steric interference at the positions marked * , and a study of models of the structure show that this is feasible (62).



XXII

In the above-mentioned paper (25), Tietz and McEwen described repetitions of some previous hydrogenations. Repeating their own experiments on the hydrogenation of crude dehydrohalorubremedine, they found that it absorbed about 1.8 molar proportions of hydrogen. It is noteworthly that the hydrogen absorbed was not an approximately integral molar proportion. This infers that the reaction was not straightforward. It is possible that some of the hydrogen was absorbed by aromatic rings. Moreover, the starting material was crude, and the yields of product isolated were small. It is thus the opinion of the present author that no deductions of significance can be made from this hydrogenation, particularly since other quantitative hydrogenations recorded by these authors have

subsequently been proved inaccurate (84). Tietz and McEwen also repeated Karrer's preparation (22) of orth-dihydrodehydroemetine, and its hydrogenation to tetrahydrodehydroemetine and "isotetrahydrodehydroemetine." They repeated the catalytic hydrogenation (23) of rubremetinium chloride. After the initial uptake of hydrogen, they added fresh catalyst, and continued the hydrogenation for a much longer period. They found that this increased the hydrogen uptake from one to two moles. From the product, they isolated tetrahydrodehydroemetine, and "isotetrahydrodehydroemetine." They showed that the latter was identical with α-dihydrorubremetine, as Openshaw and Wood had already suggested (23). By interrupting the hydrogenation after one mole of the gas had been absorbed, Tietz and McEwen were able to isolate β-dihydrorubremetine. This was subjected to further hydrogenation, in ethanol containing glacial acetic acid; it absorbed another molar proportion of hydrogen quite readily. Karrer's formula XI, apparently no longer in favour, was not even mentioned in this paper. Instead, experiments were interpreted in terms of Woodward's formula XXII: β-dihydrorubremetine was regardedasa dihydrorubremetine, and tetrahydrodehydroemtine and α-dihydrorubremetine were both regarded as tetrahydro-derivatives, with the structure XVII (p.16). This structure had already been assigned to the α- and β-dihydrorubremetines by Openshaw. It is interesting to note that, in the case of α-dihydrorubremetine, Tietz and McEwen's formula is the same as Openshaw's though derived by

quite different reasoning.

The evidence so far presented leaves room for widely differing views regarding the structure of the rubremetinium ion; but recent work (1955) by Openshaw (27) has greatly clarified the situation. Openshaw first reviewed the properties of the α and β-dihydrorubremetines. (Openshaw's formula: XVII, p.16). Both are formed from rubremetinium chloride with the absorption of almost exactly one molar proportion of hydrogen. Both products analyse as dihydrorubremetines. Both are readily reoxidised to rubremetinium salts, and when this reaction is carried out with iodine, both consume about the same amount of reagents: 1.16 and 1.29 molar proportions respectively. More recently, both have been hydrogenated to tetrahydrodehydroemetine. The α-compound melts at 198°, and the β-compound at 202°. The rotation of the α-compound is $[\alpha]_D = -395°$; that of the β-compound is $[\alpha]_D = +406°$. When a mixture of the two compounds is recrystallised from methanol, a complex forms. The rotation of the complex is $[\alpha]_D = +81°$. (All rotations were measured in acetone). Analysis of the complex is consistent with its formulation as:

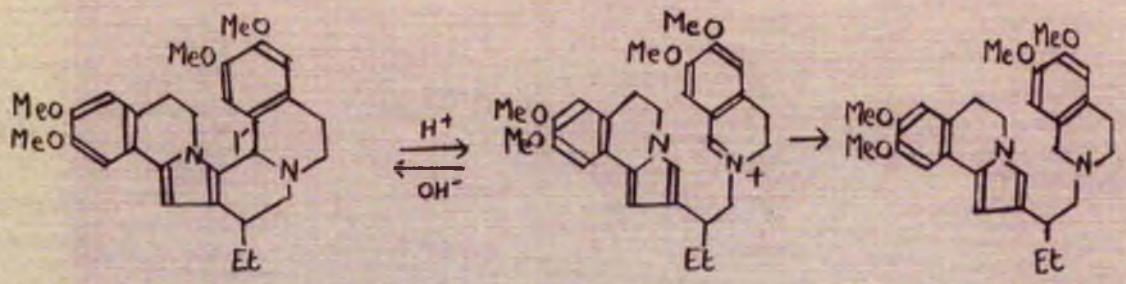
α-isomer. β-isomer. 2 methanol

Taken together, these facts constitute very sound evidence that the α- and β-compounds are diastereoisomeric dihydrorubremetines, (probably differing in their configuration at $C_{1'}$). Furthermore, the reduction of the α-compound to tetrahydrodehydroemetine disposes

of the statement of Tietz and McEwen that the α-and tetra-compounds are steroisomeric. Openshaw also repeated the lithium aluminium hydride reduction performed by Karrer, and showed the product "ortho-dihydrorubremetine" to be a mixture of the α-and β-dihydrorubremetines.

Openshaw had previously (23) noted that the α-and β-dihydrorubremetines resist catalytic hydrogenation in ethanolic solution. He now (27) reinvestigated the hydrogenation with the ethanol replaced by glacial acetic acid. Hydrogen was absorbed rapidly at first, but at a gradually decreasing rate. More than one molar proportion of hydrogen was absorbed, which implies that the aromatic rings of the molecule were being reduced at an appreciable rate. Thus, if the hydrogenation is stopped after the absorption of one mole of hydrogen, an appreciable amount of dihydrorubremetine remains unreduced, and can be isolated. It is mainly α-dihydrorubremetine (Karrer's "isotetrahydrodehydroemetine") which is evidently less readily reduced than the β-compound.

Both α- and β- dihydrorubremetine are reduced to the same product: tetrahydrodehydroemetine. Therefore, the reduction must be a hydrogenolysis involving C_1, (XXIII). Infra-red measurements showed the absence of an >NH group in the product, hence there must have been fission of a carbon-carbon bond. This suggested that the reduction might be represented by the transformations XXIII → XXV, the latter being the structure of tetrahydrodehydroemetine.



XXIII (=XVII) XXIV XXV

The above theory of Openshaw's is supported by the following:

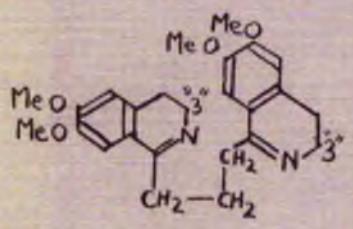
(i) Both the dihydrorubremetines undergo mutarotation in normal hydrochloric acid. In each case the rotation tends towards an equilibrium value of -130°, which is reached in about three hours. This is evidently due to equilibration through the common cation XXIV.

(ii) As will be shown later in the thesis (p. 51), cotarnine reacts with pyrrole, to form a substance which has been named anhydrocotarninepyrrole. This product is hydrolysed by acids, and the cotarnine and pyrrole may be recovered. These changes are analogous to the equilibrium XXIII ⇌ XXIV.

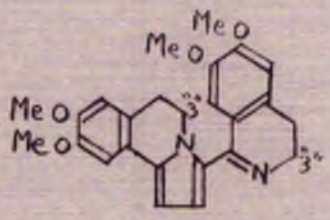
(iii) The hydrogenation of the dihydrorubremetines is extremely slow in a neutral solvent (alcohol); it is more rapid in glacial acetic acid, and even more rapid in alcoholic hydrochloric acid. This is in full agreement with the above theory.

(iv) The theory provides a structure for tetrahydrodehydroemetine which is consistent with its properties.

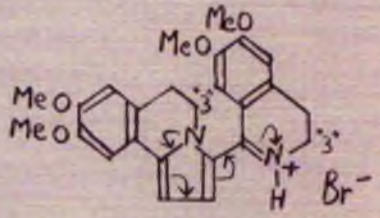
Battersby and Edwards' (27) have also provided some evidence which has a bearing on the structure of the rubremetinium ion. By oxidising the synthetic compound XXVI with mercuric acetate in dilute acetic acid, they obtained a colourless base. This base formed a bright red, crystalline hydrobromide, the absorption spectrum of which was very similar to that of rubremetinium bromide. On catalytic hydrogenation in ethanol, in the presence of sodium acetate, the hydrobromide readily absorbed 1.03 molar proportions of hydrogen. The absorption spectrum of the product was very similar to that of the dihydrorubremetines. It is inferred that these reactions are analogous to those of the rubremetinium salts: that the structure of the colourless base is XXVII, and that of the hydrobromide XXVIII.



XXVI

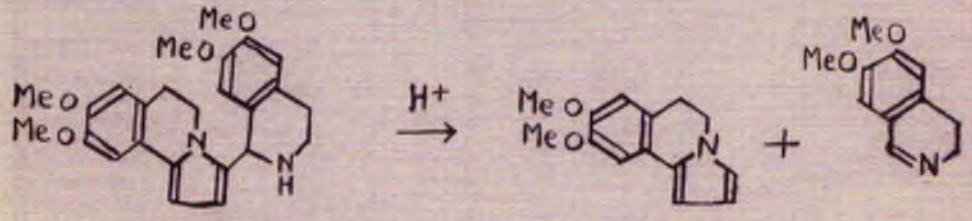


XXVII



XXVIII

Battersby and Edwards' have shown more recently that their reduced base (presumed to be XXVIIIa) is split by acid as indicated below, thus confirming the hypothesis on p.27 (88).



XXVIIIa

LXXVII

We are now in a better position to compare the merits of the structure proposed for the rubremetinium ion by Karrer (XI), Openshaw (XVIII), and Woodward (XXII). As regards Karrer's structure, the objections listed on p. 14 provide sufficient grounds for its rejection. In addition, however, it may be noted that Karrer's structure is unable to account for much of the experimental evidence of the last few paragraphs.

This leaves us with the structures of Openshaw (XVIII) and Woodward (XXII). To these we may apply the following criteria:

(i) Analysis. (a). Analysis of the rubremetinium salts. Openshaw's structure possesses 33 hydrogen atoms while Woodward's possesses 31. It might thus have been expected that analysis would indicate the correct structure. In practice, however, the results are unreliable. The present author gathered a large proportion (16 in number) of the analyses published in the literature (3, 9, 17), and expressed all the percentages of hydrogen as values calculated for anhydrous rubremetinium chloride. The mean value was found to be 6.78%, with a standard deviation of 0.21%. H_{33} (Openshaw's structure) corresponds to 6.42%; H_{31} (Woodward's) corresponds to 6.06%. The mean value thus differs considerably from both of the values suggested by chemical evidence, and this suggests that the error involved in the analyses is not entirely random. The error may be attributed to the large molecular weights of the salts, and the difficulty of obtaining them anhydrous without causing

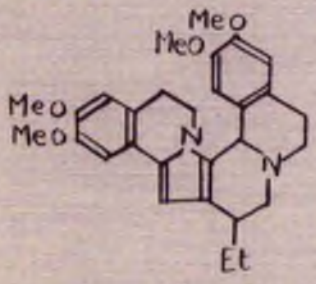
slight decomposition. The above analyses are slightly in favour of Openshaw's structure, but can not be said to constitute an effective criterion.

(i) (b) The analysis of tetrahydrodehydroemetine (20). This analysis indicated the formula $C_{29}H_{36}O_4N_2$. It has never been widely disputed that the substance is a tetrahydroderivative of rubremetinium salts. (And Openshaw's reduction of the dihydro-rubremetines seems to establish the point). This infers H_{33} for the rubremetinium ion, agreeing with Openshaw's structure.

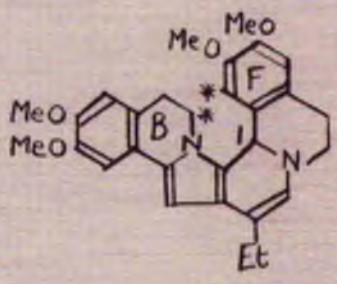
(ii) Considering the recent evidence (p.29) (27) of Battersby and Edwards , it may be noted that their starting material (XXVI) possesses no double bonds at the Δ^3-position of the isoquinoline rings. Furthermore, such double bonds are not likely to be introduced by the action of mercuric acetate in dilute acetic acid (23). It therefore seems safe to assume that there are no Δ^3 double bonds in the product (assumed to be XXVII) or its hydrobromide (assumed to be XXVIII). The hydrobromide has an absorption spectrum which was remarkably similar to that of the rubremetinium salts; and this suggests that the two chromophoric systems are identical. It would follow that the rubremetinium ion does not possess a Δ^3 double bond, as is assumed in Woodward's structure.

(iii) The author's own work, soon to be considered, favours Openshaw's structure.

(iv) The dihydrorubremetines. Strong evidence has been presented (p.26) for the existence of two diastereoisomeric dihydrorubremetines. The effect of sodium acetate in assisting the hydrogenation of rubremetinium chloride suggests that the quaternary nitrogen is involved. On the basis of Openshaw's structure (XVIII) or Woodward's (XXII), therefore, the dihydro-compounds would be XXIX or XXX respectively. In XXIX, there are two centres of asymmetry: with this structure, two dihydrorubremetines mights well be formed. In XXX, hindrance is still possible, as models show; but the orientation of "overlap" of rings B and F, and the configuration at C_1, would probably be interdependent: it is probable that only one dihydro-rubremetine would be formed. The existence of two dihydrorubremetines therefore favours Openshaw's structure XVIII.



XXIX (=XVII)



XXX

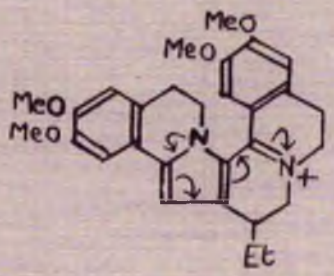
(v) Tetrahydrodehydroemetine (see also (i)(b)). (a) Ehrlich's Reaction. Tetrahydrodehydroemetine reacts with Ehrlich's reagent in the cold (85). This suggests not only that it contains a pyrrole ring, but also that this ring has a free α-position. Tietz and McEwens' structure (= XXIX) for tetrahydrodehydroemetine

does not possess a free ∝-position.

(v) (b). Later in the thesis, the author will provide spectral evidence supporting Openshaw's structure XXV for tetrahydrodehyroemetine.

Points (a) and (b) thus suggest that tetrahydrodehydroemetine has the structure XXV, derived from Openshaw's structure for the rubremetinium ion, rather than XXIX, derived from Woodward's structure for the ion.

The above points (i)-(v) comprise most of the evidence which discriminates between the structures proposed by Openshaw (XVIII) and Woodward (XXII) for the rubremetinium ion. From the very quantity of the evidence offered, it will be understood that no decisive proof is yet available. It is the opinion of the present author, however, that the evidence presented weighs strongly in favour of Openshaw's structure for the ion: XXXI (=XVIII).

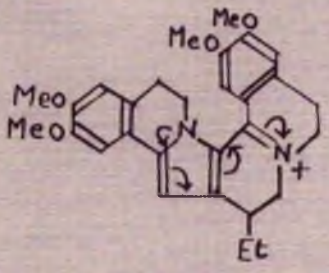


XXXI (=XVIII)

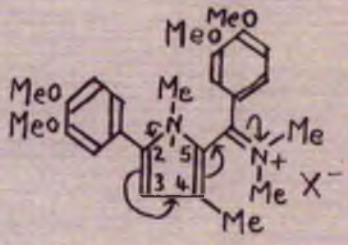
PART III

THE AUTHOR'S WORK: THEORETICAL DISCUSSION

As explained in Part II (p.23), the author set out to confirm that the rubremetinium ion has the structure XXXII (=XVIII), by synthesis of a model compound (e.g. XXXIII, = XXI) with the chromophoric system of XXXII, and comparison of the spectrum of the model compound with that of rubremetinium salts. A close similarity between the two spectra, in conjunction with the evidence already available, would provide a good confirmation of the proposed structure.



XXXII (=XVIII)

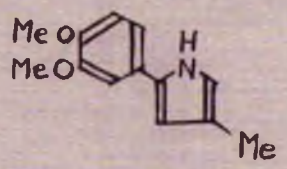


XXXIII (=XXI)

The reactions which were studied are shown, using structural formulae, in a Reaction Index at the end of the thesis. The reactions are arranged in roughly the order in which they were performed, and numbered in this order. The same order is used in discussing the reactions in parts III and IV of the thesis. In part III, the reactions are linked together by discussions, each discussion summarising the results of the previous few reactions

and introducing the next few.

A brief summary of the main trends in the research now follows. It was initially decided that XXXIII would probably be a convenient model compound to synthesise. It will be noted that it is a 1:2:4:5-tetrasubstituted pyrrole. The first synthesis to be considered depended on a "Knorr" synthesis of the pyrrole ring. A closely related reaction was attempted (reaction 3), and was unsuccessful, so this first synthesis was abandoned. In a second synthesis suggested, 4-methyl-2-veratrylpyrrole (XXXIV) was an essential intermediate.

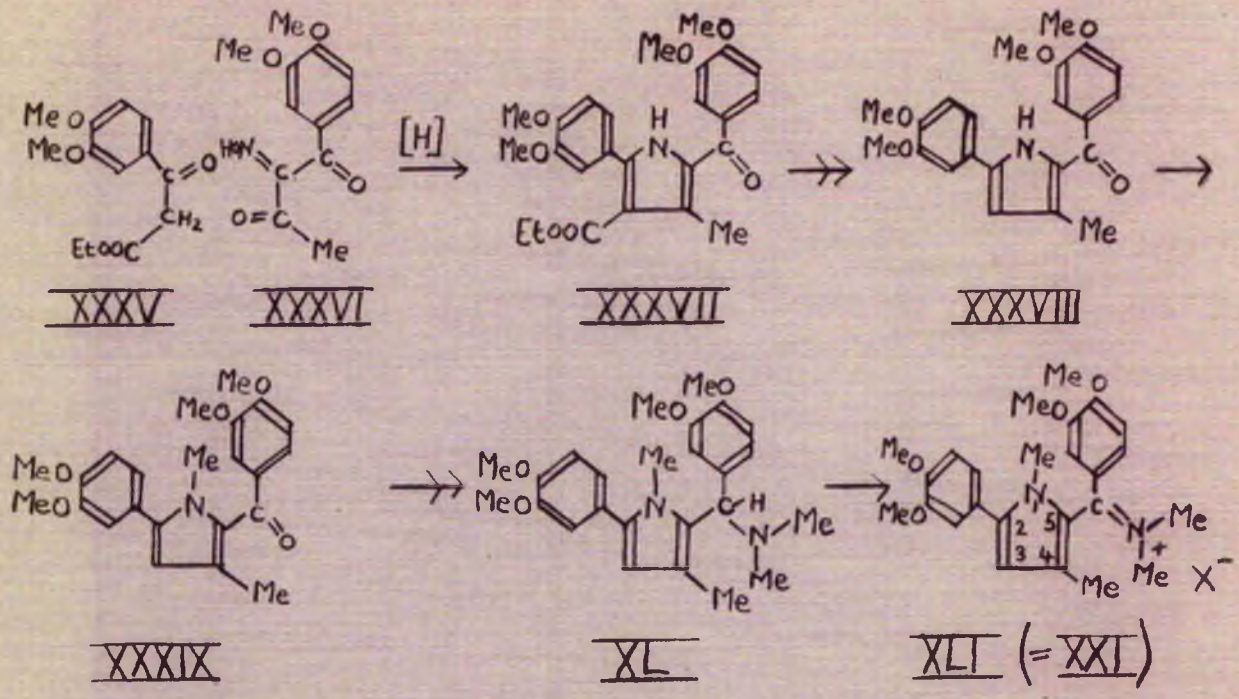


XXXIV

After some trial reactions, this intermediate was prepared (reactions 10-15). Attempts were then made to attach a suitable 5-substituent. The first two methods considered were shown by test reactions (16 and 18) to be unpromising, but the use of dimethyl veratramide with phosphorus oxychloride (reaction 32) gave an encouraging result. The introduction of the 1-substituent was also studied, and it was found possible to modify the synthesis of XXXIV to give 1:4-dimethyl-2-veratrylpyrrole (reactions 33-35). The latter was now treated with dimethylveratramide and phosphorus oxychloride in an attempt to prepare the model compound XXXIII, and

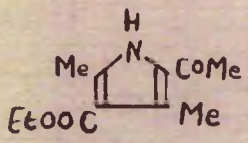
the absorption spectrum of the crude product was compared with that of rubremetinium salts. The resemblance between the two curves was not very pronounced; it was sufficient, however, to justify the preparation of further model compounds, the structures of which would approximate more closely to that (XXXII) postulated for the rubremetinium salts. A second amide was therefore prepared (reactions 37-41), and a second pyrrole (reactions 43-45). In reaction 48, a model compound was prepared, isolated and analysed, and its absorption spectrum was found to be very similar to that of rumbremetinium salts. The work will now be discussed in detail.

The first model compound to be considered was XLI (= XXI). The following synthesis was proposed for it :

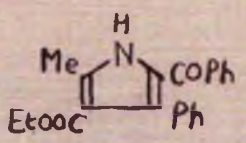


The literature was surveyed to assess the feasibility of the first of these reactions : a "Knorr" synthesis of XXXVII. The survey revealed (29) that the related substances XLII, XLIII and XLIV had been prepared. The substance required however, (XXXVII), was a 2-arylpyrrole, and no "Knorr" synthesis of a 2-arylpyrrole was recorded. Accordingly, a model synthesis of XLV was attempted (R.3)*, using the readily prepared intermediates ethyl benzoylacetate (R.1) and isonitrosoacetylacetone. (R.2).

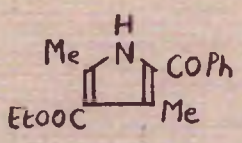
* "R." = "reaction"



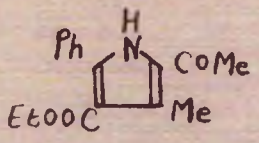
XLII
(in 74% yield)



XLIII
(51%)



XLIV
(56%)



XLV

Reaction 3

Between Ethyl Benzoylacetate and Isonitrosoacetylacetone

The basis of the Knorr synthesis is the condensation of a reactive ketone (such as a β-keto-ester) with an α-amino-ketone. Because of the lability of the latter, it is usually produced in situ by reduction of an isonitroso-ketone.

In the present case reduction both by zinc and acetic acid (60) and catalytically (29) was tried, but neither method yielded the desired pyrrole.

This route was therefore abandoned.

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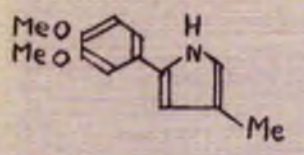
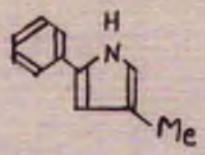
The synthesis was now approached in a different manner. The methods available for inserting the different substituents into the pre-formed pyrrole nucleus were considered and it seemed that the methods for inserting 1- and 5-substituents were the more reliable. It was therefore decided that the introduction of these substituents

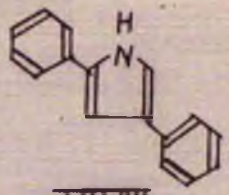
should be left until the later stages of the synthesis. The initial aim was thus to prepare 4-methyl-2-veratrylpyrrole (XLVI, = XXXIV).



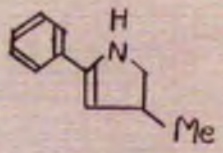
XLVI (=XXXIV)



XLVII

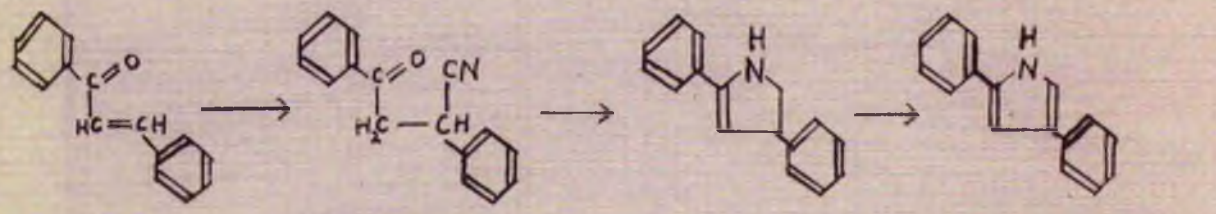


XLVIII



XLIX

This compound has not been described previously, but syntheses of two related pyrroles (XLVII and XLVIII) are recorded. The pyrrole XLVII was made (30) by prolonged reaction between acetophenone and amino-acetone in aqueous sodium hydroxide, but in low yield. The pyrrole XLVIII was prepared (31,32) via L, LI and LII. The yield in the first two conversions was high, and that in the third was 55%. This latter method therefore appeared to be the more suitable.



L LI LII LIII (= XLVIII)

The necessary intermediate, crotonoveratrone, was not mentioned in the literature. Before embarking on its preparation,

therefore, it was thought advisable to carry out a trial synthesis of the already known (30, 75) 4-methyl-2-phenylpyrroline XLIX and 4-methyl-2-phenylpyrrole (XLVII) from the more readily available crotonophenone.

Two methods are described in the literature for the preparation of crotonophenone: by the Friedel-Crafts reaction between benzene and crotonyl chloride, assisted by ultra-violet irradiation (33, 34), and by the condensation of acetophenone with acetaldehyde (35, 36).

The first method (R.5) gave only an 18% yield, instead of the reported 61%, and, as will appear later, the product was probably not crotonophenone. This poor result may have been due to inefficient irradiation through the use of a glass reaction vessel for want of a suitable quartz one.

The second method was also used (R.6): acetophenone and acetaldehyde in methanol, with a small amount of aqueous potassium hydroxide as catalyst, were allowed to stand at room temperature. An oily intermediate product, β-methoxybutyrophenone, was precipitated. This was decomposed by heating with zinc chloride, giving crotonophenone in 16% overall yield. Experiments in which the potassium hydroxide was replaced by triethylamine or pyridine did not yield any product.

Reaction 7

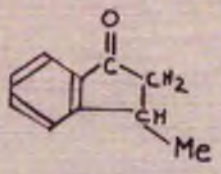
The Preparation of α-Methyl-β-benzoylpropionitrile from Crotonophenone and Hydrogen Cyanide

The initial experiment was carried out (31) with the supposed crotonophenone from reaction 5. It gave a crystalline product m.p. 71-72.5° having the correct analysis for the desired product, but in low yield. (The desired product was not mentioned in the literature).

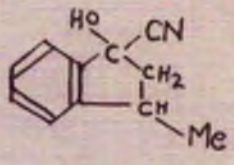
All subsequent preparations, however, gave a different product, m.p. 42.5-43°. This caused a good deal of confusion until it transpired that this lower-melting compound was, in fact, the desired material: besides having the correct analysis it gave (R.8) the expected 4-methyl-2-phenylpyrroline on hydrogenation (as shown by the melting-point of the picrate). It was derived from crotonophenone prepared by reaction 6, about the authenticity of which there could be little doubt.

It thus appeared that the product obtained in reaction 5 was not crotonophenone. When the product (m.p. 71.0-72.5) formed by addition of hydrogen cyanide was hydrogenated, a base was formed which was not the desired pyrroline. The nature of these products was not definitely established. It seems likely, however, that the product of reaction 5 was 3-methyl-1-indanone (LIV): benzene, acrylyl chloride and aluminium chloride are known to give indenone (83), and though an analogous reaction with crotonyl chloride is

not recorded, such a reaction seems feasible. The product m.p. 71.0-72.5° would then be the cyanhydrin LV, a substance which is unfortunately not mentioned in the literature.



LIV



LV

Reaction 8

The Preparation of 4-Methyl-2-phenyl- Δ^2-pyrroline by Hydrogenating α-Methyl-β-benzoylpropionitrile

The nitrile was hydrogenated in ethyl acetate solution with a Raney Nickel catalyst, and at room temperature and atmospheric pressure (c.f. 32). A sample of the product was converted to a picrate, and this had a melting-point (189-192°) close to that (192°) recorded in the literature (75) for the picrate of 4-methyl-2-phenyl- Δ^2-pyrroline. The yield of pyrroline was 89%.

Reaction 9

The Preparation of 4-Methyl-2-phenylpyrrole by Dehydrogenating 4-Methyl-2-phenyl- Δ^2-pyrroline

The dehydrogenation was first attempted by heating the pyrroline with selenium, as in the literature preparation (32) of 2:4-

diphenylpyrrole (LIII). The melting-point of the product (149-152°) was near to that (152°) recorded in the literature (30) for 4-methyl-2-phenylpyrrole, but the yield was only 14%. The dehydrogenation was then attempted by heating with palladium-charcoal. The same product was obtained, and in the greatly improved yield of 49%.

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The above trial synthesis, apparently successful, had now to be adapted to the synthesis of 4-methyl-2-veratrylpyrrole (XLVI). The first step was the preparation of crotonoveratrone, and it was decided to use the method of reaction 5: it promised to be the quicker, and a reasonable yield was expected with the benzene replaced by the more reactive veratrole. The product of reaction 5 was not as yet suspect.

The necessary veratrole was made (R.10), in 55% yield, by methylating catechol with dimethyl sulphate and potassium hydroxide in aqueous methanol (37,38).

Reaction 11

The Preparation of Crotonoveratrone from Crotonyl Chloride and Veratrole

Like reaction 5, this was a Friedel-Crafts type of reaction. Two products were isolated: crotonoveratrone, and, on one occasion, a chlorine-containing product.

The reaction product was always liquid, and the isolation of solid crotonoveratrone difficult (perhaps both the cis- and trans-

isomers were present). This, however, did not seriously affect the next reaction of the synthesis: the preparation of the nitrile (R.12), since many liquid crotonoveratrone fractions gave almost as high a yield of nitrile as did pure solid crotonoveratrone.

Owing to the difficulty of isolation, the yields of crotonoveratrone could not be determined precisely. In contrast, the nitrile crystallised readily, and was easy to purify. The overall yields of nitrile thus offer a convenient measure of the relative usefulness of the various reaction conditions employed in the present reaction. These yields, however, cannot be assumed to correspond to the yields of crotonoveratrone, since (R.13) the chlorine-containing product is also convertible to the nitrile.

In all the preparations, a mixture of crotonyl chloride, veratrole, aluminium chloride and a solvent was allowed to stand at 0°. The mixture was then poured into dilute hydrochloric acid, extracted with ether or chloroform, and fractionated.

Benzene was the first solvent tried. A crude solid product was obtained in 22% yield. It was recrystallised, and the resulting material (m.p. 52-53°) was shown by its analysis and chemical properties to be the desired product (which is not listed in the literature).

A tetrachloroethane-nitrobenzene solvent (39) gave the crude solid product in 20% yield, and also some liquid fractions. The overall yield of nitrile was 33%.

With tetrachloroethane as the solvent, no solid was isolated; but the overall yield of nitrile was 42%.

When tetrachloroethane was employed a second time there was some delay between the extraction and fractionation stages, during which a considerable amount of crystalline material separated. This, after recrystallisation, had a much higher melting point (99.5-100.5°) than crotonoveratrone. Analysis suggested that this substance might be an adduct of crotonoveratrone with hydrogen chloride: α-methyl- β-veratroylethyl chloride (not mentioned in the literature). This was confirmed by reacting it with potassium cyanide (R.13), which converted it in good yield to a nitrile identical with the above. The crontonoveratrone fractions were converted to the nitrile (R.12) in an overall yield of 43%, and the α-methyl- β-veratroylethyl chloride was converted to the same nitrile (R.13), in an overall yield of 15%. The total overall yield of nitrile was therefore 58%.

Reaction 12

The Preparation of α-Methyl- β-veratroylpropionitrile from Crotonoveratrone and Hydrogen Cyanide

Most of the occasions on which this reaction was performed have already been noted in reaction 11.

The method was based on the analogous reaction 7 (and hence on reference 31). A mixture of crotonoveratrone, acetic acid,

potassium cyanide, and aqueous alcohol was left standing at room temperature for 12 hours. The product, which crystallised out, analysed correctly for the desired material. The yield was about 88%.

Reaction 13

Between α-Methyl- β -veratroylethyl Chloride and Potassium Cyanide

This reaction was originally carried out to confirm that the chlorine-containing product of reaction 11 was α-methyl- β -veratroylethyl chloride. Later, however, the reaction found use as a preparative method.

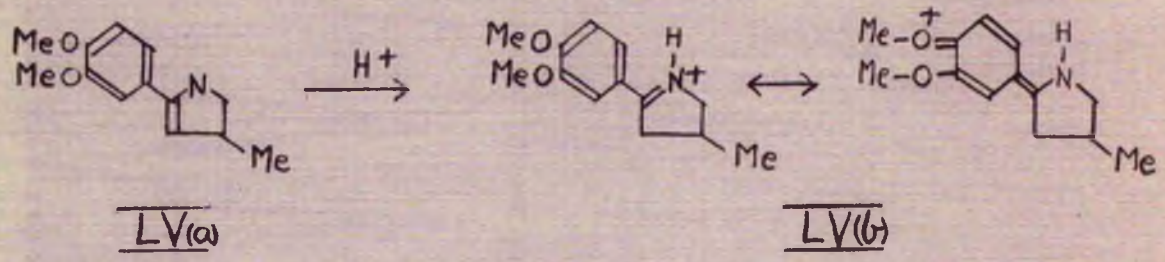
The chloride was refluxed with potassium cyanide in aqueous ethanol; on cooling, a crystalline product appeared. A "mixed melting point" showed that this product was identical with the nitrile prepared in reaction 12. The yield was 87%.

Reaction 14

The Preparation of 4-Methyl-2-veratryl-Δ^2-pyrroline by Hydrogenating α-Methyl- β -veratroylpropionitrile

The analogous reaction 8 had employed ethyl acetate as the solvent, but the present nitrile was only sparingly soluble in ethyl acetate. Acetic acid is a good solvent for the nitrile, but when the hydrogenation was attempted with this solvent, the major product was a tar. It was then discovered that a good yield of product could be obtained by hydrogenating a suspension of the

nitrile in ethyl acetate: as the reaction proceeded, the solid dissolved. Evidence that the product was the desired pyrroline was obtained by analysis of the product, analysis of its picrate, and by studying its ultra-violet absorption spectra. The spectrum in neutral solution corresponds with that of a dimethoxy-styrene. When the solution is acidified, the spectrum changes, and the change can be accounted for by a shift of structure from LV (a) to LV (b), (41).



LV(a) LV(b)

Reaction 15

The Preparation of 4-Methyl-2-veratrylpyrrole by Dehydrogenating 4-Methyl-2-veratryl-Δ^2-pyrroline

Catalytic dehydrogenation under the conditions used earlier for the model compound (R.9) gave the desired product (as shown by analysis), but in poor yield. Other dehydrogenation methods (mercuric acetate[15,24], chloranil[42]) gave no pyrrole at all, while the use of a solvent (xylene) in the catalytic method reduced the yield. Working on the micro-scale, a study was made of the effectiveness of

various dehydrogenation methods and at various temperatures. This suggested that the best results would be obtained by operating with palladium catalyst, at a high temperature and for a short time. In the method adopted, the pyrroline was heated with palladium catalyst at 260° for 3 minutes.

The micro tests were carried out as follows. A mixture of pyrroline and the agent or catalyst under test was put into a capillary (melting-point) tube. The tube was then heated, and observed, in an electrical melting-point apparatus. After heating, the tube was broken, the residue washed with benzene on to a filter paper, and the filter paper tested with Ehrlich's reagent. The intensity of the resultant blue colouration gave an indication of the effectiveness of the dehydrogenation. Materials tested included: palladium charcoal, palladium black, Raney nickel, selenium, sulphur and iodine.

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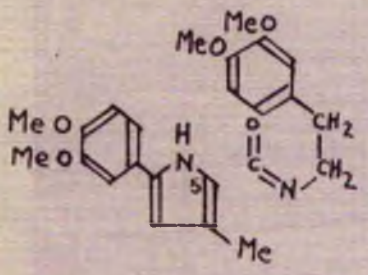
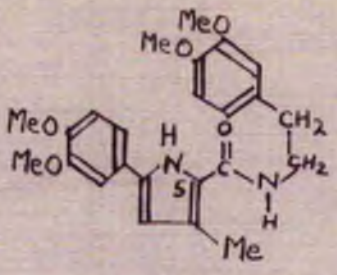
To complete the synthesis proposed (p. 38), the 1- and 5-substituents had now to be attached.

The 5-substituent was considered next. Substituents introduced into a pyrrole ring normally enter an α-position, so in the case of 4-methyl-2-veratrylpyrrole it seemed likely that any substituent would enter the 5-position. Treibs (43) showed that a number of pyrroles react with isocyanates to give amides, and this suggested that a suitable 5-substituent might be attached by the transformations

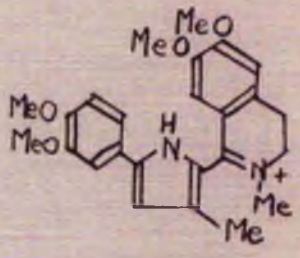
LVI → LIX. The 5-substituent of LIX is different from that originally proposed (in model compound XVI), but is in fact superior to it, since the resemblance to the appropriate part of XVIII is greater.



LVI (=XXXIV)



LVII



LVIII

LIX

Before making the isocyanate LVII, it was decided to attempt a model reaction (R.16) between 4-methyl-2-veratrylpyrrole and a readily available isocyanate: phenyl isocyanate.

Reaction 16

Between 4-Methyl-2-veratrylpyrrole and Phenyl Isocyanate

Treibs (43) found that the reactivity of a pyrrole to an isocyanate may be greatly affected by the substituents attached to the pyrrole nucleus. In particular, pyrroles possessing phenyl groups tended to be unreactive. It thus seemed possible that the present reaction might need rather vigorous reaction conditions.

In one experiment the pyrrole was heated with a slight excess of the isocyanate at 100° for 6 hours, while in a second experiment,

carried out under similar conditions, a large excess of isocyanate was used. The two experiments yielded different products. The product from the first experiment, however (m.p. 243-244°), was obtained in such a poor yield (corresponding to 5.5%) that there was not enough of it to prepare a pure analysis specimen. The product from the second experiment (m.p. 149.0-149.5°) was obtained in somewhat better yield (corresponding to 27%), but analysis indicated that it was not the desired product.

The above results were not encouraging, so the reaction was abandoned.

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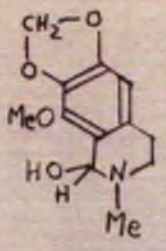
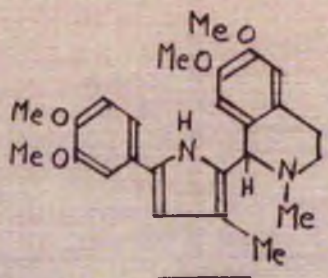
Other methods were now considered for attaching a 5-substituent to 4-methyl-2-veratrylpyrrole. Cotarnine (LXIII), a pseudo-base, has been found to react with active hydrogen atoms in a variety of organic compounds. These compounds include (44): ethanol, acetone, acetophenone; various 1:3 dicarbonyl compounds, esters and phenols; fluorene, nitromethane, nitroethane, ortho-nitrotoluene, phthalimide, aniline and para-toluidine; various pyrazolones and nitriles, and (45) α-methylindole.

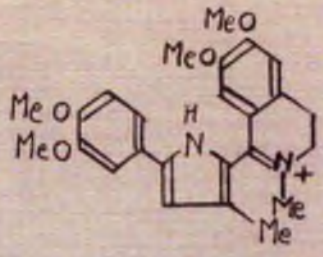
These reactions suggested that it might be possible to condense 4-methyl-2-veratrylpyrrole with the appropriate analogue of cotarnine, and obtain the substance LXIV. This could probably be oxidised to LXV, which possesses a 5-substituent of the desired type.



LXIII



LXIV



LXV

The cotarnine analogue in question was not readily available, so a test reaction was attempted (R.18) with cotarnine itself. No reactions between cotarnine and simple pyrroles were mentioned in the literature, so attempts were also made to react cotarnine with pyrrole (R.17), indole (R.19), 2:4-dimethylpyrrole (R.21), and N-methylpyrrole (R.23). These reactions necessitated the preparation of 2:4-dimethylpyrrole (R.20) and N-methylpyrrole (R.22).

Reaction 17

Between Cotarnine and Pyrrole.

Cotarnine and pyrrole reacted readily on mixing in the cold. Neither solvent nor heating was required. Analysis indicated that the product was the desired product: anhydrocotarninepyrrole. The yield was almost quantitative. The reaction was also carried out with chloroform as a solvent, when a good yield of the same product was obtained.

The stability of the product to acids was studied, as this was of interest in connection with the structure XXV proposed by Openshaw for tetrahydrodehydroemetine. Experiments suggested that the product is decomposed slowly by boiling ethanolic picric acid or cold dilute hydrochloric acid, or rapidly by hot dilute or cold concentrated hydrochloric acid. The decomposition products seem to be pyrrole and the cotarnine salt of the acid.

Reaction 18

Between Cotarnine and 4-Methyl-2-veratrylpyrrole

In the first experiment the reactants were heated together at 100° for 30 minutes; the mixture fused, and seemed to evolve some water. No product could, however, be isolated. In a second experiment, a solution of the reactants in chloroform (c.f. R.17) was left standing at room temperature for 7 days; while in a third experiment, the solution in pyridine was left standing for 12 hours. These attempts were also unsuccessful. In a fourth experiment, a solution of the reactants in triethylamine and pyridine was left standing at room temperature for 3 weeks, an inert atmosphere being employed to avoid air oxidation. A product (m.p. 219-221°) was isolated, but in low yield (the yield of crude product, m.p. 200-202°, corresponding to 2%). This product was found to be only slightly soluble in ethanol, so in the next attempt, an ethanolic

solution of the reactants was refluxed for 2 hours. This, however, gave no product. In the sixth experiment, heating without a solvent was again tried. In the first experiment, conducted at 100°, the reaction mixture had never become mobile, so it was felt that a higher temperature might be beneficial. Cotarnine, however, slowly decomposes at its melting-point: 132-133°. A temperature of 115° was therefore employed, and the reaction was also carried out under reduced pressure, so as to remove any water which might be formed. A white, powdery product (m.p. 216-218°) was obtained in a yield corresponding to 15%.

Two products were thus isolated: that obtained by using triethylamine and pyridine, and that obtained by heating the reactants at 115°. These two products were probably identical since their melting-points (219-221°, 217.5-218°) were close, and neither product gave a colouration with Ehrlich's reagent in the cold, while both gave an intense blue colouration in the hot. The latter product was analysed and the result unfortunately indicated that it was not the desired product. (Found C, 66.79; H, 6.52; N, 5.88; $C_{25}H_{28}O_5N_2$ requires C, 68.82; H, 6.47; N. 6.42). The nature of the product was not established, but the analysis is consistent with the formula $C_{13}H_{15}O_3N$ (requires C, 66.95; H, 6.44; N, 6.01), which corresponds to 4-methyl-2-veratrylpyrrole plus one oxygen atom. This suggests that the product may have been a result of oxidation of the pyrrole by the cotarnine.

Reaction 19

Between Cotarnine and Indole

An ethanolic solution of the reactants was allowed to stand at room temperature (45), and a product crystallised out over a period of several hours. This product was recrystallised from benzene, then analysed, and the results indicated that it was the desired product. The yield of crude product (m.p. 130-131° dec.) was 91.5%.

Reaction 20

The Preparation of 2:4-Dimethylpyrrole

This pyrrole was made (47) by heating 2:4-dimethyl-3:5-dicarbethoxypyrrole with concentrated aqueous alkali at 130°. The yield obtained (2%) was very much smaller than that given in the literature (57-63%). This may have been due to a delay in the working up (the pyrrole is very readily oxidised) or to the fact that superheated steam (47) was not available for the steam distillation.

Reaction 21

Between Cotarnine and 2:4-Dimethylpyrrole

A solution of the pyrrole and cotarnine in the minimum of ethanol (45) was left standing at room temperature, in a sealed

vessel and in an inert atmosphere. Even after 1 year there was no precipitate (c.f. R.19) or any other sign that the desired reaction had taken place.

Reaction 22

The Preparation of N-Methylpyrrole

This was first attempted by the destructive distillation of methylamine mucate, with glycerine as a solvent (51) (c.f. similar methods for pyrrole itself: references 48, 49, 50). The yield (24%) was lower than the literature yield (39%), and it was also noted that a considerable amount of a by-product was formed: N-methylpyrrole-2-carboxylmethylamide (52).

The literature was surveyed to see whether this amide by-product might be converted to the desired N-methylpyrrole. It was found that this amide has been converted to the potassium salt of the corresponding acid by heating with ethanolic potassium hydroxide at 120-130° (52); a subsequent decarboxylation by heating seemed feasible. Also, by analogy with the case of pyrrole (53). it seemed likely that the by-product would be formed in greater quantity if the distillation were done more slowly. Thus, in a second preparation of N-methylpyrrole, glycerine was omitted, and the methylamine mucate was dry-distilled comparatively slowly. Concentrated alkali was then added and the mixture heated strongly,

giving a further distillate. The yield from the combined distillates was 39%.

Reaction 23

Between Cotarnine and N-Methylpyrrole

In the first experiment a solution of the reactants in chloroform (c.f. R.17) was allowed to stand at room temperature for 2 days. A crystalline product (m.p. 113-115°) was isolated in poor yield.

In the second experiment the reactants were heated, without a solvent, at 115° (c.f. R18) for 30 minutes. No product could be isolated.

In a third experiment, similar to the first, but with the reaction time increased, the chloroform solution was allowed to stand for 8 weeks. Recrystallisation of the crude product (m.p. 93-113.5°) gave a product m.p. 113.5-114°. Analysis of the latter showed that it contained chlorine, and hence could not be the desired product. The figures suggested that the substance was a condensation product of cotarnine with chloroform: anhydrocotarninechloroform (not mentioned in the literature). This was confirmed by the failure of the substance to give a colouration with Ehrlich's reagent, which indicated that the pyrrole ring was absent. The yield (calculated from the cotarnine) of crude anhydrocotarninechloroform (m.p. 93-113.5°)

was 31%. The melting-points suggest that the same product had been obtained in the first experiment.

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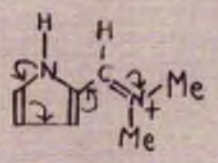
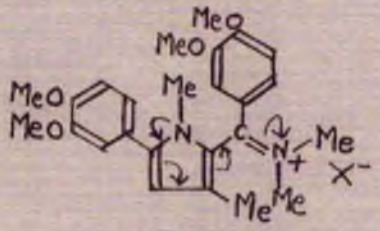
The test reaction (R.18) between cotarnine and 4-methyl-2-veratrylpyrrole had given inconclusive results: it still remained to find a method for introducing a 5-substituent into this pyrrole.

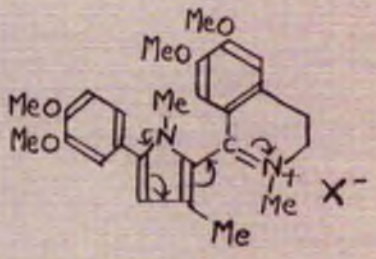
Smith (55) has shown that pyrrole reacts with dimethylformamide and phosphorus oxychloride to give the mesomeric ion LXVI. The yield is high, since the ion can be hydrolysed to 2-formylpyrrole in high overall yield (83%). Smith's work suggested that analogous reactions might be used for the preparation of the model compounds LXVII (=XXI) and LXVIII.



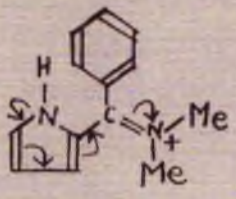
LXVI



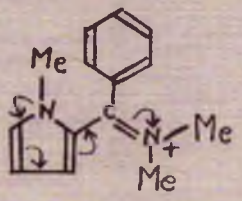
LXVII (= XXI)



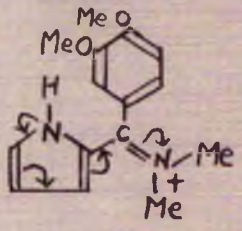
LXVIII



LXIX



LXX



LXXI

Once again, it seemed desirable to try a series of test reactions. Preparations of the ions LXIX, LXX and LXXI were

were therefore attempted (R.25, 26 and 31 respectively). Reactions 25 and 26 required the preparation of dimethylbenzamide (R.24), and reaction 31 required the preparation of dimethylveratramide (R.27-30)

N:N-Dimethylbenzamide was prepared (R.24) in 79% yield, by reacting dimethylamine with benzoyl chloride in the presence of alkali (56).

Reaction 25

Between N:N-Dimethylbenzamide, Phosphorus Oxychloride and Pyrrole

The amide employed by Smith (55), was dimethylformamide, a liquid. Smith used a considerable excess of this amide, so that it also served as a solvent. The amide in the present reaction, dimethylbenzamide, is a solid. Nevertheless, it also gave a stable, homogeneous solution with less than one molar proportion of phosphorus oxychloride, no other solvent being needed.

In the first experiment, phorphorus oxychloride (1 molar proportion) was added to dimethylbenzamide (2.4 molar proportions). On slight warming, a solution was formed, and when this was cooled it deposited no solid. The cold solution was treated with pyrrole (1 molar proportion), which dissolved readily. The mixture was allowed to stand at room temperature for 2 days. It was then added to ice, and the resulting mixture washed with benzene to remove starting materials. This gave a yellow aqueous solution,

which, it was hoped, contained the desired ion LXIX.

To confirm this, and to estimate the yield, the yellow solution was treated with an excess of alkali, and allowed to stand in the cold. A crystalline product (m.p. 73-75°) precipitated, and this crude material was recrystallised, giving a product melting at 75-77°. 2-Benzoylpyrrole (57) melts at 77-78°. An oxime was prepared from the product and this melted at 146-148°. 2-Benzoylpyrrole oxime (78) melts at 147°. These facts indicate that the crystalline hydrolysate was 2-benzoylpyrrole, and that the yellow solution did contain the desired ion LXIX. Some of the crude benzoylpyrrole was accidentally lost but the yield isolated (m.p. 73-75°) was 69%. Thus, the yield of the ion LXIX was greater than 69%.

In a second experiment, similar to the first, the reaction mixture was allowed to stand for 16 days. The yield of crude 2-benzoylpyrrole (m.p. 73-75°) was 92%.

Reaction 26

Between N:N-Dimethylbenzamide, Phosphorus Oxychloride and N-Methylpyrrole

As in the previous reaction, a mixture of the amide, phorphorus oxychloride and the pyrrole was allowed to stand at room temperature for several days. After pouring onto ice and extracting the starting materials, a yellow solution was again obtained.

For characterisation, the solution was treated with alkali. An

oil was formed, but this did not crystallise. Two products were isolated from it. The first product was a white crystalline solid, m.p. 94.5-95.5. It was analysed, and a 2:4-dinitrophenylhydrazone (m.p. 208-209°) was prepared and analysed. The analyses were consistent with the product being a methylbenzoylpyrrole. The second product was a colourless liquid, $n^{17°} = 1.6220$; its analysis was also consistent with its being a methylbenzoylpyrrole.

The above two products were evidently the two possible 1-methyl-benzoyl-pyrroles. The literature mentions 1-methyl-2-benzoylpyrrole but not the 3-benzoyl isomer. 1-Methyl-2-benzoylpyrrole has been made (58) by methylating 2-benzoylpyrrole, and hence the position of the benzoyl group in this material is unequivocal. The material thus prepared was a liquid, and had $n_{D}^{15°} = 1.6225$. The evidence presented is inconclusive, but suggests that, in the present reaction, the first product (m.p. 94.5-95.5°) was 1-methyl-3-benzoylpyrrole and the second product 1-methyl-2-benzoylpyrrole.

The yield of the crude second product corresponded to 50%, and the yield of the crude first product (m.p. 70-85°) to 20%. Thus, the yellow aqueous solution probably contained the desired ion LXX in more than 50% yield, and its 3-isomer in more than 20% yield.

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N:N-Dimethylveratramide was prepared as follows. Vanillin was methylated (59) giving veratric aldehyde in 79% yield (R.27). The aldehyde was oxidised (60) to veratric acid in 94% yield (R.28).

Veratric acid was converted (61) to the acid chloride in 95% yield (R.29), and this was reacted with dimethylamine (as in R.24) giving dimethylveratramide in 81% yield (R.30).

Reaction 31

Between N:N-Dimethylveratramide, Phosphorus Oxychloride and Pyrrole

As in reactions 25 and 26, the reactants formed a homogeneous solution at room temperature, and no additional solvent was needed. This solution, however, was considerably more viscous than those of reactions 25 and 26. It was left standing at room temperature for 2 days then treated as in the two above reactions, giving a dark yellow aqueous product.

For characterisation, and to estimate the yield, the yellow solution was treated with an excess of alkali. A sticky solid (m.p. approx. 110°) was precipitated. One recrystallisation gave a product m.p. 125-126.5°, and further recrystallisation gave the pure product, m.p. 127.5-128.0°. The desired product, 2-veratroyl-pyrrole, is not mentioned in the literature. When the above product was analysed, the carbon and hydrogen values agreed well with those calculated for 2-veratrylpyrrole, but two nitrogen values (5.28%, 5.42%) both differed considerably from the calculated value (6.06%). The analysis figures, however, do not correspond to any of the other products which might have been expected in this reaction, and it seems possible that the lowness of the nitrogen values was

due to the method of assay. The colour of the yellow aqueous product in the present reaction was similar to that of reaction 25, suggesting that the two products were similar. On the whole, the evidence suggests that the solid product (m.p. 127.5-128.0°) was 2-veratroyl-pyrrole, and that the yellow aqueous product contained the desired ion LXXI. The yield of the once-recrystallised solid product (m.p. 125.0-126.5°) was 41%, which suggests that the yield of the ion LXXI was greater than 41%.

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Using the above methods, an attempt was now made to insert a 5-substituent into 4-methyl-2-veratrylpyrrole.

Reaction 32

Between N:N-Dimethylveratramide, Phosphorus Oxychloride and 4-Methyl-2-veratrylpyrrole

In this reaction and in some later reactions, no attempt was made to isolate the reaction products. Instead, the ultra-violet absorption spectra of the crude products were measured, and the results evaluated by studying these spectra. This method, though having certain disadvantages, permitted a rapid assessment of the results, and consumed only small amounts of the reactants.

The first experiment was conducted at room temperature, and a solvent was found to be necessary. Chloroform was used, since it is

comparatively inert, and it is a good solvent for the reactants. A solution of dimethylveratramide, phosphorus oxychloride and 4-methyl-2-veratrylpyrrole was left standing at room temperature for 1 day. The reaction mixture was then added to water and the resulting mixture washed with benzene (to remove the starting materials) then with chloroform (to remove the benzene); this gave an aqueous product. The ultra-violet absorption of the product was found to be very small, suggesting that the desired reaction had not occurred to an appreciable extent. This experiment was useful as a control for subsequent experiments: it showed that the method of isolating the product had removed most of the light-absorbing starting materials without introducing much light-absorbing contaminant.

A second experiment which was carried out was similar to the above, except that the reaction mixture was heated at 61° for 6 hours.

In a third experiment the reaction mixture was heated at 100° for 1 hour, and here it was found possible to dispense with the chloroform, and use an excess of the amide (4.3 molar proportions) as a solvent (as in R.25, 26 and 31).

The ultra-violet absorption curve from the second experiment (curve 3, p.166) possessed a well-defined maximum at 412 mμ, the shape of the maximum showing some similarity to that (440 mμ) in the spectrum of rubremetinium salts. The curve from the third experiment also possessed the 412 mμ maximum, though differing from the second curve in some other respects. This resemblance of the

second and third absorption curves to that of rubremetinium salts suggested, however tentatively, (a) that these salts did possess the structure XVIII, and (b) that in the present reaction, some of the desired 5-substituted product had been formed.

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The results of the last reaction thus suggested that a suitable 5-substituent could be attached to 4-methyl-2-veratrylpyrrole. On further consideration, however, it seemed likely that it would be simpler to insert the 1-substitutent before the 5-substituent. The direct insertion of the 1-substituent into the pyrrole might have been difficult, but a convenient alternative route was proposed: the insertion of the 1-substituent into 4-methyl-2-veratryl-Δ^2-pyrroline, followed by dehydrogenation (c.f. R.15) to the 1-substituted pyrrole. This route was attempted next (R.33 34 and35).

Reaction 33

The Preparation of 1:4-Dimethyl-2-veratryl-Δ^1-pyrrolinium Iodide from 4-Methyl-2-veratryl-Δ^2-pyrroline and Methyl Iodide

A solution of the pyrroline in ether was treated with an excess of methyl iodide, and the resulting solution left standing at room temperature. A white solid slowly precipitated; after 4 days, precipitation appeared to be complete, and the white solid was filtered off.

It seems very likely that this product (m.p. 173-176°) was the desired product (which is not in the literature); unfortunately, little direct evidence was obtained. A sample of the product was set aside, so that both this substance and the product of the following reaction could be analysed at a later date. When the sample was examined a few weeks later, however, it was found that most of it had decomposed. The presence of a considerable amount of iodine was demonstrated by standard qualitative tests.

The overall yield for this and the subsequent reaction corresponded to 92%.

Reaction 34

The Preparation of 1:4-Dimethyl-2-veratryl-Δ^2-pyrroline from 1:4-Dimethyl-2-veratryl-Δ^1-pyrrolinium Iodide

The iodide was dissolved in water, the solution was basified and extracted with chloroform, then the chloroform extract was evaporated and the residue distilled. The main fraction distilled, at 140°/3mm., as a pale yellow liquid. Attempts to crystallise it failed. It was presumed to be the desired product, though it was not analysed (see previous reaction). The overall yield for this and the previous reaction corresponded to 92%.

Reaction 35

The Preparation of 1:4-Dimethyl-2-veratrylpyrrole by Dehydrogenating 1:4-Dimethyl-2-veratryl-Δ^2-pyrroline

In the first experiment an attempt was made to dehydrogenate the pyrroline with ammoniacal silver nitrate (63), while the second experiment employed chloranil in boiling xylene (42). The products were tested with Ehrlich's reagent, and the feeble colourations produced suggested that neither experiment had yielded an appreciable amount of pyrrole.

In the third experiment, the pyrroline was heated with palladium catalyst in an inert atmosphere, at 260° for 3 minutes (as in R.15). After removing the catalyst and distilling, a gummy product was obtained. This gave an intense blue colouration with Ehrlich's reagent, suggesting that it contained a considerable amount of the desired pyrrole. The gummy product would not crystallise. The yield corresponded to 39%.

In the fourth experiment an inert solvent was employed with the palladium catalyst, to moderate its action. The pyrroline and palladium catalyst were refluxed in mesitylene (b.p. 164°) for 45 minutes. The product was fractionally distilled, and some of the fractions obtained were induced to crystalline. The crystalline fractions reacted positively to Ehrlich's reagent. The yield of crude, crystalline product (m.p. 40-48°) corresponded to 28%.

In a fifth experiment, the palladium catalyst was used with

quinoline as a solvent. It was hoped that the quinoline, besides acting as a moderator, would function as a hydrogen acceptor (c.f. this use of naphthalene : reference 64). Also, being a base, it was easier to remove than mesitylene. The pyrroline and palladium catalyst were refluxed in quinoline (b.p. 238°) for 20 minutes. After removing the quinoline and unreacted pyrroline, the product was fractionally distilled. The main fraction (distilled at 145-151°/0.3mm.) crystallised; it melted at 43-47°. This material reacted positively to Ehrlich's reagent. The yield corresponded to 52%. The melting-point suggests that this product was essentially the same as that obtained in the fourth experiment (m.p. 40-48°).

The fifth experiment was adopted as the preparative method. Further purification of the product was difficult (see Part IV of this thesis), since it was always contaminated with an oily byproduct which was difficult to remove. A very small sample of the product was prepared which melted at 51-52°. Two slightly less pure samples (m.p. 49.5-50.5°) were analysed (one sample twice). The agreement between the means of the three results and the values calculated for the desired product was fair, but the results did not agree well with one another:

	Found				$C_{14}H_{17}NO_2$ requires
	(1)	(2)	(3)	mean	
%C	72.12	73.47	71.72	72.44	72.73
%H	7.44	7.76	7.08	7.43	7.36
%N	6.30	5.71	6.00	6.00	6.06

This lack of conclusiveness was particularly unfortunate in view of the fact that the precursors of this product had not been analysed (R.33, 34). The following evidence, however, may also be considered. The product closely resembles 4-methyl-2-veratrylpyrrole (R.15) in the following properties: absorption spectrum, shade of blue colouration with Ehrlich's reagent, insolubility in dilute hydrochloric acid and solubility in the concentrated acid. This evidence suggests that the product (m.p. 51-52°) of the present reaction is structurally similar to 4-methyl-2-veratrylpyrrole. The evidence as a whole suggests that the product (m.p. 51-52°) was the desired 1:4-dimethyl-2-veratrylpyrrole.

In the course of attempts to purify the product (m.p. 51-52°) of the fifth experiment, a second product (m.p. 181-182°) was isolated. This substance gave no colouration with Ehrlich's reagent, however, suggesting, even if the substance was a pyrrole, that it did not possess a free α-position. The yield was very small, and the substance was not investigated further.

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The product (m.p. 51-52°) of the above reaction, probably the desired 1:4-dimethyl-2-veratrylpyrrole, was now reacted with dimethylveratramide and phosphorus oxychloride, in an attempt to prepare the model compound XXI:

Reaction 36

Between N:N-Dimethylveratramide, Phosphorus Oxychloride and 1:4-Dimethyl-2-veratrylpyrrole

The procedure employed was similar to that of reaction 32, and the results were again evaluated by studying the absorption spectra of the products.

In the first three experiments the reaction mixtures were maintained at room temperature (for 1 day), 61° (for 1.5 hours) and 100° (for 15 minutes) respectively. As in reaction 32, chloroform was employed as a solvent at room temperature and at 61°, while an excess of the amide was employed as a solvent at 100°. The absorption curve obtained from the first experiment indicated that little, if any, reaction had occurred. The curves from the second and third experiments had many features in common, though some differences, and both bore some resemblance to the spectrum of rubremetinium salts. (curve from second experiment: curve 4, p.166).

Control experiments were carried out for the second (61°) and third (100°) experiments above. For either experiment, one control was performed with the amide omitted, and one with the pyrrole omitted. Of the four controls, the only one yielding a product with appreciable ultra-violet absorption was that carried out at 100° with the pyrrole omitted. This suggests that at 100°, the amide forms an unwanted byproduct, but that at 61°, the only product formed is derived from both pyrrole and amide: presumably the desired

model compound. This perhaps explains the differences between the curves from the second and third experiments.

The best of the three reaction temperatures thus seemed to be 61°. Two further experiments were now performed at 61° to study the variation of yield with reaction time. The spectra obtained indicated that with reaction times of 1.5 hrs., 3 hrs., and 6 hrs., the respective yields were in the ratio 1.0: 1.5: 1.4. These results suggest that, at 61°, (a) the highest yield was obtained with a reaction time of 3 hrs., and (b) there was some decomposition of the product, which was therefore most pure when the reaction time was 1.5 hrs.

The previous two paragraphs suggest that the purest product was obtained at 61° with a reaction time of 1.5 hrs. The spectrum obtained from this experiment is shown at the back of the thesis (curve 4, p.166). The resemblance between this spectrum and that of rubremetinium salts was greater than that noted in reaction 32, and was consistent with the supposition that some of the desired model compound had been formed. It was not, however, sufficient to justify any deductions regarding the structure of rubremetinium salts.

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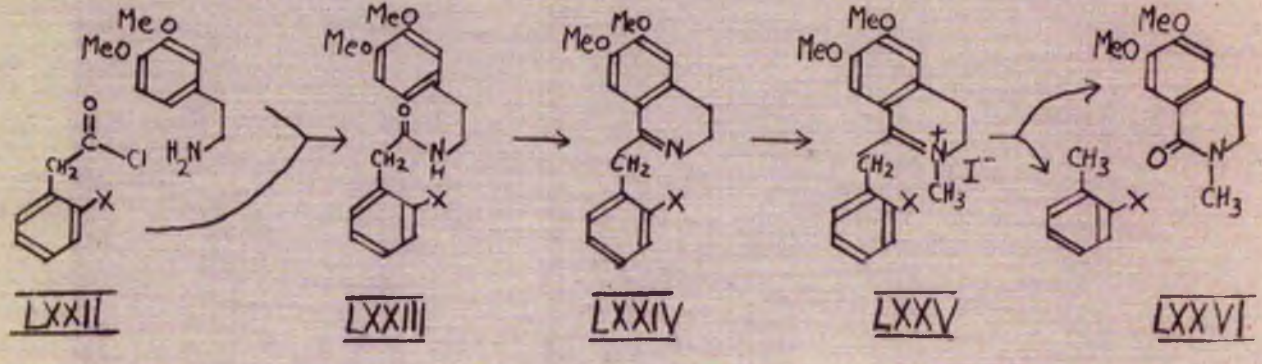
The most satisfactory explanation of the results of the last experiment seemed to be as follows: the model compound XXI had been prepared, and rubremetinium salts did have the structure XVIII

(Openshaw's structure), but the structural resemblance between the two was not sufficient for a close resemblance between the spectra.

It thus seemed desirable to synthesise a further model compound, the structure of which would approximate more closely to XVIII. Formally, the model compound XXI possesses the same chromophoric system as XVIII. In fact, however, XXI lacks three of the rings of structure XVIII, rings which may well affect resonance, and hence light absorption. It thus appeared that a model compound possessing more of the rings of structure XVIII might be more satisfactory.

It seemed likely that a model compound meeting this requirement could be prepared by a simple modification of the last reaction: by replacing the dimethylveratramide by the corresponding ring amide: N-methylcorydaldine (LXXVI).

A survey of the literature revealed that the latter had been prepared by the route LXXII to LXXVI, X = NO_2 (65).



LXXII LXXIII LXXIV LXXV LXXVI

The necessary o-nitrophenylacetyl chloride is troublesome to prepare, however, and this suggested that the preparation of the amide should be attempted by the analogous route with X = H (the same amide being formed whatever the grouping X). A further survey of the literature then showed that LXXIV (X = H) had been prepared (66,67) by a more convenient method than LXXII → LXXIV, X= H. The substance LXXIV, X = H was therefore prepared by the latter method (R.37, 38), and the conversion to N-methylcorydaldine then attempted via LXXV, X = H (R.39, 40).

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N-Homoveratrylphenylacetamide was prepared (R.37) by heating homoveratrylamine with phenylacetic acid at 190° (66). The yield of recrystallised product (m.p. 106-109°) was 81%. The conversion to 1-benzyl-6:7-dimethoxy-3:4-dihydroisoquinoline (LXXIV, X = H) was then accomplished (R.38) by refluxing with phosphorus oxychloride in toluene (66, 67). The yield of the crude base was 76%.

Reaction 39

The Preparation of 1-Benzyl-6:7dimethoxy-2-methyl-3:4-dihydroisoquinolinium Iodide from 1-Benzyl-6:7-dimethoxy-3:4-dihydroisoquinoline and Methyl Iodide

The base was dissolved in an excess of methyl iodide, and the solution allowed to stand at room temperature for 1 day (65). The

methyl iodide was then evaporated, giving the crude product (m.p. 95-99°). Recrystallising this from ethanol, even very dry ethanol, gave a material melting over a very wide range. Time could not be spared for an investigation of this behaviour. Recrystallisation from water proved to be more straightforward, and a sample (m.p. 100-102°), which had been recrystallised from water, was analysed. The result indicated that the product was the desired product (which is not mentioned in the literature), and that it had crystallised with 1 molecular proportion of water of crystallisation. The yield of the crude product (m.p. 95-99°) was about 90%.

Reaction 40

The Preparation of N-Methylcorydaldine by Hydrolysing 1-Benzyl-6:7-dimethoxy-2-methyl-3:4-dihydroisoquinolinium Iodide.

In the first experiment, the hydrolysis was attempted by the method described (65) for LXXV, X = NO_2: the iodide was refluxed with 3% (w./v.) aqueous sodium hydroxide. The reaction mixture never became homogeneous. A product which was isolated was shown by the method of "mixed melting-point" to be the desired product, but the yield was very small.

In a second experiment the concentration of hydroxide was increased (potassium hydroxide, 15% w./v.), and aqueous ethanol was employed as the solvent to give increased homogeneity. In fact,

the hot reaction mixture became completely homogeneous. On cooling, a product crystallised out as bright yellow plates m.p. 92.0-93.5°. Recrystallisation gave a product m.p. 92.5-93°, which was still bright yellow. N-Methylcorydaldine, however, is colourless, and melts at 125° (65), which indicated that the yellow product was not the desired product. This was confirmed by analysis, which also suggested that the yellow product was the methylene base corresponding to the iodide starting material. Support for the latter idea was found in the literature (68), though the methylene base in question was not listed. Attempts to isolate the desired amide were unsuccessful. The yield of the crude methylene base (m.p. 92.0-93.5°) was 91%.

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It was later noted (69) that the ease of hydrolysis of LXXV, X = NO_2 is attributed to the presence of the nitro group. This perhaps accounts for the poor result obtained above with LXXV, X = H. The literature suggested, however, that N-methylcorydaldine might be conveniently prepared by oxidising the methylene base formed above, and this was attempted next.

Reaction 41

The Preparation of N-Methylcorydaldine by Oxidising 1-Benzal-6,7-dimethoxy-2-methyl-1,2,3,4,-tetrahydroisoquinoline

The oxidation was carried out with aqueous potassium permanganate (70). The solubitity of the methylene base in water is small, so the contact between the reactants was improved by adding benzene, a solvent for the methylene base. (Benzene does not react with aqueous potassium permanganate). A mixture of the methylene base, alkaline aqueous potassium permanaganate and benzene, was shaken vigorously at room temperature for 1 hour. The benzene layer was removed, washed with alkali then acid to remove acidic and basic materials, then evaporated. The crude residue, m.p. 118-122°, was recrystallised and distilled, giving a product m.p. 125.0-125.5°. The melting-point (lit. (65) : 124 - 124.5°) and an analysis indicated that this was the desired product. The yield of the crude product (m.p. 118-122°) was 64%.

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The N-methylcorydaldine (see p.71) was now used in a further attempt to prepare a model compound.

Reaction 42

Between N-Methylcorydaldine, Phosphorus Oxychloride and 1:4-Dimethyl-2-veratrylpyrrole

The procedures used were similar to those of reactions 32 and

36, and the results were again assessed by studying the absorption spectra of the products.

In the first experiment the reactants were heated at 61°, using chloroform as a solvent. When the spectrum of the product (curve 5, p.166) was compared with that of rubremetinium salts, it was found that the resemblance was poor, and less than had been noted in reaction 36. Furthermore, the spectrum of the same product was measured a few days later and was found to have changed appreciably, showing that the product, or part of it, was decomposing. This had not occurred in reaction 36.

A control experiment (amide omitted) in reaction 36 had already indicated that the pyrrole does not form a byproduct at 61°. A control experiment was now performed with the pyrrole omitted. The spectra obtained indicated that N-methylcorydaldine does form a byproduct in the reaction at 61°, and also that the aqueous solution of the byproduct slowly decomposes on standing. The changes in the absorption curve were somewhat similar to those noted in the first experiment.

The simplest explanation of the results seemed to be that the product from the first experiment had contained two main products: (a) the desired model compound, and (b) the unstable product formed in the N-methylcorydaldine control experiment. To test this explanation, many attempts were made to effect some separation of the two postulated products. Most of the methods (see Part IV)

involved distributing the product between pairs of immiscible solvents. Spectra of different fractions were studied for any evidence of a separation. It appeared, however, that no significant separation was achieved.

A second experiment was performed, similar to the first, but at room temperature. It was hoped that the low reaction temperature would minimise the formation of any byproducts (c.f. R.32, 36). The spectrum of the product, however, was very similar to thatobtained in the first experiment, and attempts to separate two main products again failed.

The results were thus inconclusive. It was not possible to say whether one or more than one product was formed in appreciable quantity; it was equally impossible to say whether any of the desired model compound had been formed.

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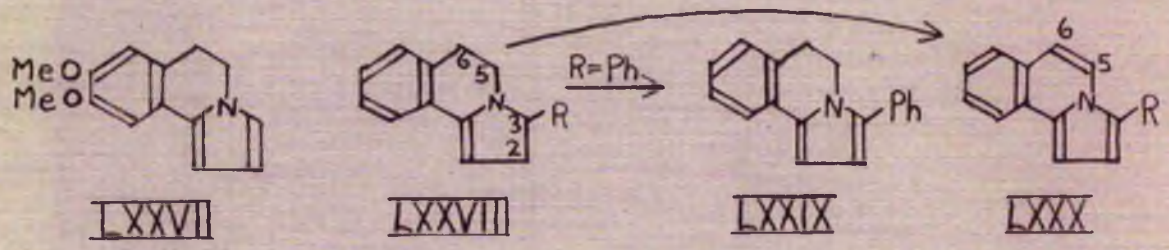
The above result was a little discouraging, but it still seemed desirable to prepare a model compound based on structure XVIII, and possessing more rings than XXI (see discussion after R.36).

The attempt to introduce an additional ring via the amide having proved unsuccessful, it was now considered whether an extra ring could be incorporated in the pyrrole.

The pyrrole possessing the appropriate additional ring is LXXVII (which may also be classed as a benzdihydropyrrocoline).

This substance was not mentioned in the literature, but the related LXXVIII R = H and R = Ph, had been prepared (71). These had been dehydrogenated to LXXX, R = H and R = Ph, and LXXVIII, R = Ph had also been partially dehydrogenated to LXXIX, the analogue of LXXVII. An attempt was now made (R.43, 44 and 45) to adapt these reactions to the preparation of LXXVII.



LXXVII LXXVIII LXXIX LXXX

Reaction 43

The Preparation of N-Homoveratryl-2-pyrrolidone from Homoveratrylamine and γ-Butyrolactone

In the first experiment the reactants were heated together in a sealed tube at 280° (71, 72). The product was a black tar accompanied by a small quantity of a brown liquid. No pure product could be isolated.

In a second experiment, a mixture of the amine and the lactone was refluxed in a slow stream of nitrogen for 3 hours. The reaction mixture was then distilled; the main fraction distilled at 164-175°/0.4mm., and a sample of this was redistilled for analysis. The analysis indicated that the desired product had been

obtained. The yield of the product distilled at 164-175°/0.4mm. was 61%.

Reaction 44

The Preparation of 8:9-Dimethoxy-2:3:5:6:-tetrahydrobenzo (g)-pyrrocoline from N-Homoveratryl-2-pyrrolidone

This reaction is a "ring-closure" of an amide.

In the first experiment the pyrrolidone was refluxed in xylene with phosphorus pentoxide (71). A red, solid product was isolated and, since it was expected (71) that this would be rather unstable, a picrate (m.p. 195.0-195.5° dec.) was prepared for analysis. The analysis result indicated that the red solid was the desired product. This conclusion was supported by the behaviour of solutions of the product (in organic solvents) when exposed to the air for a few hours: the solutions turned from colourless to deep red, the intensity of the colouration with Ehrlich's reagent (blue colouration) increasing correspondingly. This suggests that the product is readily oxidised to a material possessing a pyrrole ring. The yield of the product was estimated (via the picrate) to be about 27%.

In a second experiment, the amide was refluxed with phosphorus oxychloride in toluene (c.f. R.38). The product obtained melted at 100-103° and was shown to be identical with the product of the first experiment by carrying out a "mixed melting-point" with the

picrates. The yield was 81%.

Reaction 45

The Preparation of 8:9-Dimethoxy-5:6-dihydrobenzo(g)pyrrocoline by Dehydrogenating 8:9-Dimethoxy-2:3:5:6-tetrahydrobenzo(g)pyrrocoline

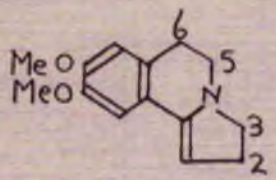
The present reaction was a partial dehydrogenation only (the conversion of LXXXI to LXXVII). An analogous dehydrogenation had been carried out catalytically on LXXVIII, R = Ph (71), but the double bond so introduced was conjugated with a phenyl group. In the catalytic dehydrogenation of LXXVIII, R = H no partially dehydrogenated product had been isolated, and since this latter example corresponds more closely with the present reaction, it seemed preferable to avoid the catalytic method.

Mercuric acetate in dilute acetic acid will not dehydrogenate 3:4-dihydro-6:7-dimethoxy-1-methylisoquinoline (23), so it seemed unlikely that it would dehydrogenate at the 5- and 6- positions in LXXI. On the other hand, the reagent is effective for the dehydrogenation of emetine (15). It was thus hoped that the reagent would perform the desired dehydrogenation at the 2- and 3- positions of LXXXI.

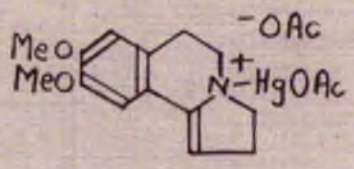
In the first experiment, then, the tetrahydropyrrocoline was heated with the stoichometric quantity of mercuric acetate in dilute acetic acid (15). There was apparently no reaction, however, and no product could be isolated.

In the second experiment, an attempt was made to apply an observation made in reaction 44: that the tetrahydropyrrocoline seems to undergo air oxidation at room temperature to a substance containing a pyrrole ring. This substance, it was hoped, was the desired product. An air oxidation was therefore attempted with the tetrahydropyrrocoline in chloroform solution. A gummy product was obtained which gave an intense blue colouration with Ehrlich's reagent, and this colouration was strikingly similar to that given by the pyrroles made in reactions 15 and 35. The product, however, would not distil at 160°/3.10^{-3}mm., whereas the pyrroles of reactions 15 and 35, which have molecular weights near to that of the desired product, distil readily at 160°/0.2 mm. This suggested that the product was not the desired product.

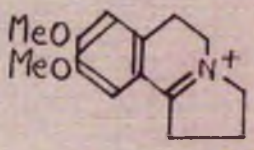
For mercuric acetate oxidations of the type attempted in the first experiment, a reaction mechanism has been proposed by Leonard (73). Applied to the present reaction, this would require addition of mercuric acetate to the tetrahydropyrrocoline with its structure as shown in LXXXI (to form the intermediate LXXXII).



LXXXI



LXXXII



LXXXIII

It seems quite possible, however, that the structure of the tetrahydropyrrocoline (in dilute acetic acid solution) is almost exclusively as shown in LXXXIII: solutions of salts of the tetrahydropyrrocoline are very stable to air oxidation; this contrasts strongly with the behaviour of the free tetrahydropyrrocoline, suggesting that very little of the free tetrahydropyrrocoline (structure LXXXI) is present in acid solutions. It appeared from this that mercuric acetate might be used with more success in a non-acid solution, when the tetrahydropyrrocoline would presumably have the structure LXXXI.

In the third experiment, therefore, the tetrahydropyrrocoline and mercuric acetate were refluxed with amyl alcohol (b.p. approx. 130°) in an inert atmosphere. A crystalline product was isolated and purified. The pure product (m.p. 131-132°) analysed correctly for the desired product; it also gave a blue colouration with Ehrlich's reagent, the shade of blue being very similar to that obtained with the pyrroles of reactions 15 and 35. The yield of the crude product (m.p. 119-121°) was 1%.

In a fourth experiment, the amyl alcohol of the previous experiment was replaced by N-propanol (b.p. 97°), but none of the desired product was obtained.

In a fifth experiment, the solvent was dispensed with, and the temperature employed was that which had been used successfully in the third experiment: 130°. The yield of crude pyrrole

Picrate. A drop of the pyrroline was added to ethereal picric acid. The picrate which precipitated was recrystallised from a mixture of ethyl acetate and ethanol, giving yellow needles m.p. 189-192°.

Reaction 9

The Preparation of 4-Methyl-2-phenylpyrrole by Dehydrogenating 4-Methyl-2-phenyl-Δ^2-pyrroline.

First Experiment A mixture of the pyrroline (1.0 g., 1.0 m.) and red selenium (1.0 g., 2.0 g.) was heated at 280° in a current of carbon dioxide. Heating was continued for 3 hours. On cooling, the product was found on the wall of the condenser as white leaflets, m.p. 149-152° (0.11g., 11%). The catalyst was extracted with hot alcohol, the extract filtered and evaporated, and the residue recrystallised from toluene. This gave a further small quantity of less pure product m.p. 143-148° (0.025g., 3%). The total yield was 14%.

Second Experiment A mixture of the pyrroline (1.0 g.) and palladium charcoal catalyst (20% 0.2 g.) was heated in a stream of carbon dioxide, at 190° and for 30 minutes. On cooling, a crystalline product m.p. 147-150° was taken from the condenser wall. The catalyst did not yield any more of the product. The yield was 0.485 g. (49%).

Reaction 10

The Preparation of Veratrole by Methylating Catechol.

A mixture of catechol (40g., 1.0m.), dimethyl sulphate (100g., 2.0m.) (74) and methanol (80ml.) was cooled to -5°. A solution of potassium hydroxide (70g., 2.3m.) in water (140ml.) was then added rapidly. A rapid, vigorous reaction ensued, and much of the methanol boiled off. After cooling, the reaction mixture consisted of an oily layer and an aqueous layer. The aqueous layer was extracted (5 times) with ether; the extracts and the oily layer were combined, and dried over sodium sulphate. The dry solution was concentrated, then cooled in a bath of ether-solid carbon dioxide. A white, crystalline precipitate of veratrole was formed. It was filtered, using a low-temperature filter (p.161), then dried in vacuo. This gave the veratrole as white crystals m.p. 19° (27.6g., 55%).

Reaction 11

The Preparation of Crotonoveratrone from Crotonyl Chloride and Veratrole

The experiments were all performed in a three-necked flask equipped with a stirrer, dropping funnel and bunsen valve. During

the addition of the crotonyl chloride, the flask was immersed in ice. After the addition of the chloride, the flask was stood in a "Dewar" containing ice, to allow the reaction to continue at 0°.

First Experiment To the three-necked flask were added benzene (20ml., dried over sodium) and powdered aluminium chloride (14.0g., 1.6m.) . With stirring a mixture of veratrole (8.8g.,1.0m.) and crotonyl chloride (6.3ml., 1.0m.; from R.5) was added over a period 1.5 hours. Stirring was discontinued, and the flask left at 0° for 2 days. The reaction mixture was then added to a mixture of ice and dilute hydrochloric acid, and the resulting mixture extracted three times with ether. The extracts were combined, washed with aqueous sodium carbonate, dried over sodium sulphate, then fractionally distilled.

Two fractions were collected :

Fraction 1), at 70-120°/2.0 mm. (4.27g.).

Fraction 2), at 120-168°/2.0 mm.

Fraction 1) was mainly veratrole. Fraction 2) partly crystallised on standing. The crystals were transferred to a porous plate and washed with a little ether, giving crude crotonoveratrone, m.p. 42-46° (2.9g., 22%). Attempts to purify it by recrystallisation from methanol, aqueous methanol, ethyl acetate or acetone were unsuccessful. Petroleum ether was more effective: two recrystallisations from petroleum ether (charcoal), cooling to 0°, gave white needles of crotonoveratrone m.p. 52-53°. (Found:

C: 70.12; H: 6.78. $C_{12}H_{14}O_3$ requires: C: 69.90; H: 6.796%).
Another effective purification was recrystallisation from ether, cooling to 0°. The recoveries in all of these recrystallisations were only about 50%.

Second Experiment To the three-necked flask were added tetrachloroethane (20ml., pure (74)), nitrobenzene (5ml., pure (74)) and aluminium chloride (16g., 1.9m.). With stirring, a mixture of veratrole (8.8g., 1.0m.) and crotonyl chloride (6.3ml., 1.0m.) was added over a period of 1.5 hours. Stirring was discontinued, and the flask was left at 0° for 2 days. The reaction mixture was then poured into a mixture of ice and dilute hydrochloric acid and worked up as before. The major high-boiling fraction distilled at 164-170°/2.0mm., weighed 9.99g., and was very viscous. By extraction with petroleum ether, it was separated into several fractions. One of these consisted of crude crotonoveratrone m.p. 43-47° (2.55g, 20%); the others were uncrystallisable liquids. The liquid fractions were combined and redistilled, but none of the fractions obtained would crystallise.

These products were reacted (R.12) with hydrogen cyanide: 1.18 g. of the crude solid gave 1.07 g. of the nitrile (an 82% conversion), and 2.69g. of the main fraction of the redistilled liquid gave 1.58 g. of the nitrile (corresponding to a 52% conversion). The total overall yield of nitrile was 33%.

Third Experiment To the three-necked flask were added

tetrachloroethane (60ml., pure (74)) and aluminium chloride (66g., 1.5 m.). With stirring, a mixture of veratrole (46g., 1.0m.), crotonyl chloride (40ml., 1.25m.) and tetrachloroethane (60ml.) was added over a period of 1.5 hours. Stirring was discontinued, and the reaction was allowed to continue at 0° for 2 days. The reaction mixture was then poured into a mixture of ice and dilute hydrochloric acid, and worked up as before. Two high-boiling fractions were collected :

Fraction 1), at 154-160°/1 mm. (36.2 g.)

Fraction 2), at 195-200°/1.5 mm. (9.8 g.), more viscous than fraction 1.

No solid crotonoveratrone was isolated.

The yields of nitrile (R.12) from these fractions were: Fraction 1) 29.7 g., (78%); 2) 2.6g., (24%).
The total overall yield of nitrile was 42%. (Though definite evidence is lacking, it seems possible that Fraction 2) was largely α-methyl-β-veratroylethyl chloride [see below]).

Fourth Experiment To the three-necked flask were added tetrachloroethane (140 ml., pure (74)), and aluminium chloride (6.3g., 1.1 m.). With stirring, a mixture of veratrole (29.0 g., 0.5 m.), crotonyl chloride (43.6 ml., 1.0m.) and tetrachloroethane (60 ml.) was added, followed by more veratrole (29.0g. 0.5m.). These two additions were spread over 1 hour. Stirring was discontinued, and the reaction allowed to continue at 0° for 2 days.

The reaction mixture was then poured into a mixture of ice and dilute hydrochloric acid. The colour changed from dark brown to salmon pink (a change also noted in the third experiment but not in the others). The mixture was extracted three times with chloroform, and the extracts were combined, dried over sodium sulphate and evaporated. The residue was divided into two halves for fractional distillation. The distillation, however, was unavoidably delayed for 8 weeks. By then, each of the two halves had deposited a considerable quantity of a crystalline solid. One half was taken, and separated by filtration into two fractions :

Fraction 1), a crude crystalline solid m.p. 98.5-100° (9.6 g.).

Fraction 2), the filtrate.

Fraction 2 was distilled, giving three fractions :

Fraction 2)a) at 164°/3.8 mm. - 172°/8.0 mm. (10.17 g.),

Fraction 2)b) at 156-158°/2.0 mm.,)
Fraction 2)c) at 153-156°/2.0 mm.,) (11.78 g.)

Fraction 2)c) crystallised; fraction 2)b) partly crystallised; fraction 2)a) would not crystallise. Fraction 1) (m.p. 98.5-100°) was evidently not crotonoveratrone (m.p. 52-53°). A sample of it was purified by recrystallising twice from ethyl acetate (charcoal). This gave white needles, m.p. 99.5-100.5°, of α-methyl-β-veratroylethyl chloride. (Found: C: 60.13; H: 6.07; Cl: 14.6.

$C_{12}H_{15}O_3Cl$ requires C: 59.38; H: 6.19; Cl: 14.64%).

Fractions 2)a), 2)b) and 2)c) were reacted (R.12) with hydrogen cyanide. The yields of nitrile from these fractions were: Fraction 2)a): 9.56 g. (83%); 2)b) and 2)c) combined: 10.17 g. (87%). The overall yield of nitrile from fraction 2) was 43%.
Fraction 1) was also found to be convertible to the nitrile, though by a different reaction (R.13): 1.50 g. of fraction 1) gave 1.14 g. (80%) of the nitrile. The overall yield of nitrile from fraction 1) was 15 %. The total overall yield of nitrile from this experiment was 58%.

Reaction 12

The Preparation of α-Methyl-β-veratroylpropionitrile from Crotonoveratrone and Hydrogen Cyanide.

A mixture of crotonoveratrone (1.15 g., 1.0 m.), ethanol (19ml.) and acetic acid (0.33 g., 1.0 m.) was treated with a solution of potassium cyanide (0.72 g., 2.0 m.) in water (2 ml.). The resulting solution was allowed to stand at room temperature. A crystalline precipitate soon began to form (c.f. R.7). After 2 hours, a considerable precipitate had formed, and after 12 hours, precipitation seemed to be complete. The mixture was cooled to 0° then filtered. After washing with a little ice-cold, aqueous ethanol and drying in a dessicator, the product consisted of pale

yellow needles, m.p. 117-119° (1.065 g., 82%). Recrystallisation from ethanol gave white needles m.p. 119.5-120°. (Found : C: 67.0; H: 6.45; N: 6.15. $C_{13}H_{15}O_3N$ requires: C: 66.9; H: 6.48; N: 6.01%. In a similar preparation, a further quantity (6%) of product was obtained by concentrating the mother liquor.

Reaction 13

Between α-Methyl-β-veratroylethyl Chloride and Potassium Cyanide

A mixture of the chloride (5.78 g., 1.0 m.), 50% aqueous ethanol (c.f. 40) (55 ml) and potassium cyanide (3.1 g., 2.0 m.) was heated under reflux. As the solvent approached its boiling point, the solid disappeared, giving a pale yellow solution. There was no further colour change. After refluxing for 1 hour, the solution was allowed to cool. α-Methyl-β-veratroylpropionitrile crystallised out as white needles m.p. 119.5-120° (4.83 g., 87%). (A "mixed melting point" showed that the product was identical with that of reaction 12).

Reaction 14

The Preparation of 4-Methyl-2-veratryl-Δ^2-pyrroline by Hydrogenating α-Methyl-β-veratroylpropionitrile

A mixture of the nitrile (R.12 or 13, 6.87 g.), ethyl acetate

(100 ml., purified by standing over Raney nickel) and Raney nickel catalyst (10 ml. of sludge) (74) was shaken vigorously with hydrogen, at room temperature and atmospheric pressure. Hydrogen was absorbed steadily, at a rate of about 1.6 ml./minute. When 1495 ml. of hydrogen had been absorbed, shaking was stopped. The solvent was colourless. While it was left in the atmosphere of hydrogen (12 hours) it remained colourless, but on exposing it to the air, it slowly turned red. The catalyst was removed by filtration (filtercel) and the red filtrate was extracted with dilute hydrochloric acid (5 x 50 ml.). On adding the acid, the filtrate turned blue. The blue colour, however, was not transferred to the acid extracts, which were brown then colourless. The acid extracts were combined, basified, and extracted with ether (4 x 40 ml.), then the ether extracts were combined, dried over potassium hydroxide (pellets), and evaporated. The residue crystallised readily. It consisted of the crude pyrroline m.p. 45-48° (5.61 g., 87%). It was recrystallised three times from benzene-petroleum ether, giving white needles, m.p. 51.5-52.5°. (Found: C: 70.9; H: 7.82; N: 6.41. $C_{13}H_{17}O_2N$ requires: C: 71.2; H: 7.80; N: 6.39%). A picrate was prepared, and twice recrystallised from ethyl acetate-ethanol, giving yellow needles m.p. 194.5-195.5° (dec.). (Found: C: 51.1; H: 4.46; N: 12.1. $C_{19}H_{20}O_9N_4$ requires: C: 50.9; H: 4.50; N: 12.5%). The pyrroline distilled at 149-153°/0.5 mm.

Reaction 15

The Preparation of 4-Methyl-2-veratrylpyrrole by Dehydrogenating 4-Methyl-2-veratryl-Δ^2-pyrroline

First Experiment Pyrroline (0.36 g.) and palladium-charcoal catalyst (0.2 g., 20%) (76) were heated together in a stream of carbon dioxide. The hydrogen evolved was collected by passing the emergent gases into an inverted burette containing concentrated alkali. The reaction vessel was heated by an oil-bath. When the oil-bath temperature had reached 145°, hydrogen was being evolved steadily, so the oil-bath was maintained at this temperature. After about 15 minutes, hydrogen was being evolved more slowly, and the apparatus was allowed to cool. The reaction mixture was extracted with hot benzene. The extract was filtered free from catalyst (filtercel), concentrated, treated with a little petroleum ether, then allowed to stand in the refrigerator. A product crystallised, m.p. 137-139° (0.16 g., 45%). It was purified by subliming at 160°/0.5 mm., followed by recrystallisation from xylene (twice, in a stream of carbon dioxide), then benzene (twice, also in a stream of carbon dioxide. The resulting product consisted of white needles, m.p. 142.5-143° (Found: C: 72.1; H: 7.00; N: 6.48. $C_{13}H_{15}O_2N$ requires: C: 71.9; H: 6.95; N: 6.45%).

Second Experiment A mixture of the pyrroline (0.5 g., 1.0 m.), mercuric acetate (1.46 g., 2.0 m.), and aqueous acetic acid (50%, 20 ml.) was heated at 100° for 7 hours. No mercurous acetate

could be isolated, and none of the products gave a colouration with Ehrlich's reagent. These results suggest that no pyrrole was formed.

Third Experiment A mixture of the pyrroline (1.0 g., 1.0 m.), chloranil (1.12 g., 1.0 m.) and xylene (25 ml., pure (74)) was refluxed in a stream of carbon dioxide for 6 hours. On cooling, some solid precipitated, but neither the solid nor the xylene solution gave any colouration with Ehrlich's reagent. This suggests that no pyrrole had been formed.

Fourth Experiment Using a similar method to that of the first experiment, the pyrroline (0.465 g.) and palladium-charcoal (0.115 g., of 20%) were heated in boiling xylene (8ml., pure (74)) for 140 minutes. The pyrrole obtained melted at 137-140°, and weighed 0.19 g. (41%).

Fifth Experiment A mixture of the pyrroline (0.40 g.) and palladium-charcoal catalyst (0.10 g., of 20%) (74) was heated in a slow stream of carbon dioxide, at 260° for 3 minutes. The reaction was vigorous at first, but soon subsided. After cooling, the reaction mixture was treated with hot benzene, and the mixture filtered to remove the catalyst. The filtrate was washed with dilute hydrochloric acid, dried over sodium sulphate, and evaporated. The residue was sublimed at 200° (Oil-bath temperature) /0.5 mm. The sublimate consisted of the crude pyrrole m.p. 133-137° (0.225 g., 57%). It was recrystallised from xylene in a stream of

carbon dioxide, giving white needles m.p. 138-140°.

The pyrrole sublimes at 120°/1×10^{-3}mm. It gives an intense blue colouration with Ehrlich's reagent. It does not form a picrate in benzene, ethanol or ether.

Reaction 16

Between 4-Methyl-2-veratrylpyrrole and Phenyl Isocyanate

First Experiment The pyrrole (200 mg. 1.0 m.) and phenyl isocyanate (0.17 ml., 1.5 m.; freshly distilled) were heated together in a sealed glass tube at 100° for 6 hours. After cooling, the reaction mixture was added to chloroform and filtered (to remove any carbanilide). The filtrate was evaporated, and the green resin which remained dissolved in hot ethanol. On cooling, the solution deposited leaf-green platelets which, after drying in vacuo, melted at 243-244° and weighed 17 mg. (corresponding to 5.5%).

Second Experiment A mixture of the pyrrole (200 mg., 1.0 m.) and the isocyanate (1.40 ml., 12.0 m.) was heated in a sealed glass tube at 100° for 6 hours. On cooling, a product crystallised out. This was filtered off, washed with ether, then dried in vacuo, giving blue platelets m.p. 141-142° (82 mg., corresponding to 27%). Two recrystallisations from ethanol raised the melting-point of this material to 149.0-149.5°, but a subsequent analysis indicated

that it was not the desired product. (Found: C: 70.7; H: 5.68; N: 10.6. $C_{20}H_{20}O_3N_2$ requires: C:71.4; H: 5.95; N: 8.33%).

Reaction 17

Between Cotarnine and Pyrrole

Cotarnine was prepared by adding aqueous potassium hydroxide to a solution of cotarnine chloride. The precipitate of cotarnine was filtered off, washed with a little water, and dried in a dessicator.

Pyrrole (0.32 ml., 1.1 m.; freshly distilled) was added to cotarnine (1.0 g., 1.0 m.). After about 2 minutes, the mixture became hot, and within several minutes it crystallised to a hard lump m.p. 146-147° (dec.). This crude product was recrystallised three times from benzene (charcoal), giving white prisms m.p. 148-149° (dec.). (Found: C: 66.8; H: 6.28; N: 9.82. $C_{16}H_{18}O_3N_2$ requires: C: 67.1; H: 6.33; N: 9.79%).

Hot solutions of the product turn brown when exposed to the air. The product gives a red colouration with Ehrlich's reagent. A picrate which was prepared in benzene melted at about 97°. When attempts were made to recrystallise this from ethanol, the only product isolated was cotarnine picrate (mixed melting-point with the authentic picrate, m.p. 143-145°). When anhydrocotarnine pyrrole was dissolved in cold dilute hydrochloric acid and left

standing for 2 hours, the solution became yellow. The colour of the solution was indistinguishable from that of a solution of cotarnine chloride. Similar yellow solutions were obtained more rapidly by using hot dilute or cold concentrated hydrochloric acid.

Reaction 18

Between Cotarnine and 4-Methyl-2-veratrylpyrrole

Fourth Experiment A mixture of cotarnine (250 mg., 1.0 m.), the pyrrole (230 mg., 1.0 m.) triethylamine (10 ml.) and pyridine (10 ml., dried over potassium hydroxide) was left standing in an atmosphere of nitrogen for 3 weeks. The solvents were then evaporated under reduced pressure. The residual brown gum was dissolved in a minimum of benzene and the solution left standing under nitrogen. After an interval of several days, a solid began to form, and after several more days precipitation seemed to have stopped. The solid material was transferred to a porous plate and washed with a little ether. The resulting product melted at 200-202° (107 mg., corresponding to 23%). A satisfactory recrystallising solvent could not be found. A sample was precipitated from its solution in benzene-ethanol by standing at 0° for 3 days. The precipitate melted at 219-221° (dec.). When viewed through a polarising microscope, it seemed to be at least partly crystalline. This product was probably identical with that of the sixth experiment.

Sixth Experiment Cotarnine (80 mg., 1.0 m.) and the pyrrole (73 mg., 1.0 m.) were intimately mixed, then heated at 113-117° and 16 mm. pressure for 30 minutes. After cooling, the brown gummy product was treated with a little warm ethanol and scratched. The gum dissolved, and a white precipitate appeared. This was filtered off, washed with a little ethanol, and dried over phosphorus pentoxide. It melted at 216-218° and weighed 19 mg. (corresponding to 15%). Reprecipitation from benzene-ethanol at 0° gave a white, probably crystalline powder m.p. 217.5-218° (dec.).
(Found: C: 66.79; H: 6.52; N: 5.88. $C_{25}H_{28}O_5N_2$ requires: C: 66.82; H: 6.47; N: 6.42%).

Reaction 19

Between Cotarnine and Indole

Cotarnine (4.05 g., 1.0 m.) was dissolved in the minimum of ethanol (18 ml.). The solution was filtered to remove a small quantity of insoluble material. Indole (2.0 g., 1.0 m.) was then added, and dissolved readily. After about 1 minute crystals appeared and grew rapidly; after several hours, crystallisation seemed to be complete. The product was filtered, washed with a little ethanol, and dried over sulphuric acid, giving pale brown prisms m.p. 130-131° (5.25 g., 91.5%). In an attempt to purify it, this product was recrytallised from ethanol (charcoal), ethanol,

ethanol; but the melting-point fell slightly. Recrystallisation from benzene (charcoal), benzene, benzene (alumina), however, gave colourless prisms m.p. 131.5-132° (dec.). (Found, mean of two analyses: C: 71.22; H: 5.67; N: 8.01. $C_{20}H_{20}O_3N_2$ requires: C: 71.42: H: 5.95; N: 8.33%). The recovery from benzene was only about 50%. The product gives a red colouration with Ehrlich's reagent.

Reaction 20.

The Preparation of 2:4-Dimethylpyrrole from 2:4-Dimethyl-3:5-dicarbethoxypyrrole

A mixture of 2:4-dimethyl-3:5-dicarbethoxypyrrole (20 g.), potassium hydroxide (45 g.), water (25 ml.) and a little sand, was heated at 130° for 4 hours. (47). After cooling, there was an unavoidable delay of 1 day, then the mixture was steam distilled. The distillate was extracted twice with ether, and the extracts were combined, dried over sodium sulphate, then fractionally distilled. The major fraction distilled at 160-165°/760 mm, and this was assumed to be the product. After redistillation it weighed 0.18 g., a yield of only 2%.

Reaction 21

Between Cotarnine and 2:4-Dimethylpyrrole

Cotarnine (0.45 g., 1.0 m.) was dissolved in the minimum of ethanol, and the solution was filtered to remove a small amount of insoluble material. 2:4-Dimethylpyrrole (0.18 g., 1.0 m.) was added, and dissolved readily. The mixture was then left standing at room temperature in an atmosphere of carbon dioxide. Even after 1 year, no solid had formed.

Reaction 22

The Preparation of N-Methylpyrrole from Methylamine Mucate

First Experiment The reaction was conducted in a distillation flask (175 ml.), with its side-arm connected to a water condenser. A plug of glass wool was inserted in the condenser to moderate the flow of gas through it. Methylamine mucate (25 g., see below for preparation) and glycerol(12 ml.) were added to the flask, and the flask was heated with a bunsen as rapidly as foaming would permit. The distillate was treated with pellets of potassium hydroxide, when a brown oil appeared. The oil was separated and dried over more potassium hydroxide. Crystals of a by-product now appeared; this was N-methylpyrrole-2-carboxylmethylamide, m.p. 82-87° (lit. (52): 89°). The pellets of potassium hydroxide

were removed, and the mixture of oil and crystals was distilled. The main fraction distilled at 110°/760 mm. (lit. N-methylpyrrole: 114-117°), and this was assumed to be N-methylpyrrole (1.78 g., 24%)

Second Experiment The above apparatus was used, but the flask was immersed in an oil-bath to give more control over the reaction temperature. Methylamine mucate (19 g.) was heated at 200° for 1.5 hours. After cooling, sodium hydroxide (20 g.) and water (10 ml.) were added to the flask. The oil-bath was then replaced by a sand-bath, and the flask was heated strongly for 0.75 hours. The combined distillates were treated with pellets of potassium hydroxide. Crude N-methylpyrrole separated, but, when this was removed and dried over more potassium hydroxide, no solid appeared (c.f. above experiment). The product was distilled; the main fraction distilled at 110°/760 mm. (2.18 g., 39%).

Methylamine Mucate Mucic acid was added to a slight excess of aqueous methylamine, giving an aqueous solution of methylamine mucate. The product was precipitated by adding several volumes of ethanol, then filtered off and dried in vacuo.

Reaction 23

Between Cotarnine and N-Methylpyrrole

First Experiment N-Methylpyrrole (0.5 g., 1.25 m.) was added to cotarnine (1.18 g., 1.0 m.). After several hours, there seemed to

have been no reaction. Chloroform (10 ml.) was added, and on warming, the reactants all dissolved. The mixture was left standing at room temperature. After 2 days, a sample of the reaction mixture was evaporated under reduced pressure. When the residual brown gum was treated with a little benzene, some solid appeared. Ethanol was added, and after standing, the solid was filtered off, washed with a little ethanol, and dried in vacuo over sulphuric acid. The resulting solid, m.p. 113-115° was probably crude anhydrocotarninechloroform. The yield was very small.

Second Experiment A mixture of cotarnine (0.695 g., 1.0 m.) and N-methylpyrrole (0.32 ml., 1.25 m.) was heated, using an oil-bath, at 115° for 30 minutes. After cooling, the reaction mixture was treated with ethanol and scratched, but no solid product could be isolated.

Third Experiment Cotarnine (3.95 g., 1.0 m.) was dissolved in a minimum of warm chloroform (18 ml.), and the solution filtered to remove a small amount of insoluble material. The warm solution was treated with N-methylpyrrole (1.64 ml., 1.1 m.), which dissolved readily. The mixture was allowed to cool, when some of the cotarnine reprecipitated. After standing for 1 week, the amount of the precipitate remaining seemed to be smaller, and after 2 weeks it had disappeared. After 8 weeks, the chloroform solution was dark red, and drops of water floated on it. The chloroform solution was

dried over sodium sulphate and evaporated under reduced pressure. The residual brown gum was covered with ethanol and scratched, whereupon it crystallised readily. The crystals were filtered, washed with a little ethanol, and dried in a dessicator containing sulphuric acid. This gave crude anhydrocotarninechloroform m.p. 93-113.5° (1.96 g., 31% from the cotarnine). The crude product was recrystallised twice from ethanol (charcoal), giving pure anhydrocotarninechloroform as large, colourless prisms m.p. 113.5-114°. (Found: C: 46.73, 46.15; H: 4.06; N: 4.08; Cl: -, 27.30, 30.1. $C_{13}H_{14}O_3NCl_3$ requires: C:46.09; H: 4.13; N: 4.13; Cl: 31.46%).

Reaction 24

The Preparation of N:N-Dimethylbenzamide from Dimethylamine and Benzoyl Chloride

To a mixture of aqueous dimethylamine (75 ml., 25% w./v., 1.25 m.), potassium hydroxide (37 g., 2.0 m.) and water (75 ml.), stirred, and maintained at 0°, benzoyl chloride (38.4 ml., 1.0 m.) was added over a period of 15 minutes. Stirring was continued for a further 5 minutes. The reaction mixture was then extracted with chloroform, and the extracts were combined, dried over sodium sulphate, and distilled. The main fraction distilled at 140-144°/16 mm; it later crystallised to a white solid, m.p. 42-43°.

This was recrystallised by dissolving it in the minimum of ether at room temperature, then cooling to -80° ; it was filtered at the same temperature (p. 161). Acetone-solid carbon dioxide was used as the refrigerant. After drying in vacuo, the product consisted of large crystals of dimethybenzamide m.p. 42.5-43.5° (lit. 43°) (39.3 g., 79%). The recovery from the recrystallisation was about 90%.

Reaction 25

Between N:N-Dimethylbenzamide, Phosphorus Oxychloride and Pyrrole.

Second Experiment Phosphorus oxychloride (1.37 ml., 1.0 m.; freshly distilled) was added to dimethylbenzamide (5.32 g., 2.4 m.). On slight warming, the mixture formed a homogeneous solution. (In contrast with the case of dimethylformamide (55), this occurred with absorption of heat). This solution was treated with pyrrole (1.00 g., 1.0 m.; freshly distilled) and the resulting solution allowed to stand at room temperature for 16 days. A sample (2.87 g.) of the brown, viscous reaction mixture was then weighed into a separating funnel, and crushed ice was added, forming a dark yellow solution. This solution was washed four times with an equal volume of benzene (a control experiment having shown that this treatment would remove virtually all starting material). The first washing was brown, the others colourless. The aqueous solution was yellow. It now gave no colouration with Ehrlich's reagent, showing that all

the pyrrole had been removed.

For characterisation, the aqueous solution was treated with a solution of sodium hydroxide (1.5 g.,) in water (3 ml.). Fine yellow globules appeared immediately; they crystallised on standing. The product was filtered off, and dried in a dessicator containing sulphuric acid. This gave crude 2-benzoylpyrrole, m.p. 73-75° (0.781 g., 92%). It was recrystallised twice, and then consisted of white needles tinged pink, m.p. 75-77° (lit. (57) 77-78°). This material gave no reaction with Ehrlich's reagent.

The preparation of the oxime (77) required a long reaction time (78): 60 hours. On cooling the reaction mixture, the oxime crystallised as thin colourless needles, m.p. 146-148°. Recrystallisation from ethanol-water (charcoal) raised the melting point to 147.5-148.5° (lit. (78): 147°).

Reaction 26

Between N:N-Dimethylbenzamide, Phosphorus Oxychloride and N-Methylpyrrole

Phosphorus oxychloride (2.26 ml., 1.0 m.; freshly distilled) was added to dimethylbenzamide (5.50 g., 1.5 m.; from R.24). On slight warming the mixture formed a homogeneous solution. The solution was treated with N-methylpyrrole (2.18 ml., 1.0 m.; freshly distilled; from R.22) and the resulting mixture was left standing in a stoppered vessel, at room temperature. After 3 days, the reaction

mixture was transferred to a separating funnel, and shaken with a mixture of ice (20 g.) and water (40 ml.). The resulting aqueous solution was washed with benzene (6 x 30 ml.). The first benzene washing was yellow and the remainder colourless; the aqueous solution remained yellow.

For characterisation, the aqueous solution was treated with a solution of potassium hydroxide (17 g.) in water (50 ml.), and heated on a steam-bath. (The literature (57) suggested that this treatment would be unlikely to harm the desired 1-methyl-2-benzoylpyrrole.) Dimethylamine, detected by its smell and action on red litmus, was evolved for at least 15 minutes. After heatingfor 30 minutes, the mixture was allowed to cool, when a brown oily product appeared. The mixture was extracted with chloroform (3 x 20 ml.), and the extracts were combined, dried over sodium sulphate, and evaporated. The brown, oily residue weighed 3.18 g. Its density ($d^{15°}$) was 1.12 (lit. [58] for 1-methyl-2-benzoylpyrrole: $d^{15°}_{4°}$ = 1.131). Its refractive index ($n^{15°}$) was 1.6208 (lit. [58]: $n^{15°}_{D°}$ = 1.6225).

A sample (0.97 g.) of the brown, oily residue was dissolved in ether (1.5 ml.), and the solution left standing at -16° (refrigerator). After 1 hour, some solid had been deposited. On filtering, two fractions were obtained :

Fraction 1) : a white solid; and

Fraction 2) : a brown filtrate.

Fraction 1) melted at 70-85° and weighed 0.309 g. Recrystallisation

from ether, ether (charcoal and alumina), ether, yielded colourless prisms m.p. 94.5-95.5°. (Found: C: 77.20; H: 5.99; N: 7.8. $C_{12}H_{11}NO$ requires C: 77.84; H: 5.95; N: 7.57%). A 2:4-dinitrophenylhydrazone was prepared (77), and after recrystallisation from n-butanol (charcoal), n-butanol, ethyl acetate, ethyl acetate, this melted at 208-209°. (Found: C: 59.07; H: 4.26; N: 19.0. $C_{18}H_{15}N_5O_4$ requires: C: 59.18; H: 4.11; N: 19.18%). The above substance m.p. 94.5-95.5° was probably 1-methyl-3-benzoylpyrrole. If so, the yield of the crude product m.p. 70-85° was 20% (from the pyrrole).

Fraction 2) was passed down a column (diameter 1.2 cm.; length 9 cm.) of alumina, using benzene-petroleum ether (1:4 by volume) as the solvent. The central fraction was evaporated, and the colourless residue distilled at 115-118° (oil-bath temperature)/0.2 mm. The distillate had $n^{15°} = 1.6220$. (Found: C: 78.27; H: 6.38; N: 7.41. $C_{12}H_{11}NO$ requires: C: 77.84; H: 5.95: N: 7.57%). A 2:4-dinitrophenylhydrazone was prepared, but could not be purified satisfactorily. Fraction 2) was probably crude, ethereal 1-methyl-2-benzoylpyrrole. If so, the yield was about 50% (from the pyrrole).

Reaction 27

The Preparation of Veratric Aldehyde by Methylating Vanillin

The reaction (59) was performed in a flask (1 L.) fitted with a stirrer, reflux condenser, and two dropping funnels. Vanillin (76 g., 1.0 m.) was added to the flask, and melted by warming with a bunsen. Stirring was then commenced, and dimethyl sulphate (59 ml., 1.0 m.; pure (74)) and a solution of potassium hydroxide (42 g., 1.2 m.) in water (75 ml.) were run in simultaneously, the addition taking 30 minutes. The reaction mixture was transferred to a beaker and allowed to stand for 12 hours. By then, the product had solidified. It was filtered off, washed with ice-cold water, and dried in a dessicator. The resulting crude product consisted of white needles, m.p. 41-43° (lit. (89) 46°). It was used (R.28) without further purification. The yield was 65.5 g. (79%).

Reaction 28

The Preparation of Veratric Acid by Oxidising Veratric Aldehyde

The reaction (60) was performed in a flask (5 L.) equipped with a stirrer and a dropping funnel. The flask was placed on a steam bath and veratric aldehyde (65.5 g.) and water (1.5 L.) were added. The mixture was heated to a temperature of 70-80°, and this

temperature was maintained throughout the reaction. With stirring, a solution of potassium permanganate (90 g.) in water (1.8 L.) was added over a period of 2 hours. Stirring and heating were continued for a further hour. The reaction mixture was then basified with 10% potassium hydroxide, and filtered (filtercel) while hot. The solid remaining in the filter funnel was washed with hot water. The filtrate and washings, were combined, and allowed to cool, then acidified (congo red) with concentrated hydrochloric acid. This precipitated a white creamy product. The product was filtered, and washed with a little ice-cold water. It was recrystallised from a mixture of ethanol (300 ml.) and water (1400 ml.). The resulting product consisted of white needles m.p. 180.5-182°. (lit. (90) 181°). It weighed 68.7 g., a yield of 94%.

Reaction 29

The Preparation of Veratroyl Chloride from Veratric Acid and Thionyl Chloride

A mixture of veratric acid (20 g.) and thionyl chloride (16 ml.) was refluxed for 2 hours, then the excess thionyl chloride was distilled off. On cooling, the residue crystallised. It was recrystallised from benzene-petroleum ether (charcoal) and dried in vacuo, giving large, pale-brown needles, m.p. 70-71° (20.86g., 95%).

Reaction 30

The Preparation of N:N-Dimethylveratramide from Veratroyl Chloride and Dimethylamine

Aqueous dimethylamine (5.62 ml. of 25% w/v., 1.25 m.) was added to a solution of potassium hydroxide (2.8 g., 2.0 m.) in water (25ml.). Veratroyl chloride (5 g., 1.0 m.) was then added in small portions with occasional agitation. The mixture became warm. The brown reaction mixture was extracted with chloroform (2 x 20 ml.), and the extracts were combined, washed with aqueous potassium hydroxide (bench, 20 ml.), dried over sodium sulphate, and evaporated. The residue was a colourless liquid. On cooling, it remained liquid for a while, then crystallised spontaneously, evolving much heat. It melted at 98-102° (lit.(91):102-3°) (4.21 g., 81%). Some of it was recrystallised from benzene-petroleum ether (charcoal), and the resulting material, consisting of white needles, m.p. 100-102° , was considered pure enough for use in the next reaction. Another portion of crude product (m.p. 98-102°) was distilled. The main fraction distilled at 205°/12 mm. Its m.p. was 102-102.5° distillation thus seems to be the better method of purification.

Reaction 31

Between N:N-Dimethylveratramide, Phosphorus Oxychloride and Pyrrole.

Phosphorus oxychloride (0.916 ml., 1.0 m.; freshly distilled)

was added to dimethylveratramide (2.092 g., 1.0m.). On warming, the mixture formed a pale yellow, homogeneous solution. This was allowed to cool, then pyrrole (0.705 ml., 1.0 m., freshly distilled) was added. The mixture was shaken and warmed to homogeneity, then again allowed to cool. It was now homogeneous, moderately viscous, and orange-coloured. The reaction vessel was carefully stoppered, and the mixture was left standing at room temperature. After standing for 1 day, some white solid which had crystallised was redissolved by warming. After standing for 2 days the reaction mixture was still viscous and was now coloured red. Part of it (1.85 g.) was weighed into a separating funnel; water (10 ml.) was added, and the funnel was shaken and warmed, forming a homogeneous solution. The solution was washed with benzene (4 x 10 ml.) (a control experiment having shown that this would suffice to remove most of the starting materials). The aqueous product was now coloured dark yellow.

For characterisation, this solution was treated with a solution of sodium hydroxide (1.25 g.) in water (2.5 ml.). A brown oil appeared. After 2 hours, the oil had crystallised to a sticky, brown solid. This solid (0.788 g.) melted in the region of 110°. It was recrystallised from methanol, giving colourless prisms m.p. 125-126.5° (0.408 g., 41%). A second recrystallisation from methanol raised the melting-point to 127.5-128°.
(Found: C: 67.80; H: 5.76; N: 5.28, 5.42. $C_{13}H_{13}NO_3$ requires: C: 67.53; H: 5.63; N: 6.06%). This product, probably

2-veratroylpyrrole, resembles 2-benzoylpyrrole in giving no colouration with Ehrlich's reagent.

Reaction 32

Between N:N-Dimethylveratramide, Phosphorus Oxychloride and 4-Methyl-2-veratrylpyrrole

It was desirable to use a minimum of the solvent, which was chloroform. The reactant with the smallest solubility in chloroform was found to be the pyrrole, which required about 7ml./g. at room temperature.

First Experiment A solution of phosphorus oxychloride (0.92 ml., 1.0 m.; freshly distilled) in chloroform (pure (74), 1.52 ml. of solution), the amide (209 mg., 1.0 m. from R. 30), and the pyrrole (217 mg., 1.0 m.; from R.15) were added to a test-tube (4.5 ml.). The tube was carefully stoppered, and left standing at room temperature for 1 day. The reaction mixture was then washed with water (5 ml.) into a separating funnel, and the resulting mixture was shaken, washed with benzene (6 x 5 ml.), and then with chloroform (pure (74), 2 x 2 ml.). The yellow aqueous solution which remained was examined for ultra-violet light absorption.

Second Experiment This was carried out like the first experiment with the difference that the reaction mixture was heated at 61°

(using boiling chloroform) for 6 hours. The ultra-violet absorption curve (curve 3) is shown on page 166.

Third Experiment In this experiment the quantities used were as follows: phosphorus oxychloride: 0.021 ml. (1.0 m.); chloroform: none, amide: 209 mg. (4.3 m.), the pyrrole: 50 mg. (1.0 m.). The reaction mixture was heated at 100° for 1 hour, then worked up as before.

Reaction 33

The Preparation of 1:4-Dimethyl-2-veratryl-Δ^1-pyrrolinium Iodide from 4-Methyl-2-veratryl-Δ^2-pyrroline and Methyl Iodide

The pyrroline (4.0 g., 1.0 m.; from R.14) was dissolved in ether (7 ml., dried over sodium) and the solution was filtered to remove a small amount of undissolved impurity. Methyl iodide (1.36 ml., 1.2 m.; decolourised with mercury, then distilled) was added, and the mixture was allowed to stand at room temperature. After 4 days, a creamy, white solid had precipitated. It was filtered off, washed with a little ether, and dried in vacuo, giving a white, microcrystalline solid m.p. 173-176°. This product was used in the next reaction without further purification. The yield in the present reaction was not estimated, but the overall yield for the present reaction and the following one was 92%. In a repeat preparation of the above material m.p. 173-176° , the product was

shown to contain much iodine, but unfortunately was not analysed at the time. It was set aside for purification and analysis at a later date, but a few weeks later it was found to be almost completely decomposed.

Reaction 34

The Preparation of 1:4-Dimethyl-2-veratryl-Δ^2-pyrroline from 1:4-Dimethyl-2-veratryl-Δ^1-pyrrolinium Iodide

The whole of the iodide prepared in reaction 33 (first preparation) was dissolved in water (50 ml.). The solution was washed with ether (2 x 50 ml.) (to remove any 4-methyl-2-veratryl-Δ^2-pyrroline), then made stongly basic with aqueous potassium hydroxide, and extracted with chloroform (3 x 50 ml.). The extracts were combined, dried over sodium sulphate, and evaporated. The residue was a pale brown liquid, presumed to be crude 1:4-dimethyl-2-veratryl-Δ^2-pyrroline (3.91 g., 92% over the two reactions). It was distilled, and the main fraction distilled at 140°/3mm., as a pale yellow liquid. This distillate was the product employed in reaction 35. It was not analysed (see the previous reaction). It resisted various attempts to crystallise it: from benzene, ether, ethyl acetate, methanol, or petroleum ether, at room temperature; or from ether at -80°. This product differed from the pyrroline of reaction 14 in at least two respects: firstly, it readily reduced

cold, ammoniacal silver nitrate; secondly, the picrate it formed was unstable to the air, degenerating over a few minutes to a dark green gum.

Reaction 35

The Preparation of 1:4-Dimethyl-2-veratrylpyrrole from 1:4-Dimethyl-2-veratryl-Δ^2-pyrroline

Third Experiment A mixture of pyrroline(1.04 g.) and palladium-charcoal catalyst (76) (20%, 0.26 g.) was heated in a stream of carbon dioxide at 260° for 3 minutes.

It was then allowed to cool. A second (equal) batch of the mixture was treated in the same way. The two reaction mixtures were combined and treated with hot benzene, and the catalyst was filtered off. The filtrate was washed with dilute hydrochloric acid, dried over sodium sulphate and then distilled. A distillate was obtained at 200° (oil-bath temperature)/0.5 mm. (0.81 g., corresponding to 39%). It could not be induced to crystallise. It gave an intense blue colouration with Ehrlich's reagent.

Fourth Experiment A mixture of the pyrroline (0.53 g.) palladium-charcoal catalyst (20%, 0.13 g.) and mesitylene (pure(74), 2.5 ml.) was refluxed in a stream of carbon dioxide for 45 minutes. After cooling, the reaction mixture was filtered to remove the catalyst, which was then extracted with boiling benzene (2 x 2.5 ml.). The

mesitylene and benzene solutions were combined, washed with dilute hydrochloric acid (3 x 5 ml.), water (2 x 5 ml.), dried over sodium sulphate, then distilled by a type of "bulb distillation" (p.162). Three fractions were distilled :

Fraction 1), at 145-148° /0.3 mm.

Fraction 2), at 148-155°/0.3 mm.

Fraction 3), at 155-173°/0.3 mm.

Fraction 1). A sample was dissolved in ether and the solution cooled to - 78° (solid carbon dioxide-ether). A white solid precipitated and a little of this solid was applied to each of the fractions 1), 2) and 3). Fraction 1) crystallised, giving white needles m.p. 44-48° (76 mg.). Fraction 2) crystallised as white needles m.p. 40-44° (71 mg.). Fraction 3) did not crystallise; its weight was very small. The total weight of crystalline material was thus 147 mg. (corresponding to 2%).

Fifth Experiment A mixture of the pyrroline (290 mg.), palladium-charcoal catalyst (72 mg., 20%) and quinoline (2 ml., distilled from catalyst, dried with catalyst over potassium hydroxide) was refluxed in a stream of nitrogen for 20 minutes. After cooling, the reaction mixture was filtered free of catalyst. The catalyst was extracted with boiling chloroform (10 ml.) then the filtered reaction mixture and chloroform were combined, and washed with dilute hydrochloric acid (4 x 12 ml.), water (2 x 6 ml.) dried over sodium sulphate, and distilled (p.162). Two fractions were

obtained :

Fraction 1), distilled at 145-151°/0.3 mm. It crystallised as white needles m.p. 43-47° (149 mg.).

Fraction 2), distilled at 151-175°/0.3 mm. It would not crystallise. It weighed very little.

The total yield of crystalline product was thus 149 mg., (corresponding to 52%). A sample of pyrrole prepared by the last method was purified and analysed (see below).

Purification of the Product A considerable number of methods was tried, but most of these were unsatisfactory for one reason or another. Recrystallisation was tried, using a variety of solvents, but none was able to remove the oily byproduct. (Acetone, benzene, ether, petroleum ether and mixtures of petroleum ether with benzene, ether, ethyl acetate, toluene or xylene were all used with cooling to - 16°. Ether, ethyl acetate, methanol and toluene were also used with cooling to -78°). Other methods found ineffective for the same reason were: extraction with petroleum ether, charcoaling the benzene solution, and column chromatography (alumina with benzene-petroleum ether). Further attempts involved the formation of derivatives. No picrate could be isolated. The pyrrole (sample m.p. 45-50°) was found to be soluble in concentrated hydrochloric acid. When the pyrrole was regenerated, however, its melting-point was lower (36-40°), indicating that this solubility could not be used to effect a purification.

It was noted that the oily byproduct appeared to be unsaturated, so a selective oxidation was attempted. A mixture of the pyrrole (143 mg., m.p. 43-45°, from a repeat of the fifth experiment), potassium permanganate (100 mg.) and acetone (5 ml., pure (74)) was left standing at room temperature for 20 minutes. The mixture was then diluted with water, extracted with benzene and the extracts dried and passed down a short column of alumina. The column was eluted with benzene-petroleum ether (1:1 by volume) and the eluate which gave a blue colouration with Ehrlich's reagent was collected and evaporated. The residue crystallised, and now melted 49.5-50.5° (23 mg., 16% recovery). A mixture of this product with the crude pyrrole (m.p. 43-45°) melted at 48-49.5°, suggesting that the pyrrole had not undergone any structural change. The product m.p. 49.5-50.5° was analysed. (Found (mean of three analyses): C: 72.44; H: 7.43; N: 6.00. $C_{14}H_{17}NO_2$ requires: C: 72.73; H: 7.36; N: 6.06%)

For routine purifications, the method adopted was as follows. The crude pyrrole (m.p. 43-45°) was warmed with petroleum ether (50 ml./g.) to 35°. Only part of the material dissolved. The petroleum ether was then decanted and cooled to -16°, when the pyrrole was deposited as white needles m.p. 48.5-49.5° (40% recovery). At a later date it was found that column chromatrography (alumina) with benzene and cyclohexane (3:7 by volume), all these materials being analytically pure, gave a sample of the pyrrole m.p. 51-52°.

The method was ineffective with the less pure solvents.

The pyrrole gives an intense blue colouration with Ehrlich's reagent. A sample of the pyrrole kept in a corked tube at room temperature for several months was found to have decomposed to a colourless solid, m.p. 80-110°.

Reaction 36

Between N:N-Dimethylveratramide, Phosphorus Oxychloride and 1:4-Dimethyl-2-veratrylpyrrole

In all the experiments and control experiments, the quantities of reactants (where used) and chloroform (where used) were the same as in the first experiment; the method of working up was also the same.

First Experiment Phosphorus oxychloride (0.23 ml., freshly distilled) was dissolved in chloroform (5 ml., pure (74)). A portion (0.20 ml., 1.0 m.) of this solution was placed in a small test-tube (2.5 ml.), and treated with the amide (20.9 mg., 1.0 m.; from R. 30), then the pyrrole (23.1 mg., 1.0 m.; from R. 35). The tube was carefully stoppered, and the mixture was allowed to stand at room temperature for 1 day. It was then shaken with water (10 ml.), and the resulting mixture washed with benzene (6 x10 ml.) to remove starting material, giving a yellow aqueous product. The ultra-violet

absorption of this aqueous product was then measured. To compensate for benzene etc., dissolved in the aqueous product (c.f. R.32), the water to be used in the spectrophotometer "solvent cell" was also washed with benzene, using the same volumes and the same number of washings as with the aqueous product.

Other Experiments In the second experiment, the mixture was allowed to react at 61° for 1.5 hours (giving absorption curve 4, p. 166). In the third experiment the chloroform was omitted, an excess of amide was employed as the solvent (totalling 46 mg., 2.0m.) and the reaction was carried out at 100° for 15 minutes. The fourth and fifth experiments were the same as the second, except that the reaction times were 3 hours and 6 hours respectively.

Reaction 37

The Preparation of N-Homoveratrylphenylacetamide from Homoveratrylamine and Phenylacetic Acid

In a boiling-tube (60 ml.), immersed in an oil-bath, a mixture of homoveratrylamine (10.07 g., 1.0m.) and phenylacetic acid (7.55 g., 1.0 m.) was heated at 190°. Steam was eliminated, and its escape was facilitated by adding porous pot. After 25 minutes, the evolution of steam had almost ceased, and after 45 minutes the mixture was allowed to cool. The cooled reaction mixture remained liquid for several hours, then crystallised spontaneously

with evolution of heat. The crude product was recrystallised from aqueous ethanol (50%, 60 ml.), giving a white, crystalline product, m.p. 106-109° (lit. (66) 111°) (13.4 g., 81%).

Reaction 38

The Preparation of 1-Benzyl-6:7-dimethoxy-3:4-dihydroisoquinoline from N-Homoveratrylphenylacetamide

A mixture of the amide (13.37 g., 1.0 m.), phosphorus oxychloride (30 ml., 13.5 m., freshly distilled) and toluene (pure (74), 50 ml.), was refluxed for 1.5 hours. On cooling, the reaction mixture deposited large, yellow crystals of a phosphate. This was filtered on a sintered glass filter, washed with a little toluene, and dried in vacuo. It weighed 15.14 g., Recrystallisation from ethanol (40 ml.) gave a white, crystalline product. This was dissolved in a minimum of cold water, and the solution treated with an excess of aqueous sodium hydroxide. The product was precipitated as a white, crystalline solid. It was filtered off, washed with a little water, and dried in vacuo; it weighed 9.59 g., (76%). This material was used in the next reaction without further purification.

Reaction 39

The Preparation of 1-Benzyl-6:7-dimethoxy-2-methyl--3:4-dihydroisoquinolinium Iodide from 1-Benzyl-6:7-dimethoxy-3:4-dihydroisoquinoline and Methyl Iodide

The isoquinoline (9.59 g.) and methyl iodide (40 ml., decolourised with mercury, thendistilled) were added to a flask (100 ml.). The flask was warmed until the isoquinoline had dissolved; it was then stoppered, and the reaction was allowed to proceed at room temperature for 1 day. On evaporating the reaction mixture a crude product was obtained, which melted at 95-99°. An attempt to recrystallise this from ethanol gave a product melting over a wide range: 103-130° (13.02 g., corresponding to 90%). A second recrystallisation raised the melting point to 122-145°. Time could not be spared for a full investigation of this behaviour, so other solvents were tried. Water (charcoal) was found to be suitable. With this solvent the above material (m.p. 122-145°) was recrystallised twice, giving sulphur-yellow needles m.p. 100-102°. Further recrystallisation did not change the melting-point significantly, so this product was assumed to be pure. (Found : C: 52.04; H: 5.38; N: 2.98; I: 26.5. $C_{19}H_{22}NO_2I.H_2O$ requires: C: 51.70; H: 5.44; N: 3.17; I: 28.8%).

Reaction 40

The Preparation of N-Methylcorydaldine by Hydrolysing 1-Benzyl-6:7-dimethoxy-2-methyl-3:4-dihydroisoquinolinium Iodide.

First Experiment A mixture of the iodide (2g., 1.0 m.) and aqueous sodium hydroxide (20 ml. of 3%, 3.2 m.) was heated under reflux. Soon after heating was commenced, the iodide turned to a brown oil. This oil remained suspended in the aqueous phase throughout the reaction, generally as a single drop. After refluxing for 45 minutes, the reaction mixture was allowed to cool. It was diluted with water (50 ml.) and extracted with benzene (3 x 25 ml.). A portion (15 ml.) of the extract was washed with dilute hydrochloric acid (5 x 5 ml.), with water (5 ml.), dried over sodium sulphate and evaporated. The residue could not be induced to crystallise. It was therefore distilled at 160° (oil-bath temperature)/0.2 mm. The distillate was recrystallised from benzene-petroleum ether (charcoal), then ether. The product obtained was shown (by performing a mixed m.p. with authentic amide from R.41) to be the desired amide. (m.p. of product: 123-125°; authentic amide: 125.5-127°; mixture: 123-126°). The yield was very small.

Second Experiment A mixture of the iodide (1g., 1.0m.), potassium hydroxide (7.5 g., 55 m.), water (37.5 ml.) and ethanol (12.5 ml.), was heated under reflux. The reaction mixture became homogeneous, boiling at 80°. After refluxing for 1.5 hours, the mixture was allowed to cool. Bright yellow crystals appeared,

leaving a colourless mother liquor. The mother liquor was treated like the reaction mixture above, but none of the desired amide was obtained. The yellow product was the methylene base : 1-benzal-6,7-dimethoxy-2-methyl-1,2,3,4,-tetrahydroisoquinoline, m.p. 92.5-93.0° (0.63 g., 91%). Recrystallisation from ethanol gave yellow plates m.p. 92.5-93.0°. (Found: C: 76.68; H: 6.98; N: 4.8. $C_{19}H_{21}NO_2$ requires: C: 77.29; H: 7.12; N: 4.75%).

Reaction 41

The Preparation of N-Methylcorydaldine by Oxidising 1-Benzal-6,7-dimethoxy-2-methyl-1,2,3,4,-tetrahydroisoquinoline.

A solution of the base (230 mg., 1.0 m., from R.40) in benzene (10 ml.), and a solution of potassium permanganate (240 mg., 2.0 m.) in bench dilute sodium hydroxide (5 ml.) and water (50 ml.), were shaken vigorously together. At first, the reaction mixture was purple; after 15 minutes it was green, and after 60 minutes, brown. Shaking was stopped. More benzene (10 ml.) was added, and the mixture shaken again for a few seconds; the benzene layer was then separated. The aqueous layer was extracted twice more with benzene (2 x 20 ml.). The benzene fractions were combined, washed with dilute sodium hydroxide (10 ml.), dilute hydrochloric acid (3 x 5 ml.: yellow, pale yellow, colourless), water (10 ml.), dried over sodium sulphate and evaporated. The residue crystallised very

readily; it melted at 118-122° (110 mg., 64%). It was recrystallised from benzene-petroleum ether (charcoal), benzene-petroleum ether, then distilled at 2 mm., and the distillate recrystallised from ether. The resulting product melted at 125-125.5° (lit. (65): 124-125°). (Found: C: 65.36; H: 6.71; N: 6.2. $C_{12}H_{15}NO_3$ requires: C: 65.16; H: 6.79; N: 6.33%).

Reaction 42

Between N-Methylcorydaldine, Phosphorus Oxychloride and 1:4-Dimethyl-2-veratrylpyrrole.

In both of the experiments, and in the control experiment, the quantities of reactants (where used), and of solvents, were the same as in the first experiment; the method of working up was also the same.

First Experiment Phosphorus oxychloride (0.23 ml., freshly distilled) was dissolved in chloroform (5 ml., pure (74)). A portion (0.20 ml., 1.0 m.) of the solution was treated with the amide (22.1 mg., 1.0 m.; from R.41), then the pyrrole (23.1 mg., 1.0 m.; from R.35) and the resulting mixture was heated at 61° for 1.5 hours. The reaction mixture was then shaken with water (10 ml.). The mixture was washed with benzene ("Analar", 6 x 10 ml.) to remove starting materials, and with cyclohexane ("B.D.H., Spectroscopically Pure", 3 x 3 ml.) to remove the benzene. The ultra-violet absorption

of the aqueous product was then measured (curve 5 , p.166).

Other Experiments The control experiment was carried out like the above, except that the pyrrole was omitted. The second experiment was also similar to the first, but in this case the reaction was conducted at room temperature for 1 day.

The ultra-violet absorption of the product of the first experiment was found to change on standing, the change seeming to be complete after 3 days. This lead (Part III) to the hypothesis that there had been two or more main reaction products.

Attempts were therefore made to separate two or more products from the aqueous product. (To simplify matters, the change was first allowed to go to completion by letting the aqueous product stand for 3 days).

(i). A sample of the aqueous product was washed with benzene (12 portions, each of 4 times the volume of the aqueous product).

(ii). A benzene-chloroform mixture was found which could extract an appreciable amount of the yellow material (s) from the aqueous prpduct. A sample of the aqueous product waswashed with this mixture (benzene: chloroform::1:6, by volume; 3 washings, each of the same volume as the aqueous product).

Neither (i) nor (ii), however, produced any significant change in the light absorption of the aqueous product.

The second experiment gave a product possessing a light absorption curve very similar to that of the first. Following the

same hypothesis, further attempts were made to separate two or more main products :

(iii). Preliminary experiments showed that the solubility of the yellow product(s) was high in chloroform, but greatly diminished by the addition of benzene, and high in water, but greatly diminished by the addition of chloride ions (hydrochloric acid or sodium chloride). A sample of aqueous product was therefore washed with successive portions of a benzene-chloroform mixture, until practically colourless. (benzene: chloroform::1:1, by volume; 10 portions, each of the same volume as the sample.) The resulting solution possessed an absorption curve which was quite different from that of the untreated aqueous product, suggesting that a separation had been achieved.

(iv). In fact, the curve obtained in (iii) was very similar to that of the control experiment with the pyrrole omitted, suggesting that a product formed in this control experiment was preferentially soluble in the aqueous phase of the solvent system of (iii). Hence, the yellow product was transferred from a sample of the aqueous product to a mixture of benzene and chloroform (1:1), and the yellow benzene-chloroform solution washed with an aqueous solution similar to that of (iii) (prepared by adding the appropriate amount of phosphorus oxychloride to water.). The benzene-chloroform solution was washed with the aqueous solution uhtil it was practically colourless (6 washings), and the product remaining in the benzene-

chloroform solution was then transferred, by a single washing with pure water, to the aqueous phase. The resulting aqueous solution, however, did not differ significantly in light absorption from the original aqueous product.

(v). A sample of the aqueous product was washed with ether, another with ethyl acetate, and another with methylene dichloride-carbon tetrachloride (10:1, by volume). None of these treatments produced a significant change in the ultra-violet absorption of the aqueous product.

(vi). Chromatography, using alumina and chloroform-acetic acid, was also tried without success.

(vii). Freezing Aqueous Solutions of the Product. When the aqueous product of the similar reaction 36 was frozen, the solid first deposited was quite colourless; only the last portion to freeze contained any of the yellow product. Partial freezing of the aqueous product of the present reaction, however, did not yield any material possessing an appreciably different light absorption.

Reaction 43

The Preparation of N-Homoveratryl-2-pyrrolidone from Homoveratrylamine and δ-Butyrolacetone

First Experiment The reaction was carried out in a small Baskerville "bomb". A mixture of homoveratrylamine (17.0 g., 1.0 m.;

freshly distilled) and γ-butyrolactone (8.05 g., 1.0m.; freshly distilled) was heated in the bomb at 280° for 2.5 hours. It was then allowed to cool. When the "bomb" was opened, a large quantity of gas escaped. The material left in the bomb consisted of a spongy black tar mixed with a small amount of a mobile brown liquid. Neither tar nor liquid could be persuaded to crystallise.

Second Experiment A mixture of homoveratrylamine (26.01 g., 1.0m.) and γ-butyrolactone (12.30 g., 1.0 m.) was heated under reflux in a stream of nitrogen. The colour of the mixture turned to yellow, then to a deep reddish-brown. During the first 2 hours, the emerging nitrogen deposited drops of a liquid presumed to be water (mobile, colourless, ether-insoluble). After refluxing for 3 hours, the mixture was allowed to cool. It was then fractionally distilled; the same flask was used, glass wool being added to make the distillation smooth. The main fraction distilled at 164-175°/0.4mm. (21.98 g., 61%). (Found: C: 67.95; H: 7.79; N: 5.55. $C_{14}H_{19}O_3N$ requires: C: 67.47; H: 7.63; N: 5.62%). This product would not crystallise on treating with ether or methanol, either at room temperature or at -78°.

Reaction 44

The Preparation of

8:9-Dimethoxy-2:3:5:6-tetrahydrobenzo[g]pyrrocoline

from N-Homoveratryl-2-pyrrolidone

First Experiment A solution of the pyrrolidone (2.0 g., 1.0 m.) in xylene (20 ml., pure (74)) was boiled under reflux. At intervals, portions of phosphorus pentoxide (totalling 10 g., 8.0 m.) were added, over a period of 1 hour. Heating was continued for a further half-hour. The reaction mixture was then transferred to a separating funnel, ice was added, and the mixture was shaken till the ice melted. The xylene layer was removed, and the brown, cloudy aqueous layer filtered (filtercel) and made strongly alkaline with sodium hydroxide solution (the use of concentrated ammonium hydroxide reduced the yield). The alkaline solution was extracted with chloroform (3 x 40 ml.), then the extracts were combined, washed with alittle water, and dried over sodium sulphate. This gave a colourless solution. If this solution was evaporated without taking special precautions, the residue consisted of dark red crystals. But if the soltuion was evaporated at a pressure of 10 cm. and heating with a waterbath at 40°, the residue consisted of white crystals tinged with red. The yield was estimated (via the picrate) to be about 27% .

A picrate was prepared by mixing a concentrated ethanolic solution of the red product with one of picric acid. It was

purified for analysis by recrystallisation from dilute acetic acid (10%). After four recrystallisations, the product was obtained as small yellow needles, m.p. 195.0-195.5° (dec.). (Found: C: 51.21; H: 4.31; N: 12.3. $C_{20}H_{20}O_9N_4$ requires: C: 52.17; H: 4.35; N: 12.17%).

Second Experiment A solution of the pyrrolidone (2.0 g., 1.0 m.) in toluene (10 ml.) was treated with phosphorus oxychloride (4.0 ml., 5.5 m.; freshly distilled). At first, a clear solution was formed; but, after about a minute, a cloudiness spread rapidly through the solution and an oil was precipitated. The mixture was heated under reflux, and much hydrogen chloride was evolved. After refluxing for 1.5 hours, the mixture was allowed to cool. On standing, a pale brown, crystalline precipitate appeared. It was filtered off; it weighed 2.97 g. It could not be recrystallised from ethanol (c.f. R.38) or other solvents. On keeping, it degenerated to a brown gum. A sample (0.67 g.) of it was dissolved in water then treated like the "aqueous layer" of the first experiment. The red, crystalline product melted at 100-103° and weighed 0.34 g. (80%). It was shown to be identical with the product of the first experiment by performing a "mixed melting point" on the picrates.

The above product, when freshly prepared, is an almost white, crystalline solid. Its chloroform solution is colourless, and gives only a faint blue colouration with Ehrlich's reagent. After exposing to the air at room temperature for several hours, the

solution is an intense red and gives an intense blue colouration with Ehrlich's reagent. After further exposure to the air, the colour turns to orange, and there is no longer any colouration with Ehrlich's reagent. In contrast to the free base, the salts seem to resist air oxidation. The picrate does not degenerate on keeping, and an aqueous solution of the phosphate has been exposed to the air for amonth without appreciable decomposition.

Reaction 45

The Preparation of 8:9-Dimethoxy-5:6-dihydrobenzo[g]pyrrocoline by Dehydrogenating 8:9-Dimethoxy-2:3:5:6-tetrahydrobenzo[g]pyrrocoline

The tetrahydropyrrocoline was always freshly prepared, as it deteriorates rapidly.

First Experiment A mixture of the tetrahydropyrrocoline (0.35 g., 1.0 m.), mercuric acetate (0.966 g., 2.0 m.) and dilute acetic acid (5%, 10 ml.) was heated at 100°. The deep red colour of the tetrahydro-compound rapidly turned to a less intense orange. There was apparently no further colour change, and no mercurous acetate (or other solid) was precipitated. After heating for 3 hours, the mixture was cooled, saturated with hydrogen sulphide and filtered (filtercel). The filtrate was basified and extracted with chloroform (4 x 5 ml.), then the extracts were combined and dried over sodium sulphate. Neither the mercuric sulphide (filtered off)

nor the chloroform extract would give a colouration with Ehrlich's reagent. From these results, and from the above-noted absence of a precipitate of mercurous acetate, it was inferred that very little, if any, of the desired product had been formed.

Second Experiment A solution of the tetrahydropyrrocoline (2 g.) in chloroform (40 ml., pure (74)) was allowed to stand at room temperature in an open concial flask (500 ml.). The colour of the solution became a progressively deeper red. At intervals, drops of the solution were tested with Ehrlich's reagent, and after 6 hours, the intensity of the colouration obtained seemed to have reached a maximum. The red chloroform solution was washed with dilute hydrochloric acid (6 x 30 ml., to remove any starting material), giving a pale yellow solution. This solution still gave an intense blue colouration with Ehrlich's reagent, and attempts were made to isolate a product from it.

(i). A sample of the yellow solution was evaporated, but the residue could not be induced to crystallise.

(ii). A sample of the yellow solution was evaporated, and the residue distilled at 160° (oil-bath temperature)/3.10^{-3}mm. Only a small proportion distilled. The distillate gave only a faint Ehrlich reaction, while the residue still gave a strong one, indicating that the pyrrole has not distilled.

Third Experiment A mixture of the tetrahydropyrrocoline (0.4 g., 1.0 m.), mercuric acetate (1.21 g., 2.0 m.) and amyl alcohol

(50 ml., dried over calcium sulphate then distilled) was refluxed in a stream of nitrogen for 1 hour. After cooling, the mixture was filtered (filtercel) to remove a little solid and tarry material. The filtrate was treated with dilute hydrochloric acid (10 ml.), saturated with hydrogen sulphide, and filtered. This gave a residue of mercuric sulphide and a filtrate; the latter was separated into an acid layer and an alcohol layer. The alcohol layer was washed with dilute hydrochloric acid, and the acid washings were combined with the above acid layer. The mercuric sulphide was extracted with boiling chloroform (2 x 15 ml.), which was then used (3 x 10 ml.) to extract any product remaining in the combined acid fractions. The chloroform and alcohol fractions were combined, washed with water (2 x 5 ml.), dried over sodium sulphate, and evaporated in a stream of nitrogen. The residue was distilled at 120° (oil-bath temperature)/6.10^{-3}mm. The distillate crystallised, forming a pale orange crystalline powder m.p. 119-121° (0.073 g., 18%). This was recrystallised from ethanol, giving white, lustrous plates m.p. 131-132°. (Found : C: 73.11; H: 6.45; N: 6.23. $C_{14}H_{15}O_2N$ requires: C: 73.34; H: 6.59; N: 6.11%). The ultra-violet absorption curve is shown on p.164(curve 1). The purified product gave the blue colouration with Ehrlich's reagent.

Fourth Experiment This was carried out in a similar manner to the third experiment, but the amyl alcohol was replaced by N-propanol (b.p. 97°). Tests with Ehrlich's reagent indicated that the amount

of pyrrole formed was negligible.

Fifth Experiment The tetrahydropyrrocoline (216 mg. 1.0 m.), chloroform (2ml.) and mercuric acetate (600 mg., 2.0 m.) were added to a round-bottomed flask (5 ml.). The chloroform was then evaporated. (This procedure was employed to provide good contact between the pyrrocoline and the mercuric acetate. The reactants were heated at 130° and in a stream of nitrogen for 1 hour. After cooling, the reaction mixture was treated with dilute hydrochloric acid (10 ml.) and chloroform (10 ml.), then saturated with hydrogen sulphide, and basified with ammonium hydroxide. The chloroform layer was separated, and the remaining layer was extracted with more chloroform (3 x 10 ml.). The chloroform fractions were filtered (filtercel), combined, washed with water (2 x 5 ml.), dried over sodium sulphate, and distilled at 120° (oil-bath temperature)/1×10^{-3}mm. The distillate crystallised, forming a white powder m.p. 119-121° (45 mg., 21%).

Reaction 46

Between Cotarnine and 8:9-Dimethoxy-5:6-dihydrobenzo [g] pyrrocoline

In a sealed tube, a mixture of cotarnine (237 mg., 1.0 m.; freshly prepared), the dihydropyrrocoline (229mg., 1.0 m.; freshly prepared) and benzene (0.5 ml., pure (74)) was heated in the vapour of boiling ethanol for 6 hours. After cooling, a sample (0.3 ml.)

of the reaction mixture was evaporated, and the residue was treated with a little ethanol and scratched. A white powder precipitated m.p. 124-128°. It was recrystallised from ethanol, but the recrystallised product was found to be dihydropyrrocoline starting material (by performing a test with Ehrlich's reagent, and a "Mixed melting point"). No other solid was isolated.

Reaction 47

Between N:N-Dimethylveratramide, Phosphorus Oxychloride and 8:9-Dimethoxy-5:6-dihydrobenzo [g] pyrrocoline

First Experiment Phosphorus oxychloride (0.043 ml.; freshly distilled) was dissolved in chloroform (2 ml., pure (74)). A portion (0.10 ml., 1.0 m.) of the solution was treated with the amide (4.9 mg., 1.0 m., from R.30) then with the pyrrocoline (5.4 mg., 1.0 m.; from R.45). The mixture was heated at 61° for 2 hours. After cooling, it was shaken with water (10 ml.), and the resulting mixture washed with benzene ("Analar", 4 x 10 ml.), then cyclohexane ("B.D.H. Spectroscopically Pure", 3 x 4 ml.). This gave an aqueous product, the ultra-violet absorption of which was measured and graphed (identical curves 6 and 8, pages 166 and 167).

Second Experiment This was carried out like the first experiment, but the amount of amide used was increased to 10 moles/mole of pyrrole. (curve 9, p. 167).

Reaction 48

Between N-Methylcorydaldine, Phosphorus Oxychloride and 8:9-Dimethoxy-5:6-dihydrobenzo [g] pyrrocoline

The N-methylcorydaldine (1.47 g., 4.9 m.; from R.41), chloroform (1.47 ml., pure (74)), phosphorus oxychloride (0.124 ml., 1.0 m.; freshly distilled) and pyrrocoline (0.31 g., 1.0 m.; from R.45) were heated together in a sealed tube at 61° (boiling chloroform) for 3 hours. After cooling, the mixture was shaken with water (30 ml.), and the resulting aqueous solution was washed with benzene (6 x 30 ml., "Analar"). After first trying a sample, most of the aqueous product was then trated with concentrated hydrochloric acid (8 ml.), which precipitated a considerable amount of a red, crystalline product. The red product was filtered off and dried; it weighed (slightly damp) 0.737 g. (corresponding to 108%). A sample of it was recrystallised for analysis from a mixture of acetone (pure (74)) and dilute hydrochloric acid (about 2N.) (acetone : acid :: 1:4 by volume), and then from dilute hydrochloric acid (1N.). After drying, the resulting product consisted of intensely orange-red needles, which sintered at about 150° and melted at about 195-205°. Attempts were made to purify this material further (a) by using charcoal, and (b) by conversion to the iodide (using aqueous potassium iodide) followed by further recrystallisation. The absorption curves of the products, however, differed very little from that of the above product (m.p. 195-205°), which

was therefore assumed to be pure. (Found, on undried material : C: 61.20; H: 6.40; N: 6.10; Cl : 13.32; ionic Cl : 13.31. On drying at 100°, the loss in weight was 0.53%. $C_{26}H_{29}O_4N_2Cl.HCl$, containing 0.53% of water, requires: C: 61.45; H: 6.01; N: 5.51; Cl: 13.95%. The dried material gave: C: 61.84; H: 5.84. $C_{26}H_{29}O_4N_2Cl.HCl$ requires: C: 61.75; H: 5.97; N: 5.54; Cl: 14.0%.) The ultra-violet absorption curve (curve 11 p.168) was found to be very similar to that of rubremetinium salts.

ADDITIONAL NOTES

(The first two notes apply throughout the thesis; the rest apply to Parts III and IV only).

Unaccompanied Arabic numerals refer to the Bibliography.

Unaccompanied Roman numerals refer to structural formulae, or to the substances these represent.

Analyses Most of the analyses were performed by Drs. Weiler and Strauss, Oxford, but those of the products of reactions 35, 45 and 48 were performed by Mr. P. R. W. Baker, at the Wellcome Research Laboratories, Beckenham, whose assistance is gratefully acknowledged.

Temperatures All temperatures, including melting points, are uncorrected.

Yields The yield given is often the yield of the crude product. This is because the purification of the crude product frequently involved a considerable loss of material, and the yield of the crude product then gives the most satisfactory indication of the amount of product formed.

Ehrlich's Reagent Ehrlich's reagent is a solution of p-dimethylaminobenzaldehyde in dilute hydrochloric acid. This reagent reacts readily with many pyrroles, giving intense colourations. It is widely used to test for pyrroles, and was frequently used for this purpose by the author.

Two methods were employed for the test. In the first method,

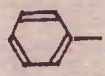
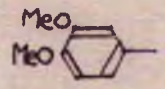
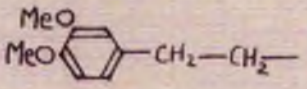
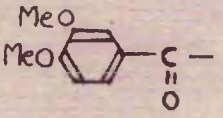
the material to be tested was obtained as a solution in a suitable solvent (e.g. water or ethanol) or solvent mixture. The solution was then treated with the reagent. In the second method, a drop of the material to be tested was put on a piece of filter paper, and the filter paper then treated with the reagent. The second method was generally more convenient; also, it was probably more sensitive.

The pyrroles prepared in reactions 15, 35 and 45 all gave deep blue colourations in this test, and the three colourations were very similar.

ABBREVIATIONS

Some of the abbreviations used occur frequently in Chemical literature.

The remainder are as follows :

R.	Reaction(s) (Where two numbers are given, these are inclusive)	
Th.	Theoretical Discussion (i.e. Part III)	
Exp.	Experimental Details (i.e. Part IV)	
m.	Molar Proportions	
dec.	Decomposes	
lit.	Literature	
(Ph-	Phenyl	: )
V-	Veratryl	: 
	Homoveratryl	: 
V-Co-	Veratroyl	: 

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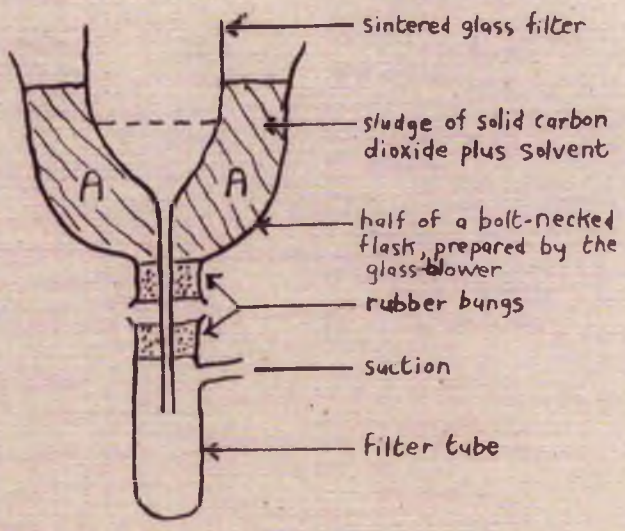
SOME APPARATUS USED

A Low-Temperature Filter

Used in : Reactions 7, 10, 24.

Procedure : The apparatus was generally used in recrystallisations at -78°, using solid carbon dioxide. The material to be recrystallised was dissolved in a suitable solvent (often ether or methanol), and the resulting solution was allowed to stand in a sludge of solid carbon dioxide plus the same solvent. When crystallisation seemed to be complete the space "A" was filled with more of the sludge, and the filter was left a few moments to allow it to cool. The product was then filtered.



Bulb Fractionation of Small Amounts of Material

Used In : Reaction 35.

Procedure : This apparatus was made from a piece of medium-bore glass tubing. The material to be distilled was dissolved in the minimum of chloroform, then, using a long pipette, the solution was transferred to the lowest bulb. The chloroform was carefully evaporated (porous chip). Glass wool was added to the residue through a glass tube. The top of the tube was connected to the vacuum pump and the tube was lowered into a bath of glycerol to just below the highest bulb. The bath was then heated, and the first fraction distilled into the highest bulb. By raising the tube to the appropriate height, other fractions were then distilled into the other bulbs. After the distillation, the fractions (as their benzene solutions) were removed with a bent pipette.

A large round-bottomed flask was used to contain the glycerol. The apparatus seemed to function more effectively with the receiving bulb just above the top of the flask, and the level of the glycerol adjusted to be near the top.

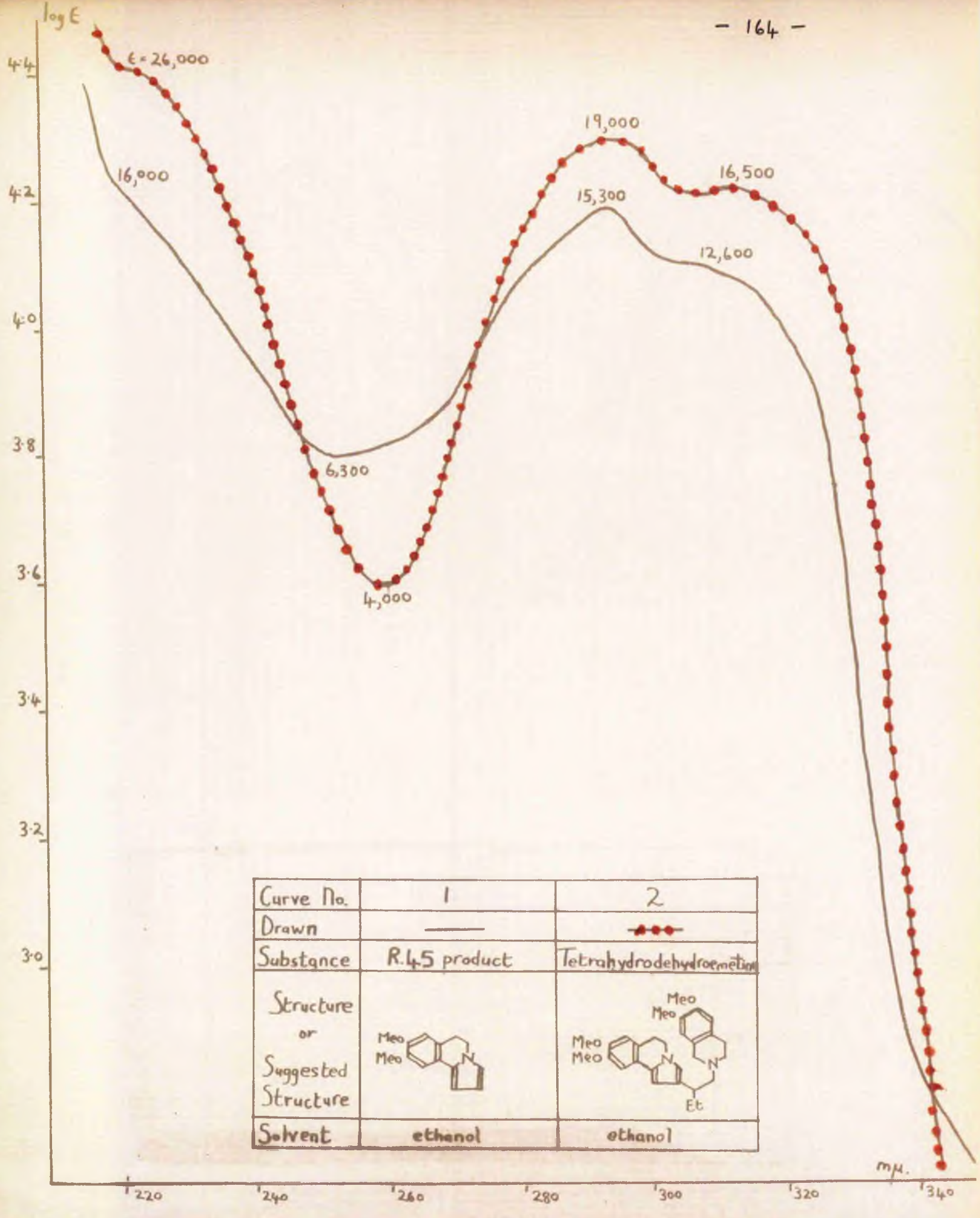
ULTRA-VIOLET ABSORPTION CURVES

In some of the reactions concerned, the products were not isolated. In such cases, the quantity plotted against the wavelength is : log (Optical Density) + an arbitrary constant, (the constant being chosen so that the curve lies near that of rubremetinium salts). In such cases, therefore, the height of the curve above the wavelength axis has no significance, and inferences can only be drawn from the shape of the curve.

The curves of rubremetinium salts, tetrahydrodehydroemetine and of the products of reaction 48, were measured on a Hilger "Uvispek" by Dr. A. J. Everett (of the Wellcome Research Laboratories, Beckenham) to whom I am grateful.

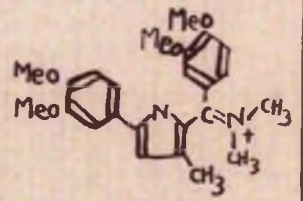
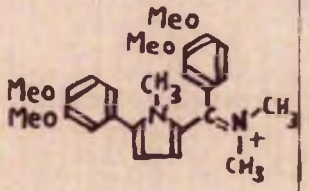
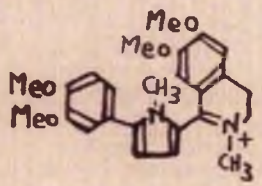
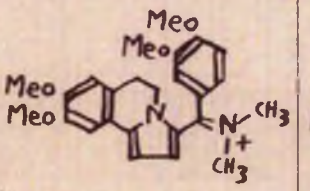
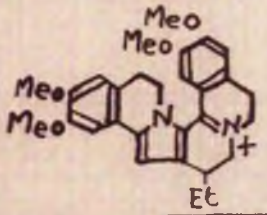
LIST OF CURVES

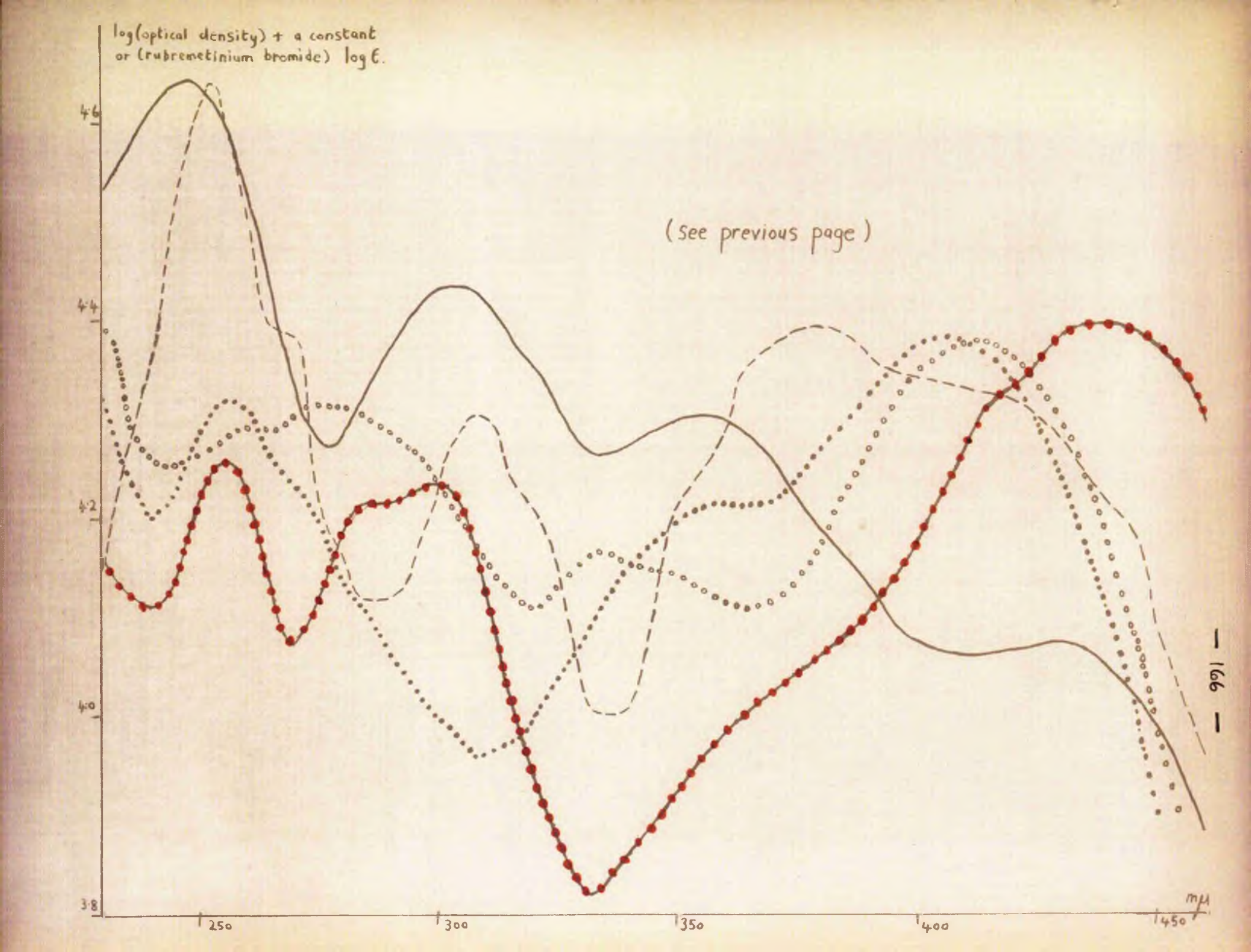
Curve		Page
1	R.45 product	164
2	Tetrahydrodehydroemetine	
3	R.32 (second experiment) product	166
4	R.36 (second experiment) product	
5	R.42 (first experiment) product	
6	R.47 (first experiment) product	
7	Rubremetinium Bromide	
8	R.47 (first experiment) product	167
9	R.47 (second experiment) product	
10	Rubremetinium Bromide	
11	R.48 product	168
12	Rubremetinium Bromide	



Curve No.	1	2
Drawn	——	●●●
Substance	R.45 product	Tetrahydrodehydroemetine
Structure or Suggested Structure		
Solvent	ethanol	ethanol

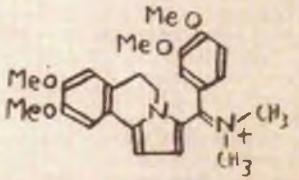
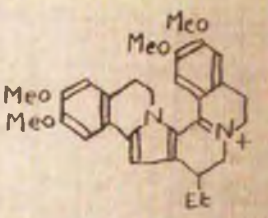
The table below refers to the following page:

Curve No.	3	4	5	6	7
Drawn	ooooooo	• • • • •	– – – – –	——	●●●
Substance	R.32 (2nd. exp) product	R.36 (2nd. exp) product	R42 (1st. exp.) product	R47 (1st. exp) product	Rubremetinium Bromide.
Desired or Suggested Structure					
Solvent	distilled water	distilled water	distilled water	distilled water	distilled water



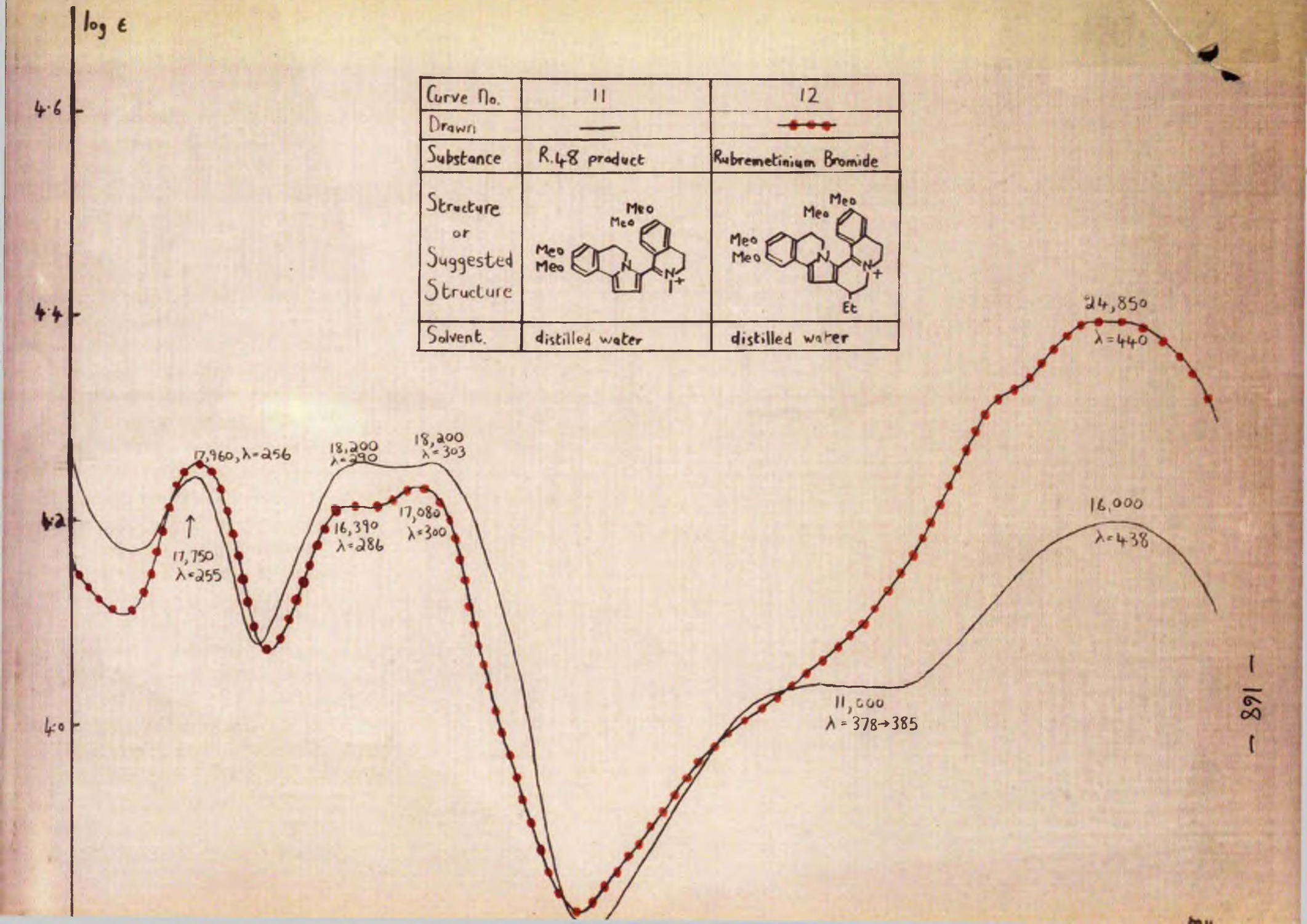
(see previous page)

log (optical density) + a constant
or (rubremetinium bromide) log ε

Curve No.	8	9	10
Drawn	– – – – –	———	●●●
Substance	R.47 (1st exp) product	R.47 (2nd exp) product	Rubremetinium Bromide
Suggested or Desired Structure			
Solvent	distilled water	distilled water	distilled water

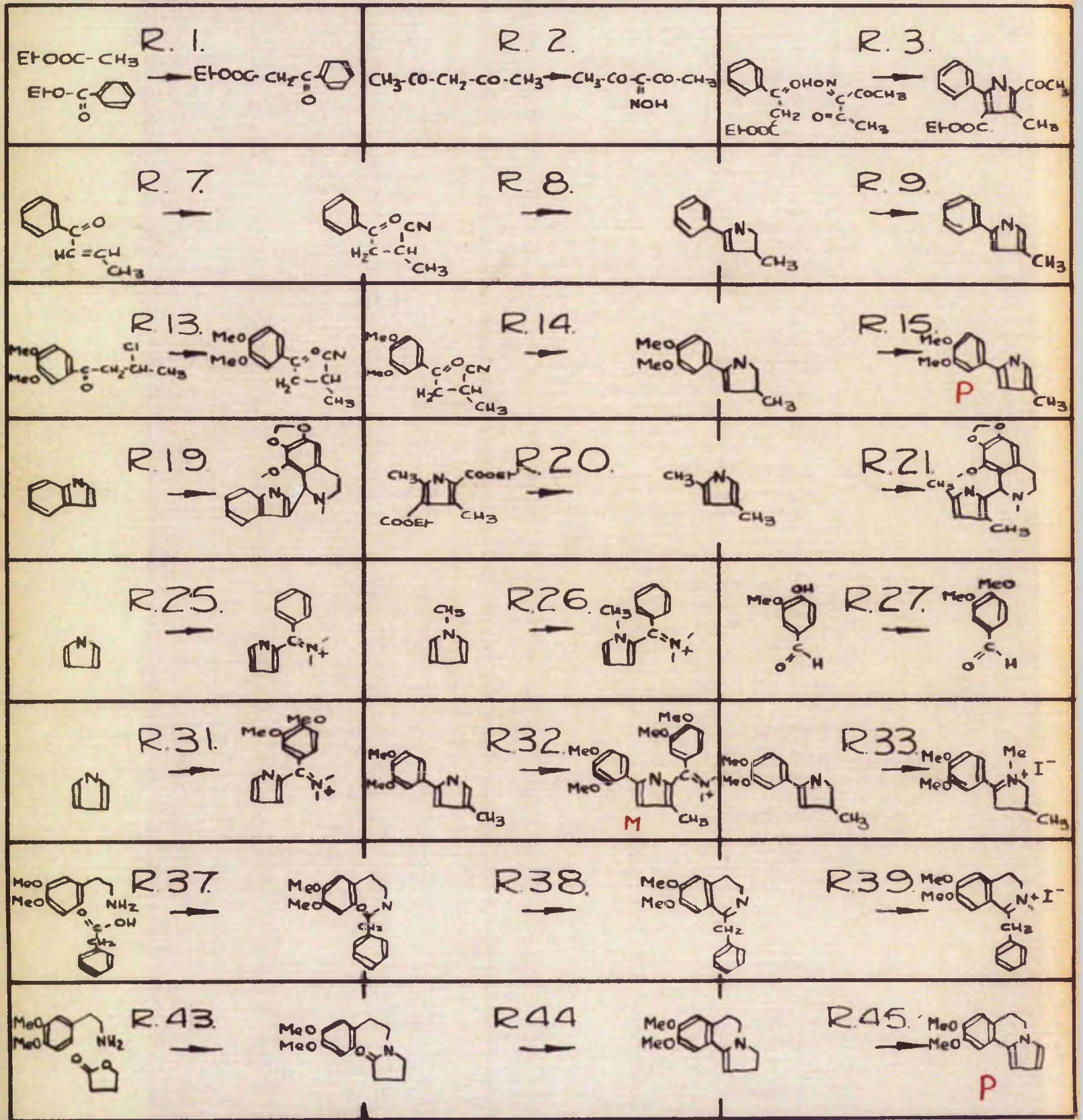
4·6
4·4
4·2
4·0
3·8

300
350
400
450
mμ


log ε
4·6
4·4
4·2
4·0
17,960, λ=256
17,750
λ=255
18,200
λ=290
16,390
λ=286
18,200
λ=303
17,080
λ=300
11,000
λ=378→385
24,850
λ=440
16,000
λ=438
MeO
MeO
MeO
MeO
N
N+
I−
Et
Curve No.
11
12
Drawn
Substance
R.48 product
Rubremetinium Bromide
Structure or Suggested Structure
Solvent.
distilled water
distilled water
- 891 -

Discussions of these reactions in Parts III or IV of the thesis may be located by scanning the top centre of the pages in the appropriate part of the thesis. "Th." signifies the Theoretical Discussion, ie Part III discussion, of the reaction stated; "Exp" signifies the Experimental Details, i.e. Part IV discussion, of the reaction stated.

REACTION



INDEX

Below:- A "—" is occasionally used for "—Me."

An "M" placed beside a structure indicates t
is one of the "model compounds". "P" indicates
a structure is one of the pyrrole derivative
which these model compounds were prepa