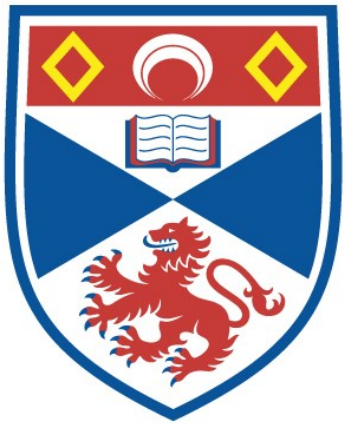
EXPERIMENTS IN CONNECTION WITH THE STRUCTURE OF EMETINE

Geoffrey Norcross

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



1949

EXPERIMENTS IN CONNECTION WITH

THE STRUCTURE OF EMETINE

being a Thesis

presented by

GEOFFREY NORCROSS, M.Sc.,

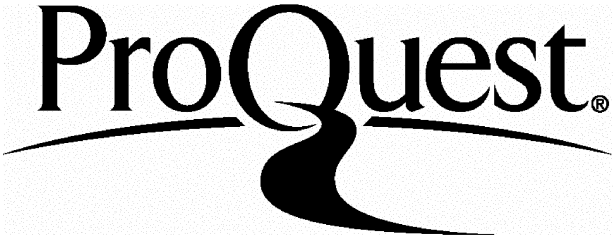
to the

UNIVERSITY OF SAINT ANDREWS

in application for

the

DEGREE OF DOCTOR OF PHILOSOPHY



DECLARATION

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

The investigations were carried out in the Chemical Research Laboratory of the United College under the direction of Doctor H. T. Openshaw.

CERTIFICATE

I hereby certify that Mr. Geoffrey Norcross, M.Sc., has spent eight 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 Doctor of Philosophy.

Director of Research.

UNIVERSITY CAREER and RESEARCH EXPERIENCE

I entered the Victoria University of Manchester in October, 1943, and graduated B.Sc. with First Class Honours in Chemistry in January, 1946.

Thereafter, I undertook original research at Manchester under the direction of Doctor H.T. Openshaw, proceeding with him to St. Andrews in October, 1946. In July, 1947, I was awarded the degree of Master of Science by the University of Manchester.

The researches described in the present Thesis were carried out in the United College, St. Andrews, within the period January, 1947, until December, 1948.

C O N T E N T S

GENERAL

1. References to the bibliography of original literature are made by enclosing the number of the reference in brackets, as (42).

2. References to pages of the present Thesis are made by preceding the page number by p. and enclosing in brackets, as (p. 34).

HISTORICAL

INTRODUCTION

Emetine is the principal alkaloid of ipecacuanha root which is obtained from the plant known botanically as Psychotria Ipecacuanha, also called Cephaelis Ipecacuanha, indigenous to Brazil, and from Psychotria Acuminata found in Colombia, both members of the Rubiaceous Order. In this root emetine is accompanied by cephaeline and, in much smaller amount, by psychotrine, O-methylpsychotrine and emetamine, the five alkaloids being closely related to each other chemically.

The two chief medicinal properties of ipecacuanha root, namely its emetic effect and its ability to alleviate dysentery, have long been known, the name "ipecacuanha" itself being derived through Portugese from a native word meaning "road-side sick-making plant".

The earliest recorded account of the root which is extant occurs in a book published in 1625 (1) and written by a Portugese friar who had resided in Brazil. He refers to "Igpecaya" or "Pigaya", without doubt the plant now known as ipecacuanha, as being a remarkable remedy for the bloody flux, the condition whose modern name is dysentery. Some years later Piso and Marcgrav (2) described the ipecacuanha plant and its medicinal properties, in the account of their scientific exploration in Brazil.

Although in common use in Brazil, ipecacuanha was not employed in Europe before the year 1672 when Legras imported a quantity of the root to Paris. Legras, however, damaged rather

than enhanced the reputation of the new drug through administration of excessive quantities, and in developing its use in Paris Helvetius kept the nature of his medicine secret. Following the successful treatment by Helvetius of the Dauphin of France, who had become infected with dysentery, Louis XIV negotiated the purchase from Helvetius of his secret for 1,000 Louis d'or and made it public.

By 1912, when Vedder (3) finally proved that the alkaloids, particularly emetine and cephaeline, were the active components in the treatment of dysentery, it had become generally realised that of the several forms of dysentery known only that termed "amoebic" responded to the drug, although more recently emetine has been used with some success against bilharzial dysentery when the usual treatment has been inapplicable due to antimony intolerance, or when both forms of dysentery have occurred together.

Amoebic dysentery is caused by a parasite, Entamoeba histolytica, which burrows into the intestinal mucosa causing large ulcers, and which enters the liver setting up a secondary condition known as hepatic liver abscess. There are two forms of the parasite, the cystic or resting form which is present in chronic dysentery, and the active form whose prevalence gives rise to the symptoms of acute dysentery. It is during the acute stage of the disease that treatment is most effective, since the gut is then hyperaemic and the blood has easy access to the amoebae. In the chronic or carrier condition, however, the drug is less able to attack the cysts, walled in by the gut tissue, which by this

time has often undergone considerable fibrosis and thickening.

Recent developments in the treatment of amoebic dysentery have aimed at reducing to a minimum the nausea and vomiting accompanying the use of ipecacuanha. According to current theory, the emetic effect of ipecacuanha is due entirely to its irritant action on the gastric mucous membrane rather than to direct action on the vomiting centre in the medulla. This has led to the administration of isolated emetine instead of crude ipecacuanha, since this is the least irritating of the alkaloids in the root, and also to hypodermic injection, since larger quantities of emetine may be injected without ensuing emesis than can be taken orally. Hypodermic injection of emetine hydrochloride was first carried out by Rogers (4) and this salt has remained to the present day the one most commonly injected.

Eradication of the cysts from the substance of the bowel wall requires a very large concentration of emetine in the intestine for prolonged periods. To bring this about, and yet avoid the ill effects of the drug, Du Mez (5) suggested the oral administration of the double iodide of emetine and bismuth. This compound was introduced under the erroneous impression that it was completely insoluble in physiological acid so that it could not be attacked in the stomach but that solution with decomposition and liberation of emetine would occur in the intestine. If emetine bismuth iodide is to reach the duodenum undecomposed, it must be coated with a suitable preparation, for example salol.

The modern treatment of amoebic dysentery involves the intramuscular injection of a solution of emetine hydrochloride in distilled water, coupled with the oral administration of emetine bismuth iodide.

Although it is in the case of amoebic dysentery that ipecacuanha finds by far its most important application, its local irritant nature leads to three further uses, namely as an emetic, as an expectorant and as a purgative. Ipecacuanha was formerly used to quite a large extent as an emetic, but owing to its relatively slow action it has been largely superseded, especially in cases of poisoning where speed is essential, by apomorphine which acts directly upon the vomiting centre in the medulla and whose effect is immediate on injection. On the other hand, ipecacuanha is probably the safest emetic and is valuable in broncho-pneumonia in children to empty the air passages by vomiting. Although possessing emetic properties, the vinous preparation of the drug in two to three minim doses allays the vomiting in pregnancy.

In small doses, ipecacuanha increases the secretion of the bronchial mucous membrane rendering the mucus more fluid and facilitating expectoration. It is employed as an expectorant in acute bronchitis when the sputum is scanty and gives great relief in the dry cough of laryngitis and trachitis. It is well tolerated by children and is used in croup and whooping cough.

Combined with opium to allay vomiting, as in Dover's Powder,

ipecacuanha is of use as a diaphoretic in the early stages of febrile infections and especially to abort incipient colds. Emetine has been used in the treatment of chronic alcoholism.

The increasing importance of ipecacuanha in medicine has led to its cultivation in South America and, since the latter part of the nineteenth century, in India. It has also led to the chemical investigation of the potent principles contained in the drug, the natural outcome of which have been the attempts, reported by Pyman and Child (6) between 1929 and 1937, to synthesise compounds structurally related to emetine but more amoebicidal and less toxic than the alkaloid. These workers based their syntheses on tentative structures which had been proposed for emetine in 1927 as the culmination of research in different schools, but although a compound was finally prepared which was three to five times as amoebicidal as emetine in vitro at a pH of 6.2 to 6.3, and at least as active as emetine in the presence of blood, it was clinically useless on account of the intense irritation produced on injection.

It is with the investigations into the constitution of the ipecacuanha alkaloids, and particularly with the modern work in this field, that we are concerned in the present dissertation. From considerations of space, in the historical survey much must necessarily be disregarded which to the present author seems irrelevant to the main issue, and in particular an account of the work of many early investigators will be omitted because in no way do their results appear to have disclosed anything of

fundamental importance. A chapter is to be included recording the development, scope and modern position of the technique of dehydrogenation, a technique which forms the basis of a large section of the present investigation of which this thesis is a record.

THE EARLY HISTORY OF THE CHEMISTRY OF IPECACUANHA

It is to Pelletier and Magendie that we are indebted for the first recorded chemical investigation of the ipecacuanha root. In a paper (7) published in 1817, they were able to show that the medicinal properties of the drug were due to a "matière vomitive" which they called "émétine" on account of its emetic nature, but this substance had an acidic instead of a basic reaction, was obtained in 16% yield, approximately eight times as much as the total alkaloid now known to be present in the root, and was in fact an alcoholic extract of the drug rather than a distinct chemical compound.

In 1823, Pelletier and Dumas (8) reported the isolation from ipecacuanha of a basic substance for which they retained the name emetine, although its physiological activity was three times as great as that of their earlier material and evidently differed markedly from it.

Several workers were attracted to this field during the next fifty years, but it was not until 1876, when Glénard (9) liberated the base from its purified hydrochloride, that a pure specimen of the alkaloid emetine, as at present understood, was finally obtained.

Although the investigations of Lefort and Wurtz (10), Podwyssotzki (11) and Kunz-Krause (12), which followed the work of Glénard, did not advance the subject to any great extent, the preliminary work carried out prepared the way for the systematic examination of the chemical properties of the drug,

reported by Paul and Cownley in 1893 and 1894.

Operating with Brazilian root, these authors (13) were able to isolate two distinct alkaloids from the ethereal extract of the total base, which had been regenerated from acid solution by the addition of ammonia, by making use of the fact that one of these alkaloids was soluble, but the other insoluble, in caustic alkali solution. The latter was present in the greater amount, and for this the name emetine was retained, the other alkaloid, soluble in solutions of strong alkalis, being called cephaeline.

Paul and Cownley (14) also showed that there occurs in the root a third alkaloid which is insoluble in ether and remained behind in the aqueous ammoniacal layer after extraction of emetine and cephaeline. To this third alkaloid, which is present only in very small amount relative to the other two, the name psychotrine was given.

Following the decisive separation of the three main alkaloids of the ipecacuanha, the study of the root was continued during the next twenty years by Paul and Cownley in collaboration with Hesse (15), by Frerichs and de Fuentes Tapis (16) and by Keller (17, 18). The findings of Paul and Cownley were confirmed and some knowledge gained as to the rôles played by the atoms of oxygen and nitrogen, which analyses had shown to be present in the molecules of the alkaloids.

CHARACTERISATION OF THE ALKALOIDS

During the period of almost a century since Pelletier and Magendie published the first paper on the chemistry of ipecacuanha, a large number of workers had undertaken the investigation of the drug. The knowledge they gained, however, was not in keeping with the time and labour expended and even the more recent investigators had failed to obtain a clear understanding of the chemical properties of the three alkaloids. It was left to Carr and Pyman, not only to clarify the results previously obtained, but to carry the investigations a significant step forward.

These workers (19, 20) were able to obtain many crystalline salts of the three alkaloids and from these the bases themselves were liberated in a high state of purity. They carried out a large number of analyses of the bases and their salts and the results obtained, taken in conjunction with those from the analyses of a large number of simple derivatives, led them to the conclusion that emetine had the formula $C_{29}H_{40}O_4N_2$, cephaeline $C_{28}H_{38}O_4N_2$ and psychotrine $C_{28}H_{36}O_4N_2$. Previous investigators had analysed the alkaloids but the formulae they put forward had been conflicting and have been abandoned in favour of those of Carr and Pyman which are accepted as correct at the present day. Molecular weight determinations carried out by these latter workers were, on the whole, in agreement with their proposed formulae.

Emetine was described as an amorphous, white powder, melting

point 74°. Cephaeline and psychotrine on the other hand were both obtained crystalline, the former melting at 120 - 130° and the latter at 138° with previous sintering. The solubilities of the three alkaloids in various solvents and the specific rotations of solutions of the alkaloids and their salts were measured.

The mode of combination of the oxygen atoms in the molecules was readily accounted for, since emetine was found to contain four methoxyl groups, whilst cephaeline and psychotrine each contained three methoxyl and one phenolic hydroxyl group. Treatment of cephaeline with dimethyl sulphate and sodium methoxide, leading to the formation of emetine among the products of methylation, and the observation that hydrolysis of emetine and of cephaeline with concentrated hydrochloric acid at 130 - 140° leads, in both cases, to the same totally demethylated product, noremetine hydrochloride, $C_{25} H_{32} O_4 N_2$. 2HCl, confirmed the idea, arising from the fact that the formula of emetine exceeds that of cephaeline by CH_2, that emetine is the methyl ether of cephaeline. The relationship existing between the formulae of psychotrine and of cephaeline suggested that this latter alkaloid is dihydropsychotrine, and cephaeline was indeed isolated when psychotrine was reduced with sodium and alcohol.

Carr and Pyman showed that of the two nitrogen atoms in emetine and, since emetine is the methyl ether of cephaeline, in cephaeline also, one was tertiary and the other secondary. On treatment with benzoic anhydride, emetine readily yielded a crystalline compound, benzoylemetine $C_{29} H_{39} O_4 N_2$. COPh, which

was a monacid tertiary base. That it was a N-benzoyl derivative was shown by its stability to hydrolysis.

They were of the opinion that psychotrine was ditertiary, but in a later paper Pyman (21) was able to show that psychotrine, like the other two alkaloids, is a secondary-tertiary base. Carr and Pyman detected no N-methyl group in any of the three alkaloids.

The results of the Hofmann degradation on emetine, described by Karrer (22) in 1916, are in harmony with the secondary-tertiary nature of the alkaloid. His starting material, N-methylemetine dimethiodide, was given the formula $C_{30}H_{42}O_4N_2.2CH_3I$, which supports the composition $C_{29}H_{40}O_4N_2$ assigned to emetine by Carr and Pyman. Two complete treatments of this dimethiodide in the Hofmann manner were required to split out the first nitrogen atom in the form of trimethylamine, showing that it must be present in a ring, whilst the other nitrogen atom, retained in the molecule after the two treatments, must be common to two rings. The former was the secondary and the latter the tertiary nitrogen atom of the emetine molecule.

Contemporaneously with the publication of the work of Carr and Pyman, Hesse (23) described a lengthy investigation of the ipecacuanha and claimed to have isolated two new alkaloids from the drug. They were stated to accompany emetine in the ether-soluble, non-phenolic fraction of total alkaloid and were named ipecamine and hydroipecamine. Pyman, however, was of the opinion that the method used by Hesse to separate these alkaloids

from emetine and from each other, and also the description of their properties, were not such as to inspire confidence in their homogeneity and in his paper (21) of 1917 he was able to report the successful isolation from the emetine fraction of two further alkaloids which he characterised fully.

The non-phenolic, ether-soluble alkaloids of ipecacuanha were converted into the hydrobromides and crystallised from water, when emetine hydrobromide separated. A hydrogen oxalate, prepared from the bases remaining in the mother liquors, proved to contain two alkaloids whose separation by fractional crystallisation of salts presented some difficulty, but it was eventually found advantageous to separate them by fractional extraction from chloroform solution by dilute acid.

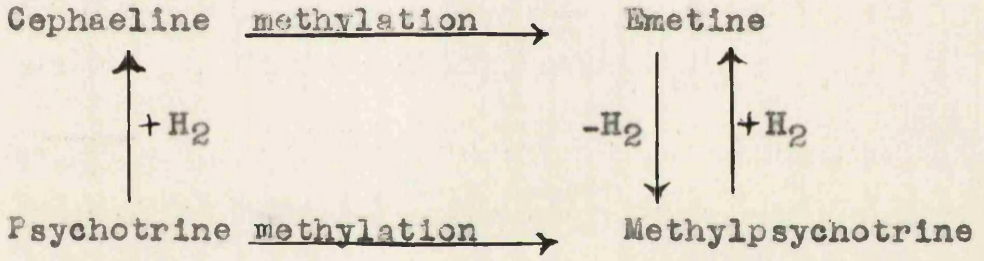
Pyman showed that the more basic alkaloid, which was extracted first, was O-methylpsychotrine which he isolated as an amorphous powder (although in 1927, in collaboration with Brindley (24), he succeeded in obtaining it in the form of prisms, melting point 123 - 124°). Analyses of its salts showed that the alkaloid had the composition $C_{29}H_{38}O_4N_2$, that it contained no N-methyl but four methoxyl groups and was a diacidic base. These results at once gave rise to the suspicion that it was the O-methyl ether of psychotrine and this structure was established on the partial synthesis of the compound by methylation of psychotrine.

Methylpsychotrine was also formed by the gentle oxidation of emetine by means of alcoholic iodine, but the yield was small.

Since cephaeline could be formed by the reduction of psycho-

trine (p. 10) with sodium and alcohol, it was to be expected that methylpsychotrine would yield emetine under similar conditions and this proved to be the case.

The relationship of methylpsychotrine to the previously known alkaloids of the ipecacuanha was clear, and the interconversions of the four alkaloids which had been realised experimentally may be recorded diagrammatically as follows:



When heated with benzoic anhydride, methylpsychotrine yielded a mono-N-benzoyl derivative which was a monacidic base. It therefore followed that methylpsychotrine, and consequently psychotrine itself, contained an imino group, and it was on this basis that Pyman was able to refute the statement made in his earlier paper (20) that psychotrine was a ditertiary base (p. 11).

For the alkaloid which he obtained from the least basic fraction of its mixture with O-methylpsychotrine, Pyman proposed the name <u>emetamine</u>. It formed colourless needles melting at 155 - 156°, and analyses of the base and of its salts gave figures intermediate between those required for the formulae $C_{29}H_{36}O_4N_2$ and $C_{30}H_{36}O_4N_2$. Emetamine was found to contain no N-methyl but four methoxyl groups and to be non-phenolic and a diacidic base. It gave no benzoyl derivative on heating with

benzoic anhydride, but the product of its reduction with sodium and alcohol could be benzoylated with the formation of the benzoyl derivative of isoemetine, an isomer of emetine which is also formed, together with emetine, by the reduction of methylpsychotrine (p. 13) with sodium and alcohol.

These facts made it probable that emetamine was best represented by the formula $C_{29}H_{36}O_4N_2$ and that it differed from emetine in containing two unsaturated linkings, one of them connecting two carbon atoms and the other a carbon atom and a nitrogen atom. In their paper of 1927, Brindley and Pyman (24) were able to confirm this latter formula for emetamine, which they further characterised by the preparation of a number of salts.

The alkaloids ipecamine and hydroipecamine, which Hesse (23) claimed to have isolated (p. 11) from the ether-soluble, non-phenolic fraction, are now disregarded in favour of the O-methyl-psychotrine and emetamine of Pyman, so that five alkaloids are at present recognised as occurring in the ipecacuanha root.

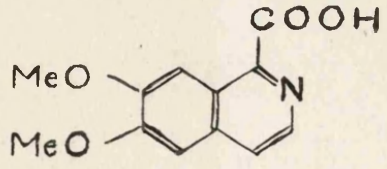
All five alkaloids have been found present in each variety of ipecacuanha examined, and although both the percentage of total alkaloid present in the different species of the plant, and the amounts of the alkaloids relative to each other, may vary by a factor of approximately three, it is yet possible to give some idea of their relative abundance by means of the following table, in which average values are given:-

Alkaloid	Percentage of the Alkaloid in the Root
Emetine	1·2
Cephaeline	0·7
Psychotrine	0·05
Methylpsychotrine	0·02
Emetamine	0·004

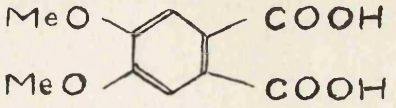
INVESTIGATIONS INTO THE STRUCTURES OF THE ALKALOIDS

The investigations described up to the present have been concerned with the isolation of the alkaloids from the ipecacuanha root, and with the elucidation of the relationship existing between the five compounds.

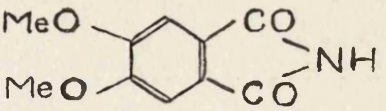
Prior to 1914, the attempts which were made by alkali fusion (12), by dry distillation and zinc dust distillation (18), and by oxidation with permanganate (25) to gain some insight into the structures of the alkaloids were without significant result. In that year, however, Carr and Pyman (20) reported the isolation of 6:7-dimethoxyisoquinoline-1-carboxylic acid (I) and m-hemipinic acid (II) from the products of oxidation of emetine using an aqueous acetone solution of potassium permanganate. The formation of m-hemipinic acid and of its imide (III), by oxidation of emetine with permanganate, was reported in the same year by Windaus and Hermans (26).



I



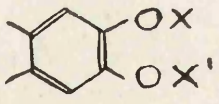
II



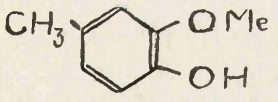
III

These results showed that the alkaloids are derivatives of 6:7-dimethoxyisoquinoline, a fact which is in harmony with the statement made by Carr and Pyman in the same paper that noremetine (p. 10) gave a catechol coloration with ferric chloride.

In 1914 also, Dobbie and Fox (27) pointed out that the absorption spectrum of emetine bore a remarkable resemblance to the spectra of a number of isoquinoline alkaloids. The structural differences in these latter alkaloids occur in the reduced part of their molecules, whereas they resemble oneanother in each containing two unreduced benzene rings of the type (IV) where the symbols X and X' represent hydrogen atoms, methyl groups or a methylene group. As a result of this observation, these authors decided that emetine must also contain two such unreduced rings of the catechol type, the deduction being made at a time when there was no knowledge of the structure of emetine, apart from the fact that it contained four methoxyl groups.



IV

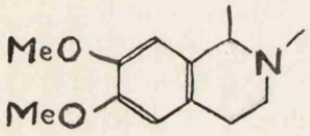


V

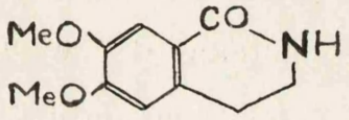
The isolation of m-hemipinic acid (II, p. 16) by Carr and Pyman from the products of oxidation of emetine shows the presence of at least one catechol group in the alkaloid, and the existence of two such groups, as suggested by Dobbie and Fox above, was rendered highly probable by the presence of four methoxyl groups in the molecule, coupled with the fact that the spectrum of one molecular proportion of emetine coincided with that of two molecular proportions of creosol (V).

Although the other oxidation product isolated by Carr and Pyman, 6:7-dimethoxyisoquinoline-1-carboxylic acid (I, p. 16), contains a catechol group, it gave a spectrum entirely different

from that afforded by catechol, and Dobbie and Fox suggested that in emetine the isoquinoline group occurs in a partially reduced condition (VI) but that oxidation deprived it of part of its hydrogen and converted it to the unreduced acid (I, p. 16).



VI

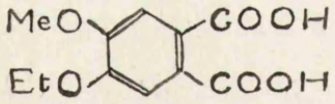


VII

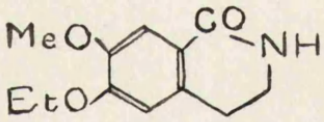
Striking confirmation of this suggestion of Dobbie and Fox was provided by the appearance of corydaldine (VII), a derivative of tetrahydroisoquinoline, among the products of a mild oxidation of emetine employing 2% faintly alkaline permanganate, which was reported by Späth and Leithe (28) in 1927. Their oxidation also furnished m-hemipinic acid (II, p. 16) in yields which led them to conclude that emetine contained two structural units capable of oxidation to this acid, and support was lent to the idea when it was found that a similar oxidation of cephaeline, which contains only three methoxyl groups and therefore at most one dimethoxyisoquinoline nucleus, gave only half the yields of corydaldine and m-hemipinic acid that were obtained from emetine.

The best evidence that emetine contained two dimethoxy-tetrahydroisoquinoline ring systems, and incidentally two rings of the catechol type as suggested by Dobbie and Fox (p. 17), was obtained by Späth and Leithe (28) from a study of O-ethyl-cephaeline, which differs from emetine only in that one of the methoxyl groups of the latter alkaloid has been replaced by an

ethoxyl group. These authors subjected O-ethylcephaeline to their mild oxidation with permanganate, from which reaction an inseparable mixture was obtained, further oxidation of this mixture leading to the formation both of m-hemipinic acid (II, p. 16) and the anhydride of 4-methoxy-5-ethoxyphthalic acid (VIII). Since these two different phthalic acid derivatives had originated from the single compound, O-ethylcephaeline, and because of the close relationship existing between this substance and emetine, it followed that the alkaloid must contain two ring systems capable of oxidation to m-hemipinic acid.



VIII



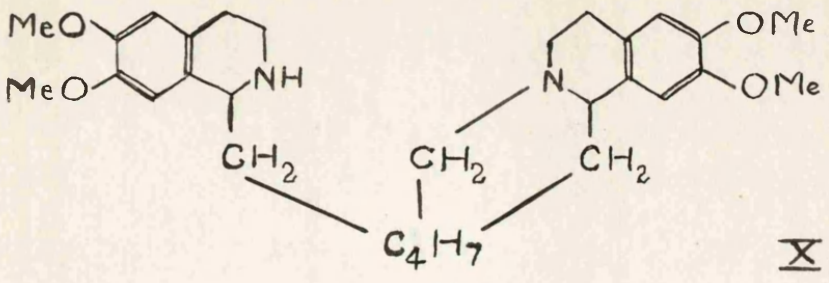
IX

The melting point of the inseparable mixture, obtained by the direct oxidation of O-ethylcephaeline, was found to be raised by admixture both with corydaldine (VII, p. 18) and 1-keto-7-methoxy-6-ethoxy-1:2:3:4-tetrahydroisoquinoline (IX), and the melting points of derivatives of this mixture were similarly raised by admixture with the corresponding derivatives of the two compounds. On this evidence, Späth and Leithe assumed that the two compounds mentioned were actually present in the inseparable mixture, since this would account for the formation of m-hemipinic acid and 4-methoxy-5-ethoxyphthalic acid on further oxidation, as explained in the previous paragraph.

Whilst it must be admitted that Späth and Leithe were unable

fully to characterise the corydaldine and 1-keto-7-methoxy-6-ethoxy-1:2:3:4-tetrahydroisoquinoline which they assumed were present in the mixture, the deductions which they made on that assumption have stood the test of time and have been supported recently by work (29, 30) to which reference will shortly be made. These deductions were that since the two different isoquinoline derivatives had been formed from O-ethylcephaeline, then this latter substance, and also emetine itself, must contain two tetrahydroisoquinoline nuclei, and since in both the products of the oxidation the C-1 was obtained in oxidised state, then in the O-ethylcephaeline and in emetine the 1-position must be the point of attachment of the rest of the molecule to each tetrahydroisoquinoline nucleus, as in the structure (VI, p. 18).

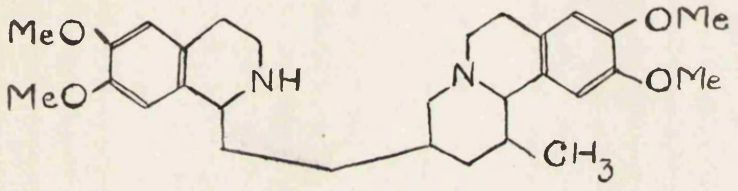
On the basis of these deductions, and bearing in mind that emetine was known, from the results of degradation experiments in the Hofmann manner (p. 11), to contain a secondary nitrogen atom present in a single ring and a tertiary nitrogen atom which was common to two rings, Späth and Leithe in 1927 put forward for emetine the partial structure (X).



X

Although at that time there was no experimental evidence available to throw light on the nature of the hydrocarbon chain

connecting the two isoquinoline residues, Brindley and Pyman (24), in the same year, published a complete structure (XI) for the alkaloid which was in harmony with that proposed by Späth and Leithe but which had been derived independently of the results of these latter authors.

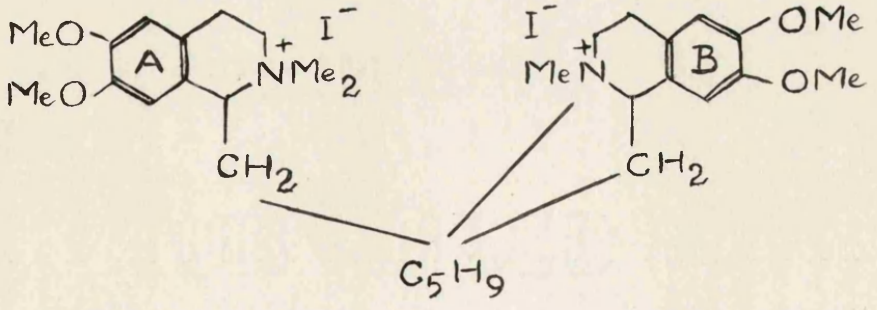


XI

The speculative formula of Brindley and Pyman, based on the hypothetical phytochemical origin of the isoquinoline alkaloids, was able to afford an explanation of the properties of emetine which were known at that time, and from this formula the authors deduced satisfactory constitutions for the derivatives of emetine, including the four remaining ipecacuanha alkaloids. Only with the recent publication of the results of Späth and Pailer (29, 30) has the formula proposed by Brindley and Pyman become untenable.

MODERN DEVELOPMENTS IN THE CHEMISTRY OF EMETINE

For a number of years, researches under the direction of Dr. H. T. Openshaw have been performed with a view to elucidating the structure of that part of the emetine molecule lying between the isoquinoline nuclei in the partial formula (X, p. 20), proposed by Späth and Leithe (28) in 1927. By employing the exhaustive methylation technique of Hofmann and oxidising certain nitrogen-free substances so obtained, considerable light has been thrown on the arrangement of the seven carbon atoms in question. Within the last twelve months, Späth and Pailer (29, 30) have described independent, but closely parallel, experiments and in the present discussion reference will be made to the reports of these authors, since the results of the British workers still await publication.

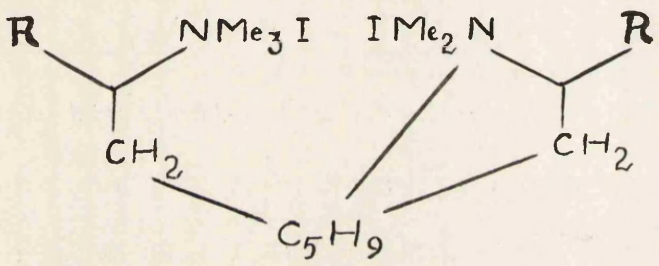


XII

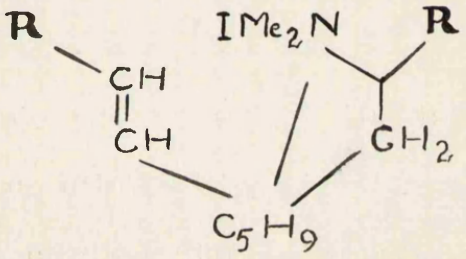
Emetine was completely methylated (29) using methyl iodide, with the formation of N-methylemetine dimethiodide (XII). The dimethiodide was converted by means of silver oxide into the corresponding diquaternary base and this decomposed, with removal of two molecules of water, by heating under reduced pressure. The resulting methine base contained two double bonds which were

saturated by catalytic hydrogenation.

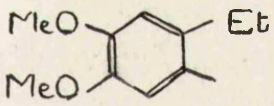
On boiling the reduced methine base for six hours with methyl iodide in methyl alcohol, there was formed not the expected dimethiodide (XIII) but the monomethiodide (XIV), together with trimethylamine hydriodide.



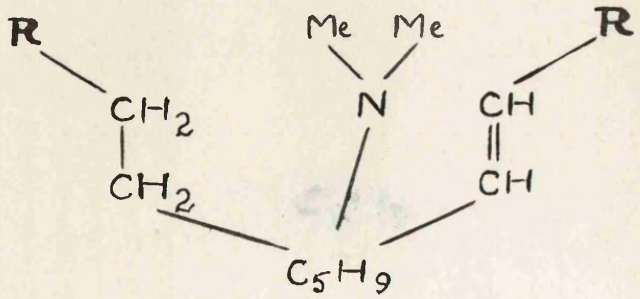
XIII



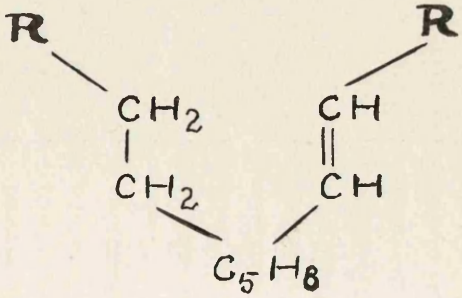
XIV

R– = 

The elimination of nitrogen normally occurs only on heating the quaternary hydroxide and this instability of the methiodide (XIII) presented a special case of the Hofmann degradation which had not been previously described.



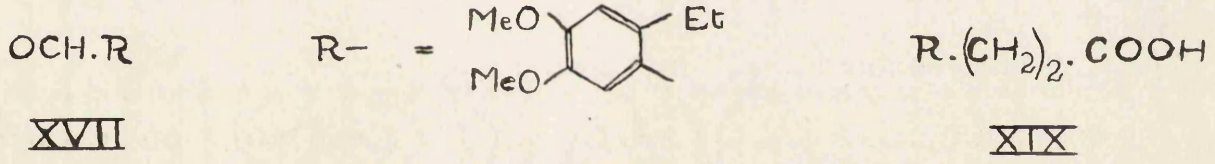
XV



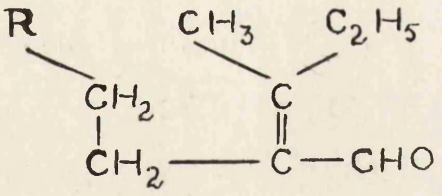
XVI

The unsaturated monomethiodide (XIV) was converted into the corresponding methochloride and hydrogenated, the quaternary base liberated by means of silver oxide and decomposed by heat in the normal Hofmann manner, to give the singly unsaturated

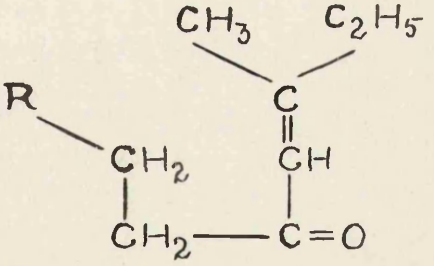
base (XV). The next step of the Hofmann degradation, carried out on the base (XV) without preliminary reduction of the double bond, furnished the nitrogen-free compound (XVI), containing two unsaturated linkages, and this was subjected to ozonolysis. Among the products of decomposition of the ozonide were detected 3:4-dimethoxy-6-ethylbenzaldehyde (XVII) and an unsaturated ketonic compound (XVIII), whose semicarbazone was shown by analysis to have the constitution $C_{19}H_{29}O_3N_3$.



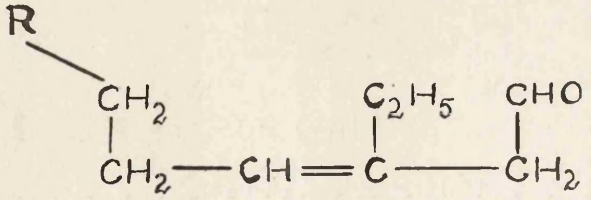
XVII XIX



XVIII A



XVIII B

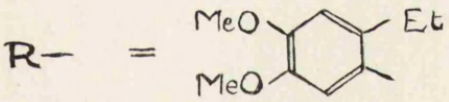


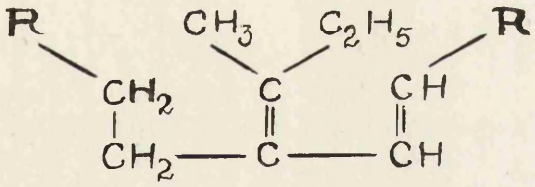
XVIII C

Three formulae (XVIIIA, XVIIIB and XVIIIC) are possible for this ketonic compound which would explain the formation from it, by further oxidation, of methyl ethyl ketone and 3:4-dimethoxy-6-ethylhydrocinnamic acid (XIX), although Späth and Pailer consider only the formulae (XVIIIA and XVIIIB). The formation of methyl ethyl ketone by oxidation of an aldehyde of structure (XVIIIC)

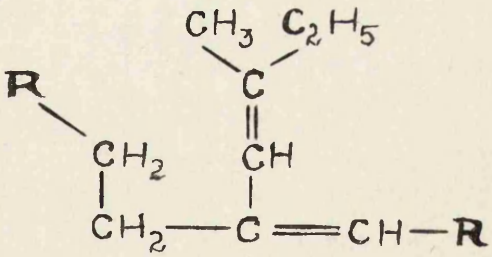
could come about by decarboxylation of the primary oxidation product, propioacetic acid.

Further, it is possible to deduce from the structures (XVIII) three formulae (XVIA, XVIB and XVIC) for the final degradation product, the ozonolysis of which gave rise to 3:4-dimethoxy-6-ethylbenzaldehyde (XVII) and to the ketonic compound (XVIII). The fully saturated, final Hofmann degradation product is thus represented by one or other of the formulae (XXA, XXB and XXC) of which only two (XXA and XXB) are proposed by Späth and Pailer.

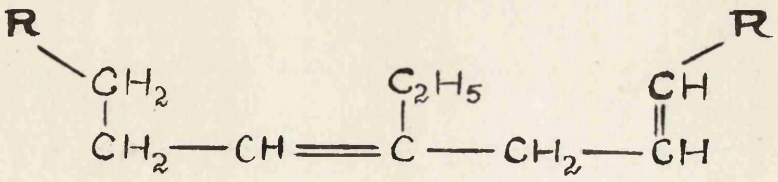




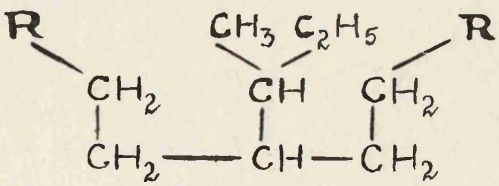
XVI A



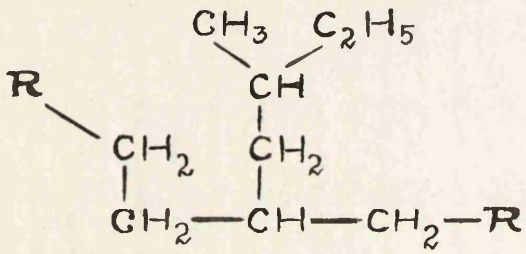
XVI B



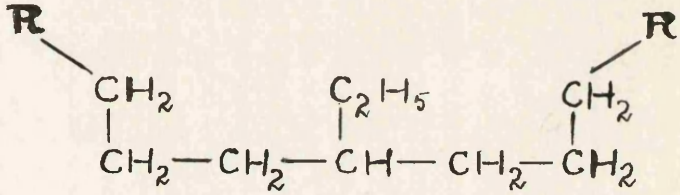
XVI C



XX A

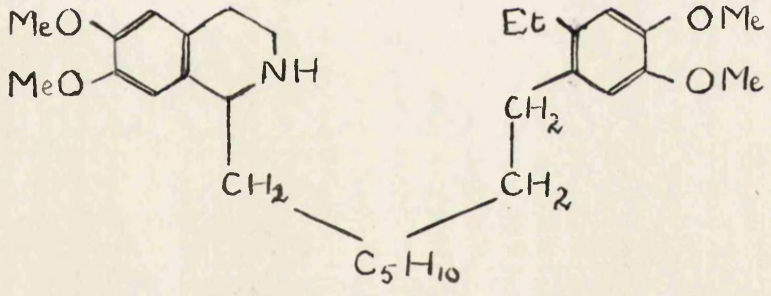


XX B



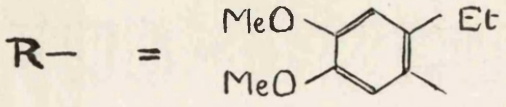
XX C

From the results described in a further paper by the latter author (30), it is possible to distinguish between the symmetrical formulae (XXA and XXC) and the unsymmetrical formula (XXB). After acetylation to protect the secondary nitrogen atom, emetine was subjected to the Hofmann degradation and in this way Pailer ensured that the nitrogen atom eliminated as trimethylamine was that which had been the tertiary nitrogen atom of emetine. Hydrogenation and deacetylation furnished the free isoquinoline base (XXI).



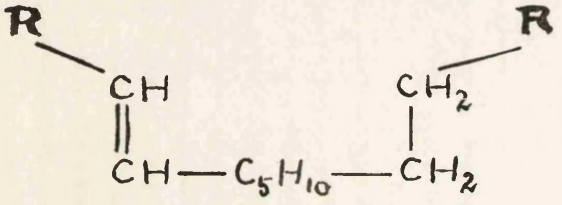
XXI

By continuing the Hofmann degradation on this base, and hydrogenating only after the first of the two remaining steps, he finally obtained the unsaturated, nitrogen-free compound (XXII)

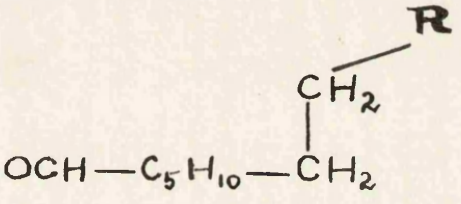


R.CHO

XVII



XXII



XXIII

Cleavage of the ethylenic bond by ozonolysis furnished 3:4-dimethoxy-6-ethylbenzaldehyde (XVII) and the saturated ketonic body (XXIII) which was proved, by direct comparison of the semicarbazones, to be identical with the ketone resulting from the hydrogenation of the unsaturated ketonic body (XVIII, p. 24).

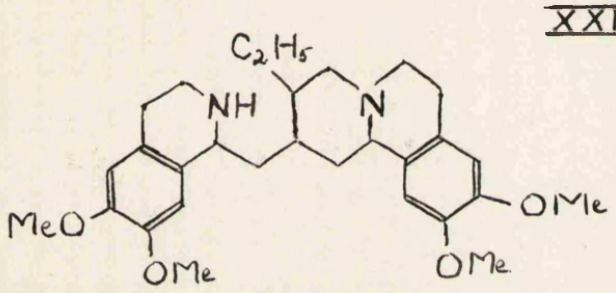
On account of the identity of these two cleavage fragments, in which the ethylveratryl residue is derived in the first instance from ring A and in the second instance from ring B of the structure (XII, p. 22), the unsymmetrical constitution (XXB, p. 25) for the saturated, nitrogen-free Hofmann degradation product of emetine is eliminated.

The fact that, during degradation in the Hofmann manner, 6-ethylveratryl residues are formed from both ends of the emetine molecule is additional evidence of the presence in the alkaloid of two dimethoxytetrahydroisoquinoline nuclei, with the rest of the molecule attached in both cases at the 1-position. This further confirms the correctness of the assumptions (p. 20) underlying the deductions made by Späth and Leithe (28) from the results of their oxidative degradations of emetine and its derivatives, in putting forward their partial formula (X, p. 20).

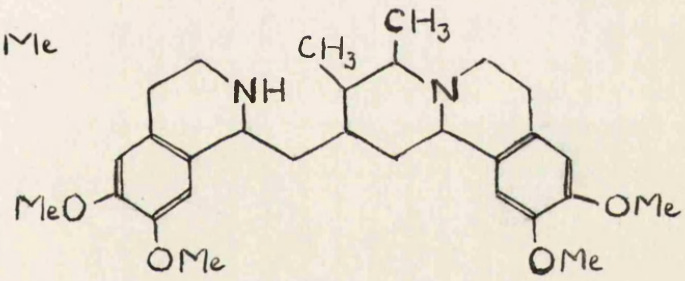
With the knowledge that exhaustive methylation in the Hofmann manner, followed by hydrogenation, finally results in the formation of a symmetrical, nitrogen-free compound (XXA or XXC, p. 25), the partial formula (X, p. 20) of Spath and Leithe may now be modified to include the information which has been gained with regard to the portion of the molecule lying between

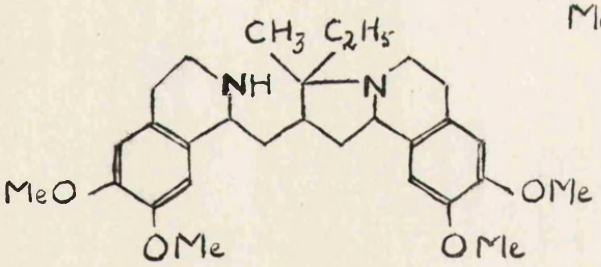
the two tetrahydroisoquinoline nuclei. There are three constitutions possible for emetine (XXIV, XXV and XXVI) which would account for the production of the compound (XXA, p. 25), and one (XXVII) from which could be derived the compound (XXC, p. 25), in the Hofmann degradation.

XXIV

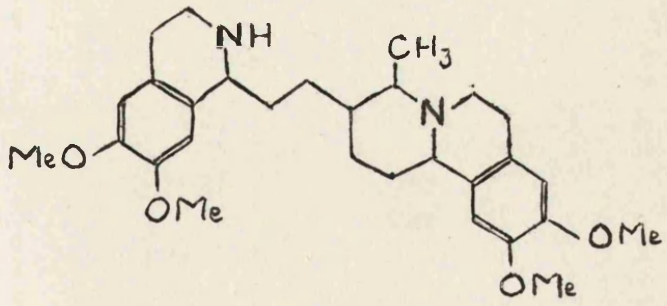


XXV





XXVI



XXVII

Of these four structures, none coincides with the speculative formula (XI, p. 21) put forward by Brindley and Pyman in 1927. With the appearance of the results of Späth and Pailer, therefore, the formula (XI) was eliminated from further consideration.

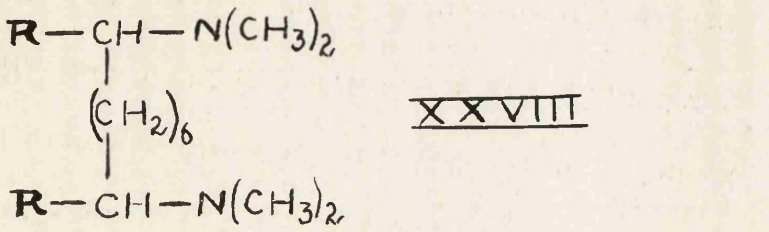
Two possibilities (XXV and XXVII) have been made untenable

by researches, as yet unpublished (33), carried out at St. Andrews. Exhaustive methylation in the Hofmann manner, hydrogenating after each stage except the last, furnished a compound from which the two nitrogen atoms had been eliminated and which contained one double bond. This singly unsaturated, nitrogen-free material could be formulated in seven different ways from a consideration of the steps involved in its production from emetine, itself capable of representation in four ways.

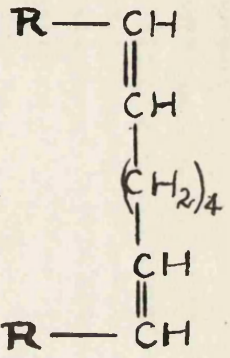
Ozonolysis of this singly unsaturated, nitrogen-free material derived from emetine gave a complex ketone, together with formaldehyde, and inspection of the seven possible structures for the unsaturated material showed that only that derived from the emetine formula (XXIV) and one of the three derived from the formula (XXVI) were capable of fission to formaldehyde and a complex ketone under such conditions. Two of the proposed structures for emetine were thereby eliminated and only the formulae (XXIV and XXVI) remain between which a decision must yet be made.

In course of the description of the researches performed by Späth and Pailer (29), it was pointed out (p. 23) that the unexpected decomposition of the methiodide (XIII) derived from emetine presented a special case of the Hofmann degradation which had not been previously described. Pailer and Bilek (31) studied this reaction in the cases of two derivatives of benzylamine (XXVIII and XXIX), which were easily obtained synthetically, in order to establish whether the splitting off of nitrogen from a methiodide under such mild conditions was to

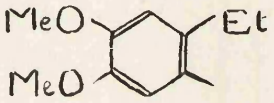
be ascribed to the influence of the special structure of emetine, or whether this was a general reaction of such methiodides.

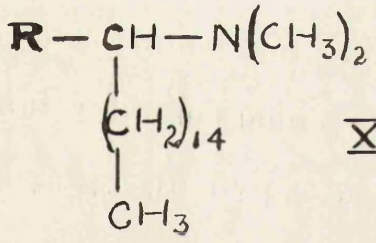


XXVIII

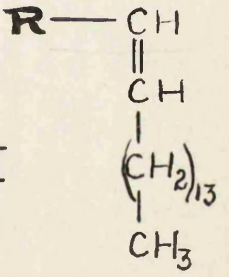


XXX

R = 



XXIX

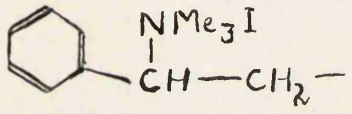


XXXI

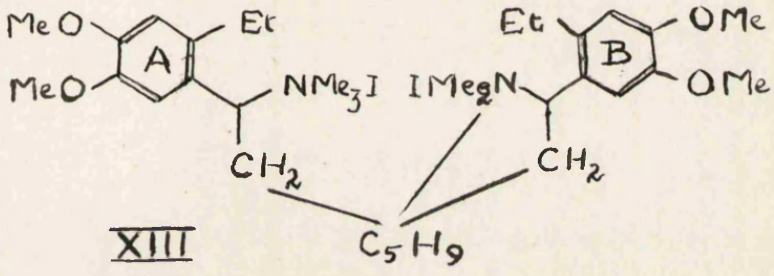
When the compound (XVIII) was heated for twelve hours with methyl iodide and methyl alcohol in a sealed tube at 95 to 100°, almost complete removal of the two nitrogen atoms occurred, with formation of the unsaturated compound (XXX) together with trimethylamine hydriodide. Similar treatment of the base (XXIX) caused complete cleavage of the nitrogen and the compound (XXXI) was isolated. In neither case was any reaction observed if the heating was carried out in the absence of methyl iodide, showing that cleavage was dependent on the formation of methiodide.

Model experiments, somewhat analogous to those of Pailer and Bilek just described, have been carried out by the present

author and formed the basis of a previous thesis (32). With a view to elucidating the reasons for the unexpected instability of the dimethiodide (XIII) derived from emetine, which had been detected (33) independently of Späth and Pailer, a study was made of the behaviour at 100° of a number of methiodides containing the ∝-alkylbenzylamine structure.



XXXII



XIII

Whereas Pailer and Bilek (31) deduced from the study of their two methiodides that thermal instability was a property common to substances containing the structure (XXXII), in our experiments only in certain cases was cleavage of trimethylamine hydriodide observed, and from the results obtained we were able to show that the instability of the dimethiodide (XIII) is due mainly to the presence in the benzylamine ring A of a methoxyl group in the position para to the side-chain carrying the nitrogen.

DEHYDROGENATION

Introduction

In the broadest sense, dehydrogenation is any reaction to which a compound may be subjected which furnishes a product less rich in hydrogen than the original material. This definition includes, not only the usual conversions of hydroaromatic to aromatic compounds, but also the conversion (34) of benzylamine into benzonitrile by passing over catalytic nickel at 300 to 350°, and the conversion (35) of alcohols into aldehydes and ketones by means of copper at 250 to 300°, reactions which involve the direct removal of hydrogen from the starting materials and which are therefore justly to be termed dehydrogenations. The definition also includes, however, the classical conversion of alcohols into aldehydes by the action of dichromate and acid which is not normally considered to be a dehydrogenation, although Hans Meyer (36), in his list of dehydrogenation methods, includes the common oxidising agents such as chromic acid, manganese dioxide and nitric acid.

Reactions involving the conversion of hydroaromatic to aromatic compounds have long been known. In 1879, Hofmann (37) was first led to suspect a close relationship between pyridine and piperidine when he obtained, by the action of bromine on the latter base, a dibromohydroxypyridine. During the next few years the oxidation of piperidine to pyridine was performed by a number of reagents, including concentrated sulphuric acid at 300° (38) and nitrobenzene at 260° (39). Konowaloff (40) in

1887 and Markovnikoff (41) in 1892 were able to convert homologues of cyclohexane to brominated aromatic hydrocarbons by means of bromine and aluminium bromide, a reaction which formed the basis of von Baeyer's exhaustive bromination technique (42) for the derivation of ring structure in the terpene field.

The very numerous reagents used by the early workers have been superseded, however, by the modern dehydrogenation agents sulphur, selenium and catalytic metals, although a variety of methods still finds application in particular cases, an example being the exhaustive bromination technique of von Baeyer which has recently been employed (43) for the conversion of hydroaromatic ketones to phenols.

In the present account, discussion will largely be confined to those reactions in which sulphur, selenium, the catalytic metals or others of the small number of recently developed reagents are used to bring about the conversion of cyclic compounds relatively rich in hydrogen into their aromatic counterparts, the aromatic substances concerned being either homo- or heterocyclic.

The catalytic method

Of the dehydrogenation methods in general use at the present time, that involving the metallic catalysts was the first to be studied systematically.

In the early years of the present century Sabatier (44) decided, on theoretical grounds, that the catalysts with which

he had successfully carried out the hydrogenation of a large variety of substances must be capable of facilitating the reverse change. He was able to verify his deduction experimentally and by the action of finely divided nickel on cyclohexanol and upon cyclohexylamine above 350° he obtained phenol and aniline respectively. The dehydrogenation of piperidine to pyridine (45) over the same catalyst was found to proceed at 250°, and the ease of conversion of piperidine to pyridine was correlated by Sabatier (44) with the difficulty experienced in bringing about the reverse change, hydrogenation of pyridine over nickel at 120 to 220° having led (45) merely to ring cleavage with formation of amylamine and, at higher temperatures, of n-pentane and ammonia. In the case of benzene, Sabatier and Mailhe found (46) that this substance was formed from cyclohexane over nickel at 270 to 280°, but that methane appeared as a byproduct. In the presence of hydrogen and at 180° (44) the reverse reaction occurred.

Following up these investigations, Zelinsky (47) in 1911 observed that the dehydrogenating activity of the noble metals on cyclohexane and its homologues was appreciable at 170 to 200°, within which range Sabatier had demonstrated hydrogenation over nickel, and became maximal at about 300°, the reaction proceeding smoothly without ring fission and the formation of methane. The noble metals brought about the rapid reduction of benzene to cyclohexane at 100° and Zelinsky later showed (48) that, whereas attempted hydrogenation of pyridine to piperidine

over nickel had caused only ring fission, quantitative formation of piperidine occurred over platinum and palladium catalysts at 150°, and by raising the temperature to 250° piperidine was smoothly converted to pyridine.

Platinum, palladium and nickel are the most fully investigated of the dehydrogenation catalysts, the first two being the most satisfactory on account of the lower temperatures at which they act, and owing to the risk of elimination of hydrocarbon fragments and other side reactions attendant upon the use of the last metal. There seems to be no fundamental difference between the behaviour of platinum and that of palladium, and in any particular experiment the choice between the two is usually made on the basis of their availability and current prices.

Sulphur

Of the "chemical" dehydrogenating agents, we are indebted to Ruzicka for the first systematic investigation of the capabilities of sulphur in this respect, although there are many isolated instances in the literature of dehydrogenations carried out by means of the element before the studies of this author began in 1921. As early as 1874, Curie (49) had noted the formation of a crystalline hydrocarbon when sulphur was heated with colophony and the same hydrocarbon, later recognised (50) as retene, was obtained by Kelbe (51) by analogous treatment of the rosin oil formed on dry-distillation of colophony. In 1903, Vesterberg showed (52) that it was from the dehydrogenation of abietic acid, the chief compound present in colophony, that the

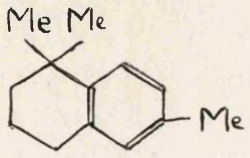
retene observed by the earlier workers was derived.

At that time, however, the general importance of the dehydrogenation method was not realised, and it was in the hands of Ruzicka that the method achieved its first great success, in the sesquiterpene field. In a review (53) of his researches in this field, Ruzicka points out that up till 1921 very little progress had been made in the chemistry of the sesquiterpenes, since the complex molecules of these substances were open to attack by oxidising agents at several points at once. Oxidative degradation, the method usually employed in researches into the structures of these materials, frequently led, therefore, either to the formation of inseparable mixtures or to the isolation of no tangible product of molecular weight higher than that of acetic acid or carbon dioxide.

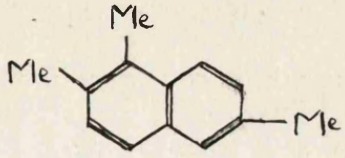
By employing the dehydrogenation method in the study of the constitutions of the sesquiterpenoid compounds, Ruzicka hoped to convert the complex molecules, where there was a suitable arrangement of the carbon skeleton, into basal aromatic bodies with the same disposition of the carbon atoms. These aromatic molecules, being more strongly built than those from which they were derived, should yield more characteristic degradation products and also be easier to synthesise. With a knowledge of the fundamental carbon skeleton, the second problem, the elucidation of the position of the double bonds and oxygen-containing substituents in the terpene molecules, would be greatly facilitated.

At that period the three principal methods available for

the conversion of hydroaromatic into the corresponding aromatic compounds were catalytic dehydrogenation, exhaustive bromination and heating with sulphur. Of these catalytic dehydrogenation, despite its cleanness, was rejected by Ruzicka because of certain disadvantages inherent in the method, which were particularly undesirable in the sesquiterpene field. The reaction temperature for instance, lying between 250 and 300°, was too high to exclude the possibility of a change in the carbon skeleton of these compounds during dehydrogenation. Again, Zelinsky (54) showed that the presence of quaternary carbon atoms in a ring, as for example in 1:1-dimethylcyclohexane, hindered dehydrogenation over metallic catalysts. The exhaustive bromination method was also rejected by Ruzicka on account of the possibility of side reactions, and because of the observation of von Baeyer and Villiger (55) that in the presence of a quaternary carbon atom dehydrogenation by this method took place with wandering of a methyl group, ionene (XXXIII) thus giving rise to 1:2:6-trimethylnapthalene (XXXIV).



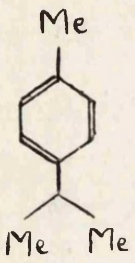
XXXIII



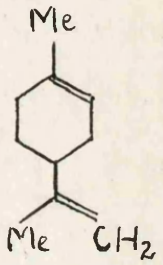
XXXIV

Before applying the technique of dehydrogenation with sulphur to the problem of structure determination in the sesquiterpene field, Ruzicka realised the necessity for testing the method on known compounds, since it had been so seldom

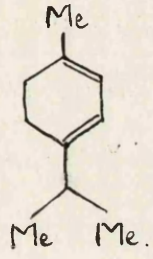
applied previously. Since p-cymene (XXXV) resulted from the dehydrogenation with sulphur of the simple monoterpenes limonene (XXXVI) and terpinene (XXXVII),



XXXV



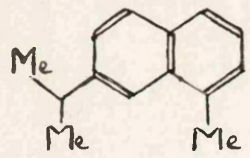
XXXVI



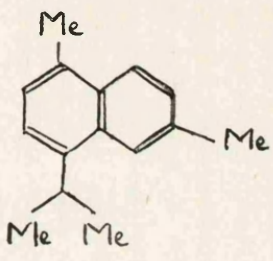
XXXVII

it followed that no alteration of the carbon skeleton accompanied the loss of hydrogen, and the method using sulphur was trustworthy in this respect. Ruzicka noticed that the yield of p-cymene from terpinene (50%), in which the double bonds both lie in the ring, was greater than the yield from limonene (15%), in which one double bond is exocyclic.

On applying the method to natural compounds, Ruzicka was able to show (56) that all the known dicyclic sesquiterpenes could be converted by the action of sulphur at about 200° into one of the two derivatives of naphthalene, either eudalene (XXXVIII) or cadalene (XXXIX), whose structures were shown by synthesis (57).

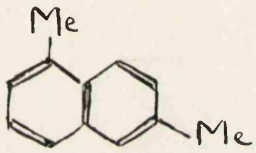


XXXVIII

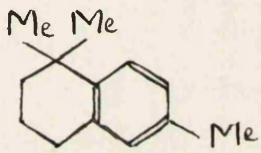


XXXIX

The fact that widely varying yields of cadalene and eudalene resulted from dehydrogenation of the natural materials, was attributed to the various endocyclic or exocyclic locations of the ethylenic linkages of the sesquiterpenes, since the position of the double bonds had been shown to exert an influence on the ease of dehydrogenation of the monoterpenes limonene and terpinene, as mentioned in the previous paragraph.



XL



XXXIII

In 1927, Ruzicka and Rudolph (58) were able to demonstrate the formation of 1:6-dimethylnaphthalene (XL) in 10% yield by dehydrogenation of ionene (XXXIII) with sulphur at 180 to 250°. This they took as an indication of the superiority of the sulphur method over the exhaustive bromination method and that involving the catalytic metals, since dehydrogenation by the last mentioned procedure was known from Zelinsky's work on 1:1-dimethylcyclohexane (p. 37) to be hindered by the presence in a ring of a quaternary carbon atom, and dehydrogenation of ionene by exhaustive bromination (p. 37) had been accompanied by migration of a methyl group, whereas using sulphur the hindering group was cleanly eliminated. It must be borne in mind, however, that Linstead and Thomas (59) have recently dehydrogenated ionene (XXXIII) with palladised charcoal at 310° with elimination of the hindering methyl group and formation of 1:6-dimethylnaphthalene (XL) in 89% yield.

Selenium

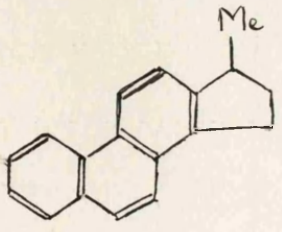
The use of selenium as a dehydrogenation agent was first recorded by Diels, Gädke and Körding (60) in 1927. In the course of their researches on cholesterol, Diels and Gädke (61) had observed the formation of large amounts of chrysene by the dehydrogenation of this sterol with palladised charcoal and they were of the opinion that the chrysene had not been built up by a complex pyrosynthesis from simple molecules, since its appearance had also been observed in the catalytic dehydrogenation of the hydrocarbon $C_{19}H_{18}$, obtained by pyrolysis of cholesteryl chloride, but that it had been derived in some way from the skeleton of cholesterol, perhaps with intervention of the side chain.

In view of these results, it appeared to them of great importance to seek a dehydrogenation method which would work more mildly and at a lower temperature than the catalytic procedure, and which would thereby furnish products of value in determining the structure of cholesterol. Sulphur was first considered, but the use of this element was excluded in the case of cholesterol and its derivatives on account of the unpleasant properties which it was known to exhibit. On the one hand dehydrogenation with sulphur frequently proceeded too far, occasionally to carbonisation, and on the other hand often led to the introduction of sulphur into the organic molecule. More recent examples of this latter tendency are cited by Fieser (62) and by Ruzicka and van Veen (63).

Turning to selenium, Diels and his co-workers found (60) in this element, which had not previously been employed for this purpose, an extremely useful dehydrogenation agent. As had been

the case with sulphur (p. 38), the course of dehydrogenation reactions using selenium had first to be studied on known compounds, and from the results of such trial experiments these authors were able to report that the new material had shown itself superior to sulphur in all cases. They claimed that not only did selenium succeed in many instances where sulphur had failed, but that the yields of the dehydrogenation products obtained by the use of selenium were often multiples of those observed when sulphur was the reagent.

Although the assertion that selenium was superior to sulphur in all cases has not since proved unexceptionable, nevertheless selenium has found wide application as a dehydrogenation agent. On applying it to cholesterol and its derivatives, Diels (60) noted the formation in all cases of a well crystalline hydrocarbon $C_{18}H_{16}$ as the main product, the hydrocarbon which now bears his name and which has been proved (64) to have the structure (XLI).



XLI

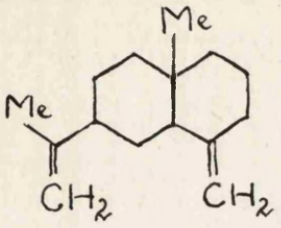
The nature of the materials resulting from such experiments led Rosenheim and King (65) and Wieland and Dane (66), in 1932, to a new and now generally accepted formulation of the entire sterol chemistry.

Dehydrogenation of alicyclic compounds

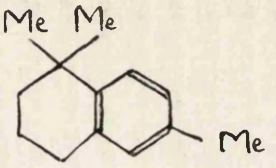
The use of dehydrogenation in the examination of natural products of complex hydroaromatic structure has increased very greatly during the past twenty-five years, during which period information has gradually been accumulating on the control of the various dehydrogenation processes by the study of substances of known structure. The large and scattered literature on this subject which had grown up prior to 1936 was admirably reviewed by Linstead (67) in that year, and more recent work is described in modern text-books (68). A recapitulation of these writings would be out of place in the present discussion and mention need only be made of the salient features which emerge therefrom.

Dehydrogenation with sulphur is usually carried out in the temperature range 180 to 250°, whereas selenium, being less reactive, requires heating to between 280 and 300°, but usually results in better yields and less side reaction. Catalytic dehydrogenation is accomplished in a temperature range similar to that of selenium.

Fully hydrogenated compounds are more resistant to dehydrogenation than those less distantly removed from the aromatic state, this being especially true in the case of sulphur and selenium. Thus tetralin is rapidly dehydrogenated catalytically at 185° (69) whereas decalin requires a temperature of 300° (70). In the case of selenium this latter compound is scarcely affected even at 350° (71).



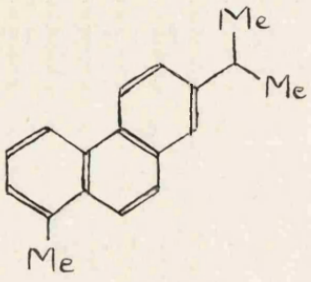
XLII



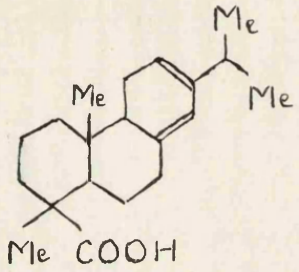
XXXIII

In some cases dehydrogenation is hindered by the presence of groups, such as the methyl and the geminal dimethyl groups of selinene (XLII) and ionone (XXXIII) respectively, attached to a quaternary carbon atom which is a member of a ring. These groups cannot survive the reaction and are normally eliminated during dehydrogenation with sulphur, but the yields are lower than would be obtained from similar compounds not containing such groups, and therefore capable of conversion to the aromatic state without the necessity for fission of C-C bonds. In the case of selenium, these hindering groups are eliminated in like manner providing that the starting material is not fully saturated, in which case dehydrogenation by this reagent is resisted. The work of Zelinsky gave support to the original supposition that catalytic dehydrogenation was completely inhibited by the presence of quaternary methyl groups, and although recent results, of which the most striking was the isolation of retene (XLIII) in 90% yield by Ruzicka and Waldmann (72) from the catalytic dehydrogenation of abietic acid (XLIV), do not confirm this opinion, nevertheless substances containing groups attached to quaternary carbon atoms offer considerable resistance towards dehydrogenation over metallic catalysts and

in many cases the reaction cannot be realised.



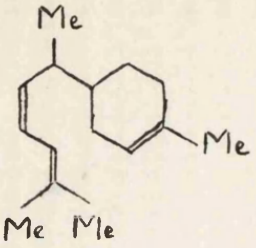
XLIII



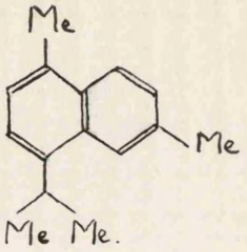
XLIV

Non-quaternary methyl groups are not eliminated during dehydrogenation but heavier side chains usually are, particularly at the relatively high temperatures normally employed with selenium or the catalytic metals, the best known example of this being the formation of chrysene from cholesterol (p. 40). On the other hand, a number of dehydrogenation products have been reported containing isopropyl, n-propyl, t-butyl (73) and even heavier side chains (74). Where the side chains are retained, exocyclic double bonds are reduced.

When dehydrogenation is used for structural determination work, it is fundamentally important that migration of methyl groups, cyclisation, ring fission and other rearrangements should not occur, and fortunately this is usually found to be the case when dealing with six-membered rings. Cyclisation such as that of zingiberene (XLV) to cadalene (XXXIX) during sulphur dehydrogenation is uncommon, although several examples of the



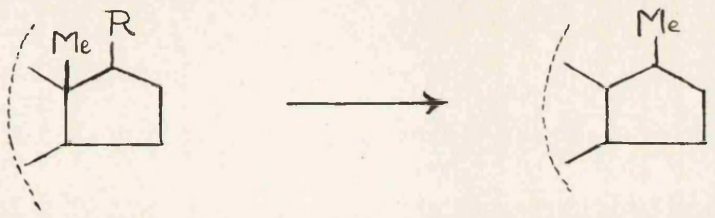
XLV



XXXIX

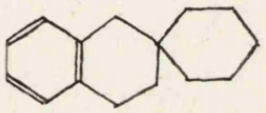
formation of new rings have been reported when selenium has been employed, but usually only at temperatures in the region of 420°. Cyclisation is occasionally observed under the conditions of catalytic dehydrogenation, one example being the formation of phenanthrene (75) from $\alpha\beta$-diphenylethane over palladised charcoal at 300°.

The migration of methyl groups without the simultaneous elimination of some other group is very uncommon, although conflicting results have been obtained by Haworth and co-workers (76) using selenium. Migrations accompanying the elimination of a neighbouring group, such as hydroxyl or a hydrocarbon side chain, are frequent, the best known example being the change in ring D on dehydrogenation of the sterols with the formation of Diels' hydrocarbon. Representing the side chain by R, this change may be symbolised:

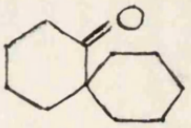


Rearrangement is frequently observed with spiro compounds. Thus 1:2:3:4-tetrahydronaphthalene-2:1'-spirocyclohexane (XLVI)

yields (77) phenanthrene on dehydrogenation with selenium, and naphthalene is formed on similar treatment of the ketone (XLVII) and the corresponding hydrocarbon (78).



XLVI



XLVII

Of the rings other than six-membered, the cyclopropane and cyclobutane rings are normally opened under the conditions of dehydrogenation, whereas five-membered rings are unaffected. The cycloheptane and cyclooctane rings resist the action of selenium at 350°, but rearrangements occur at higher temperatures. Over a platinum catalyst at 420°, 1:1:2-trimethylcycloheptane has been dehydrogenated (71) to a trimethylbenzene.

The fate of oxygen-containing groups during dehydrogenation by the different reagents is various. Selenium is particularly prone to reduce or eliminate such groups, but cases are known of the survival of aromatic methoxyl groups and of the formation of phenols from hydroaromatic ketones. There is a decided tendency for the reduction of ketonic and alcoholic groups during catalytic dehydrogenation, but the oxygen is sometimes preserved with the formation of a phenol. Methoxyl groups on aromatic rings survive, as occasionally do carboxyl groups. Sulphur on the other hand normally splits off methoxyl groups, whereas carboxyl groups are not generally affected and this element has been widely used for the dehydrogenation of

carboxylic acids derived from tetralin and tetrahydrophenanthrene. Here again ketones are usually reduced, but phenol formation is not unknown.

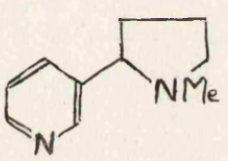
Although the reaction mechanism of dehydrogenation is but little understood, empirical deductions, based on observations of the type just described, enable prediction to be made as to the probable course of the reaction in particular cases. Linstead (67) suggests that the catalytic and "chemical" processes must be essentially different. Catalytic dehydrogenation probably comes about by preliminary activation of the hydrogen of the starting material by the metal, followed by elimination of this hydrogen as such, or by its addition to an unsaturated centre (but not an aromatic centre) in the same or a neighbouring molecule. On the other hand, dehydrogenation by means of sulphur or selenium probably involves an addition of the reagent to an unsaturated or an aromatic centre, followed by an elimination of hydrogen sulphide or selenide. Such a difference in mechanism would account among other things for the fact that saturated hydroaromatic compounds are dehydrogenated smoothly over catalysts, but not by sulphur or selenium under normal conditions.

The dehydrogenation of heterocyclic compounds

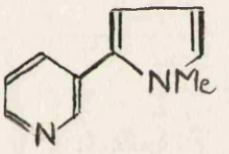
Although the major portion of the observations made in the previous section with respect to alicyclic compounds are equally applicable to the heterocyclic bodies, nevertheless some points of interest may be mentioned which particularly

concern these latter substances, of which those containing nitrogen have been fairly thoroughly investigated.

It has been remarked (p. 35) that piperidine may be smoothly dehydrogenated to pyridine over noble metal catalysts. The five-membered rings of pyrrolidine (79) and nicotine (XLVIII) (80) are likewise dehydrogenated with the formation of pyrrole and nicotyrine (XLIX) respectively, in striking contrast to the stable five-membered homocyclic rings (p. 46).

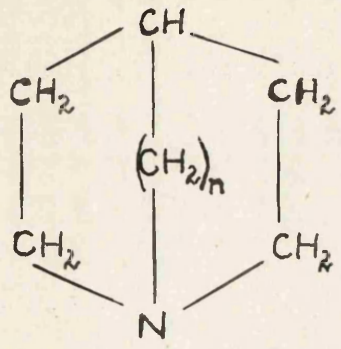


XLVIII

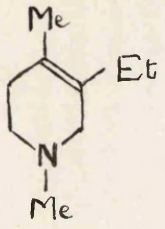


XLIX

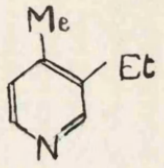
The presence of a tertiary nitrogen atom in a piperidine ring presents an analogy with the case of hindering groups attached to quaternary carbon atoms (p. 43) in that fission of a N-C bond must accompany dehydrogenation. That such fission can occur is exemplified in recent work by Prelog, in which the compound (L, n = 1) and quinuclidine (L, n = 2) were converted (81) by palladised charcoal at 320° and by selenium at 350° to to γ-picoline and 4-ethylpyridine respectively. Similarly, 1:4-dimethyl-3-ethyl-1:2:5:6-tetrahydropyridine (LI) furnished (82) β-collidine (LII) using selenium at 350°.



L

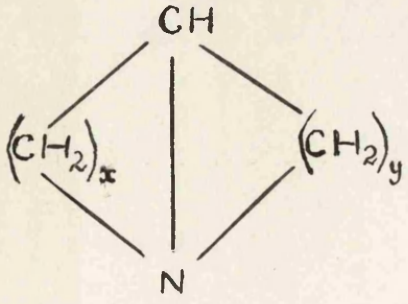


LI

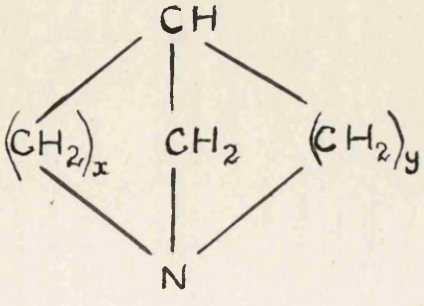


LII

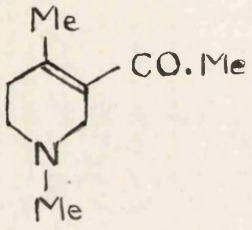
In other cases where the fission of a C-C or a C-N bond would be required in order to give an aromatic compound, results were not so favourable. Thus (81) octahydropyridocoline (LIII, x = y = 4) gave but a trace of quinoline and the bases (LIII, x = 3 or 4, y = 3) and bases (LIV, x = 2 or 3, y = 3) gave no definite products.



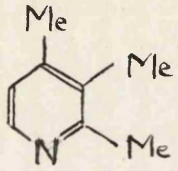
LIII



LIV



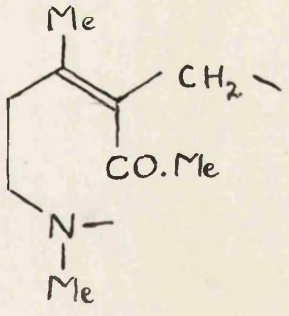
LV



LVI

An interesting example of a rearrangement accompanying dehydrogenation of a reduced pyridine ring was reported by the same school. Dehydrogenation of 3-acetyl-1:4-dimethyl-1:2:5:6-tetrahydropyridine (LV), using both selenium, either at 300° or in boiling xylene, and palladised charcoal at 300°, gave (83) 2:3:4-trimethylpyridine (LVI) in place of the expected

LVII



3-acetyl-4-methylpyridine. The rearrangement similarly occurred with the fully saturated ketone derived from the base (LV), whereas no rearrangement took place in the absence of the keto group, dehydrogenation of the partially reduced pyridine (LI) having led (p. 48) to the formation of the expected product, β-collidine (LII). These two latter cases indicate that the presence of the keto group, but not of the ethylenic linkage, was a necessary condition for rearrangement and in the same and in a following (84) paper, experiments on further compounds are

described which support this view. The suggestion was made (83) that the rearrangement came about by preliminary fission of the bond between the nitrogen atom and the carbon atom β- to the carbonyl group, leading to the formation in the case of the compound (LV) of the intermediate product (LVII), cyclisation and dehydrogenation following.

Applications of Dehydrogenation

By far the most important application of the technique of dehydrogenation is to the problem of the determination of the structure of complex molecules, in which application the aims are those outlined by Ruzicka (p. 36) in the particular case of the sesquiterpenes. Nevertheless, for the sake of completeness mention must be made of the use of this technique in analysis and in synthetic work.

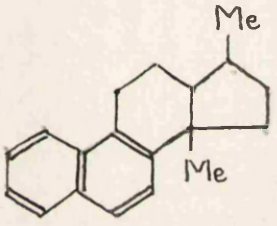
In describing the dehydrogenation activities of the noble metals in 1911, Zelinsky pointed out (47) that of the six- and five-membered aromatic rings only the former were dehydrogenated below 300°, pentamethylene and methylpentamethylene remaining unaffected, as also were the open-chain aliphatic hydrocarbons such as hexane. Twelve months later this author was able to report (85) the successful isolation of pure methylcyclopentane from an artificial mixture of this compound with cyclohexane. After distilling the mixture three times over platinum black at 300° evolution of hydrogen had ceased, and during the process 93% of the hydrogen theoretically available from the cyclohexane had been released. The resulting benzene was removed from the

mixture by shaking with fuming sulphuric acid and methyl-cyclopentane was thereby obtained in the pure state, as was shown by comparison of its physical constants with those of the original synthetic specimen. It was suggested that some of the cyclohexane had doubtless escaped from the apparatus during the reaction, thus accounting for the insufficient evolution of hydrogen. In the same and in a further paper (86), Zelinsky goes on to describe the successful application of the principle of "selective" catalysis to the analysis of mineral oil fractions.

According to Tausz and Putnoky (87), an estimate may be made of the quantity of cyclohexane in a mixture with hexane by measuring the volume of hydrogen liberated over palladium black at 300°. The authors point out, however, that even open-chain aliphatic hydrocarbons slowly liberated hydrogen at that temperature in the presence of their catalyst, so that if the percentage of cyclohexane were low, measurement of the hydrogen evolved did not permit even qualitative detection of this hydrocarbon in the original mixture. The limits of sensitivity of the method were exceeded if the original mixture contained less than one per cent. of cyclohexane and the presence of this latter compound could then be demonstrated only by the detection of benzene in the product of dehydrogenatio

The development of the use of dehydrogenation for the derivation of the structure of complex molecules has led to the necessity for reference substances for comparison with the products obtained in this work. These products are normally

of the polycyclic, aromatic type and the methods developed for their synthesis often involve the dehydrogenation, in the final stage, of more saturated polycyclic materials. Thus, in the synthesis (64) of Diels' hydrocarbon (XLI, p. 41), the last step consisted of the dehydrogenation with selenium of the hydrocarbon (LVIII).



LVIII

In the heterocyclic field, the preparation of substances not readily available otherwise has often been facilitated by the application of the technique of dehydrogenation. Späth and his collaborators have obtained (88) a series of quinoline derivatives by the catalytic dehydrogenation, in over 90% yield, of the corresponding dihydro derivatives, formed by the ring-closure in the Bischler-Napieralski manner of various acyl derivatives of β-phenylethylamine. They similarly obtained (89) papaverine by dehydrogenation of dihydropapaverine, a substance synthetically available (90), and thus opened the way to the technical manufacture of the alkaloid. This latter dehydrogenation has recently been studied by Harlay (91), who concluded that of the catalysts palladium oxide was the most effective, giving 85% conversion, whereas sulphur or (better) selenium gave papaverine in a yield of 50%.

The fact that the nitrogen-containing ring of decahydro-

quinoline parts with hydrogen during dehydrogenation more readily than does the homocyclic ring finds application in the preparation of 5:6:7:8-tetrahydroquinoline, which may be obtained (92) by the partial dehydrogenation of decahydroquinoline. The compound is unobtainable by the partial hydrogenation of quinoline since this process furnishes (93) the 1:2:3:4-tetrahydro derivative of the last mentioned base.

Dehydrogenation agents of recent introduction

In the effort to discover dehydrogenation agents milder in action than those normally employed but yet capable of bringing about the desired result, a number of organic substances have recently been introduced. Although favourable results have often been achieved by their application, in other cases experiments have not been successful, and closer study will be necessary before these new reagents can safely be used in the degradation of natural products.

One of the more frequently applied of the new reagents is chloranil, by means of which Arnold and co-workers (94,95) were able to dehydrogenate a series of partially reduced di- and tricyclic aromatic hydrocarbons. Crawford and Nelson have obtained (96) 70% of 2:3-diphenylnaphthalene from its dihydro derivatives, and note that using selenium the yield was only 55%. Dehydrogenation by chloranil has been successfully applied to a large number of derivatives of tetrahydrocarbazole by Barclay and Campbell (97), who report yields of the corresponding carbazoles lying, in most cases, between

75 and 95%.

Favourable results using isoamyl disulphide have been obtained by Ritter and Sharpe (98). By means of this reagent they were able to convert tetralin into naphthalene in 70% yield and the dehydrogenation of ionene (XXXIII, p. 39) to 1:6-dimethylnaphthalene (XL, p. 39), a process involving fission of a C-C bond, was achieved in a yield of 32% whereas, using sulphur, this latter change furnished only 10% of 1:6-dimethylnaphthalene. The isoamyl mercaptan formed in these reactions was reoxidised to isoamyl disulphide by means of hydrogen peroxide.

Within the last year, Barnes (99) has applied N-bromosuccinimide to the dehydrogenation of a number of partially reduced di- and tricyclic aromatic aromatic hydrocarbons, but although a clean reaction usually took place, the formation of brominated products was observed in some cases.

Conclusion

Apart from its useful applications in analysis and synthesis, since 1921 when, in the hands of Ruzicka, it achieved its first great success in the study of the structure of complex molecules the technique of dehydrogenation has grown steadily in importance, and has been established as a most useful tool for these investigations. Although first applied as such in the sesquiterpene field, it has been responsible for many of the recent advances made in the chemistry of natural compounds including the sterols and bile acids, the D vitamins, the alkaloids and the carcinogenic hydrocarbons.

The results of dehydrogenation experiments on natural substances must be interpreted with discretion owing to the many changes which may occur in the carbon skeleton, particularly where the reaction has been carried out at temperatures above 300°. On the other hand, these changes usually conform to a definite pattern and, with the knowledge which has been derived from experiments on a great number of substances of known structure, they may sometimes be avoided by a judicious choice of reagent and conditions or, alternatively, allowance may be made for them in the interpretation of results.

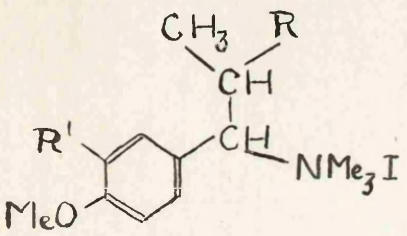
Few methods can compete with dehydrogenation in the determination of the carbon nuclei of complex natural products and as our understanding of the nature of the process increases, so will grow the usefulness of this technique.

THEORETICAL

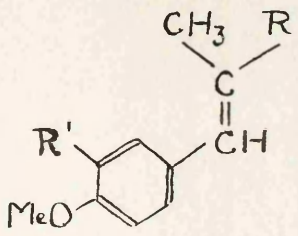
INTRODUCTION

The experimental work which forms the basis of the present thesis may conveniently be divided into four sections.

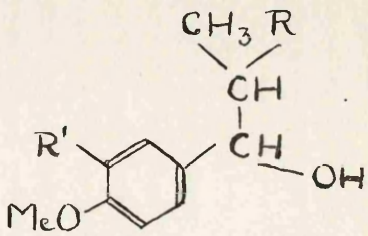
1. It has been pointed out (p. 31) that work carried out by the present author and forming the subject of a previous thesis (32) was directed towards the elucidation of the reasons for the unexpected instability of the dimethiodide (XIII, p. 31) derived from emetine, this instability having been detected (33) independently of Späth and Pailer. The attempt was made through a study of the stability of a number of quaternary iodides containing the α-alkybenzylamine structure, and in three cases (LIX, R = CH_3 and R' = MeO, R = H and R' = MeO, R = CH_3 and R' = H) it was shown that the model substences underwent decomposition in boiling, aqueous solution. The trimethylamine liberated when decomposition occurred was satisfactorily characterised but only in one case was the neutral product of fission isolated in a crystalline state.



LIX



LX

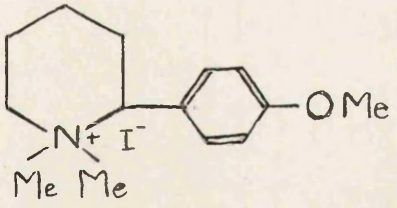


LXI

Since decomposition of the dimethiodide (XIII) derived from emetine led (p. 33) to the formation of the unsaturated compound (XIV), the neutral products obtained by fission of the model methiodides were expected to be the derivatives of styrene represented in the formula (LX). The results of analyses did not support the formulation (LX) for these neutral products, however, but suggested that they consisted mainly of alcohols of the type (LXI).

An attempt has been made to synthesise these alcohols for comparison with the materials resulting from the decomposition of the methiodides.

2. The second section concerns an examination of the stability of 2-p-methoxyphenyl-1-methylpiperidine methiodide (LXII).



LXII

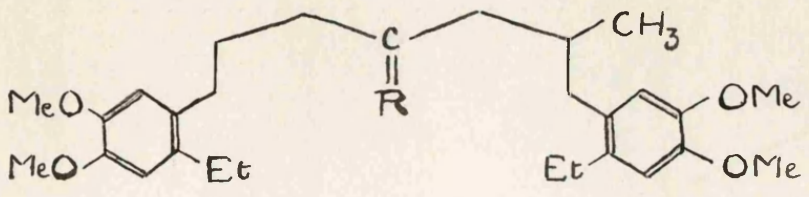
It had been noted that, whereas the secondary nitrogen atom of emetine was completely removed (p. 23) from the molecule on heating the dimethiodide (XIII), there was no indication of the cleavage of a N-C bond at the other side of the molecule. The only obvious difference between the environments of the two nitrogen atoms in the dimethiodide (XIII) is that the atom which remains in the molecule is involved in a ring, whilst the other is not.

From a consideration of the emetine formula (XI, p. 21), it was surmised that the ring in question was six-membered,

and a study has been made of the stability of the methiodide (LXII) to discover whether the presence of the nitrogen atom in a piperidine ring is sufficient to stabilise the N-C bond of a benzylamine system which fulfils the conditions for instability if the nitrogen atom is attached only to an open carbon chain.

3. The synthetic work which forms the basis of the third section of the research was undertaken with a view to obtaining a compound which it was thought might also result from the degradation of emetine.

Application to the alkaloid of the exhaustive methylation technique of Hofmann, reducing at each stage except the last the ethylenic linkages arising on fission of the N-C bonds, should eventually lead to the formation of a nitrogen-free, singly unsaturated substance. Assuming for emetine the structure (XI, p. 21), which at that time had not yet been made untenable, this singly unsaturated compound would be expected to have the constitution (LXIII, R = CH_2).



LXIII

Mild oxidation of this material should furnish, among other products, a ketone (LXIII, R = O) derived by elimination of the methylene group and its replacement by an oxygen atom. If analyses of crystalline derivatives of such a ketone showed

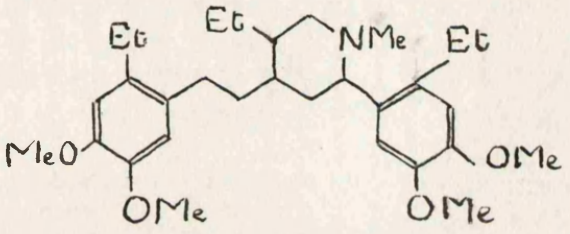
it to contain one carbon atom less than the expected final Hofmann degradation product, this would be an indication of the correctness of the formula (LXIII, R = CH_2) for the degradation product and would also constitute a check on the progress of the degradation.

It was hoped to obtain synthetically workable quantities of a compound with the structure (LXIII, R = CH_2) and by means of oxidation experiments to discover the best method for the isolation of the ketone (LXIII, R = O) and of its crystalline derivatives. A knowledge of this method should be of great assistance in characterising the ketone expected on oxidation of the final Hofmann degradation product of emetine, it being anticipated that this degradation product would be obtainable only in very small quantity.

4. The final section deals with the study of dehydrogenation applied to model substances with a view to the employment of this technique in the case of a substance derived from emetine. It was pointed out (p. 22) that conversion of the dimethiodide (XII) into the corresponding diquaternary base, followed by heating of this under reduced pressure, results in the loss of two molecules of water and the formation of a doubly unsaturated, methine base. This base may be transformed (33) by hydrogenation of the ethylenic links and treatment with methyl iodide in the cold into a mixture of a monomethiodide, whose non-quaternary nitrogen atom was the tertiary nitrogen atom of emetine, together with the dimethiodide (XIII, p. 23). Heating of the monomethiodide causes cleavage of the quaternary nitrogen atom,

and reduction of the resulting, singly unsaturated compound furnishes a saturated, tertiary base.

Assuming the formula (XXIV, p. 28) for emetine, this saturated tertiary base must have the structure (LXIV) which contains a piperidine ring. The structures derived for the



LXIV

saturated, tertiary base from the emetine formulae (XXV and XXVII) similarly contain piperidine rings, whereas that derived from the formula (XXVI) contains a pyrrolidine ring.

Dehydrogenation of the tertiary base should result in the formation of a substance containing either a pyridine ring or a pyrrole ring, according as emetine is represented by one of the formulae (XXIV, XXV or XXVII), or by the formula (XXVI). The detection of a pyrrole ring in a dehydrogenation product of the base would therefore constitute strong evidence in favour of the structure (XXVI) for emetine. Should a compound containing a pyridine ring result from such a dehydrogenation, vigorous oxidation would be expected to yield a pyridine carboxylic acid, the positions of the carboxyl groups indicating the points of attachment of other portions of the molecule to the piperidine ring of the saturated, tertiary base. A knowledge of these points of attachment would enable a decision to be made between the three formulae (XXIV, XXV and XVII) for emetine.

Dehydrogenation of the heterocyclic ring of the tertiary base to the aromatic state would entail the loss of the N-methyl group if the ring were six-membered. The fission of N-C bonds is not unknown (p. 48) where aromatisation would otherwise be unattainable, but the conditions of dehydrogenation required to bring about such fission might be expected also to endanger the stability of the bonds connecting the heavy side chains (p. 44) to the heterocyclic ring.

In this final section are described, therefore, experiments carried out on model substances in an attempt to determine the best conditions under which to dehydrogenate the heterocyclic ring of the saturated, monacidic, tertiary base derived from emetine, without further decomposition of the molecule.

SYNTHESES OF THE ALCOHOLS REQUIRED FOR COMPARISON PURPOSES

α-3:4-dimethoxypenylisobutyl alcohol

The neutral product from the decomposition in boiling, aqueous solution of α-3:4-dimethoxyphenylisobutyltrimethylammonium iodide (LIX, R = CH_3, R' = MeO. p. 57) was isolated (32) as a white solid, crystallising in needles. Analyses agreed with the constitution α-3:4-dimethoxphenylisobutyl alcohol (LXI, R = CH_3, R' = MeO. p. 57) and this formulation has been confirmed by synthesis of the alcohol.

Veratraldehyde was reacted with the magnesium derivative of isopropyl bromide, from which reaction it was possible to isolate a crystalline material whose identity with the product of decomposition of the methiodide was shown by the identity of the melting points of the two products and of their mixture. Taken in conjunction with the analytical results which had been given by the decomposition products, this synthesis constituted proof of the formulation of the material as α-3:4-dimethoxyphenylisobutyl alcohol.

Decomposition of α-3:4-dimethoxyphenylisobutyltrimethylammonium iodide, by the refluxing of its solution in diethyl ketone instead of in water, had produced a strongly unsaturated oil giving analytical results in agreement with the formulation 3:4-dimethoxy-ββ-dimethylstyrene (LX, R = CH_3, R' = MeO. p. 57).

Support for this formulation may be derived from a consideration of the synthesis of the compound. Distillation of the oil, obtained together with the alcohol from the Grignard reaction between veratraldehyde and isopropyl bromide, furnished a strongly unsaturated distillate whose method of preparation indicated the constitution 3:4-dimethoxy-$\beta\beta$-dimethylstyrene. Its physical properties were in close agreemen with those of the unsaturated product of decomposition of the methiodide.

α-p-methoxyphenylisobutyl alcohol

The decomposition of α-p-methoxyphenylisobutyltrimethylammonium iodide (LIX, R = CH_3, R' = H. p. 57) in boiling, aqueous solution had resulted (32) in the formation of a colourless and odourless, neutral oil which did not react with a solution of bromine in carbon tetrachloride. On the basis of the results just described in the case of α-3:4-dimethoxyphenylisobutyltrimethylammonium iodide, the oil was expected to be α-p-methoxyphenylisobutyl alcohol (LXI, R = CH_3, R' = H. p. 57) but the results of analyses were unsatisfactory. On boiling under reduced pressure, it developed a strong odour of aniseed and became unsaturated.

This saturated, neutral oil was available in a quantity to small for further study and α-p-methoxyphenylisobutyl alcohol has therefore been prepared by the method of Tiffeneau and Lévy (100), in order to compare its behaviour with that of the oily product of decomposition. The reaction between

anisaldehyde and isopropyl magnesium bromide furnished an odourless oil which was almost completely saturated but which, on distillation, developed a strong odour of aniseed and became saturated.

β-Methylanethole (LX, R = CH_3, R' = H. p. 57) is described by Perkin (101) as possessing an odour of aniseed and it is apparent that distillation of the α-p-methoxyphenyl-isobutyl alcohol resulting from the Grignard reaction causes dehydration with the formation of this unsaturated compound. Since the neutral product of fission of α-p-methoxyphenyl-isobutyltrimethylammonium iodide also gave the same odour on distillation, support is lent to the view that the primary product of decomposition consisted largely of the expected alcohol but that heating resulted in dehydration and the formation of the styrene derivative.

Attempst to prepare a crystalline phenylurethane of the synthetic alcohol proved unsuccessful.

A method of titration with bromine has been developed to give an indication of the amount of unsaturated material in these synthetic products. By means of such titration it was shown that the undistilled α-p-methoxyphenylisobutyl alcohol resulting from the Grignard reaction contained only about 5% of the substance considered to be β-methylanethole, but that the distillate contained almost equal quantities of the alcohol and of the unsaturated material.

α-3:4-dimethoxyphenyl-n-propyl alcohol

Among the products of thermal decomposition of α-3:4-dimethoxyphenyl-n-propyltrimethylammonium iodide (LIX, R = H, R' = MeO. p.57) had been detected (32) O-methylisoeugenol (LX, R = H, R' = MeO. p. 57) and a neutral, slightly unsaturated oil had been obtained which furnished, on distillation, a material analysing as a mixture of O-methylisoeugenol and α-3:4-dimethoxyphenyl-n-propyl alcohol (LXI, R = H, R' = MeO. p. 57) containing approximately 35% of the unsaturated substance.

The product obtained from the interaction of ethyl magnesium iodide and veratraldehyde was an oil, shown by titration with bromine to contain approximately 15% of the styrene derivative. A single distillation increased the proportion of the unsaturated material to approximately 30%, a degree of unsaturation in harmony with that obtained by a single distillation of the product of decomposition of the methiodide, as mentioned in the previous paragraph.

THE THERMAL STABILITY OF 2-p-METHOXYPHENYL-1-METHYLPIPERIDINE METHIODIDE

The required 2-p-methoxyphenyl-1-methylpiperidine methiodide (LXII, p. 58) was synthesised from p-anisidine and pyridine which were coupled (102) by means of a diazonium reaction and the resulting 2-p-methoxyphenylpyridine separated from the 4-substituted pyridine by fractional crystallisation of the picrates from acetone. The heterocyclic ring was reduced with sodium and alcohol and the piperidine base fully methylated by heating with excess methyl iodide in an aqueous solution of sodium carbonate.

A sample of pure 2-p-methoxyphenyl-1-methylpiperidine methiodide was refluxed in aqueous solution for 48 hours. Fission of the bond between the nitrogen atom and the carbon atom carrying the aromatic ring would result in the formation of the hydriodide of a tertiary base but, after making alkaline, extraction of the aqueous solution with ether removed only an insignificant quantity of material. On the other hand, an almost quantitative yield of the unchanged methiodide was recovered from the aqueous solution.

The stability of 2-p-methoxyphenyl-1-methylpiperidine methiodide presents an interesting contrast with the thermal instability of the methiodides represented in the structure, (LIX, R = CH_3 or H, R' = MeO or H. p. 57) in which the nitrogen atom is attached to an open carbon chain.

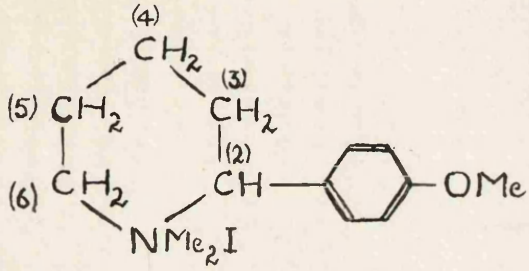
The experimental results previously obtained had shown (32)

that the instability of the latter methiodides was due to the presence of the methoxyl group in the aromatic ring in the position para to the carbon atom carrying the nitrogen, and that fission of the C-N bond was facilitated by alkylation of the β-carbon atom since the methiodides (LIX, p. 57) having R = CH_3 were decomposed more rapidly than the one having R = H.

It was suggested (32) that decomposition took place by initial fission of the N-C bond, according to the E1 mechanism of Hughes, Ingold and Patel (103), the mesomeric effect of the p-methoxyl group and the inductive effect operating in the hydrocarbon side chain serving to increase the electron density on the α-carbon atom carrying the nitrogen, thus weakening the N-C bond and stabilising the carbonium ion formed on cleavage of trimethylamine. The alcohols represented in the formula (LXI, p. 57) were postulated as resulting from the ~~aqueous~~ combination of this carbonium ion with a hydroxyl ion from the aqueous solution and the styrene derivatives (LX, p. 57) from loss of a proton by the carbonium ion.

The reason for the stability of 2-p-methoxyphenyl-1-methylpiperidine methiodide is not apparent, since it resembles the unstable methiodides in that a methoxyl group is present in the aromatic ring in the position para to the carbon atom attached to the nitrogen, this carbon atom also carrying a hydrocarbon chain. It may be that the N-C fission process is a reversible one and that, whereas in the case of the open-chain compound the two products of fission can easily separate, with the cyclic compound the restraining action of the ring prevents rapid separation of the nitrogen atom and the carbon atom at

either end of the dissolving bond and allows recombination.



LXII

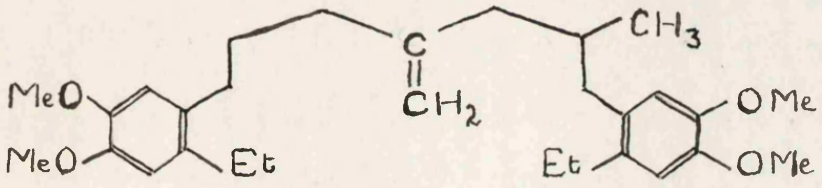
On the other hand the presence of the chain C-5 and C-6 on the side of the nitrogen atom remote from C-2 may cancel the contribution towards the electronegativity of C-2 of the inductive effect in the chain C-3 and C-4, and thereby reduce the electron density on C-2 to an extent sufficient to cause stabilisation.

Whether the stability of 2-p-methoxyphenyl-1-methylpiperidine methiodide is to be ascribed to either of these possibilities, to a combination of them both or to some other factor could only be settled by further study involving an examination of the stability of quaternary ammonium compounds, on the one hand related in structure to 2-p-methoxyphenyl-1-methyl-piperidine methiodide and carrying a heavy alkyl substituent such as a t-butyl group on C-3 of the piperidine ring, and on the other hand related to the unstable, open-chain methiodides and carrying such an alkyl group on the nitrogen atom.

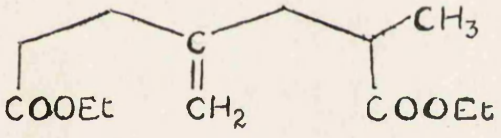
In any case, the fact that 2-p-methoxyphenyl-1-methyl-piperidine methiodide does not decompose in boiling, aqueous solution whereas α-p-methoxyphenylisobutyltrimethylammonium iodide (LIX, R = CH_3, R' = MeO. p. 57) does so decompose

indicates that the presence of the nitrogen atom in a piperidine ring is sufficient to stabilise the N-C bond of a benzylamine system which fulfils the conditions for instability if the nitrogen atom is attached to an open, carbon chain. All this is in harmony with the observation (p. 23) that if the dimethiodide (XIII, p. 31) derived from emetine be heated cleavage occurs of the nitrogen atom attached to the open chain adjacent to ring A, whereas the cyclically-linked nitrogen atom adjacent to ring B remains unaffected.

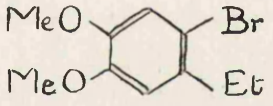
THE ATTEMPTED SYNTHESIS OF THE SUBSTANCE (LXV)



LXV



LXVI

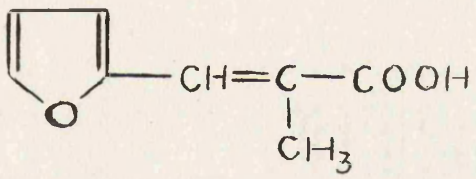


LXVII

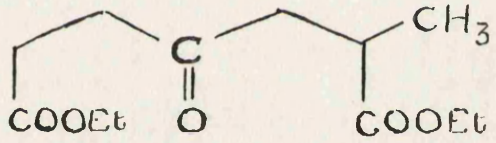
For the synthesis of the substance (LXV) two compounds were required, ethyl α-methyl-γ-methylenylpimelate (LXVI) and 1-bromo-3:4-dimethoxy-6-ethylbenzene (LXVII), which it was intended should be coupled by means of a Grignard reaction between the magnesium derivative of the halide and the acyl chloride or amide derived from the ester, the resulting diketone to be converted into the substance (LXV) by reduction in the Kischner-Wolff manner.

Attention was directed towards the preparation of the ester (LXVI) and it was noticed that a method of fission of the heterocyclic ring of β-furylacrylic acid, described by Marckwald (104), opened a convenient route to a compound possessing the required carbon chain. Application of this

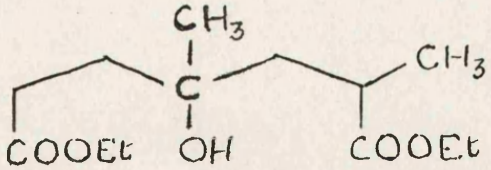
technique to β-furyl-α-methylacrylic acid (LXVIII) would be expected to furnish ethyl γ-keto-α-methylpimelate (LXIX). For the conversion of this substance (LXIX) into the ester (LXVI) it was decided to attempt in the first place the formation of the tertiary alcohol (LXX) by the action of methyl magnesium iodide on the central ketone group, in the hope that the double bond resulting from dehydration of this alcohol would not lie in the chain but between the chain and the required methylene group.



LXVIII



LXIX



LXX

β-Furyl-α-methylacrylic acid (LXVIII) was obtained in a yield of 48.5% by means of a Perkin reaction between furfural, propionic anhydride and potassium propionate, the experimental details being adapted from those given by Johnson (105) for the preparation of β-furylacrylic acid. Accumulation of the acetic acid formed during a Perkin reaction using acetic anhydride and potassium acetate is known (106) to be deleterious but, whereas in the case of the lower homologue the acetic acid formed during the reaction distils out, no such removal of the byproduct took place during the formation of β-furyl-

α-methylacrylic acid owing to the higher boiling point of propionic acid. During a second experiment, from which no better yield resulted, reduced pressure was applied to the reaction mixture with a view to removing the propionic acid as it was formed, but the distillate which slowly collected was shown by titration to contain less than half its bulk of the acid, the remainder apparently consisting of furfural, and it is clear that careful fractionation would be required to remove the propionic acid alone.

Three consecutive attempts to convert β-furyl-α-methylacrylic acid into ethyl γ-keto-α-methylpimelate by the method of Marckwald, involving the action of gaseous hydrogen chloride upon the alcoholic solution of the acid, resulted in the formation of much tar and yielded only 12, 21 and 27% respectively of the required ester. On the other hand, considerable quantities of material of lower boiling point were obtained and fractional distillation yielded a product which was proved, by quantitative hydrolysis followed by isolation of the corresponding acid, to consist largely of ethyl β-furyl-α-methylacrylate. Further yields of ethyl γ-keto-α-methylpimelate were obtained by treating these fractions of lower boiling point with hydrogen chloride and by treating similarly the material resulting from acidification of the alkaline washings of the original reaction product.

Since the reaction had been known to furnish better yields (33, Thesis) in the case of the lower homologue, the method was tested with β-furylacrylic acid and in three runs

the formation of 23, 44 and 69% of ethyl γ-ketopimelate was recorded. Large amounts of tar were produced as in the previous case but the quantities of material of lower boiling point were this time insignificant. An oil, obtained on acidification of the alkaline washings of the reaction product, solidified and was shown to be the monoethyl ester of γ-ketopimelic acid.

It is apparent, from the fact that more favourable yields of the required product were observed and that much less of the ester of low boiling point containing an unopened furan ring was obtained, in the case of β-furylacrylic acid than with the higher homologue, that the presence of the α-methyl group in the latter material in some way hinders the ring-fission process. From the experience gained, however, which indicated that the hydrogen chloride must be led into the reaction mixture at an extremely vigorous rate, especially at the beginning, it was possible in a final run to obtain ethyl γ-keto-α-methylpimelate from β-furyl-α-methylacrylic acid in a yield of 34.5% of the theoretical amount.

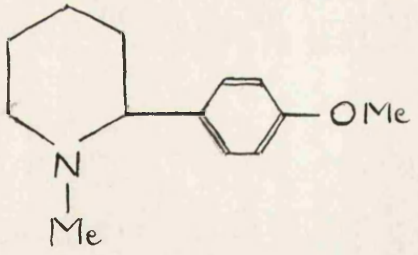
For the conversion (p. 72) of ethyl γ-keto-α-methylpimelate (LXIX) into the alcohol (LXX) it was hoped, by means of a "reverse Grignard" procedure in which the solution of the calculated quantity of the Grignard reagent is slowly added to the solution of the other reactant with vigorous stirring, to confine the attack of the methyl magnesium iodide to the reactive ketone group, leaving the ester groups unaffected During a trial experiment using ethyl γ-ketopimelate, however,

stirring was made ineffective by the large quantities of a sticky, yellow solid which were formed during the addition of the ethereal solution of methyl magnesium iodide to the solution of the ketonic ester (23g.). On decomposing the product with ammonium chloride solution, only 16 grams of oil were extractable by ether and proved to consist largely of the unchanged ketonic ester. It would seem that due to insufficient mixing local excesses of the Grignard reagent were developed which reacted exhaustively with a small proportion of the ethyl γ-ketopimelate and, on decomposition of the product with aqueous ammonium chloride, gave rise to polyhydric alcohols unextracted from the aqueous solution by ether.

Further investigation would have been directed towards increasing the efficiency of mixing, but at this point the results of Späth and Pailer appeared and made untenable for emetine the formula (XI, p. 21), as explained above (p. 28). Hofmann degradation of the alkaloid could no longer be expected to yield a nitrogen-free product with the structure (LXV) and the attempt to synthesise the compound was therefore discontinued.

STUDIES ON DEHYDROGENATION

A convenient model substance, the study of whose dehydrogenation might afford an idea as to the conditions most suitable for application in the case of the saturated, tertiary base derived from emetine, was seen in 2-p-methoxyphenyl-1-methylpiperidine (LXXI) which contains the required N-methylated piperidine ring carrying a heavy substituent and which was obtainable from the 2-p-methoxyphenylpyridine, prepared on an earlier occasion.



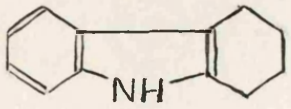
LXXI

For the conversion of 2-p-methoxyphenylpyridine into 2-p-methoxyphenyl-1-methylpiperidine, hydrogenation of the methosulphate of the former base appeared to be the most direct route. Five attempts were made to obtain the required, quaternary salt using dimethyl sulphate alone and also in solution in benzene and in methyl alcohol, but no success was achieved. Tarry products resulted, together with a sticky solid containing substantial quantities of the sulphate of the unchanged pyridine base. On the other hand, 2-p-methoxyphenylpyridine methiodide was obtained crystalline and in good yield. Conversion of this salt into the methochloride, followed by hydrogenation, furnished the required 2-p-methoxy-

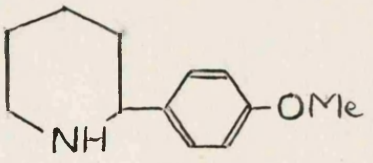
phenyl-1-methylpiperidine.

The catalytic method was chosen as the cleanest and most convenient means of dehydrogenation, palladised charcoal being selected as the catalyst on account of the suggestion of Linstead and Thomas (59) that this form of the metal is more active than palladised asbestos or palladium black. Dehydrogenation was carried out in a flask of 10 milliliters capacity which was heated by means of a metal bath under a condenser set for refluxing. Carbon dioxide gas, generated from the solid compound in a Dewar vessel, was led into the reaction mixture in order to sweep the evolved gases into a nitrometer containing caustic potash solution.

Before attempting the dehydrogenation of 2-p-methoxyphenyl-1-methylpiperidine, it was resolved to test the apparatus and the method on the simpler compounds, tetrahydrocarbazole (LXXII) and 2-p-methoxyphenylpiperidine (LXXIII),



LXXII



LXXIII

this latter substance being readily obtained by reduction of 2-p-methoxyphenylpyridine with sodium and alcohol. In the first run using tetrahydrocarbazole, the quantity of hydrogen collected was 78% of the theoretical amount, and using 2-p-methoxyphenylpiperidine and its hydrochloride, only about 50% of the theoretical amount of hydrogen was obtained.

Since the formation of carbazoles by the catalytic

dehydrogenation of tetrahydrocarbazoles had been reported (107) in yields of the order of 90-95% of the theoretical quantity, it was considered desirable to improve the method of dehydrogenation, as used in these preliminary runs, before applying it to 2-p-methoxyphenyl-1-methylpiperidine. In the course of seven further attempts to dehydrogenate tetrahydrocarbazole, however, varying the conditions on each occasion, no great increase was observed in the proportion of hydrogen evolved, and in some cases this proportion was considerably less.

No definite conclusions could be reached as to reason for the low evolution of hydrogen, but evidence was forthcoming, from these experiments and from a further attempt using the piperidine base, which suggested that when evolution of hydrogen ceased very little, if any, of the starting material remained. Thus, a colour reaction failed to reveal the presence of tetrahydrocarbazole in a product of dehydrogenation, and in the case of 2-p-methoxyphenylpiperidine the pyridine base, formed in the dehydrogenation, solidified spontaneously on washing from the catalyst with ether and evaporating the solvent. Cessation of dehydrogenation was not thought to be due to poisoning of the catalyst since, when evolution of the hydrogen had ceased, no further liberation of the gas was achieved by the addition, on one occasion, of a fresh portion of the catalyst.

The reason for the insufficient evolution of hydrogen is not apparent. In the cases where a solvent was used, it

may be that a certain proportion of the nascent gas served to hydrogenate some small quantity of the solvent. Disproportionation of hydrogen between the molecules of the reactant may perhaps have occurred, and with the piperidine base it is possible to visualise rupture of the molecule between the two rings followed by the escape of piperidine from the reaction-mixture. The possibility of a leak in the apparatus must also be borne in mind, a particularly dangerous spot being the ground-glass joint between the reaction-vessel and the condenser, this being a region which suffers wide variation in temperature during the reaction and whose lubrication is not, therefore, completely trustworthy.

The trial runs using tetrahydrocarbazole and 2-p-methoxyphenylpiperidine indicated that dehydrogenation was swifter, and the isolation of the products much facilitated, when the reaction was carried out in the absence of a solvent. Also indicated was the fact that a rapid flow of carbon dioxide, and actual bubbling of the gas through the reaction-mixture instead of its passage over the surface of the liquid, aided evolution of hydrogen. This last observation is in harmony with the statement of Linstead and Michaelis (69) that no catalytic dehydrogenation of tetralin takes place in the tranquil liquid at 200°, but that the hydrocarbon is readily dehydrogenated when actually boiling, even though the ebullition may be made to occur below the normal boiling point of tetralin (206°) by the application of reduced pressure or by the addition of a diluent.

2-p-methoxyphenyl-1-methylpiperidine was dehydrogenated much more slowly than 2-p-methoxyphenylpiperidine, as was anticipated, since the formation from the former base of 2-p-methoxyphenylpyridine requires the fission of a N-C bond. The pyridine base was, in fact, formed during the reaction and was isolated in the solid, but not completely pure, state. The melting point of a mixture of this product with an authentic specimen of 2-p-methoxyphenylpyridine fell between the melting points of the separate materials, and a similar observation was made in the case of the corresponding picrates.

With the successful dehydrogenation of this model substance, the reaction was applied to the saturated, tertiary base derived from emetine and evolution of hydrogen was observed. The product of the dehydrogenation is at present in course of investigation.

EXPERIMENTAL

GENERAL

1. Melting points (m.p.) are corrected.

2. Analyses are by Dr. G. Weiler and Dr. F. B. Strauss, with the exception of one figure (indicated by the initials D.J.L.) for which the author is indebted to Mr. D. J. Lloyd.

α-3:4-Dimethoxyphenylisobutyl alcohol

Magnesium turnings (3.8g.), previously washed with ether and dried at 100° under reduced pressure, were covered with sodium-dried ether (10ml.) in a flask fitted with a stirrer, a dropping-funnel and a condenser set for refluxing and closed by a drying-tube containing calcium chloride. A small portion of a solution of calcium chloride-dried isopropyl bromide (15.5g.) in dry ether (15ml.) was added and was followed, when the reaction had set in, by the rest of the bromide solution. Addition was complete in 40 minutes, after which the mixture was gently refluxed for 1 hour causing solution of the major portion of the magnesium.

A solution of veratraldehyde (16.5g., prepared from vanillin by the method of Barger and Silberschmidt (108), m.p. 38°) in dry ether (40ml.) was added during 30 minutes with vigorous stirring and the resulting, white paste allowed to stand overnight. The intermediate complex was decomposed with water and ice (70g.) containing ammonium chloride (10g.) and filtered, the residue being extracted with ether. The aqueous and ethereal layers (100 and 200ml. respectively) were shaken together, separated and the aqueous layer extracted further with ether (2 x 30ml.).

Unchanged veratraldehyde was removed from the ethereal solution by shaking with saturated sodium bisulphite solution (3 x 50ml.) and the precipitated bisulphite compound filtered off. After washing with water (2 x 50ml.) and drying over sodium sulphate, evaporation of the ether left a brown oil

(6.8g.) which was seeded with the product obtained from the decomposition of α-3:4-dimethoxyphenylisobutyltrimethylammonium iodide in boiling, aqueous solution. On standing below 0° for a few days, the product partially solidified and separation of the solid and oily constituents was effected with difficulty, by vacuum filtration followed by pressing of the solid on a porous plate.

This latter material crystallised from light petroleum (b.p. 40 - 60°) in colourless needles whose melting point, 65.5 - 67°, was undepressed on admixture with the decomposition product of the quaternary iodide (m.p. 65.5 - 66.5°).

3:4-Dimethoxy-ββ-dimethylstyrene

Distillation of the oily filtrate, separated from the solid product in the previous preparation, took place over the range 140 - 155°/17mm., giving rise to a water-white oil which distilled at 151 - 152°/15mm. The distillate had $n_D^{17°}$ = 1.5565 and immediately decolourised a solution of bromine in carbon tetrachloride.

The unsaturated oil obtained by decomposition of α-3:4-dimethoxyphenylisobutyltrimethylammonium iodide in diethyl ketone had distilled at 150 - 151°/13mm. and had $n_D^{17°}$ = 1.5565.

Titration against Bromine

The method adopted for measuring the approximate degree of unsaturation of the products obtained during the synthesis of the alcohols consisted in dissolving a weighed quantity of the product in carbon tetrachloride and adding a solution of bromine in carbon tetrachloride of known concentration until a definite coloration by the bromine was observed. To determine the quantity of bromine absorbed, an aqueous solution containing 10% of potassium iodide was added and shaken, and the liberated iodine back-titrated against standard sodium thiosulphate solution, starch being employed to detect the end-point. Hydrogen bromide, liberated when substitution occurred apart from the addition of bromine to the unsaturated linkages, was detected by adding aqueous potassium iodate to the solution, causing liberation of iodine and reappearance of the blue, starch coloration. Titration against the thiosulphate solution was then continued, giving a measure of the amount of this hydrogen bromide for which allowance could be made in calculating the quantity of bromine absorbed by ethylenic bonds.

The bromine solution was contained in a micropipette, enclosed at the top by a rubber cap, and the solution was ejected as required by squeezing this cap. It was found that, as the level of the bromine solution in the pipette fell, the concentration decreased by almost 10% owing to evaporation of bromine into the space above the surface of the liquid, thus necessitating standardisation of the solution

for each level in the pipette.

The degree of unsaturation of a product is expressed in the following pages as a percentage, the figure representing the amount of bromine absorbed additively by the sample as compared with the amount which would be so absorbed by an equal weight of the pure styrene derivative obtained on dehydration of the alcohol.

α-p-Methoxyphenylisobutyl alcohol (cf. Sosa (109))

The alcohol was prepared by a Grignard reaction (cf. Tiffeneau and Lévy (100)) in a manner analogous to that employed for the preparation of α-3:4-dimethoxyphenylisobutyl alcohol above.

An ethereal solution of isopropyl bromide (30.5g.) was added during 70 minutes to magnesium turnings (7.5g.) in ether and the mixture refluxed for a further 1⅓ hours. An ethereal solution of anisaldehyde (27.7g., b.p. 131 - 132°/21mm.) was added during 2½ hours with stirring and the intermediate complex decomposed with ammonium chloride solution, as before. After extraction of the product with ether and removal of unchanged anisaldehyde by shaking with saturated sodium bisulphite solution and filtering, the alcohol was obtained as an odourless, brown oil (7.7g.), shown by titration with bromine to contain some 5% of the related, unsaturated compound.

The product distilled over the range 125 - 140°/16mm., the distillate being a pale yellow oil which possessed a

strong odour of aniseed and which was approximately 55% unsaturated.

α-3:4-Dimethoxyphenyl-n-propyl alcohol (cf. Müller, Raltschewa and Papp (110))

A Grignard reaction (cf. Béhal and Tiffeneau (111)) between magnesium (7.5g.), ethyl iodide (39.9g.) and veratraldehyde (27.0g.) furnished the alcohol, after removal of unchanged aldehyde by means of sodium bisulphite, as a clear, brown oil (18.1g.), which titration with bromine showed to be approximately 15% unsaturated.

A sample of this oil (4.0g.) was distilled under high vacuum and a colourless, limpid liquid (1,8g., 30% unsaturated) was collected over the range 78 - 120°/0.013 - 0.005mm. A higher fraction (1.7g.), which distilled up to 175°/10^{-3}mm., was an extremely viscous oil, also 30% unsaturated, and may well have contained substantial quantities of the dimer of O-methylisoeugenol (109).

2-p-Methoxyphenylpyridine

The base was prepared according to the method of Haworth, Heilbron and Hey (102).

p-Anisidine (123g.) was diazotised, coupled with pyridine and the resulting mixture (113g.) of 2- and 4-p-methoxyphenylpyridines separated by fractional crystallisation of the picrates from acetone, giving 2-p-methoxyphenylpyridine picrate (82.4g., m.p. 191 - 195°). Liberated from the

salt by means of aqueous sodium hydroxide and extracted with ether. 2-p-methoxyphenylpyridine was obtained as a white solid (35.6g.) which crystallised from light petroleum (b.p. 40 - 60°) in a felt of fine, colourless needles (28.5g., m.p. 54 - 55.5°). Concentration of the mother liquors gave two further crops of the base (5.5 and 0.2g.) melting at 53 - 54.5 and 52 - 54° respectively. (Haworth, Heilbron and Hey (102) give the m.p. 49 - 50°).

The total weight of the required base obtained in the crystalline state (34.2g.) represents a yield of 18.5% of that theoretically available from the p-anisidine used, if all were converted into the correct isomer.

2-p-Methoxyphenylpiperidine

Sodium (12.5g.) was added portionwise during 20 minutes to a solution of 2-p-methoxyphenylpyridine (5.3g.) in ethyl alcohol (98%, 40ml.) with refluxing of the solvent, more alcohol (3 x 20ml.) being added at intervals to maintain a vigorous reaction. Unreacted sodium was then destroyed by the gradual addition of aqueous alcohol (50%, 40ml.) and finally of water (10ml.). The alcohol was evaporated under reduced pressure and the residual, solid base separated from the water by extraction with ether.

The extract was washed with water (20ml.) and a slow stream of carbon dioxide passed through the ethereal solution for one hour in order to precipitate 2-p-methoxyphenylpiperidine in the form of its carbonate, leaving the pyridine base in

solution. The white, flocculent precipitate was filtered off, washed with ether (50ml.) and dried. Solution of the amine carbonate (5.0g.) in excess of 2N hydrochloric acid, followed by evaporation to dryness, furnished 2-p-methoxyphenylpiperidine hydrochloride (4.7g., m.p. 202.5 - 205°).

The ethereal filtrate and washings from the carbonate were treated again with carbon dioxide and the process repeated until precipitation was complete, fresh ether being added from time to time to replace losses by evaporation. Small quantities of water were also necessary to ensure that the ethereal solution remained permanently moist. In this way, further crops of carbonate resulted which gave rise to more of the hydrochloride (0.9g., m.p. 196.5 - 199.5°). The total amount of hydrochloride obtained was thus 5.6g. (86%).

Recrystallisation of 2-p-methoxyphenylpiperidine hydrochloride from water furnished colourless, prismatic needles, m.p. 204 - 206°. (Found: C, 63.0; H, 7.9; N(D.J.L.), 5.9. $C_{12}H_{17}ON.HCl$ requires C, 63.3; H, 7.95; N, 6.15%).

Liberated from an aqueous solution of the hydrochloride as an oil by means of sodium hydroxide, the base soon solidified and the resulting, pale brown mass melted at 52 - 55° to a cloudy liquid, clearing at 95°. Distillation of the pale brown mass at 155 - 158°/13mm. gave a colourless oil which solidified, repeated crystallisation from light petroleum (b.p. 40 - 60°) furnishing rosettes of colourless needles

melting at 35.5 - 36.5° to a clear liquid. The melting point of the hydrochloride prepared from this latter product was undepressed on admixture with the hydrochloride which gave rise to the solid melting at 52 - 55°.

(van der Zanden (112) describes 2-p-methoxyphenylpiperidine as melting at 57.5° to a cloudy liquid, analyses agreeing with the constitution $C_{12}H_{19}O_2N$, which is the hydrated form of the base).

2-p-Methoxyphenyl-1-methylpiperidine methiodide

A mixture of 2-p-methoxyphenylpiperidine (1.4g.) and methyl iodide (1 ml.) was heated under reflux for 15 minutes in a solution of sodium carbonate (0.7g.) in water (10ml.). The oily, lower layer, remaining after evaporation of the methyl iodide, was taken up in ether (2 x 10ml.) and the aqueous solution extracted with chloroform (3 x 10ml.) and the aqueous solution extracted with chloroform (3 x 10ml.).

The ether was driven off and the oil returned to the chloroform-extracted, aqueous solution, where it was again warmed under reflux with methyl iodide (2ml.) for ½ hour. The methyl iodide was distilled off and the aqueous solution extracted with ether (2 x 10ml.) followed by chloroform (3 x 10ml.).

The combined chloroform solutions (60ml.) were dried over anhydrous sodium sulphate and evaporated,

leaving a brown syrup (2.3g., 90%) which crystallised to a cream-coloured solid, m.p. 156 - 161°, on trituration with ether. After crystallisation from anhydrous acetone, 2-p-methoxyphenyl-1-methylpiperidine methiodide was obtained as colourless, deliquescent, rectangular plates, m.p. 160 - 161° (Found: C, 48.55; H, 6.6; N, 3.7. $C_{14}H_{22}ONI$ requires C, 48.4; H, 6.4; N, 4.0%).

The stability of 2-p-methoxyphenyl-1-methylpiperidine methiodide

1. The quaternary nature of the salt was first demonstrated by extracting with ether (5 x 5ml.) a solution of the salt (0.17g.), made alkaline with sodium hydroxide. Evaporation of the solvent left only a trace (4mg.) of brown oil, whereas extraction of the aqueous, alkaline solution with chloroform (5 x 5ml.), washing of the extract with water (2 x 5ml.) and re-extraction of the washings with chloroform (2 x 5ml.) followed by evaporation of the solvent, gave a glass (0.06g.) converted to a white, amorphous mass on trituration with ether. Crystallisation from dry acetone gave a product, m.p. 160 - 161°, undepressed on admixture with the original methiodide.

2. 2-p-methoxyphenyl-1-methylpiperidine methiodide (0.24g., m.p. 160 - 161°) was dissolved in water (15ml.) and boiled under reflux for 48 hours.

After cooling, the solution was made alkaline with sodium hydroxide and extracted with ether (4 x 5ml.), the extract washed with water, dried and evaporated, leaving a negligible residue (0.8mg.). The aqueous, alkaline solution was neutralised with 2N hydrochloric acid, evaporated to dryness under reduced pressure and the residue extracted by heating under reflux with acetone (3 x 12ml.) for periods of ½ hour. The filtered, acetone extracts were evaporated to dryness leaving a cream-coloured solid (0.23g., m.p. 149 - 153°). After crystallisation from dry acetone, the product (0.15g.) melted at 159 - 161°, the melting point being undepressed on admixture with an authentic specimen of the original 2-p-methoxyphenyl-1-methylpiperidine methiodide.

β-Furyl-α-methylacrylic acid

Furfural (25.3g.), propionic anhydride (34.3g.), both freshly distilled, and pulverised, freshly fused potassium propionate (20.5g.) were stirred for 2½ hours in a flask heated by a bath at 150 - 170° and fitted with a condenser set for distillation. After cooling somewhat, the reaction mixture was boiled for ten minutes with water (300ml.) and norit (2.5g.), this latter coagulating to a tar. The aqueous liquid was decanted off and boiled again with fresh norit.

After filtering hot, the pale brown solution was acidified to Congo red with hydrochloric acid (6N, 40ml.) and deposited a felt of yellowish brown needles on cooling slowly. The β-furyl-α-methylacrylic acid was collected, washed with small amounts of iced water and sucked dry (19.4g., 48.5%, m.p. 107.5 - 109.5°). The product sublimed giving tiny needles, m.p. 118.5 - 119.5°, crystallisation of the sublimate from water furnishing long, silky, pale fawn needles, m.p. 118 - 119°. (Schmidt (113) gives the melting point 107° and Kasiwagi (114) the melting points 110.5 - 111 and 116°).

β-Furyl-α-methylacryloyl chloride was obtained by refluxing the acid with an excess of thionyl chloride and distilled at 115°/12mm. (Buu-Hoï et al. (115) give the b.p. 127°/12mm.)

β-Furyl-α-methylacrylamide, resulting from the action of concentrated ammonia solution on the acid chloride, crystallised from 98% ethyl alcohol in colourless plates, m.p. 138.5 - 140° (Buu-Hoï et al. (115) give the m.p. 137°).

Ethyl γ-ketopimelate

β-Furylacrylic acid (34.5g., m.p. 139 - 140°) was dissolved in absolute alcohol and treated with gaseous hydrogen chloride according to the method of Marckwald (104). The alcohol was evaporated under reduced pressure, the residual brown oil dissolved in ether (250ml.) and washed with aqueous sodium carbonate (4%, 2 x 50ml.), and the washings re-extracted with ether (30ml.)

The combined ethereal solutions were washed with water (20ml.), dried over anhydrous sodium sulphate, evaporated and the tarry residue distilled under reduced pressure. After a short forerun (3.5g., b.p. 150 - 170°/15mm.), ethyl γ-ketopimelate was collected as a pale brown oil (39.9g., 69.4%. b.p. 172 - 174°/15mm.).

The semicarbazone crystallised from aqueous alcohol in colourless, prismatic needles, m.p. 89.5 - 90.5°, undepressed on admixture with an authentic specimen.

The alkaline washings of the original reaction product were acidified to Congo red with 6N hydrochloric acid and extracted with ether. The extracts were dried over anhydrous sodium sulphate and evaporated, giving a dark brown, viscous oil which solidified to a chocolate-brown mass, m.p. 40 - 50°. This was boiled with norit in water and the solution filtered hot, an oil separating on cooling which also solidified, giving a pale brown material.

Extraction of the product with hot petroleum (b.p. 100 - 120°) left a tarry residue and, on cooling, the solution in

petrol deposited a colourless solid, m.p. 62 - 67°. Recrystallation of the latter from a mixture of light petroleum (b.p. 40 - 60°) and benzene furnished colourless needles, m.p. 67 - 69° (Marckwald (116) describes the monoethyl ester of γ-ketopimelic acid as crystallising from a mixture of benzene and ligroin in needles, m.p. 67 - 68°).

Ethyl γ-keto-α-methylpimelate

β-Furyl-α-methylacrylic acid (26.8g., m.p. 113 - 117.5°) was dissolved in absolute alcohol (100ml.), saturated rapidly with hydrogen chloride under reflux (cf. Marckwald (104)) and finally heated on the steam bath for 3 hours with the gas passing through in a slow stream. The solvent was distilled off under reduced pressure, the residue taken up in ether (100ml.) and the ethereal solution washed with aqueous sodium carbonate (4%, 2 x 50ml.), the washings being re-extracted with ether (20ml.). After washing with water (20ml.), the extract was dried over anhydrous sodium sulphate, the solvent removed and the tarry residue distilled. Three fractions were collected:

Fraction (A), 4.0g., b.p. 130 - 134°/15mm.

Fraction (B), 7.0g., b.p. 135 - 166°/15mm.

Fraction (C), 14.85g., b.p. 165 - 171°/14mm. (mostly 170 - 171°)

of which fraction (C) was taken as ethyl γ-keto-α-methylpimelate (34.5% yield).

The semicarbazone prepared from fraction (C) crystallised from absolute ethyl alcohol in colourless rods, m.p. 97 - 97.5°. (Found: C, 52.0; H, 7.6; N, 14.4. $C_{13}H_{23}O_5N_3$ requires C, 51.8; H, 7.7: N, 13.9%).

A sample of fraction (C) was hydrolysed using standard methyl alcoholic potassium hydroxide, the excess alkali being back-titrated against standard hydrochloric acid. Two such determinations gave 119 and 120, respectively, as the equivalent weight of fraction (C) in hydrolysis. The equivalent weight calculated for ethyl γ-keto-α-methylpimelate is 122.

A sample of fraction (A) was similarly hydrolysed, the results of two determinations showing the equivalent weight of the fraction to be 173 and 174, respectively. Ethyl β-furyl-α-methylacrylate requires 180. Concentration of the neutralised hydrolysates from fraction (A), followed by acidification with 6N hydrochloric acid, precipitated a solid which crystallised from water in pale fawn needles, m.p. 116.5 - 118°, undepressed on admixture with β-furyl-α-methylacrylic acid. A sample of fraction (A) was allowed to stand for three months with concentrated ammonia solution. The material which separated crystallised from 98% ethyl alcohol in large, colourless, rectangular plates, m.p. 139 - 141°, undepressed on admixture with β-furyl-α-methylacrylamide.

The combined, low-boiling fractions (39.3g., b.p. 130 - 170°/14mm.), from three conversions of β-furyl-α-methylacrylic acid into ethyl γ-keto-α-methylpimelate, were dissolved in 98% ethyl alcohol (140ml.) and water added (4ml.). After

treating with gaseous hydrogen chloride and isolating the product as a tarry oil, distillation yielded two fractions:

Fraction (i), 18.6g., b.p. 132 - 170°/16mm. (mostly 135°)

Fraction (ii), 12.5g., b.p. 168 - 175°/16mm. (mostly 173 - 174°)

of which fraction (ii) was taken as ethyl γ-keto-α-methylpimelate.

The combined, alkaline washings of the reaction product from three conversions of β-furyl-α-methylacrylic acid into ethyl γ-keto-α-methylpimelate were acidified to Congo red with 6N hydrochloric acid and extracted with ether. Removal of the solvent left a dark brown, viscous oil (13.2g.) which was dissolved in 98% alcohol (50ml.) and treated with gaseous hydrogen chloride. After isolation, the tarry product was distilled and two fractions collected:

Fraction (a), 1.0g., b.p. 132 - 170°/16mm.

Fraction (b), 7.2g., b.p. 173 - 178°/18mm. (mostly 176 - 177°)

of which fraction (b) was taken as ethyl γ-keto-α-methylpimelate.

2-p-Methoxyphenylpyridine methiodide

2-p-Methoxyphenylpyridine (8.35g.) was heated under reflux with methyl iodide (15ml.) for 5½ hours. The methyl iodide was evaporated and the residual, white solid crystallised from 98% ethyl alcohol in colourless, hexagonal prisms (14.15g., 96%. m.p. 167 - 168.5°). Further crystallisation of

2-p-methoxyphenylpyridine methiodide from alcohol gave a product, m.p. 168 - 168.5°(Found: C, 48.1; H, 4.4; N, 4.4. $C_{13}H_{14}ONI$ requires C, 47.7; H, 4.3: N, 4.3%).

2-p-Methoxyphenyl-1-methylpiperidine

A suspension of silver chloride, freshly prepared from an aqueous solution of silver nitrate (13.25g.) by treatment with 11N hydrochloric acid (8ml.) followed by washing of the precipitate with water (6 x 100ml.) until the washings were neutral to litmus, was stirred briskly for 2 hours at 50 - 100° in water (75ml.) with 2-p-methoxyphenylpyridine methiodide (13.25g.). The suspended silver salts were filtered off, washed with water and the combined filtrate and washings concentrated to 80ml. by evaporation under reduced pressure.

After addition of crystalline sodium acetate (10.05g.), the clear, colourless solution of the methochloride was hydrogenated in a glass apparatus using Adams' platinum oxide catalyst, slightly more than the theoretical quantity of hydrogen being absorbed (2814 instead of 2776ml., N.T.P.). The hydrogenated mixture was filtered, made alkaline to phenolphthalein with sodium hydroxide and the oily base which separated taken up in ether (4 x 50ml.). Dried over anhydrous potassium carbonate, the solvent was evaporated leaving 2-p-methoxyphenyl-1-methylpiperidine as a brown oil (7.7g.) which was distilled (b.p. 141 - 142°/10mm.). The clear, colourless distillate crystallised spontaneously in hexagonal plates (7.1g., 85%. m.p. 30 - 32°), the melting point remaining

unchanged on recrystallisation from light petroleum (b.p. 100 - 120°).

The hydrochloride was precipitated from an ethereal solution of the base as a gum which solidified on scratching and standing. Crystallisation from acetone gave a product, m.p. 189.5 - 191° (Found: C, 65.0; H, 8.0; N, 5.9. Calculated for $C_{13}H_{20}ONCl$, C, 64.6; H, 8.3; N, 5.8%). (Lee et al. (117) describe 2-p-methoxyphenyl-1-methylpiperidine hydrochloride as separating from ether in white crystals, m.p. 170°).

The dehydrogenation of tetrahydrocarbazole

The procedure is described above (p. 77). The three samples A, B and C of 10% palladised charcoal were prepared on different occasions according to the method of Hartung (118). The solvents, diphenyl ether and 1-methylnaphthalene, were purified by distillation from Raney nickel.

I. Tetrahydrocarbazole (0.094g., m.p. 116.5 - 117.5°) was dissolved in diphenyl ether (4ml.) and palladised charcoal (0.094g., A) added. Carbon dioxide was passed through the mixture until the bubbles collecting in the nitrometer had become micro, whereupon the nitrometer was completely filled with the 50% potassium hydroxide solution and the reaction mixture heated, the temperatures given referring to the metal-bath.

During 2 hours at 127, rising steadily to 260°, the

evolution of hydrogen was at first rapid but soon slackened, a total of 18.5ml. being collected in the nitrometer. A further 2 hours at 210 - 220° produced 1.1ml. of gas and another 3 hours at 240° an additional 0.7ml. The total evolution of hydrogen was thus 20.3ml. at 14°/754mm. (78%).

II. Tetrahydrocarbazole (0.103g., m.p. 116.5 - 118.5°) was dissolved in diphenyl ether (4ml.) and palladised charcoal (0.106g., B) added. The carbon dioxide was this time led in above the surface of the melt and not bubbled through the reaction mixture.

During 1 hour at 230 - 240°, 7.5ml. of hydrogen were collected but an additional 2 hours at the same temperature produced only 0.6ml., the total evolution in 3 hours thus being 8.1ml. at 16°/765mm. (29%).

III. Tetrahydrocarbazole (0.103g., m.p. 116.5 - 118.5°) was mixed with palladised charcoal (0.109g., B) and diphenyl ether (4ml.) poured on to the mixture without attempting to dissolve the tetrahydrocarbazole. The carbon dioxide was again passed over the surface of the melt.

During 1 hour at 200, steadily rising to 250°, the evolution of hydrogen, at first rapid, soon slackened 13.3ml. being collected. A further 2½ hours at 250 - 280° produced only 0.3ml. The total quantity of hydrogen liberated in 3½ hours was thus 13.6ml. at 17°/762mm. (47.5%).

IV. Tetrahydrocarbazole (0.100g., m.p. 116.5 - 118.5°) was dissolved in diphenyl ether (4ml.) and palladised charcoal (0.108g., A) added. The condenser was surrounded by a water-jacket to increase the efficiency of condensation of the solvent which had been occasionally carried past the condenser by the moving gases. The carbon dioxide was bubbled through the reaction mixture in this and in succeeding experiments.

During 15 minutes at 200, steadily rising to 240°, 19ml. of hydrogen were collected, a further 4 hours at 240 - 290° increasing the total to 22.8ml. at 17°/764mm. (82.5%).

The reaction mixture was dissolved in hot benzene (20ml.) which had been freshly heated under reflux with 11N hydrochloric acid, separated and distilled. The catalyst was filtered off and the filtrate extracted with 11N hydrochloric acid (3 x 10ml.), the acidic extract washed with benzene (5ml.) and evaporated to dryness, leaving a minute brown residue.

The absence of tetrahydrocarbazole in the residue was indicated by a colour test using as reagent a solution of p-dimethylaminobenzaldehyde in a mixture of 11N hydrochloric acid and 98% alcohol:

Liquid	Cold	Hot
Solution of the residue in the reagent.	Clear, pale green.	Faintly cloudy, pale green.
Reagent.	Clear, pale green.	Faintly cloudy, pale green.
Solution of tetrahydrocarbazole in the reagent.	Clear, pale green.	Deep, olive green.

It was demonstrated that tetrahydrocarbazole remaining in the reaction mixture would have been extracted by the acid from the solution in benzene. A solution of tetrahydrocarbazole (0.088g.) in benzene (20ml.) was extracted with 11N hydrochloric acid (2 x 10ml.). Evaporation of the benzene layer left only a small residue (8mg.) whereas evaporation to dryness of the aqueous solution resulted in almost quantitative recovery of the tetrahydrocarbazole (0.083g.).

V. Tetrahydrocarbazole (0.101g., m.p. 114.5 - 116.5°) was dissolved in diphenyl ether (4ml.) and palladised charcoal (0.107g., C) added. Up to this point, control of the flow of carbon dioxide had been effected by means of a tap between the reaction vessel and the nitrometer. This tap was now left permanently, fully open and the stream of carbon dioxide controlled by means of a tap inserted between the mercury safety-valve and the reaction vessel. The change was made on account of the danger of loss of gas through the safety-valve attendant upon fluctuations of pressure which occurred in the reaction vessel and which, in previous runs, had caused momentary reversal of the direction of flow of the carbon dioxide entering this vessel.

During 15 minutes at 210, steadily rising to 255°, 17.5ml. of hydrogen were collected, the total being increased to 17.9ml. by a further hour at 255 - 280°.

After cooling of the reaction mixture and addition of a

further quantity of catalyst (0.111g., C), heating was continued for 2 hours at 265 - 285°, 0.25ml. of gas being evolved. That this extra volume of gas came from the catalyst itself and not from further dehydrogenation of the tetrahydrocarbazole was demonstrated by a blank experiment in which palladised charcoal (0.112g., C) was heated in the apparatus with diphenyl ether (4ml.) for 2 hours at 260°, with the production of 0.2ml. of gas.

VI. Tetrahydrocarbazole (0.102g., m.p. 113 - 117°) was heated in the absence of a solvent with palladised charcoal (0.102g., C) for 10 minutes at 160 - 180°, whereby 20ml. of hydrogen were collected. This total was increased by an additional 2 hours at 180, steadily rising to 250°, to 23.7ml. (21°/752mm., 81.5%). The carbazole which sublimed into the condenser as a white deposit had m.p. 246.5 - 248°.

VII. Tetrahydrocarbazole (0.103g., m.p. 114 - 116°) was dissolved in 1-methylnaphthalene (4ml.) and palladised charcoal (0.118g., C) added.

During 1 hour at 200, steadily rising to 240°, 20ml. of hydrogen were liberated, this total being increased to 21.8ml. (21°/749mm., 74%) by a further hour at the same temperature.

VIII. Tetrahydrocarbazole (0.106g., m.p. 114 - 116°) was dissolved in 1-methylnaphthalene (0.5ml.) and palladised

charcoal (0.115g., C) added.

During 1 hour at 180, steadily rising to 230°, 16ml. of hydrogen were evolved, the total being increased to 19.6ml. (14°/761mm., 67%) by an additional 3 hours at 250°.

The dehydrogenation of 2-p-methoxyphenylpiperidine

The method used was that described in the case of tetrahydrocarbazole.

I. 2-p-Methoxyphenylpiperidine (0.098g., m.p. 35 - 37.5°) was dissolved in diphenyl ether (2ml.) and palladised charcoal (0.127g., A) added.

In 1 hour at 215°, 7.5ml. of hydrogen were evolved, another 3ml. being collected as the temperature was gradually raised to 270°during the next hour. The total was increased to 19.3ml. (18°/746mm., 51.5%) by a further 18 hours at 260 - 280°.

Solution of the reaction mixture in ether (40ml.), filtration and extraction of the ethereal filtrate with 2N hydrochloric acid (5 x 20ml.) gave a solution from which the basic material was precipitated with sodium hydroxide and taken up in ether (4 x 50ml.). The extract was evaporated to 20ml., washed with water (2ml.) and carbon dioxide bubbled through, no precipitation of carbonate occurring, however.

Removal of the solvent left an oil (0.022g.) which gave a picrate, m.p. 168 - 192°. Crystallisation of the salt from acetone gave silky, yellow needles, m.p. 193.5 - 195.5°,

undepressed on admixture with the picrate of 2-p-methoxyphenylpyridine.

II. 2-p-Methoxyphenylpiperidine hydrochloride (0.100g., m.p. 203.5 - 206.5°) was suspended in diphenyl ether (2ml.) and palladised charcoal (0.133g., B) added.

During 45 minutes at 220°, 2ml. of hydrogen were evolved. Raising the temperature to 250° produced a further 4ml. of the gas in 5 minutes, the total being increased to 15.15ml. (N.T.P., 51.2%) by a further 4½ hours at 250 - 285°.

Extraction of the reaction product with acid, filtration, addition of sodium hydroxide followed by ether-extraction of the liberated base and evaporation of the solvent gave rise to an oil (0.021g.) which solidified spontaneously, m.p. 49 - 51°. The mixed melting point with authentic 2-p-methoxyphenylpyridine (m.p. 54 - 55.5°) was 51 - 53°. The picrate of the dehydrogenation product crystallised from acetone in yellow needles, m.p. 193.5 - 195.5°, undepressed on admixture with 2-p-methoxyphenylpyridine picrate.

III. 2-p-Methoxyphenylpiperidine (0.101g., m.p. 35.5 - 37°) was mixed with palladised charcoal (0.101g., C) in the absence of a solvent.

In 20 minutes at 120 - 140°, 22.7ml. of hydrogen were evolved, the total being raised to 27.7ml. (16°/763mm., 74%) by a further 8½ hours at 140, steadily rising to 220°.

2-p-Methoxyphenylpyridine (0.025g., m.p. 51 - 52.5°)

solidified spontaneously in the condenser and a further crop (0.015g.), which similarly solidified, was obtained by ether-extraction of the catalyst. This second crop had the m.p. 49 - 52°, the mixed m.p. with an authentic specimen being 53.5 - 55°.

The dehydrogenation of 2-p-methoxyphenyl-1-methylpiperidine.

2-p-Methoxyphenyl-1-methylpiperidine (0.116g., m.p. 26 - 29°) was mixed with palladised charcoal (0.100g., C) in the absence of a solvent. The procedure was that described in the previous cases.

In 1 hour at 185 - 205°, 6ml. of gas were collected, an additional 9ml. appearing during the following 5 hours at 205 - 225°. The total was increased to 24.2ml. (17°/762mm., 60%) by a further 21 hours at 220, gradually rising to 300°.

Extraction of the material from the condenser gave an oil (0.044g.) which solidified on seeding with 2-p-methoxyphenylpyridine. Crystallised from light petroleum (b.p. 40 - 60°), the product had m.p. 40 - 46° and a mixed m.p. with an authentic specimen (m.p. 53.5 - 55°) gave 47 - 54.5°.

A picrate of the dehydrogenation product, after crystallisation from acetone, had the m.p. 186.5 - 191.5°. The mixed m.p. with an authentic specimen of 2-p-methoxyphenylpyridine picrate (m.p. 193.5 - 194.5°) gave 188.5 - 191.5°.

A further quantity of oil (0.023g.) was extracted from the catalyst with ether but failed to solidify. The picrate, crystallised from acetone and then 98% ethyl alcohol, had the

m.p. 185.5 - 188.5°, the mixed melting point determination with 2-p-methoxyphenylpyridine picrate giving 187.5 - 190°.

The dehydrogenation of the saturated, tertiary base derived from emetine

The tertiary base (0.247g., m.p. 78 - 79.5°) was mixed with palladised charcoal (0.142g., C) in the absence of a solvent. The procedure was that described in the previous cases.

In 2 hours at 220, steadily rising to 260°, 19ml. of gas were evolved, a further hour at 270° giving only 3.1ml. The reaction was then discontinued since the rate of dehydrogenation was too slow to warrant longer heating, with the accompanying risk of thermal decomposition of the molecule. The total amount of gas evolved (22.1ml., 19°/761mm.) represents 60.0% of that theoretically available if the piperidine ring of the base were to undergo complete dehydrogenation.

The reaction mixture was extracted with ether and the product isolated as a dark brown gum (0.193g.) which is at present in course of investigation.

B I B L I O G R A P H Y

BIBLIOGRAPHY

1. TRISTRAM. Pilgrimes IV, p. 1311, Published by Purchas (1625).
2. PISO, MARCGRAV. Historia rerum naturalium Braziliae (1648).
3. VEDDER. Trans. 2nd. Cong. Far Eastern Assoc. Trop. Med., (1912), p. 87.
4. ROGERS. Ind. Med. Gaz., (1914), 49, 85.
5. DU MEZ. Phillipine Journal of Science, (1915), (B), 10, 73.
6. CHILD, PYMAN. J.C.S., (1929), 132, 2010.
   CHILD, PYMAN. J.C.S., (1931), 134, 36.
   PYMAN. J. Soc. Chem. Ind., (1937), 56, 789.
7. PELLETIER, MAGENDIE. Ann. Chim. Phys., (1817), (ii), 4, 172.
8. PELLETIER, DUMAS. Ann. Chim. Phys., (1823), (ii), 24, 163.
9. GLÉNARD. Ann. Chim. Phys., (1876), (v), 8, 233.
10. LEFORT, WURTZ. Ann. Chim. Phys., (1877), (v), 12, 277.
11. PODWYSSOTZKI. Pharm. J., (1880), (iii), 10, 642.
12. KUNZ-KRAUSE. Arch. Pharm., (1887), (iii), 225, 461.
    KUNZ-KRAUSE. Arch. Pharm., (1894), (iii), 232, 466.
13. PAUL, COWNLEY. Pharm. J. Trans., (1893), 53, 61.
    PAUL, COWNLEY. Pharm. J., (1894), (iii), 25, 111, 373.
14. PAUL, COWNLEY. Pharm. J., (1894), (iii), 25, 690.

15. PAUL, COWNLEY, HESSE. Pharm. J., (1898), (iv), 7, 98.

16. FRERICHS, DE FUENTES TAPIS. Arch. Pharm., (1902), 240, 390.

17. KELLER. Arch. Pharm., (1911), 249, 512.

18. KELLER. Arch. Pharm., (1913), 251, 701.

19. CARR, PYMAN. Proc. Chem. Soc., (1913), 29, 226.

20. CARR, PYMAN. J.C.S., (1914), 105, 1591.

21. PYMAN. J.C.S., (1917), 111, 419.

22. KARRER. Ber., (1916), 49, 2057.

23. HESSE. Annalen, (1914), 405, 1.

24. BRINDLEY, PYMAN. J.C.S., (1927), 1067.

25. KUNZ-KRAUSE. Schweiz. Wochenschrift f. Pharm., (1896), 34, 358.

26. WINDAUS, HERMANNS. Ber., (1914), 47, 1470.

27. DOBBIE, FOX. J.C.S., (1914), 105, 1639.

28. SPÄTH, LEITHE. Ber., (1927), 60, 688.

29. SPÄTH, PAILER. Monatsh., (1948), 78, 348.

30. PAILER. Monatsh., (1948), 79, 127.

31. PAILER, BILEK. Monatsh., (1948), 79, 135.

32. NORCROSS. M.Sc. Thesis, Manchester, (1947).

33. BATTERSBY. M.Sc. Thesis, Manchester, (1947).

BATTERSBY, OPENSHAW. Part I, J.C.S. (in press).

34. SABATIER, GAUDION. Compt. Rend., (1917), 165, 224.

35. SABATIER, SENDERNS. Compt. Rend., (1903), 136, 738, 921, 983.

ARMSTRONG, HILDITCH. Proc. Roy. Soc., (1920), (A) 97, 259.

36. MEYER. Analyse und Konstitutionsermittlung Org. Verbb., 5th Edition, (1931), p. 247.

37. HOFMANN. Ber., (1879), 12, 984.

38. KOENIGS. Ber., (1879), 12, 2341.

39. LELLMANN, GELLER. Ber., (1888), 21, 1921.

40. KONOWALOFF. J. Russ. Phys. Chem. Soc., (1887), 1, 255.

41. MARKOVNIKOV. Compt. Rend., (1892), 115, 440.

42. BAEYER, VILLIGER. Ber., (1898), 31, 1401.

43. FIESER, DUNN. J.A.C.S., (1936), 58, 572.

44. SABATIER. Ber., (1911), 44, 1984.

45. SABATIER, MAILHE. Compt. Rend., (1907), 144, 784.

46. SABATIER, MAILHE. Compt. Rend., (1903), 137, 240.
SABATIER, MAILHE. Bull. Soc. Chim., (1903), (iii), 29, 974.

47. ZELINSKY. Ber., (1911), 44, 3121.

48. ZELINSKY, BORISOFF. Ber., (1924), 57, 150.

49. CURIE. Chem. News, (1874), 30, 189.

50. D.R.P. (1887), 43802.

51. KELBE. Ber., (1878), 11, 2174.

52. VESTERBERG. Ber., (1903), 36, 4200.

53. RUZICKA. Fortschr. der Chem. Phys., (1928), 19, Heft 5, 1.

54. ZELINSKY. Ber., (1923), 56, 1716.

55. BAEYER, VILLIGER. Ber., (1899), 32, 2429.

56. RUZICKA, MEYER. Helv. Chim. Acta, (1921), 4, 505.
RUZICKA, MEYER, MINGAZZINI. Helv. Chim. Acta, (1922), 5, 345.

57. RUZICKA, SEIDEL. Helv. Chim. Acta, (1922), 5, 369.
RUZICKA, STOLL. Helv. Chim. Acta, (1922), 5, 923.

58. RUZICKA, RUDOLPH. Helv. Chim. Acta, (1927), 10, 915.

59. LINSTEAD, THOMAS. J.C.S., (1940), 1127.

60. DIELS, GÄDKE, KÖRDING. Annalen, (1927), 459, 1.

61. DIELS, GÄDKE. Ber., (1927), 60, 140.

62. FIESER. J.A.C.S., (1933), 55, 4977.

63. RUZICKA, van VEEN. Annalen, (1929), 476, 70.

64. HARPER, KON, RUZICKA. J.C.S., (1934), 124.

65. ROSENHEIM, KING. Chem. and Ind., (1932), 51, 464, 954.

66. WIELAND, DANE. Z. Physiol. Chem., (1932) 210, 268.

WIELAND, DANE, MARTIUS. Z. Physiol. Chem.,(1933),215,15.

67. LINSTEAD. Ann. Rep. Chem. Soc., (1936), 33, 294.

68. For example: PLATTNER (translated by ARMSTRONG). Newer Methods of Preparative Organic Chemistry,p.21, Interscience Publishers, Inc.,New York, 1948.

69. LINSTEAD, MICHAELIS. J.C.S., (1940), 1134.

70. LINSTEAD, MILLIDGE, THOMAS, WALPOLE. J.C.S.,(1937),1146.

71. RUZICKA, SEIDEL. Helv. Chim. Acta,(1936), 19, 424.

72. RUZICKA, WALDMANN. Helv. Chim. Acta,(1933), 16, 842.

73. BARBOT. Bull. Soc. Chim., (1930), (iv), 47, 1314.

74. COOK, HEWETT. J.C.S., (1936), 62.

75. ZELINSKY, TITZ, GAVERDOWSKAJA. Ber., (1926), 59, 2590.

76. HAWORTH, MAVIN, SHELDRICK. J.C.S., (1934), 454.

77. SEN-GUPTA. J. Ind. Chem. Soc., (1942), 19, 467.

78. CLEMO, ORMSTON. J.C.S., (1933), 352.

79. ZELINSKY, YUR'EV. Ber., (1931), 64, 101.

80. FRANK, HOLLEY, WIKHOLM. J.A.C.S., (1942), 64, 2835.

81. PRELOG, BALENOVIC. Ber., (1941), 74, 1508.

82. PRELOG, KOMZAK. Ber., (1941), 74, 1705.

83. PRELOG, KOMZAK, MOOR. Helv. Chim. Acta, (1942),25,1654.

84. PRELOG, MOOR, FÜHRER. Helv. Chim. Acta, (1943),26,846.

85. ZELINSKY. Ber., (1912), 45, 3678.

86. ZELINSKY. Ber., (1923), 56, 1718.

87. TAUSZ, PUTNOKY. Ber., (1919), 52, 1573.

88. SPÄTH, BERGER, KUNTARA. Ber., (1930), 63, 134.

89. SPÄTH, BURGER. Ber., (1927), 60, 704.

90. PICTET, GAMS. Ber., (1909), 42, 2943.

91. HARLAY. Compt. Rend., (1947), 224, 568.

92. EHRENSTEIN, BUNGE. Ber., (1934), 67, 1715.

93. HÜCKEL, STEPF. Annalen, (1927), 453, 163.

94. ARNOLD, COLLINS. J.A.C.S., (1939), 61, 1407.

95. ARNOLD, COLLINS, ZENK. J.A.C.S., (1940), 62, 983.

96. CRAWFORD, NELSON. J.A.C.S., (1946), 68, 134.

97. BARCLAY, CAMPBELL. J.C.S., (1945), 530.

98. RITTER, SHARPE. J.A.C.S., (1937), 59, 2351.

99. BARNES. J.A.C.S., (1948), 70, 145.

100. TIFFENEAU, LÉVY. Bull. Soc. Chim., (1926), (iv),39,763.

101. PERKIN. J.C.S., (1879), 35, 136.

102. HAWORTH, HEILBRON, HEY. J.C.S., (1940), 358.

103. HUGHES, INGOLD, PATEL. J.C.S., (1933), 526.

104. MARCKWALD. Ber., (1887), 20, 2811.

105. JOHNSON. Org. Synth. (1940), 20, 55.

106. KALNIN. Helv. Chim. Acta, (1928), 11, 977.

107. HORNING, HORNING, WALKER. J.A.C.S., (1948), 70, 3935.

HOSHINO, TAKIURA. Bull. Chem. Soc. Japan,(1936),11,218.

108. BARGER, SILBERSCHMIDT. J.C.S., (1928), 133, 2919.

109. SOSA. Ann. Chim., (1940), 14, 5.

110. MÜLLER, RALTSCHEWA, PAPP. Ber., (1942), 75, 692.

111. BÉHAL, TIFFENEAU. Bull. Soc. Chim., (1908),(iv),3,301.

112. van der ZANDEN. Rec. Trav. Chim., (1942), 61, 365.

113. SCHMIDT. Ber., (1881), 14, 574.

114. KASIWAGI. Bull. Chem.Soc. Japan, (1927), 2, 310.

115. BUU-HOÏ, CAGNIANT, JANICAUD, FINIGER. Bull. Soc. Chim., (1943), 10, 137.

116. MARCKWALD. Ber., (1888), 21, 1398.

117. LEE, ZIERING, BERGER, HEINEMAN. Emil Barell Jubilee Volume, (1946), p. 264, Published by Frederick Reinhardt, Ltd., Basle.

118. HARTUNG. Quoted by ALEXANDER, COPE. J.A.C.S., (1944), 66, 888, footnote 7.

ACKNOWLEDGEMENTS

The author wishes to express his gratitude to Doctor H. T. Openshaw for his constant interest and valuable criticism throughout the course of the author's training in research.

His thanks are also due to Professor John Read, F.R.S., for the provision of facilities to carry out the present investigations and to the Wellcome Foundation for financial assistance during this period.