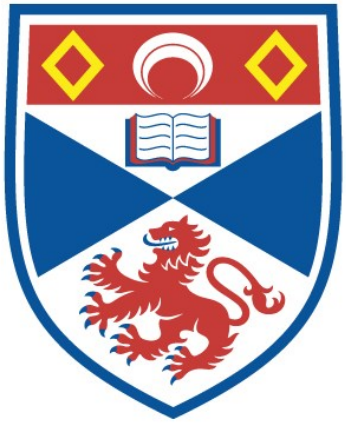
RESEARCHES INTO THE STRUCTURE OF EMETINE

Alan Rushton Battersby

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



1949

RESEARCHES INTO THE STRUCTURE OF EMETINE.

being a Thesis

presented by

ALAN RUSHTON BATTERSBY. B.Sc., M.Sc.

to the

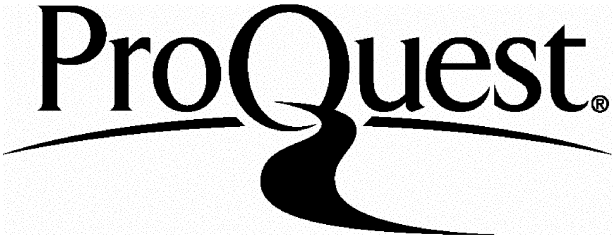
UNIVERSITY OF SAINT ANDREWS

in application for the

Degree of

DOCTOR OF PHILOSOPHY.

April, 1949.



I wish to express very sincere thanks to my teacher Dr. H.T. Openshaw for his invaluable assistance and wise counsel throughout the conduct of this research. His encouragement and keen interest in the work have helped me at all times. I am also indebted to Mr. D.J. Lloyd, Miss A. Doherty, and Drs. G. Weiler and F.B. Strauss for carrying out the micro-analyses recorded in the Thesis. The Department of Scientific and Industrial Research provided a Maintenance Grant, for which I am most grateful.

DECLARATION.

I hereby declare that the following Thesis is a record of experiments carried out by me, that the Thesis is my own composition and has not previously been presented for a Higher Degree.

The investigation was carried out in the Chemical Research Laboratory of the University of St. Andrews, under the direction of H.T. Openshaw, M.A., D. Phil.

CERTIFICATE.

I hereby certify that Mr. Alan R. Battersby, B.Sc., M.Sc., has spent nine 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.

Director of Research.

UNIVERSITY CAREER AND RESEARCH EXPERIENCE.

I entered the University of Manchester in October, 1943, pursuing the course of study leading to the Degree of B.Sc., and was awarded First Class Honours in Chemistry in 1946.

In January, 1946, I obtained the Mercer Chemistry Research Scholarship and a D.S.I.R. grant, which I held until the end of the year. During this period, I was engaged upon research in Manchester and in St. Andrews under the direction of Dr. H.T. Openshaw, and was awarded the Degree of M.Sc. (Manchester) in 1947.

I was admitted as a Research Student of the University of St. Andrews in January, 1947, under the same supervisor, and was the holder of second and third year D.S.I.R. grants until October, 1948. At this time, I was appointed Lecturer in Chemistry in the United College, St. Andrews.

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(I) INTRODUCTION.

The first crude preparation of the alkaloid emetine was obtained in 1817 by Pelletier (1) from the plant species Cephaelis ipecacuanha. Since that day many workers have turned their attentions to the structural problem presented by this alkaloid, among them being such famous chemists as Karrer, Pyman, Späth, and Reichstein.

Their failure to complete the elucidation of the structure cannot be ascribed to a lack of time or to the substance being uninteresting in itself, for, during the century or so that emetine has been known, the structures of many alkaloids with considerably more complex molecules have been solved. Furthermore, emetine has always aroused considerable interest because of its unique position as therapeutic agent for the treatment of amoebic dysentery (2). It seems more probable that the great difficulty experienced by the early workers of obtaining pure emetine accounts partly for the slow rate of progress; the reluctance of the derivatives and degradation products of the alkaloid to crystallise, must also be taken into account. Again, the oxidation technique, so powerful a weapon with many other alkaloidal problems, failed to cast any light on what might be called the core of the molecule.

A knowledge of the structure of emetine will obviously be of considerable value in view of its

/pharmacological

pharmacological properties, and the present researches have been planned with that end in view. The mode of attack, different from those previously employed, will be described in this thesis. Part of the author's early work on the emetine problem was presented for a Higher Degree (M.Sc., Manchester), and will be described briefly in this historical survey.

II. THE CHEMISTRY AND STRUCTURE OF EMETINE AND RELATED ALKALOIDS.

(a). FORMULA AND FUNCTIONAL GROUPINGS.

The early workers (3) in this field obtained analytical results for emetine and its derivatives, which could not be brought into agreement with any one molecular formula for the alkaloid. It is now quite clear that the controversy arose because of the impurity of the specimens which were employed for analysis. In contrast, the exemplary researches of Carr and Pyman (4) showed, beyond any doubt, that emetine possesses the molecular formula $C_{29}H_{40}O_4N_2$. These workers carried out many analyses on the alkaloid, its salts and simple derivatives, and, in addition, their molecular weight determinations by both the ebullioscopic and cryoscopic methods lend support to the above formula.

As with the molecular formula, there was dispute concerning the function of the four oxygen atoms in emetine, and it was once more left to Carr and Pyman to construct order out of confusion. Numerous analyses by these authors gave conclusive proof of the presence of four methoxyl groups; the function of all the oxygen atoms is thereby known.

The two nitrogen atoms in the molecule must now be considered, and the first definite evidence as to their function was brought forward by Keller (5). He found that a solution of emetine in hydrochloric acid yielded a nitrosamine

/on treatment

on treatment with sodium nitrite. This product gave a positive Liebermann reaction, which indicated the presence of at least one imino grouping in the alkaloid.

Keller's work was followed by that of Pyman, who studied the action of benzoic anhydride on emetine. The analyses of the acylated product agreed with a molecular formula $C_{36}H_{44}O_5N_2$, and thereby showed that only one benzoyl residue had entered the molecule. Furthermore, this material, named N-benzoylemetine, proved to be a monoacidic base; the secondary nitrogen atom must therefore have been benzoylated, whilst the other nitrogen atom, unaffected in the reaction, must be in the tertiary state.

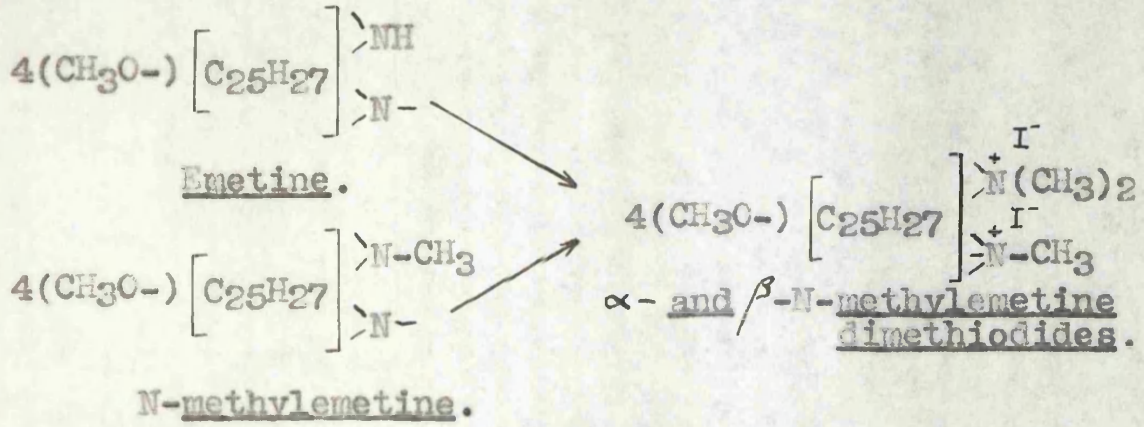
The view that emetine contains one secondary and one tertiary nitrogen atom, conveniently designated N(a) and N(b) respectively, was fully supported by a study of the N-alkylation of the alkaloid. Methylation, with dimethyl sulphate and sodium methoxide, yielded the ditertiary base N-methylemetine $C_{30}H_{42}O_4N_2$, with the introduction of only one methyl group. The expected result of complete methylation of emetine was realised by Keller (5), who heated a suspension of the base in dilute, aqueous sodium carbonate with methyl iodide, to yield a quaternary dimethiodide. The molecular formula of this salt, m.p. 225-6°, was shown to be $C_{32}H_{48}O_4N_2I_2$ by Carr and Pyman (4), and the normal

/methylimino

methylimino estimation proved that three methyl groups were linked to nitrogen. Since the action of excess methyl iodide upon N-methylemetine afforded the same quaternary diiodide (4), its constitution was established as N-methylemetine dimethiodide.

Later work by one of the same authors (6) has shown that a second N-methylemetine dimethiodide, of m.p. 262°, is formed in the complete methylation of emetine, isomeric with the one already described. Pyman classes these two salts as stereoisomers, differing only in the spatial configuration at the asymmetric, quaternary nitrogen atom, that is, at N(b). There can be no doubt that this is the true explanation of the observed facts, as the later development of the survey will show. In accordance with the usual practice, the isomer with the lower melting point is designated the α-salt, and the other, the β-compound.

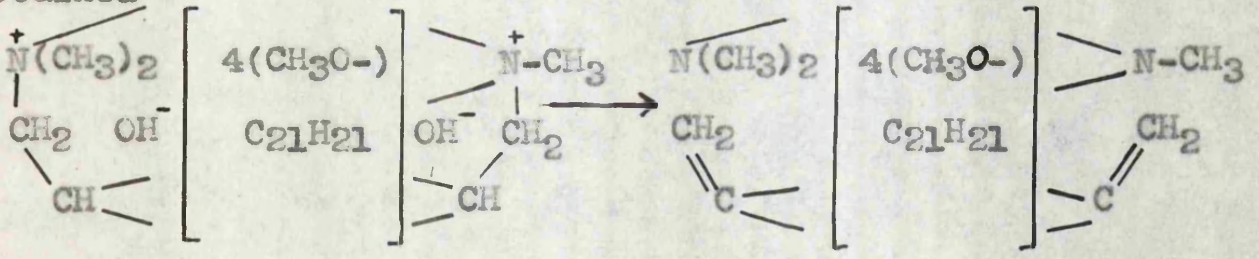
One can represent the changes which have occurred in the formation of these two isomers, by the following partial structures:-



/At this

At this stage in the investigations, the way in which the nitrogen atoms are built into the emetine molecule was still unknown, and since alkylimino groupings were shown to be absent (4), that valuable, investigational tool, the Hofmann degradation, was applied to emetine.

Hesse (7) was the first to study this degradation, but it was Pyman (8), who satisfactorily characterised the product. This author converted ∝-N-methylemetine dimethiodide to the corresponding diquaternary hydroxide, by means of moist silver oxide, and then decomposed it thermally, as indicated by the partial formulae below. In this way, he obtained



a ditertiary base, which was named N-methylemetinemethine $C_{32}H_{46}O_4N_2$.

The difference between the ∝- and β-N-methylemetine dimethiodides has been said to lie only in the spatial arrangement at the asymmetric nitrogen atom, and therefore, both salts should yield the same methine, when the asymmetry is destroyed in the Hofmann degradation. Pyman tested this experimentally, and it was found to be the case; his proposed relationship for the two salts was thereby firmly established.

/It is of

It is of great importance that the N-methylemetine-methine retains the two nitrogen atoms, for it shows that both must have been linked in cyclic systems in the alkaloid.

Karrer carried the exhaustive methylation procedure one stage further, by converting N-methylemetinemethine, by way of the dimethiodide, to the dimethohydroxide, which was heated (9). The oil so formedwas distilled, but Karrer failed to isolate any crystalline salts; however, the analysis of the amorphous hydrochloride indicated a molecular formula $C_{31}H_{41}O_4N$. Whilst the analysis of an amorphous salt cannot be said to establish a molecular formula, in this case it does show that one nitrogen atom has been split out of the molecule. Two complete steps of the Hofmann degradation are therefore necessary to remove N(a), whilst N(b) is still linked to the main skeleton after this treatment. It follows directly, that N(a) must have been part of one ring in the emetine molecule, whilst N(b) must have been a member of two heterocycles.

The first stage of the Hofmann degradation must now be considered further, in the light of the knowledge so far outlined. Ring fission at N(a) could occur in two ways, and at N(b) in three ways, and therefore many different methines could be formed. In this case, however, the present author found that one substance makes up at least 90%

/of the total

of the total methine base (see p.42), and Pyman (8) was able to isolate 77% of the same material from his total product. One direction of fission must therefore be strongly favoured, a circumstance of no mean importance in the long series of degradative reactions used in the present work.

The carbon skeleton now remains to be considered, and information regarding the number of C-methyl groups was afforded by a study of the Kuhn-Roth oxidation of the base. Approximately one molecular proportion of acetic acid was formed (10, 11), which suggests the presence of one C-methyl grouping, though the possibility that there are two such groups cannot be ruled out on this evidence alone; this important problem has received attention in the present author's researches. The alkaloid is recovered largely unchanged, when reduction is attempted with tin and hydrochloric acid, or with sodium and ethanol, using vigorous conditions (4). This result, and the results of many catalytic hydrogenations of emetine degradation products, carried out in the present work, all lead to the conclusion that the structure contains no olefinic linkages.

Sufficient information is now available about the general features of the emetine molecule, to be able to apply the usual numerical consideration to the formula $C_{29}H_{40}O_4N_2$. The structure must obviously include several rings, and at

/this stage

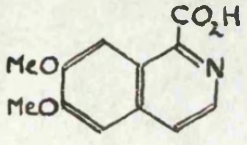
this stage it suffices to say that the presence of five rings, with two in the aromatic state, is the only arrangement which satisfactorily explains the hydrogen content of the molecule.

The researches described in this section have shown that emetine contains four methoxyl groups, and that the two nitrogen atoms are secondary, and tertiary, due to being members of one, and two, cyclic systems, respectively. Furthermore, the molecule possesses one C-methyl group, or possibly two such groups, and has no olefinic linkages; it follows that the structure contains several cyclic systems.

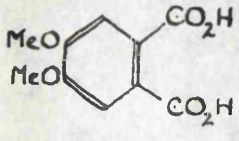
II. (b). OXIDATIVE AND SPECTROSCOPIC INVESTIGATIONS.

Of the many processes used in the study of alkaloids, those involving oxidation have probably been of the greatest value. It is not surprising then, that several workers turned their attentions to the oxidation of emetine and its derivatives; the results they obtained can conveniently be considered in two parts. Firstly, there are those involving a degradation of the molecule to yield small fragments, and secondly, those in which hydrogen is removed and no fission of the skeleton occurs.

Carr and Pyman (4) were the first workers to satisfactorily characterise any oxidation products from the alkaloid. Using potassium permanganate as the oxidising agent, they were able to isolate two crystalline substances, one of which was amphoteric, and the other acidic, in nature. The former proved to be 6:7-dimethoxy-isoquinoline-1-carboxylic acid (I), whilst the latter was metahemipinic acid (II).



I

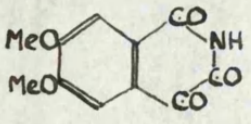


II

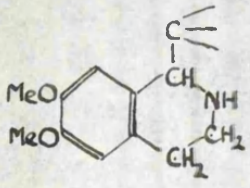
/These results

These results were of great importance, for not only did the isolation of the substance (I) show that emetine belongs to the large class of isoquinoline alkaloids, but also, the position of at least two methoxyl groups in emetine is settled. Furthermore, since the carboxyl group is located at C_1 of the heterocycle, it is through this position that linkage to the rest of the molecule must have taken place in the original alkaloid.

This work was closely followed by that of Windaus and Hermanns (12), who described their oxidation of emetine by chromic acid, and by potassium permanganate. Using the first reagent, they isolated 4:5-dimethoxyphthalonimide (III) from the reaction mixture, but the acid (I) was not detected; with potassium permanganate, only metahemipinic acid was obtained. It can be seen that the isolation of (III)



III



IV

supports the conclusions of Carr and Pyman with respect to the orientation of two of the methoxyl groups in the alkaloid, and is consistent, at least, with their view regarding the linkage point to the rest of the molecule. It seems reasonable, however, that (III) would be derived from a

/tetrahydro-

tetrahydroisoquinoline residue (IV) in emetine, rather than from the aromatic isoquinoline residue, which is suggested by Pyman's isolation of (I). Fortunately the study of absorption spectra of alkaloids was sufficiently advanced at this time, to be of great assistance in the case of emetine.

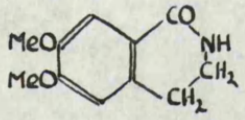
Dobbie and Fox (13) found that the extinction curve for creosol (4-hydroxy-3-methoxytoluene) was strikingly similar to the curves for laudanosine, tetrahydropapaverine, and corydaline. Since each of these alkaloids contains two catechol residues, the results given by two molecular proportions of creosol were compared with those using one molecular proportion of the alkaloid. A totally different extinction curve was observed, however, when the isoquinoline nucleus was present in the unreduced state, as in papaverine, for example. In the case of emetine, it was found that the curve was very similar to that obtained for two molecular proportions of creosol, whilst that of (I) was entirely different. Dobbie and Fox therefore suggested, that emetine contains two 1:2:3:4-tetrahydroisoquinoline residues, and that (I) arises by a dehydrogenation of one, or both, of these residues, in the course of the oxidation. These views have stood the test of time, and of further experiment.

It now remains to describe how quantitative

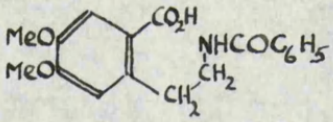
/chemical

chemical investigations gave very strong support to the suggestions of Dobbie and Fox; this work was carried out by Späth and Leithe, and was published in 1927 (14).

These workers studied the results of a mild oxidation of emetine with potassium permanganate, and were well rewarded, when corydaldine (V) was isolated from the reaction mixture. Not only did the formation of this lactam agree with the results of the earlier workers (p.10), but it also provided the first direct chemical evidence for the presence of at least one 1:2:3:4-tetrahydroisoquinoline residue in the alkaloid. It cannot be assumed at this stage,



V



VI

however, that the nitrogen atom of (V) is the N(a) of emetine, since tetrahydropalmatine, in which the nitrogen atom is tertiary, affords the same product (V) on oxidation. The problem had therefore to be investigated further.

N-benzoylemetine was oxidised by potassium permanganate and it was expected, by analogy with similar oxidations (15,16), that fission of the ring would occur, to afford the N-benzoylamino acid (VI). Späth and Leithe succeeded in isolating a crystalline compound, which gave

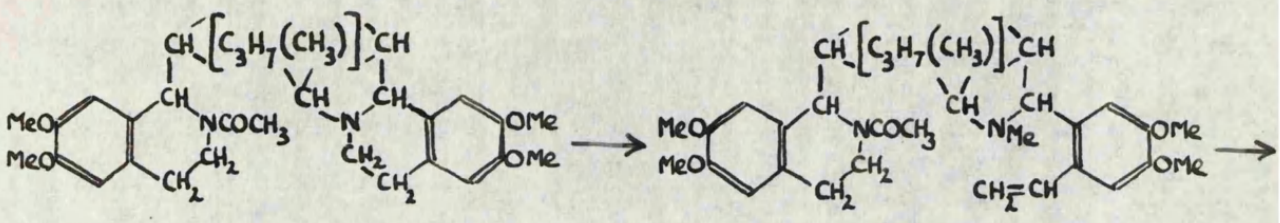
/substantially the

substantially the correct analysis for $C_{18}H_{19}O_5N$, and its properties were well represented by the structure (VI). They obtained additional support for their view regarding the structure of the oxidation product, by heating the substance in vacuo, when benzoic acid was split off. With this evidence the authors were satisfied, and no synthetic specimen of (VI) was prepared for comparison.

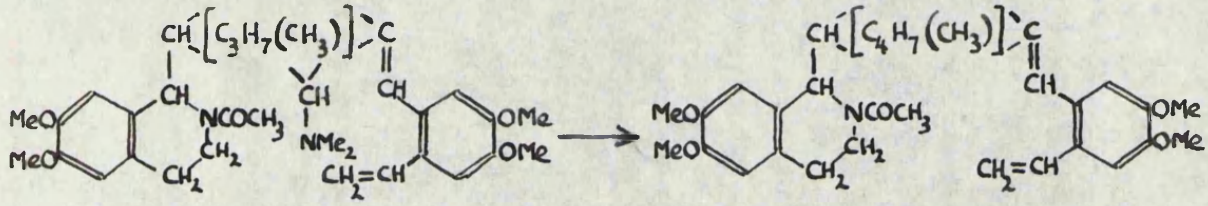
In the opinion of the present author, the evidence was not sufficient, and it is fortunate that the linkage of N(a) into a 6:7-dimethoxy-1:2:3:4-tetrahydroisoquinoline ring system was proved conclusively, at a later date, by Ahl and Reichstein (17). By carrying out a partial Hofmann degradation upon N-acetylemetine, these workers were able to eliminate the tertiary nitrogen atom from the molecule, as illustrated in the scheme below. It can be seen that three complete applications of Hofmann's procedure were necessary to remove N(b), confirming that this atom is common to two rings.

In the final degradation of the methiodide of the base (VII), carefully controlled conditions were necessary in order to avoid a rapid decomposition of the organic material; this difficulty was probably due to the highly unsaturated nature of the substances involved. The final

/product



N-acetylemetine (see p. 19).



VII VIII

product (VIII) was oxidised with acidified potassium permanganate, to afford metahemipinic acid (II) and 4:5-dimethoxyphthalonimide (III). Since the imide (III) was also obtained by the oxidation with chromic acid of 6:7-dimethoxy-1:2:3:4-tetrahydroisoquinoline, or its N-acetyl derivative, it follows, unequivocally, that N(a) is contained in a 6:7-dimethoxy-1:2:3:4-tetrahydroisoquinoline ring system. Karrer has recently given added support to this conclusion, by the isolation of 1-methyl-6:7-dimethoxyisoquinoline from the products of the distillation of VIII with zinc dust (11).

/The question

The question now arises, whether emetine contains a second isoquinoline residue or not. Späth and Leithe found that the oxidation of bases containing only one dimethoxyisoquinoline residue yielded about half the quantity of metahemipinic acid, which was obtained when the equivalent quantity of emetine was oxidised. For example, palmatine afforded 34% of the theoretical quantity of metahemipinic acid, and the oxidation of papaverine, under the same conditions, gave only 25% of this acid. The formation of 65% of the theoretical amount of metahemipinic acid, by a similar oxidation of emetine, suggested strongly that two, dimethoxylated benzene nuclei are present in the alkaloid.

This suggestion gained strong support when emetine was oxidised mildly to corydaldine (V), which was estimated, and the mother liquors oxidised further to metahemipinic acid; the equivalent of 96% of this acid was isolated in this way.

Späthe and Leithe suggested that the second benzene nucleus was present, like the first, as part of a 1:2:3:4-tetrahydroisoquinoline residue, basing their proposal upon a consideration of the alkaloids of known structure. Experimental support for this proposal was sought, using a secondary alkaloid of Ipecacuanha, named cephaeline $C_{28}H_{38}O_4N_2$, which previously had been shown to be a phenolic

/base (3)

base (3). The difference of CH_2 between the molecular formulae of emetine and cephaeline suggested very strongly that the two alkaloids are closely related, and the nature of this suspected relationship was elucidated, when Carr and Pyman (4) made the important discovery, that emetine is the O-methyl ether of cephaeline (X, p.20).

With this knowledge, it can readily be seen, that by ethylating the free phenolic grouping in cephaeline, a product is obtained having the carbon skeleton and general features of emetine, whilst differing in one important respect. This is, that the two benzene nuclei now carry different substituents. It should be noted that alkylation of the free phenolic grouping in cephaeline was essential, in order to protect both aromatic nuclei against oxidation; in the case of cephaeline itself, the aromatic nucleus carrying the phenolic group was completely destroyed by oxidation, as was expected. In this latter experiment, the amounts of corydaldine and metahemipinic acid which were obtained, were equivalent to 30% of the theoretical yield of metahemipinic acid, showing that only one benzene nucleus survived the oxidation; further chemical evidence thereby was given for the view that emetine, and cephaeline possess two aromatic nuclei.

When O-ethylcephaeline (XI, P. 20) was oxidised

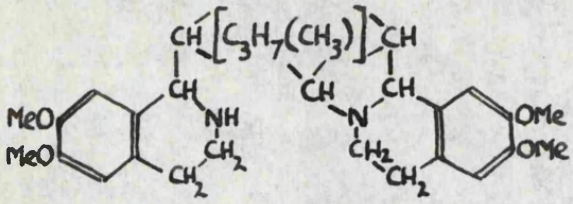
/under the

under the same conditions, a product was obtained, very similar in properties to corydaldine, but having a lower melting point, which, furthermore, was not sharp. This melting point was raised, when the oxidation product was mixed both with corydaldine and with 7-methyl-6-ethyl-norcorydaldine; corresponding derivatives of the three substances showed this same melting point behaviour when mixed. These results led Späthe and Leithe to the conclusion, that the corydaldine-like substance was composed of corydaldine itself and 7-methyl-6-ethyl-norcorydaldine, a conclusion which was confirmed by a vigorous oxidation of the supposed mixture. Metahemipinic acid and 4-methoxy-5-ethoxy-phthalic acid (XII p.20) were isolated from the products of this reaction, and further quantities of these two acids were obtained by an oxidation of O-ethylcephaeline, under more drastic conditions than had hitherto been employed.

It is quite clear, at this stage, that the emetine molecule contains one secondary, and one tertiary, nitrogen atom, each contained in a 6:7-dimethoxy-1:2:3:4-tetrahydro-isoquinoline nucleus; these nuclei are linked together by a carbon chain attached at their 1-positions. Furthermore, the work of Carr and Pyman, and Karrer (p.6,7) showed that the tertiary nitrogen atom is built into two rings, whilst

/our work

our work, and that of Karrer, has shown the presence of at least one C-methyl group (p. 8). These facts can be represented by the partial structure (IX).

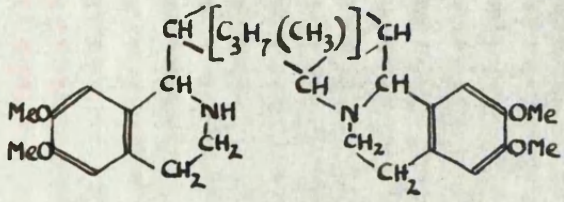


IX

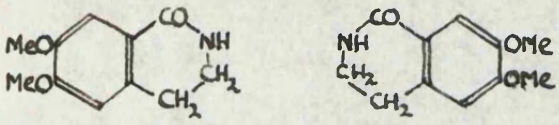
On this basis, the primary products of the mild oxidations of emetine, cephaeline and O-ethylcephaeline, described above, can be indicated in the scheme on the next page, in which the accepted position of the phenolic hydroxyl group in cephaeline has been used for simplicity.

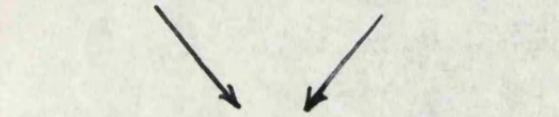
It now remains to consider those oxidations of emetine and its derivatives, which remove hydrogen from the molecule, but which do not cause fission of the carbon skeleton; these reactions are more correctly termed dehydrogenations. Using aqueous ferric chloride, Carr and Pyman (4) oxidised emetine hydrochloride to a red, crystalline salt $C_{29}H_{33}O_4N_2Cl$, which was named rubremetine hydrochloride. The molecular formula shows, that, with the elimination of eight atoms of hydrogen, one nitrogen atom has lost its basic character; the function of the other nitrogen atom was not fully understood. The behaviour of the red, dehydrogenation

/product

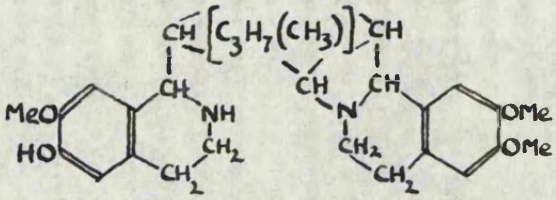


Emetine (1·0g.).

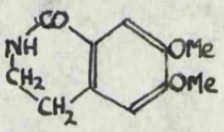




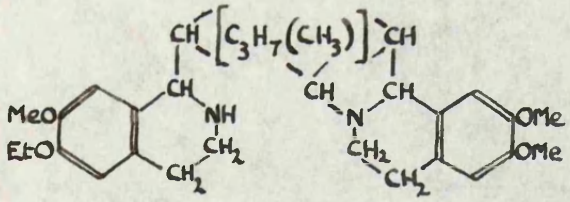
Pure corydaldine (0·12g.)



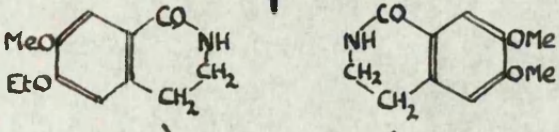
Cephaeline (1·0g.) X.



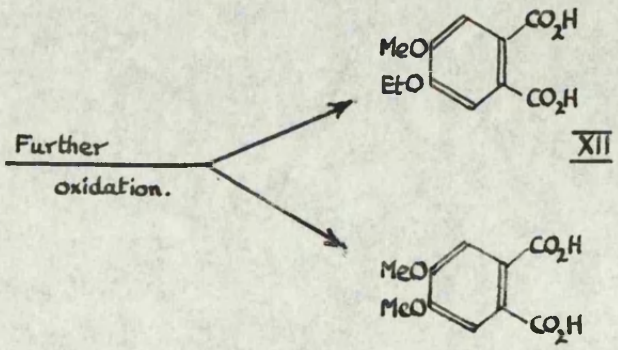
Pure corydaldine (0·05g.)



O-ethylcephaeline (1·0g.) XI.



Corydaldine-like mixture (0·09g.)



XII

product with alkalies suggested that this second nitrogen atom is in the quaternary state, although the contradictory nature of the statements in the literature did not allow any sound conclusions to be drawn. For instance, Karrer (9) found that treatment of a solution of rubremetine hydriodide with silver oxide, gave a halogen-free solution, which, on evaporation, yielded an amorphous, yellow varnish, readily soluble in water, to give a neutral solution. Carr and Pyman (4), on the other hand, observed that the halogen-free solution, prepared by the same method, would not yield the base to ether or benzene, but chloroform readily removed it. Evaporation of the chloroform gave rubremetine hydrochloride, derived from the decomposition of the chloroform by the base.

The early researches by the present author (18) proved conclusively that the red oxidation product is a quaternary salt. By means of a potentiometric titration using 0·01N sodium hydroxide, a curve was obtained for "rubremetine hydrochloride", almost identical with that for an equimolar solution of potassium chloride, whilst that for a similar solution of ammonium chloride differed considerably. Furthermore, the alkaline solution showed no fall in pH on standing, indicating that no appreciable quantity of pseudo-base is formed under these conditions.

The red oxidation product can therefore be called rubremetinium chloride, as suggested by Brindley and Pyman (19),

and the salts of the parent base, with any other acid, named accordingly.

The action of silver oxide upon a solution of rubremetinium chloride was also re-investigated, at the same time (18), and the results obtained were a confirmation and an extension of those of Carr and Pyman. The resulting, deep-red, halogen-free solution, filtered from silver chloride and excess silver oxide, was strongly alkaline in reaction, and by acidification of a sample with hydrochloric acid , the chloride was recovered in 88% yield.

When the solution was evaporated in an atmosphere of nitrogen, two products were obtained. One, a bright orange-red, microcrystalline solid was shown to be the quaternary hydroxide, since it dissolved in water to give an alkaline solution, from which the chloride was recovered by acidification. The second substance was insoluble in water but soluble in ether, and was obtained, from its solution in the latter solvent, as a clear, orange-yellow gum. It dissolved in dilute hydrochloric acid, but concentration of the dark red solution yielded only tarry products, and no rubremetinium chloride could be isolated. These results, together with the fact that solutions of this second substance rapidly darken and resinify on standing, suggest that it is a pseudo-base or anhydro-base.

Turning now to the various alternative methods for

/the preparation

the preparation of rubremetine$^{\phi}$, one finds that two, very interesting by-products can be obtained. Employing iodine as the oxidising agent in alcoholic solution, Carr and Pyman (4) isolated rubremetine, together with a base having one ethylenic linkage, and having the molecular formula $C_{29}H_{38}O_4N_2$. This substance already had been shown to be one of the minor alkaloids of Cephaelis ipecacuanha and had been named O-methylpsychotrine (8); it will be discussed in some detail, in a later section. At this stage, it is interesting to note, that since O-methylpsychotrine is dehydrogenated to rubremetine in good yield using bromine in chloroform (8), this base is an intermediate stage in the oxidation of emetine to rubremetine.

Battersby and Openshaw (18) oxidised emetine with mercuric acetate in boiling, dilute, aqueous acetic acid solution, the principal product being rubremetine, isolated in 45% yield. This is the most convenient method which has been recorded for the preparation of rubremetine, and moreover, gives the highest yield. A second product of the oxidation was a base having the molecular formula $C_{29}H_{36}O_4N_2$, which indicates the presence of two ethylenic linkages; this was

/confirmed by

ϕ It is often convenient to use the general term rubremetine in place of rubremetinium chloride, rubremetinium bromide, etc.

confirmed by micro-hydrogenation. The substance may therefore be termed tetradehydroemetine. This base is very unstable, and even in the form of a salt, gradually turns pink on exposure to the atmosphere, a change which is accelerated by sunlight. When subjected to the further action of mercuric acetate, tetradehydroemetine was converted to rubremetine, and thus represents a second intermediate stage in the dehydrogenation of emetine.

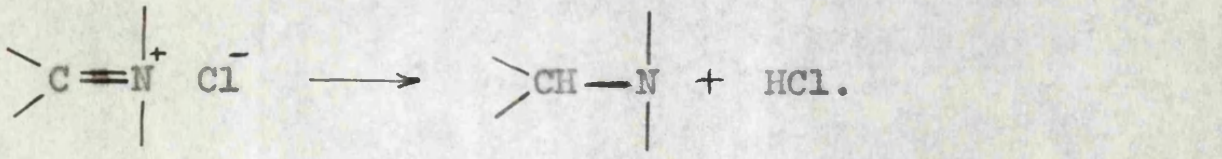
In arriving at any proposed structure for emetine, due consideration must be given to the two partially dehydrogenated products, described in the previous paragraphs. Still more important is the requirement, that any proposed structure must be capable of accounting for the formation of rubremetine.

It was a recognition of the importance of this latter requirement, that led Brindley and Pyman (19) to make a further study of the dehydrogenation of emetine and its derivatives. These workers found that no substance analogous to rubremetine could be prepared from N-methylemetine, a result which is of considerable significance; this matter will be discussed further in the later development of the present dissertation.

The statement made previously that eight atoms of hydrogen are removed in the change from emetine hydrochloride

/to rubremetinium

to rubremetinium chloride, rests entirely upon the analyses of Carr and Pyman. Whilst these analyses were undoubtedly carried out most carefully, the necessity of drying hydrated samples of rubremetinium salts for analysis, the slight instability of these salts, and their high molecular weight, leave the true hydrogen content of rubremetine in some doubt. Battersby and Openshaw (18) therefore investigated the catalytic hydrogenation of rubremetinium chloride in an endeavour to remove this uncertainty, but the substance resisted complete reduction. Hydrogenation of rubremetinium chloride, in the presence of sodium acetate in alcohol, ceased when one molecular proportion of hydrogen had been absorbed; the solution was then almost colourless. When alcohol alone was employed as the solvent, the uptake of hydrogen was very slow, and ceased when about 0·6 mole of hydrogen had been absorbed. The beneficial effect of the sodium acetate on the reduction suggests that the quaternary nitrogen atom is involved.

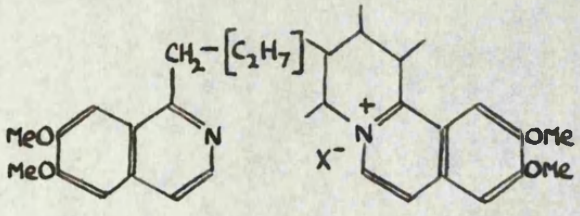


Attempts to isolate the reduction product proved abortive, as its solution was re-oxidised to the orange-red, starting material by atmospheric oxygen, passing through an intermediate green stage.

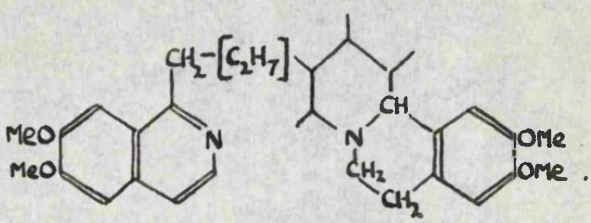
/Karrer

Karrer, Eugster and Rüttner (11) are the only workers to have had any success with the reduction of rubremetine using chemical methods; these methods, unfortunately, cannot give direct information concerning the amount of hydrogen absorbed. By reduction with zinc dust and acetic acid, they obtained a crystalline base, which was optically active; it follows that rubremetine must also possess at least one asymmetric centre. The single analysis carried out on the new base was in agreement with the molecular formula $C_{29}H_{36}O_4N_2$; this suggests that it contains four atoms of hydrogen more than rubremetinium chloride. The new compound was not reduced by hydrogen in the presence of platinum black, under mild conditions, which suggests that the two remaining double bonds are present in an aromatic ring system, or, alternatively, are sterically hindered. With methyl iodide, the reduction product yielded a crystalline monomethiodide.

On the basis of this work, Karrer and his collaborators put forward the partial structures (XIII) and (XIV) for rubremetine and its reduction product, respectively.



XIII

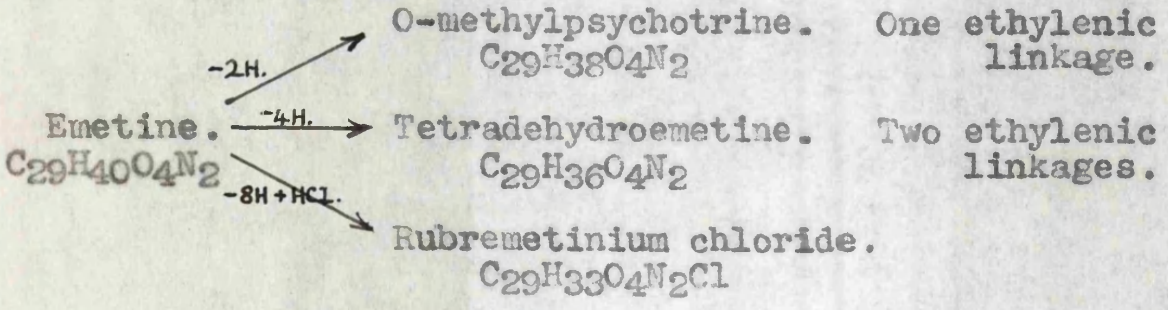


XIV

/These

These proposals are open to so many serious objections that they are, without any doubt, incorrect. Most of these objections will be discussed in the Theoretical Section, and it is sufficient here to mention two. Firstly, there is no reason why the structure (XIII) should be deep red, since isoquinolinium salts are colourless or pale yellow, and secondly, the nitrogen atom N(a) in (XIII) must have the normal basic character. In contrast, the non-quaternary nitrogen atom in rubremetine has lost its basic function completely. The rejection of Karrer's proposal raises the problem of providing more acceptable suggestions; this problem can be discussed only when all the information concerning the structure of emetine has been considered.

The dehydrogenations of emetine which have been reviewed can be represented by the following scheme.



III. (c). THE CHEMISTRY AND INTERRELATIONSHIP OF THE MINOR ALKALOIDS OF IPECACUANHA.

Paul and Cownley (3), and later Pyman, with Carr and Brindley (4,19), are to be credited with the thorough investigation of the total, alkaloidal material of Cephaelis ipecacuanha. Five bases were found to be present, of which mention has already been made of cephaeline $C_{28}H_{38}O_4N_2$ and O-methylpsychotrine $C_{29}H_{38}O_4N_2$, in addition to the principal alkaloid emetine $C_{29}H_{40}O_4N_2$. The remaining two had the molecular formulae $C_{28}H_{36}O_4N_2$ and $C_{29}H_{36}O_4N_2$, and were named psychotrine and emetamine, respectively.

Psychotrine was found to resemble cephaeline in having one phenolic group, whilst it was similar to O-methylpsychotrine in having one olefinic linkage. Emetamine was shown to contain four methoxyl groups, as does emetine, but differed from the other bases in having two double bonds; it also differed in being a ditertiary base, as shown by its failure to react with benzoic anhydride (8).

Since the alkaloids isolated from one plant species are often closely related, Pyman and his collaborators (4,6, 8,19) sought to establish the interrelationship of the five bases from Ipecacuanha. In this they were helped, and spurred on, by the close relationship of the five molecular formulae. Thus emetine contains a CH_2 group more than does

/cephaeline,

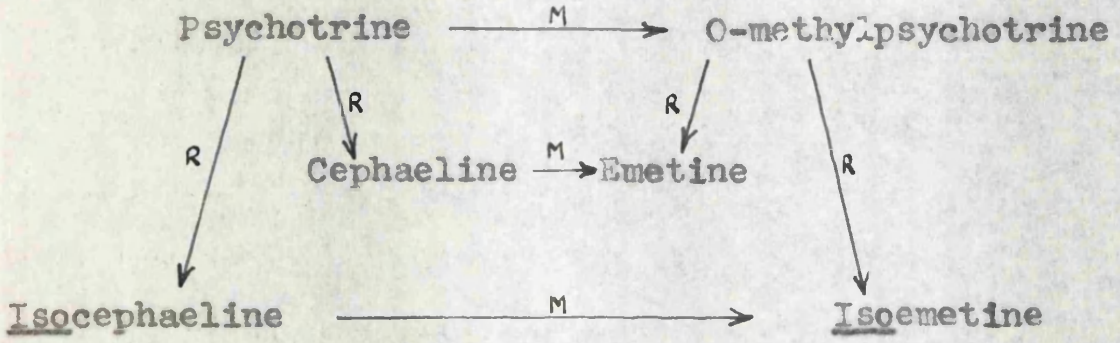
cephaeline, and it has been stated previously that emetine is the O-methyl ether of cephaeline; therefore they have the same relationship as codeine and morphine.

The molecular formulae of psychotrine and O-methylpsychotrine suggested the relationship which is disclosed by the naming of the latter alkaloid. In this case, not only did the methylation of the phenolic group in psychotrine yield O-methylpsychotrine, but partial demethylation of the natural O-methylpsychotrine afforded psychotrine, in good yield.

A study of the reduction of psychotrine, O-methylpsychotrine and emetamine completed the network of relationships. When psychotrine was reduced with sodium and ethanol, a mixture of bases was obtained, from which cephaeline and a new substance $C_{28}H_{38}O_4N_2$ were isolated; this new base is isomeric with cephaeline and is named <u>isocephaeline</u> on this account. By analogy, O-methylpsychotrine would be expected to yield O-methylcephaeline, that is, emetine, when reduced in the same way, and this was found to be the case. Moreover, the base corresponding to <u>iso</u>cephaeline was isolated from the same reduction product and was named <u>isoemetine</u>, $C_{29}H_{40}O_4N_2$. In this connection, mention must be made of Karrer's recent work (11) on the catalytic hydrogenation of O-methylpsychotrine, which showed that emetine or <u>iso</u>emetine was obtained, according to the conditions employed.

/The results

The results discussed so far are summarised in the diagram below, which includes the additional fact that methylation of isocephaeline yielded isoemetine.



R = Reduction. M = Methylation.

The formation of two isomeric bases by reduction of O-methylpsychotrine, suggests strongly that a new asymmetric centre is produced in the molecule by the addition of a hydrogen atom. If it be taken as a working hypothesis, that emetine and isoemetine differ only in the spatial arrangement at a newly formed asymmetric centre, then two experiments to test the hypothesis are apparent. Firstly, one can attempt to convert emetine to isoemetine or to bring about the reverse change, and secondly, attempt to dehydrogenate both emetine and isoemetine to O-methylpsychotrine. In the first experiment, a positive result is strong evidence in favour of the hypothesis, but a negative one is inconclusive, since many stereoisomerides resist attempts at racemisation. Pyman (6) carried out these two experiments and from the first he obtained no evidence of interconversion, using fairly drastic

/conditions.

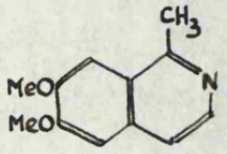
conditions. The second experiment, however, proved that the hypothesis is true, for isoemetine gave rise to O-methylpsychotrine, using the same conditions under which this latter alkaloid is formed from emetine (p. 23).

The conclusion which has been derived for O-methylpsychotrine is equally valid for the reduction of psychotrine, because of the close relationship of the two bases; it follows that only the relationship of emetamine to any one of the other four alkaloids need be known, in order to complete our knowledge.

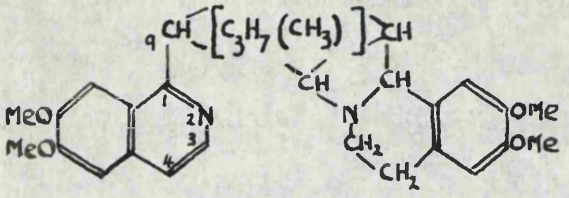
When emetamine was reduced, using the method which was employed for psychotrine (8), a mixture of bases was obtained containing isoemetine; this substance was isolated by means of its benzoyl derivative. All attempts to separate emetine from the reduction product proved abortive. The isolation of isoemetine is sufficient, however, to bridge the gap between emetamine and the rest of the alkaloids, and this work was to be fully confirmed by the researches of Ahl and Reichstein (17). Whilst the chemical dehydrogenation of emetine and O-methylpsychotrine had yielded no trace of emetamine (4,8), these workers detected emetamine in the complex mixture of substances formed when emetine is dehydrogenated catalytically. It is of interest to note that 1-methyl-6:7-dimethoxyisoquinoline (XV) was isolated from the same reaction mixture; this affords still further evidence

/in support

in support of the partial structure (IX p. 19).



XV



XVI

Any proposed structure for emetamine must accord with the facts that it can be reduced to isoemetine, that it is formed by dehydrogenation of emetine, with the loss of four atoms of hydrogen, and also that it is a ditertiary base, more feebly basic than is O-methylpsychotrine. The difference in basicity was shown by a fractional extraction, with dilute acid, of a mixture of O-methylpsychotrine and emetamine in ethereal solution, when the former base was removed first (8).

In considering possible structures for emetamine, Brindley and Pyman (19) did not benefit by the work of Ahl and Reichstein, since it was carried out many years later, but their proposal was fully supported by these more recent researches. They suggested that emetamine contains one unreduced 6:7-dimethoxyisoquinoline residue, so that the alkaloid can be represented by (XVI),.which is in harmony with all the facts mentioned in the foregoing paragraph. It is also in agreement with the reduction of emetamine to

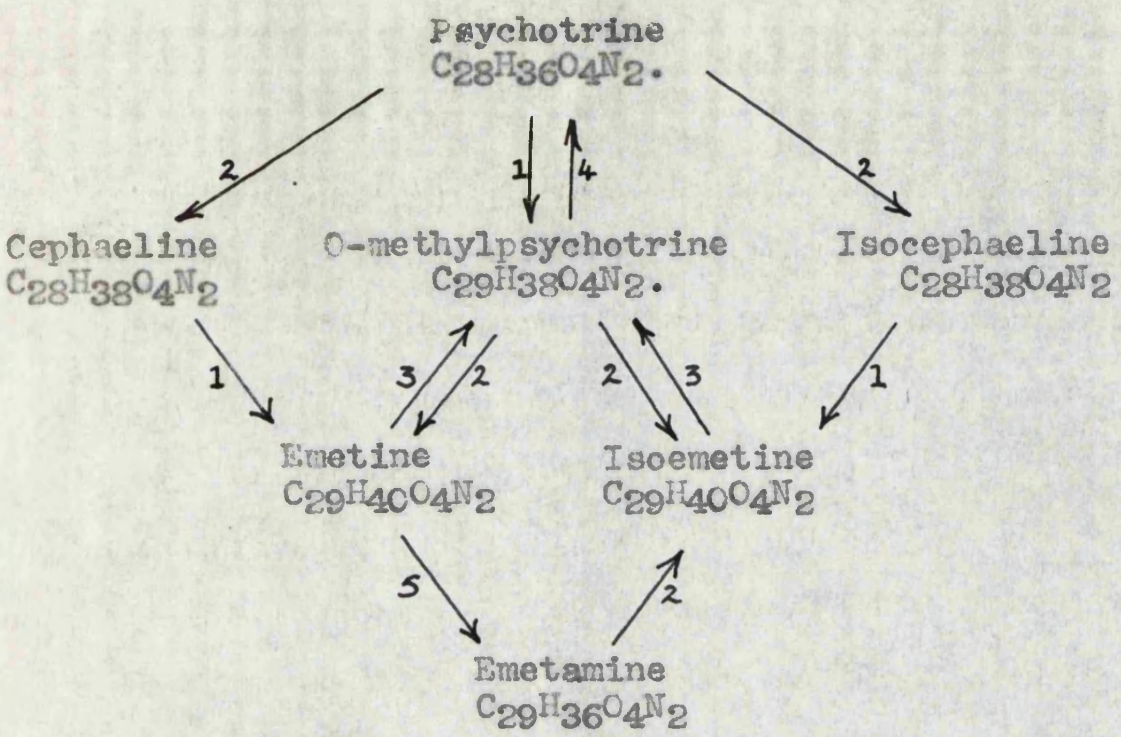
/isoemetine,

isoemetine, due to the formation of a new asymmetric carbon atom at C_1. On this basis, emetine and isoemetine differ only in the configuration at this carbon atom, and the double bond in O-methylpsychotrine must lie between the carbon atoms 1 and 9, or between carbon atom 1 and nitrogen atom 2; further evidence will be presented relating to these matters.

It now remains to discuss the dehydrogenation of emetamine, which was studied by Brindley and Pyman (19). These workers treated emetamine with two molecular proportions of bromine, using the conditions under which this agent had converted O-methylpsychotrine and emetine to rubremetine (8, 20). No rubremetine could be isolated, but a small quantity of a red, micro-crystalline solid was obtained, resembling rubremetinium bromide in colour and solubility properties, but differing in melting point. Karrer (11) has recently confirmed the non-identity of the two salts, by comparing their light extinction curves.

Any proposals regarding the structure of rubremetine must therefore take into account these results on the dehydrogenation of emetamine, a requirement totally unfulfilled by Karrer's proposed structure (XIII).

Having discussed the methods by which the five alkaloids were related one to the other, it will be convenient to summarise the results in diagrammatic form.

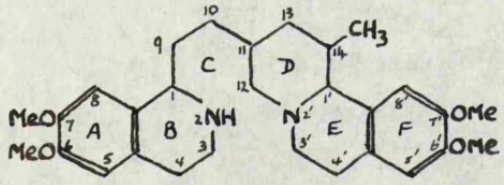


(1) O-methylation
(2) Reduction
(3) Chemical dehydrogenation
(4) Demethylation
(5) Catalytic dehydrogenation

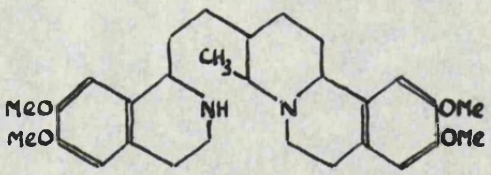
III. (d). THE FIRST COMPLETE PROPOSALS FOR THE STRUCTURES OF EMETINE AND THE RELATED ALKALOIDS.

In 1927, it was known how the atoms in a large portion of the emetine molecule were arranged, the dehydrogenation of the alkaloid to rubremetine had been examined in some detail, and theories regarding the biogenesis of alkaloids were being advanced. The time was therefore ripe for speculations upon the complete structure of emetine and its congeners.

Brindley and Pyman (19), in this year, published an important paper on the structure of the Ipecacuanha alkaloids, in which they suggested that emetine possesses the structure (XVII). This, they derived by modifying Robinson's proposal (XVIIA), which had been made on biogenetic grounds, in 1925.



XVII



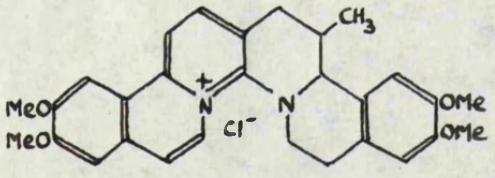
XVIIA

The structure (XVII) accorded with all the known chemistry of emetine, and furthermore, afforded a neat explanation of the formation of rubremetine. No satisfactory explanation of this kind was evident on the basis of the structure (XVIIA), which can be seen to differ from (XVII) only in the position

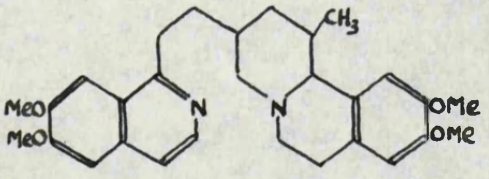
/of the

of the C-methyl group. It should be pointed out, that the C-methyl group was placed on C_{14} (XVII) in analogy to the corydaline structure; on this basis, location of the group at position 9 is equally probable.

When emetine hydrochloride is dehydrogenated to rubremetinium chloride, eight atoms of hydrogen are removed from the molecule to yield a salt, in which one nitrogen atom is quaternary (18) and the other is non-basic. Brindley and Pyman suggested that the change involves an oxidative ring closure between carbon atom 12 and nitrogen atom 2, together with aromatisation of rings B and C, to give (XVIII). The loss of basicity of one of the nitrogen atoms is



XVIII



XIX

attributed to the amidine formation in (XVIII).

Staub (20) pointed out that this proposed structure for rubremetine contains two atoms of hydrogen fewer than the number required by the analytical results. It was mentioned earlier, however, that the degree of unsaturation of rubremetine is not known with any great certainty, and Staub's objection did not interfere with the general acceptance of structure (XVIII).

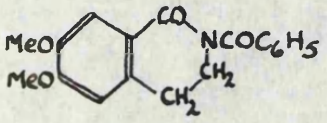
/On the

On the basis of their proposed structure for emetine, Brindley and Pyman were able to deduce acceptable structures for the minor alkaloids of Ipecacuanha. Their proposal for emetamine has been represented already in the partial structure (XVI p. 32), which now can be expanded to (XIX).

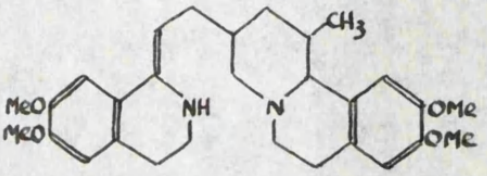
The location of the double bond in O-methylpsychotrine between C_1 and C_9 or C_1 and N_2 has also been mentioned, and Brindley and Pyman chose the former position for the following reasons. It was found that when O-methylpsychotrine was reduced to emetine and isoemetine (p. 29), a third substance, $C_{28}H_{38}O_3N_2$, could be isolated, which contained only three methoxyl groups. This substance, named Base C, was taken to be derived from O-methylpsychotrine by the replacement of one methoxyl group by a hydrogen atom, and saturation of the olefinic linkage. The replacement of alkoxy groups, in this way, was known to occur at the para position of styrene derivatives (21,22), and thus support was given to the proposed structure for O-methylpsychotrine. Brindley and Pyman considered that the double bond could not lie between C_1 and N_2, because the alkaloid yielded a mono-N-benzoyl derivative, when treated with benzoic anhydride, and is therefore apparently a secondary-tertiary base. Karrer (11) has recently provided further experimental evidence by his

/oxidation of

oxidation of N-benzoyl-O-methylpsychotrine to N-benzoyl-corydaldine (XX). The suggested structure for the alkaloid



XX



XXI

therefore can be represented by (XXI).

Both Karrer and Pyman, however, overlook the fact that tautomerism can occur between $-\underset{R}{C}=\underset{R}{C}-NH-$ and $-\underset{R}{CH}-\underset{R}{C}=N-$, which would permit a migration of the unsaturated linkage from the alternative position between C_1 and N_2, as the N-benzoyl derivative is formed. A sound decision between the two possible positions for the double bond cannot be made at this stage, and any arguments by Brindley and Pyman for the structures of the other alkaloids, based directly upon the structure (XXI), must be judged accordingly.

Turning now to the structure of cephaeline, it has been pointed out that this alkaloid yields emetine by O-methylation, and therefore only the position of the single phenolic group requires consideration. In this connection, evidence, which had been obtained in the researches of Carr

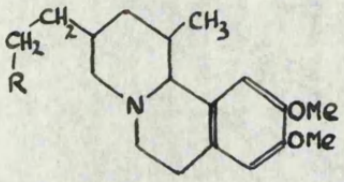
/and Pyman (4),

and Pyman (4), was brought forward upon the oxidation of cephaeline by ferric chloride. No compound analogous to rubremetine was formed, but small amounts of two crystalline hydrochlorides, Product A $C_{18}H_{18}O_3NCl.HCl$ and Product B $C_{20}H_{27}O_3NCl_2.HCl$, were isolated. Only the second product is of value in deriving the structure for cephaeline.

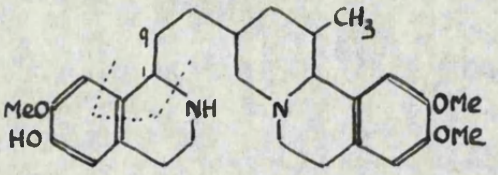
Two of the oxygen atoms in Product B are contained in methoxyl groups, and the two chlorine atoms were readily eliminated by the action of cold, aqueous sodium hydroxide. The resultant product was a crystalline solid $C_{20}H_{29}O_5N$, which was soluble in water, neutral to litmus and amphoteric in character. It is quite clear that the two chlorine atoms in Product B have been replaced by hydroxyl groups, and since the final product was amphoteric, a molecular rearrangement was suspected. Spectroscopic evidence (13) showed that Product B contains only one benzene ring, which must carry the two methoxyl groups; the nucleus which contained the phenolic grouping in cephaeline has therefore been destroyed. One of the nitrogen atoms also has been split out of the molecule, as the analysis shows, and the other was shown to be tertiary, by its failure to yield a nitrosamine.

These facts could be brought into agreement only with one structure (XXII, R= $-CO.CHCl_2$) for Product B, derived from cephaeline by the destruction of Ring A, as shown

/by the



XXII



XXIII

by the dotted line in structure (XXIII). The amphoteric substance, which was obtained from Product B by treatment with alkali, was formulated as (XXII, R= —CH(OH)COOH), and was considered to be produced from the glyoxal (XXII, R= —CO.CHO), formed initially, by a change analogous to the transformation of methyl glyoxal to lactic acid. It follows directly, that the phenolic hydroxyl group in cephaeline is carried by ring A, and position 6 was taken to be more probable than the possible, alternative position 7.

This proposal was given strong support by the researches of Späth and Leithe (p. 13), and also by a study of the partial hydrolysis of O-methylpsychotrine; the preparation of psychotrine by this hydrolysis has been mentioned previously. The relationship of psychotrine to cephaeline leads directly to the result that the phenolic hydroxyl group in the former base is situated on Ring A. Position 6 is again favoured, since the selective hydrolysis

/of one

of one ether grouping in O-methylpsychotrine could be explained only on the basis of activation of the para position of (XXI) by the substituted vinyl residue.

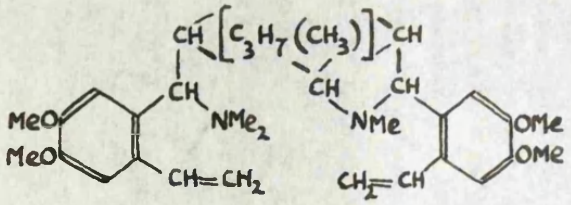
All the evidence, from several independent experiments, supports the choice of position 6 for the phenolic hydroxyl group in cephaeline and psychotrine; the former base was represented by (XXIII), and the latter by (XXIII, with a double bond between C_1 and C_9), because of its relationship to O-methylpsychotrine.

In conclusion, it can be stated that the proposals of Brindley and Pyman for the structures of the Ipecacuanha alkaloids, have acted as a valuable stimulus to further research. These detailed structures, however, rest on speculative considerations, and the facts which are known with certainty, in the case of emetine, only give rise to the partial structure (IX).

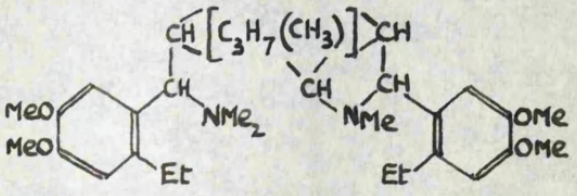
III. (e). THE HOFMANN DEGRADATION OF EMETINE.

This section deals briefly with the work of the present author, which was presented to the Victoria University of Manchester in 1947, for the Degree of Master of Science. These researches were carried out as the first part of a series of investigations planned to establish the structure of emetine, and the new work, a continuation of that described herein, will be discussed in the Theoretical Section.

In order to avoid the difficulties encountered by Ahl and Reichstein in their multi-stage degradation of emetine (p. 14), which are probably due to the accumulation of ethylenic linkages in the molecule, it was decided to hydrogenate the product at each stage of the Hofmann degradation. The first step was carried out on a mixture of α- and β-N-methylemetine dimethiodides, using the method described by Pyman (8). The N-methylemetinemethine (XXIV) so obtained, was



XXIV



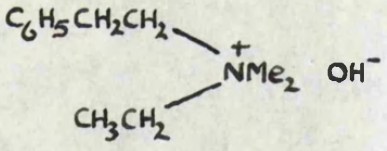
XXV

hydrogenated, using platinum catalyst, to N-methylemetine-tetrahydromethine (XXV), characterised as the sparingly

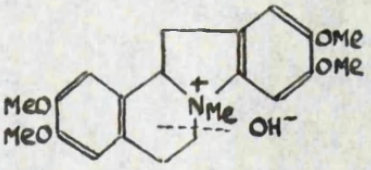
/soluble

soluble, crystalline perchlorate. The yield of this salt was 90% of the theoretical quantity, and the conclusion of Pyman (p. 8.), that the methine (XXIV) consists mainly, if not entirely, of one substance, is thereby confirmed.

The assignment of the structure (XXIV) to N-methylemetinemethine requires the assumption that the ring fission has occurred between the nitrogen atom and C_3 in both isoquinoline nuclei. This assumption was based upon the known ease with which β-phenylethylamine derivatives undergo such fission; for example, the substance (XXVI) eliminates styrene in preference to ethylene, when decomposed thermally.



XXVI



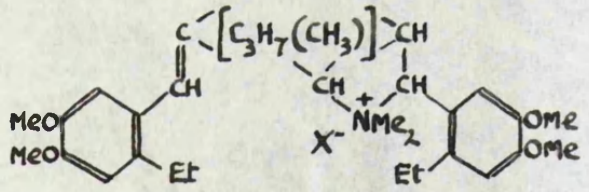
XXVII

Support for the structure (XXIV) also is given by the fact that the dibenztetrahydropyrrocoline (XXVII) undergoes ring fission between the nitrogen atom and C_3 of the isoquinoline residue (23). A complete proof of the structure (XXIV), by chemical methods, will be described in the Theoretical Section.

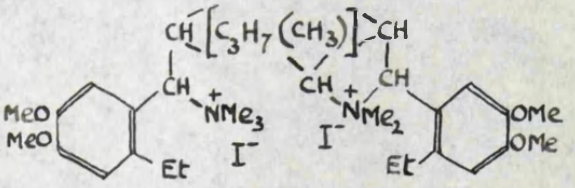
When the preparation of the dimethiodide of the

/tetrahydromethine

tetrahydromethine (XXV) was attempted by Dr. H.T. Openshaw (10), using methyl iodide in hot alcoholic solution, an unexpected decomposition occurred. The product obtained was a mixture of trimethylamine hydriodide and a singly unsaturated monomethiodide, named des-N(a)-emetine-tetrahydromethine methiodide (XXVIII, $X^- = I^-$). The yield of the methiodide (XXVIII, $X^- = I^-$) was not good, however, and a considerable quantity of gummy material was formed as a by-product. An alternative method for the preparation of this salt, therefore, was investigated in the present researches. When the methylation of the tetrahydromethine (XXV) was carried out with methyl iodide in cold ethereal



XXVIII

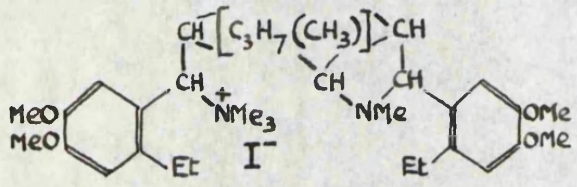


XXIX

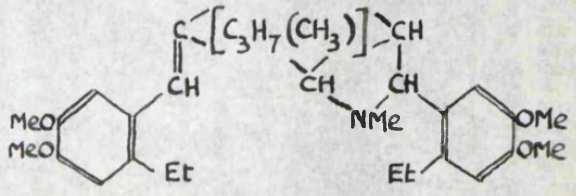
solution, the normal dimethiodide (XXIX) was obtained, together with an impure mixture of salts, which was thought to contain the monomethiodide (XXX) of the tetrahydromethine. A complete investigation of the nature of this mixture of salts will be described in the Theoretical Section.

The separation of the dimethiodide (XXIX) from the total product of the methylation, was facilitated by the fact that (XXIX) forms a crystalline complex with ethylene

dichloride (apparently $C_{34}H_{56}O_4N_2I_2.C_2H_4Cl_2$), very sparingly soluble in that solvent. On heating a solution of the pure dimethiodide in diethyl or methyl propyl ketone at 100° for three hours, decomposition occurred to give the monomethiodide (XXVIII, $X^- = I^-$), in 81% yield, and trimethylamine hydriodide, which was characterised by converting the volatile base to its



XXX



XXXI

known <u>picrate</u>.

The presence of the monomethiodide (XXX) in the crude methylation product was suspected as a result of one experiment in which the decomposition of a very impure specimen of the dimethiodide was studied. In addition to the monomethiodide (XXVIII, $X^- = I^-$), a small amount of a tertiary base was isolated as its crystalline <u>hydriodide</u>. The crystalline salt with perchloric acid was also used to characterise the base. When the <u>methochloride</u> (XXVIII, $X^- = Cl^-$), prepared from the corresponding methiodide by the action of freshly precipitated silver chloride, was decomposed thermally, it was found to afford this same base

/in excellent

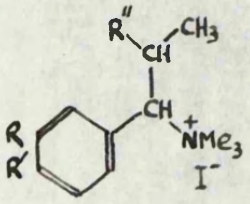
in excellent yield. Moreover, the base was reconverted to the methiodide (XXVIII, $X^- = I^-$) by methyl iodide in cold, ethereal solution, and full support, therefore, is given to the representation of the base, named des-N(a)-emetine-tetrahydromethine, by the structure (XXXI). This substance must have arisen from the monomethiodide (XXX) by a similar decomposition to that which has been described for the normal dimethiodide (XXIX).

The facile decomposition of N-methylemetine-tetrahydromethine dimethiodide (XXIX) is of great interest. It is also of considerable value, for by this circumstance it has been possible to eliminate one nitrogen atom from the molecule, and to leave the other still bound in the single nitrogenous ring D. It can be seen that the tertiary base (XXXI) and its methiodide (XXVIII, $X^- = I^-$) are suitable starting materials for the determination of the size of this remaining ring.

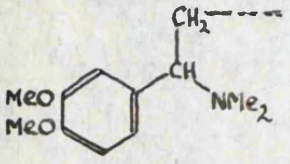
Two decompositions, that of the alkaloid gramine (24) and that of pavinemethine methiodide (25), are analogous to the one which has been described, and a consideration of these reactions indicated that the decomposition of the methiodide (XXIX) could be attributed to the presence of an activated benzylamine structure. This theory was confirmed by a study of model substances (26). Substances of the type

/(XXXII,

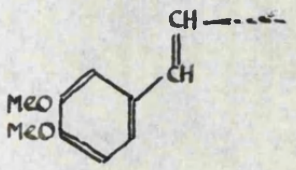
(XXXII, R = H or CH_3O, R′ = CH_3O, R″ = H or CH_3) were found to be unstable in boiling aqueous solution, whilst the



XXXII



XXXIII



XXXIV

substances which differed by having R = H and R′ = H were stable under these conditions. Recent work by Pailer and Bilek (27) has shown that the methiodides of bases containing the residue (XXXIII) decompose at 100° to trimethylamine hydriodide together with the unsaturated products (XXXIV).

Since an odour of volatile amine was always observed during the handling of the tetrahydromethine (XXV), attempts were made (10) to bring about its decomposition to des-N(a)-emetinetetrahydromethine (XXXI), a reaction analogous to the decomposition of the dimethiodide (XXIX) to (XXVIII, X^- = I^-). The base (XXV) was heated alone, and under a variety of acid and alkaline conditions, but in no case was any appreciable amount of dimethylamine liberated. The starting material was usually recovered unchanged, except that partial demethylation of the methoxyl groups occurred when strongly acid conditions were employed. The model bases (XXXIII) of Pailer and Bilek were found to be stable

/in methanol

in methanol at 100°, a result which is in agreement with our findings.

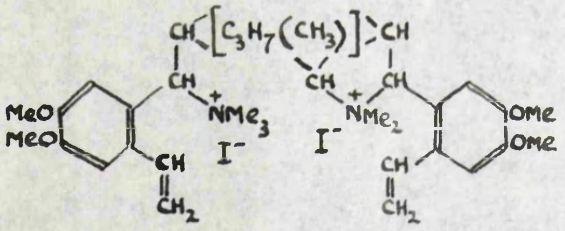
A further study of the degradation of emetine by the Hofmann procedure, and also by oxidation, forms the basis of the researches to be described in the next section.

IV. THEORETICAL SECTION.

The present series of investigations can be divided into three sections; firstly, a study of the preparation and properties of N-methylemetinemethine, secondly, degradative work, which has completed the elucidation of the structure of emetine, and lastly certain synthetical investigations.

STUDY OF N-METHYLEMETINEMETHINE.

When the Hofmann degradation of emetine was investigated by Karrer (9), he prepared N-methylemetinemethine dimethiodide (XXXV) in the amorphous state. His paper gives



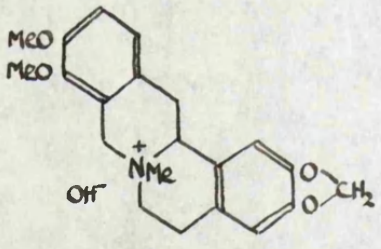
XXXV

no indication that this salt is thermo-labile in the manner which has been described for its tetrahydro derivative (XXIX p. 43). It was considered of interest, therefore, to prepare a sample of the dimethiodide (XXXV) in order to test its stability, and accordingly, N-methylemetinemethine (XXIV p. 42) was treated with excess of methyl iodide in cold

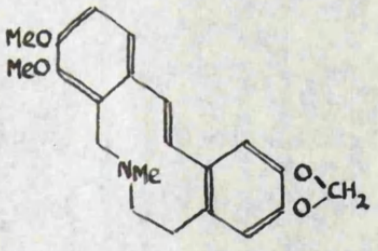
/ethereal

ethereal solution. The amorphous product crystallised from ethylene dichloride. On heating in diethyl ketone at 100°, this dimethiodide yielded 13% of the theoretical quantity of trimethylamine, characterised as the picrate, whilst the rest of the material was converted to a dark tar, probably due to the sensitivity of the two dimethoxylated styrene residues. This result is in sharp contrast to the decomposition of the corresponding tetrahydro derivative, which gives a high yield of the pure fission products.

The stability of N-methylemetinemethine itself (XXIV p. 42) was also investigated, the base being heated in aqueous ethanol. In the case of the methine (XXXVII) derived



XXXVI

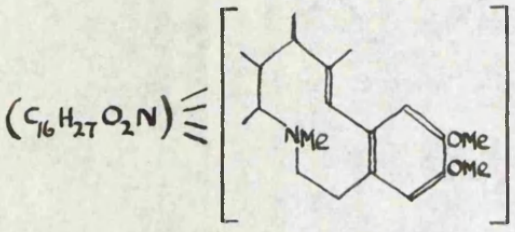


XXXVII

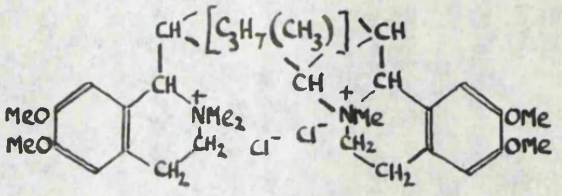
from 1-camadine metho-hydroxide (XXXVI), a reversal of the ring opening occurred under these conditions, to afford the original, quaternary hydroxide (28). As this change progressed, the solution gradually became strongly alkaline, due to the formation of (XXXVI), in contrast to the faintly alkaline character of the original solution of (XXXVII).

/Emetine

Emetine is similar to canadine in having the tertiary nitrogen atom common to two rings, and it is possible for the first stage of the Hofmann degradation to yield some, or all, of



XXXVIII



XXXIX

the methine (XXXVIII); when this work was carried out, no direct chemical evidence was available to support the structure (XXIV) for N-methylemetinemethine. The aqueous alcoholic solution of the N-methylemetinemethine did not become strongly alkaline when it was heated, and furthermore, evaporation of the aqueous alcoholic solution under reduced pressure yielded a residue which dissolved readily in ether. Thus, there is no evidence for any reversibility of the Hofmann degradation in the case of the methine from emetine, which indicates that the base does not have the structure (XXXVIII); this indication was completely confirmed by later work.

The last problem to be discussed in this section concerns the Emde degradation of emetine. Späth and Leithe (14) carried out this degradation upon N-methylemetine dimethochloride (XXXIX), but did not prepare any crystalline

/derivatives

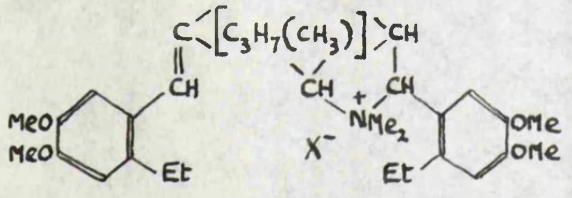
derivatives of the product. They then repeated the Emde procedure twice upon the crude product from the first stage, and obtained a mixture of one part of nitrogen-free material and three parts of base. The first stage of this degradation was repeated by the present author, in order to determine whether or not the ring opening occurs at the same point as in the Hofmann degradation. If the two methods do open the ring at the same point, then the product from the Emde degradation will be N-methylemetinetetrahydromethine (XXV), which has been well characterised. When N-methylemetine dimethochloride, prepared from the corresponding diiodide by the action of silver chloride, was treated with sodium amalgam, the basic product was found to be unsaturated. The unsaturated material must arise by the occurrence of the normal Hofmann degradation of the methochloride under the alkaline conditions prevailing. Micro-hydrogenation of the total basic product from the degradation showed the presence of 0·66 double bond per mole; some 33% of the product from the Hofmann degradation must be present, therefore, in the mixture. It can be seen from the foregoing discussion, that if the two reactions open the ring at the same point, then the product, after hydrogenation, must be pure N-methylemetinetetrahydromethine (XXV). This was shown not to be the case, for the perchlorate of the hydrogenated material was amorphous, and no crystalline salt

/could be

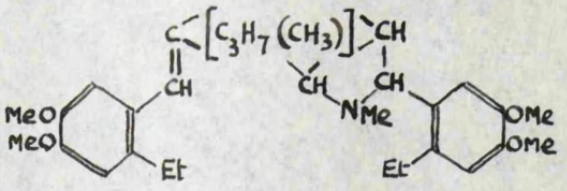
could be obtained from it, even after seeding. The Emde degradation must therefore open the ring at a different point from the Hofmann, probably between C_1 and N in each ring.

DEGRADATIVE INVESTIGATIONS.

In researches which were described in the Historical Section (p. 42), the degradation of emetine by the Hofmann procedure was carried to the point at which one nitrogen atom was removed from the molecule. The main product was des-N(a)-emetinetetrahydromethine methiodide (XXVIII, X^- = I^-), but a small amount of des-N(a)-emetine-tetrahydromethine (XXXI) was obtained as a by-product.



XXVIII



XXXI

The ultra-violet extinction curve for the methiodide (XXVIII, X^- = I^-) showed that the double bond is conjugated with the benzene nucleus, and since this salt has been shown to be the methiodide of the base (XXXI), this base must have the double bond similarly conjugated.

That stage of the degradation involving the preparation and decomposition of the methiodides of

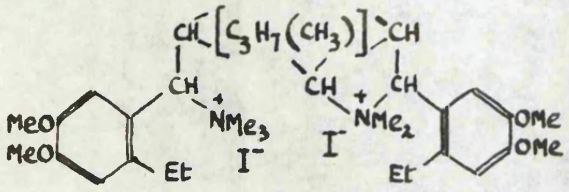
/N-methylemetine-

N-methylemetinetetrahydromethine was fully re-investigated at the start of the work to be described below. Special attention was given to the problem of increasing the yield of the important tertiary base (XXXI), and it was envisaged that this could be realised by treating the tetrahydromethine with a limited amount of methyl iodide. When this was carried out in cold ethereal solution, an amorphous mixture of methiodides was obtained, which was shown to contain about 30% of the dimethiodide (XXIX). In the experiments reported earlier, in which a large excess of methyl iodide was employed, at least half of the methiodide mixture proved to be the dimethiodide; the amount of this product, therefore, is considerably reduced by using a limited quantity of methyl iodide. The separation of the dimethiodide was carried out using ethylene dichloride, as was mentioned previously.

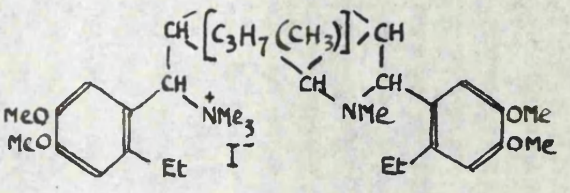
Considerable difficulty was experienced in purifying the methiodide which was soluble in ethylene dichloride, and which therefore remained in the mother liquors from the crystallisation of the dimethiodide. This crude methiodide afforded small crops of crystals from alcohol, which melted at widely different temperatures. A partially purified sample was analysed, however, and the result indicated that the crystalline material was not the expected N-methylemetine-tetrahydromethine-N(a)-methiodide (XXX), but was the

/hydriodide

hydriodide of (XXX), probably contaminated by trimethylamine



XXIX



XXX

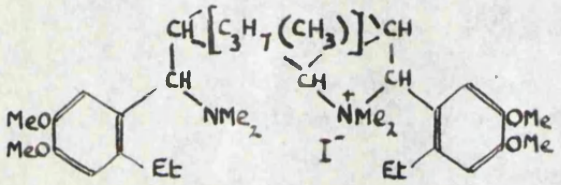
hydriodide and by (XXX) itself. The hydriodic acid of the salt which was analysed, must be derived from trimethylamine hydriodide, this being derived in turn, from the slight decomposition of the methiodides of the tetrahydromethine during handling. This shows quite clearly why it was possible to isolate only small, impure crops of the methiodide-hydriodide in the exploratory experiments. This discovery made it possible to isolate (XXX) as its hydriodide quite readily, by dissolving the crude methiodide, from the mother liquors above, in alcohol or acetone, and acidifying with hydriodic acid; the methiodide hydriodide then crystallised rapidly in almost the pure state, and in good yield.

After isolating the dimethiodide (XXIX) by means of the complex with ethylene dichloride, and the methiodide (XXX) as the hydriodide, the remaining, amorphous material was decomposed in methyl propyl ketone at 110°; small amounts of the base (XXXI) and its methiodide (XXVIII, $X^- = I^-$) were

/obtained.

obtained. In this way, pure products were obtained, equivalent to 92% of the mixture of methiodides obtained from the tetrahydromethine and methyl iodide.

It is interesting to note, that whilst the monomethiodide (XXX) could be isolated in considerable amounts, no trace of the alternative monomethiodide (XL) could be detected. This indicates that methiodide formation is more



XL

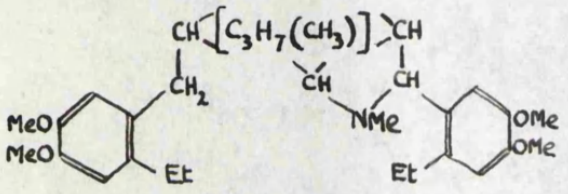
difficult at N(b) than at N(a), probably due to steric hindrance.

The N-methylemetinetetrahydromethine-N(a)-methiodide (XXX), as the hydriodide, was decomposed by heating in diethyl or methyl propyl ketone under reflux for three hours. It yielded 90% of the theoretical quantity of des-N(a)-emetine-tetrahydromethine (XXXI), isolated as the perchlorate, together with trimethylamine hydriodide, which was characterised by conversion to the picrate. The characterisation of the base (XXXI) was completed by converting a portion, recovered from the perchlorate, to the methiodide, which was identical with

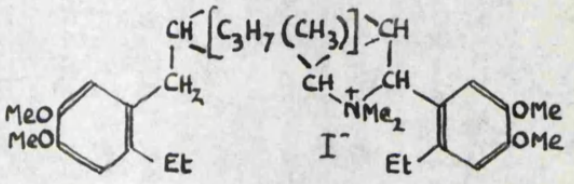
/(XXVIII,

(XXVIII, $X^- = I^-$). This method of preparation made it possible to obtain the valuable base (XXXI) in quantity; it was shown to be optically active.

Catalytic hydrogenation of des-N(a)-emetine-tetrahydromethine (XXXI) proceeded readily in acetic acid, using platinum catalyst, to yield the saturated, crystalline, tertiary base (XLI), named <u>des</u>-N(a)-<u>emetinehexahydromethine</u>.



XLI



XLII

One molecular proportion of hydrogen was absorbed, which accords with the structure (XXXI) for the starting material, and the ultra-violet extinction curve for the hydrogenated base (XLI) showed the absence of styrene residues.

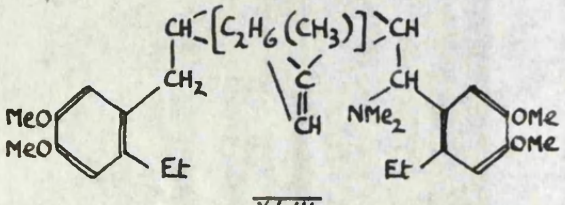
The methiodide (XLII), <u>des</u>-N(a)-<u>emetine-hexahydromethine methiodide</u>, corresponding to the saturated base (XLI), was obtained by two methods. The first was to convert the unsaturated methiodide (XXVIII, $X^- = I^-$) to the corresponding chloride (XXVIII, $X^- = Cl^-$), by the action of freshly precipitated silver chloride, and to hydrogenate this quaternary chloride using platinum catalyst. Isolation of the reduction product was carried out by precipitating the

/crystalline

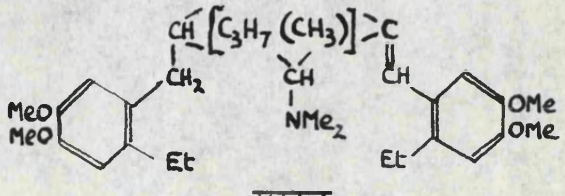
crystalline methiodide (XLII). This same methiodide was obtained by the prolonged action of hot methyl iodide upon the saturated base (XLI). It is interesting to note, that when the preparation of (XLII) was attempted by treating a cold ethereal solution of the base (XLI) with methyl iodide, only a trace of the methiodide had separated after seventeen hours. This is a further instance of the resistance to methylation shown by N(b) in its present environment.

By degrading fifty grammes of emetine hydrochloride in the manner which has been described above, a sufficient quantity of des-N(a)-emetinehexahydromethine methiodide (XLII) was obtained to enable the degradation to be pursued further. This methiodide (XLII) was degraded by the normal Hofmann procedure to yield a mixture of basic and neutral substances. The main product was a tertiary base, which afforded a beautifully crystalline picrate; analyses of the base and the picrate agreed with the expected molecular formula $C_{31}H_{47}O_4N$. A micro-hydrogenation of this base, which had been purified through its picrate, showed the presence of one ethylenic linkage, and the ultra-violet extinction curve indicated that this is conjugated with the benzene nucleus.

The Hofmann degradation of the methiodide (XLII)



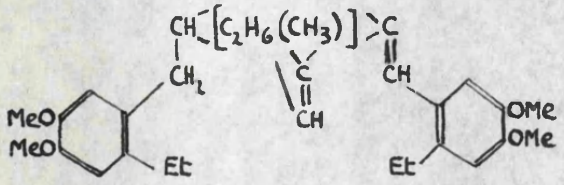
XLIII



XLIV

/could

could give rise to two bismethines (XLIII) and (XLIV), and the evidence already presented shows that the one which was obtained has the structure (XLIV), designated des-N(a)-emetinehexahydrobismethine. This base was shown to be optically active. Further support for the structure (XLIV) was sought by preparing the amorphous methiodide of the bismethine. This was readily carried out with cold, ethereal methyl iodide and thus, with fission of the ring, the hindrance of methylation at N(b), which was mentioned earlier, is removed. The methiodide so obtained, was stable at 100° over a period of three hours, whereas the methiodide of the possible alternative bismethine (XLIII) would have decomposed to trimethylamine hydriodide and the neutral fission product (XLV), in analogy to the decompositions of



XLV

the mono- and di-methiodides of N-methylemetine-tetrahydromethine (p.45). The two fission products were sought by methods capable of detecting very small quantities, but no trace of either substance was found. Support is

/thereby given

thereby given to the structure (XLIV) for the bismethine, and further evidence for this structure is adduced below.

The mother liquors from the picrate of the bismethine (XLIV) contained small quantities of a base, which eventually crystallised. It was different from the bismethine (XLIV), since the picrate would not crystallise, even after seeding with the picrate of (XLIV), and the melting point of this new base suggested its identity with des-N(a)-emetinehexahydromethine (XLI). This was shown to be so, when the two bases melted separately, and in admixture, at exactly the same temperature. This base (XLI) is obviously derived from the metho-hydroxide (XLII, $I^- = OH^-$) by loss of methanol, a common side-reaction in the Hofmann degradation, and the extent of the side-reaction was found to depend upon the conditions which were employed. Considerably more by-product was obtained when the metho-hydroxide (XLII, $I^- = OH^-$) was decomposed by distillation in high vacuo at 140°, than when the decomposition was conducted at 100° and 15 m.m. pressure. The final stage in the Hofmann degradation of emetine to give the nitrogen-free molecule, was found to behave in the same way.

The formation of neutral matter in the Hofmann degradation of des-N(a)-emetinehexahydromethine methiodide (XLII) has been mentioned previously, and it was isolated in

/two portions.

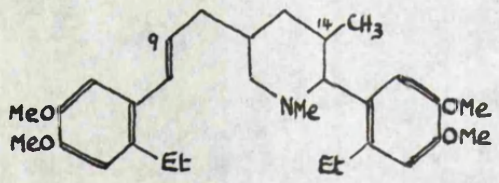
two portions. One fraction was isolated from the product of the distillation of the total basic product from the degradation, and therefore appears to be derived from one or both of the two possible bismethines (XLIII) and (XLIV). It is difficult, however, to explain the formation of the neutral substance from either possible source. The problem was not studied further, because of the extremely small quantity of this neutral material. A second portion of neutral substance remained when the total crude product from the degradation of the metho-hydroxide was freed from basic substances. A clear gum, weighing some 200 mgs., was obtained in this way. The analysis of the gum, distilled in a high vacuum, was in agreement with the molecular formula $C_{29}H_{40}O_4$, and the ultra-violet extinction curve showed that one ethylenic linkage is conjugated with a benzene nucleus. These results accord with a structure (XLV) for the neutral substance, but micro-hydrogenations of the remaining neutral matter did not yield consistent results. Further experiments upon larger samples of this substance will be necessary before any sound conclusions regarding its nature can be drawn, and at this stage, speculation upon possible mechanisms of its formation would be of little value.

The two substances, des-N(a)-emetinetetrahydromethine (XXXI) and des-N(a)-emetinehexahydrobismethine (XLIV), are of

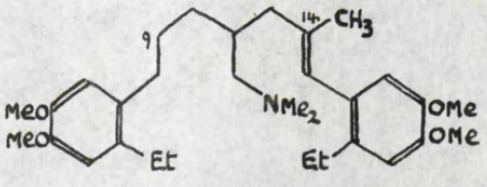
/great importance

great importance for further degradative experiments, because of the ethylenic linkage which each contains. These unsaturated linkages are points of ready attack by oxidising agents, and the molecules can be split into two parts by this means.

On the basis of the structure proposed by Brindley and Pyman for emetine (XVII p.35), again assuming the one direction of ring fission in the first Hofmann degradation which has been used hitherto, the structures of the tetrahydromethine and the hexahydrobismethine can be represented by (XLVI) and (XLVII) respectively. A profitable comparison might be made of these structures with the partial structures



XLVI



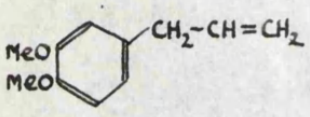
XLVII

(XXXI) and (XLIV), which have been used previously. It must be stressed, however, that whilst the emetine structure proposed by Brindley and Pyman was considered to be a very probable one in its essentials, at this stage, the location of the C-methyl group at C_9 is just as probable as at the proposed C_{14}. The importance of the oxidative degradation of

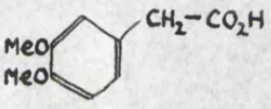
/the two bases

the two bases (XLVI) and (XLVII) is now apparent, for not only should this procedure yield direct chemical evidence upon the point of ring fission in the first Hofmann degradation, but it should also cast light upon the position of the C-methyl group.

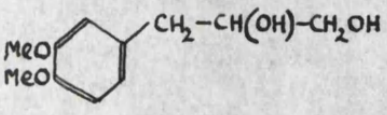
Accordingly, trial experiments were carried out upon O-methyleugenol (XLVIII) as the model substance, this being



XLVIII



XLIX



L

prepared from eugenol by a modification of the procedure used for the methylation of vanillin (29). The eugenol which was employed, was shown to be free from any appreciable quantity of isoeugenol, which is inseparable by ordinary distillation, by the melting point of its benzoyl derivative and by its refractive index; the refractive index of the O-methyleugenol prepared from it, also indicated the absence of O-methyl-isoeugenol. Two products were obtained when the pure O-methyleugenol (XLVIII) was oxidised in a cooled, aqueous suspension, by the gradual addition of dilute, aqueous potassium permanganate (cf. 30). The main product proved to be the known, crystalline glycol, 1-(3:4-dimethoxyphenyl)-propane-2:3-diol (L), and homoveratric acid (XLIX) was isolated

/in smaller

in smaller quantity.

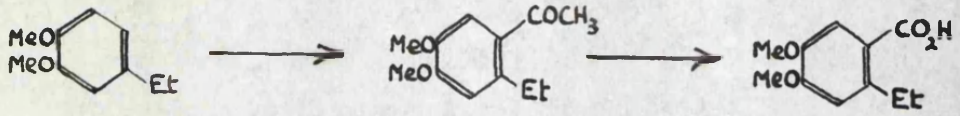
From the experience gained in these trial experiments, it was decided to split the ethylenic linkages in the two degradation products from emetine by a one stage oxidation, rather than to attempt to isolate the intermediate glycols for further oxidation.

The oxidation of des-N(a)-emetinetetrahydromethine (XLVI) was carried out by the gradual addition, over many hours, of cold, aqueous barium permanganate to a solution of the base in aqueous acetone. The quantity of the oxidising agent which was added was equivalent to four atomic proportions of oxygen, and the rate of addition was so adjusted, that no appreciable concentration of unreacted permanganate was present at any time. Barium permanganate was employed in preference to the more readily available potassium salt, because, with the former reagent, it is readily possible to remove inorganic ions from the solutions, a property of no mean importance when water soluble acids or amino-acids are the expected products.

One, crystalline, acidic product from the oxidation was extractable by ether from the aqueous solution. It melted at 141°, was soluble in hot water, and sublimed readily in vacuo; furthermore, the analysis indicated a molecular formula $C_{11}H_{14}O_4$. These results left little doubt that the acidic

/substance

substance was 6-ethylveratric acid (LIII), 44% of the theoretical quantity being isolated; a synthetic specimen was prepared by a procedure which is a considerable improvement



LI LII LIII

on the method described by Shinoda and Sato (31).

4-ethyl-5-acetoveratrone (LII) was first prepared from 4-ethylveratrole (LI) and acetyl chloride, by the Friedel-Crafts reaction; the orientation of (LII) had been proved by oxidation to metahemipinic acid with potassium permanganate (31). The methyl ketone (LII) was then oxidised to the required 6-ethylveratric acid (LIII), in very high yield, using alkaline sodium hypochlorite. This synthetic specimen was identical in every way with the acid from the degradation of emetine, and with this, the first union of the synthetic and degradative investigations in the present researches had been made. The isolation of 6-ethylveratric acid, by oxidation of the base (XLVI), proves conclusively that the ring containing N(a) is opened between N and C_3 in the Hofmann degradation of emetine. Furthermore, the spectroscopic evidence upon the position of the double bond in the starting material (XLVI) is completely confirmed.

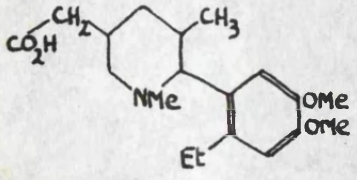
/Two further

Two further products from the oxidation of the base (XLVI) were examined, the first being the mixture of substances isolated as the neutral and basic fraction. This mixture was found to contain only a trace of basic substances, which suggests that the C-methyl group is not at C_9 in (XLVI); had it been there, a considerable amount of the basic methyl ketone would have been expected from the oxidation. The neutral fraction was found to afford a small quantity of 6-ethylveratric acid when it was oxidised by hydrogen peroxide or by the atmosphere, derived, without doubt, from the corresponding 6-ethylveratraldehyde. The remaining neutral matter was fractionated in a molecular still, but no pure products could be isolated. It is interesting to note, however, that this neutral material contains nitrogen, which is probably present as an amide residue $-CO-N<$, formed by oxidation of the carbon atom adjacent to the tertiary nitrogen atom.

A search for amino acids was made in that remaining fraction from the oxidation of (XLVI) which contained the water soluble acids. By careful addition of sulphuric acid to the aqueous solution, the barium ions were removed, and the solution, now free from inorganic matter, was evaporated to dryness. A method was developed to esterify the crude acids so obtained, which was an improvement upon many of the

/procedures

procedures described in the literature, and had the additional advantage that it was successful with very small quantities of acid. The esterification was carried out in anhydrous methanol, using concentrated sulphuric acid as the catalyst. By pouring the acid solution into dry chloroform and shaking with excess anhydrous barium hydroxide, the free ester was liberated, and was then recovered from the chloroform and distilled in high vacuum. The salts of the ester could not be induced to crystallise. It was therefore hydrolysed with a known quantity of aqueous barium hydroxide, and the solution freed from barium ions by a careful titration with standard sulphuric acid. In this way, a beautifully crystalline amino acid was obtained, the ethyl ester of which, prepared by the above procedure from the pure acid, analysed in agreement with the expected molecular formula $C_{21}H_{33}O_4N$. Satisfactory analytical figures were not obtained for the acid itself, the difficulty probably being due to tenaciously held water of crystallisation. On the basis of structure (XLVI), this amino acid can be represented by (LIV).



LIV

/Since the

Since the oxidation of the tetrahydromethine (XLVI) yielded 6-ethylveratric acid and an amino acid $C_{19}H_{29}O_4N$, without loss of carbon atoms, the ethylenic linkage must be of the type $R-CH=CH-R'$; the C-methyl group therefore cannot be situated at C_9.

The question now arises whether or not the C-methyl group is situated at C_{14}, and an oxidation of the hexahydrobismethine (XLVII), similar to that described above, was carried out to provide an answer. In the first experiment, the quantity of oxidising agent added was equivalent to three atomic proportions of oxygen, since it seemed probable that the C-methyl group would be found at C_{14}, after it was known with certainty not to be at C_9. The oxidation product was found to contain 6-ethylveratric acid (LIII), identical with the synthetic specimen of this acid.

It seemed possible, though unlikely in view of the mild conditions employed in the oxidation, that the 6-ethylveratric acid might have arisen by fission of the saturated left-hand portion of the molecule, as it is represented by (XLVII). The oxidation of 4-n-propylveratrole, prepared by the catalytic hydrogenation of O-methyleugenol, was therefore studied under the conditions used for the oxidation of the hexahydrobismethine (XLVII). A trace of veratric acid was isolated, the quantity showing that in the

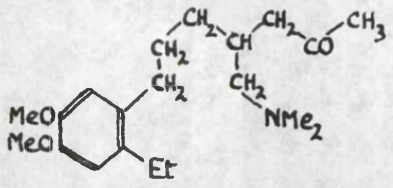
/analogous

analogous oxidation of (XLVII), less than a fiftieth of the amount of 6-ethylveratric acid which was obtained, could have arisen from the saturated left-hand portion of the molecule. This 6-ethylveratric acid must be derived, therefore, from the right-hand portion of (XLVII), by attack at the double bond. It follows that the fission in the isoquinoline residue containing N(b) must occur between N and C_3 in the Hofmann degradation of emetine, as it does in the ring containing N(a). Thus the structure (XXV p. 42) for N-methylemetinetetrahydromethine is fully proven, and the position of the double bond in des-N(a)-emetinehexahydrobismethine (XLVII) is confirmed; this work also provides independent proof of the existence of two dimethoxytetrahydroisoquinoline ring systems in emetine.

The oxidation product from the hexahydrobismethine (XLVII) contained neutral matter, which yielded a little 6-ethylveratric acid after mild oxidation with hydrogen peroxide. This acid must be derived from the corresponding 6-ethylveratraldehyde. Analysis of the neutral matter showed the presence of nitrogen, which is probably linked into the system $-CO-NMe_2$.

On the basis of structure (XLVII) for the hexahydrobismethine, the oxidation product accompanying the 6-ethylveratric acid was expected to be a methyl ketone (LV).

/This substance



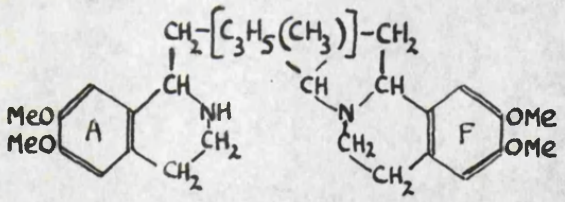
LV

This substance was sought in the basic products from the oxidation, which were fractionated in a molecular still, to yield four portions. In order to detect methyl ketones in these fractions, a micro-scale procedure for the iodoform reaction was worked out, which gave sufficient iodoform from 5 mgs. of laevulinic acid to allow purification and identification. Each of the four fractions from the oxidation gave a negative iodoform reaction, which suggested strongly that the C-methyl group is not at C_{14}.

The amino acid fraction from the oxidation, was therefore examined by the method which was described for the isolation of the crystalline amino acid from the tetrahydromethine (p.66), but no pure substance could be separated from it. However, it was mentioned earlier that the double bond in the hexahydrobismethine was thought to be of the type $R-C(CH_3)=CH-R'$ (see XLVII), and the amount of oxidising agent employed was therefore only three quarters of that required for $R-CH=CH-R'$. Since the first oxidation had

/shown that

shown that, in all probability, the double bond in the hexahydrobismethine is of the type $R-CH=CH-R'$, a second oxidation of this base was carried out using a quantity of barium permanganate equivalent to four atomic proportions of oxygen. Greater quantities of both 6-ethylveratric acid and the amino acid fraction were obtained from this experiment than from the previous one. The amino acid, purified through its methyl ester, could not be crystallised, but the methyl ester analysed in agreement with the expected molecular formula $C_{21}H_{35}O_4N$. This work shows that the C-methyl group is not situated at C_{14} or at C_9, and as a result, the partial structure for emetine can be extended to (LVI); the proposed



LVI

structure for emetine, put forward by Brindley and Pyman, is thereby excluded.

Whilst this last oxidation was being completed, the work of Späth and Pailer (32, 33) came available to us. These workers degraded emetine by a similar process to that described in the foregoing paragraphs, to yield a product free

/from nitrogen.

from nitrogen. In the final stage of the Hofmann degradation, they did not hydrogenate the substance we have named des-N(a)-emetinehexahydrobismethine (XLIV p.58) and, as a result, the nitrogen-free product contained two double bonds. This final product was obtained in the crystalline state, which was fortunate, for only one intermediate degradation product was isolated in the pure crystalline state. Their description of the properties of this latter substance, which was des-N(a)-emetine-tetrahydromethine methiodide (XXVIII, $X^- = I^-$ p.44), is in complete agreement with our findings (10). The other crystalline degradation products which have been described in this Thesis, were either not detected by Späth and Pailer, or were obtained in the amorphous state.

The method employed by these workers, starting with N-methylemetinemethine, which they prepared by the method of Pyman (8), is shown in the following scheme. The nomenclature used in this Thesis is continued, and the intermediate and final crystalline substances are marked with an asterisk. Repetition of the last two stages upon the tertiary base

N-methylemetinemethine (XXIV p.42) $\xrightarrow[\text{Reduction.}]{\text{Catalytic}}$

N-methylemetinetetrahydromethine (XXV p.42) $\xrightarrow[\text{MeI.}]{\text{Heat with}}$

des-N(a)-emetinetetrahydromethine methiodide* (XXVIII, $X^- = I^-$ p.44)

Convert to methochloride and hydrogenate. → des-N(a)-emetinehexahydromethine methochloride (XLII $I^- = Cl^-$ p.57)

Hofmann degradation. → des-N(a)-emetinehexahydrobismethine (XLIV p.58)

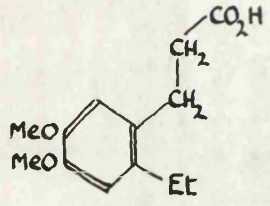
Heat with MeI. → des-N(a)-emetinehexahydrobismethine methiodide.

Hofmann degradation. → Nitrogen-free product $C_{29}H_{40}O_4$* and a tertiary base.

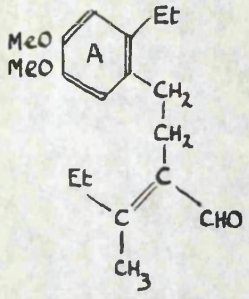
yielded a further quantity of the neutral product; this substance was shown to contain two double bonds by a micro-hydrogenation.

The ozonolysis of the neutral product afforded very valuable results. 6-ethylveratraldehyde and a carbonyl compound $C_{18}H_{26}O_3$ were isolated, the latter substance by means of its crystalline semicarbazone. A consideration of the method by which the neutral product was prepared, shows clearly that the 6-ethylveratraldehyde must be derived from ring F of emetine (LVI), ring A being contained in the carbonyl compound. This carbonyl compound contained one double bond, as shown by micro-hydrogenation to a dihydro derivative $C_{18}H_{28}O_3$, which yielded a crystalline semicarbazone. On further oxidation by ozone, and by potassium permanganate, the unsaturated carbonyl compound yielded methyl ethyl ketone, and 3:4-dimethoxy-6-ethylhydrocinnamic acid (LVII), respectively.

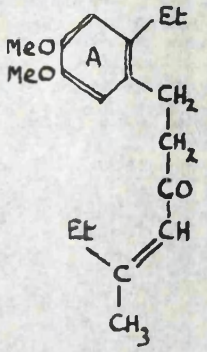
/The isolation



LVII



LVIII



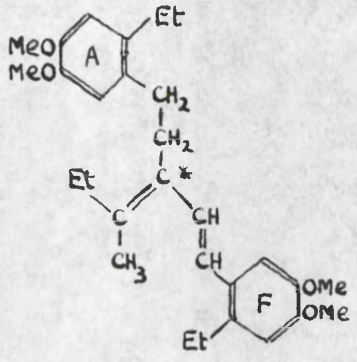
LIX

The isolation of these substances leads to two possible structures (LVIII) and (LIX) for the carbonyl compound, with the assumption that the two double bonds in the neutral product are conjugated with each other and with a benzene nucleus. The present author showed that the double bonds are so arranged, as will be described later.

Späth and Pailer did not attempt to eliminate one of the two possible structures (LVIII) and (LIX) by showing that their carbonyl compound was, or was not, an aldehyde, which is rather surprising. Instead, Pailer (33) argued that if (LVIII) is the correct structure, then the neutral product must be (LX), and the <u>fully saturated</u> neutral product will have the structure (LX, with the double bonds reduced). The fully saturated molecule can be seen to be symmetrical about the carbon atom marked with an asterisk in (LX), and this leads to an interesting possibility. If the ring A of emetine can be split off by a suitable degradative process, then a product should be obtained, which can be compared with those obtained

/above by

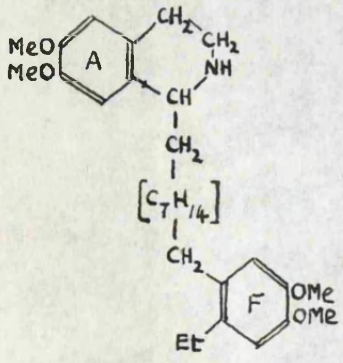
above by the elimination of ring F. The structure derived for the fully saturated final neutral product , if (LIX) is



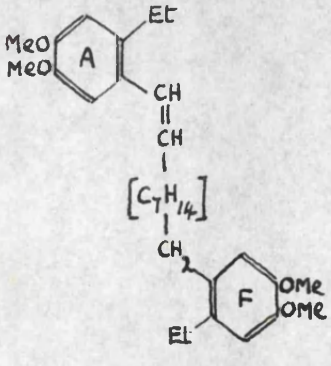
LX

the true structure for the carbonyl compound, is obviously not symmetrical in any way.

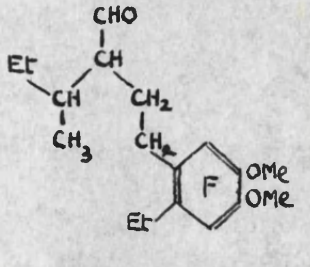
Accordingly, Pailer (33) repeated the partial Hofmann degradation of N-acetylemetine (p.14), hydrogenating the product after the first and after the third Hofmann degradations, to obtain the fully saturated substance (LXI) with the elimination of N(b).



LXI



LXII

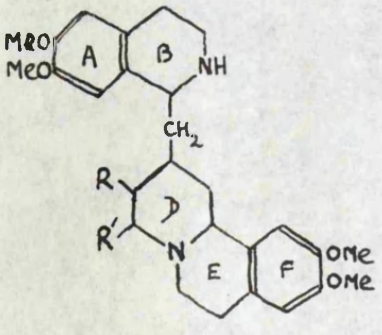


LXIII

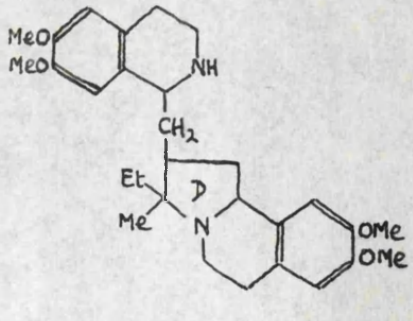
/Two applications

Two applications of Hofmann's process upon (LXI), with hydrogenation after the first, split out the nitrogen atom N(a), and afforded the singly unsaturated neutral product (LXII). This substance was oxidised with ozone to yield 6-ethylveratraldehyde and a carbonyl compound $C_{18}H_{28}O_3$, which proved to be identical with that obtained by hydrogenation of the unsaturated carbonyl compound (LVIII) or (LIX). Since the same saturated carbonyl compound is obtained by fission of either benzene nucleus from the degradation products, this carbonyl compound must be (LXIII), and the corresponding unsaturated substance must be (LVIII), and not (LIX).

Recently Pailer (34) has synthesised the aldehyde (LXIII) and has shown that it is identical with the carbonyl compound obtained by degradation. The synthesis was by



LXIV R = Et, R' = H.
LXV R = R' = Me.



LXVI

standard methods and need not be reported here.

/It is

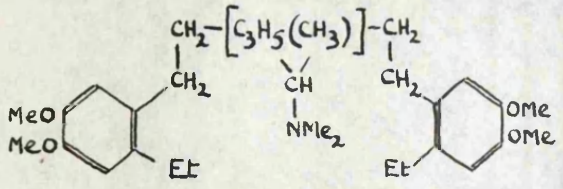
It is remarkable that Späth and Pailer did not put forward any proposals for the structure of emetine, as their work leads to three possible alternative structures (LXIV), (LXV), and (LXVI), the structure (LXVI) being the least probable. Robinson has pointed out (35) that the structure (LXIV) is consistent with current theories of biogenesis; it is difficult, however, to reconcile the two alternative structures (LXV) and (LXVI) with these theories.

C-methyl determinations upon emetine, although consistent with (LXIV), do not rule out the structures (LXV) and (LXVI) because of the quantity of acetic acid obtained; we obtained 0·94 mol. (10) and Karrer 1·1 mol. (11). The further degradation of emetine was therefore planned with a view to the final elucidation of its structure.

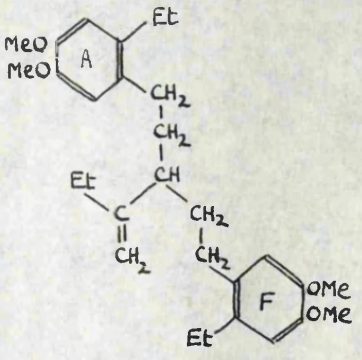
Before proceeding with the degradation, it was considered prudent to show that the neutral substance (LX) obtained by Späth and Pailer (32), does contain a 3:4-dimethoxyphenylbutadiene residue, as assumed. Accordingly, the hexahydrobismethine (XLIV p.58) was treated with methyl iodide in cold, ethereal solution, and the amorphous methiodide so obtained, degraded by Hofmann's method. The product was a mixture of basic and neutral substances, and the base was shown to be recovered hexahydrobismethine, by conversion to the crystalline picrate; this base must arise by loss of methanol from the intermediate metho-hydroxide.

The neutral product crystallised from petrol as colourless needles and its properties are substantially those described by Späth and Pailer (32). Its ultra-violet extinction curve showed that the two double bonds are conjugated in a phenylbutadiene system, as shown in (LX). Späth and Pailer described their product as yellow, and the substance obtained by the present author gradually became yellow on exposure to light. When a deep yellow sample was analysed, the proportion of carbon was found to have decreased, probably due to an uptake of oxygen. Such a behaviour is expected, when a substance of this type is handled.

The further degradation of emetine was now pursued by repeating the hydrogenation of des-N(a)-emetinehexahydro-bismethine (XLIV p. 58) on a macro scale; the quantitative micro-hydrogenation of this base has been mentioned previously. The product was the saturated, tertiary base des-N(a)-emetine-octahydrobismethine (LXVII) which was shown to be optically active.



LXVII



LXVIII

/Treatment

Treatment of (LXVII) with methyl iodide in cold, ethereal solution afforded an amorphous methiodide, which, by conversion to the metho-hydroxide and on being heated, underwent the Hofmann degradation. The product consisted of a mixture of neutral and basic substances, the base probably being recovered octahydrobismethine, in analogy to the Hofmann degradation of the hexahydrobismethine above. A direct comparison could not be made in the case of the octahydrobismethine, since this base failed to yield crystalline salts. The amount of recovered base was considerably greater when the metho-hydroxide was decomposed by distillation in a high vacuum, than when the decomposition was carried out at 100°, under 15 m.m. pressure; a similar observation has been noted previously (p. 60).

Analysis of the neutral substance supported the expected molecular formula $C_{29}H_{42}O_4$, and micro-hydrogenation showed the presence of one olefinic linkage. Furthermore, the substance was found to be optically inactive within the limits of experimental error.

This neutral substance reacted with ozone at −78° in ethyl chloride, to yield an ozonide which, on decomposition with water, afforded formaldehyde, isolated in 33% yield as the dimedone derivative, together with an involatile, viscous oil. In trial experiments upon O-methyleugenol as the model substance, 27% of the theoretical quantity of formaldehyde was isolated in the same manner. The yield of formaldehyde from

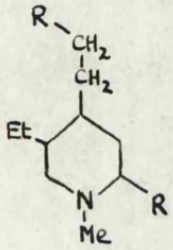
the degradation product, therefore, compares favourably with that from a known substance containing $\geq C=CH_2$. For this work, a small glass apparatus, with standard joints, was devised and built by the present author, which enabled the preparation, isolation, and decomposition of the ozonide to be carried out in the same apparatus.

The involatile oil from the decomposition of the ozonide was shown to be a carbonyl compound, since it formed a sparingly soluble, amorphous 2:4-dinitrophenylhydrazone, when treated with 2:4-dinitrophenylhydrazine. It did not, however, restore the colour to Schiff's reagent, nor did it reduce ammoniacal silver nitrate, and with the dianisidine test for aldehydes (37) it gave a negative result. These results show quite clearly that the substance is a ketone. It follows that the optically inactive, singly unsaturated, neutral product, which on ozonolysis yields formaldehyde together with a ketone, must have the structure (LXVIII). This is derived from (LXIV) or, less likely, from (LXVI), but not from (LXV); the structure (LXV) is thereby excluded.

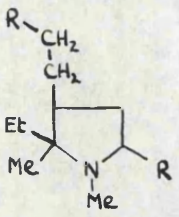
Inspection of the two remaining possible structures for emetine, (LXIV) and (LXVI), shows that a determination of the size of ring D will distinguish between them. A study was therefore made of the catalytic dehydrogenation of des-N(a)-emetinehexahydromethine (XLI, p. 57) which is represented by

/(LIXa)

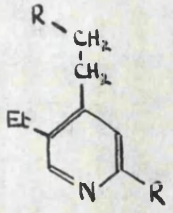
(LIXa), derived from structure (LXIV), or (LXa), derived from (LXVI).



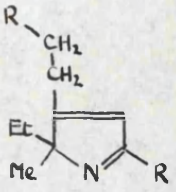
LIXa



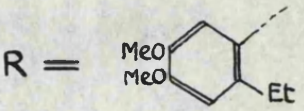
LXa



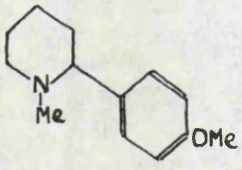
LXIa



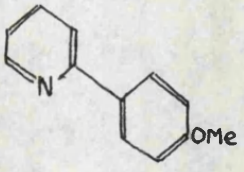
LXIIa



In the first place, it was decided to search for a suitable method for the separation of mixtures of a substituted pyridine with the corresponding N-methylpiperidine, since this was expected to be the nature of the product from the dehydrogenation experiments. It was found that 1-methyl-2-(p-methoxyphenyl)-piperidine (LXIIIa) and 2-(p-methoxyphenyl)-pyridine (LXIVa) could be separated quantitatively, by shaking



LXIIIa



LXIVa

an ether solution of a mixture of the two bases with a buffer solution of suitable acidity. The piperidine was removed into the aqueous phase, whilst the pure pyridine, being weakly basic, was recovered by evaporation of the ether layer. Mr. G. Norcross, M.Sc., kindly supplied the two bases used in these model experiments.

The catalytic dehydrogenation of the hexahydromethine (LIXa or LXa) was then studied, using palladium catalyst. The reaction proceeded smoothly at 270°, and the volume of gas evolved was 55-60% of that theoretically expected for the change from (LIXa) to the corresponding, demethylated pyridine derivative (LXIa). Almost all the dehydrogenation product was basic in character, but a small amount of neutral matter was isolated, which gave an intense purple colour in the cold with Erlich's reagent (p-dimethylaminobenzaldehyde), and also a red pine splint reaction. The neutral matter must therefore contain a substance, or substances, in which there is a pyrrole nucleus, but even if all the neutral matter is composed of substituted pyrroles, which seems unlikely, the small amount of this material suggests that it arises by a rearrangement of the ring, rather than by dehydrogenation of a structure such as (LXa).

No separation was achieved, when an attempt was made to remove the more basic substances from the dehydrogenation product, by shaking in ether with the same buffer that was successful in the model experiments. This is probably due to the fact, that the bases from emetine are more soluble in ether, and much less soluble in water, than are the model substances. However, by trial, a suitable buffer, more acidic than the previous one, was found, and the weakly basic substances

/isolated

isolated by its use. This weakly basic fraction afforded a crystalline picrate, which analysed in agreement with the molecular formula $C_{29}H_{37}O_4N.C_6H_3O_7N_3$, and the crystalline base recovered from it, gave the correct analysis for $C_{29}H_{37}O_4N$.

In trial experiments, silver acetate was found to dehydrogenate the acetate of the base (LXIIIa), when heated with it at 180° in a sealed tube (cf. 37), to yield the corresponding methylpyridinium acetate. This product, by treatment with hydrochloric acid, was converted to the methochloride of (LXIVa), which was decomposed thermally. In this way, the pyridine base (LXIVa) was obtained almost pure, and in quantity corresponding to 50% of the theoretical yield. This method has the advantage over the catalytic dehydrogenation procedure, in that the intermediate product is quaternary in character, and thus is readily separable from the unchanged basic material.

The total non-quaternary matter from the dehydrogenation, gave negative tests for the pyrrole nucleus with both Erlich's reagent, and a pine splint. It follows, that a change in ring size to a substituted pyrrole does not occur, even to a small extent, under the conditions of the reaction.

The series of reactions, described in the last paragraph, was repeated successfully upon the hexahydromethine (LIXa or LXa). The base obtained by the thermal decomposition

/of the

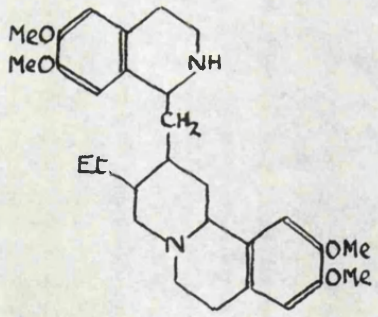
of the intermediate methochloride, formed a crystalline picrate, identical with that from the catalytic dehydrogenation experiments. In addition, the non-quaternary substances, from the crude total dehydrogenation product, gave a negative test for the pyrrole nucleus with Erlich's reagent.

The base, recovered from the pure picrate, was a stable substance, and showed no tendency to resinify during handling. It had the weakly basic properties expected for a substituted pyridine, and was stable to dilute potassium permanganate in cold, aqueous acetone. Furthermore, reduction was very slow when the base, dissolved in glacial acetic acid, was shaken with hydrogen in the presence of Adam's platinum catalyst. In 34 hours the uptake of hydrogen was equivalent to 3·56 mol. and was still proceeding when the experiment was stopped. This argues strongly against the presence of isolated double bonds in the structure, and suggests that aromatic systems are being reduced. These properties are those expected for a substance with the structure (LXIa) whilst one with the structure (LXIIa), a conceivable though it seems an unlikely dehydrogenation product of structure (LXa), would not be expected to behave in this way. The structure (LXIIa) can be seen to be an $\alpha\beta$-unsaturated cyclic ketimine, and not a structure stabilised by resonance. It would not be expected to have the stability which the dehydrogenation

/product

product shows, nor its resistance to oxidation and reduction. This evidence suggests very strongly that (LXIa) is the correct structure for the dehydrogenation product and this was shown to be the case by a study of absorption spectra. It was found that the extinction curve for the dehydrogenation product was similar to that for the model substance (LXIVa), (p. 144).

The nitrogenous ring in des-N(a)-emetinehexahydromethine is therefore shown to be six-membered, and this base can be represented by the structure (LIXa). It follows that, of the two structures for emetine (LXIV) and (LXVI) which were possible before the studies on dehydrogenation were carried out, (LXVI) is excluded and (LXIV) is fully supported.

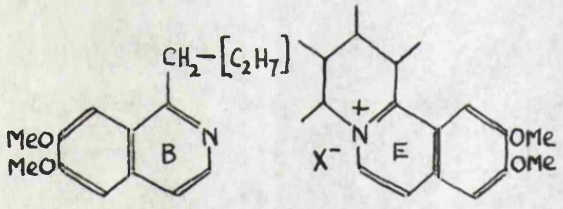


LXVa

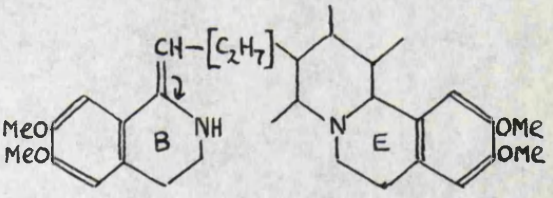
The structure of emetine can thus be represented by (LXVa), and experiments are in progress to confirm this structure by synthesis.

DISCUSSION OF THE STRUCTURES OF RUBREMETINE AND THE MINOR ALKALOIDS.

The problem of providing an explanation of the nature of rubremetine on the basis of the structure (LXVa) is one that must be faced. Karrer's proposal (LXVIa) was rejected as completely unsound (p. 27), and to the two objections raised in the earlier discussion, the following can be added. The proposed structure cannot explain the catalytic reduction of rubremetine with the uptake of one mole of hydrogen to yield a product which resists further reduction (p. 25). Also, if rubremetine had Karrer's structure, then it would be formed readily from emetamine



LXVIa

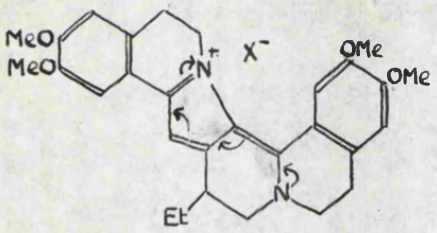


LXVIIa

(XVI p. 32), but this is known not to be so (p. 33). Lastly, Karrer explained the dehydrogenation of O-methylpsychotrine (LXVIIa) to rubremetine (LXVIa) by assuming the migration of the ethylenic linkage as shown, followed by aromatisation of rings B and E. The present author found, however, that 1-n-butyl-3:4-dihydroisoquinoline was not dehydrogenated by mercuric acetate using the conditions under which this reagent readily dehydrogenates emetine to rubremetine (38).

/A structure

A structure (LXVIIIa) was put forward for rubremetine by Battersby, Openshaw and Wood (38), which explains all the known chemistry of this interesting substance. This structure is formed from emetine by the loss of eight atoms of hydrogen



LXVIIIa

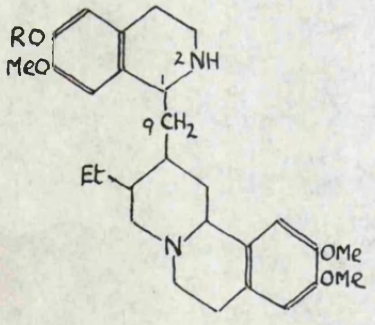
and on this basis, rubremetine is a resonance hybrid similar to a cyanine dye, as indicated by the curved arrows. The intense colour of rubremetinium salts is thus accounted for, and like the cyanine dyes, one nitrogen atom will be apparently quaternary and the other non-basic. The structure (LXVIIIa) could not be obtained by the dehydrogenation of emetamine or N-methylemetine, again in accordance with the known facts.

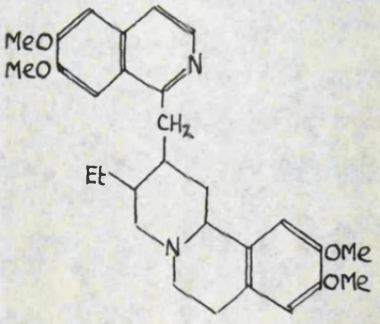
It seemed probable that the properties of Karrer's reduction product from rubremetine (p. 26), which was resistant to catalytic hydrogenation, could be explained by the presence of an intact pyrrole nucleus in the structure. Mr. H.C.S. Wood, B.Sc., repeated Karrer's reduction of rubremetine, and the crude product gave pyrrole reactions with Erlich's reagent and with a pine splint. Furthermore, he repeated the catalytic

/hydrogenation of

hydrogenation of rubremetine reported in this thesis, to obtain a base which also gave pyrrole reactions.* This work proves the presence of a five-membered nitrogenous ring in rubremetine, and affords strong support for the structure (LXVIIIa).

Turning now to the minor alkaloids of Ipecacuanha, the task is, in the main, one of deriving their structures from (LXVa), using the information which was available before the elucidation of the structure of emetine. Thus the structures of cephaeline and emetamine can be represented by (LXIX) and (LXX) respectively; in these, Pyman's proposals (p. 36,40) have been modified to accord with the emetine structure (LXVa). By this same method of derivation, the





LXIX R = H.

LXXI R = Me, double bond C_1 to C_9.

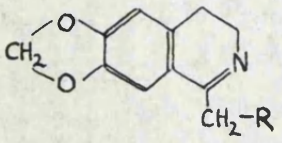
LXXII R = Me, " " C_1 to N_2.

LXXIII R = H, " " C_1 to N_2.

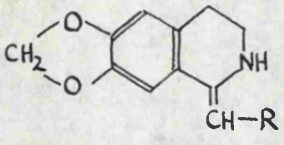
LXX

*I am most grateful to Mr. Wood for his permission to refer to these results in order to make the account complete.

structure of O-methylpsychotrine would be represented by (LXXI). However, recent work (39) upon the absorption spectra of substances of the type (LXXIV, R = H or C_6H_5) has



LXXIV



LXXV

shown that they exist in this form, and not as the alternative structure (LXXV, R = H or C_6H_5), even though the double bond in (LXXV) when R = C_6H_5, would be conjugated with two benzene nuclei. Thus there must be a strong tendency for the double bond to be endocyclic as in (LXXIV), and it seems most probable that this is also the case for O-methylpsychotrine. Its structure can therefore be represented by (LXXII), and the closely related psychotrine by (LXXIII). The ultra-violet absorption spectrum of O-methylpsychotrine will have to be studied before these most probable structures (LXXII) and (LXXIII) can be firmly established.

The ultra violet absorption spectra of some of the emetine derivatives which have been mentioned in this Thesis were measured by Dr. A.E. Gillam, to whom the author expresses his sincere thanks. The interpretations of the results collected here were given in the discussions of the substances, and need not be repeated.

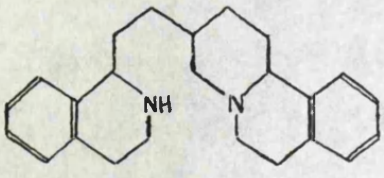
/Compound.

Compound.	$\lambda_{max.}$	ε.
Des-N(a)-emetinetetrahydromethine methiodide (XXVIII, $X^- = I^-$)	2665 3030*	15,900 7,240
Des-N(a)-emetinehexahydromethine (XLI)	2840	6,900
Des-N(a)-emetinehexahydrobismethine (XLIV)	2650 3030*	12,600 3,560
Neutral matter (XLV) from Hofmann degradation of des-N(a)-emetinehexahydromethine methiodide.	2655 3040*	16,100 6,160
Final doubly unsaturated neutral product (LX)	2280 2910	24,800 19,100

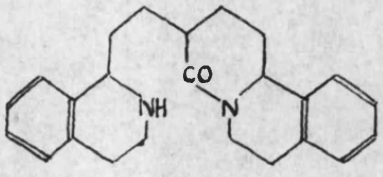
*Inflexion

SYNTHETICAL INVESTIGATIONS.

In the author's early work, attempts were made to synthesise the structure (LXXVI) by various routes, and this work was continued in the present researches. The structure (LXXVI) can be seen to be the main skeleton of Brindley and



LXXVI

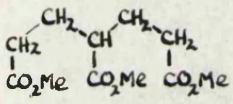


LXXVII

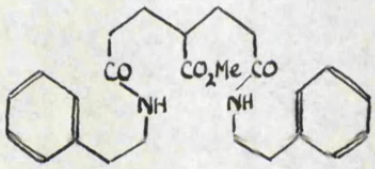
Pyman's proposal (XVII p. 35) for emetine, and it was thought that a synthesis of (LXXVI) could be modified to give emetine itself, should (XVII) prove to be correct. A comparison of the properties of (LXXVI) with those of emetine, and the possibility of studying its oxidation by mercuric acetate,

were also factors which prompted the start of the synthesis.

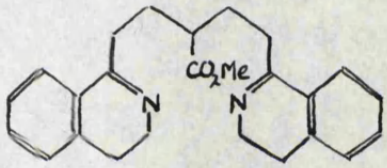
After two routes to (LXXVI) had been investigated and abandoned (40), a most promising one was found. It was based upon the preparation of methyl pentane-1:3:5-tricarboxylate (LXXVIII) as the key substance. Malonic ester was condensed with formaldehyde and the resulting ethyl pentane-1:1:3:3:5:5-hexacarboxylate yielded pentane-1:3:5-tricarboxylic acid on hydrolysis and decarboxylation, this acid being esterified to give (LXXVIII) (41).



LXXVIII



LXXIX



LXXX

It was envisaged that the two primary carbomethoxyl groups in (LXXVIII) would react more readily with β-phenylethylamine than would the secondary group. The tri-ester was therefore heated in tetralin, and two molecular proportions of the amine dropped in gradually over many hours; in this way, no appreciable concentration of unreacted amine was present at any time. From the reaction product, the diamide (LXXIX) was isolated in the crystalline state, together with smaller quantities of the mono- and tri-amides, also crystalline.

/The diamide

The diamide was to have been subjected to the Bischler-Napieralski reaction to bring about ring closure to the bis-3:4-dihydroisoquinoline (LXXX), which on reduction was expected to yield (LXXVII). The last stage in the synthesis, the reduction of the lactam (LXXVII) to (LXXVI), is one which can be brought about very readily by lithium aluminium hydride (42). However, before the ring closure of the diamide had been fully investigated, the Brindley and Pyman proposal for the structure of emetine was shown to be incorrect, and as a result, this synthetic work was discontinued.

GENERAL INFORMATION

Note 1. Analyses marked * were carried out by Mr. D.J. Lloyd and Miss A. Doherty, of Manchester University; and the remainder by Drs. Weiler and Strauss, Oxford.

Note 2. All solids were dried in vacuo at room temperature over phosphoric oxide, unless otherwise stated.

Note 3. Solutions of products in ether or chloroform were dried with sodium sulphate, unless otherwise stated.

(V) EXPERIMENTAL SECTION.

Preparation of N-methylemetinemethine dimethiodide (XXXV).

The methine (XXIV) (1.33 g.) was dissolved in anhydrous alkali-free ether (12 c.c.) and treated with excess of dry methyl iodide (1.5 c.c.). After 24 hrs. at room temperature, the amorphous precipitate was collected and washed with anhydrous ether, (1.73 g.) m.p. 132-135°, with effervescence, after sintering from 110°. A second crop (86 mg.) was obtained by adding methyl iodide (2 c.c.) to the filtrate, and allowing to stand for a further 24 hrs.; only 42 mg. of residue remained when the final filtrate was evaporated.

A portion of the first crop (1.072 g.) was dissolved in ethylene dichloride (4 c.c.) and allowed to stand. Crystallisation occurred after scratching, and the solid (0.356 g.) was washed with ethylene dichloride, m.p. 137-138° dec. with effervescence; the crystals were seen to be trapezoidal prisms under the microscope. On recrystallisation twice from acetone, the m.p. of the colourless, short prisms so obtained, was 151-153°, after slight previous sintering, to a clear melt which soon became cloudy. The m.p. was unchanged by a further recrystallisation from acetone to give the analysis specimen, which was dried for 2 hrs. in vacuo at

/room temperature

room temperature over phosphoric oxide. No further loss occurred on redrying the specimen to constant weight under these same conditions, before analysis.

Found:* C,48.6; H, 6.4; N, 3.1.

$C_{34}H_{52}O_4N_2I_2.2H_2O$ requires C,48.43; H, 6.70; N,3.32.

Thermal stability of N-methylemetinemethine dimethiodide (XXXV).

(XXXV) (66 mg.) was dissolved in dry diethyl ketone (5 c.c.) and heated at 100-110° for 3 hrs., whilst nitrogen, dried by conc. sulphuric acid, was bubbled through the solution. The nitrogen stream was freed from diethyl ketone vapours by a reflux condenser, and volatile bases, carried through by the nitrogen, were trapped by a bubbler containing dil. hydrochloric acid (10 c.c.). At the end of the heating, the acid from the trap was evaporated to dryness, and the residue treated with dil. sodium hydroxide. Air was aspirated through the apparatus and led into saturated ethereal picric acid, when a small precipitate formed. This was collected, washed thoroughly with ether, and dried in vacuo (3 mg. = 13%) m.p. 213-218° after sintering from 150°; one recrystallisation from ethanol raised the m.p. to 217-218°, alone and in admixture with authentic trimethylamine picrate.

The diethyl ketone solution, which had darkened in colour considerably during the heating, was diluted with acetone, water (3 c.c.) added, and the organic solvents

/boiled off.

boiled off. An aqueous suspension of tarry matter was thereby obtained, which was cooled, basified, and air aspirated through it into ethereal picric acid, as previously described. No precipitate formed in the ethereal solution, and the aqueous suspension was therefore warmed to ca. 40°; after 10 mins. aspiration, there was still no precipitate. The diethyl ketone solution therefore contained no trimethylamine hydriodide.

Stability of N-methylemetinemethine (XXIV).

The methine (0.497 g.) was dissolved in 50% aqueous ethanol (30 c.c.) to yield a solution which was alkaline to cresol red, but not to phenol phthalein. After being heated for 4 hrs. under reflux, the solution still failed to give the "alkaline" colour with phenol phthalein, and the solvent was evaporated under reduced pressure. The residue, freed from traces of water by re-evaporating with absolute ethanol, was a pale yellow gum. This dissolved readily in ether, save for a trace of insoluble matter, (less than 1 mg.) which merely rendered the solution faintly cloudy.

The Emde degradation of N-methylemetine dimethochloride (XXXIX).

A solution of N-methylemetine dimethiodide (0.524 g.), in warm 50% aqueous ethanol (15 c.c.), was stirred with silver chloride (from 0.6 g. silver nitrate) for 1 hr. The filtered solution was evaporated to 10 c.c. under reduced pressure, and

/5% sodium

5% sodium amalgam were added, and six portions (10 g. each) were added over a further period of 5 hrs. The base was extracted with three portions of ether, washing each ether layer once with water. The ether was dried and evaporated to leave a clear, pale yellow gum (0.223 g.). A portion, dissolved in aqueous acetone, was readily oxidised by dilute aqueous permanganate.

The rest of the gum was distilled at 160° (bath) 3×10^{-5} m.m. and the distillate dissolved in ether, to ensure a thorough mixing of the two components. After evaporating the ether, the residue was freed from traces of solvent by heating at 100°/10^{-4} m.m. for 1 hr. Two samples were micro-hydrogenated.

1. Wt. = 60.2 mg. Catalyst, 30 mg. PtO_2. T = 11°, p = 781 m.m. Uptake of hydrogen = 1.73 c.c. Theoretical uptake for two double bonds at above p/T = 5.23 c.c.
   ∴ Amount of Hofmann product = 33.1%.
2. Wt. = 36.3 mg. Catalyst, 25 mg. PtO_2. T = 12°, p = 776 m.m. Uptake of hydrogen = 1.03 c.c. Theoretical uptake for two double bonds at above p/T = 3.18 c.c.
   ∴ Amount of Hofmann product = 32.4%.

The solvent in each case was absolute ethanol, previously distilled from Raney nickel.

The two solutions were combined, filtered free from catalyst ("Filtercel"), and evaporated to dryness. On

/dissolving the

dissolving the residue in dilute hydrochloric acid and adding excess of 20% perchloric acid, the amorphous perchlorate of the hydrogenated product was precipitated. This was worked up carefully in various solvents, but crystallisation could not be induced even by seeding with the perchlorate of N-methylemetinetetrahydromethine (XXV).

Isolation of N-methylemetinetetrahydromethine-N(a)-methiodide (XXX).

The tetrahydromethine base (XXV, 4.837 g.) was dissolved in anhydrous, alkali-free ether (150 c.c.) and methyl iodide (1.4 c.c.; approx. 2.5 mols) was added. After 40 hours at room temperature, the solid precipitate (1.55 g.) was collected and washed with ether. Treatment of the filtrate with further portions (1.5, 2.5 and 2.5 c.c.) of methyl iodide, and collection of the product before each fresh addition, at intervals of 2, 3 and 2 days, gave three further crops (1.54, 2.41 and 0.93 g. respectively). The first two crops were combined (3.09 g.) and crystallised from ethylene dichloride (25 c.c.) to yield the solvated dimethiodide (XXIX, 0.598 g.), m.p. 131-132° (sintered at 129°). The mother liquor was evaporated to dryness under reduced pressure and the residual gum was crystallised from acetone to which a crop of concentrated hydriodic acid was added. The crystals (0.643 g.) were washed with acetone and dried in a vacuum; m.p. 143-144° (cloudy melt). Most of this material

/subsequently

subsequently decomposed in attempted purification, since its nature was not understood at this time. The third and fourth crops of crude methiodide gave, on treatment with ethylene dichloride, solvated dimethiodide (2.083 g.), m.p. 128-129° (with decomposition and previous sintering). The mother liquors, treated as before, gave a crystalline solid (0.305 g.), m.p. 154-156° (cloudy melt). This material, together with a little of the earlier crop (0.34 g.) was suspended in water and made alkaline to phenolphthalein with caustic soda, when a clear solution was obtained. Extraction four times with ether removed only a trace (2 mg.) of non-quaternary material. After aspiration with air to remove ether and a trace of trimethylamine, the solution was extracted four times with chloroform. The extract was washed once with water, dried and evaporated in a vacuum below room temperature. The residual yellow gum (0.336 g.) was dissolved in alcohol (5 c.c.), and, on adding two drops of concentrated hydriodic acid, crystallisation occurred. After collecting, washing with alcohol, and drying at room temperature, the product (0.262 g.) had m.p. 159-160° (cloudy melt), with previous sintering. A second crop (13 mg.; m.p. 160-162° with previous sintering) was obtained by concentrating the mother liquor in a vacuum desiccator. The first crop was recrystallised by dissolving as rapidly as possible in warm alcohol, cooling immediately to

/room temperature

room temperature and finally to 0°. The crystals (200 mg.) had m.p. 163-165° (cloudy melt). Half of this crop was dissolved in cold alcohol, shaken with charcoal and filtered ("Filtercel"), and the filtrate was concentrated in a desiccator. The hydriodide of (XXX, 63 mg.) formed short, blunt-ended, colourless prisms, m.p. 162-164° (cloudy melt). For analysis, the substance was crystallised again in a similar fashion, and dried for 2 hours over phosphorus pentoxide in a vacuum at room temperature (23 mg., m.p. 163-164°), cloudy melt).

Found: C, 49.8; H, 6.9; N, 3.2; I, 31.3.

$C_{33}H_{53}O_4N_2I.HI$ requires C, 49.7; H, 6.8; N, 3.5; I, 31.8.

In a further experiment, the tetrahydromethine (36.85 g.) was treated with methyl iodide, in the manner described above, to give a mixture of amorphous methiodides (51.72 g.). Crystallisation was carried out in four portions (15.22, 17.73, 13.88 and 4.90 g.) from ethylene dichloride (135, 130, 100 and 60 c.c. respectively) to yield the solvated dimethiodide (30.97 g. in all), m.p. 128-130° dec. The mother liquors were evaporated to dryness under reduced pressure at room temperature, the gummy residue dissolved in acetone (100 c.c.), and concentrated hydriodic acid added until acid to litmus. Crystallisation occurred rapidly, and after being washed with acetone and dried, the hydriodide of (XXX, 14.45 g.) had m.p. 159-161° (cloudy melt).

/The mother

The mother liquor from the methiodide hydriodide was evaporated almost to dryness under reduced pressure, and the residue dissolved in chloroform. By shaking first with 2N sodium carbonate, then with aqueous sodium thiosulphate, and finally with water, the hydriodic acid and traces of iodine were removed. The dried chloroform solution was evaporated to dryness under reduced pressure, and the residue, a yellow resin was decomposed by being heated under reflux for 5 hrs. in methyl propyl ketone (100 c.c.). Evaporation of the ketone left a gum, which was dissolved in the minimum quantity of ethanol, and poured into excess of 0.5N sodium hydroxide. The precipitated base was extracted with ether (1x200 c.c., 3x100 c.c.), washing each ether layer once with water. After being dried, the ether solution was evaporated, and the gummy base (5.60 g.) converted to the perchlorate by being dissolved in very dilute hydrochloric acid followed by addition of excess of 20% aqueous perchloric acid. This salt was crystallised from aqueous acetone to yield the perchlorate of des-N(a)-emetinetetrahydromethine (XXXI, 5.96 g.), m.p. 131-133°.

The aqueous alkaline solution from the extraction of the bases by ether, was shaken with four portions of chloroform, to isolate the quaternary products. After washing the chloroform solution once with water, it was dried and evaporated under reduced pressure, to leave a yellow resin (2.5 g.). By crystallisation from aqueous acetone, the

/monomethiodide

monomethiodide (XXVIII, $X^- = I^-$) was obtained (0.99 g.), m.p. 229-231°.

The amounts of the dimethiodide (XXIX), the hydriodide of the monomethiodide (XXX), the base (XXXI), and the

monomethiodide (XXVIII, X^- = I^-), isolated in the pure state above, are equivalent to 92% of the crude mixture of methiodides from the tetrahydromethine.

Decomposition of N-methylemetinetetrahydromethine-N(a)-methiodide (XXX).

A solution of the salt as the hydriodide (90 mg.) in diethyl ketone (4 c.c.) was heated in a bath at 100-110° for 3 hours, a slow stream of nitrogen being passed through the solution and then through a trap containing dilute hydrochloric acid. The contents of the trap were evaporated to dryness, and the small crystalline residue was identified as trimethylamine hydrochloride by conversion to the picrate in the usual manner (9 mg., m.p. and mixed m.p. 216-218°). The diethyl ketone solution was evaporated under reduced pressure, and the residue was dissolved in acetone (4 c.c.) and water (2 c.c.). By evaporation under reduced pressure the acetone was removed, leaving the product as a gum from which the water was decanted. The gum was dissolved in a little alcohol and the solution poured into aqueous sodium hydroxide. The liberated base was isolated by thorough extraction with ether; on evaporation, the base (54 mg.; 100%) remained as a clear yellow gum, which was characterised by conversion to the perchlorate of the base (XXXI), by the procedure used in previous cases (54 mg.), m.p. and mixed m.p. 128-130°. The base was recovered from a portion of the

/perchlorate by

perchlorate by suspending it in warm aqueous sodium hydroxide, and extracting four times with ether. After drying and evaporating the ether, the recovered base was heated under reflux for 4 hrs. with methyl iodide (0.5 c.c.) and 5% aqueous sodium carbonate (2 c.c.). The excess of methyl iodide was then evaporated, and the aqueous layer decanted from the gummy product. This gum was dissolved in the minimum volume of hot ethanol, the solution poured into the aqueous layer decanted above, and basic substances were removed by shaking twice with ether. Three extractions of the aqueous solution with chloroform removed the quaternary substances, which were recovered by evaporation of the chloroform under reduced pressure. Two crystallisations of the product from acetone yielded the pure methiodide (XXVIII, $X^- = I^-$) m.p. 230-231°, alone and in admixture with an authentic specimen.

In an experiment carried out on a larger scale, the methiodide (XXX), as the hydriodide (14.45 g.), was heated as above in methyl propyl ketone (300 c.c.). The product was worked up by essentially the same procedure as that used on the small scale, to yield a yellow basic gum (8.53 g.), which was converted to the perchlorate. Crystallisation from aqueous acetone afforded the perchlorate of the base (XXXI), (9.63 g.), m.p. 131-133°, together with a second crop (0.20 g.), m.p. 129-130°. Total yield was 9.83 g. = 90%.

/Specific

Specific rotation of des-N(a)-emetinetetrahydromethine perchlorate (Perchlorate of XXXI).

The perchlorate, of m.p. 131-133°, was dried in vacuo over phosphoric oxide at 78° for 3 hrs.; previous analyses (40) had shown that this treatment produces the monohydrate.

l = 4 dm. c = 3.492. α_D = +2.61°. Solvent = Acetone.

$$[\alpha]_D^{19} = +18.7° \pm 0.2°.$$

Preparation of des-N(a)-emetinehexahydromethine (XLI).

Des-N(a)-emetinetetrahydromethine (XXXI; 4.37 g.), recovered as above from the perchlorate, was dissolved in glacial acetic acid (30 c.c.), which had been distilled from a chromic acid. This solution was shaken in the presence of platinic oxide (100 mg.) with hydrogen at 17°/746 m.m. Reduction ceased after 20 mins., when 1.04 mol. of hydrogen had been absorbed. After filtering off the catalyst ("Filtercel") and washing it with acetic acid, the solution was evaporated to dryness under reduced pressure. The residue was dissolved in water, aqueous sodium hydroxide was added until the solution was alkaline to phenol phthalein, and the liberated base was extracted with four portions of ether. Evaporation of the dried ether solution left a clear gum (XLI; 4.38 g.), which crystallised from 40-60° petrol as rosettes of colourless needles (3.96 g.) m.p. 78-79.5°. A sample was distilled at 140° (bath)/2×10^{-5} m.m. and the

/distillate

distillate was crystallised from 40-60° petrol. After drying at 56° for 1 hr. over phosphoric oxide in a vacuum, the product, m.p. 79-80.5°, was analysed.

Found C, 74.45; H, 9.5; N, 3.05, 2.95.

$C_{30}H_{45}O_4N$ requires C, 74.47; H, 9.40; N, 2.9.

Preparation of des-N(a)-emetinehexahydromethine methiodide (XLII).

(a) From des-N(a)-emetinetetrahydromethine methochloride (XXVIII, X^- = Cl^-).

The corresponding methiodide (XXVIII, X^- = I^-; 4.79 g.) was stirred in warm 50% aqueous ethanol (300 c.c.) with freshly precipitated silver chloride (from 4.5 g. of silver nitrate) for 1¼ hours. After filtering ("Filtercel"), the solution was concentrated under reduced pressure until free from alcohol, and platinic oxide (0.1 g.) was added. The suspension was shaken with hydrogen at 18°/754 m.m., and absorption of hydrogen (1.00 mol.) was complete in 80 mins. Since the catalyst had become partially colloidal, the solution was acidified to bring about coagulation, and the platinum was then filtered off ("Filtercel"). The filtrate was concentrated to 100 c.c. under reduced pressure, and the methiodide (XLII) was precipitated by the addition of potassium iodide (4 g.) in a little water. It crystallised from aqueous ethanol as pale yellow short prisms, which were washed with the solvent mixture and dried (4.43 g.) m.p. 126-129°. A portion of the product was dried at 110° in a vacuum over

/phosphoric

phosphoric oxide for 3 hrs., and then recrystallised from dry acetone, to yield colourless short prisms m.p. 169-170°. A sample of this methiodide was redried at 110° to give the monohydrate†.

Found:* C, 58.0; H, 7.7; Loss 118°, 2.6.

$C_{31}H_{48}O_4NI.H_2O$ requires C, 57.8; H, 7.8; H_2O, 2.8.

Found in anhydrous substance* C, 59.1; H, 7.6; N, 2.1

$C_{31}H_{48}O_4NI$ requires C, 59.4; H, 7.7; N, 2.2

(b) From des-N(a)-emetinehexahydromethine (XLI)

This base (106 mg.) was dissolved in methyl alcohol (1 c.c.), and methyl iodide (2 c.c.), and was heated under reflux for 12 hours. The methyl alcohol and excess of methyl iodide were then evaporated, and the residue dissolved in the minimum quantity of hot ethanol. By pouring this solution into aqueous sodium hydroxide and extracting thrice with ether, a trace of basic material was removed. The aqueous solution was then extracted thrice with chloroform, the three portions were combined, and were washed once with water. After being dried, the chloroform was evaporated under reduced pressure, to leave a colourless resin (137 mg.). It was crystallised from aqueous ethanol, washed with this solvent mixture, and dried (132 mg.) m.p. 123-125°. This

/product

† This sample was prepared by Dr. H.T. Openshaw.

product was dried at 100° over phosphoric oxide in a vacuum for 2 hrs., and then at 110° under these conditions for 3 hours. Recrystallisation of the dried sample from dry acetone afforded the monohydrate of (XLII) m.p. 169-170°, alone and in admixture with the product from (a) above.

Hofmann degradation of des-N(a)-emetinehexahydromethine methiodide (XLII).

This salt (4.05 g.) was stirred in warm 50% aqueous ethanol (100 c.c.) with freshly precipitated silver oxide (from 2 g. of silver nitrate) for 45 mins. The solids were removed by filtration ("Filtercel"), and the clear solution, shown to be free from iodide ion, was evaporated to dryness under reduced pressure. The residue was heated at 100° for 1½ hrs. under 10 m.m. pressure, and the gum so obtained, partitioned between water and ether; it was not completely soluble in either solvent alone. After extracting the aqueous layer once with ether, it was evaporated to dryness, and the residue was heated as above. The product was again partitioned between water and ether, and in this case the aqueous layer was extracted thrice with ether. All the ether solutions were combined, dried, and evaporated to afford a clear, yellow gum (3.43 g.).

This gum was treated with N hydrochloric acid (7.5 c.c.) and sufficient water was added to dissolve the salt.

/Extraction

Extraction twice with ether removed a crude brown neutral gum (97 mg.), which was not further examined. The aqueous solution was made alkaline to phenol phthalein with sodium hydroxide, and the liberated base taken up by extraction with four portions of ether, washing each ethereal layer once with water. Evaporation of the combined dried ether solutions, left a yellow gum (2.75 g.; "basic fraction"). The aqueous solution, after ether extraction, was shaken with four portions of chloroform, the combined organic layers being washed once with water, and then dried. Removal of the chloroform under reduced pressure left a crude brown gum (0.322 g.; "chloroform extract").

The basic fraction was distilled at 155-160° (bath)/ 5×10^{-4} m.m. to give a clear, pale yellow, viscous gum, which was dissolved in ethanol and picric acid (1.27 g.; 1 equiv.) was added. The precipitated solid was redissolved by heating and adding more ethanol; on cooling the picrate of des-N(a)-emetinehexahydrobismethine (XLIV) separated as rosettes of golden yellow needles (3.45 g.; 74%) m.p. 158-159°, after slight sintering. Repeated recrystallisation from ethanol raised the m.p. to 159-160°, and the sample for analysis was dried at 100° over phosphoric oxide for 2 hrs. in a vacuum.

/Found:

Found: C, 60.9; H, 6.9; N, 7.6.

$C_{31}H_{47}O_4N.C_6H_3O_7N_3$ requires C, 61.14; H, 6.94; N, 7.71.

The base (XLIV) was recovered by suspending the picrate (1.223 g.) in aqueous sodium hydroxide, and extracting with four portions of ether (200 c.c. each); this treatment extracted some picric acid from the aqueous solution. After concentrating the ether to 200 c.c., it was shaken four times with 20% aqueous sodium hydroxide (10 c.c. portions) to remove picric acid, washed once with water, and then dried. Evaporation of the ether yielded the base (XLIV) as a clear gum (0.84 g.; 100%). A portion was distilled at 150° (bath)/ 10^{-5} m.m. for absorption spectrum measurements (p. 90) and for analysis.

Found: C, 74.6, 74.9; H, 9.4, 9.1; N, 3.0.

$C_{31}H_{47}O_4N$ requires C, 74.76; H, 9.53; N, 2.82.

The chloroform extract above was partitioned between water and ether, and the ether solution, after being dried and evaporated, left a brown gum (0.244 g.). Distillation at 140-150° (bath)/5×10^{-4} m.m. afforded a clear, yellow gum (0.221 g.), which was dissolved in ethanol, and picric acid (0.102 g.; 1 equiv.) was added to it. Only a little (26 mg.) of the picrate of (XLIV) separated, this being washed with ethanol and dried, m.p. 154-156°, after previous sintering. The mother liquor was concentrated and poured into dilute hydrochloric acid; three extractions of this solution with

/ether

ether removed the neutral matter and most of the picric acid. After making the aqueous solution alkaline to phenol phthalein with sodium hydroxide, the bases (10 mg.) were extracted by four portions of ether followed by four portions of chloroform. The ether solution containing the neutral matter was freed from picric acid by being shaken with four portions (15 c.c. each) of 30% aqueous sodium hydroxide, and then once with water. This treatment gave a colourless solution which was dried, and the ether distilled to leave a pale yellow, neutral gum (0.198 g.); aqueous potassium permanganate rapidly oxidised this product in stabilised acetone. The gum was heated at 80-100° (bath)/4×10^{-5} m.m. in a short-path distillation apparatus to remove any moderately volatile products; only a very small quantity distilled, and this was rejected. Distillation was continued at 150-160° (bath)/4×10^{-5} m.m. to yield a pale yellow gum, which was redistilled at 150° (bath)/3×10^{-5} m.m. for absorption spectrum measurements (p. 90) and analysis.

Found: C, 76.9; H, 9.0; N, None.

$C_{29}H_{40}O_4$, (XLV) requires C, 76.93; H, 8.93; N, None.

Two micro-hydrogenations of this neutral matter were carried out at room temperature and pressure, in pure ethanol using platinic oxide catalyst. The first sample absorbed 0.83 mol. of hydrogen, and the second sample, 1.38 mol.; it

/seems probable

seems probable that the neutral substance is not homogeneous.

The mother liquors from the preparation of the picrate of the hexahydrobismethine (XLIV) were concentrated, poured into aqueous sodium hydroxide, and the suspension was shaken with four portions (100 c.c. each) of ether. Picric acid was removed from the combined ether solution by being shaken with four lots (15 c.c. each) of 20% aqueous sodium hydroxide, and once with water. The ether solution was shaken with N hydrochloric acid (1x20 c.c., 3x10 c.c.), and after shaking the combined acid solutions once with ether, the ether solutions were combined, washed once with water, and dried. On evaporation, a yellow-brown, neutral gum remained (101 mg.). The acid solution was made alkaline to phenol phthalein with sodium hydroxide, and the basic matter, a clear, yellow gum (250 mg.), was extracted with four portions of ether in the usual fashion. A portion (31 mg.) was converted to the picrate, by being treated with picric acid (15 mg. 1 equiv.) in ethanol, but crystallisation could not be induced, even on seeding with the picrate of (XLIV). The rest of the basic matter gradually crystallised, and the solid was found to be very soluble in acetone, ether, and ethyl acetate. It was possible to recrystallise it from 40-60° petrol (charcoal) to yield feathery needles, which were washed with petrol and dried (110 mg.), m.p. 75-76°. A portion was distilled at 120° (bath)/10^{-4} m.m. and the distillate was crystallised from

/40-60° petrol,

40-60° petrol, washed with this solvent, and dried, m.p. 78-79.5°; in admixture with des-N(a)-emetinehexahydromethine (XLI) m.p. 79-80.5° prepared above, the m.p. was 79-80°.

Experiments with des-N(a)-emetinehexahydrobismethine (XLIV)

The pure base was recovered from the picrate as described above, and the gum so obtained, was distilled at 150° (bath)/2×10^{-5} m.m.; the following investigations were carried out upon the distillate.

a) Micro-hydrogenations.

Wt.-20.2 mg. Solvent=5 c.c. glacial acetic acid. Catalyst=20 mg. PtO_2.

Uptake of hydrogen = 1.02 c.c. at 15° and 754 m.m.(1.04 mol.) This uptake was complete in 20 mins. and then very slow steady absorption of hydrogen occurred, due to attack at the benzene nuclei. It was known that benzene nuclei are reduced by this sample of catalyst, from the result of a reduction of cinnamic acid (29.0 mg.) in ethanol (5 c.c.) carried out previously. The uptake of hydrogen was complete in 7 hrs. (18.99 c.c.; 4.02 mol.), the first molecular proportion being absorbed in 15 mins. The solution of the reduction product was filtered, evaporated to dryness, and the residue distilled at 100° (bath) /0.9 m.m. to yield an oil $n_D^{20} = 1.4642$; Zelinsky (43) gives $n_D^{20} = 1.4634$ for 2-cyclohexylpropionic acid.

b) Specific rotation.

l = 2 dm. C = 3.194. $\alpha_D = +0.33°$. Solvent = Ethanol.

$$[\alpha]_D^{20} = +5.2° \pm 0.3°.$$

/c) Stability

c) Stability of the methiodide.

The base (123 mg.) was dissolved in alkali-free ether (5 c.c.), and excess of methyl iodide (0.5 c.c.) was added. After 94 hrs. at room temperature, the amorphous methiodide was collected and washed well with ether (154 mg.; 98%). Attempts to crystallise this salt from alcohol, acetone, and ethylene dichloride were abortive. A portion of the methiodide (85 mg.) was heated under reflux with water (10 c.c.) for 3 hrs., whilst nitrogen was passed through the solution and into a trap containing dilute hydrochloric acid (10 c.c.). The methiodide, which had dissolved in the hot water, separated on cooling, and the suspension was extracted thrice with ether. After washing the ether solution once with water, it was dried and evaporated to leave only a trace of red-brown gum (2 mg.). The acid from the trap was evaporated to dryness, and the residue tested for trimethylamine hydrochloride in the manner already described; it was found to be absent.

Preparation of O-methyleugenol (cf. 29).

The purity of the eugenol employed was shown to be high, by its refractive index, n_D^{13}, being 1.5432 (44 gives $n_D^{14.5}$ = 1.5439), and by the m.p. of its benzoyl derivative being 67-68°, unchanged by one recrystallisation from aqueous ethanol (45 gives 69.5°).

Eugenol (82 g.) was weighed into a flask fitted with

/stirrer,

stirrer, two dropping funnels, and a reflux condenser, and heated on the steam bath to ca. 80°. With vigorous stirring, a solution of potassium hydroxide (42 g., 1.5 moles) in 75 c.c. of water was run in gradually, so that the whole addition took 20 mins. About 20 secs. after the addition of potassium hydroxide had been started, dimethyl sulphate (60 c.c. = 79 g., 1.25 moles) was gradually added, at such a rate that it was nearly finished when all the alkali had been added. Before use, the dimethyl sulphate had been shaken with ice-water (60 c.c.), and then with cold saturated sodium bicarbonate solution (20 c.c.). After the reactants had been added, the heating and stirring were continued for a further 15 mins., when the reaction mixture was cooled. The aqueous layer was made strongly alkaline to litmus by adding dilute sodium hydroxide, and the two layers were shaken together. After diluting the organic layer with a little ether, it was separated and shaken twice with dilute sodium hydroxide solution to remove phenols. The aqueous solution was extracted thrice with ether, shaking the combined organic solutions with dilute sodium hydroxide; the ether solution was then dried and evaporated. Distillation of the residue under reduced pressure through a short column, yielded pure O-methyleugenol (83.5 g., 94%) b.p. 131.5-132° at 14 m.m. $n_D^{15.5} = 1.535$. (47 gives $n_D^{17} = 1.5383$, $n_D^{20} = 1.532$).

/Oxidation

Oxidation of O-methyleugenol (cf. 30).

O-methyleugenol (11.46 g.) was stirred vigorously with water (100 c.c.) below 5°, until a coarse emulsion formed. Aqueous potassium permanganate (6.8 g. in 700 c.c., equiv. to one atom of oxygen) cooled to below 10°, was then added dropwise over 2½ hrs., and at the end of this period the reaction mixture was heated to coagulate the manganese dioxide. The solution was filtered ("Filtercel"), washing the cake twice with hot water, to give a filtrate containing a little suspended oil. Finally the manganese dioxide was washed with 4 x 50 c.c. portions of boiling ethanol, the washings being evaporated to low bulk before they were added to the main solution; this was then concentrated under reduced pressure to remove the alcohol. After acidifying the solution to Congo Red with dilute hydrochloric acid, it was evaporated to dryness under reduced pressure; the distillate contained suspended oil and was therefore reserved.

The dry residue was extracted with ether ethanol, and finally with ethanol alone, concentrating the extracts to near dryness before diluting with ether. Acidic material was then extracted by shaking twice with dilute sodium carbonate, this aqueous alkaline layer being extracted four times with ethyl acetate. After drying the combined ethyl acetate and ether solutions above, the solvents were evaporated under

/reduced pressure.

reduced pressure. The viscous residue (5.86 g.), on distillation, afforded mainly the fraction 176-182° at 0.35 m.m. (4.9 g.), which was crystallised from anhydrous ether and washed with this solvent. The colourless prisms of the glycol (L), (4.69 g., 55%) melted at 69-70°. The glycol was readily soluble in cold ethyl acetate, ethanol, acetone, and water, sparingly soluble in cold ether, but readily so in the hot.

The aqueous distillate above, containing the suspended oil afforded unchanged O-methyleugenol (3.70 g.) b.p. 132-134°, 14 m.m. by ether extraction and distillation. The percentage yields of the products are based upon the weight of unrecovered O-methyleugenol.

When the aqueous sodium carbonate extract above was acidified to Congo Red and extracted thrice with ether, a crystalline acid was obtained (1.114 g.). This was recrystallised from aqueous ethanol (charcoal), to afford slightly off-white crystals (0.991 g.) m.p. 76-78°; the acid was dried at 56° over phosphoric oxide for 3 hrs. in vacuo, when the m.p. rose to 92-93°, and by one recrystallisation from ether, the anhydrous acid (XLIX) was obtained m.p. 96-97.5° (48 gives 98°).

Oxidation of des-N(a)-emetinetetrahydromethine (XXXI).

The base (0.89 g.), regenerated from the pure perchlorate, was dissolved in acetone (30 c.c.), and water (30 c.c.) was added. The mixture was cooled at 0° and stirred

/whilst aqueous

whilst aqueous barium permanganate (122.5 c.c. containing 4 atomic proportions of oxygen) was gradually added, the rate of addition being controlled so that no appreciable concentration of unreacted permanganate was present at any time. After the addition of the first quarter of the solution (15 minutes) a further quantity of acetone (20 c.c.) was added to maintain homogeneity. The total time of addition was 7 hours. After stirring for a further hour, when there remained no unchanged permanganate, the mixture was rendered alkaline to phenolphthalein by the addition of barium hydroxide. The manganese dioxide was coagulated by heating and removed by filtration ("Filtercel"). The filter-cake was thoroughly extracted with boiling water (total, 350 c.c.) and boiling alcohol (400 c.c.). The alcoholic extract on evaporation left only a small residue, which was added to the combined aqueous solutions. After concentrating to 150 c.c., a small quantity of insoluble material was removed by extracting five times with ether (total, 500 c.c.); evaporation of the dried ether solution left a brown gum (0.247 g.; "neutral and basic fraction").

The aqueous solution was rendered acid to Congo red with hydrochloric acid and extracted six times with ether. Evaporation of the extract, finally under reduced pressure, left a residue which largely crystallised on cooling. On

/recrystallisation from

recrystallisation from hot water colourless needles (124 mg.) were obtained, m.p. 142° after slight previous sintering. Small additional amounts were obtained from the mother liquors by evaporation and sublimation of the residue in a vacuum, and from the "neutral and basic fraction" where the acid was probably formed by atmospheric oxidation of the related aldehyde. The total yield was 172 mg. (44%). After further purification by sublimation at 0.05 mm. from a bath at 80-90°, the m.p. was 140.5-141.5°, undepressed in admixture with synthetic 6-ethylveratric acid (LIII) of the same m.p. Before analysis, the acid was again crystallised from water and resublimed.

Found: C, 63.1; H, 6.65.

$C_{11}H_{14}O_4$ requires C, 62.8; H, 6.7.

The neutral and basic fraction was dissolved in ether and shaken with three portions of 0.5N hydrochloric acid (20 c.c. each) to remove the basic substances. These were recovered from the acid solution, after it had been extracted thrice with ether, by making it alkaline to phenol phthalein with sodium hydroxide and extracting four times with ether. The dried ether solution, on evaporation, left a brown gum (20 mg.). The combined ether solutions from the acid solution above were washed once with water and then shaken twice with 2N sodium carbonate (total, 40 c.c.). After drying the ether solution, it was evaporated to yield a brown

/gum

gum (120 mg.; "neutral fraction").

The acids were recovered from the aqueous alkaline extract as a brown semi-crystalline mass (72 mg.), by rendering it acid to Congo red with hydrochloric acid and thoroughly extracting with ether. This product was heated in a sublimation apparatus at 70-80°/0.05 m.m. for 15 hrs., when a white crystalline sublimate was obtained (37 mg.) m.p. 139-140°, alone and in admixture with synthetic 6-ethylveratric acid.

A Lassaigne test was carried out on a portion of the neutral fraction and nitrogen was found to be present. The remaining material (100 mg.) was distilled in a molecular still, three fractions (12 mg., 4 mg., 7 mg.) being collected after 2½, 6 and 13 hrs. respectively, at 70-75° (bath)/0.1 m.m., and one fraction (32 mg.) after 6½ hrs. at 110-115° (bath)/0.05 m.m. The residue did not distil. These fractions were worked up in various solvents, but no pure substances could be isolated.

Considerable difficulty was experienced when attempts were made to isolate the amino acid from the reaction mixture. A second oxidation was therefore carried out upon the base (XXXI, 1.5 g.), repeating the process described above as far as the isolation of the neutral and basic fraction. It was then modified by adding sulphuric acid to the aqueous solution from this fraction until it was acid to Congo red. The precipitated barium sulphate was digested at 100° for ½ hr.,

/and removed

and removed by filtration ("Filtercel"), washing the pad thoroughly with boiling water (400 c.c. in all). After concentrating the clear filtrate to 200 c.c. under reduced pressure, it was extracted five times with ether (total, 600 c.c.), each extract being washed once with water. The combined extracts were dried and evaporated to yield a brown crystalline solid (0.362 g.), which was examined for 6-ethylveratric acid in the manner described above.

The acid solution from the last ether extraction was titrated with dilute barium hydroxide until a sample showed that a slight excess of Ba^{++} was present. This solution was then freed from barium sulphate as described previously, and the filtrate evaporated to dryness under reduced pressure, to yield a yellow resin containing a little crystalline material. Esterification of the crude acid was carried out by dissolving it in absolute methanol (30 c.c.), adding concentrated sulphuric acid (1 c.c.), and heating under reflux for 2 hrs. The solution was then poured into dry chloroform (150 c.c.) and shaken with dry, finely powdered barium hydroxide (5 g.) for 10 mins.; the barium hydroxide had been dried at 150° in vacuo over phosphoric oxide for 6 hrs. After filtering off the solids, and washing the pad thoroughly with boiling chloroform (total, 200 c.c.), the filtrate was evaporated to dryness under reduced pressure to yield a yellow, basic-smelling gum (0.671 g.). This was treated with ether,

/filtering to

filtering to remove a little insoluble matter, and the solution evaporated to dryness in a short-path distillation apparatus. By distillation at 100-110° (bath)/2×10^{-5} m.m., a clear, pale yellow gum (577 mg.) was obtained.

A portion of this product was shown to resist hydrolysis by being heated with excess water under reflux for 16 hours. All the ester was therefore combined and heated under reflux for 5 hrs. with 0.1N aqueous barium hydroxide (20 c.c.). The exact equivalent of 0.05N sulphuric acid was then added, and the precipitated barium sulphate digested at 100° for 1 hour. It was removed by filtration ("Filtercel") and the pad washed thoroughly with boiling water (total, 200 c.c.). Ether extraction of the clear filtrate removed only a trace of gum (2 mg.). The aqueous solution was concentrated under reduced pressure to yield the amino acid (LIV) as colourless, glistening prisms (427 mg., 40%) m.p. 218-221°, with darkening.

Before analysis, the acid was recrystallised twice from water without change in m.p.; it was dried at 110° for 2 hrs. over phosphoric oxide in a vacuum.

Found: C, 62.1; H, 8.15; N, 3.47.

$C_{19}H_{29}O_4N.2H_2O$ requires C, 61.5; H, 9.0; N, 3.78.

In order to avoid difficulties in analysis due to partial hydration, the ethyl ester was prepared by dissolving the pure acid (74 mg.) in absolute ethanol (5 c.c.), adding

/concentrated

concentrated sulphuric acid (0.2 c.c.) and heating under reflux for 3 hours. The ester was isolated by the procedure described above for the methyl ester, and then distilled at 120° (bath)/4×10^{-3} m.m. Before analysis it was redistilled to afford a clear, colourless gum.

Found: C, 69.2; H, 8.95; N, 4.2.

$C_{21}H_{33}O_4N$ requires C, 69.36; H, 9.16; N, 3.85.

Synthesis of 6-ethylveratric acid (LIII).

(This preparation was carried out by Miss M.L. Donaldson.) 4-Ethylveratrole (LI, 5 g.) and pure, anhydrous benzene (20 c.c.) were stirred at room temperature with powdered aluminium chloride (3.5 g.), and a solution of acetyl chloride (3 g.) in benzene (5 c.c.) was added during the course of an hour. After being heated under reflux for a further hour, the aluminium chloride complex was decomposed in the usual manner. The benzene solution of the product was extracted twice with dilute sodium hydroxide solution, and the phenolic material thus removed was remethylated by shaking the alkaline extract with dimethyl sulphate (2 portions of 2 c.c.), and extracting the oil thus produced with benzene. The combined benzene extracts were dried and distilled, giving 4-ethyl-5-acetoveratrone (LII, 4.88 g.; 78%), b.p. 133-138°/1 mm., as a colourless oil which rapidly solidified. A sample, recrystallised from aqueous alcohol, formed rosettes of colourless needles, m.p. 62-63° (Shinoda and Sato (31), give m.p. 63°).

/The alkaline

The alkaline sodium hypochlorite solution obtained from aqueous sodium hydroxide (4.4. g. in 30 c.c.) and chlorine (3.2 g.) was heated to 55° and stirred, and the ketone (2.08 g.) was added. After reaction started, the temperature was held at 60-70° by occasional warming for 30 minutes, and the mixture was stirred for a further 30 minutes without the application of heat. Excess of hypochlorite was destroyed by adding sufficient sodium bisulphite, and the cooled solution was acidified with concentrated hydrochloric acid. The precipitated 6-ethylveratric acid (LIII, 1.9 g.; 90%), m.p. 141-141.5° after slight previous sintering, was collected. After sublimation under reduced pressure it had m.p. 141.5° (Shinoda and Sato give m.p. 142°.)

Oxidation of des-N(a)-emetinehexahydrobismethine (XLIV).

The base (0.942 g.) was dissolved in stabilised acetone (50 c.c.), to which water (30 c.c.) was added, and the solution was cooled to 0°. With stirring, barium permanganate (103.7 c.c. of M/50; equiv. to 3.2 atomic proportions of oxygen) was run in gradually over 8½ hrs., acetone (10 c.c., 20 c.c.) being added after 6½ and 7½ hrs. respectively, to preserve homogeneity. The oxidation products were examined by the improved procedure which was used above, in the oxidative experiments upon des-N(a)-emetinetetrahydromethine. The neutral and basic fraction (0.757 g.) was a brown gum, whilst the acidic matter, extractable by ether from the acidified

/solution, was

solution, was a brown crystalline solid (121 mg.). This acidic material was heated with water, a brown tar which failed to dissolve was removed, and the solution was filtered (charcoal). The silky needles (61 mg.) which separated on cooling, were collected, washed with water, and dried m.p. 140.5-141.5°, after sintering at 138°. After sublimation at 100-110° (bath)/0.1 m.m., a colourless product was obtained m.p. 140.5-141.5°, alone and in admixture with synthetic 6-ethylveratric acid. A further quantity of this acid (10 mg.) was isolated from the "neutral and basic fraction" by dissolving this mixture in ether and shaking with two portions of 2N sodium carbonate. The alkaline solution was shaken twice with ether, then combined with the alkaline extract from the mild oxidation of the neutral matter (see below), acidified to Congo red with hydrochloric acid, and extracted with ether (4x100 c.c. portions). On evaporation, the dried ether solution, containing the acidic matter, left a gummy residue (44 mg.), which was heated in a sublimation apparatus at 100-110° (bath)/0.05 m.m. for 9 hours. A pasty substance (32 mg.) was obtained which was crystallised from water (charcoal), to afford the 6-ethylveratric acid (10 mg.) mentioned above, m.p. 137-139°, mixed m.p. with synthetic 6-ethylveratric acid, 139-141°.

The ether solution of the "neutral and basic fraction", now freed from acidic substances, was shaken with 0.25N

/hydrochloric acid

hydrochloric acid (4x10 c.c. portions), shaking the combined aqueous layer twice with ether. After washing the combined ether solutions once with water and drying, the solvent was removed to leave the brown gummy neutral matter (0.271 g.). The basic matter (0.432 g.), as a brown gum, was recovered from the aqueous acid solution in the usual way. The neutral matter was dissolved in acetone (30 c.c.), and treated with 40 vol. hydrogen peroxide (30 c.c.) and sufficient 2N sodium carbonate to render the solution strongly alkaline to litmus. After 48 hrs. at room temperature, the solution was heated on the water bath until free from hydrogen peroxide and acetone; it was then extracted thrice with ether, washing each ether layer once with water. The aqueous alkaline solution was combined with one of a similar nature as noted above, whilst the dried ether solution was evaporated to leave a yellow-brown, neutral gum (0.20 g.); this was found to contain 0.94% of nitrogen.

The basic matter was heated in a short-path distillation apparatus, collecting two fractions (130 mg., 27 mg.; yellow oil), after 3 and 9 hrs. respectively, at 100° (bath)/ 8×10^{-5} m.m., a third fraction (97 mg.; yellow gum), after 8 hrs. at 120° (bath)/8×10^{-5} m.m., and a fourth (157 mg.; yellow glass), after 5 hrs. at 150° (bath)/8×10^{-5} m.m. A red-brown resin did not distil. None of the fractions gave any precipitate when treated with 2:4-dinitrophenylhydrazine

/sulphate in

sulphate in solution in methanol. Each fraction was tested for the iodoform reaction, using a modified form of the procedure recommended by Kamlet (49). The following experiment is a typical example of the ones carried out. Laevulinic acid (5.3 mg.) in dioxan (15 drops; purified by the method of Hess and Frahm, 50) was treated with 10% aqueous sodium hydroxide (6 drops). Iodine reagent (1 g. of I_2 in a solution of 2 g. KI in 16 c.c. of water) was then added dropwise until a brown colour persisted, when the reaction mixture was warmed in a water bath at 60° for 90 secs., adding one drop of the iodine solution. After cooling, the excess of iodine was removed by adding a few drops of 10% sodium hydroxide, and on adding water (1.5 c.c.), the iodoform separated. This was collected and dried (5.8 mg.) m.p. 119-121°. All four fractions of basic material from the oxidation gave completely negative iodoform tests when portions (approx. 20 mg. of each fraction) were examined in the above manner.

The aqueous solution from the oxidation, containing the amino acids, was freed from inorganic matter in the way that was described in the second oxidation of the tetrahydromethine (XXXI) above. Evaporation of the aqueous solution left a pale brown gum (123 mg.), which was converted to the crude methyl ester (84 mg.), by the procedure previously described. A portion of this (18 mg.) was insoluble ether, and the soluble matter was separated from it, and distilled

/at 110-

at 110-120° (bath)/4x10^{-5} m.m.; a pale yellow gum was obtained (56 mg.). This was heated under reflux for 15 hrs. with water (5 c.c.), and the ester which had not been hydrolysed (20 mg.) was removed by three extractions with ether. Evaporation of the aqueous solution left a colourless gum (38 mg.), which could not be induced to crystallise.

The above oxidation of des-N(a)-emetinehexahydrobismethine (0.867 g.) was repeated, adding in this case a volume of barium permanganate equivalent to 4.1 atomic proportions of oxygen, over 11 hours. The products of the oxidation were examined as in the previous case, when a neutral and basic fraction (0.475 g.; brown gum) and an acidic fraction (0.136 g.; brownish crystals) were obtained. Recrystallisation of the latter from water, followed by sublimation at 100° (bath)/0.1 m.m. gave a colourless product (86 mg.), m.p. 141-2°, alone and in admixture with 6-ethylveratric acid. The crude amino acid fraction (280 mg.) from the oxidation was converted to the methyl ester in the usual way, and distilled to yield a clear, yellow gum (181 mg.). A portion (approx. 110 mg.) was hydrolysed by being heated under reflux with 0.1N barium hydroxide (20 c.c.) for 9 hours. The acid was then isolated in the manner described on p.120, but all attempts to bring about crystallisation were abortive. The rest of the methyl ester was therefore distilled twice at 140° (bath)/8x10^{-5} m.m., and submitted for analysis.

/Found:

Found: C, 69.1; H, 9.8.

$C_{21}H_{35}O_4N$ requires C, 69.0; H, 9.66.

Oxidation of 4-n-propylveratrole.

The substance required for this oxidation was prepared by shaking O-methyleugenol (5.02 g.), in ethanol (10 c.c.), with hydrogen in the presence of platinum oxide (150 mg.), when 1.00 mol. of hydrogen was absorbed in 20 mins. After filtering, the solution was freed from alcohol under reduced pressure, and the residue distilled, a fraction b.p. 119.5-121.5° being collected at 10 m.m. (4.61 g.; n_D^{15} 1.5185).

4-n-propylveratrole (1.92 g.) was dissolved in 50% aqueous acetone (200 c.c.), and treated dropwise at 0° with M/50 barium permanganate; the rate of addition was such that a slight excess of MnO_4^- was always present. After 10 hrs., the addition was stopped, 17.5 c.c. of the permanganate solution having been added. The acidic matter from the oxidation was isolated as gummy crystals (17 mg.), by the method used on p.116. Sublimation of this product at 70-80° (bath)/0.03 m.m. yielded a white pasty solid (9 mg.), which on crystallisation from water gave impure veratric acid (5 mg.), m.p. 173-177°; pure veratric acid has m.p. 181°.

Hofmann degradation of des-N(a)-emetinehexahydrobismethine (XLIV).

A modification of the process described by Späth and Pailer (32) was used. The base (0.472 g.) was dissolved

/in dry

in dry ether (10 c.c.) and treated with dry methyl iodide (1 c.c.). After 60 hrs. at room temperature, the ether was decanted from the precipitated methiodide, which was washed with ether. The salt was then dissolved in 50% aqueous ethanol (20 c.c.), was heated to 50°, and stirred for 1 hr. with silver oxide (from 0.5 g. of silver nitrate). The solids were removed by filtration ("Filtercel") and the clear filtrate, free from iodide ion, was evaporated to dryness under reduced pressure. The residual metho-hydroxide was decomposed by being heated at 180-200°/0.1 m.m. for 1 hr., and the products were then distilled at 180°/4×10^{-3} m.m. A clear, pale yellow distillate was obtained, which was dissolved in ether, and the solution was shaken twice with 2N hydrochloric acid (10 c.c. portions). After washing the ether solution once with water, the total acid solution was shaken with ether (2x50 c.c.), washing each ether layer once with water. The dried ether solution was evaporated to leave a pale yellow, neutral gum (0.239 g.), which was crystallised from 40-60° petrol, to afford rosettes of needles (LX, 142 mg.) m.p. 66-67.5°, after sintering at 64°, raised to 68-69° by one further crystallisation from the same solvent. This product was colourless, but slowly became yellow. Before analysis, it was distilled at 130-140° (bath)/8×10^{-5} m.m. and crystallised from 40-60° petrol; the final sample was dried at 35° for 2 hrs. over phosphoric oxide in a vacuum,

/m.p. 69-70°

m.p. 69-70° after slight sintering. This sample was also used for absorption spectrum measurements.

Found:	C, 76.2; H, 8.9.
$C_{29}H_{40}O_4$ requires	C, 76.93; H, 8.93.
Repeat on deep yellow sample	C, 74.6; H, 9.2.

The basic products (0.137 g.; colourless gum) were recovered from the acid solution above in the usual manner, and a portion (51 m.g.) was treated with picric acid (24 mg., 1 equiv.) in ethanol. The picrate was collected, washed with ethanol, and dried (66 mg.) m.p. 158-9°, alone and in admixture with the picrate of (XLIV).

Preparation and Hofmann degradation of des-N(a)-emetineoctahydrobismethine (LXVII).

The hexahydrobismethine (XLIV; 3.276 g.) was dissolved in glacial acetic acid (30 c.c.) and shaken with hydrogen in the presence of platinum oxide (80 mg.) at room temperature and pressure. Reduction was complete in 20 mins., when 1.05 mol. of hydrogen had been absorbed. The catalyst was filtered off ("Filtercel") and the clear filtrate was evaporated to dryness under reduced pressure, to leave a residue which was dissolved in water. After rendering the solution alkaline to phenol phthalein with sodium hydroxide, the base was extracted by three portions of ether (1x100, 2x50 c.c.), washing each ether layer once with water. The dried ether solutions were evaporated, and the residual pale yellow gum (3.265 g.) was distilled at 180° (bath)/$5x10^{-6}$ m.m.

/to yield

to yield a colourless gum. Attempts to prepare crystalline salts of this base (LXVII) with picric, perchloric, and hydriodic acids were unsuccessful. $\alpha_D = -0.49^\circ$, C = 2.444, l = 4 dm., $[\alpha]_D^{13.5} = -5.0 \pm 0.2^\circ$.

All the above product, and a small quantity from a previous preparation, were dissolved in ether (50 c.c.), and treated with excess of dry methyl iodide (3 c.c.). After 46 hrs. at room temperature, the ether was decanted from the the yellow gum, which was washed with fresh ether. Evaporation of the ether solution left a negligible residue. The methiodide was dissolved in 50% aqueous ethanol (60 c.c.) and the solution was stirred with silver oxide (from 4 g. of silver nitrate) for ¾ hr. at 50°. After filtering ("Filtercel") the solution, free from iodide ion, was evaporated to dryness, and the residue heated at 150° (bath)/0.2 m.m. for 1 hr., and then at 180° (bath)/2×10^{-5} m.m. until distillation was complete. A pale yellow gum (3.405 g.) was obtained. This was separated into neutral and basic fractions (0.779 g., 2.685 g. respectively; pale yellow gums) as described on p.128. The process was repeated upon the recovered basic matter, but in this case, the metho-hydroxide was heated for 2 hrs. at 100°/15 m.m. before being distilled at 180-190° (bath)/2×10^{-5} m.m. to give a clear gum (2.606 g.). This was separated into neutral matter (LXVIII; 1.237 g., pale yellow gum) and basic matter (1.339 g., nearly colourless gum) as before. After

/heating the

heating the first fraction of the neutral matter at 50° (bath)/10^{-5} m.m. for ½ hr. to remove ether, it was dissolved in ethanol (c = 1.874) for a determination of the specific rotation, using "Hg green"; $\alpha = +0.018 \pm 0.032°$. The second fraction of neutral matter was distilled at 180° (bath) /2×10^{-5} m.m. and the pale yellow distillate treated as before; c = 2.008, $\alpha = -0.028 \pm 0.02°$. A further portion of this distillate was redistilled at 140° (bath)/5×10^{-6} m.m. and submitted for analysis; a micro-hydrogenation was also carried out on this specimen.

Found: C, 76.5; H, 9.15; No nitrogen.

$C_{29}H_{42}O_4$ requires C, 76.80; H, 9.33; N = Zero.

Wt. for hydrogenation = 30.8 mg. Solvent = 5 c.c. glacial acetic acid. Catalyst = 20 mg. PtO_2. Uptake = 1.64 c.c. at 17°/749 m.m. (= 1.00 mol.)

Ozonolysis of the final neutral matter (LXVIII).

This substance (0.852 g.) was dissolved in ethyl chloride (15 c.c.) and the solution was cooled to −78°. Ozonised oxygen (1440 c.c. of 3.51%, equiv. to 1.2 mol.) was led in for 24 mins., the removal of ozone being almost quantitative, as shown by passing the gas from the reaction vessel into a trap containing aqueous potassium iodide. The ethyl chloride was evaporated under reduced pressure, and the gummy residue was treated with water (20 c.c.), to which silver nitrate (15 mg.) and zinc dust (0.2 g.) were added. This supension was heated under reflux for 5 mins., whilst

/nitrogen was

nitrogen was bubbled through it and into a trap containing an aqueous alcoholic solution of dimedone (100 c.c. of a solution of 1.5 g. dimedone in 200 c.c. of water and 40 c.c. of ethanol). At the end of this period, the reflux condenser was removed, and water was allowed to distil slowly into the dimedone solution, with the nitrogen stream still passing, for ½ hour. More water (20 c.c.) was then added to the reaction mixture, and the condenser was replaced to allow the suspension to be heated under reflux for ½ hour. The condenser was removed and the slow distillation of water was continued for ½ hr., after which, the solution of dimedone, now containing a white precipitate, was allowed to stand overnight. The precipitate was collected, washed with water and dried (184 mg., 33%) m.p. 180-184°, after previous sintering. One recrystallisation from aqueous ethanol raised the m.p. to 187-8°, and a second yielded a product m.p. 188-9°, alone and in admixture with the dimedone derivative of formaldehyde, which melted at this same temperature.

The aqueous suspension of the non-volatile products was extracted thrice with ether, and the ether solution, after being filtered to remove zinc dust, was shaken thrice with 10% aqueous sodium carbonate (20 c.c. portions). The aqueous, alkaline solution was shaken twice with ether, washing each

/ether layer

ether layer once with water. The ether layers were then combined and, after being dried, were evaporated to leave a yellow gum (745 mg.). Distillation at 140-150° (bath)/5x10^{-6} m.m. afforded a pale yellow gum (637 mg.) which was collected in two portions (345 mg. and 292 mg.). Attempts to prepare the crystalline semicarbazone, 2:4-dinitrophenylhydrazone, and p-nitrophenylhydrazone of portions of the first fraction were unsuccessful, but the formation of sparingly soluble, amorphous products in each case showed that a carbonyl compound was being handled.

A small amount of the first fraction (approx. 10 mg.) was added to Schiff's reagent (decolorised 0.1% aqueous fuschin; 0.3 c.c.), but after ½ hr. there was no pink coloration. A further portion was added to a solution prepared by adding sodium hydroxide (0.3 c.c. of 2N) to silver nitrate (0.3 c.c. of 2N), the precipitate just being redissolved by the addition of dilute ammonium hydroxide. After being warmed to ca. 50° for 5 mins., there was no reduction to silver, nor did any occur after the solution had stood for ½ hour. The last test employed was that using dianisidine (36), which was purified by dissolving the hydrochloride in dilute hydrochloric acid (charcoal), filtering hot and adding concentrated hydrochloric acid to the filtrate. This was repeated until colourless crystals were obtained. A little of this salt (50 mg.) was dissolved in a saturated solution of sodium acetate in glacial

/acetic

acetic acid (0.3 c.c.) with warming, and the ozonolysis product (10 mg.) added to the cooled solution. Only a very faint, yellow colour was produced after ½ hr. at room temperature; warming the solution brought about no significant change. The three reagents employed above were shown to be very sensitive to known aldehydic compounds.

Separation of a N-methylpiperidine (LXIIIa) from the related pyridine (LXIVa).

The N-methylpiperidine (54 mg.) and the pyridine compound (79 mg.) were mixed, and dissolved in ether (60 c.c.). By trial, it was found that (LXIIIa) was removed by shaking this ether solution four times with a buffer solution of pH 5.9 (20 c.c. portions). The ether solution, after washing with water, was dried and evaporated to leave a crystalline base (LXIVa, 79 mg.) m.p. 52-53.5°, m.p. of pure (LXIVa) in the same bath = 55-55.5°.

Dehydrogenation of des-N(a)-emetinehexahydromethine (LIXa) with palladium.

The crystalline base (544 mg.) was mixed with 10% palladised charcoal (436 mg.) and heated without solvent at 260-270° for 3 hrs., with a stream of pure carbon dioxide sweeping through the reaction vessel into a nitrometer containing 50% aqueous potassium hydroxide. The volume of gas collected (46.9 c.c., at 20°/750 m.m.) is 56.5% of that theoretically expected for the change from (LIXa) to (LXIa).

/A second

A second experiment, using a similar quantity of base (599 mg.), yielded 55% of the quantity of gas theoretically expected. The two products were dissolved in ethanol and filtered ("Filtercel") into the same flask, washing the pad thoroughly with hot solvent. Evaporation of the clear filtrate under reduced pressure left a brown gum (883 mg.), which gave a purple colour with Erlich's reagent; the loss in weight is probably due to fission of the molecule to some extent (cf. 17).

This gum was dissolved in ether (450 c.c.) and trial showed that a strongly basic fraction could be removed by shaking this solution with M/50 citric acid (1x150 c.c., 2x75 c.c.). After shaking the ether solution thrice with N hydrochloric acid (1x40 c.c., 2x20 c.c.) to remove the weak bases, it was evaporated to 80 c.c. and shaken again with N hydrochloric acid (2x20 c.c.). The ether was then washed once with water, and once with 2N sodium carbonate, after which it was dried, and evaporated to leave the neutral matter as a cloudy brown gum (154 mg.). This gave a slight purple colour with Erlich's reagent, but in one earlier experiment, the neutral matter was isolated by dissolving the total dehydrogenated product in ether, extracting exhaustively with N hydrochloric acid, and evaporating the ether to dryness, after washing the ether solution with water to remove acid. In this case, the neutral matter gave an intense purple colour

/with Erlich's

with Erlich's reagent; evidently any pyrrole derivatives which are present are sensitive to heat in the presence of even traces of mineral acid.

The aqueous extracts containing the strongly basic substances above, were made alkaline to phenol phthalein with sodium hydroxide, and extracted with ether (1x200 c.c., 2x100 c.c.). After washing the ether solution once with water, it was dried, and evaporated to leave a pale brown gum (349 mg.). This was dissolved in 40-60° petrol, the solution filtered, and then seeded with the starting material (LIXa); crystallisation ensued, and the product (164 mg.) had m.p. 74-7°, whilst the mixed m.p. with pure (LIXa, m.p. 78-79.5°) was 76-9°.

The weakly basic substances were recovered from the acid extracts above by the addition of sodium hydroxide to render the solution alkaline to phenol phthalein, followed by three extractions with ether. Each ether layer was washed once with water, and the combined solutions were dried and evaporated; a clear brownish gum remained (358 mg.). This was dissolved in methanol and picric acid (178 mg., 1 equiv.) was added. Crystallisation occurred after some time, and the product was collected, washed with methanol, and dried (407 mg.) m.p. 106-9°, after sintering at 104°. The salt was dissolved in ethyl acetate, the solution filtered hot, and allowed to cool when the picrate crystallised as rosettes of yellow needles m.p. 121-3°. Three further recrystallisations

/from ethyl

from ethyl acetate raised the m.p. to 124.5-126°, the sample for analysis being dried at 100° over phosphoric oxide in a vacuum for 2½ hours.

Found: C, 60.95; H, 6.0; N, 8.0.

$C_{29}H_{37}O_4N.C_6H_3O_7N_3$ requires C, 60.65; H, 5.84; N, 8.09.

The base was recovered from the picrate (388 mg.) by suspending it in 2N sodium hydroxide and extracting with ether (1x75 c.c., 2x50 c.c.), washing each ether layer once with water. Picric acid was then removed from the ether solution by shaking it thrice with 20% sodium hydroxide (15 c.c. portions), and washing once with water. The dried ether solution was evaporated to leave a clear gum (260 mg., 100%) which was distilled at 160-170° (bath)/$8x10^{-5}$ m.m. to give a clear colourless gum. A portion of the distillate was sent for absorption spectrum measurements (p. 144), and a second portion (13.4 mg.) was hydrogenated in glacial acetic acid (5 c.c.) by shaking with hydrogen at 13°/752 m.m. in the presence of platinum oxide (20 mg.). Uptake of hydrogen was slow, and 3.56 mol. had been absorbed after 34 hours; there was no appreciable change in the rate of absorption of hydrogen after 2 or 3 mol. had been taken up.

The pure base, obtained above, eventually crystallised, and on recrystallisation from ether, it was obtained as rosettes of colourless needles m.p. 101.5-102.5°, raised to 102-102.5° by two further crystallisations from ether. This

/sample was

sample was dried at 78° for 2 hrs. over phosphoric oxide in a vacuum and submitted for analysis.

Found: C, 74.9; H, 8.05; N, 3.32.

$C_{29}H_{37}O_4N$ requires C, 75.17; H, 8.06; N, 3.02.

A portion of this product, dissolved in aqueous acetone at room temperature, was completely stable to the action of potassium permanganate over 30 minutes.

Action of silver acetate upon 1-methyl-2-(p-methoxyphenyl)-piperidine (LXIII$_a$).

The base (0.5 g.) was mixed with silver carbonate (2.19 g.; 3.25 moles) in a Carius tube, to which was added glacial acetic acid (3 g.) and water (3 c.c.). When the evolution of gas had ceased, the tube was sealed, and then heated for 6 hrs. at 180-190°. The solution in the tube was filtered ("Filtercel"), and the pad was washed thoroughly with hot water. After making the orange-red filtrate alkaline with sodium hydroxide, the neutral and basic products were extracted with four portions of ether, each ether layer being washed once with water. The dried ether solution left a red-brown gum (135 mg.) on evaporation, which was shown to be free from pyrrole compounds by the Erlich and pine splint tests.

The aqueous solution from the ether extraction was acidified with hydrochloric acid, and after filtration, was evaporated to dryness under reduced pressure. Hydrochloric acid (15 c.c. of a solution made by adding 30 c.c. of conc.

/acid

acid to 70 c.c. of water) was added to the residue, and after evaporation to dryness as before, the organic matter was extracted from the sodium chloride with ethanol. The filtered alcoholic solution left a thick, brown gum (441 mg.) when it was evaporated under reduced pressure. A small portion of this product dissolved readily in water and no cloudiness resulted when sodium hydroxide was added, showing that it is a quaternary chloride. The rest of this salt was decomposed, with steady effervescence, by heating at 170-175° (bath)/35 m.m. for ½ hr. and the product was then sublimed at 170° (bath)/ 0.03 m.m. A crystalline product was obtained, m.p. 47-53°, after slight sintering, this being dissolved in ether, and shaken once with dilute sodium hydroxide, and once with water, to remove traces of quaternary substances. The aqueous extracts were shaken twice with ether, washing each ether layer once with water, and after drying, the ether solution was evaporated to afford a crystalline base (LXIVa) 248 mg.; 55%) m.p. 51-3°. The m.p. was raised to 52-4° by one recrystallisation from 40-60° petrol, and to 54.5-55.5°, alone and in admixture with the authentic base (LXIVa) of m.p. 55-55.5°, by one sublimation at 70° (bath)/0.02 m.m.

Action of silver acetate upon des-N(a)-emetinehexahydromethine (LIXa).

This base (1 g.) was mixed with silver carbonate (1.72 g.; 3 moles) in a Carius tube as in the previous

/experiment

experiment, the amounts of glacial acetic acid and water being 2.4 g. and 15 c.c. respectively. The sealed tube was heated at 180° for 7½ hrs., and the product examined in the way described above. The neutral and basic products (545 mg.) formed a dark brown resin, which gave no colour reaction with Erlich's reagent, and the crude quaternary chloride (401 mg.) was obtained as a dark brown resin. This latter substance was decomposed by being heated at 180° (bath)/0.1 m.m. for ½ hr.; a steady effervescence occurred during this period. Distillation of the product at 180° (bath)/5×10^{-4} m.m. yielded a yellow glass, which was freed from traces of quaternary matter as in the previous experiment. The base so obtained was a clear, pale yellow glass (162 mg.), which was dissolved in methanol and treated with picric acid (78 mg., 1 equiv.). Crystallisation occurred slowly to give a crop of yellow needles (203 mg.), m.p. 110-112°, after sintering at 104°, raised by two recrystallisations from ethyl acetate to 124-125°, after sintering at 123°. The mixed m.p. with the picrate (m.p. 124.5-126°) from the dehydrogenation of (LIXa) with palladium, was 124-125.5°, after sintering at 123°.

The neutral matter (106 mg.; mixture of brown and colourless gums) and the weak bases (125 mg.; brown-yellow gum) were separated from the neutral and basic matter above, which had been combined with a further portion (211 mg.) from a second, similar experiment, by the technique, using citric

/acid,

acid, described in the palladium dehydrogenation. No coloration was obtained when the neutral matter was treated with Erlich's reagent. The weak bases, with picric acid (63 mg., 1 equiv.) in methanol, gave a crystalline picrate (77 mg.) m.p. 104-107°, after previous sintering, raised to 124-125.5° by two recrystallisations from ethyl acetate.

Preparation of the di-β-phenylethylamide (LXXIX).

Methyl pentane-1:3:5-tricarboxylate (LXXVIII, 6.82 g.) in tetralin (20 c.c.) was heated in a bath at 190°, whilst β-phenylethylamine (7.04 g., 2 moles), dissolved in tetralin (40 c.c.) was dropped in over 6 hours. The bath temperature was then raised to 210° for 1 hr., after which the tetralin was distilled under reduced pressure. Water was added to the residue, and by steam distillation, the last traces of tetralin were removed. Extraction of the aqueous suspension thrice with chloroform removed the mixed amides, which were freed from acidic and basic substances by shaking the chloroform solution twice with 2N sodium hydroxide, then twice with 2N hydrochloric acid, and finally once with water. The dried chloroform solution was evaporated to leave a gum (10.10 g.), which was separated into mono-, di-, and tri-amides by a procedure worked out in the trial experiments.

The gum was dissolved in chloroform (25 c.c.) and the solid which separated was collected, washed with chloroform, and dried; it was a brown waxy substance (0.965 g.) and two

/products

products were isolated from it. One (0.548 g.), sparingly soluble in cold acetone, was isolated by recrystallisation of the waxy product from acetone-ethanol, and by repeated crystallisation of this substance from the same solvent mixture, the pure tri-amide m.p. 174-5° was obtained as colourless short prisms. The analysis specimen was dried at 100° for 3 hrs. over phosphoric oxide in a vacuum.

Found: C, 75.0; H, 7.7; N, 7.9.

$C_{32}H_{39}O_3N_3$ requires C, 74.8; H, 7.66; N, 8.18.

The second substance was isolated from the mother liquors from the tri-amide, by evaporating to dryness under reduced pressure and dissolving the residue in ethyl acetate. After washing the solid which separated with ethyl acetate, it was dried (94 mg.) m.p. 96.5-98°. The main quantity of this product was isolated from the chloroform mother liquor which had deposited the waxy solid. Evaporation of this mother liquor to dryness under reduced pressure left a gummy residue, which was dissolved in ethyl acetate (50 c.c.). Crystallisation occurred, and the solid, after being washed thrice with ethyl acetate, was colourless (3.42 g.) m.p. 95-7°; several small crops from mother liquors raised the total yield to 3.67 g. (30%). One crystallisation from benzene and two from ethyl acetate gave the pure diamide (LXXIX) m.p. 97.5-98.5°, as short blunt-ended prisms. The analysis specimen was dried at 78° for 3 hrs. over phosphoric oxide in a vacuum.

/Found:

Found: C, 70.75; H, 7.65; N, 6.4.

$C_{25}H_{32}O_4N_2$ requires C, 70.70; H, 7.61; N, 6.60.

The ethyl acetate mother liquor from the main crop of the diamide was evaporated to dryness to leave a viscous brown oil (5.26 g.), which was fractionated under reduced pressure. After collecting a first fraction, b.p. 128-132°/ 0.5 m.m. (0.57 g.) of unchanged methyl pentane -1:3:5- tricarboxylate, and an intermediate one, b.p. 170-220°/0.5 m.m. (0.62 g.), the main fraction was obtained, b.p. 225-237°/ 0.5 m.m. (2.60 g.). The residue in the flask afforded a little of the diamide (153 mg.) m.p. 84-94°, when it was crystallised from ethyl acetate.

The high boiling fraction, consisting of the mono- amide, was redistilled, and the middle fraction b.p. 195°/ 3×10^{-3} m.m. was collected, to be redistilled in a short-path apparatus at 140° (bath)/10^{-5} m.m. for analysis.

Found: C, 64.3; H, 7.5; N, 4.35.

$C_{18}H_{25}O_5N$ requires C, 64.44; H, 7.52; N, 4.18.

After long standing, this substance crystallised, and from ether was obtained as colourless triangular plates m.p. 42-43°. A sample of this product was converted to the tri-amide in 72% yield by being heated with excess of β-phenylethylamine in a bath at 180° for 2 hrs., and then at 200° for 2 hrs. The product was freed from acidic and basic

/substances

substances as in the previous case, and was crystallised once from aqueous ethanol, and once from acetone-ethanol. The m.p. was then 172-5°, alone and in admixture with the authentic tri-amide.

Absorption spectrum measurements. (See p. 137).

	$\lambda_{max.}$	ε.
Dehydrogenation product (LXIa)	2490*	12,910.
	2850	11,250.
2-(p-methoxyphenyl)-pyridine (LXIVa)	2600	14,490.
	2820	16,870.

*Inflexion.

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