THE MORPHINE GROUP. PART I.
A DISCUSSION OF THE CONSTITUTIONAL PROBLEM.

BY

JOHN MASSON GULLAND

AND

ROBERT ROBINSON.

Publication. I

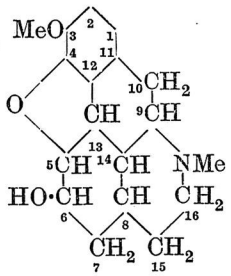
From the Transactions of the Chemical Society, 1923. Vol. 123.

CXII.—*The Morphine Group. Part I. A Discussion of the Constitutional Problem.*

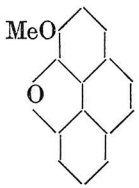
By John Masson Gulland and Robert Robinson.

Largely on account of the migration phenomena encountered in the study of this group of alkaloids, the morphine puzzle has absorbed the interest of many chemists in two generations, and in the case of no other natural product have so many different constitutional formulæ been proposed or such a volume of experimental work, directed to the elucidation of constitution, recorded. It is therefore only because the present authors are convinced that insufficient attention has been paid to certain aspects of the

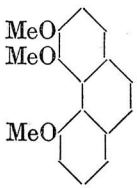
subject that they venture to advance still another suggestion. The present communication is intended to be the introduction to a series of experimental investigations, and is explanatory of a working hypothesis which we have adopted as the result of a review of the whole subject.



(I.)



(II.)



(III.)

In order to provide a basis for discussion, formula (I) may be assumed to represent a possibly hypothetical dihydrocodeine, and the various structural elements in this expression call for brief examination. The phenanthrene skeleton, the tertiary –NMe– group attached to a chain of two atoms not included in the phenanthrene nucleus, the aromatic character of the upper benzene nucleus, the position of the alcoholic hydroxyl and methoxyl groups, and the existence of an ether-bridge have all been proved at some stage or other of the work of Vongerichten, Knorr, Pschorr, Freund, and others. There is, however, an element of ambiguity in regard to all other points involved, although we believe that the case for the assumption that (I) is derived from codeine by the addition of two hydrogen atoms is an almost unanswerable one. The first question is the position of the oxygen bridge, and the arguments which can be used to support the usual view expressed in formula (I) are the following:

(1) Attachment of oxygen to 4 * is certain, hence further attachment to 5 is the most natural assumption on stereochemical grounds. (2) Codeine may be degraded to methylmorphenol (II) by simple processes and the constitution of morphenol is proved by its conversion on fusion with potassium hydroxide into 3 : 4 : 5-trihydroxyphenanthrene, the trimethyl ether (III) of which has been synthesised by Pschorr.† (3) The stability of the oxide ring towards reducing

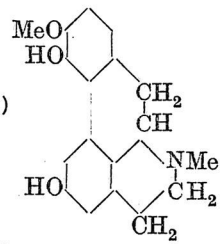
* Reference is made to the various positions, numbered as in formula (I) by means of simple numerals; for example, 6 instead of position 6 or "the carbon atom in position 6."

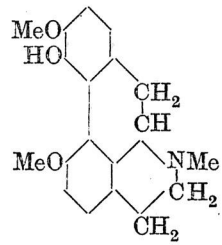
† A bibliography of relevant literature bearing directly on the morphine problem is appended.

agents is very much diminished when a keto-group appears at 6 as in codeinone. This clearly indicates attachment of oxygen of the ether link to 5 or 7, and of these the latter presents no advantages whatever.

The attachment of the nitrogen atom to 9 follows from the results obtained by Knorr on the methine derived from hydroxycodeine and by comparison with other alkaloids and phenanthrene bases (glaucine, bulbocapnine, dicentrine, laurotetanine, etc.) of proved and analogous constitution. The point of attachment of the 2-carbon chain, which, it may be remarked, cannot have the ethylidene arrangement –NMe·CHMe·, to the phenanthrene nucleus is the most controversial point included in the expression (I). Indeed in the greater number of morphine formulæ suggested in recent years the example of Knorr has been followed and 15 has been joined to 5. Nevertheless, the proof given by Pschorr of the constitution of *apo*morphine and of morphothebaine (IV) must be taken into account and in addition the relation of morphine, codeine, and thebaine to the bases which accompany them in the plant. In this connexion, particular attention may be directed to the alkaloid *iso*thebaine, which has formula V, in which the only doubtful features are the positions assigned to the hydroxyl and methoxyl groups. This base occurs in the root of *Papaver orientale* after the period of blooming and withering of the aërial parts. During the time of vigorous growth of the plant, however, thebaine is the only alkaloidal constituent which can be isolated. It has been inferred that thebaine is actually converted into *iso*thebaine, and as the latter substance is proved to belong to the aromatic phenanthrene group and to have a carbon atom of the side chain linked to 8, it is clear that thebaine should be similarly constituted.

(IV.)



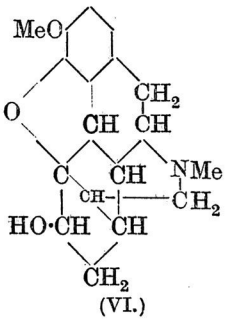


(V.)

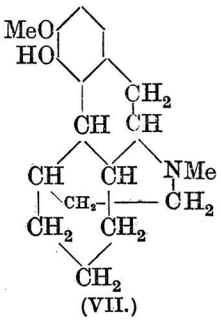
For the above reasons, we consider it very probable that (I) represents codeine plus two hydrogen atoms and although, as has been indicated, this conclusion is by no means based on decisive experiments, it must be admitted that the assumption is in harmony with the broad lines of the chemistry of these alkaloids and is especially attractive if weight is attached to the argument connected

*

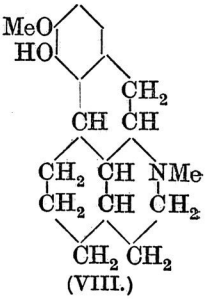
with their natural occurrence side by side with bases of proved *iso*quinoline structure. The chief reason why the fundamental basis afforded by this expression has been abandoned by many investigators is that it was supposed to be impossible to use it to develop a satisfactory formula for codeine, and it is the purpose of the present communication to remove this objection. The further problems which confront us are the determination of the manner in which the codeine formula is to be evolved from (I) by the removal of two hydrogen atoms, and the consistent explanation of the remarkable transformations which have been observed in this group with the aid of the expression so deduced. In the first place, it seems certain that codeine does not contain an ethylene linkage. The ultimate failure of the Pschorr formula was due to the fact that the morphine chemistry could not be explained on the basis of a structure derived from (I) and containing a double bond and even when the $\cdot CH_2 \cdot CH_2 \cdot NMe \cdot$ chain is attached to 5 as in the Knorr formula there are grave disadvantages attached to every possible position for a double linking. These arise chiefly in regard to the relations of the isomeric methylmorphimethines, but the point need not be laboured, as there is positive evidence available that codeine contains an alicyclic bridge. Freund, Melber, and Schlesinger have prepared two isomeric tetrahydrodeoxycodeines in regard to both of which the following statements are true. (1) The alcoholic hydroxyl is replaced by hydrogen. (2) Two hydrogen atoms are added at the oxygen bridge because these substances are phenolic in character. (3) These reduced deoxycodeines are tertiary bases, and therefore the C–NMe link is not broken. The α-form results when deoxycodeine (or α- or β-chlorocodide) is first reduced electrolytically at a lead cathode and the dihydrodeoxycodeine then treated with hydrogen in presence of palladium. The β-isomeride is obtained by the reduction of deoxycodeine hydrochloride by means of hydrogen in presence of palladium in aqueous solution.



(VI.)



(VII.)

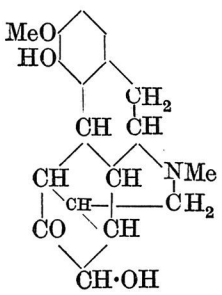


(VIII.)

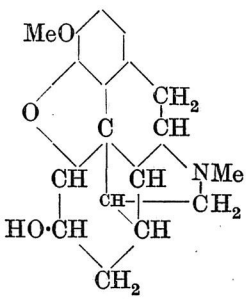
These results are with reason attributed by Freund and Speyer to the breaking of the bridge-ring system of codeine in two directions as shown in formulæ VI for codeine and VII and VIII for the isomeric tetrahydrodeoxycodeines. A second example of isomerism which must be due to the fission of the bridge-ring in two directions is dealt with in Part II of this investigation (p. 998). A further strong argument tending to prove the non-existence of a double bond in codeine is derived from the fact that the ketone codeinone can be obtained from the secondary alcohol codeine by oxidation with potassium permanganate in acetone solution. It is difficult to believe that this could be the case if codeine were unsaturated, and, moreover, in addition to codeinone, the chief product of the oxidation of codeine is a hydroxycodeine in which the new hydroxyl group occurs at 9 or 10, very probably 10, and for other reasons it is certain that the carbon atoms in these positions are saturated. Finally, in this connexion, it may be noted that the behaviour of thebaine towards ozone shows that this base, $C_{19}H_{21}O_3N$, is attacked by the reagent at one point only, since it is converted into an aldehyde or ketone, $C_{19}H_{21}O_5N$, termed *thebaizone*, which appears to be the methyl ester of a carboxylic acid. Thebaine is thus oxidised at the ethylene linkage or readily ruptured bridge which is produced in that enolic or other tautomeric form of codeinone of which the base is the methyl ether. In view of the close relation of thebaine to codeine, as proved by the hydrolysis of the former to codeinone and methyl alcohol, it may be inferred that what may be called the codeinoid unsaturation is of the polycyclic type. The researches of Freund on the oxidation of thebaine to hydroxycodeinone and on the attempted reduction of phenyldihydrothebaine lead to the same conclusion.

The next stage in our inquiry is to attempt a decision as to the position of the new ring which it is clearly necessary to introduce into the structure (I), and it is at this point that we wish to lay stress on a consideration to which, in our opinion, quite insufficient weight has been hitherto attached. Of the reactions encountered in the study of the chemistry of morphine and its allies none are more remarkable and surprising than those in which an aromatic phenanthrene system and an aminoethanol derivative are simultaneously produced. It is generally recognised that these degradations involve the break of a carbon-to-carbon union, and they occur in various types of morphine derivatives. It is not merely a case of a singular reaction occurring in one or two particular substances; the process is so common that its cause must be sought in some general property of the morphine structure. The driving force behind the change is doubtless the tendency to produce an aromatic nucleus, because the extrusion of the side-chain is never

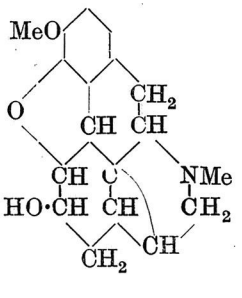
observed independently of the formation of the true phenanthrene derivative. But the obvious consequence has not previously been stated. *The formation of the aromatic phenanthrene derivative cannot take place for structural reasons unless the ethanamine side-chain is displaced in favour of a hydrogen atom or hydroxyl group.* Actually the displacement is normally in favour of a hydrogen atom. It is equally clear that the only structural condition which could inhibit aromatic ring formation is that the side-chain is attached to a quaternary carbon atom, one of those (13, 14) which are shared by two nuclei in the resulting phenanthrene derivative. An analogous case is that of abietic acid, which always loses a methyl group when it is converted into retene. The explanation in this example is accepted that the methyl group is attached to one of the carbon atoms common to two rings, but unaccountably the same deduction has not been drawn in relation to morphine and none of the current formulæ for the substance satisfies the above requirement. Applying it, we find that the bridge must be 8–15–13 or 8–15–14. It cannot be 8–15–5, because Knorr and Pschorr have observed degradative formation of phenanthrene derivatives in the case of methylthebainonemethine, and in this substance the oxide ring is broken and both 5 and 8 bear a hydrogen atom. If the bridge were 8–15–5, we should here have loss of the side chain without the alleged compelling reason and an explanation other than that now advanced would have to be found. That the position of the C·C·N chain presents an obstacle to the formation of a true aromatic ring follows also from the stability of hydroxythebainone. If this substance had the constitution (IX) assigned to it by its discoverers, it should pass into an aromatic compound such as morphothebaine (IV) with facility, and yet it is prepared from hydroxycodeinone by the action of a solution of stannous chloride in concentrated hydrochloric acid in a sealed tube at 100°. In agreement with these views, the alternative expressions for the constitution of codeine are X and XI and it will be convenient



(IX.)



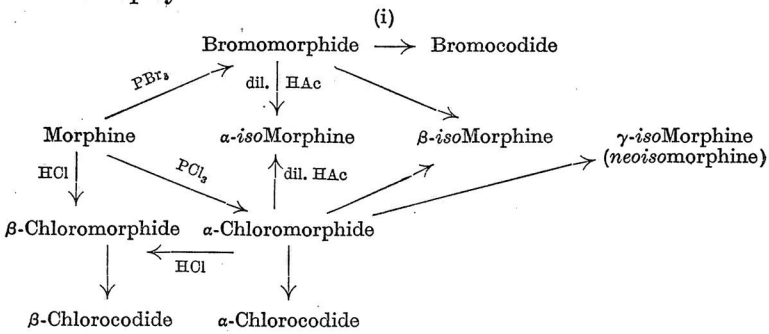
(X.)

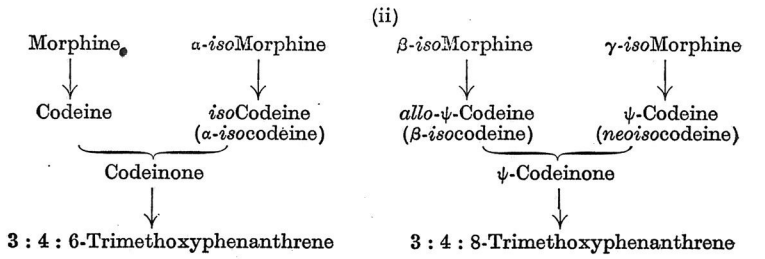


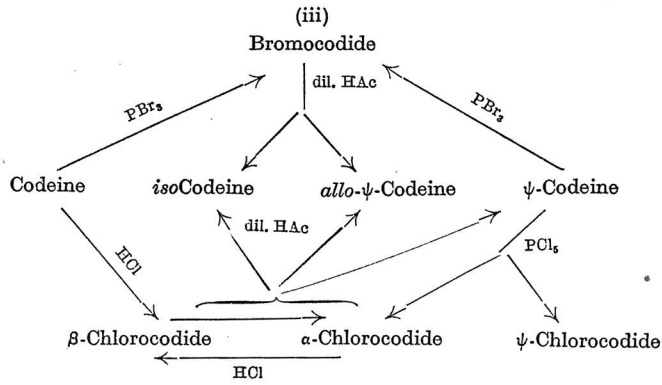
(XI.)

to discuss, in the first place, the explanation of the transformations of this group of bases with the aid of the pinene-like formula X.

The Isomerides of Morphine and Codeine.—The relation of morphine and codeine with their halide derivatives and isomerides is illustrated in the following tables. The names given in brackets are not employed in the text.







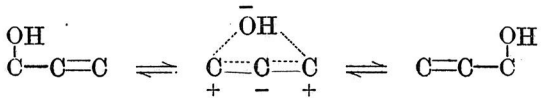
It has been abundantly proved that the alcoholic hydroxyl in the stereoisomeric pair, codeine and *iso*codeine, is at 6, whilst *allo*-ψ-codeine and ψ-codeine, also stereoisomerides, are structurally different from codeine and have a secondary alcoholic group at 8.

It is not known to which of the two series the various halogeno-morphides and -codides belong. The tables show how often it is necessary to recognise the migration of hydroxyl from an α- to a γ-position and it will be noticed that the transformation can be reversed. In searching the literature for analogies, we encountered several cases of a very similar nature, and perhaps the best known of these concerns the relations of geraniol (XII) and linalool (XIII).

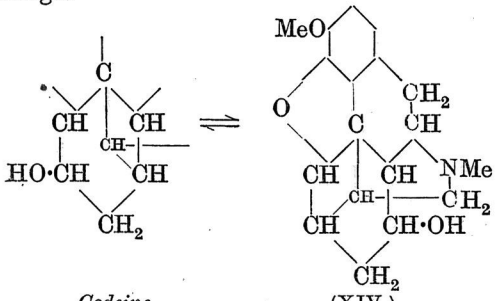
(XII.) $Me_2C{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}OH$

(XIII.) $Me_2C{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe(OH){\cdot}CH{:}CH_2$

These alcohols are interconvertible in several ways. Linalool may be obtained from geraniol by heating with water at 200° under pressure, by hydrolysing the chlorides obtained from geraniol, and by passing steam into an aqueous solution of geranyl hydrogen phthalate. On the other hand, linalool may be converted into geraniol by hydrolysis of the products of the action of hydrochloric acid, by treatment with half a per cent. of sulphuric acid in acetic acid solution, and best of all by means of acetic anhydride, which produces geranyl acetate. The molecular changes involved in these reactions are illustrated in the scheme:



On the partial valency cycle theory of intramolecular re-arrangement this example belongs to the considerable group (including the Beckmann change) which involves a four-ring intermediate stage. The conversion of codeine into ψ-codeine (XIV) can be quite analogously represented and the intermediate stage is given in the part-formula (XV) for purposes of comparison. It is a decided advantage of the bridge formulation of codeine (X) and the attachment of the bridge carbon to 8 that we are thus able to represent this characteristic wandering of oxygen as an interchange.



Codeine. (XIV.) (XV.)

Both the codeine and ψ-codeine structures can be set up on models of the Engler type and are found to be relatively unstrained arrangements. On inspection, it is seen that the formation of *iso*codeine (6—OH series) from ψ-codeine through β-chlorocodide is most readily explicable if it is assumed that the hydroxyl and the bridge are in *trans*-relation in codeine. The argument of Knorr that codeine and ψ-codeine must have the same carbon skeleton because they may be converted into one and the same deoxycodeine has little weight, since the deoxycodeine is not obtained directly but through the halogeno-codides. Obviously a transformation of the more labile into the more stable series is not excluded and it would appear from this evidence that such a change does, in fact, occur during the formation as well as during the hydrolysis of the halogeno-codides.

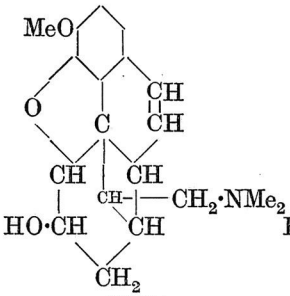
The Isomeric Methylmorphimethines.

These substances are obtained by the decomposition of the codeine methohydroxides, and each of the codeines gives rise to a distinct methylmorphimethine. Those derived from codeine and *iso*codeine may be converted into isomerides by the action of alcoholic alkali and in other ways, whereas those derived from *allo*-ψ-codeine and ψ-codeine are not convertible into isomerides. It is very important to note that none of the methylmorphimethines can have more than one benzene ring because they are all unsaturated and the formula X is the first codeine formula to be proposed which offers an explanation of this fact. The occurrence of a second aromatic nucleus is, of course, inhibited by the attachment of the side chain to 13. The following table exhibits the relations and nomenclature of the six methylmorphimethines.

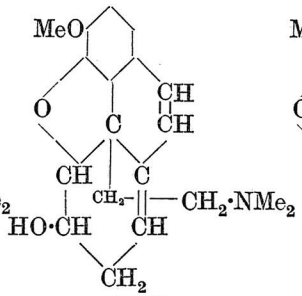
Methohydroxide from

Codeine	*iso*Codeine	*allo*-ψ-Codeine	ψ-Codeine
↓	↓	↓	↓
α-	γ-	ζ-	ϵ-
↓	↓		
β-	δ-Methylmorphimethine.		

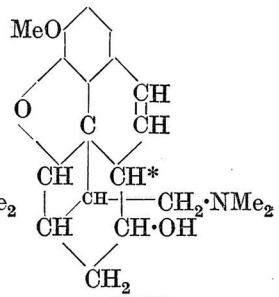
It has been clearly proved that the hydroxyl group in α-, β-, γ-, and δ-methylmorphimethines is at 6 and in the ϵ- and ζ-isomeridse at 8. The codeine formula (X) allows the change of α into β and γ into δ to be explained in a simple manner as shown in the formulæ XVI and XVII for the α- and β-isomerides, respectively.



(XVI.)

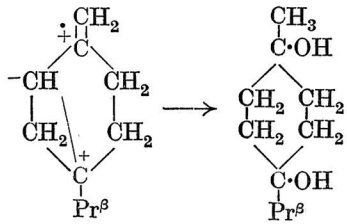


(XVII.)

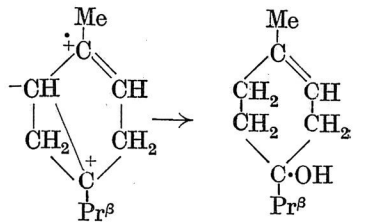


(XVIII.)

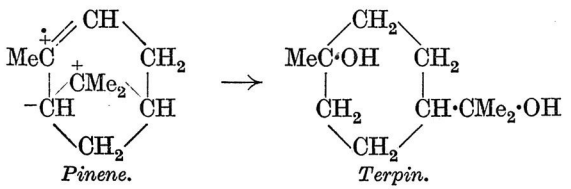
ε- and ζ-Methylmorphimethines receive the formula XVIII and the stability of these substances towards alcoholic potassium hydroxide is easily understood when it is considered that the more unstable bridge link is removed in this expression from the double bond and the tendency to form a conjugated system of two ethylene linkages has little scope. Examples culled from the terpene group show that a bridge breaks down with especial facility when in so doing it can directly produce a conjugated system. The formation of carvenone from carone, carvotanacetone from thujone, and eucarvone from carvone hydrobromide may be cited in this connexion. If, however, the bridge is connected to a carbon atom in the α-position with respect to a carbonyl or ethylene group, a conjugated system is not formed, because the α-carbon is negative and the β-atom positive. This point is illustrated in the schemes :



Sabinene. 1 : 4-*Terpin.*



Thujene. *Terpinenol.*



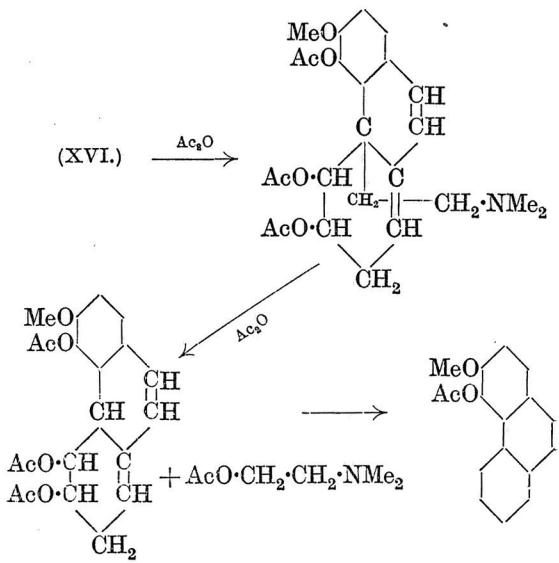
Pinene. *Terpin.*

The ease with which a double bond is formed in the conjugated position to an unsaturated group by a break away from the β-position and not from the α-position is analogous to the ready

decomposition of hydracrylic acid and the stability of lactic acid. From the above it will be seen that in the α- and γ-methylmorphimethines we have the ideal conditions for the break of the bridged ring which is favoured both by the tendency to form a conjugated system and by the considerations connected with polarity. It may be remarked that we should expect ε-methylmorphimethine to be more stable towards acids than the ζ-isomeride, because in the former substance the hydroxyl group and the hydrogen atom marked with an asterisk in formula XVIII are in *trans*-relation. As a matter of fact, derivatives of *allo*-ψ-codeine have been little investigated.

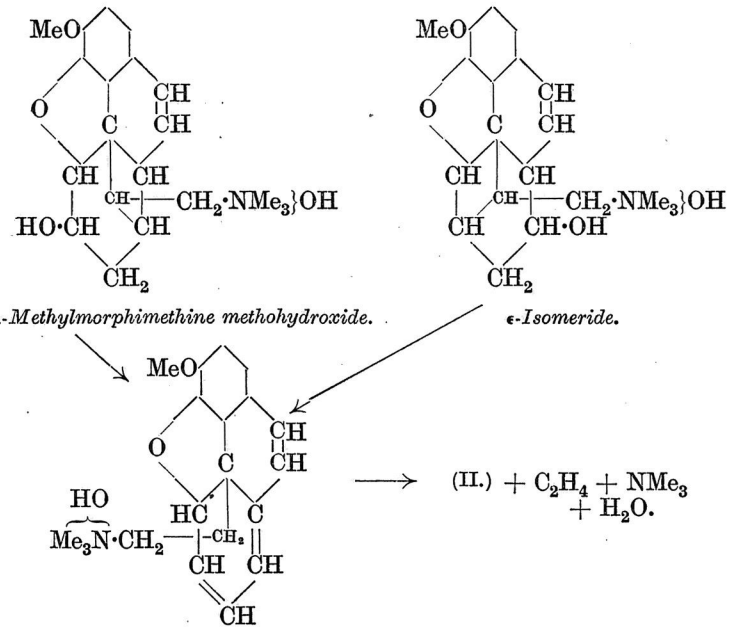
The Degradation to Morphol Derivatives.

This fission takes place under a variety of conditions and the basic side chain is removed in various forms, which include dimethylaminoethanol and its acetate, dimethylaminoethyl ether, and tetramethylethylenediamine. The last substance results from the addition of dimethylamine to vinyldimethylamine. A single example will suffice and the stages represented are, of course, hypothetical and designed to show that formula X provides a natural explanation. The point which is stressed is the compulsory removal of the ethylene side chain in order that the aromatic ring may be formed. A by-product of the reaction chosen is the acetyl derivative of β-methylmorphimethine.



Production of Morphenol from Methylmorphimethine Methohydroxides.

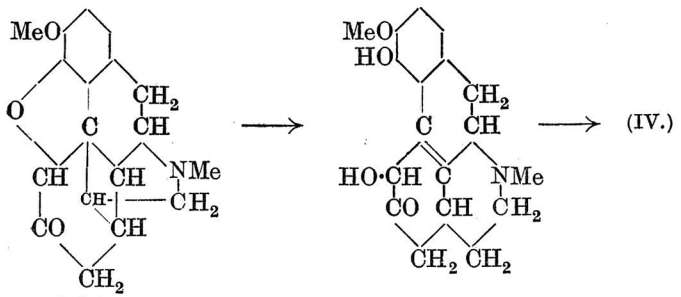
The state of oxidation of a tertiary base is increased by its conversion into a methohydroxide, and the methylmorphimethine methohydroxides are, for this reason, able to change to an aromatic phenanthrene without the opening of the oxide ring. The following is self-explanatory:



apo*Morphine and Morphothebaine.*

The severance of the 8–15-binding leading to the formation of non-nitrogenous phenanthrene derivatives is experimentally readily recognised, because the products are not basic and often are easily separated and purified. In many cases, however, there has been observed the production of phenanthrene bases and this is due to the breaking of the union of 15 to 13. The reason for the elimination of the ethylene group is then non-existent. The formation of morphothebaine from codeinone by the action of hot concentrated hydrochloric acid furnishes one of the smoothest known processes of this kind and the production of *apo*morphine

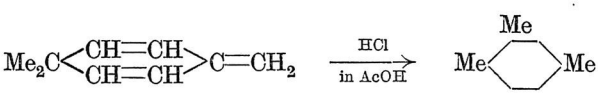
from chlorocodide, for example, is an entirely similar reaction. The former case may be chosen as an example :



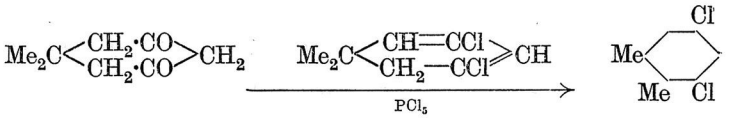
Codeinone.

Thebenine.

This base is formed by the action of hot dilute hydrochloric acid on thebaine, or the first product of its hydrolysis, namely, codeinone, and from ψ-codeinone by a similar method. It has been conclusively proved by Pschorr to have the formula XIX (R = $CH_2 \cdot CH_2 \cdot NHMe$) and therefore it is remarkable that it should be obtainable both from codeinone (CO at 6) and ψ-codeinone (CO at 8), especially since the reaction is facile in the former case and somewhat difficult to bring about in the latter. There are only two conceivable explanations whatever the constitution of morphine may be. Either oxygen wanders and this is very unusual in the case of oxygen of a carbonyl group, or the lower ring revolves about 180° at some stage. We take first the formation from ψ-codeinone in which the oxygen is already in the correct position. There are two ways in which blocked hydroaromatic substances having a suitable state of oxidation are known to pass into aromatic compounds. One is by displacement of a group from the molecule altogether and the other, almost as common, is by the wandering of a group to an adjacent carbon atom. We believe that the formation of thebenine involves such a migration and formula X for codeine leads to an explanation of the reaction for which there are many analogies. The following will serve to illustrate this point :

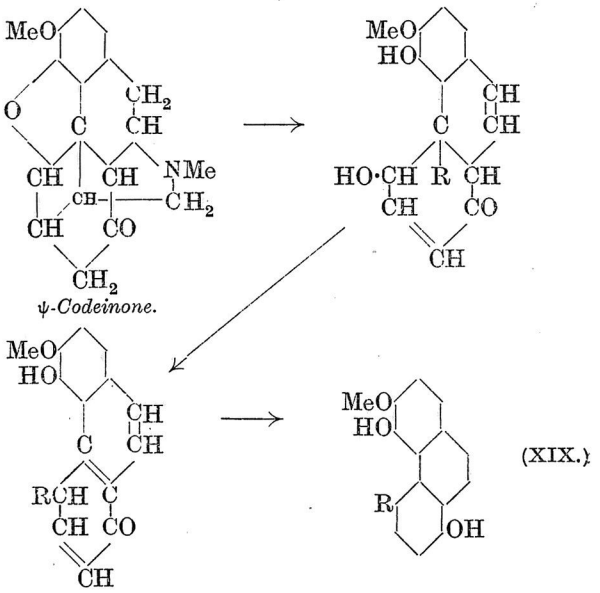


(von Auwers and Ziegler, *Annalen*, 1921, **425**, 217).



(Crossley and Le Sueur, T., 1902, **81**, 827, 1533).

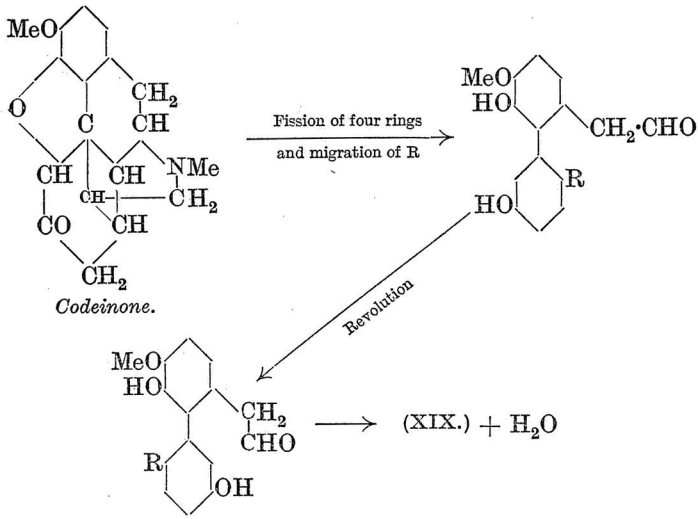
The stages in the production of thebenine can be represented in the following manner (R = ·CH_2·CH_2·NHMe):



(XIX.)

The molecular rearrangement is of the *iso*borneol-camphene type. Probably the difficulty experienced in the conversion of ψ-codeinone into thebenine is connected with the initial stages, because the bridge in the ψ-series is, in other reactions, more difficult to break than in the codeine series.

In the formation of thebenine from codeinone (thebaine) we may, of course, assume a similar mechanism plus migration of oxygen from 6 to 8 and in this respect formula X for codeine labours under no disadvantage from which other formulæ are free. The following mechanism seems, however, more probable and we put it forward with the reservation that the acceptance of this detail is not essential to our case.



If this is correct, the two schemes given are related in that the group R prefers to migrate to that adjacent carbon atom which is most remote from the carbonyl group. A careful examination of the whole of the literature relating to morphine and its allies has not disclosed any facts which are not in harmony with formula X for codeine, nor any which demand a special explanation, as in the case of thebenine.

The problem of thebainone is considered in Part II. Having now reviewed the facts on the basis of formula X, it remains to consider whether the alternative XI is equally satisfactory as a summary of the relations of these alkaloids. In our opinion, this is not so, although the arguments are not of a decisive character. If XI represents the molecule of codeine, ψ-codeine would be a *cyclo*pentane derivative and the difference in stability of the ring systems should be considerable, so that the reversibility of the codeine–ψ-codeine transformation presents a difficulty. The isomerisation of α- and γ-methylmorphimethines would not receive a very natural explanation and there would be no apparent reason why the ϵ- and ζ-isomerides are unattacked by alcoholic potassium hydroxide. The formation of thebenine from codeinone would necessarily involve rotation of the lower ring, and from ψ-codeine it would involve rotation and wandering of oxygen as well. For these reasons, we propose formula X as being, in all probability, the best representation of the constitution of codeine. Thebaine is the methyl ether of a tautomeric form of codeinone and on the basis of the codeine constitution now brought forward several

alternatives call for consideration. It is hoped that the matter will be discussed in detail in a future communication, but it may be stated now that we regard thebaine as dehydrocodeine methyl ether, in the molecule of which the carbon atoms at 6 and 14 are directly connected by a bond. This conclusion has been drawn mainly as the result of a study of hydroxycodeinone, a base prepared by Freund by the oxidation of thebaine with hydrogen peroxide. The formulæ proposed hitherto as symbols of the behaviour of hydroxycodeinone and its derivatives have all contained the group $-CH(OH)-CO-$ in spite of the fact that it reduces neither Fehling's solution nor ammoniacal silver nitrate and cannot be converted into an osazone. If the hydroxyl group is not situated in the α-position with respect to carbonyl, it is equally certain that hydroxycodeinone and hydroxydihydrocodeinone are not β-hydroxyketones, because they are very much too stable and exhibit no tendency to lose the elements of water. Similar arguments can be cited to show that the only tenable hypothesis is that this oxidation product of thebaine is 14-hydroxycodeinone and this leads to the unexpected and remarkable thebaine formula which has been indicated above. Inspection of the models shows that the arrangement is not particularly strained, although more so than in codeine, and that carbon atoms in the alicyclic portion of the molecule occur at seven of the corners of a cube. A further interesting point is that the benzene ring is constrained and most naturally assumes the boat-shaped configuration recently suggested by Sir William Bragg as the probable arrangement existing in the crystal molecules of aromatic compounds. Finally, it may be pointed out that the pinocean formula for morphine is in reality a modification of Pschorr's original "pyridine" formula, and although we refrain from using the fact as an argument, a proceeding which would be an inversion of the logical order of development, it could have been printed without any modification of the text in place of the Pschorr formula in the scheme developed by one of us to represent the genetic relationships of the *iso*quinoline group of the alkaloids. It is merely a question of the direction of elimination of one molecule of water so as to produce a bridge instead of a double bond. The experimental work on which we are engaged in connexion with this subject is designed to provide crucial tests of the suggestions now advanced and is greatly facilitated by a generous gift of material from Professor W. H. Perkin, to whom we tender our warmest thanks. In collaboration with Dr. C. F. van Duin, one of us is also attacking the problem of the constitution of neopine, a rare opium alkaloid discovered by T. and H. Smith, and investigated by Dobbie and Lauder. This base was known

only as a gum which yielded a crystalline hydrobromide and it was thought to be a hydroxycodeine. Dr. van Duin has luckily succeeded in crystallising the substance and it is a new isomeride of codeine. We are greatly indebted to Messrs T. and H. Smith for a supply of this unique material and for the trouble which they have taken in preparing it in a state of purity.

Summary.

A new formula for codeine (morphine methyl ether) is suggested, the main stages in the argument being the following :

1. Codeine is not unsaturated but contains a bridged ring.

2. The position of the bridge is deduced from (*a*) degradation of morphine or codeine to *apo*morphine and of codeine or thebaine to morphothebaine, (*b*) the relation of the morphine group to other opium alkaloids, (*c*) the consideration that in the decompositions leading to non-nitrogenous aromatic phenanthrene derivatives the breaking of a carbon-to-carbon union occurs because the point of attachment of the ethanamine chain offers a structural obstacle to the formation of aromatic nuclei.

3. The formula so deduced provides a natural explanation of the codeine–ψ-codeine transformation, the isomerisation of α- and γ-methylmorphimethines, the production of methylmorphol, morphenol, morphothebaine, etc., in the course of various degradations.

4. Thebenine is regarded as owing its production from codeinone and ψ-codeinone to a molecular rearrangement analogous to that of *iso*borneol into camphene.

5. A conceivable alternative constitutional formula accommodating the condition mentioned in (2, *c*) is found to be not so satisfactory a summary of the chemistry of morphine and its derivatives as that which is adopted.

References.

Isomeric Morphines and Codeines, Halogeno-morphides and -codides : Anderson, *Annalen*, 1851, **77**, 356; Armstrong, *ibid.*, 1871, **159**, 391; Grimaux, *Compt. rend.*, 1881, **92**, 1140, 1228; Dott, *Pharm. J. Trans.*, 1882, **12**, iii, 1009; Merck, *Arch. Pharm.*, 1891, **229**, 161; Göhlich, *ibid.*, 1893, **231**, 235; Schryver and Lees, T., 1900, **77**, 1024; 1901, **79**, 563; Lees and Tutin, P., 1906, **22**, 253; Lees, P., 1907, **23**, 200; T., 1907, **91**, 1408; Knorr and Hörlein, *Ber.*, 1906, **39**, 4409; 1907, **40**, 376, 2032, 3341, 4883, 4889; 1908, **41**, 969; Knorr and Roth, *Ber.*, 1907, **40**, 3355; Knorr, Hörlein, and Grimme, *Ber.*, 1907, **40**, 3844; Ach and Steinbock, *Ber.*, 1907, **40**, 4281; Oppé, *Ber.*, 1908, **41**, 975; Knorr, Butler, and Hörlein, *Annalen*, 1909, **368**, 305.

Morphimethines and Methylmorphimethines : Grimaux, *Compt. rend.*, 1881, **93**, 591; Hesse, *Annalen*, 1884, **222**, 203; Knorr, *Ber.*, 1889, **22**, 181, 1113; 1894, **27**, 1144; Vongerichten, *Ber.*, 1896, **29**, 65; 1897, **30**, 2439; 1899, **32**, 1047, 2379; Schryver and Lees, T., 1901, **79**, 563; Knorr and

Smiles, *Ber.*, 1902, **35**, 3009; Knorr and Hawthorne, *ibid.*, p. 3010; Knorr, *Ber.*, 1904, **37**, 3494; Pschorr, Roth, and Tannhäuser, *Ber.*, 1906, **39**, 19; Knorr and Hörlein, *Ber.*, 1906, **39**, 4412; Vongerichten and Hübner, *Ber.*, 1907, **40**, 2827; Knorr, Hörlein, and Grimme, *Ber.*, 1907, **40**, 3844; Vongerichten and Densdorff, *Ber.*, 1907, **40**, 4146; Pschorr, Dickhäuser, and D'Avis, *Ber.*, 1911, **44**, 2633; Knorr and Roth, *Ber.*, 1911, **44**, 2754; Pschorr and Dickhäuser, *Ber.*, 1912, **45**, 1570; Pschorr, *Ber.*, 1912, **45**, 2212.

Morphol and Derivatives: Fischer and Vongerichten, *Ber.*, 1886, **19**, 792; Knorr, *Ber.*, 1889, **22**, 181, 1113; 1894, **27**, 1144; Vongerichten, *Ber.*, 1897, **30**, 2439; 1898, **31**, 51, 2924, 3198; 1899, **32**, 1521; 1900, **33**, 352, 1824; Pschorr and Sumuleanu, *Ber.*, 1900, **33**, 1810; Knorr and Pschorr, *Ber.*, 1905, **38**, 3172; Barger, T., 1918, **113**, 218.

Morphenol and Derivatives: Vongerichten and Schrötter, *Ber.*, 1882, **15**, 1487; Vongerichten, *Ber.*, 1897, **30**, 2439; 1898, **31**, 51, 3198; 1899, **32**, 1521; 1900, **33**, 352; 1901, **34**, 2722; Pschorr and Sumuleanu, *Ber.*, 1900, **33**, 1810; Schryver and Lees, T., 1901, **79**, 578; Vongerichten and Dittmer, *Ber.*, 1906, **39**, 1718; Pschorr, Zeidler, Dickhäuser, Treidel, and Koch, *Annalen*, 1912, **391**, 40.

Oxidation of Codeine: Ach and Knorr, *Ber.*, 1903, **36**, 3067; Knorr and Schneider, *Ber.*, 1906, **39**, 1414; Knorr and Hörlein, *Ber.*, 1906, **39**, 3252; 1907, **40**, 2042; Pschorr and Einbeck, *Ber.*, 1907, **40**, 1980; Pschorr, Vogtherr, Kuhtz, and Roth, *Ber.*, 1906, **39**, 3130.

Degradation of Codeinone and ψ-Codeinone: Knorr, *Ber.*, 1904, **37**, 3501; 1903, **36**, 3074; 1905, **38**, 3171; Pschorr, Seidel, and Stöhrer, *Ber.*, 1902, **35**, 4400; Vongerichten, *Ber.*, 1902, **35**, 4410; Knorr and Hörlein, *Ber.*, 1907, **40**, 2035, 2039, 3350; Pschorr and Busch, *Ber.*, 1907, **40**, 2001.

apo*Morphine:* Matthieson and Wright, *Annalen*, 1870, Suppl. 7, 172; Mayer, *Ber.*, 1871, **4**, 121; Liebert, *Jahresbericht Fortschr. Chem.*, 1872, 755; Oberlin, *J. Pharm. Chim.*, 1876, [iv], **21**, 89; Pschorr, Jaeckel, and Fecht, *Ber.*, 1902, **35**, 4377; Pschorr and Karo, *Ber.*, 1906, **39**, 3124; Pschorr, *Ber.*, 1907, **40**, 1984; Pschorr, Einbeck, and Spangenberg, *Ber.*, 1907, **40**, 1998; Pschorr and Busch, *Ber.*, 1907, **40**, 2001.

Morphothebaine: Howard, *Ber.*, 1884, **17**, 527; Freund and Holthoff, *Ber.*, 1899, **32**, 168; Knorr, *Ber.*, 1903, **36**, 3074; Freund, *Ber.*, 1899, **32**, 173; Knorr and Pschorr, *Ber.*, 1905, **38**, 3153; Pschorr and Halle, *Ber.*, 1907, **40**, 2004; Pschorr and Rettberg, *Annalen*, 1910, **373**, 51; Pschorr and Knöffler, *Annalen*, 1911, **382**, 50.

Thebaol: Freund and Göbel, *Ber.*, 1895, **28**, 941; Freund, Göbel, and Michaels, *Ber.*, 1897, **30**, 1357; Pschorr, Seidel, and Stöhrer, *loc. cit.*; Vongerichten, Ber., 1902, **35**, 4410.

Thebenine: Freund and Michaels, *Ber.*, 1897, **30**, 1357; Freund and Holthoff, *Ber.*, 1899, **32**, 168; Knorr, *Ber.*, 1903, **36**, 3074; Pschorr and Massaciu, *Ber.*, 1904, **37**, 2780; Knorr and Pschorr, *Ber.*, 1905, **38**, 3153; Knorr and Hörlein, *Ber.*, 1907, **40**, 2037; Pschorr, Loewen, and Rettberg, *Annalen*, 1910, **373**, 51; Pschorr and Zeidler, *Annalen*, 1910, **373**, 75.

Indications of $\cdot CO \cdot CH_2 \cdot$ *in Derived Ketones:* Knorr and Hörlein, *Ber.*, 1907, **40**, 3349, 3353; Schneider, *Dissertation*, Jena, 1906; Herrschmann, *Dissertation*, Berlin, 1906.

Deoxycodeine and the Isomeric Tetrahydrodeoxycodeines: Knorr and Hörlein, *Ber.*, 1907, **40**, 376, 2032, 3352, 4883; Knorr and Waentig, *Ber.*, 1907, **40**, 3860; Göhlich, *Arch. Pharm.*, 1893, **231**, 235; Lees, T., 1907, **91**, 1408; Skita and Franck, *Ber.*, 1911, **44**, 2862; Freund, Melber, and Schlesinger, *J. pr. Chem.*, 1920, [ii], **101**, 1.

Further References to Reduction of the Alkaloids : Freund and Holthoff, *Ber.*, 1899, **32**, 168; Pschorr, Pfaff, and Herrschmann, *Ber.*, 1905, **38**, 3160; Oldenburg, *Ber.*, 1911, **44**, 1829; Mannich, *Arch. Pharm.*, 1916, **254**, 349; Mannich and Löwenheim, *Arch. Pharm.*, 1920, **258**, 295; Freund, Speyer, and Guttman, *Ber.*, 1920, **53**, [*B*], 2250; Speyer and Siebert, *Ber.*, 1921, **54**, [*B*], 1519; Skita, Nord, Reichert, and Stukart, *ibid.*, p. 1560; Speyer, Selig, and Heil, *Annalen*, 1922, **430**, 1.

Codeinone and Derivatives from Thebaine : Knorr and Hörlein, *Ber.*, 1906, **39**, 1409; Freund, *Ber.*, 1906, **39**, 844; Freund and Speyer, *J. pr. Chem.*, 1916, [ii], **94**, 135; *Münch Med. Woch.*, 1917, **64**, 380.

Phenyldihydrothebaine : Freund, *Ber.*, 1905, **38**, 3234; Freund and Speyer, *Ber.*, 1916, **49**, 1287. *Thebaizone :* Pschorr and Einbeck, *Ber.*, 1907, **40**, 3652. iso*Thebaine :* Gadamer, *Z. angew. Chem.*, 1913, **26**, 625; *Chem. Zentr.*, 1913, ii, **4**, 2046; Klee, *Arch. Pharm.*, 1914, **252**, 211. *Relation of morphine to other opium alkaloids :* Robinson, T., 1917, **111**, 892. *Papers in which morphine formulæ are propounded :* Knorr, *Ber.*, 1889, **22**, 1113; 1899, **32**, 742; 1903, **36**, 3074; Knorr and Pschorr, *Ber.*, 1905, **38**, 3172; Knorr and Hörlein, *Ber.*, 1906, **39**, 1414; 1907, **40**, 2042, 3341; Pschorr, Jaeckel, and Fecht, *Ber.*, 1902, **35**, 4377; Pschorr, *Ber.*, 1905, **38**, 3160; Pschorr and Einbeck, *Ber.*, 1907, **40**, 3652; Pschorr, Dickhäuser, and D'Avis, *Ber.*, 1912, **45**, 2212; Freund, *Ber.*, 1897, **30**, 1357; 1905, **38**, 3234; Freund and Speyer, *Ber.*, 1916, **49**, 1287; Vis, *J. pr. Chem.*, 1893, [ii], **47**, 584; Vongerichten, *Ber.*, 1900, **33**, 335; Bucherer, *J. pr. Chem.*, 1907, [ii], **76**, 428; von Braun, *Ber.*, 1914, **47**, 2312; Faltis, *Pharm. Post*, 1906, **39**, 497; *Arch. Pharm.*, 1917, **255**, 85; Gadamer, *loc. cit.*; Wieland and Kappelmeier, *Annalen*, 1911, **382**, 306.

The above is not a complete list of the publications dealing with the chemistry of morphine and related alkaloids.

UNITED COLLEGE,
THE UNIVERSITY, ST. ANDREWS. [*Received, February 23rd*, 1923.]

PRINTED IN GREAT BRITAIN BY RICHARD CLAY & SONS, LIMITED,
BUNGAY, SUFFOLK.

THE MORPHINE GROUP. PART II. THEBAINONE, THEBAINOL, AND DIHYDROTHEBAINONE.

BY

JOHN MASSON GULLAND

AND

ROBERT ROBINSON.

Publication 2.

The whole of the work described in this paper was carried out by me.

From the Transactions of the Chemical Society, 1923. Vol. 123.

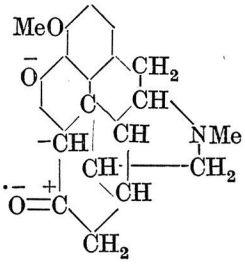
CXIII.—*The Morphine Group. Part II. Thebainone, Thebainol, and Dihydrothebainone.*

By John Masson Gulland and Robert Robinson.

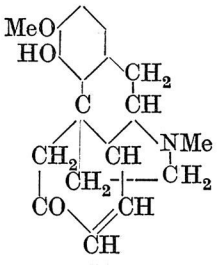
Thebainone is an isomeride of codeine which was first prepared by Pschorr, Pfaff, and Herrschmann (*Ber.*, 1905, **38**, 3160) by the reduction of thebaine by means of stannous chloride and hydrochloric acid at 100° and subsequently by Knorr (*ibid.*, 3171) by the application of a similar method to codeinone. It is derived from codeinone by the addition of two atoms of hydrogen, and the general character of the substance is readily deduced because the tertiary base is also a phenolic ketone, which has a pale yellow colour and dissolves in water to an intense yellow solution, whilst in alkalis it yields an orange solution. These properties recall the

behaviour of salicylideneacetophenone and there can be little doubt that thebainone is an αβ-unsaturated ketone.

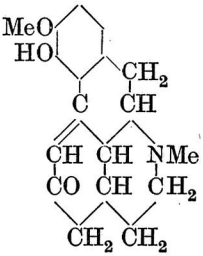
Evidently the production of the substance from codeinone involves the opening of the oxide ring by reduction and simultaneously the bridged system is broken with formation of an ethylene linkage. On the basis of the formulæ proposed in the preceding communication, codeinone (I) could undergo this transformation in two conceivable directions and thebainone might have either of the structures II and III. The + — signs in the codeinone formula are intended to indicate an explanation of the reducibility of the oxide ring in this substance.



(I.)



(II.)

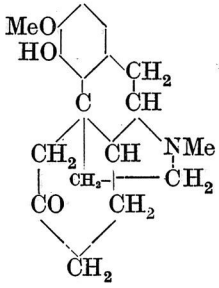


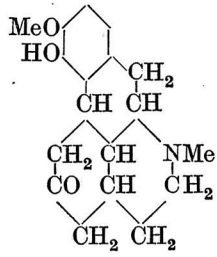
(III.)

Knorr and Pschorr (*Ber.*, 1905, **38**, 3172) have, however, shown that methylthebainonemethine may be degraded to dimethylmorphol, and consistently with the arguments advanced in Part I we must therefore prefer the constitution II, because III provides no explanation of the loss of the ethanamine chain in the course of the formation of the aromatic nucleus. When thebainone is reduced in aqueous solution by means of sodium amalgam, the orange colour of the liquid is gradually discharged and a dihydroderivative is obtained. This substance was first prepared by Pschorr (*loc. cit.*) and regarded by him as the secondary alcohol corresponding to thebainone and hence named thebainol. It was crystallised from methyl alcohol and melted at 50—54°; the crystals contained solvent of crystallisation, but were dried before analysis. We have had no difficulty in preparing this product, but by crystallisation from dry ether have also obtained pure thebainol in colourless prisms melting at 135—136°. No proof of the secondary alcoholic character of thebainol was advanced by Pschorr, and the substance is in reality a ketone yielding a *semicarbazone* melting at 215—216°. Thebainol is therefore derived from thebainone by addition of two hydrogen atoms to the double bond and should have the constitution IV. An isomeride of thebainol has been prepared by Freund, Speyer, and Guttmann (*Ber.*, 1920, **53**, [*B*],

2250) and in a purer condition by Skita, Nord, Reichert, and Stukart (*Ber.*, 1921, **54**, [*B*], 1560) by the reduction of thebaine in acetic acid solution by hydrogen in presence of palladium or platinum. This ketone melts at 137—138°, but it is lævorotatory, whereas thebainol is dextrorotatory. Its semicarbazone melts at 225—226°, and a mixture with thebainol semicarbazone at about 205°. The two substances are quite distinct. The compound has unfortunately been called dihydrothebainone, although its relation to thebainone has never been proved in any way and in our opinion is non-existent. We propose, however, to retain for the present the misnomers thebainol and dihydrothebainone in order to avoid confusion, but at some later stage it may be desirable to replace the name thebainol by dihydrothebainone and dihydrothebainone by dihydro*iso*-thebainone. Dihydrothebainone is a tertiary basic, phenolic ketone. The phenolic hydroxyl must be at 4 and the carbonyl group at 6, so that the isomerism with thebainol can only be explained by the assumption that the bridged system has been broken down in each of the two conceivable directions and dihydrothebainone must have the constitution V. The possibility that thebainol and dihydrothebainone are stereoisomerides has not been overlooked, but the hypothesis does not appear to offer any consistent explanation of the facts.

(IV.)



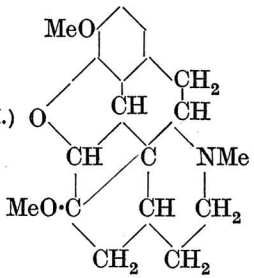


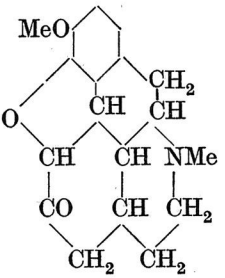
(V.)

This case of isomerism would be inexplicable if codeine contained one and thebaine two double bonds and the relation of thebainol to dihydrothebainone is quite analogous to that existing between the two tetrahydrodeoxycodeines (Part I., p. 983). The former two substances are, in fact, 6-keto-derivatives of the latter two. In the reduction of thebaine to dihydrothebainone it has been shown that an intermediate product is a dihydrothebaine (m. p. 162—163°) which is not phenolic and in accordance with our view of the nature of dihydrothebainone and of thebaine is to be represented by the formula VI. This dihydrothebaine yields on hydrolysis a dihydrocodeinone (VII) crystallising in columns melting at 197—198° and

forming an oxime decomposing at 264°. Mannich and Löwenheim (*Arch. Pharm.*, 1920, **258**, 295) have apparently obtained the same substance (prisms, m. p. 193—194°; oxime, m. p. 266°) by the reduction of codeinone with hydrogen in presence of palladium.

(VI.)





(VII.)

On further reduction by Clemmensen's method, this dihydrocodeinone yields a tetrahydrodeoxycodeine the description of which by Mannich and Löwenheim does not quite coincide with that of either the α- or β-tetrahydrodeoxycodeine by Freund, Melber, and Schlesinger (*J. pr. Chem.*, 1920, [ii], **101**, 1). Clearly, a direct comparison would allow of the determination of the relation of the α- and β-isomerides to thebainol and dihydrothebainone and so provide interesting information in regard to the direction of scission of the ring system under various conditions. The structural distinction between thebainol and dihydrothebainone is further of interest in connexion with the constitution of codeinone.

Although it is usually assumed that the relation of codeinone to codeine is that of ketone to secondary alcohol, there is no satisfactory proof of this. Ach and Knorr (*Ber.*, 1903, **36**, 3067), in the introduction to their paper, state that codeinone may be reduced to codeine, but no experimental details have been published and, as mentioned above, catalytic reduction produces a new ketone, dihydrocodeinone. Further it is stated in some text-books that codeinone undergoes the Claisen condensation and therefore must contain the group $-CH_2 \cdot CO-$. But definite benzylidene and *iso*nitroso-derivatives have only been obtained from ψ-codeinone, and our experiments have convinced us that codeinone, probably because of its instability in presence of acids or alkalis, does not yield similar compounds. The sole evidence that codeinone contains a reactive methylene group is furnished by the formation of azo-derivatives, but this is not decisive because the azo-compound might be of the form $Ar-N_2-C-CO-$ instead of $Ar-N_2-CH-CO$ or $Ar-N_2-C{=}C(OH)-$. In order to make this test a more stringent one, we have examined the behaviour of the azo-compounds on treatment with alkali. Comparison of a large number of cases shows

that if there is a mobile hydrogen atom in the *p*-nitrobenzeneazo-derivatives especially, as, for example, in those obtained by coupling with phenols or ketones containing the group $-CH_2 \cdot CO-$, an intense coloration is developed on the addition of potassium hydroxide to an alcoholic solution. No such colour is obtained by similar treatment of ethers of the nitrobenzeneazophenols or other *p*-nitrobenzeneazo-compounds not containing a mobile hydrogen atom in the system. The results show that codeinone forms azo-derivatives capable of passing into more intensely coloured modifications in presence of alcoholic potassium hydroxide and therefore the substance must contain the group $-CH_2-CO-$. Apart from these observations, the quite possible alternative is that codeinone is unsaturated and not related in a simple manner to codeine. But in that case codeinone would clearly have the same carbon skeleton as thebainone, into which it passes by reduction. We should thus have the following related series all having the same carbon skeleton : thebainol, thebainone, codeinone, dihydrocodeinone, dihydrothebaine, dihydrothebainone. If the view that thebainol and dihydrothebainone are structural isomerides is justified, it follows that codeinone cannot be an unsaturated ketone, but must contain the same alicyclic bridge as codeine. Inspection of the formulæ suggested for thebainone (II), thebainol (IV), and dihydrothebainone (V) shows that the first contains the group $-CH_2-CO-$ and the latter two the group $-CH_2-CO-CH_2-$. It appeared to be of great importance to confirm these deductions, because the occurrence of such a structure in both thebainol and dihydrothebainone would be inconsistent with a morphine formula in which the ethanamine chain is attached to 5, as in the Knorr formula or the dicyclic modification of this due to Freund and Speyer. Knorr and Hörlein (*Ber.*, 1907, **40**, 3349) state that Herrschmann (*Dissertation*, Berlin, 1906) had found that benzaldehyde condenses with thebainone, but no further publication has been made. We have now prepared and analysed benzylidenethebainone and piperonylidenethebainone and a methylenedioxyquinoline derivative obtained by condensation of thebainone with 6-aminopiperonal (Rilliet and Kreitmann, *Helv. Chim. Acta*, 1921, **4**, 588). Piperonylidenethebainone is an amorphous, pale yellow powder which exhibits the typical halochromy of a monopiperonylidene-$\alpha\beta$-unsaturated ketone. It gives a reddish-purple solution in concentrated sulphuric acid closely resembling that given by benzylidenepiperonylideneacetone, but not so blue as the solution of dipiperonylideneacetone in sulphuric acid. The condensation of thebainol with piperonal in alcoholic solution containing sodium ethoxide was followed by observing the halochromy of the product. Apparently a monopiperonylidene

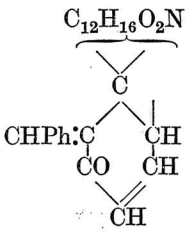
derivative was quickly produced and this gave a red colour in concentrated hydrochloric acid and thus resembled a monopiperonylidene saturated ketone. On prolonged treatment, the solution became bluer and ultimately a product was isolated, a yellow amorphous powder, which appears to be dipiperonylidenethebainol with $2H_2O$. This substance dissolves in hydrochloric acid to a pure blue solution which becomes green and then yellow on dilution with water. Dipiperonylidenethebainol methyl ether and dipiperonylidenedihydrothebainone methyl ether have also been prepared, but could not be crystallised. They exhibit the typical behaviour of dipiperonylidene-*cyclo*-ketones. The amorphous character of these substances is doubtless due to the fact that they are mixtures of stereoisomerides and it may be recalled that Haber has shown that the condensation of piperonal and acetone leads to both *cis*- and *trans*-piperonylideneacetones (*Ber.*, 1891, **24**, 617). We are at present engaged in experiments designed to overcome this difficulty, but in the meantime there can be little doubt but that both thebainol and dihydrothebainone contain the group $-CH_2-CO-CH_2-$. If this is so, the ethanamine chain cannot be attached to 5 and thebenine must owe its formation from codeinone to molecular rearrangement as suggested in the preceding communication.

EXPERIMENTAL.

Note on the Preparation of Thebainone.

As mentioned by Pschorr (*loc. cit.*), exceedingly troublesome emulsions are formed during the extraction of the base with chloroform, and the following slight modification avoids this difficulty without affecting the yield. Thebaine, stannous chloride, and hydrochloric acid in the proportions recommended by Pschorr were placed in a wide bomb tube closed by a tightly fitting rubber stopper, kept in position by wires. This was immersed during twenty minutes in boiling water and at the end of this period rapidly cooled by the addition of cold water to the bath. The mixture was then added to 800 c.c. of water, well shaken, and treated with aqueous sodium hydroxide (10 per cent.) until a permanent milkiness was produced and the solution was very faintly acid to Congo-red. There is no difficulty in gauging this point, because the thebainone is itself an indicator, and if too much alkali has been added the colour changes from yellow to orange-red. Neutralisation was then completed by means of successive small amounts of sodium bicarbonate and the precipitate allowed to settle over-night. The clear orange solution was decanted, treated twice with animal charcoal, filtered, and extracted by gently shaking with chloroform. Two extractions

removed the whole of the thebainone, which was purified in the manner described by Pschorr.

Benzylidenethebainone, 

A solution of thebainone (1 gram), benzaldehyde (1·2 grams; 3 mols.), and potassium hydroxide (0·5 gram, dissolved in the minimum of water) in ethyl alcohol (10 c.c.) was boiled during two hours under reflux. The colour of the solution rapidly changed from light red to crimson. After the addition of water (100 c.c.), the liquid was just acidified with dilute hydrochloric acid and thoroughly extracted with ether in order to remove benzaldehyde. The orange-red solution was freed from ether by means of a current of air, neutralised by sodium carbonate, and the yellow precipitate collected, washed with water, and dried in a vacuum over sulphuric acid. The yield was 90 per cent. of that theoretically possible. The substance is very readily soluble in most organic solvents and could not be crystallised. It was purified by precipitation from benzene solution with light petroleum and obtained as a yellow powder which softened at 114° and melted at 120—123° (Found: C = 77·3; H = 6·8. $C_{25}H_{25}O_3N$ requires C = 77·5; H = 6·8 per cent.). The solutions of the substance in concentrated hydrochloric acid and sulphuric acid are deep red and become yellow on dilution with water. The picrate crystallises from alcohol in radiating clusters of short needles. It melts with decomposition at 194° after darkening at 191°. The methiodide crystallises from ethyl acetate in yellow, tubular columns which melt indefinitely, beginning at 195°.

Piperonylidenethebainone.

This substance was prepared in the same way as the benzylidene derivative, replacing the benzaldehyde by piperonal (1·6 grams). The bright yellow powder which separated on the addition of light petroleum to a benzene solution of the derivative softens at 118° and melts at 128—130° (Found: C = 72·4; H = 6·2. $C_{26}H_{25}O_5N$ requires C = 72·4; H = 5·8 per cent.). The solution in concentrated hydrochloric or sulphuric acid is intense reddish-purple and becomes pale yellow on dilution with water. Crystalline derivatives could

not be obtained. Piperonylidenethebainone was reduced in 5 per cent. acetic acid solution by means of hydrogen in presence of palladium. The colourless solution gave no coloration with concentrated hydrochloric acid, but still gave an orange solution on the addition of sodium hydroxide. The product was therefore in all probability homopiperonylthebainone. The whole was rendered alkaline and reduced by means of sodium amalgam until the orange colour disappeared. The liquid was then just acidified with acetic acid, rendered alkaline by the addition of ammonia, and the colourless, sticky precipitate taken up in ether. After removal of the solvent, a colourless oil remained and this could not be crystallised. It gives coloured solutions neither in strong acids nor in dilute alkali, and is probably essentially homopiperonylthebainol. On condensation with piperonal in the usual manner, a yellow product was obtained and this gave a deep red solution in concentrated hydrochloric or sulphuric acid and is probably piperonylidenehomopiperonylthebainol. The series of reactions confirms the view that piperonylidenethebainone contains the group

$$CH_2O_2{:}C_6H_3{\cdot}CH{:}C{\cdot}CO{\cdot}CH{:}C-.$$

Dianhydro-6-aminopiperonalthebainone Dihydrobromide.

A solution of sodium ethoxide (0·5 gram Na) in alcohol (10 c.c.) was added to thebainone (1·1 grams) and 6-aminopiperonal (0·6 gram) dissolved in alcohol (10 c.c.), and the mixture boiled under reflux during six hours. The red solution was added to water (200 c.c.) and after filtration the phenolic base was precipitated by means of carbon dioxide. The yellow substance which separated dissolved as the passage of the gas was continued, but was redeposited on standing over-night exposed to the air. The precipitate was collected and dried (1·0 gram). All attempts to crystallise this quinoline derivative were unsuccessful, but a crystalline hydrobromide was obtained by the addition of concentrated hydrobromic acid to a solution of the base in a little acetic acid. The salt was crystallised from dilute aqueous hydrobromic acid and dried in a vacuum over sulphuric acid (Found: Br = 25·2; loss at 130° = 8·5. $C_{26}H_{24}O_4N_2,2HBr,3H_2O$ requires Br = 24·9; H_2O = 8·4 per cent.). The glistening, orange-yellow, rectangular plates decompose at 258—260° and dissolve in sulphuric acid to a solution which exhibits bright emerald-green fluorescence.

Thebainol and its Semicarbazone.

This substance was prepared by the method of Pschorr (*loc. cit.*), which depends on the reduction of thebainone by means of sodium

amalgam. The product, crystallised from methyl alcohol, melted at 50—54°, but long standing of a 10 per cent. dry ethereal solution provided a small crop of colourless prisms which were used to seed an approximately 20 per cent. solution in the same solvent. The well-formed, rectangular prisms melted at 135—136° (Found: C = 71·6; H = 7·5. $C_{18}H_{23}O_3N$ requires C = 71·8; H = 7·6 per cent.). Thebainol is one of the few morphine derivatives which, like deoxycodeine, are dextrorotatory. In ethyl alcohol, $c = 8·71$, $l = 0·5$ dcm., $\alpha = +2·92°$; whence $[\alpha]_D^{25°} = +67·05°$. In 5 per cent. acetic acid, $c = 2·368$, $l = 2·0$ dcm., $\alpha = +1·58°$; whence $[\alpha]_D^{25°} = +33·07°$.

On crystallisation of the product, m. p. 135—136°, from methyl alcohol, the melting point was again found to be 50—54°, but the substance resolidified and melted finally at about 135°. When the substance was mixed with dihydrothebainone (Freund, Speyer, and Guttmann's preparation), the melting point was depressed to 110°. Thebainol is readily soluble in dilute aqueous sodium hydroxide, but with a concentrated solution yields a precipitate of a colourless, crystalline sodium derivative.

Thebainolsemicarbazone was prepared in dilute acetic acid solution by the action of an excess of semicarbazide hydrochloride and sodium acetate. The mixture was warmed to 80°, then allowed to cool and, after five minutes, the solution was neutralised by sodium carbonate. The precipitate was collected and the derivative crystallised from aqueous alcohol and then from a mixture of ethyl alcohol and ethyl acetate. An identical product was obtained from pure thebainol, m. p. 135—136°, and from the original material having the properties recorded by Pschorr (Found: N = 15·8. $C_{19}H_{26}O_3N_4$ requires N = 15·6 per cent.). Rapid cooling of a solution in ethyl alcohol and ethyl acetate causes the separation of a cloud of globules which are so small that they may only be discerned under the higher powers of the microscope. Slow cooling produces frond-like bundles of slender needles and if crystallisation is very slow twinned prismatic needles are obtained. The substance melts at 215—216° as ordinarily prepared. After drying during four hours at 100° under 100 mm., there was no perceptible loss of weight, but the melting point rose to 217—218°. A mixture of thebainolsemicarbazone and dihydrothebainonesemicarbazone (m. p. 225—226°) melted at about 205°.

Thebainol Methiodide.—This derivative was obtained very readily by gently warming an alcoholic solution of thebainol and methyl iodide and allowing to remain during an hour. The addition of ether precipitated the substance in an amorphous condition and crystals were first obtained by the careful addition of ethyl acetate

to a solution in methyl alcohol. The crude product was then dissolved in methyl alcohol and addition of a crystal to the hot solution induced the crystallisation of most of the salt, which when pure is sparingly soluble in methyl alcohol. The substance was recrystallised from ethyl alcohol and obtained in colourless columns melting at 243° with decomposition [Found: I = 28·5, 28·9 (by titration). $C_{19}H_{26}O_3NI$ requires I = 28·6 per cent.]. The salt is dextrorotatory in aqueous solution: $c = 2{\cdot}061$, $l = 0{\cdot}5$ dcm., $\alpha = +0{\cdot}48°$; whence $[\alpha]_D^{25°} = +46{\cdot}56°$.

Dihydrothebainonesemicarbazone.

In the preparation of dihydrothebainone from thebaine it was observed that the mother-liquors deposited a small crop of crystals which, after recrystallisation from alcohol, were colourless, prismatic tablets melting at 219° and at the same temperature when mixed with pure cryptopine. Evidently cryptopine occurs as an impurity in thebaine, but cannot be detected by the characteristic reaction with sulphuric acid because the colour is masked by the deep orange due to thebaine itself. The specimen of thebaine employed began to melt at 188°, whereas pure thebaine melts at 193°. On one occasion, the palladium catalyst was inefficient and the main product of the reduction was dihydrothebaine, m. p. 165°. The substance crystallised from methyl alcohol in rectangular prisms and was proved to be identical with the dihydrothebaine, m. p. 162—163°, of Freund, Speyer, and Guttmann (*loc. cit.*) because it yielded dihydrocodeinone, m. p. 197—198°, on hydrolysis with concentrated hydrochloric acid. *Dihydrothebainonesemicarbazone* was prepared in the manner prescribed above for thebainolsemicarbazone. It crystallises from aqueous alcohol in colourless, elongated prisms melting at 224—225°. The substance, dried in a vacuum over sulphuric acid, lost 9·6 per cent. at 110—115° and then melted at 226—227° (Found, in anhydrous substance: N = 15·7. $C_{19}H_{26}O_3N_4,2H_2O$ requires $H_2O = 9{\cdot}1$; $C_{19}H_{26}O_3N_4$ requires N = 15·6 per cent.).

Dipiperonylidenethebainol.

A solution of thebainol (1 gram), piperonal (2 grams), and potassium hydroxide (0·5 gram) in ethyl alcohol (10 c.c.) was boiled under reflux. The yellow colour rapidly changed to red and a sample withdrawn after twenty minutes gave a bright red solution in concentrated hydrochloric acid. After two hours, the base was isolated exactly as described above in the case of benzylidenethebainone. The yellow powder gave a purple colour

with concentrated hydrochloric acid. It was noticed, however, that the initial treatment with dilute hydrochloric acid failed to dissolve a small quantity of brown material, which gave a bright blue colour with concentrated hydrochloric acid. It seemed probable, therefore, that thebainol condenses readily with one molecule of piperonal and forms a dipiperonylidene derivative with much greater difficulty. The product was accordingly dissolved in ethyl alcohol (10 c.c.) and, after the addition of piperonal (2 grams) and potassium hydroxide (0·5 gram, dissolved in a little water), the mixture was boiled during twenty hours. The colour in concentrated hydrochloric acid gradually changed from reddish-purple to pure blue and at the end of the period mentioned the dark red solution was added to water (150 c.c.) and carefully acidified with ice-cold dilute hydrochloric acid. The reddish-brown tar was collected on a glass rod, well washed with ether, and dissolved in acetic acid. On dilution with water, a precipitate was obtained and, after neutralisation of the acid present, this was collected, dried, and the substance purified by repeated precipitation from chloroform solution by means of light petroleum. The orange-yellow powder could not be crystallised and was dried in a vacuum over sulphuric acid (Found: C = 67·4; H = 6·0; N = 2·4. $C_{34}H_{31}O_7N,2H_2O$ requires C = 67·9; H = 5·8; N = 2·4 per cent.). The substance dissolved in concentrated sulphuric acid to a purple solution and in concentrated hydrochloric acid to a deep pure blue solution which became green and then pale greenish-yellow on dilution with water. The substance is readily soluble in acetone, chloroform, ethyl acetate, or alcohol, sparingly soluble in benzene, and almost insoluble in ether or light petroleum. The condensation of dihydrothebainone with piperonal was also carried out with similar results.

Dipiperonylidene Derivatives of Thebainol Methyl Ether and Dihydrothebainone Methyl Ether.

Methylation of thebainol and dihydrothebainone was effected by means of diazomethane, which was prepared by the method of Werner (T., 1919, **115**, 1098) from nitrosomethylurea. The decanted ethereal solution of the reagent was found to be unsuitable for use in these examples and was distilled. Moreover, methylation did not proceed in ether alone and it was found necessary to add the solution of diazomethane (6 mols.) to a 10 per cent. solution of the phenolic base in pure ethyl alcohol. The use of *iso*amyl ether was not advantageous. After allowing to remain at the ordinary temperature during twenty-four hours, during which time bubbles of nitrogen were evolved, the solvent was removed by distillation

and the oily residue triturated with dilute sodium hydroxide to separate any unchanged material. The oil was then taken up in ether and the solution washed, dried, and evaporated. The pale yellow, viscid residue, consisting either of thebainol methyl ether or of dihydrothebainone methyl ether, could not be crystallised. Thebainol methyl ether exhibited a curious behaviour on standing. Although completely soluble in ether when first prepared, some process of auto-condensation or oxidation occurred and when treated with the solvent there was a flocculent residue. After evaporation of the filtered solution and allowing to remain for a further period, more of this insoluble material was produced; the process was repeated five times with the same result and apparently would proceed indefinitely. The average yield of the methyl ethers was 60 per cent. of that theoretically possible.

Methylthebainol methiodide was obtained by the addition of a little more than one molecular proportion of methyl iodide to a solution of the ether in ethyl acetate. The precipitated oil solidified on rubbing with ether and acetone, and the substance crystallised from methyl alcohol in irregular prisms which melted at about 245° with decomposition [Found, in material dried at 100° in a vacuum: I = 27·8 (by titration). $C_{20}H_{28}O_3NI$ requires I = 27·8 per cent.].

Methyldihydrothebainone methiodide separated in clusters of boat-shaped crystals when methyl iodide was added to a solution of the base in ethyl acetate. The derivative was recrystallised from methyl alcohol and obtained in diamond-shaped prisms which darkened slightly at 257—258° [Found, in material dried at 100° in a vacuum: I = 27·8, 27·7 (by titration). $C_{20}H_{28}O_3NI$ requires I = 27·8 per cent.].

The condensation of thebainol methyl ether and of dihydrothebainone methyl ether with piperonal gave identical results. The base (1·6 grams) and piperonal (3·1 grams) were dissolved in ethyl alcohol (25 c.c.) and after the addition of a solution of sodium ethoxide (0·5 gram of sodium in 10 c.c. of alcohol) the mixture was boiled under reflux during twelve hours. A further quantity of piperonal (1·5 grams) was then added and the boiling continued during twelve hours. The dark red liquid was poured into moderately concentrated brine, and the reddish-brown precipitate collected, washed, and dried. After a preliminary purification by precipitation from a filtered chloroform solution by means of light petroleum, the yellow powder was dissolved in a large volume of hot alcohol, the solution treated with animal charcoal, filtered, and concentrated. The compound separated in microscopic, transparent, yellow globules and in a similar condition from ethyl acetate.

The derivative from methylthebainol softened at 149° and began to melt at 156°; that from methyldihydrothebainone softened at 160° and began to melt at 166°. For analysis, the substances, which tend to retain water to a marked degree, were dried at 110° (Found: for dipiperonylidenemethylthebainol, C = 71·2, 71·5; H = 5·5, 5·7; for dipiperonylidenemethyldihydrothebainone, C = 71·9; H = 6·1; N = 2·4. $C_{35}H_{33}O_7N,0{\cdot}5H_2O$ requires C = 71·4; H = 5·8; N = 2·3 per cent.). The colour reactions of the two compounds are identical. In sulphuric acid, a rich purple solution is produced, and addition of hydrochloric acid to a solution in glacial acetic acid develops an intense green coloration, which is also obtained from dipiperonylidenetropinone under similar conditions.

Interaction of Bromocodeinone and Hydrogen Iodide.

A solution of bromocodeinone hydrobromide (0·1256 gram) in ethyl alcohol (20 c.c.) and water (20 c.c.) was freed from air by boiling and passing a current of carbon dioxide. Potassium iodide (1·0 gram) was then added, and after cooling to 40° air-free 2*N*-hydrochloric acid (10 c.c.) was introduced and the mixture maintained at 45° in the neutral atmosphere during three and a half hours. The free mineral acid in the cooled solution was neutralised by the addition of potassium acetate, and the iodine set free in the reaction required 10·2 c.c. of 0·0252*N*-sodium thiosulphate. Hence one molecule of bromocodeinone hydrobromide liberates 0·97 atom of iodine. This is half the amount anticipated on the assumption that the process is a straightforward reduction to codeinone, but this substance, if formed, would be converted in the acid solution into thebenine to some extent and loss of halogen as the result of substitution in this phenol is a natural consequence. On the other hand, the reaction may follow an abnormal course such that one molecule of iodine is produced from two molecules of bromocodeinone. An experiment was carried out under the conditions described above but without bromocodeinone hydrobromide and no trace of iodine was liberated.

Coupling of Codeinone with Diazonium Salts.

The diazonium salt in aqueous solution in presence of excess of sodium acetate was added to an alcoholic solution of codeinone; subsequently alcoholic potassium hydroxide was introduced. Very dilute solutions were employed and under similar conditions codeine gave either no coloration or very pale shades unchanged in tone by the addition of alkali.

Base.	Colour produced.	After addition of KOH.
p-Toluidine	Yellow	Orange-red
p-Phenetidine	Yellow	Yellowish-brown
Cresidine	Yellow	Brownish-red
o-Nitroaniline	Yellow	Purplish-brown
m-Nitroaniline	Yellow	Reddish-brown
p-Nitroaniline	Orange-yellow	Reddish-violet
p-Nitro-*o*-toluidine	Yellow	Brownish-orange
Nitrocresidine	Brown	Brownish-violet
Picramic acid	Orange-yellow	Deep brown
2 : 4-Dinitro-*m*-toluidine	Lemon-yellow	Brownish-red tending to violet
p-Aminobenzoic acid	Pale yellow	Red
Aminosulphosalicylic acid	Greenish-yellow	Reddish-orange
Aminoazobenzene	Red	Dark brown
α-Naphthylamine	Orange-brown	Brownish-red
Naphthionic acid	Orange	Crimson
Tolidine	Orange-red	More intense
Dianisidine	Bluish-red	More intense
Diaminoveratrone	Orange-brown	Reddish-brown

Attempts to condense codeinone with benzaldehyde, anisaldehyde, piperonal, and nitrosodimethylaniline in the presence of various catalysts and under a variety of conditions were fruitless.

One of us (J. M. G.) desires to express his thanks to the Carnegie Trust for a scholarship which has enabled him to take part in this investigation.

CHEMISTRY RESEARCH LABORATORY,
THE UNITED COLLEGE OF ST. SALVATOR AND ST. LEONARD,
THE UNIVERSITY, ST. ANDREWS. [*Received, February 23rd,* 1923.]

PRINTED IN GREAT BRITAIN BY RICHARD CLAY & SONS, LIMITED,
BUNGAY, SUFFOLK.

From Volume 69 of "MEMOIRS & PROCEEDINGS OF THE MANCHESTER LITERARY AND PHILOSOPHICAL SOCIETY," *Session 1924-1925.*

The Constitution of Codeine and Thebaine

BY

JOHN MASSON GULLAND, Ph.D.

AND

PROF. R. ROBINSON, D.Sc., F.R.S.

Publication 3.

The whole of the work described in this paper was carried out by me.

MANCHESTER
36, GEORGE STREET.

Price Two Shillings.

July 23rd, 1925.

Manchester Memoirs, Vol. lxix. (1924-25), *No.* 10.

X. The Constitution of Codeine and Thebaine.

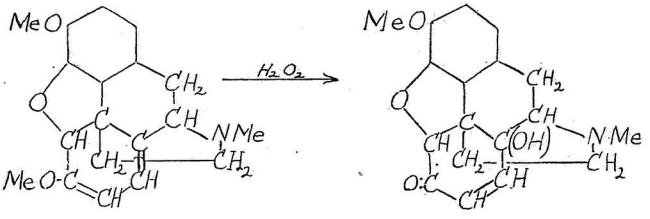
By JOHN MASSON GULLAND, PH.D., and
Prof. R. ROBINSON, D.SC., F.R.S.

WHEN thebaine, which is the methyl ether of a tautomeric form of codeinone, is oxidised with hydrogen peroxide it yields hydroxycodeinone (Freund and Speyer, *J. Pr. Chem.*, 1916 (ii.), **94**, 135), and the change has usually been represented as the transformation of the group $-C(OMe)=CH.$ to $-CO-CH(OH)-$.

This formulation of hydroxycodeinone as an α-hydroxyketone is, however, quite unjustified by the evidence and, in particular, the high degree of stability exhibited by the base towards alkaline cupric and silver solutions is not in harmony with the hypothesis. Nor, in view of the difficulty of dehydrating hydroxycodeinone and its derivatives, can the substance be a β-hydroxyketone, and it does not appear to be possible to construct a thebaine formula which can, in any plausible manner, give rise to a β-hydroxyketone having the composition of hydroxycodeinone. Nothing can be urged against the remaining alternative—namely, that hydroxycodeinone is a γ-hydroxyketone—and we consider that the substance is 14-hydroxycodeinone (II.) The relation to codeinone follows from the observations that bromocodeinone (*ex* thebaine) and hydroxycodeinone yields the same hydroxycodeinone oxime (Freund, *Ber.*, 1906, **39**, 844; Freund and Speyer, *loc. cit.*), and that bromocodeinone may be reduced to codeinone (Freund, *loc. cit.*). The experiments which we describe below indicate that hydroxycodeinone does not contain the group $-CO-CH_2-$, but that dihydrohydrocodeinone does, and this is best explained by the occurrence of the group $-CO-CH=C-C(OH)-$ in hydroxycodeinone. Working back to thebaine it is obvious that this base must contain the group $-C(OMe)=CH-C=C$, and that the pro-

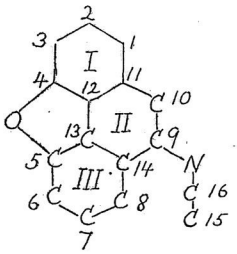
July 23rd, 1925.

duction of hydroxycodeinone from it is an example of addition to a conjugated system. In an earlier memoir we have suggested (*J. Chem. Soc.*, 1923, **123**, 980) formulæ for morphine, codeine and thebaine, the most novel feature of which related to the attachment of the ethanamine chain (15, 16) to position 13 in ring III rather than to position 5 as in Knorr's formula. On further study our arguments in this connexion appear to have lost none of their force, and we are convinced that in this detail the new expressions constitute a real advance. The assumption of a bridge-ring in these alkaloids in place of ethylene linkages now seems unnecessary, however, and we regard codeine as an unsaturated substance. In accordance with the above argument respecting the formation of hydroxycodeinone the formula I is proposed for thebaine.

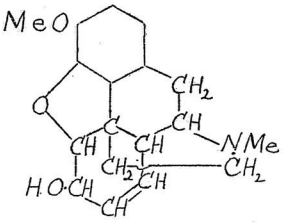


(I) (II)

Through hydroxycodeinone (II.) and codeinone (IV.) we find that codeine should be represented by the expression III. This modification of the formula suggested in our earlier papers (*loc. cit.*) has the great advantage that

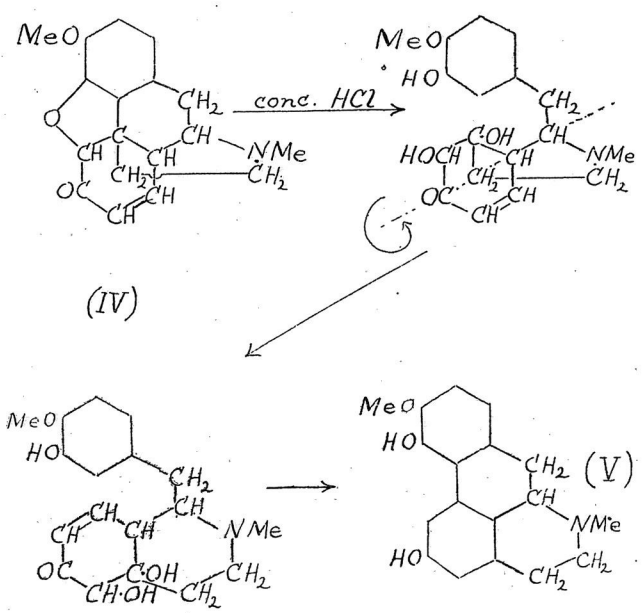


Numbering Scheme.



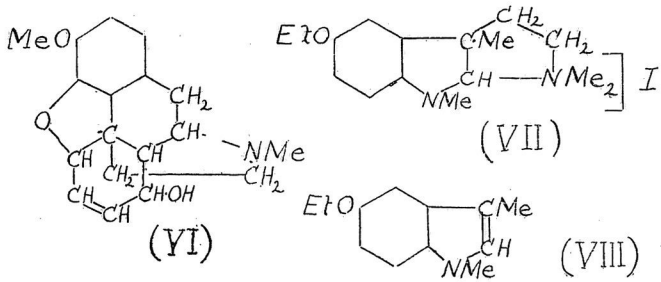
(III.)

the codeine—ψ-codeine and similar transformations are now seen to be strictly analogous to the geraniol—linalool type of isomeric change. Furthermore, it is of much interest to note that the papaverine skeleton is contained in III., and in order to appreciate this fact one must imagine the bond 12—13 to be broken and ring III to be rotated through 180° about the axis 6—14. In order to satisfy the requirements of genetic relationship it is quite sufficient if the morphine molecule can be shown to contain a papaverine carbon skeleton. A similar break of the bond 12—13 and rotation of ring III, followed by attachment of the unsaturated carbon at 8 to position 12, explains in a perfectly satisfactory manner the production of *apo*morphine and morphothebaine (V.) from chlorocodide and codeinone (IV.) respectively. In the annexed representation the stages at which the elements of water are eliminated can be varied.



The existence of the isomeric pairs α- and β-tetrahydrodeoxycodeines and thebainol and dihydrothebainone constituted for us in 1923 a convincing argument in favour of the double bridged-ring formula for codeine, but the ever-increasing number of cases of isomerism of the decahydronaphthalene type (compare Annual Reports, 1924, XXI., 92) suggests the possibility of a stereochemical explanation of these anomalies. The fact that codeine is not only instantly oxidised by potassium permanganate but, as Professor E. Späth has pointed out to us, is also extremely readily reduced to a dihydro-derivative by means of hydrogen in presence of palladium, neutralises the effect of the argument that codeine should be saturated because it can be oxidised to codeinone. Finally, the work of Vongerichten, Hübner and Densdorff (*Ber.*, 1907, **40**, 2827, 4146) on the action of bromine on α-methylmorphimethine, and of Pschorr (*Ber.*, 1912, **45**, 2212) on the action of bromine on the methyl ethers of α- and ε-methylmorphimethines includes details which are most easily explained on the assumption that the halogen attacks an unsaturated centre in ring III. The main object of Pschorr's work, for example, was to bring ring III. into such a state of oxidation that the methoxy group in position 6 would not be eliminated in the course of a degradation to a non-nitrogenous phenanthrene derivative, and in this he was wholly successful. The greater number of our earlier suggestions are unaffected by the modifications we now propose. The formulæ for β-methylmorphimethine, thebainone and thebainol remain the same whilst the degradation mechanisms are only altered in relatively unimportant respects. ψ-Codeine (allo-ψ-codeine) will have the formula VI. and here we encounter a difficulty, since on this basis ψ-codeinone would not contain the group $-CO-CH_2-$. Possibly the double bond moves to the position 5—6 in the course of the condensation reactions. In conclusion, we note that the conception underlying our new formulæ for the bases of the morphine group—namely, that the ethanamine chain is removed in the course of degradations because it "blocks" the formation of an aromatic nucleus—is strongly supported by the behaviour of etheserole methiodide (VII.). Just as a

morphine derivative suffers loss of the ethanamine chain with formation of a phenanthrene, so the methiodide VII. is similarly degraded to the indole derivative VIII. (Stedman, *J. Chem. Soc.*, 1924, 125, 1373; Stedman and Barger, *ibid.*, 1925, 127, 247).



Experimental.

Hydroxycodeinone and dihydrohydroxycodeinone do not reduce Fehling's solution or an ammoniacal solution of silver oxide, even on warming, and both bases were recovered largely unchanged from solutions in 30 per cent. aqueous sulphuric acid which had been boiled under reflux during two and a half hours. In the preparation of dihydrohydroxycodeinone by means of Freund and Speyer's hydrosulphite method the mother liquors from the crystallisation of the base gave a *by-product* crystallising from alcohol containing a little chloroform in colourless columns, m.p. 210-211°, insoluble in aqueous sodium hydroxide and yielding a colourless solution in sulphuric acid. The fact that bromocodeinone can be converted into hydroxycodeinone oxime has been confirmed. The oxime from bromocodeinone was obtained after one crystallisation from alcohol in cigar-shaped crystals, melting unsharply at 258°. A second crystallisation gave chisel-shaped needles, m.p. 269-270°, and finally hexagonal prisms, m.p. 278°, were obtained. The oxime from hydroxycodeinone separated first in rectangular prisms, m.p.

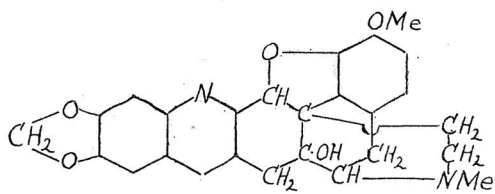
275°, and then in hexagonal prisms, m.p. 279°, and mixed with the specimen from bromocodeinone, m.p. 278°.

Condensation of Hydroxycodeinone and Dihydrohydroxycodeinone with Benzaldehyde and Piperonal. The condensations were carried out in boiling ethyl alcoholic solution in presence of sodium ethoxide, and the product isolated by addition of dilute hydrochloric acid, removal of unchanged aldehyde by means of ether and addition of ammonia to the separated aqueous layer. None of the substances could be crystallised and they were purified by successive precipitations from benzene solution with light petroleum.

Piperonylidenedihydrohydroxycodeinone is an amorphous yellow powder (Found: in material dried in a vacuum; C, 69.9, 69.5; H, 6.2, 6.3; N, 3.2. $C_{26}H_{25}O_6N$ requires C, 69.8; H, 5.6; N, 3.1 per cent.). The solution in concentrated hydrochloric acid is red and in sulphuric acid purplish red. The corresponding solutions of *benzylidenedihydrohydroxycodeinone* are colourless and red respectively. The colour reactions of the *benzylidene* and *piperonylidene* derivatives derived from hydroxycodeinone were identical with those of the dihydro compounds, but the analyses indicated the occurrence of reduction as well as condensation. Both hydroxycodeinone and dihydroxycodeinone condense with salicylaldehyde in presence of potassium hydroxide in alcoholic solution, giving the orange-red solution characteristic of the salts of most salicylidene-ketones.

Condensation of Hydroxycodeinone with 6-Aminopiperonal. A mixture of hydroxycodeinone (1.g.), 6-aminopiperonal (0.56 g.) and alcohol (35 cc.) containing sodium ethoxide (from 0.2 g. of sodium) was boiled gently for fifteen minutes and then added to water. The pink precipitate was collected, dried, dissolved in hot benzene, charcoaled therein, and the filtered solution concentrated to about 5 cc. Pale pink crystals separated and, after two recrystallisations from benzene, the substance was obtained in rectangular plates, m.p. 243-244°, which lose 14.9 (14.2) per cent. at 140° (Found: in material dried at 140°; C, 69.9, 69.9; H, 5.9, 5.9; N, 6.2, 6.3;

$C_{26}H_{26}O_5N_2$, C_6H_6 requires C_6H_6, 14.9 and $C_{26}H_{26}O_5N_2$ requires C, 70.0; H, 5.8; N, 6.3 per cent.). The compound thus appears to be formed by the elimination of two molecules of water from one molecule of aminopiperonal and one of hydroxycodeinone with the addition of four atoms of hydrogen. It is a non-phenolic base which contains a methylenedioxy group since it responds to Gadamer's test (*Arch. Pharm.*, 1920, **258**, 148). The substance is readily soluble in acetone, alcohol and chloroform, rather sparingly soluble in benzene and ether, and sparingy soluble in light petroleum.



Dianhydro-6-aminopiperonal-dihydrohydroxycodeinone. A solution of dihydrohydroxycodeinone (1.6 g.) and 6-aminopiperonal (0.85 g.) in alcohol (45 cc.) containing sodium ethoxide (from 0.3 g. of sodium) was boiled for fifteen minutes and then added to water. The precipitate was collected, dried, treated in hot benzene solution with animal charcoal and the filtered liquid concentrated to 10—15 cc. The crystals (1.7 g.) which separated were twice recrystallised from benzene, in which the substance is sparingly soluble. The colourless rectangular prisms melted with decomposition at 282-283°. After drying in a vacuum, there was no loss in weight at 110° during three hours (Found: C, 69.8; H, 5.1; N, 6.4. $C_{26}H_{24}O_5N_2$ requires C, 70.2; H, 5.4; N, 6.3 per cent.). This compound is insoluble in aqueous sodium hydroxide and readily soluble in dilute acids to colourless solutions. It is readily soluble in chloroform, but rather sparingly soluble in methyl and ethyl alcohols, ethyl acetate, ether, acetone, benzene and heavy petroleum. Gadamer's test indicated the presence of a methylenedioxy group. The colourless solution in con-

centrated sulphuric acid does not exhibit fluorescence, and we should certainly regard this as anomalous in the case of all simple methylenedioxyquinoline derivatives. In this example, however, the attached groups constitute the greater part of the molecule, and it would appear to be unwise to dogmatise in regard to the anticipated optical properties of the complex.

SYNTHETICAL EXPERIMENTS IN THE NAPHTHYRIDINE GROUPS.

BY

JOHN MASSON GULLAND

AND

ROBERT ROBINSON.

Publication 4

The whole of the work described in this paper was carried out by me.

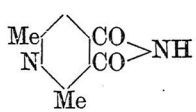
Reprinted from the Journal of the Chemical Society, Volume 127, 1925.

Reprinted from the Journal of the Chemical Society,
Volume 127, 1925.

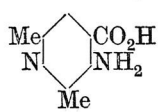
CC.—*Synthetical Experiments in the Naphthyridine Groups.*

By John Masson Gulland and Robert Robinson.

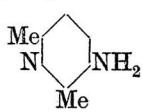
The sodamide method of Tschitschibabin (*J. Russ. Phys. Chem. Soc.*, 1914, **46**, 1216; 1915, **47**, 835) has rendered many α- and γ-aminopyridine derivatives readily accessible, but it is still difficult to obtain β-aminopyridines in quantity. We have utilised the fact that 2 : 6-dimethylcinchomeronic acid is easily prepared (Mumm and Hüneke, *Ber.*, 1917, **50**, 1568) in devising a method of preparation of 3-amino-2 : 6-lutidine (III). 2 : 6-Dimethylcinchomeronimide (I), obtained from the acid by heating with carbamide (compare Herzog, *Z. angew. Chem.*, 1919, **32**, 301; Lawson, Perkin, and Robinson, J., 1924, **125**, 634), is converted by potassium hypobromite and potassium hydroxide into a salt of 3-amino-2 : 6-dimethyl*iso*nicotinic acid (II). This acid yields the aminolutidine on distillation with soda-lime. The product is quite different



(I.)

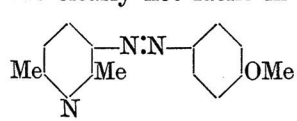


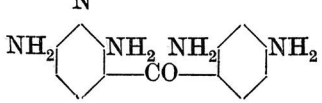
(II.)

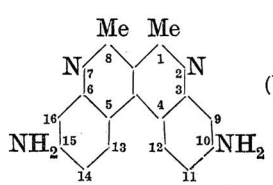


(III.)

from 4-amino-2 : 6-lutidine (Marckwald, *Ber.*, 1894, **27**, 1325), and this fact establishes the constitution of the new base. We have made many fruitless attempts to convert this aminolutidine into 1 : 7-naphthyridine derivatives, for example, by condensation with acetylacetone and by application of the Doebner-Miller synthesis. The reactivity of the nucleus appears to be feeble. The diazonium salt derived normally from the base couples with phenol with formation of lutidineazophenol, the *O*-methyl ether (IV) of which was examined by the method of Jacobson for the semidine transformation on reduction. No evidence of this was obtained, and as regards the benzidine transformation, Friedl (*Monatsh.*, 1913, **34**, 765) has prepared 3-hydrazopyridine, but makes no mention of a molecular rearrangement of this substance. Intramolecular changes of these types are clearly not facile in the pyridine series.

(IV.)


(V.)




(VI.)

The copyrine synthesis from derivatives of *oo*-diaminobenzophenone and 1 : 3-diketones described by Lawson, Perkin, and Robinson (*loc. cit.*) involves a very satisfactory reaction from the point of view of yield and convenience, but the number of available diaminobenzophenones is limited. We have now obtained 2 : 4 : 2′ : 4′-*tetra-aminobenzophenone* (V), and from it, by condensation with acetylacetone, a *diaminodimethyldibenzocopyrine* (VI).

Further brief indications of synthetical schemes will be found in the experimental section.

EXPERIMENTAL.

2 : 6-*Dimethylcinchomeronimide* (I).—In the preparation of 2 : 6-dimethylcinchomeronic acid (Mumm and Hüneke, *loc. cit.*) the isolation of the ester was found to be unnecessary. The product of the condensation of ethyl acetylpyruvate (83 g.) with ethyl β-aminocrotonate (69·3 g.) in ether (40 c.c.) was, after 15 hours, hydrolysed with potassium hydroxide (25 g.) dissolved in 70% alcohol (150 c.c.). Following steam distillation, the liquid was acidified with respect to Congo-red, and sodium acetate added to neutralise the mineral acid. The acid, m. p. 274° (pure 275°), crystallised from the solution in quantitative yield. The conversion into the *imide* by heating the ammonium salt at 230°, as described by Mumm and Hüneke, is troublesome, and the following process is far more convenient. The acid (10 g.) and carbamide (5 g.) were heated together with stirring at 225° until ammonia was no longer evolved (about 5 minutes), then at 230° for a few moments, and the mass was cooled and extracted with alcohol. The substance, m. p. 230° (Mumm and Hüneke give m. p. 230°), crystallises from the solution in yellow needles (yield 81%).

3-*Amino*-2 : 6-*dimethylisonicotinic Acid* (II). (Compare Gabriel and Colman, *Ber.*, 1902, **35**, 2832, for the preparation of 3-amino-*iso*nicotinic acid from cinchomeronimide).—Finely-powdered 2 : 6-dimethylcinchomeronimide (20 g.) dissolved when it was gradually added to a well-stirred, ice-cold solution of potassium hypobromite prepared from bromine (18·2 g.) and 10% aqueous potassium hydroxide (300 c.c.). After 2 hours, 10% potassium hydroxide (160 c.c.) was added and the mixture heated for 10 minutes on the steam-bath. The solution was acidified with respect to Congo-red with hydrochloric acid and evaporated to dryness under diminished pressure on the steam-bath. The residue was extracted twice with boiling alcohol, and the filtered solutions were concentrated to a small bulk, dilute hydrochloric acid (20 c.c.) being added to prevent the separation of inorganic salts. The *hydrochloride* of the amino-acid, which crystallised on cooling, was washed, dried (yield 16 g.

or 60%), and recrystallised from dilute hydrochloric acid, separating in slender, pale yellow needles, decomp. 248° (Found in material dried over sulphuric acid: Cl, 14·9; loss at 110°, 8·4; loss at 130°, 15·2. $C_8H_{11}O_2N_2Cl,2H_2O$ requires Cl, 14·9; $1H_2O$, 7·6; $2H_2O$, 15·1%). The long, yellow needles which separate from alcohol have m. p. 253—255° with previous slight darkening. This salt is readily soluble in water and sparingly soluble in dilute hydrochloric acid. The amino-group can be diazotised and coupling with β-naphthol produces a red azo-compound.

Sodium acetate was added to a concentrated aqueous solution of the hydrochloride, and the pale yellow, oblique-ended prisms of the *acid* which slowly separated were washed, and dried over sulphuric acid (Found: loss at 110°, 5·1; in material dried at 110°, C, 57·9; H, 6·1. $C_8H_{10}O_2N_2,0{\cdot}5H_2O$ requires H_2O, 4·9. $C_8H_{10}O_2N_2$ requires C, 57·8; H, 6·0%). The acid is sparingly soluble in neutral organic solvents, more readily soluble in water, and easily soluble in alcohol; it melts at 295° after darkening at 285°. The *copper* salt occurs in yellow, prismatic needles, moderately soluble in water, and the *lead* salt in colourless, quadrilateral or hexagonal prisms which do not melt at 315°.

3-*Amino*-2 : 6-*lutidine* (III).—A mixture of the hydrochloride of aminodimethyl*iso*nicotinic acid (15 g.) with powdered soda-lime (5 parts) was strongly heated in a combustion tube in a stream of hydrogen. The distillate, which solidified (6·4 g.), crystallised from benzene in colourless needles, m. p. 122°, and from water in needles which melted indistinctly between 70° and 75° and lost 14·4% on drying over potassium hydroxide in a vacuum; they then melted at 122° (Found: C, 68·7; H, 8·4; N, 22·9. $C_7H_{10}N_2$ requires C, 68·8; H, 8·2; N, 22·9% and $C_7H_{10}N_2,H_2O$ requires H_2O, 14·7%).

This strong base has a characteristic odour and is readily soluble in most organic solvents, although somewhat sparingly soluble in ether. The *hydrochloride* is very readily soluble in water and separates from alcohol in flat needles, m. p. 235°.

3-p-*Hydroxybenzeneazo*-2 : 6-*lutidine* (corresponding with IV).—3-Aminolutidine (4·2 g.) was diazotised below 2° in hydrochloric acid (13·7 c.c.; *d* 1·16) and water (80 c.c.) with sodium nitrite (3·6 g.) in water (50 c.c.). The diazo-solution was slowly added to a cold, agitated solution of phenol (3·2 g.) and sodium hydroxide (6·9 g.) in water (100 c.c.), and, after 5 minutes, the dark red solution was saturated with carbon dioxide. The orange-brown precipitate, after being washed and dried (yield 6·7 g. or 86%), crystallised from toluene in flat, orange needles, m. p. 240° (decomp.) (Found in material dried at 110°: C, 68·9; H, 5·9; N, 18·6. $C_{13}H_{13}ON_3$ requires C, 68·7; H, 5·7; N, 18·9%). The substance is sparingly

soluble in ether, benzene, or chloroform, and is moderately readily soluble in alcohol, acetone, or ethyl acetate. The solutions in concentrated sulphuric and hydrochloric acids are bright red and the *hydrochloride* crystallises from dilute hydrochloric acid in orange-yellow needles, m. p. 239—240° (decomp.) (depressed by admixture with the base). In caustic alkalis, an orange-red solution is obtained, but the compound is less readily soluble in aqueous ammonia than benzeneazophenol.

The *methyl* ether (IV), which could not be obtained by the action of methyl sulphate on the phenol, since methylation of the tertiary nitrogen atom ensued, was prepared by Pyman's method (J., 1918, **113**, 227) for the *O*-methylation of phenolic bases; the conversion of benzeneazophenol into benzeneazoanisole by this process was found to be 75%. The lutidineazophenol (2 g.) and sodium methyl sulphate (3·6 g.; 3 mols.) were added to a solution of sodium *iso*amyloxide (from 0·2 g. of sodium) in *iso*amyl alcohol (20 c.c.), and the mixture was boiled under reflux for 2 hours, the colour changing from red to dark brown. Ether and dilute sodium hydroxide solution were added to the cold mixture, and the ethereal layer was washed with dilute alkali and water, filtered, and the solvent removed by distillation and steam distillation. The residue crystallised on cooling (yield 1·86 g. or 87·7%); 0·25 g. of unchanged phenol was recovered. *Lutidineazoanisole* is rather readily soluble in organic solvents and crystallises from light petroleum in elongated, diamond-shaped, red plates, often forming radiating clusters; it melts at 81—82° and solidifies to a yellow mass on cooling. When the bright red crystals were collected, they became yellow in places, but the change did not progress on keeping (Found: C, 69·6, 69·4; H, 6·2, 6·2. $C_{14}H_{15}ON_3$ requires C, 69·7; H, 6·2%). The *hydrochloride*, orange needles, sparingly soluble in dilute hydrochloric acid, melts to a paste at 112°, but, after drying at 100°, has m. p. 183—185° (decomp.). The semidine transformation was attempted by treatment of the ether both with acid reducing agents, such as alcoholic stannous chloride and hydrochloric acid, and with neutral reducing agents, such as aluminium–mercury and alcohol, and hydrogen in presence of palladium, followed by treatment with acids. The products gave no trace of triazole derivatives on treatment with nitrous acid. The failure of the semidine rearrangement also involved the breakdown of an otherwise feasible synthesis of harmine.

Derivatives of 3-*Amino*-2-*methylcinchoninic Acid*.—The object in view in making the experiments described below was the conversion of the accessible 3-amino-2-methylcinchoninic acid (Lawson, Perkin, and Robinson, *loc. cit.*) into a 1 : 7-naphthyridine derivative

by applying the Camps synthesis of 2 : 4-dihydroxyquinoline from anthranilic acid (*Arch. Pharm.*, 1899, **237**, 659). The attempt was abandoned on account of the difficulties encountered, and indicated in the sequel, but also because Seide (*Ber.*, 1924, **57**, 1806) failed to obtain a naphthyridine derivative in a similar manner from 2-aminonicotinic acid.

Methyl 3-Amino-2-methylcinchoninate.—The acid is not esterified when its solution in dry methyl alcohol (25 g. in 500 c.c.) is saturated with hydrogen chloride and heated under reflux for 3·5 hours. This phenomenon is not abnormal, since the conditions for the exercise of powerful steric hindrance are present, whilst, in addition, the basic character of the substance operates against the exhibition of oxonium character by the oxygen atoms of the carboxyl group.

A mixture of the acid (10 g.), sulphuric acid (10 c.c.), and methyl alcohol (100 c.c.) was boiled under reflux for 7 hours. Barely 1 g. of the *ester* was ultimately isolated as a viscous, yellow oil which soon solidified; it crystallised from light petroleum (b. p. 60—80°) in canary-yellow needles, m. p. 83—84° (Found : C, 66·4; H, 5·6. $C_{12}H_{12}O_2N_2$ requires C, 66·7; H, 5·6%). The substance exhibits brilliant blue fluorescence in ethereal solution, and is readily soluble in dilute hydrochloric acid and most organic solvents. The *acetyl* derivative was apparently not produced by the action of boiling acetic anhydride alone, but when the ester was boiled with an excess of acetic anhydride and fused sodium acetate for 10 minutes a substance was isolated in about 35% yield, which crystallised from benzene–light petroleum in pale yellow needles, m. p. 169°. This is doubtless *methyl 3-acetylamino-2-methylcinchoninate*, but the method of preparation is very unsatisfactory and attempts, unfortunately fruitless, were made to reverse the order of the operations.

3-Acetylamino-2-methylcinchoninic acid. A mixture of amino-methylcinchoninic acid (10 g.), fused sodium acetate (10 g.), and acetic anhydride (30 c.c.) was gently heated over a free flame until a vigorous reaction set in and the yellow colour disappeared. After being heated to incipient ebullition for a minute, the product was cooled, decomposed with water, and the precipitate collected and dried (10 g.). The material was a mixture, and an acidic fraction was separated from a neutral fraction (A) by means of dilute aqueous sodium carbonate. The acid precipitated from the filtered alkaline solution was at first gelatinous, but became crystalline when the mixture was heated on the steam-bath for about 10 minutes. The substance crystallises from much hot water in small, colourless needles which, after drying in a vacuum, lose 10·3% at 100° and then have m. p. 286° (Found in material dried at 100° : C, 64·2; H, 4·9. $C_{13}H_{12}O_3N_2,1{\cdot}5H_2O$ requires H_2O, 9·6% and $C_{13}H_{12}O_3N_2$

requires C, 63·9; H, 4·9%). This compound is sparingly soluble in most organic solvents, but dissolves in dilute hydrochloric acid at about 40° and separates again on cooling. The acetyl group was not removed when a solution of the substance in dilute aqueous sodium hydroxide was boiled for 4 hours; a sodium salt separated in silky needles from the cooled solution and by treatment with dilute acetic acid gave the unchanged acid, m. p. 286°.

A curious result followed an attempt to esterify the acid. A mixture of 3-acetylamino-2-methylcinchoninic acid (2 g.), sulphuric acid (3 c.c.), and methyl alcohol (20 c.c.) was boiled under reflux for 3·5 hours. After distillation of half the methyl alcohol, the mixture was added to water and ammonia and extracted with ether, which removed nothing. The ammoniacal solution was then acidified with hydrochloric acid and, on keeping, 1·9 g. of a yellow substance separated which crystallised from water in feathery, yellow needles, m. p. 217° (decomp.) [Found: loss at 100°, 14·3; in material dried at 100°, C, 64·8; H, 5·1. $C_{24}H_{22}O_5N_4(2C_{11}H_{10}O_2N_2 + C_2H_4O_2 - H_2O)$ requires C, 64·6; H, 4·9% and $C_{24}H_{22}O_5N_4,4H_2O$ requires H_2O, 13·9%). When the acetylamino-acid was boiled with concentrated hydrochloric acid it was quickly converted into an acid, devoid of basic properties, which, crystallised from dilute hydrochloric acid and then from alcohol, formed bright yellow needles, m. p. 234—235° (Found in material dried in a vacuum: loss at 100°, 5·6; in material dried at 100°, C, 63·1, 63·4; H, 5·5, 5·6; N, 12·8%). Both substances, m. p. 217° and m. p. 234—235°, are acids which are readily soluble in aqueous sodium carbonate, and the latter was shown to be unaffected by boiling dilute aqueous sodium carbonate in ½ hour. We have not reached any definite conclusion as to the nature of these substances.

Anhydro-3-acetylamino-2-methylcinchoninic Acid.—The material (A) obtained in the course of the acetylation of aminomethylcinchoninic acid crystallised from alcohol or benzene in colourless needles, m. p. 199—200° (Found: C, 69·1; H, 4·6; N, 12·2. $C_{13}H_{10}O_2N_2$ requires C, 69·0; H, 4·4; N, 12·4%). On boiling with water, the substance is slowly hydrated, but more rapidly in presence of sodium hydroxide, with the formation of 3-acetylamino-2-methylcinchoninic acid, m. p. 286°. The substance resembles acetylanthranil (compare Schroeter and Eisleb, *Annalen*, 1909, **367**, 124), and its constitution is probably analogous (O instead of NPh) to that of the pyrimidine derivative described below.

1-*Keto*-2-*phenyl*-3 : 5-*dimethyl*-1 : 2-*dihydro*-2 : 4 : 6-*naphthaiso*-*triazine*, $C_9H_4MeN<^{CO\cdot NPh}_{N=CMe}$.—A mixture of anhydro-3-acetylamino-2-methylcinchoninic acid (0·7 g.) and aniline (2 c.c.) was

boiled for 2 minutes and cooled, and the product was washed with alcohol and crystallised from much alcohol, separating in yellow needles, m. p. 235° (Found: C, 75·6; H, 5·3. $C_{19}H_{15}ON_3$ requires C, 75·7; H, 5·0%). This sparingly soluble substance is a weak base and is precipitated unchanged on addition of water to its solution in concentrated hydrochloric acid.

2 : 4 : 2′ : 4′-*Tetra-aminobenzophenone* (V).—Schöpff's method of tetra-nitration of diphenylmethane (*Ber.*, 1894, **27**, 2318) resulted in inferior yields, and the following method effected a considerable improvement. Molten diphenylmethane (53 g.) was added drop by drop to a stirred solution of potassium nitrate (128 g.) in sulphuric acid (360 g.) maintained below 25°. An equal quantity of potassium nitrate was then introduced and the mixture frequently shaken and heated on the steam-bath for 30 minutes. The isolation was by the method of Schöpff, and the yield 70%. The oxidation of tetranitrodiphenylmethane with chromic and acetic acids as described by Städel (*Annalen*, 1883, **218**, 341) proved a most unsatisfactory process and, after numerous trials, we finally adopted the following conditions. Tetranitrodiphenylmethane (10 g.) was dissolved in concentrated sulphuric acid (90 g.) and water (10 g.), and a concentrated aqueous solution of chromic acid (5·8 g.) added with vigorous agitation, the temperature being maintained below 40°. The mixture was finally heated for an hour on the steam-bath, added to water, and the precipitate collected and dried (7·5 g. or 72%). A specimen crystallised from acetic acid melted at 224—225° and for ordinary purposes the crude product can be satisfactorily purified by extraction with hot ethyl acetate. A good criterion of purity is the absence of the blue coloration with alcoholic potassium hydroxide which is so characteristic of tetranitrodiphenylmethane.

The tetranitrobenzophenone (10 g.) was suspended in a mechanically stirred mixture of acetic acid (100 c.c.) and concentrated hydrochloric acid (65 c.c.), and granulated tin (45 g.) gradually added. After about 20 hours, the liquid contained no solid nitrocompound in suspension and gave a clear solution with water. Sufficient water to dissolve the tin salt was added, and the filtered solution rendered strongly alkaline by the addition of sodium hydroxide. After a few hours, the black sludge and yellow needles were collected, dried, and extracted several times with hot alcohol. Dull, yellow prisms (3 g.) separated on cooling the concentrated extracts; the base, recrystallised from alcohol, had m. p. 202° (Found: C, 64·5; H, 6·0; N, 23·2. $C_{13}H_{14}ON_4$ requires C, 64·5; H, 5·8; N, 23·1%). Tetra-aminobenzophenone is readily soluble in acetone, ethyl acetate, or methyl alcohol, sparingly soluble in

benzene or chloroform, and very sparingly soluble in ether. Just above its m. p. the substance evolves ammonia; the residue dissolves in dilute hydrochloric acid, the yellow solution exhibiting bluish-green fluorescence. This behaviour indicates the formation of diaminoacridone. On treatment of an acid solution with sodium nitrite, a brown precipitate is thrown down and the solution contains a diazonium salt.

10 : 15-*Diamino*-1 : 8-*dimethyldibenzocopyrine* (VI). — Concentrated hydrochloric acid (5 c.c.) was added to a mixture of 2 : 4 : 2′ : 4′-tetra-aminobenzophenone (1 g.), acetylacetone (1 g.), and water (25 c.c.), and the whole gently heated. In about ½ minute orange crystals separated and the mixture was then boiled for a minute and cooled. The crystals were collected, washed with alcohol, and dried in a vacuum (Found: Cl, 26·6. $C_{18}H_{16}N_4$,3HCl requires Cl, 26·7%). This *hydrochloride* occurs in orange-red, rectangular plates, which decompose without melting at 310°. It crystallises in beautiful leaflets when hydrochloric acid is added to an aqueous solution. The yield in the preparation is almost quantitative if account be taken of the small amount of base recoverable from the original filtrate. In order to obtain the free base, the salt was dissolved in boiling dilute acetic acid and potassium hydroxide added until crystals began to separate. The heating was then discontinued and the remainder of the base precipitated by the further addition of potassium hydroxide. The substance was collected, washed, dried, and dissolved in a large volume of hot alcohol (charcoal). The filtered solution was concentrated by distillation and, at a certain stage, pale brown cubes were deposited from the hot solution (Found: C, 75·2; H, 5·6; N, 19·2. $C_{18}H_{16}N_4$ requires C, 75·0; H, 5·6; N, 19·4%). The substance is sparingly soluble in most organic solvents and its alcoholic solution exhibits a weak green fluorescence. It begins to decompose at about 305°, but does not melt at 340°. The base can be normally tetrazotised and coupled with β-naphthol to produce a crimson azo-compound.

An attempt to shorten the preparation was made, the product of reduction of tetranitrobenzophenone (1 mol.) being treated with zinc to eliminate tin and then with acetylacetone (3 mols.) on the steam-bath. After the red precipitate had been treated with successive quantities of cold alcohol, the residue consisted of the above-mentioned trihydrochloride. The alcoholic filtrates were evaporated to dryness; the residue crystallised from dilute hydrochloric acid in dark red needles which, air-dried, lost 19·6% at 130°, leaving a purplish-brown mass with a green reflex. This salt exhibits a most brilliant green fluorescence in solution and contains a diazo-

tisable amino-group. The amount of material at our disposal did not permit of further investigation.

Benzoylveratroylmethane, $PhCO{\cdot}CH_2{\cdot}CO{\cdot}C_6H_3(OMe)_2$. — Ethyl veratrate (10·5 g.) and acetophenone (7·5 g.) were condensed together by means of granulated sodium (2·3 g.) under dry ether (50 c.c.), and the diketone was isolated as the *copper* salt (5 g.) in the usual manner. This substance crystallised from benzene in pale green leaflets, m. p. 250° (Found: Cu, 10·1. $C_{34}H_{30}O_8Cu$ requires Cu, 10·1%). The *benzoylveratroylmethane* obtained by its decomposition with dilute sulphuric acid in presence of ether crystallised from methyl alcohol in pale yellow plates, m. p. 67°, and was readily soluble in most organic solvents (Found: C, 71·7; H, 5·6. $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·6%). An alcoholic solution is coloured greenish-brown on the addition of ferric chloride.

Ethyl Benzoylveratroylacetate, $(MeO)_2C_6H_3{\cdot}CO{\cdot}CH(CO_2Et){\cdot}COPh$. —As the yield of benzoylveratroylmethane was rather poor in the direct process, this ester was prepared, but it could not be hydrolysed so as to yield the desired product.

Solutions of sodium ethoxide (from 8·7 g. of sodium) in alcohol (147 c.c.) and of veratroyl chloride (39·5 g.) in benzene (500 c.c.) were prepared. Half the sodium ethoxide solution was added to ethyl benzoylacetate (37·8 g.), and the mixture stirred and cooled to 0°. Half the veratroyl chloride solution was added during 15 minutes, and the mixture allowed to remain for 30 minutes. The cycle of operations was repeated several times, on each occasion one-half of the volume of the solution which remained being added. After 12 hours, the dense, yellow precipitate of crude sodium salt was collected, washed with benzene, dried in the air, and decomposed in aqueous solution with 2*N*-hydrochloric acid. The bulky, white precipitate of the ester was taken up with ether and the extract rapidly dried and concentrated, when, on standing, most of the product separated in colourless nodules. The substance was recrystallised by addition of light petroleum to a benzene solution (at about 50°), the long, slender needles obtained having m. p. 125—126° (Found: C, 68·9; H, 5·8. $C_{20}H_{20}O_6$ requires C, 68·9; H, 5·7%). Ferric chloride added to an alcoholic solution developed a red coloration. When the ester (15 g.) was boiled with aqueous ammonia (10·8 c.c.; *d* 0·880) in water (100 c.c.) for 5 minutes, the chief products were benzamide and ethyl veratroylacetate; veratramide, veratric acid, and acetophenone were also formed. Benzoic acid and acetoveratrone did not appear to be among the products of hydrolysis.

2 : 4-*Dinitro*-3′ : 4′-*methylenedioxystilbene*.*—We have prepared

* This work on some derivatives of stilbene was carried out in collaboration with William Stafford.

some stilbene derivatives in order to attempt to obtain 2 : 6-naphthyridine derivatives by the dehydration of *oo*-diacylaminostilbenes.

A molten mixture of piperonal (23 g.), 2 : 4-dinitrotoluene (27 g.), and piperidine (30 drops) was heated on the steam-bath for 3 hours, when the mass became solid. The very sparingly soluble product crystallised from acetic acid in bright salmon prisms, m. p. 180° (Found: C, 57·3; H, 3·2. $C_{15}H_{10}O_6N_2$ requires C, 57·3; H, 3·2%).

4-*Nitro*-2-*amino*-3′ : 4′-*methylenedioxystilbene*.—A cooled solution of dinitromethylenedioxystilbene (20 g.) in acetic acid (300 c.c.) was mixed with a solution of crystallised stannous chloride (40 g.) in acetic acid containing hydrogen chloride and stirred in the cold for 6 hours. The orange-yellow tin salt obtained was digested with water, and from the free, red amino-derivative produced the hydrochloride was prepared in alcoholic solution, and decomposed by water. The base crystallised from alcohol in dark red prisms, m. p. 213° (Found: C, 63·3; H, 4·4. $C_{15}H_{12}O_4N_2$ requires C, 63·4; H, 4·2%). Its constitution may be inferred from the results of Thiele and Escales (*Ber.*, 1901, **34**, 2842) relating to the semi-reduction of 2 : 4-dinitrostilbene combined with the fact that ammonia and hydrogen sulphide reduced dinitromethylenedioxystilbene to a quite different isomeric base.

2 : 4-*Dinitro*-2′ : 3′-*dimethoxystilbene* was prepared from 2 : 4-dinitrotoluene (18 g.), 2 : 3-dimethoxybenzaldehyde (17 g.), and piperidine (20 drops) as described above. It crystallised from acetic acid in bright yellow prisms, m. p. 165° (yield 31 g.; 94%) (Found: C, 57·9; H, 4·4. $C_{16}H_{14}O_6N_2$ requires C, 58·2; H, 4·3%).

2-*Nitro*-4-*amino*-2′ : 3′-*dimethoxystilbene*.—The conditions for the satisfactory preparation of 2-nitro-4-aminostilbene itself have been studied and the following method gives good results (compare Thiele and Escales, *loc. cit.*). Hydrogen sulphide was led for 3 hours through a gently refluxing mixture of dinitrostilbene (20 g.), alcohol (250 c.c.), and aqueous ammonia (30 c.c.; *d* 0·880). The cooled solution was filtered, and the hydrochloride precipitated with hydrogen chloride; the base obtained from the salt separated from alcohol in red crystals, m. p. 110°.

Nitrostilbenediazonium hydrogen sulphate is readily isolable in the crystalline condition and on decomposition with aqueous potassium iodide gives 4-*iodo*-2-*nitrostilbene*, bright yellow crystals, m. p. 105°. A similar reduction process was applied to dinitro-2′ : 3′-dimethoxystilbene and orange-red needles, m. p. 121—122°, were obtained (Found: C, 63·6; H, 5·2. $C_{16}H_{16}O_4N_2$ requires C, 64·0; H, 5·3%).

2 : 4-*Dinitro*-3′ : 4′-*dimethoxystilbene*, prepared from veratraldehyde and 2 : 4-dinitrotoluene, crystallises from acetic acid in

stout, maroon prisms, m. p. 143°, sparingly soluble in alcohol (Found : C, 58·0; H, 4·4. $C_{18}H_{14}O_6N_2$ requires C, 58·2; H, 4·3%). When triturated with acetic acid (35 c.c.) and nitric acid (25 c.c.; *d* 1·42), the substance (19 g.) became yellow; the product crystallised from acetic acid in short, yellow prisms, m. p. 192° (Found : N, 11·3. $C_{16}H_{13}O_8N_3$ requires N, 11·2%).

2 : 4 : 6′-*Trinitro*-3′ : 4′-*dimethoxystilbene* is readily soluble in acetone, but sparingly soluble in most other organic solvents.

2 : 4-*Dinitro*-2′-*hydroxystilbene* is obtained in poor yield from 2 : 4-dinitrotoluene and salicylaldehyde in presence of piperidine. It crystallises from ethyl alcohol in light brown, irregular granules, m. p. 179—181° (Found : C, 58·6; H, 3·6. $C_{14}H_{10}O_5N_2$ requires C, 58·7; H, 3·5%), is readily soluble in most organic solvents, develops no coloration with alcoholic ferric chloride, and dissolves in aqueous sodium hydroxide to a red solution.

2 : 4-*Dinitro*-3′-*methoxy*-4′-*hydroxystilbene*, produced (yield 67%) by condensation of 2 : 4-dinitrotoluene and vanillin in presence of piperidine, crystallises from acetic acid in stout, vermilion prisms, m. p. 193° (Found : C, 57·0; H, 3·8. $C_{15}H_{12}O_6N_2$ requires C, 56·7; H, 3·9%).

We desire to thank the Carnegie Trust for the Universities of Scotland for a Scholarship which enabled one of us (J. M. G.) to take part in this investigation.

THE UNIVERSITIES OF ST. ANDREWS
AND MANCHESTER. [*Received, April 17th*, 1925.]

PRINTED IN GREAT BRITAIN BY RICHARD CLAY & SONS, LIMITED,
BUNGAY, SUFFOLK.

DERIVATIVES OF HOMOCATECHOL.
PART I.

BY
FRANZ ROBERT GRAESSER-THOMAS,
JOHN MASSON GULLAND,
AND
ROBERT ROBINSON.

Publication 5

With the exception of three minor experiments (marked G-T), the whole of the work described in this paper was carried out by me at Oxford, without the collaboration of Professor Robinson.

Reprinted from the Journal of the Chemical Society
August, 1926.

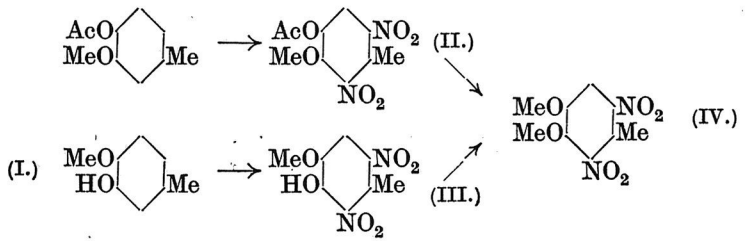
Reprinted from the Journal of the Chemical Society, 1926.

CCLXII.—*Derivatives of Homocatechol. Part I.*

By Franz Robert Graesser-Thomas, John Masson Gulland, and Robert Robinson.

A recent publication of Oberlin (*Arch. Pharm.*, 1925, **263**, 641) includes a description of the preparation of 2 : 6-dinitrohomoveratrole (IV) from creosol by successive acetylation, nitration, hydrolysis and methylation. We therefore submit an account of experiments in this field in which we have been engaged during the past 10 years with the ultimate object of synthesising *apo*morphine.

The annexed scheme indicates the methods which have been employed.



Pollecoff and Robinson (J., 1918, **113**, 645) showed that 2-methoxyphenyl carbonate is nitrated in the *o*- and *p*- positions with respect to the methoxyl groups alone, and this observation suggested the extension to the preparation of 2 : 6-dinitrocreosol. *iso*Creosol (I) was first obtained in poor yield by Limpach (*Ber.*, 1889, **22**, 350) by the decomposition of diazotised *m*-cresidine and was described as a yellow oil, b. p. 185°. De Vries (*Rec. trav. chim.*, 1909, **28**, 276) showed, however, that the substance has b. p. 220—222° and m. p. 35·5°, and we now submit details of a satisfactory method of preparation and confirm the properties quoted by de Vries. The phenol yields its dinitro-derivative when submitted to the action of nitrous acid or its decomposition products in ethereal solution.

Experimental.

iso*Creosol* (I).—The *m*-cresidine employed in this preparation must be of good quality, since impurities cause a decrease in the yield quite disproportionate to their amount.

Sodium nitrite (25 g.) dissolved in water (150 c.c.) was gradually added to a mechanically stirred solution of 3-amino-4-methoxytoluene (50 g.) in water (400 c.c.) and sulphuric acid (57 c.c.; *d* 1·84), maintained below 10°. The diazo-solution * was diluted with half its volume of water and dropped gradually on hydrated copper sulphate (100 g.) contained in a 1½-litre round-bottomed flask fitted with a condenser, a steam jet passing to the bottom of the vessel, and a thermometer with the bulb touching the copper sulphate. The flask was heated at 170° and a fine jet of steam was blown through the liquid in the flask during the reaction. This had the effect, not only of removing the *iso*creosol formed from the mixture, but also of breaking up the tarry scum on the surface

* In later experiments the diazo-solution was neutralised at a low temperature by the addition of copper carbonate; more regular yields (about 65%) were thus obtained.

and thus allowing the diazo-solution to come into immediate contact with the copper sulphate. The internal temperature remained almost constant at 103°. A light brown oil passed over with the steam, and the rate of addition was regulated so as to be equal to that of distillation. The addition occupied 2 hours and the steam was passed for ½ hour longer. The oil was isolated by means of ether and distilled. The fraction b. p. 200—220° (about 30 g.) was sufficiently pure for most purposes and on distillation gave 24 g., b. p. 217—218°. The colourless oil rapidly crystallised in large plates, m. p. 35—36° (Found: C, 69·5; H, 7·3. Calc. for $C_8H_{10}O_2$: C, 69·5; H, 7·2%).

*iso*Creosol gives with alcoholic ferric chloride a transitory green coloration, quickly becoming bluish-green.

Acetyl derivative. The phenol was acetylated by a boiling mixture of twice its weight of acetic anhydride and its own weight of sodium acetate for 3 hours (yield almost theoretical). The substance crystallised from a mixture of acetic acid (5 vols.) and water (3 vols.) in colourless needles, m. p. 56—57° (Found: C, 66·4; H, 6·7. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%). The crystals which separate from aqueous alcohol and from light petroleum are flat prisms and long needles respectively.

The *benzoyl* derivative, obtained by the usual method, crystallised from alcohol in colourless, hexagonal plates, m. p. 80—81° (Found: C, 73·8; H, 5·8. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8%).

2 : 6-*Dinitro*-iso*creosol* (III).—A mixture of concentrated hydrochloric acid (170 c.c.) and water (200 c.c.) was gradually added with shaking to a solution of sodium nitrite (100 g.) in water (400 c.c.) underlying one of *iso*creosol (10 g.) in ether (300 c.c.). The ethereal layer became deep red and brown fumes were copiously evolved. On the following day, the ethereal solution was separated, washed with water and aqueous sodium acetate, and stirred in a concentrated solution of sodium carbonate. The precipitated yellow sodium salt was collected, washed with ether, and dried (10 g.). Its solution in water was acidified and the *dinitro*iso*creosol* precipitated was employed in further experiments.

The substance crystallises from water in pale yellow needles, m. p. 152—153° (decomp.) or from benzene–light petroleum in flat, yellow needles of the same m. p. (Found in material dried at 100°: N, 12·3. $C_8H_8O_6N_2$ requires N, 12·3%). The compound gives a reddish-brown coloration with alcoholic ferric chloride and its solution in sulphuric acid is orange. The yellow *sodium* salt crystallises from alcohol in felted needles and gives red solutions.

When the reaction described above was interrupted after 6 hours,

a mixture of nitrophenols could be isolated, but separation was not effected. After methylation, however, pure 6-nitrohomoveratrole, m. p. 117°, was obtained and identified.

The dinitro*iso*creosol was readily soluble in cold acetic anhydride, but was not acetylated. Reaction occurred on boiling the solution, and the resulting *acetyl* derivative crystallised from alcohol in colourless needles, m. p. 106° (Found: C, 44·9; H, 3·8; N, 10·3. $C_{10}H_{10}O_7N_2$ requires C, 44·4; H, 3·7; N, 10·4%). It gave the original compound on hydrolysis with 2*N*-sodium hydroxide on the steam-bath. It is therefore improbable that either of the nitro-groups is in the *o*- or *p*- position with respect to the methoxyl. On reduction and condensation with phenanthraquinone no phenanthraphenazine derivative was produced.

The *phenylhydrazine* salt was prepared in toluene solution and crystallised from alcohol in flat, orange needles, m. p. 109° with evolution of gas (Found: C, 45·5; H, 5·4; N, 15·8. $C_8H_8O_6N_2,C_6H_8N_2,2H_2O$ requires C, 45·2; H, 5·4; N, 15·1%). It was partially hydrolysed by boiling water and was resolved into its constituents by acids or alkalis. The *hydroxylamine* salt crystallised from water in bright orange needles which became pasty at 166° and melted to a brown liquid at 208°, a sequence not affected by recrystallisation from water or ethyl acetate (Found: C, 36·2; H, 4·4. $C_8H_8O_6N_2,NH_3O$ requires C, 36·8; H, 4·2%). On heating at 100°, the salt lost hydroxylamine, and the residue, m. p. 151°, consisted of pure dinitro*iso*creosol.

G-T. 2 : 6-*Dinitroacetylcreosol* [2 : 6-*Dinitro*-4-*acetoxy*-m-*tolyl methyl ether*] (II).—Beechwood creosote was distilled through an efficient column and the fraction, b. p. 210—223°, was redistilled, the portion, b. p. 219—222°, being collected. The sodium salt was then isolated and the phenol recovered and distilled; the material, b. p. 219—221°, consisted of creosol which was sufficiently pure to be employed for most purposes.

(A) G-T. 6-*Nitroacetylcreosol* [6-*nitro*-4-*acetoxy*-m-*tolyl methyl ether*] (Cardwell and Robinson, J., 1915, **107**, 256) is best prepared by one of the following methods. (A) Acetylcreosol (25 g.) was gradually added to nitric acid (200 c.c.; *d* 1·42) cooled to — 10° and mechanically stirred. The product was precipitated by the addition of water (500 c.c.) and isolated. The nitric acid employed was previously boiled, but a trace of sodium nitrite was added just before the experiment was commenced. (B) A solution of nitric acid (10 g.; *d* 1·42) in acetic anhydride (5 c.c.) to which a crystal of urea had been added was gradually introduced into a mixture of acetylcreosol (10 g.) and acetic anhydride (10 c.c.) cooled to —10°. Water was added 15 minutes later, and the product collected. This

material (which can be used for the next stage) crystallised from alcohol in colourless, silky needles, m. p. 136—137°.

When, however, the crude product was extracted from a benzene solution with aqueous sodium hydroxide, a by-product could be isolated. The red alkaline solution was acidified with hydrochloric acid and extracted with chloroform. On evaporation of the dried extract there remained 2 g. of a yellow, crystalline mass, which crystallised from water, in which it was moderately readily soluble, in stout, yellow, hexagonal prisms, m. p. 172° (decomp.) (Found: N, 13·1. $C_7H_6O_6N_2$ requires N, 13·1%). This indicated a *dinitrohomocatechol*, and the deep cherry-red colour of its solution in aqueous alkalis as well as the rich bluish-green coloration which it gave with ferric chloride confirmed this view. On methylation with a large excess of methyl iodide and boiling alcoholic sodium ethoxide, 2 : 6-dinitrohomoveratrole, m. p. 92° (see below), was obtained. This by-product is therefore 2 : 6-*dinitrohomocatechol*. It is difficult to explain the demethylation which must have occurred.

6-Nitroacetylcreosol (4 g.) was nitrated in 1 hour by means of nitric acid (30 c.c.; *d* 1·5) below 10°. The substance crystallised from alcohol in hexagonal plates, m. p. 103° (Found: N, 10·3. Calc. for $C_{10}H_{10}O_7N_2$: N, 10·4%). On hydrolysis with 2*N*-sodium hydroxide or, better, with hot aqueous alcoholic sodium carbonate, 2 : 6-*dinitrocreosol* was obtained; this crystallised from benzene in yellow, prismatic needles, m. p. 108° (Found: C, 42·4; H, 3·6; N, 12·3. $C_8H_8O_6N_2$ requires C, 42·1; H, 3·5; N, 12·3%). When this phenol was treated with cold nitric acid (*d* 1·42), and the solution diluted with water, no precipitation occurred, but addition of a solution of quinoline in dilute sulphuric acid precipitated characteristic, bright red prisms of a *quinoline* salt; this crystallised from acetic acid in chocolate-brown, rectangular, prismatic needles, m. p. 110° (decomp.). The *quinoline* salt of 3 : 5 : 6-trinitroguaiacol (Pollecoff and Robinson, *loc. cit.*) was prepared for comparison and this crystallised from alcohol in slender, yellow needles, m. p. 185° (decomp.) (Found: N, 14·4. $C_{16}H_{12}O_8N_4$ requires N, 14·4%).

2 : 6-*Dinitrohomoveratrole* (IV) was obtained by methylation of dinitro*iso*creosol and of dinitrocreosol. In the latter case (compare Oberlin, *loc. cit.*) the aqueous alkali–methyl sulphate and the xylene–methyl sulphate–potassium carbonate method both give excellent results. A mixture of the sodium salt of dinitro*iso*creosol, anhydrous potassium carbonate (½ mol.), and methyl sulphate (about 2·5 mols.) was heated at 125° for 2 hours (yield almost quantitative). 2 : 6-Dinitrohomoveratrole crystallises from alcohol or light

petroleum (b. p. 60—80°) in colourless needles, m. p. 92° (Found : C, 44·6; H, 4·3; N, 11·5. Calc. for $C_9H_{10}O_6N_2$: C, 44·5; H, 4·1; N, 11·5%).

Anhydrocotarnine-2 : 6-dinitrohomoveratrole,

$$CH_2O_2{:}C_6H(OMe)\text{—}CH\cdot CH_2\cdot C_6H(OMe)_2(NO_2)_2$$
$$\qquad\qquad\qquad\quad CH_2\text{—}CH_2\text{—}NMe$$

—A mixture of 2 : 6-dinitrohomoveratrole (3 g.), cotarnine (3 g.), and methyl alcohol (20 c.c.) was boiled under reflux. Crystals appeared in about 5 minutes and the reaction was completed in 10 minutes. After cooling, the substance was collected, washed with methyl alcohol, and dried in a vacuum (yield, 4·5 g.). The base crystallised from ethyl alcohol in orange-yellow, diamond-shaped plates, often arranged in stellar aggregates, m. p. 141° to a red liquid (Found : C, 54·4; H, 5·0. $C_{21}H_{23}O_9N_3$ requires C, 54·7; H, 5·0%). This substance is moderately readily soluble in benzene and, on boiling with glacial acetic acid, it is decomposed with formation of its generators.

We wish to thank the Chemical Society for a grant which has defrayed a part of the cost of the work.

THE UNIVERSITIES OF OXFORD,
LIVERPOOL, AND MANCHESTER. [*Received, June 1st*, 1926.]

PRINTED IN GREAT BRITAIN BY RICHARD CLAY & SONS, LIMITED,
BUNGAY, SUFFOLK.

DERIVATIVES OF HOMOCATECHOL. PART II.

BY
JOHN MASSON GULLAND
AND
ROBERT ROBINSON.

Publication 6

The whole of the work described in this paper was carried out by me, without the collaboration of Professor Robinson.

Reprinted from the Journal of the Chemical Society, August, 1926.

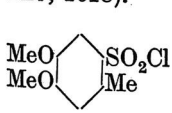
Reprinted from the Journal of the Chemical Society, 1926.

CCLXIII.—*Derivatives of Homocatechol. Part II.*

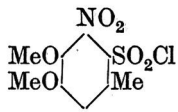
By John Masson Gulland and Robert Robinson.

The experiments here described were made with the object of preparing 2-nitrohomoveratrole, and the following points arising from the investigation require comment.

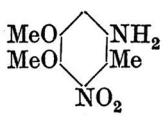
The nitration of homoveratrole-6-sulphonyl chloride (I) yields its 5-nitro-derivative (II) in agreement with the rule of Jones and Robinson (J., 1917, **111**, 907; compare Rây and Robinson, J., 1925, **127**, 1618).



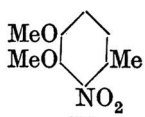
(I.)



(II.)



(III.)



(IV.)

Oberlin (*Arch. Pharm.*, 1925, **263**, 641) reduced 2 : 6-dinitrohomoveratrole with ammonium sulphide and obtained a nitroamine, m. p. 92—93°, or 104—105°, which he considered to be homogeneous and converted into an oily nitrohomoveratrole by deamination.

Since, on oxidation, 2-nitroveratric acid was obtained, the above substances were regarded as 2-nitro-6-aminohomoveratrole (III) and 2-nitrohomoveratrole (IV), respectively.

We had traversed independently much the same ground, but our compounds were undoubtedly mixtures. Employing sodium sulphide as the reducing agent, we obtained a nitroaminohomoveratrole of m. p. 90—100°, and oxidation of the oily nitrohomoveratrole therefrom gave a mixture of nitroveratric acids.

Experimental.

5-Nitrohomoveratrole-6-sulphonyl Chloride (II).—Chlorosulphonic acid (80 c.c.) in chloroform (100 c.c.) was gradually added to a cooled, mechanically stirred solution of homoveratrole (100 g.) in chloroform (100 c.c.); as the sulphonic acid crystallised in needles, more chloroform (100 c.c.) was added. After 15 minutes, 137 g. of phosphorus pentachloride were added in four portions. The mixture was gently heated and after an hour the solution was shaken with ice-cold water, dried, and the solvent removed. The residue was triturated with light petroleum, dried (140 g.; yield 85%), and recrystallised from this solvent, homoveratrole-6-sulphonyl chloride being obtained in glistening plates, m. p. 75° (Found: S, 13·0. Calc. for $C_9H_{11}O_4ClS$: S, 12·8%). Homoveratrole-6-sulphonamide, prepared from the chloride, had m. p. 193—194° (Brown and Robinson, J., 1917, **111**, 955, describe the chloride as an oil yielding a sulphonamide, m. p. 191°).

Powdered homoveratrolesulphonyl chloride (10 g.) was gradually added to stirred nitric acid (60 c.c.; *d* 1·46), maintained below 10°, and 15 minutes later the mixture was poured into water. The product (yield, 72%) crystallised from benzene in colourless prisms, m. p. 140—141° (Found: C, 36·8; H, 3·6; N, 4·9. $C_9H_{10}O_6NClS$ requires C, 36·5; H, 3·4; N, 4·7%). To determine the position of the nitro-group, a hot solution of nitrohomoveratrolesulphonyl chloride (6 g.) in aqueous potassium hydroxide (3 g. in 80 c.c.) was cooled, the potassium salt of the sulphonic acid crystallising in elongated, rectangular plates, and concentrated sulphuric acid (70 c.c.) introduced. Superheated steam removed a yellow oil, which solidified (3·7 g.) and was then crystallised from alcohol. (i) The yellow needles (2·8 g.) were recrystallised and had m. p. 57—59° (Found: C, 54·4; H, 5·3%); after removal of a minute amount of a nitrophenol, the substance crystallised from alcohol in colourless, flat needles, which, alone or mixed with 5-nitrohomoveratrole prepared by Cousin's method (*Ann. Chim.*, 1898, **13**, 537), melted at 59° (Found: C, 54·4; H, 5·5. Calc. for $C_9H_{11}O_4N$: C, 54·8; H, 5·6%). (ii) The alcoholic mother-liquor was evaporated, the

residue extracted with cold aqueous sodium hydroxide, and the solution filtered (residue, 0·3 g. of nitrohomoveratrole). The precipitate (0·5 g.) obtained on acidification and cooling in ice crystallised from aqueous alcohol in long, orange needles, m. p. 80° (Found: N, 7·8. Calc. for $C_8H_9O_4N$: N, 7·7%). This substance yielded the above-described nitrohomoveratrole, m. p. 59°, on methylation and was unaltered in m. p. when mixed with 5-nitrocreosol (compare Oberlin, *loc. cit.*), m. p. 79—80° (Found: N, 7·6%), prepared by the nitration of creosol in ethereal solution.

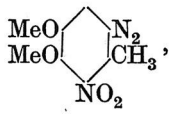
Nitration of Acetylisocreosol [3-*Acetoxy*-p-*tolyl methyl ether*].—A series of experiments was made on the nitration of *iso*creosol in ethereal solution under various conditions and small quantities of a compound which was volatile in steam were isolated. The substance crystallised from water in needles, m. p. 166—167°, and gave a red solution in aqueous alkali, but the amount obtained did not allow of complete investigation. Under some conditions 2 : 6-dinitro*iso*creosol was obtained.

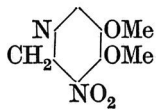
Acetyl*iso*creosol (7 g.) was gradually added to mechanically stirred and ice-cooled nitric acid (100 c.c.; *d* 1·42), the temperature being maintained below 5°. After 15 minutes, the product was precipitated by ice-water as an oil which solidified over-night (6 g.). Fractional crystallisation from alcohol gave two products. (A) The more sparingly soluble substance (yield 5 g.) crystallised from 80% alcohol in flat, yellow needles, m. p. 104—105° (Found: C, 51·0; H, 4·2; N, 6·6. $C_9H_9O_5N$ requires C, 51·2; H, 4·3; N, 6·6%). The compound gave a reddish-brown colour with ferric chloride and dissolved in aqueous alkalis to permanganate-coloured solutions. These properties and the analytical figures suggest that the substance is a nitroacetylhomocatechol the production of which would involve demethylation. After treatment for 15 minutes with boiling 2*N*-alcoholic potassium hydroxide a nitrophenol was obtained which crystallised from water in golden-yellow leaflets, m. p. 80° (unsharp), and then from light petroleum in golden-yellow needles; these melted at 82—83°, and at the same temperature when mixed with an authentic specimen of 5-nitrohomocatechol (Cousin, *loc. cit.*). In all probability, therefore, the substance, m. p. 104—105°, is 5-nitro-3-acetoxy-*p*-cresol. (B) The more soluble constituent (yield 1 g.), which was to some extent obtained from the solution by the addition of water, crystallised from light petroleum in lemon-yellow prisms, m. p. 60—61° (Found: N, 6·2. $C_{10}H_{11}O_5N$ requires N, 6·2%). It was insoluble in cold alkalis, but on boiling dissolved to an orange-red solution. The compound is doubtless a nitroacetyl*iso*creosol and very probably it is 5-*nitro*-3-*acetoxy*-p-*tolyl methyl ether*.

2-*Nitro*-6-*amino*isocreosol, $MeO{\cdot}C_6HMe(OH)(NH_2){\cdot}NO_2$.—Sodium sulphide (5 mols.) was added to a boiling solution of 2 : 6-dinitro-*iso*creosol (1 mol.) in the calculated quantity of 2% aqueous sodium hydroxide. After ¾ hour, the liquid was just acidified with hydrochloric acid, filtered while hot from sulphur, cooled, and treated with sodium acetate until it was no longer acid to Congo-red. The feathery needles obtained (yield, 25%) crystallised from methyl alcohol and then from benzene–light petroleum in orange-yellow prisms, m. p. 168—169° (decomp.) (Found : C, 49·3; H, 5·1. $C_8H_{10}O_4N_2$ requires C, 48·5; H, 5·0%). This compound is very prone to discoloration as the result of oxidation; its solution in aqueous alkalis is deep red, and it gives a green colour with alcoholic ferric chloride. The *acetyl* derivative, readily produced by the action of acetic anhydride, crystallised from water in colourless needles, m. p. 183° after slight softening at 180°. After drying in a vacuum the substance lost 6·0% at 110° (Found in dried material: N, 11·7. $C_{10}H_{12}O_5N_2,H_2O$ requires H_2O, 6·9%. $C_{10}H_{12}O_5N_2$ requires N, 11·7%). Its solution in aqueous sodium hydroxide is bright red and, on cooling to 0°, deposits the sodium salt in yellow needles. Clearly the acetyl group is attached to nitrogen, and the non-formation of a benzoxazole is one of the reasons for the assignment of the *p*-aminophenol structure to the semi-reduction product of dinitro*iso*creosol.

Nitroaminohomoveratroles and Various Derivatives.—A hot solution of crystallised sodium sulphide (25 g.) and sulphur (7·5 g.) in water (100 c.c.) was added to a boiling mixture of 2 : 6-dinitrohomoveratrole (10 g.), alcohol (50 c.c.), and water (400 c.c.). The whole was boiled under reflux for 1¼ hours, then cooled, and the precipitate of golden-yellow needles was collected and freed from sulphur by solution in hot dilute hydrochloric acid and reprecipitation by ammonia. The dry product (7·5 g.; 85%) crystallised from aqueous alcohol in golden-yellow needles, m. p. 90—100°, and no separation was effected by recrystallisation (Found : N, 13·4. Calc. for $C_9H_{12}O_4N_2$: N, 13·2%). There is no doubt that this substance is a mixture, the chief constituent of which is 2-nitro-6-aminohomoveratrole (III). The *hydrochloride*, m. p. about 210°, is hydrolysed by hot water, giving golden-yellow needles, m. p. 90—92°. The *acetyl* derivative, colourless needles, m. p. 173—175°, from alcohol, on hydrolysis yielded the original base, m. p. 90—100°. 6-*Bromo*-2-*nitrohomoveratrole*, obtained in good yield by the Sandmeyer reaction (along with a sparingly soluble *by-product*, orange needles, m. p. 241°, from ethyl acetate), crystallised from ethyl acetate in buff columns, m. p. 102° (Found : N, 5·3. $C_9H_{10}O_4NBr$ requires N, 5·1%). The action of sulphurous acid on the diazo-sulphate

from nitroaminohomoveratrole in presence of copper powder led to the production of two substances, one of which was neutral and crystallised from alcohol in golden-yellow needles, m. p. 142° (Found in material dried at 100°: C, 45·9; H, 4·3; N, 14·3; S, 6·6. $C_{18}H_{19}O_9N_5S$ requires C, 44·9; H, 4·0; N, 14·6; S, 6·7%). This curious compound, which constitutes the major product, is stable in boiling 2*N*-sodium hydroxide and dissolves in sulphuric acid to a purple solution which quickly becomes red. Apparently the following fragments



, S, O,


must be pieced together by suitable rearrangements in order to construct a possible constitutional formula for the substance, and this can be done in many ways. The second product from the reaction was a small amount of nitrohomoveratrolesulphinic acid. This was oxidised by permanganate, and the resulting sulphonic acid hydrolysed with superheated steam in presence of sulphuric acid. An alkali-insoluble oil and a nitrophenol, crystallising from light petroleum in needles, m. p. 62° (Found: N, 7·6. $C_8H_9O_4N$ requires N, 7·6%), were obtained. Since this nitrophenol is volatile in steam, gives a red solution in aqueous sodium hydroxide, and a green coloration with ferric chloride, it is probably 2-*nitro*-3-*hydroxy*-p-*tolyl methyl ether*. The nitrohomoveratrolediazonium chloride was reduced by stannous chloride; the resulting *nitrohydrazino-homoveratrole* crystallised from methyl alcohol in orange leaflets, m. p. 146—166°. The *piperonylidene* derivative of this hydrazine crystallised from alcohol as a mixture of small, orange-yellow tablets and large, orange-yellow plates, m. p. 171—175°. On repeated crystallisation a small amount of the plates was obtained in a homogeneous condition, m. p. 172—173°.

Nitroaminohomoveratrole itself was condensed with piperonal, and a considerable quantity of an apparently homogeneous *piperonylidene* derivative obtained which crystallised from methyl alcohol in lemon-yellow needles, m. p. 130—132° (Found: C, 59·3; H, 4·7. $C_{17}H_{16}O_6N_2$ requires C, 58·9; H, 4·7%). On hydrolysis this purified material gave a nitroaminohomoveratrole, m. p. 90—92° (Found: C, 51·2; H, 5·7. Calc. for $C_9H_{12}O_4N_2$: C, 50·9; H, 5·7%). The hydrazine prepared from this specimen crystallised from alcohol in orange leaflets, m. p. 147—149°, and in a second physical modification, m. p. 163—164° after softening at 148° (Found: N, 18·4. $C_9H_{13}O_4N_3$ requires N, 18·5%). On oxidation with copper sulphate

in dilute acetic acid solution, the last-mentioned specimen of the hydrazine gave an almost colourless oil, volatile in steam. This afforded, on oxidation with potassium permanganate, a substance, crystallising from water in needles and plates, m. p. 180—198°, which proved to be a mixture of 2-nitro- and 6-nitro-veratric acids.

We desire to thank the Chemical Society for a grant which defrayed a part of the expense of the investigation.

THE UNIVERSITIES OF OXFORD AND MANCHESTER.

[*Received, June 1st,* 1926.]

PRINTED IN GREAT BRITAIN BY RICHARD CLAY & SONS, LIMITED, BUNGAY, SUFFOLK.

STRYCHNINE AND BRUCINE. PART V.

BY

JOHN MASSON GULLAND,

WILLIAM HENRY PERKIN, Junr.,

AND

ROBERT ROBINSON.

Publication 7

The whole of the work described in this paper was carried out by me.

Reprinted from the Journal of the Chemical Society, July, 1927.

Reprinted from the Journal of the Chemical Society, 1927.

CCXI.—*Strychnine and Brucine. Part V.*

By John Masson Gulland, William Henry Perkin, jun., and Robert Robinson.

The present communication contains the description of part of a general investigation of the reduction products of brucine, our knowledge of which is comparatively scanty. Reduction by hydrogen in presence of colloidal palladium yields dihydrobrucine (Skita and Franck, *Ber.*, 1911, **44**, 2864), and Tafel and Naumann (*Ber.*, 1901, **34**, 3291) have described the preparation by electrolytic reduction of a substance which they designate " tetrahydrobrucine."

The starting point of the research now to be described is brucidine, a substance which Tafel and Naumann (*loc. cit.*) claim to have prepared from " tetrahydrobrucine " by the elimination of water at 215°. The two substances were thus considered to be analogous to tetrahydrostrychnine and strychnidine and were represented by the scheme :

$$(MeO)_2(C_{20}H_{20}O)(:N)\leqslant^{CH_2\cdot OH}_{NH} \longrightarrow (MeO)_2(C_{20}H_{20}O)(:N)\leqslant^{CH_2}_{N}$$

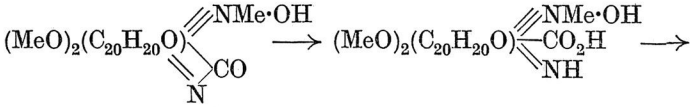
Tetrahydrobrucine. *Brucidine.*

The properties of these substances as described by Tafel are extremely similar, and he was unable to demonstrate by the preparation of a nitrosoamine the presence of an imino-group in the secondary amine, tetrahydrobrucine. We have repeated the electrolytic reduction of brucine, using the modified apparatus described in a previous communication (J., 1924, **125**, 1798), and our results show that Tafel's " tetrahydrobrucine," m. p. 200—201°, should be re-named brucidine. It is clear, however, that his " brucidine," m. p. 198°, was correctly named, although it was not quite homogeneous and was identical with his supposed " tetrahydrobrucine." We have now obtained two products, (i) *brucidine*, m. p. 203—203·5°, which shows all the properties of Tafel's " tetrahydrobrucine," and (ii) *tetrahydrobrucine*, m. p. 177°, which is a secondary amine yielding a *nitrosoamine*. The second substance, moreover, yields brucidine when dehydrated by means of phosphorus

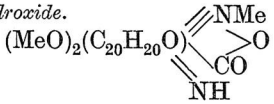
oxychloride, and the two compounds are thus entirely analogous to the corresponding derivatives of strychnine. Tafel's analyses of " tetrahydrobrucine " are in agreement with the theory for brucidine containing a molecule of methyl alcohol, and we have found that the base when crystallised from methyl alcohol does in fact retain one molecule of the solvent.

Tetrahydrobrucine and brucidine are di-acid bases each of which forms a *dihydrochloride* and a *dihydriodide*, but only a monomethiodide when heated with an excess of methyl iodide in boiling methyl alcohol.

The starting materials in the experiments described in this communication are the brucidine metho-salts, and of these the *methosulphate*, prepared by the direct combination of the base with methyl sulphate, is the most easily obtained in practice. Brucidine metho-salts, however, have also been prepared by the electrolytic reduction of methylbrucine. This substance was first obtained (Moufang and Tafel, *Annalen*, 1899, **304**, 42) by the decomposition of brucine methiodide with silver sulphate, followed by the removal of the sulphuric acid by baryta, and Tafel represented it as a betaine according to the scheme :



Brucine methohydroxide.



Methylbrucine.

Leuchs and Anderson (*Ber.*, 1911, **44**, 3046), however, prepared this compound more simply by the action of sodium hydroxide on brucine methosulphate, and we have employed a slight modification of their method. The electrolytic reduction of methylbrucine in dilute sulphuric acid is followed by the removal of the sulphuric acid by means of barium carbonate. In this way, *brucidine methohydrogencarbonate* is obtained, and from it may be prepared *brucidine methohydroxide* by the action of alkali, and also *brucidine methiodide* by means of sodium iodide. This methiodide is identical with a specimen prepared by the interaction of the base with methyl iodide, and it is therefore evident that the nitrogen atom which is involved in the production of brucidine metho-salts is not that which forms part of the group –CO–N: of brucine.

When brucidine methochloride or methosulphate,

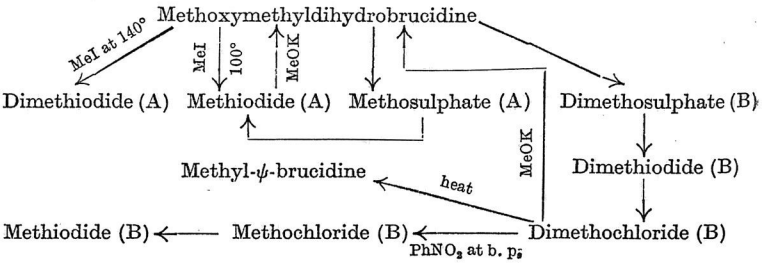
$$C_{23}H_{28}O_3N_2,Me_2SO_4,$$

is digested with methyl-alcoholic potassium hydroxide it is converted into *methoxymethyldihydrobrucidine*, $C_{25}H_{34}O_4N_2$, m. p. 115°, which is derived from brucidine by the introduction of a methyl group and the addition of methyl alcohol. Unlike the corresponding derivative of strychnidine, this substance is a di-acid base, yielding a *dihydriodide*, but here, as in the case of brucidine, one molecule only of methyl iodide enters easily into combination with the base. The formation of this *methiodide* (A) by the action of methyl iodide at 100° takes place smoothly in the absence of a solvent, but when methyl alcohol is employed in the preparation, a small quantity of *oxymethoxymethyldihydrobrucidine*, $C_{25}H_{34}O_5N_2$, m. p. 277°, is produced, and a little of the same substance may be isolated from the mother-liquors when the methiodide, prepared in the absence of a solvent, is recrystallised from methyl alcohol. By far the greater proportion of the product of the action of methyl iodide on methoxymethyldihydrobrucidine under either set of conditions is the methiodide (A), and in this the brucidine derivative differs greatly from the parallel strychnidine one (compare this vol., p. 1591). Indications have been obtained of the formation in these reactions of a second iodine-free *base*, melting at about 218°, which may correspond to oxymethoxymethyldihydrostrychnidine (A), but this substance has not been obtained in a pure condition, because recrystallisation from methyl alcohol converts it into oxymethoxymethyldihydrobrucidine, m. p. 277°. Oxymethoxymethyldihydrobrucidine is probably formed by an atmospheric oxidation which is catalysed by small quantities of iodine, since it has recently been obtained in much greater yield when an ethyl-alcoholic solution of methoxymethyldihydrobrucidine containing a few small crystals of iodine is exposed to the air for some days. A parallel experiment in which the iodine was omitted yielded no oxymethoxymethyldihydrobrucidine in the same space of time.

Further atmospheric oxidation takes place in boiling methyl-alcoholic solution, and a *dioxymethoxymethyldihydrobrucidine* (X), $C_{25}H_{34}O_6N_2$, m. p. 270°, has been isolated. This substance is isomeric with two *dioxymethoxymethyldihydrobrucidines*, namely (Y) and (Z) (p. 1631), which are produced by oxidation of methoxymethyldihydrobrucidine by permanganate. The investigation into the constitution of these substances, their relationship, and the significance of their formation has not yet been completed.

Methoxymethyldihydrobrucidine combines readily at 100° with one molecule of methyl iodide, as has been stated above, but when the temperature is raised to 140° and the reaction prolonged for some hours, the *dimethiodide* (A), m. p. 215°, is formed. In a similar way, methoxymethyldihydrobrucidine reacts slowly with methyl

sulphate at 100° to form the *monomethosulphate* (A), but if the reaction is continued for a day the base is converted quantitatively into the *dimethosulphate* (B). This substance has not been obtained in a crystalline form, but when sodium iodide is added to its aqueous solution the *dimethiodide* (B), m. p. 290°, is precipitated and easily obtained in a pure condition. The *dimethochloride* (B), prepared from the dimethiodide by the action of silver chloride, is a horny mass which has been decomposed in three different ways. When boiled with methyl-alcoholic potassium hydroxide, it loses two molecules of methyl chloride, and methoxymethyldihydrobrucidine is regenerated. When the dimethochloride is heated for a short time in boiling nitrobenzene, the chief product is *methoxymethyldihydrobrucidine methochloride* (B), produced by the liberation of one molecule of methyl chloride. Sodium iodide converts this substance into the *methiodide* (B), which is isomeric with the methiodide (A) mentioned above. When, thirdly, the dry dimethochloride (B) is heated, it loses two molecules of methyl chloride and one of methyl alcohol and yields *methyl-ψ-brucidine* (p. 1631). It will be observed that methoxymethyldihydrobrucidine not only forms two series of metho-salts, depending probably upon which of the two nitrogen atoms is involved, but also two series of dimetho-salts, which are probably stereoisomeric. The relationships existing in this complex group of substances are readily understood from the following scheme:



A consideration of the colour reactions of the reduced brucidine derivatives, especially that given with ferric chloride (see p. 1661), leads to the conclusion that the methiodide (A) has the formula $(MeO)_2(C_{20}H_{20}O)(OMe)(:NMe)\left\langle \begin{matrix} CH_2 \\ | \\ NMe \end{matrix} \right\rangle I$, whilst the methiodide (B) is $(MeO)_2(C_{20}H_{20}O)(OMe)(:NMe_2)\left\langle \begin{matrix} CH_2 \\ | \\ N \end{matrix} \right\rangle I$. This is noteworthy and implies that the more basic of the two nitrogen atoms of brucidine becomes the less basic of the two nitrogen atoms of methoxymethyldihydrobrucidine.

Dilute nitric acid has apparently little oxidising action on

methoxymethyldihydrobrucidine, as this reagent at 100° yields only *nitromethoxymethyldihydrobrucidine*, $C_{25}H_{33}O_6N_3$. When, however, the oxidation is brought about by means of potassium permanganate in acetone, two isomeric *dioxymethoxymethyldihydrobrucidines*, $C_{25}H_{34}O_6N_2$, are produced, namely (Y), m. p. 185—186°, and (Z), m. p. 110—111°. The first of these substances (Y) is a base and yields a *methiodide*, which has the interesting property of existing simultaneously in two interconvertible forms; one contains solvent of crystallisation, the other does not. This base is not altered by boiling for a short time with acetic anhydride, and attempts to form a semicarbazone resulted in a dark red, uncrystallisable oil. The second substance (Z) shows more feebly basic properties, since, although it is readily soluble in dilute hydrochloric acid, it does not react with methyl iodide at 100°.

In order to determine whether a process similar to the formation of methoxymethyldihydrobrucidine would occur if ethyl alcohol were substituted for the methyl alcohol used in the preparation of this substance, brucidine methosulphate was digested with sodium ethoxide in ethyl alcohol. A sandy powder was obtained which showed no tendency to crystallise, and was therefore analysed in the form of its crystalline methiodide. This proved to be *ethoxymethyldihydrobrucidine methiodide*, $C_{26}H_{36}O_4N_2$,MeI. The reaction thus follows a course similar to that observed when methyl alcohol is used, but the product was not further investigated.

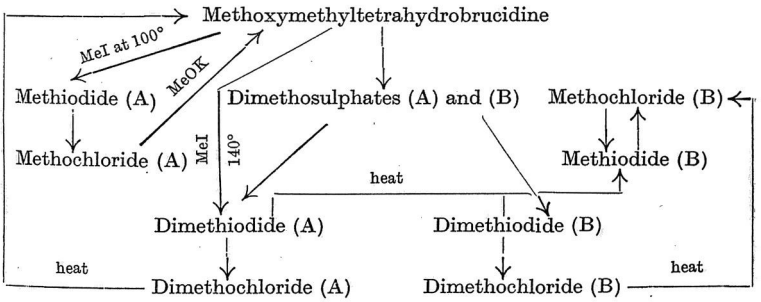
When methoxymethyldihydrobrucidine is boiled with dilute sulphuric acid, methyl alcohol is eliminated, and as no precipitate is formed on the addition of ammonia or sodium hydroxide the solution evidently contains a quaternary sulphate. On addition of an excess of sodium iodide *methyl*neo*brucidinium iodide*, $C_{24}H_{31}O_3N_2I$, m. p. 298°, is precipitated, and the investigation of the mother-liquors yielded only a further quantity of the same iodide. It would thus appear that, in contrast to the behaviour of methoxymethyldihydrostrychnidine under similar conditions (this vol., p. 1593), only one iodide is formed, which, it should be noted, is isomeric with brucidine methiodide, m. p. 322°. *Methyl*neo*brucidinium chloride*, prepared from the iodide by means of silver chloride, may be decomposed in two ways. When digested with methyl-alcoholic potassium hydroxide, it gains methyl alcohol and loses hydrogen chloride, forming methoxymethyldihydrobrucidine. On the other hand, if the dry chloride is heated it loses hydrogen chloride, forming *methyl-ψ-brucidine*.

Methyl-ψ-brucidine, $C_{24}H_{30}O_3N_2$, m. p. 198—199°, is obtained either in the manner described above, or by heating methoxymethyldihydrobrucidine dimethochloride (B). It is a base, forming a

dihydriodide, but only a *methiodide* when combined directly with methyl iodide in the cold. Small quantities of the base and also of its methochloride are formed during the decomposition of methoxymethyldihydrobrucidine dimethochloride (B) in boiling nitrobenzene; the methochloride, which was not isolated, yields the above-mentioned methiodide when treated with sodium iodide. Methyl-ψ-brucidine is unchanged by electrolytic reduction or by shaking in an atmosphere of hydrogen in presence of colloidal palladium, but it is readily oxidised by potassium permanganate to brucidone, $C_{23}H_{28}O_5N_2$, one atom of carbon being lost during the process. This most interesting substance, the analogue of strychnidone, is unfortunately an oil, but a crystalline *monosemicarbazone* was obtained and analysed. The stability of methyl-ψ-brucidine towards reducing agents is noteworthy and cannot, at present, be explained.

Methoxymethyltetrahydrobrucidine, $C_{25}H_{36}O_4N_2$, m. p. 133—135°, is derived from methoxymethyldihydrobrucidine by electrolytic reduction. It is characterised by the facility with which it crystallises, and also shows greater stability to light and air than the methoxydihydro-derivative. It is a di-acid base yielding a *dihydrochloride* and a *dihydriodide*, and like the methoxydihydro-derivatives it forms two series of metho-salts, namely (A) and (B), and also two series of dimetho-salts, namely (A), which are comparatively low-melting, and (B), which are high-melting. The *methiodide* (A) is produced by the direct combination of the base with methyl iodide at 100°, and in contrast to the behaviour of methoxymethyldihydrobrucidine under similar conditions no oxidation accompanies this reaction (compare p. 1629). This methiodide yields the *methochloride* (A) by the action of silver chloride, and it was observed that both of these substances readily revert to the parent base. The methiodide loses methyl iodide quantitatively at 170°, whilst methyl chloride is eliminated when the methochloride is boiled with methyl-alcoholic potassium hydroxide. Methoxymethyltetrahydrobrucidine combines slowly with methyl sulphate when heated with an excess of the reagent in dry benzene for 24 hours, and yields a glassy mass which is a mixture of two *dimethosulphates*, namely, (A) and (B). These have not been separated, but the addition of sodium iodide to their aqueous solution precipitates the *dimethiodide* (B), m. p. 287°, the isomeride (A) remaining in solution. The dimethiodide (B) and the *dimethochloride* (B), which is prepared from it by means of silver chloride, each lose one molecule of methyl iodide, or methyl chloride, when heated, and yield respectively the *methiodide*, or *methochloride*, of the series (B). Attempts to prepare methyl-ψ-dihydrobrucidine by further decomposition of the dimethochloride (B) or the metho-

chloride (B) were unsuccessful, because decomposition of the rest of the molecule precedes the elimination of methyl chloride; this behaviour is in marked contrast to that of the corresponding strychnidine derivatives (compare this vol., p.1592). *Methoxymethyltetrahydrobrucidine dimethiodide* (A), m. p. 230—232°, is precipitated in a very crude condition by the addition of a large excess of potassium hydroxide to the mother-liquors from the preparation of the dimethiodide (B). It may also be obtained by the direct combination of the base with methyl iodide at 140°. When heated at its melting point, it loses one molecule of methyl iodide with the formation of the methiodide (B), and it is converted by silver chloride into the *dimethochloride* (A). When this substance is heated, two molecules of methyl chloride are liberated and methoxymethyltetrahydrobrucidine is regenerated. The relationships of these substances are illustrated by the following scheme :—



The ferric chloride reactions suggest that the metho-salts (A) and (B) are constituted analogously to the related series from methoxymethyldihydrobrucine.

The methiodide (A) will have the formula

$$(MeO)_2(C_{20}H_{22}O)(OMe)(:NMe)\left\langle \begin{matrix} CH_2 \\ | \\ NMe \end{matrix} \right\rangle I,$$

whilst the methiodide (B) should be

$$(MeO)_2(C_{20}H_{22}O)(OMe)(:NMe_2)\left\langle \begin{matrix} CH_2 \\ | \\ N \end{matrix} \right\rangle I.$$

This is in agreement with the production of the methiodide (B) from each of the stereoisomeric dimethiodides (A) and (B), since the decomposition, on the suggested hypothesis, occurs at the nitrogen atom which becomes asymmetric (*Nabcd*) on the formation of the dimethiodides. A glance at the formula of the dimethiodides, $(MeO)_2(C_{20}H_{22}O)(OMe)(:NMe_2)\left\langle \begin{matrix} CH_2 \\ | \\ NMe \end{matrix} \right\rangle I_2$, will show that the $:NMe_2$ group is not a new asymmetric centre, whilst the nitrogen atom of the

$-CH_2-\overset{/}{\underset{\backslash}{N}}Me$ group can give rise to enantiomorphism. If the formulæ for the methiodides (A) and (B) were transposed, we should anticipate that the dimethiodides (A) and (B) would give rise to stereoisomeric methiodides on decomposition.

The *methyl*neo*dihydrobrucidinium salts* could not be prepared directly from methoxymethyltetrahydrobrucidine because this substance, unlike the methoxydihydro-base, is unaffected by boiling dilute sulphuric acid. Attempts to obtain these salts by the reduction of the methyl*neo*brucidinium salts were unsuccessful, as the sulphate was unchanged by electrolytic reduction. Methoxymethyltetrahydrobrucidine dihydrochloride, however, decomposes above its melting point in boiling mesitylene, yielding hydrogen chloride, methyl alcohol, and *methyl*neo*dihydrobrucidinium chloride.* This substance is amorphous, and its aqueous solution forms no precipitate with ammonia or potassium hydroxide. When the dry chloride is heated, it decomposes without producing methyl-ψ-dihydrobrucidine (compare this vol., p. 1592). The crystalline *methyl*neo*dihydrobrucidinium iodide* is prepared from the chloride by means of sodium iodide.

A number of efforts were made to prepare *methyl-ψ-dihydrobrucidine* by heating either (i) methoxymethyltetrahydrobrucidine methochloride (B), or (ii) methoxymethyltetrahydrobrucidine dimethochloride (B), or (iii) methyl*neo*dihydrobrucidinium chloride In each case, it was evident that decomposition of the rest of the molecule preceded the liberation of methyl chloride or of hydrogen chloride as the case might be, although the corresponding derivatives of strychnidine yield methyl-ψ-dihydrostrychnidine. We hoped, therefore, that the less stable *methoxymethyltetrahydrobrucidine dimethohydrogencarbonates* would decompose more readily, and this proved to be the case. The *dimethohydrogencarbonates* (A) and (B) may be prepared by evaporating in an open basin aqueous solutions of the corresponding *dimethohydroxides*, prepared by the action of silver hydroxide on the dimethiodides (A) and (B). They are also obtained by the action of silver carbonate on the dimethiodides. When heated over a flame, the dimethohydrogencarbonate (A) regenerates methoxymethyltetrahydrobrucidine, whilst the dimethohydrogencarbonate (B) yields methyl-ψ-dihydrobrucidine, $C_{24}H_{32}O_3N_2$, m. p. 220—221°, which has been characterised further by the preparation of a *dihydriodide*. When heated less vigorously (at 135°), the dimethohydrogencarbonate (B) loses only one molecule of carbon dioxide and forms *methoxymethyltetrahydrobrucidine methohydrogencarbonate* (B), which was not purified, but was isolated in the form of the methiodide (B) by the action of sodium iodide.

Experimental.

Brucine Methosulphate.—Leuchs and Anderson (*Ber.*, 1911, **44**, 3046) have described the preparation of small quantities of this substance by the combination of brucine with methyl sulphate in chloroform. The following process was found convenient for large-scale operations. Pure methyl sulphate (50 c.c.) is added to a suspension of brucine (125 g.) in methyl alcohol (200 c.c.). The base dissolves with evolution of heat, and the methosulphate, which separates over-night, is collected, washed with a little methyl alcohol, and dried first in a vacuum and then at 100°. A further quantity is obtained on concentrating the mother-liquors (total yield, about 90%). The methosulphate crystallises from ethyl alcohol in colourless needles, m. p. 278° (decomp.) (Found : C, 58·2; H, 6·5. Calc. : C, 58·5; H, 6·5%). Leuchs and Anderson give m. p. 268°.

Brucine methiodide is obtained by adding sodium iodide solution to an aqueous solution of the methosulphate. It crystallises from water in needles, m. p. 295° (decomp.), after drying at 100° (Found : C, 53·4; H, 5·4. Calc.: C, 53·7; H, 5·4%). Claus and Röhre (*Ber.*, 1881, **14**, 772) prepared this compound by the interaction of brucine and methyl iodide, and give the melting point as 290° (decomp)., whereas Hanssen (*Ber.*, 1884, **17**, 2267) gives 270°.

Brucine methohydrogencarbonate is prepared from the methiodide by shaking a hot aqueous solution with excess of silver carbonate, evaporating the filtrate to dryness under reduced pressure on the water-bath, and crystallising the residue from ethyl alcohol. It forms creamy-yellow plates, m. p. 202—203° (decomp.), which retain a molecule of alcohol after drying in a vacuum desiccator, and dissolve readily in water (loss at 120°, 10·5. 1EtOH requires loss, 9·8%. Found in dried material : C, 63·6 ; H, 6·5. $C_{23}H_{26}O_4N_2$, $MeHCO_3$ requires C, 63·8 ; H, 6·4%).

The Electrolytic Reduction of Brucine. Brucidine and Tetrahydrobrucine.

The success of this reduction depends largely on the temperature of the cathode chamber. Thus at 18°, the lowest temperature at which the battery of cells could be kept during a prolonged period in the absence of ice-cooling, about 68% of the weight of brucine used was isolated in the form of practically pure brucidine and tetrahydrobrucine. If, on the other hand, the temperature rose to 21°, the yield dropped to about 55% of the weight of brucine, and further the isolation of the tetrahydrobrucine was made more difficult by the presence of gummy substances, which caused the products to

become red when exposed to light and air. The formation of these could never be entirely avoided, but their amount was diminished considerably at the lower temperature. Tafel and Naumann (*loc. cit.*) were troubled by similar unstable by-products if their reduction was carried out above 15°.

The following is a description of a typical experiment, but it must be realised that variations occurred in the yields from different preparations. A solution of brucine (100 g.) in dilute sulphuric acid (300 g. of concentrated acid in 300 c.c. of water) is reduced in the usual apparatus (J., 1924, **125**, 1798) for 16 hours by a current of 5 amps., while the temperature is maintained at 17—18° by immersing the cells in running water. The contents of the cathode chambers and the aqueous washings of the cells are diluted to about twice the volume of the original solution, filtered in order to remove some lead sulphate, mixed with ice, and rendered alkaline by ammonia (*d* 0·880). Any rise of temperature is carefully avoided by the addition of ice and by cooling in a freezing mixture. A pale pink gum separates and adheres to the walls of the vessel. The liquid is decanted, extracted three times with chloroform (300 c.c. in all), and the mixed extracts are then used to dissolve the gum. The chloroform solution is washed with water, dried by potassium carbonate, and distilled. In order to remove the last traces of chloroform, the gummy residue is dissolved in boiling methyl alcohol (150 c.c.), and the solution evaporated to dryness on the water-bath. The product (100 g.), now a solid, is dissolved in boiling methyl alcohol (250 c.c.), and, on cooling, an almost colourless mass of crystals separates; this is collected and dried on the water-bath (45 g.). It melts at about 199° and is practically pure brucidine (see below). The mother-liquors are evaporated to dryness on the water-bath, the last traces of solvent being removed under reduced pressure; on boiling the semi-solid mass with pure ethyl acetate, a part remains undissolved, and after cooling is collected, washed with ethyl acetate, and dried in a vacuum (23 g.). It melts at 174° and is practically pure tetrahydrobrucine (see below). The mother-liquors contain the oily by-products, together with some crystalline substances, and their investigation is in progress.

Brucidine.—The product obtained from the reduction is crystallised from methyl alcohol, from which it separates in colourless needles, which, after being dried in a vacuum desiccator, shrink at 188—190° and melt at 203—203·5° without decomposition. On drying at 105° brucidine loses one molecule of methyl alcohol of crystallisation, and then melts at 203—203·5° without decomposition (loss at 105°, 7·7. 1MeOH requires loss, 7·9%. Found in dried material: C, 72·7; H, 7·3. $C_{23}H_{28}O_3N_2$ requires C, 72·6; H, 7·4%). It is

very slightly soluble in boiling water, and the solution reacts alkaline to litmus. It dissolves readily in chloroform, less easily in methyl alcohol and ethyl acetate, and only very sparingly in ether. The colourless solution of a pure specimen in dilute hydrochloric acid slowly acquires a faint olive-green colour; on addition of a few drops of sodium nitrite a dark green coloration appears, which becomes reddish-brown on standing. When now excess of sodium carbonate is added, the colour changes to a very intense claret, which passes entirely into chloroform when the liquid is shaken with that solvent. These properties agree well with the reactions of the substance which Tafel and Naumann describe as "tetrahydrobrucine." A solution of brucidine in 60% sulphuric acid * to which a drop of an aqueous solution of potassium dichromate has been added becomes green on standing. The addition of ferric chloride to a solution in dilute hydrochloric acid produces a dark blue-green colour, which appears pink when examined in thin layers. These colour reactions are also shown by many derivatives of brucidine (see p. 1661) and in many cases dilute nitric acid causes the development of a similar green-pink colour.

The corresponding colour reactions of brucine may be given here for comparison. A drop of dichromate imparts a deep red colour to a solution in 60% sulphuric acid, but the addition of ferric chloride to brucine in dilute hydrochloric acid does not produce a coloration.

The *dihydrochloride* is formed when a little concentrated hydrochloric acid is added to a solution of the base in hot methyl alcohol. On cooling, the liquid sets to a mass of needles, which are collected and recrystallised from methyl alcohol. This salt forms colourless needles which begin to darken at 285°, and melt at 310° (decomp.) after drying in a vacuum desiccator. A satisfactory analysis of this substance was not obtained, as it appears to lose hydrogen chloride on drying. There is no doubt, however, that the base combines with two molecules of hydrogen chloride. A solution of the dihydrochloride in methyl alcohol is colourless, but on exposure for a short time to air it becomes green; the solution then appears pink when examined in thin layers.

The *dihydriodide*, prepared by adding sodium iodide to a solution of the base in dilute hydrochloric acid, crystallises from water in shining, grey needles, m.p. 255° (decomp.), which are only very sparingly soluble in hot water.

The methosulphate. A short, vigorous reaction occurs when pure methyl sulphate (8 c.c.) is added to a slightly warm suspension of

* In the case of brucine and its derivatives the colour reactions are well shown in dilute sulphuric acid of 60% by weight, and not by volume (compare Part IV, this vol., p. 1599).

* *

powdered brucidine (20 g.) in methyl alcohol (80 c.c.), and when this has subsided the mixture is heated on the water-bath for a few moments until the base has completely dissolved. On cooling the green solution in ice, the methosulphate separates in excellent yield as a mass of colourless needles, which are collected, washed with methyl alcohol, and dried in a vacuum desiccator. It is essential that the methyl sulphate should be pure and freshly distilled; the presence of acid greatly reduces the yield. When prepared in this way, the methosulphate is sufficiently pure for most purposes. It may be recrystallised from methyl alcohol in colourless needles which begin to darken at 270° and melt at 291° (decomp.), are readily soluble in water, and become purple or green when kept for some time.

The *methiodide* is obtained either by the addition of sodium iodide to an aqueous solution of the methosulphate, or by adding methyl iodide to an ethyl-alcoholic solution of the base. In either case, the crystals which separate are recrystallised from water. The methiodide forms colourless needles, m. p. 322° (decomp.), which are sparingly soluble in methyl or ethyl alcohol (Found : C, 55·1; H, 6·0. $C_{23}H_{28}O_3N_2$,MeI requires C, 55·2; H, 5·9%).

Tetrahydrobrucine.—The product obtained from the electrolytic reduction (p. 1636) is recrystallised from ethyl acetate, in which it is sparingly soluble. When prepared in this way, tetrahydrobrucine forms colourless needles, m. p. 177° (Found : C, 69·1; H, 7·7. $C_{23}H_{30}O_4N_2$ requires C, 69·4; H, 7·5%), but one of its characteristic properties is the power of retaining solvent of crystallisation with the resulting production of comparatively low-melting crystalline forms. It melts in boiling water, dissolves fairly readily to a solution which is alkaline to litmus, and on cooling crystallises in colourless needles; after drying for a short time in a vacuum desiccator, these melt to a pasty mass at 90—92°, and evolve water briskly at 100° (loss at 100°, 14·8. $4H_2O$ requires loss, 15·3%). It is rather easily soluble in methyl alcohol, but when a concentrated solution is cooled, it crystallises in colourless needles, which, after being dried in a vacuum desiccator, melt to a pasty mass at 90—95° (loss at 100°, 10·4. MeOH requires loss, 10·8%), harden on further heating, and melt again at 177°. When crystallised from ethyl alcohol, tetrahydrobrucine forms colourless needles, which soften at 115° and melt at 120° after drying in a vacuum desiccator. These contain one molecule of ethyl alcohol which is not lost at 90° (Found in material dried at 90° : C, 68·4; H, 8·3. $C_{23}H_{30}O_4N_2$,EtOH requires C, 68·2; H, 8·2%), but is liberated at 120° (loss at 120°, 10·0. 1EtOH requires loss, 10·4%). A solution of a pure specimen in dilute hydrochloric acid is colourless, but becomes bright green

on the addition of a few drops of ferric chloride; this solution does not, however, show the pink tinge in thin layers which is characteristic of brucidine and its derivatives.

The *dihydrochloride* is rather readily soluble, but is obtained when a little concentrated hydrochloric acid is added to a concentrated solution of the base in methyl alcohol. On standing over-night, it separates in colourless needles, which are collected, washed with methyl alcohol, and dried at 100°. This salt darkens at 280° and melts at 305° (decomp.) (Found: C, 58·4; H, 7·0. $C_{23}H_{30}O_4N_2$,2HCl requires C, 58·6; H, 6·8%).

The *dihydriodide* is prepared by adding sodium iodide to a solution of tetrahydrobrucine in dilute hydrochloric acid. The green colour of the solution disappears, and a yellow gum separates which slowly crystallises on rubbing. When recrystallised from ethyl alcohol, it forms colourless plates, which darken at 220° and melt at 225° (decomp.).

The *methiodide* is readily obtained by warming a solution of the base and an excess of methyl iodide in methyl alcohol for a few moments until crystallisation begins. After cooling, the colourless needles of the methiodide are collected, washed, and dried in a vacuum desiccator; they then melt at 290° (decomp.) (loss at 100°, 5·3. 1MeOH requires loss, 5·5%. Found in material dried at 100°: C, 53·5; H, 6·3. $C_{23}H_{30}O_4N_2$,MeI requires C, 53·3; H, 6·1%).

The nitrosoamine. Sodium nitrite (0·5 g.) in a little water is added gradually to a cooled solution of tetrahydrobrucine (2 g.) in hydrochloric acid (20 c.c. of 2*N*). The yellow crystals are collected, washed with dilute hydrochloric acid, and recrystallised from ethyl alcohol. *Tetrahydrobrucine nitrosoamine hydrochloride* forms buff-coloured needles, which, after drying in a desiccator, darken and shrink at 190°, have become black at 250°, and melt at 288° (decomp.) (loss at 100°, 8·5. 1EtOH requires loss, 9·0%. Found in material dried at 100°: Cl, 7·5. $C_{23}H_{29}O_5N_3$,HCl requires Cl, 7·6%).

When sodium carbonate is added to an aqueous solution of the hydrochloride, the *nitrosoamine* separates in needles. It is collected, washed, and recrystallised from dilute ethyl alcohol, separating in lemon-yellow needles which shrink at 205° and melt at 213—214° (decomp.) (Found: C, 64·2; H, 6·7. $C_{23}H_{29}O_5N_3$ requires C, 64·6; H, 6·8%). It is readily soluble in ethyl alcohol, and gives Liebermann's nitroso-reaction.

The Conversion of Tetrahydrobrucine into Brucidine.

A mixture of tetrahydrobrucine (5 g.) and phosphorus oxychloride (50 g.) is warmed on the water-bath for about 30 minutes; hydrogen chloride is evolved, whilst the base becomes gummy, partly dissolves,

and soon changes to a mass of crystals. The excess of phosphorus oxychloride is removed by distillation on the water-bath under reduced pressure, and the residue is dissolved in water (25 c.c.), much heat being produced. After cooling and addition of ice, the solution is mixed with potassium hydroxide, and the semi-solid precipitate is collected on a glass rod, drained as thoroughly as possible, and boiled with a little methyl alcohol. The product becomes crystalline, and after cooling it is collected, washed with methyl alcohol, and dried at 100° (yield 3·6 g.; 75% of that theoretically possible). The crystals melt at 203—203·5° either alone or when mixed with a specimen of brucidine.

The Electrolytic Reduction of Methylbrucine. Brucidine Metho-hydroxide and Metho-salts.

Methylbrucine.—The conversion of brucine methosulphate into methylbrucine does not take place under conditions similar to those under which strychnine methosulphate yields methylstrychnine (this vol., p. 1624), because the methosulphate is precipitated unchanged by the alkali. If, however, a higher temperature and more concentrated potassium hydroxide are used, the liquid sets to a gelatinous mass, which certainly contains methylbrucine, but which can be neither crystallised nor purified. Methylbrucine was therefore prepared by a modification of the method of Leuchs and Anderson (*loc. cit.*, p. 3047), who used less concentrated alkali. Hot, dilute sodium hydroxide solution (200 c.c. of 2·5*N*) is added in one batch to a hot solution of brucine methosulphate (10 g.) in water (50 c.c.), and the mixture is heated on the water-bath for 5 minutes. On cooling, the yellow solution does not gelatinise (compare Leuchs and Anderson); sodium hydroxide (20 c.c. of 30%) is now added, and the mixture set aside. Next day, the needles, which fill the liquid, are collected, and are sufficiently pure for the purpose of the reduction described below. When purified by the addition of acetone to a concentrated aqueous solution, and dried at 100°, methylbrucine forms colourless needles, m. p. 300° (decomp.) when heated quickly. Leuchs and Anderson give the melting point as 300° (decomp.).

The reduction. A solution of methylbrucine (20 g.) in sulphuric acid (100 c.c. of 60%) is reduced in the usual apparatus for 6 hours with a current of 5 amps., while the temperature is kept at 18° by cooling in running water. The liquid is diluted with an equal volume of water, heated on the water-bath, and neutralised by an excess of barium carbonate. The deep red filtrate, mixed with the washings of the barium precipitate, is evaporated to dryness under reduced pressure on the water-bath. The dark red, glassy residue

dissolves readily in water or methyl or ethyl alcohol, and shows very little tendency to crystallise. A small specimen, however, was obtained in a crystalline condition from methyl alcohol by cooling in ice. It was recrystallised once from that solvent in colourless nodules of needles, m. p. 265° (decomp.) after drying in a vacuum desiccator, and appears from analysis to be *brucidine methohydrogencarbonate* containing two molecules of water (Found: C, 60·3; H, 7·1. $C_{25}H_{32}O_6N_2,2H_2O$ requires C, 61·0; H, 7·3%). This view is confirmed by the conversion of this substance into brucidine methiodide and methohydroxide (see below), and also by its interaction with dilute hydrochloric acid. Carbon dioxide is evolved, and the substance dissolves to a green solution; the addition of ferric chloride intensifies this colour, and gives it the pink tinge in thin layers which is characteristic of brucidine and its derivatives.

When sodium iodide is added to an aqueous solution of the methohydrogencarbonate, brucidine methiodide is formed. It separates from water in colourless needles, m. p. 322° (decomp.), and is identical with a specimen prepared from brucidine (p. 1638).

Brucidine methohydroxide is obtained by grinding the crude methohydrogencarbonate with 30% potassium hydroxide solution. The resulting crystalline paste is filtered, and the solid recrystallised twice from water, in which it dissolves very readily. Brucidine methohydroxide forms colourless, hair-fine needles, m. p. 268° (decomp.), which retain two molecules of water after drying in a vacuum desiccator (Found: C, 64·1; H, 7·6. $C_{23}H_{28}O_3N_2,MeOH,2H_2O$ requires C, 64·3; H, 8·0%). The same substance was prepared for comparison from brucidine methiodide. An aqueous solution of the methiodide was shaken with an excess of silver carbonate, and the dark red filtrate evaporated to dryness under reduced pressure on the water-bath. The residual dark red glass (not purified) was dissolved in water, and mixed with 50% potassium hydroxide solution; brucidine methohydroxide then separated in crystalline form, and was recrystallised from a little water in colourless needles, m. p. 268° (decomp.).

The specimen obtained from the reduction of methylbrucine was converted into brucidine methiodide either (i) by adding sodium iodide to a solution in dilute hydrochloric acid, or (ii) when a solution of the methohydroxide (4 g.) and methyl iodide (10 c.c.) in ethyl alcohol (30 c.c.) was boiled for 10 minutes, and then cooled. In either case, the crystalline precipitate which separated was recrystallised from water, and formed colourless needles, m. p. 322° (decomp.) (Found: C, 55·1; H, 6·1. $C_{23}H_{28}O_3N_2,MeI$ requires C, 55·2; H, 5·9%). The identity of this substance with brucidine methiodide was confirmed by converting it into methoxymethyldihydrobrucidine

(see below), which is formed by heating brucidine metho-salts with methyl-alcoholic potassium hydroxide. Brucidine methochloride (not purified), prepared by shaking with an excess of silver chloride an aqueous solution of the methiodide obtained above, and evaporating the filtrate to dryness under reduced pressure on the water-bath, was heated with a large excess of 25% methyl-alcoholic potassium hydroxide for 30 minutes, cooled, mixed with water, and the precipitate collected. Crystallisation from ethyl alcohol yielded colourless needles, m. p. 115° either alone or mixed with an authentic specimen of methoxymethyldihydrobrucidine.

Methoxymethyldihydrobrucidine.—A mixture of brucidine metho-sulphate (30 g.) and methyl-alcoholic potassium hydroxide (150 c.c. of 25%) is heated on the water-bath for 30 minutes in an open flask so that the methyl alcohol partly evaporates. The initial yellow solution gradually clouds and deposits a solid precipitate which increases on cooling in running water. Water (500 c.c.) is added, and the precipitate is collected after 1 hour, washed with water, and dried roughly on porous tile. The crude product is crystallised from ethyl alcohol, from which about 20 g. of pure material separate, and the addition of water to the mother-liquor yields a further quantity of practically pure substance (total yield, *ca.* 90%). *Methoxymethyldihydrobrucidine* forms colourless needles, m. p. 115° without decomp. after drying in a vacuum [Found: C, 70·2; H, 7·8; OMe, 21·9. $C_{25}H_{34}O_4N_2$ requires C, 70·4; H, 8·0; $(OMe)_3$, 21·8%]. It distils without decomposition at 265—267°/1·5 mm., and is rather readily soluble in the usual solvents except light petroleum. A solution in glacial acetic acid is not precipitated on addition of water. The base and its solutions become red on keeping, especially if exposed to laboratory fumes.

The dihydriodide. The addition of sodium iodide to a solution of methoxymethyldihydrobrucidine in dilute sulphuric acid produces a red, uncrystallisable oil, which rapidly oxidises, but when concentrated sodium iodide solution is added slowly with constant stirring to a solution of the base (5 g.) in 2*N*-sulphuric acid (20 c.c.), saturated with sulphur dioxide, an additive compound separates as a brick-red oil which soon crystallises on rubbing. This is collected (approximately 8 g.), and boiled with water until the orange colour of the solution and the smell of sulphur dioxide have disappeared; the dihydriodide then crystallises on cooling in colourless leaflets, m. p. 217—218° (decomp.) (loss at 100°, 3·5. $1\frac{1}{2}H_2O$ require loss, 3·8%. Found in material dried at 100°: C, 43·8; H, 5·3. $C_{25}H_{34}O_4N_2,2HI$ requires C, 44·0; H, 5·3%). The crystals become yellow on keeping, on exposure, or on drying, and when heated char and evolve hydrogen iodide.

The methiodide (*A*). This substance is obtained under the following conditions. (i) Methoxymethyldihydrobrucidine (10 g.) and pure methyl iodide (15 c.c.) are heated together at 100° in a sealed tube for 5 minutes. The solution becomes purple and fills with crystals, which are collected after cooling, washed with methyl iodide, and dried in a vacuum (12 g.). The mother-liquors deposit a further amount (1 g.) on standing over-night. The yield is about 98%. (ii) A mixture of methoxymethyldihydrobrucidine (15 g.) and methyl iodide (15 c.c.) is boiled under reflux for 15 minutes, and next day 13—15 g. of crude product are collected. The methiodide obtained by either method separates from methyl alcohol in creamy tablets which become chalky when dried in a vacuum; m. p. 190° (loss at 100°, 2·6. 0·5MeOH requires loss, 2·8%. Found in material dried at 100°: C, 55·1; H, 6·5; N, 4·9. $C_{25}H_{34}O_4N_2$,MeI requires C, 55·0; H, 6·5; N, 4·9%). It crystallises from water in stout prisms, m. p. 190°, or from ethyl alcohol in rectangular plates, m. p. 179°, which contain alcohol of crystallisation (loss at 100°, 3·6. 0·5EtOH requires loss, 3·9%. Found in dried material: C, 55·2; H, 6·7%). It yields the methochloride (A) when treated with silver chloride (see below).

The methyl-alcoholic mother-liquors gradually deposit a very small amount of crystalline material which does not contain iodine. This is recrystallised by dissolving it in much methyl alcohol and concentrating the solution; *oxymethoxymethyldihydrobrucidine* then separates in pink bipyramids, which shrink at 270° and melt at 277° (decomp.) (Found: C, 67·3; H, 7·6. $C_{25}H_{34}O_5N_2$ requires C, 67·9; H, 7·7%). The same substance may be obtained in greater quantity by a simpler method. When a solution of methoxymethyldihydrobrucidine in ethyl alcohol containing a few crystals of iodine is exposed to the air for some days, the solution becomes deep crimson, and gradually deposits oxymethoxymethyldihydrobrucidine as pale pink, perfectly formed prisms, which soften at 270°, melt at 277°, and are analytically pure (Found: C, 67·6; H, 7·8; N, 6·1. $C_{25}H_{34}O_5N_2$ requires N, 6·3%). It is very sparingly soluble in ethyl alcohol or acetone, but dissolves in warm benzene, and is readily soluble in chloroform. It is insoluble in boiling water or sodium hydroxide, but dissolves readily in dilute hydrochloric acid. When it is boiled with methyl alcohol (charcoal) and the filtered solution is concentrated, a slightly more soluble base separates in irregular, boat-shaped crystals, m. p. 270° (decomp.), which appear from the analysis to be *dioxymethoxymethyldihydrobrucidine* (X) (compare pp. 1647, 1648) (Found: C, 65·5; H, 7·4. $C_{25}H_{34}O_6N_2$ requires C, 65·5; H, 7·4%).

When methoxymethyldihydrobrucidine and methyl iodide inter-

act in methyl-alcoholic solution the reaction follows a course very similar to that, described above, in the absence of methyl alcohol, and the chief product is the monomethiodide (A), accompanied by small quantities of oxymethoxymethyldihydrobrucidine (compare Part IV, this vol., p. 1607). In addition to these substances, an intermediate *base*, m. p. about 210—218°, appears to be formed. This does not contain iodine, and changes into oxymethoxymethyldihydrobrucidine in boiling methyl alcohol or acetone, in which solvents it is sparingly soluble. This substance was not obtained sufficiently pure for analysis, and the change evidently takes place so readily that the intermediate product did not appear in some experiments, but had been completely converted into oxymethoxymethyldihydrobrucidine. The following is an account of an experiment in which the intermediate base was formed. A mixture of methoxymethyldihydrobrucidine (5 g.) and methyl iodide (5 c.c.) in methyl alcohol (25 c.c.) was boiled under reflux for 3 hours, and then concentrated to half its volume. The residue was cooled for several hours in ice and salt, and the crystals which had separated were collected, washed with methyl alcohol, and dried (3 g.). The mother-liquors were examined separately (see below). The crude crystals were extracted with boiling methyl alcohol (20 c.c.), and the insoluble portion was collected, washed thoroughly with methyl alcohol, and dried (0·2 g.). It consisted of indefinite crystals, m. p. 210°, which did not contain iodine. The methyl-alcoholic extract contained practically pure methiodide (A).

The methyl-alcoholic mother-liquors (see above) were mixed with water, and the solid was collected and extracted with boiling methyl alcohol. The insoluble portion (0·1 g.) formed indefinite crystals, m. p. 218°, which did not contain iodine. Oxymethoxymethyldihydrobrucidine separated in the characteristic bipyramids, m. p. 277°, when a solution of the mixed fractions, m. p. 210° and 218°, in much boiling methyl alcohol was concentrated and cooled.

The Action of Methyl-alcoholic Potassium Hydroxide on the Methiodide (A) and the Methochloride (A).—The reaction follows the same course in both cases, but takes place more readily with the methochloride. This is prepared from the methiodide by heating an aqueous solution with excess of silver chloride for 1 hour, and evaporating the filtrate to dryness on the water-bath under reduced pressure. The gummy *methochloride* crystallises in colourless needles on standing for some days. The methochloride (7 g.) and methyl-alcoholic potassium hydroxide (60 c.c. of 25%) are heated in an open flask on the water-bath for 40 minutes, and after cooling and addition of water, the precipitate is collected and dried in a desiccator (5 g.). Recrystallisation of this crude material from ethyl alcohol

yields colourless needles; m. p. 115°, either alone or mixed with a specimen of methoxymethyldihydrobrucidine (Found: C, 70·6; H, 7·8; OMe, 21·4%). A careful examination of the mother-liquors yields no other product.

Methoxymethyldihydrobrucidine methochloride (*B*) cannot be obtained directly from methoxymethyldihydrobrucidine, but it is formed when methoxymethyldihydrobrucidine dimethochloride (B) (compare p. 1647) (15 g.) is heated in boiling nitrobenzene (30 c.c.) until all has dissolved and the evolution of gas appears to have ceased—10 to 15 minutes. After standing over-night, the crystals which have separated are collected, washed with light petroleum, dried in a desiccator (10 g.), and crystallised from acetone, being thus obtained in colourless prisms, m. p. 164° (decomp.) (Found: C, 64·9; H, 7·4. $C_{25}H_{34}O_4N_2$,MeCl requires C, 65·5; H, 7·8%). This substance yields methyl-ψ-brucidine when heated gently in a test-tube over a free flame (compare p. 1651). The nitrobenzene mother-liquors contain both methyl-ψ-brucidine and methyl-ψ-brucidine methochloride; their examination is described on p. 1652.

The *methiodide* (*B*) is prepared from the methochloride with sodium iodide, but has not been obtained in any other way. It crystallises from water in colourless, coarse prisms, m. p. 291° (decomp.), and is less soluble in water and methyl or ethyl alcohol than the isomeric methiodide (A).

The *dimethiodide* (*A*) is obtained when methoxymethyldihydrobrucidine (5 g.) and pure methyl iodide (10 c.c.) are heated in a sealed tube in an oil bath at 135—140° for 7½ hours. After removal of the methyl iodide by distillation, the brown, sandy powder (8·5 g.) is crystallised from methyl alcohol (charcoal), from which the dimethiodide (4·5 g.) separates in pink leaflets which become colourless at 110°, form a pasty mass at 215°, and evolve gas freely at 230° (loss at 110°, 8·6. 2MeOH requires loss, 8·3%. Found in material dried at 110°: C, 45·3; H, 5·5. $C_{25}H_{34}O_4N_2$,2MeI requires C, 45·6; H, 5·6%).

The *methosulphate* (*A*) is formed when a solution of methoxymethyldihydrobrucidine (3 g.) and pure methyl sulphate (10 c.c.) in dry benzene (70 c.c.) is boiled under reflux for 4 hours and allowed to remain over-night. A mixture of stellar aggregates of coarse crystals and a purple gum separates, and the crystals of the monomethosulphate are easily detached and pressed on porous tile (1·7 g.). The gum consists essentially of the dimethosulphate (B) (see below). The methosulphate is crystallised from ethyl alcohol, in which it is rather readily soluble, and forms colourless, rectangular plates, m. p. 231—232° (decomp.) (Found: S, 6·0. $C_{25}H_{34}O_4N_2$,Me_2SO_4 requires S, 5·8%). This substance is

very soluble in water and is converted by sodium iodide into the methiodide (A), m. p. 190°.

The Dimethosulphate (*B*) *and the Dimethiodide* (*B*).—A solution of carefully dried methoxymethyldihydrobrucidine (60 g.) and pure methyl sulphate (150 c.c.) in dry benzene (500 c.c.) is boiled for 9 hours under reflux, carefully protected from moisture. It rapidly becomes purple, and after some time a brown gum forms slowly and increases steadily with diminution of the purple colour. After the benzene has been decanted, the gum is washed with benzene, and freed from excess of the solvent by a current of air. It undoubtedly consists essentially of the *dimethosulphate* (*B*), although traces of benzene and methyl sulphate are still present, but all attempts to crystallise it are unsuccessful, and it is therefore converted into the corresponding dimethiodide by sodium iodide. Sodium iodide (100 g.) in warm water (40 c.c.) is added to the dimethosulphate in warm water (100 c.c.) and, after cooling, the mixture is scratched and set aside over-night. The crystalline precipitate is collected, washed with water, dried in a vacuum desiccator (84 g.), and recrystallised from water. The *dimethiodide* (*B*) forms colourless columns, m. p. 290° (decomp.), with darkening below this, and is sparingly soluble in alcohol (loss at 105°, 1·0. $\frac{1}{2}H_2O$ requires loss, 1·2%. Found in dried material : C, 45·0 ; H, 5·5. $C_{25}H_{34}O_4N_2.2MeI$ requires C, 45·6 ; H, 5·6%).

The mother-liquors from the precipitation with sodium iodide are mixed with 50% potassium hydroxide solution; the caseous precipitate then soon hardens. It is washed roughly with water, and boiled with alcohol, which causes it to crystallise without passing into solution. After cooling, the crystals are collected (13 g.), and recrystallised from water, being obtained in colourless columns, m. p. 290° (decomp.), identical with those obtained by direct precipitation from the solution of the dimethosulphate with sodium iodide (loss at 105°, 1·1%. Found in dried material: C, 45·5; H, 5·4%). The total yield is 97 g., or 96% of that theoretically possible.

The dimethiodide is stable to 25% methyl-alcoholic potassium hydroxide at 120°, but reaction takes place with the corresponding dimethohydrogensulphate obtained by means of silver sulphate. The dimethiodide (10 g.) in water (75 c.c.) is heated on the water-bath for 1 hour with excess of silver sulphate, the filtrate is evaporated to dryness under reduced pressure on the water-bath, the residue taken up in methyl alcohol to eliminate silver sulphate, and the solution again evaporated to dryness. The gummy dimethohydrogensulphate thus obtained (not isolated) is mixed with methyl-alcoholic potassium hydroxide (100 c.c. of 25%) and heated in an

oil-bath for 45 minutes while the temperature is gradually raised from 110° to 130°. After cooling and addition of water, the roughly dried, sandy powder is crystallised from ethyl alcohol, and shown to be identical with methoxymethyldihydrobrucidine by mixed m. p., and by conversion into the methiodide (A), m. p. 190°.

The *dimethochloride* (*B*), prepared in the usual way from the dimethiodide by silver chloride, is a colourless glass which could not be crystallised.

Nitromethoxymethyldihydrobrucidine.—A solution of methoxymethyldihydrobrucidine (3 g.) in water (75 c.c.) and nitric acid (*d* 1·4; 7·5 c.c.) is heated under reflux on the water-bath for 2 hours. From the cooled mixture, ammonia (*d* 0·880) precipitates a negligible quantity of a base, which is discarded, and the addition of 50% potassium hydroxide solution yields a mixture of tar and crystals which is pressed on porous tile, crystallised twice from ethyl alcohol, and dried in a desiccator. *Nitromethoxymethyldihydrobrucidine* forms colourless needles, m. p. 276—278° (decomp.), which contain alcohol of crystallisation (loss at 110°, 9·6. 1EtOH requires loss, 9·8%. Found in material dried at 110°: C, 63·9; H, 7·0; N, 9·2. $C_{25}H_{33}O_6N_3$ requires C, 63·7; H, 7·1; N, 8·9%). It is rather curious that this substance exhibits the brucidine reaction with 60% sulphuric acid and potassium dichromate.

Permanganate Oxidation of Methoxymethyldihydrobrucidine. The Isomeric Dioxymethoxymethyldihydrobrucidines (*Y*) and (*Z*).

A number of experiments showed the necessity of adhering to the conditions described below. Powdered (80-mesh) potassium permanganate (20 g.; 4 atoms of oxygen) is added gradually to a solution of methoxymethyldihydrobrucidine (20 g.) in purified acetone (800 c.c.), stirred mechanically, and cooled in ice and salt so that the internal temperature remains at −10°. The manganese precipitate, collected and washed with acetone, yields with water a solution in which only oxalic acid can be detected.

The removal of the acetone by distillation yields 12—15 g. of thick, brown oil. When this is dissolved in warm alcohol (15 c.c.), cooled, and scratched, 2·5—2·8 g. of fairly pure crystalline material separate. (The examination of the mother-liquors, called M, is described on p. 1648.) Recrystallisation from ethyl alcohol yields colourless prisms, m. p. 185—186°, which appear from the analyses to be *dioxymethoxymethyldihydrobrucidine* (called Y; compare p. 1643) (loss at 100°, 4·4. ½EtOH requires loss, 4·8%. Found in dried material: C, 65·3; H, 7·6; N, 6·3. $C_{25}H_{34}O_6N_2$ requires C, 65·5; H, 7·4; N, 6·1%). This substance is insoluble in water or alkali, but readily dissolves in dilute hydrochloric acid, giving a green solution;

on addition of ammonia, the base is precipitated and the colour changes to red. The compound is recovered unchanged after boiling for a few minutes with acetic anhydride, and attempts to form a semicarbazone resulted in a dark red, uncrystallisable oil.

The *methiodide* is prepared by heating the base (2 g.) and methyl iodide (3 c.c.) in a sealed tube at 100° for 5 hours. The residue is pressed on porous tile, and separates from ethyl alcohol as a mixture of plates and needles, m. p. 223°. On recrystallisation from ethyl alcohol, both forms separate again, but when the mixture is boiled with insufficient alcohol for complete solution, the needles dissolve more rapidly, and ultimately the undissolved portion consists of plates only. These are collected and recrystallised, by seeding, from ethyl alcohol, separating in colourless plates, m. p. 225—226°, which lose nothing at 110° (Found: C, 52·3; H, 6·4. $C_{25}H_{34}O_6N_2$,MeI requires C, 52·0; H, 6·2%). When the hot alcoholic solution from the separation of plates and needles is cooled and set aside, it begins to deposit needles only, and on scratching, the material separates entirely in that form; but if allowed to remain undisturbed, the mixture of crystals again separates. The needles are recrystallised in the same form, m. p. 223—224°, from ethyl alcohol, and contain 2 molecules of alcohol of crystallisation after drying in a vacuum desiccator (loss at 110°, 12·1. 2EtOH requires loss, 13·3%. Found in material dried at 110°: C, 52·2; H, 6·4%). Both forms are sparingly soluble in ethyl alcohol, and a hot solution of each in that solvent, when cooled and seeded with the other form, deposits only that by which it has been seeded. A mixture of the two pure forms melts at 223°.

The alcoholic mother-liquors (M; p. 1647) are evaporated to dryness, and a filtered, aqueous solution of the residue is made strongly alkaline with potassium hydroxide. The oil thus precipitated is extracted as far as possible with ether, and the extract dried with potassium carbonate. The oil which remains undissolved in the ether yields no crystalline product, and is discarded. The oily residue from the evaporation of the ether is dissolved in ethyl alcohol (5 c.c.), cooled in ice and salt, and scratched frequently; crystals (3·2 g.) then separate slowly. Three recrystallisations from ethyl alcohol yield colourless, square plates, m. p. 110—111° after drying in a vacuum desiccator, which appear from analysis to be a *dioxymethoxymethyldihydrobrucidine* (called Z) (loss at 100°, 4·0. $\frac{1}{2}$EtOH requires loss, 4·8%. Found in material dried at 100°: C, 65·0, 65·1; H, 7·6, 7·5; N, 5·8. $C_{25}H_{34}O_6N_2$ requires C, 65·5; H, 7·4; N, 6·1%). This substance is sparingly soluble in cold water, dissolves readily on heating to give a neutral solution, and on cooling separates in colourless, rectangular prisms. It is readily soluble in

the usual organic solvents except light petroleum, from which it crystallises when a hot solution is cooled, and gives the same colour reactions as methoxymethyldihydrobrucidine. It dissolves rapidly in cold dilute hydrochloric acid, but no iodide separates with sodium iodide. The compound is recovered unchanged after heating with excess of methyl iodide in a sealed tube at 100° for 4 hours, and an alcoholic solution does not form a sparingly soluble picrate.

Ethoxymethyldihydrobrucidine.—This substance was prepared in order to ascertain whether alkyloxy-groups other than methoxyl can be introduced into brucidine. The action between brucidine methosulphate and sodium ethoxide follows a similar course to that described on p. 1642 with methyl-alcoholic potassium hydroxide, but the isolation of the product was not successful, and further investigation was abandoned. Brucidine methosulphate (15 g.) and a solution of sodium (10 g.) in ethyl alcohol (150 c.c.) were heated in an open flask for 1 hour on the water-bath and then for 1 hour in an oil-bath at 120°. After cooling and addition of water, the sticky precipitate was pressed on porous tile. Attempts to crystallise the sandy powder (10 g.) thus obtained were fruitless, although it probably consisted of ethoxymethyldihydrobrucidine, and it was converted into the methiodide by boiling with excess of methyl iodide in ethyl alcohol (15 c.c.) for 20 minutes. On cooling, the purple solution set to a mass of crystals, which were washed with alcohol until they became colourless. *Ethoxymethyldihydrobrucidine methiodide*, recrystallised from ethyl alcohol, forms colourless needles, m. p. 176° (decomp.) (Found: C, 55·6; H, 7·1. $C_{26}H_{36}O_4N_2$,MeI requires C, 55·6; H, 6·9%).

*Methyl*neo*brucidinium Salts.*

*Methyl*neo*brucidinium Iodide.*—When a solution of methoxymethyldihydrobrucidine (25 g.) in sulphuric acid (250 c.c. of 10% by weight) is boiled gently under reflux for 2½ hours it becomes red, and methyl alcohol is evolved and can be burnt at the neck of the flask. The solution is cooled, rendered alkaline with ammonia (no precipitate), and just acidified with sulphur dioxide. The careful addition of concentrated sodium iodide precipitates a crystalline *iodide* (22 g.), which separates from water in stout, pink columns, m. p. 298° (decomp.) (Found: C, 55·3; H, 6·0. $C_{24}H_{31}O_3N_2I$ requires C, 55·2; H, 5·9%). When prepared in this way, the salt is always red; it may, however, be obtained practically colourless by crystallisation from aqueous potassium carbonate, or from ethyl alcohol, from which it separates in leaflets, m. p. 298° (decomp.). It is sparingly soluble in cold water, acetone, or methyl or ethyl

alcohol, and crystallises unchanged when a boiling solution in 30% potassium hydroxide is cooled.

The mother-liquors from the precipitation by sodium iodide (see above) were investigated in the expectation of isolating an isomeric iodide (compare methyl*neo*strychnidinium iodide, this vol., p. 1612), but only a further quantity of the same methyl*neo*brucidinium iodide was obtained, the total yield being 90% of that theoretically possible. The mother-liquors are concentrated to quite a small volume under reduced pressure on the water-bath, and after cooling, the aqueous layer is decanted from the oil which has separated during the distillation. This oil crystallises on being boiled with a little acetone; part dissolves, crystallisation begins suddenly, and the oil soon changes into a mass of colourless needles. After cooling, these are collected, washed with acetone, and dried (5 g.); m. p. 295° (decomp.). One recrystallisation from water yields the iodide in colourless, prismatic columns, m. p. 298° (decomp.). The identity of this substance with the methyl*neo*brucidinium iodide obtained above was shown by seeding an aqueous solution with a crystal of the authentic material.

*Methyl*neo*brucidinium chloride* is prepared from the iodide in the usual way by silver chloride. When sulphur dioxide is passed into the dark red filtrate after this has been concentrated on the water-bath under reduced pressure, slightly sticky, yellow needles separate; these are triturated with hot acetone, which causes the compound to crystallise in beautiful prisms. Methyl*neo*brucidinium chloride crystallises from absolute alcohol, in which it is rather readily soluble, in colourless, anhydrous needles, m. p. 188°, which absorb moisture on keeping and then melt at about 163°. On addition of ether to an alcohol–acetone solution, the chloride forms pale yellow, waxy prisms, m. p. 163°, which retain a molecule of water of crystallisation after being heated at 100° (Found: C, 63·9; H, 7·5. $C_{24}H_{31}O_3N_2Cl,H_2O$ requires C, 64·2; H, 7·4%). It dissolves readily in water, and is precipitated unchanged as a rapidly-crystallising oil by 50% potassium hydroxide solution. The colour reactions with ferric chloride in hydrochloric acid are identical with those given by methoxymethyldihydrobrucidine, and are also produced by silver nitrate in dilute nitric acid, whilst the addition of a drop of potassium dichromate to a solution in 60% sulphuric acid develops a yellowish-brown colour which does not alter on standing. After the chloride has been heated with 25% methyl-alcoholic potassium hydroxide on the water-bath for 30 minutes in the usual way, the addition of water precipitates a base, which crystallises from ethyl alcohol in colourless needles, m. p. 115°; the base melts at the same temperature in admixture with methoxy-

methyldihydrobrucidine. The chloride yields methyl-ψ-brucidine when heated (see p. 1652). In order to test the possibility of reducing methyl*neo*brucidinium salts, the sulphuric acid solution obtained directly from methoxymethyldihydrobrucidine was reduced in the usual apparatus for 18 hours with a current of 4·5 amps. The contents of the colourless solution, which began to redden as soon as the current was switched off, were isolated as the iodide in the manner described above. This iodide formed colourless prisms, m. p. 298° (decomp.), which were identical with a very pure specimen of methyl-*neo*brucidinium iodide (Found: C, 55·6; H, 6·0%). The fact that reduction had not taken place was confirmed by converting the corresponding chloride, m. p. 188°, into methyl-ψ-brucidine by heating.

Methyl-ψ-brucidine.—This substance is prepared either (i) from methoxymethyldihydrobrucidine dimethochloride (B) or (ii) from methyl*neo*brucidinium chloride.

(i) Methoxymethyldihydrobrucidine dimethochloride (B) (27 g.), free from inorganic material, is heated gently over a flame in test-tubes in batches of 3 g. until the evolution of methyl chloride and inflammable gas ceases. The clear, glassy residue is dissolved in benzene, the solution filtered from a little charred material, and the solvent distilled; the crystalline solid (16·5 g.), m. p. 194°, thus obtained is recrystallised from ethyl alcohol. Pure *methyl-ψ-brucidine* forms colourless tablets, m. p. 198—199° without decomposition [Found: C, 72·8; H, 7·7; N, 7·4; OMe, 15·7; *M*, in camphor, 430. $C_{24}H_{30}O_3N_2$ requires C, 73·1; H, 7·6; N, 7·1; $(OMe)_2$, 14·9%; *M*, 394]. It is, however, often green, melting at about 196°, but in this condition is sufficiently pure for most purposes. It is insoluble in water, readily soluble in benzene, acetone, and dilute acetic acid, and is stable to boiling 20% potassium hydroxide solution. A solution in dilute sulphuric acid instantly decolorises permanganate, forming the characteristic green solution with the pink tinge which is also produced by ferric chloride in dilute hydrochloric acid or ethyl alcohol. The base is recovered unchanged after being electrolysed in 25% sulphuric acid for 9 hours with a current of 4·5 amps. in the usual apparatus, or after being shaken in cold dilute acetic acid solution in an atmosphere of hydrogen in presence of reduced palladous chloride and gum arabic.

The *dihydriodide*, prepared by adding sodium iodide to a solution of the base in dilute hydrochloric acid, crystallises from water in leaflets, m. p. 259° (decomp.) (Found in material dried at 100°: C, 44·1; H, 4·9. $C_{24}H_{30}O_3N_2,2HI$ requires C, 44·3; H, 4·9%).

The *methiodide* is formed (*a*) directly from methyl-ψ-brucidine, or (*b*) from methoxymethyldihydrobrucidine dimethochloride (B).

(*a*) Powdered methyl-ψ-brucidine (1 g.) and methyl iodide (3 c.c.) react at once in the cold to form a jelly which rapidly crystallises. The methiodide, obtained thus in theoretical yield, separates from methyl alcohol in colourless plates, m. p. 297° (decomp.) (Found: C, 55·8; H, 6·1. $C_{24}H_{30}O_3N_2$,MeI requires C, 55·9; H, 6·1%). Occasionally it crystallises in needles, m. p. 297°, which change slowly into plates in presence of methyl alcohol.

(*b*) The nitrobenzene mother-liquors from the action of boiling nitrobenzene on methoxymethyldihydrobrucidine dimethochloride (B) (compare p. 1645) contain a small quantity of methyl-ψ-brucidine methochloride and also a little methyl-ψ-brucidine, and these are removed separately by extraction first with water and then with dilute hydrochloric acid. The methochloride was not isolated from the aqueous extract, but was converted by sodium iodide into the methiodide. The crystalline solid thus formed crystallised from ethyl alcohol in colourless needles, m. p. 297° (decomp.) (Found: C, 56·1; H, 6·2%).

The identity of these two specimens of the methiodide was shown by causing a solution of (*b*) in methyl alcohol to deposit plates on seeding with (*a*), and also by seeding an ethyl-alcoholic solution of (*a*) with (*b*), when the methiodide separated in needles.

The Formation of a By-product by the Action of Heat on Methoxymethyldihydrobrucidine Dimethochloride (*B*).—When the dimethochloride is contaminated by inorganic matter, *e.g.*, sodium chloride if the silver chloride used in its formation has been prepared from sodium chloride, the yield of methyl-ψ-brucidine is lowered, pyridine bases are formed during the heating, and a *by-product* is obtained. For example, the dimethochloride (30 g.), containing some sodium chloride, yielded a benzene extract containing pure methyl-ψ-brucidine (10 g.) together with a residue insoluble in benzene (4 g.). The investigation of this substance is at present in progress and the results already obtained show that we have encountered here an important degradation by fission of the brucine molecule.

Methyl-ψ-brucidine (ii). This base is also obtained by heating methyl*neo*brucidinium chloride in an oil-bath at 200—210° until effervescence ceases. The dark brown glass is dissolved in dilute acid, and the base is precipitated by potassium hydroxide and crystallised from ethyl alcohol. It forms tablets, melting, either alone or mixed with an authentic specimen of methyl-ψ-brucidine, at 198°.

Permanganate Oxidation of Methyl-ψ-brucidine.

Brucidone Semicarbazone.—Powdered potassium permanganate (6·8 g.: 5 atoms of oxygen) is added gradually to methyl-ψ-brucidine (5 g.) in ice-cold, mechanically-stirred acetone (500 c.c.); the colour

of the permanganate disappears slowly, and oxidation seems to be complete at the end of the addition. The manganese precipitate is filtered off, but yields no solid product. Removal of the acetone leaves a pale yellow, gummy residue (4 g.), which has not been obtained crystalline, and which yields only oily products when heated with methyl-alcoholic potassium hydroxide, or when dissolved in concentrated sulphuric acid (compare strychnidone, this vol., p. 1615). It is therefore converted into the semicarbazone by boiling a solution of the gum, semicarbazide hydrochloride (3·4 g.), and potassium acetate (3·4 g.) in aqueous alcohol under reflux for 1½ hours. Water is added, the alcohol distilled off under reduced pressure, and the crystalline precipitate, which forms during the distillation, is recrystallised from ethyl alcohol, being obtained in colourless needles which shrink at 210° and evolve gas at 226°, without complete fusion (loss at 100°, 13·1. 1½EtOH requires loss, 12·8%. Found in dried material: C, 60·8; H, 7·0; N, 15·1. $C_{24}H_{31}O_5N_5$ requires C, 61·4; H, 6·6; N, 14·9%). This *semicarbazone* is very sparingly soluble in cold methyl or ethyl alcohol. From the analyses, it appears to be the monosemicarbazone of a ketone derived from methyl-ψ-brucidine by the loss of CH_2 and its replacement by O, and the further introduction of one oxygen atom.

The unsharp melting point suggested that this material might be a mixture, and fruitless efforts were made to obtain pure components by repeated crystallisation from methyl or ethyl alcohol. The melting point remained unaltered. Purification was also attempted by extracting the substance with boiling methyl alcohol in sufficient quantity to dissolve only half, filtering the hot solution from the residue *A*, allowing it to deposit a second fraction *B* on cooling, and obtaining a third fraction *C* when the mother-liquor had remained over-night. *A* was recrystallised, and the mother-liquor yielded a very small fraction, *D*, on standing over-night. These fractions all formed colourless needles, which were dried in a vacuum desiccator, and the analyses agreed well with the formula already suggested (see below). On the other hand, the specimens differ in melting point and contain different amounts of solvent of crystallisation. (*A*) shrinks at 200°, melts at 220—225° (decomp.), and is not changed by recrystallisation (loss at 100°, 2·3. ½MeOH requires loss, 3·3%. Found in material dried at 100°: C, 62·0; H, 6·5%). (*B*) shrinks at 245°, melts at 257° (decomp.), and is not changed by recrystallisation (loss at 100°, 11·4. 2MeOH requires loss, 12·0%. Found in dried material: C, 61·6; H, 6·6%). (*C*) shrinks at 200° and melts at 235° (decomp.); there was not enough for recrystallisation (loss at 100°, 7·5. 1MeOH requires loss, 6·4%. Found in dried material: C, 61·4; H, 6·7%). (*D*), only

0·0327 g., shrinks at 195° and melts at 245° (decomp.) (loss at 100°, 10·4%. Found in dried material : C, 59·7; H, 6·5%).

It is possible that brucidone is a mixture of isomerides or that the semicarbazone group introduces geometrical isomerism.

Methoxymethyltetrahydrobrucidine.—A solution of methoxymethyldihydrobrucidine (20 g.) in sulphuric acid (200 c.c. of 20%) is reduced in the usual apparatus for 16 hours with a current of 5 amps., the temperature being kept at 18° by cooling in water. The methoxymethyldihydrobrucidine may be used in the crude condition in which it is obtained when water is added to the product of the interaction of brucidine methosulphate and methyl-alcoholic potassium hydroxide. After the reduction, excess of ammonia (*d* 0·880) is added while the liquid is stirred and cooled in ice; the product is thus obtained as a finely divided solid, whereas precipitation without cooling yields a caseous mass which solidifies to a single hard lump. The precipitate is collected, washed, dried (18 g.), and crystallised from methyl alcohol, from which it separates in colourless needles (Found : C, 70·2; H, 8·3. $C_{25}H_{36}O_4N_2$ requires C, 70·0; H, 8·4%).

Methoxymethyltetrahydrobrucidine melts at 133—135° and distils without decomposition at 253°/2 mm. It is somewhat soluble in the usual solvents and crystallises in beautiful needles from light petroleum (b. p. 60—80°). It dissolves readily in dilute acetic or mineral acid, and does not redden on exposure nearly so quickly as methoxymethyldihydrobrucidine. Acetic anhydride seems to be without action; after the mixture has been boiled for a few minutes and water and excess of ammonia have been added, the base is recovered unchanged.

The *dihydriodide* is prepared by adding concentrated sodium iodide solution to a solution of the base in 2*N*-sulphuric acid. On scratching, the dihydriodide separates in practically quantitative yield; it crystallises from water in colourless needles, which melt at 212° to a yellow froth (Found : I, 37·3. $C_{25}H_{36}O_4N_2,2HI$ requires I, 37·1%). It is sparingly soluble in ethyl alcohol, and becomes yellow on keeping.

When a hot aqueous solution of the dihydriodide is treated with excess of silver chloride, and the filtrate is evaporated to dryness under reduced pressure on the water-bath, the *dihydrochloride* is obtained as a colourless glass, which crystallises when ether is added carefully to a solution in alcohol–acetone. It forms rectangular plates, which are very soluble in water and evolve gas at 150° without melting completely. The residue is probably methyl*neo*-dihydrobrucidinium chloride, which is produced when the dihydrochloride is decomposed in boiling mesitylene (b. p. 165°) (see p. 1659).

The *methiodide* (*A*) is prepared by heating the base (4 g.) and methyl iodide (5 c.c.) under reflux on the water-bath for 20 minutes; a crystalline precipitate is soon formed. The methyl iodide is distilled away, and the residue separates from ethyl alcohol in colourless leaflets (Found: C, 54·9; H, 7·2. $C_{25}H_{36}O_4N_2$,MeI requires C, 54·7; H, 6·8%). The methiodide dissolves rather readily in water. It melts at 166—167°, losing methyl iodide quantitatively (loss in an oil-bath at 165—170°, 24·9. $C_{25}H_{36}O_4N_2$,MeI requires loss, 24·9%), and regenerating the base, m. p. 134°, which was identified by the mixed melting-point method.

The *methochloride* (*A*), prepared in the usual way from the methiodide and silver chloride, forms a glassy mass. When it was heated with an excess of methyl-alcoholic potassium hydroxide at 120° for 1 hour, and water was added, methoxymethyltetrahydrobrucidine was regenerated, and identified by the mixed melting-point method.

The *methiodide* (*B*) is obtained by heating either (i) the dimethiodide (A) (p. 1658) or (ii) the dimethiodide (B) (p. 1656).

(i) When methoxymethyltetrahydrobrucidine dimethiodide (A) is heated in an oil-bath at 230°, it melts and evolves methyl iodide quantitatively. The glassy residue crystallises from ethyl alcohol in flattened needles or leaflets, m. p. 298° (decomp.) (Found: C, 54·9; H, 6·7. $C_{25}H_{36}O_4N_2$,MeI requires C, 54·7; H, 6·8%). This substance is sparingly soluble in ethyl alcohol and in water and crystallises from the latter in characteristic prisms, m. p. 298° (decomp.), which become chalky when dried in a vacuum desiccator.

(ii) Methoxymethyltetrahydrobrucidine dimethiodide (B) (1 g.) is heated gently in a test-tube over a flame until the evolution of methyl iodide ceases. If the heating becomes too vigorous, deep-seated decomposition takes place, and gases are evolved which burn with a luminous flame, partly condense on the cold part of the tube, and smell strongly of pyridine bases. The residue is crystallised from ethyl alcohol, and this purification is repeated if necessary until leaflets, m. p. 298° (decomp.), are obtained. This *methiodide* (*B*) separates from water in colourless, characteristic prisms, m. p. 298° (decomp.) (Found: C, 55·1; H, 6·9; I, 22·4. $C_{25}H_{36}O_4N_2$,MeI requires I, 22·3%). The identity of the specimens of the methiodide (B) obtained from the dimethiodides (A) and (B) was shown by seeding an aqueous solution prepared in one way with a crystal prepared in the other way.

The *methochloride* (*B*), prepared in the usual way from the methiodide and silver chloride, forms a colourless glass. When this is heated in a test-tube over a flame, it decomposes before methyl

chloride is split off, and no methyldihydrobrucidine can be isolated from the charred residue. When exposed to water vapour in a bell-jar, the glassy methochloride crystallises in sticky needles, which after being pressed on porous tile and dried in a vacuum desiccator, decompose without melting at about 210.°

Methoxymethyltetrahydrobrucidine Dimetho-salts.

The Dimethosulphates (A) and (B).—Methoxymethyltetrahydrobrucidine reacts with methyl sulphate even more slowly than does methoxymethyldihydrobrucidine. In this case no monomethosulphate has been isolated. A solution of dried methoxymethyltetrahydrobrucidine (46 g.) and pure methyl sulphate (100 c.c.) in dry benzene (300 c.c.) is boiled on the water-bath under reflux for 24 hours, carefully protected from moisture. The hot benzene is decanted, but the residual mixture of brown gum and needles (90 g.) still retains some methyl sulphate and a little solvent, even after being washed as thoroughly as possible with benzene, which is then blown away in a current of air. This mixture must contain two dimethosulphates, (A) and (B), since it is converted into two dimethiodides, but attempts to isolate the dimethosulphates have been fruitless, and the mixture is therefore converted into the dimethiodides (A) and (B) by sodium iodide.

The *dimethiodide* (*B*) is prepared by adding sodium iodide (100 g.) in warm water (40 c.c.) to a warm solution of the above mixture of dimethosulphates in water (60 c.c.). On cooling and scratching, crystallisation begins, and after 24 hours the solid is collected, washed with water, and dried in a vacuum (31 g.). (The mother-liquors contain the dimethiodide A together with a small quantity of the dimethiodide B, and their investigation is described on p. 1658.) One recrystallisation from water (filter : see below) is usually sufficient for the purification of this product, although on a few occasions it had an unpleasant smell, which was first removed by grinding with cold ethyl alcohol. The dimethiodide (B) crystallises from water in prismatic needles, m. p. 287° (decomp.) (Found : C, 45·3, 45·4; H, 5·5, 5·7. $C_{25}H_{36}O_4N_2,2MeI$ requires C, 45·5; H, 5·9%). It is sparingly soluble in cold water or methyl or ethyl alcohol, but dissolves readily in hot water. When an aqueous solution is saturated with sulphur dioxide, a yellow oil is formed which crystallises on standing. This additive product, which contains sulphur dioxide, is very sparingly soluble in cold water, but readily forms an orange solution on warming, which evolves sulphur dioxide when boiled and then becomes colourless. When the colourless solution is cooled, the dimethiodide separates in a pure condition. The dimethiodide is very stable to alkali, and was

recovered in good yield after being heated with a large excess of 25% methyl-alcoholic potassium hydroxide at 140° for 30 minutes.

The crude precipitate of the dimethiodide is usually mixed with a small quantity of an ochreous, amorphous substance, which remains undissolved on recrystallisation of the precipitate from water. The amount of this by-product increases to about one-tenth of the weight of the dimethiodide if the solutions of the dimethosulphates and sodium iodide are boiling when mixed. The insoluble solid from the recrystallisation of the dimethiodide (see above) is crystallised fom methyl alcohol, in which it is very sparingly soluble, by dissolving it in much boiling solvent (charcoal), concentrating the solution until crystallisation begins, and allowing it to cool. The substance thus obtained in purple-red, glistening prisms melts at 230° (decomp.) and is a *periodide* of the dimethiodide (B) (Found : I, 55·6. $C_{25}H_{36}O_4N_2$,2MeI,I_2 requires I, 52·6%). This periodide is slowly decomposed by boiling water; it is stable to cold dilute nitric acid, but is instantly decomposed on boiling, iodine being liberated. When sulphur dioxide is passed into an aqueous suspension, the crystals change into a red gum, which is collected, and boiled with water until the solution becomes colourless and the smell of sulphur dioxide is no longer perceptible; on cooling, the dimethiodide (B) separates in colourless prisms, m. p. 287°.

The *dimethochloride* (*B*) is prepared by heating an aqueous solution of the dimethiodide (B) with excess of silver iodide, and evaporating the filtrate to dryness on the water-bath under reduced pressure. The colourless, crystalline mass thus obtained separates from ethyl alcohol in plates which melt to a froth and lose solvent at 138°, after drying in a vacuum desiccator. On further heating, the froth hardens and melts at 214°. After drying at 100°, the dimethochloride has m. p. 214° (decomp.) (loss at 100°, 8·5. 1EtOH requires loss, 8·0%. Found in dried material: Cl, 13·7. $C_{25}H_{36}O_4N_2$,2MeCl requires Cl, 13·4%).

The dimethochloride loses a molecule of methyl chloride when it melts at 214°, forming methoxymethyltetrahydrobrucidine methochloride (B). After heating at 245° in an oil-bath until the evolution of methyl chloride ceased, the residual glass, consisting of the methochloride (B), was converted into the methiodide by adding sodium iodide to an aqueous solution, and crystallising the precipitate from water. The methiodide (B) separated in the characteristic prisms, m. p. 298° (decomp.), which became chalky on drying (Found : C, 54·5; H, 6·8%).

When the dimethochloride was heated in a test-tube at 300°, further decomposition took place. No methyl-ψ-dihydrobrucidine could be isolated from the residue, which consisted only of charred material

if the heating was sufficiently prolonged to allow complete elimination of the methyl chloride.

The *dimethiodide* (*A*) is obtained either (i) from the mother-liquors of the preparation of the dimethiodide (B), or (ii) by the direct combination of the base and methyl iodide.

(i) The mother-liquors from the preparation of the dimethiodide (B) (p. 1656) are mixed with 50% potassium hydroxide solution; a caseous mass then separates, and soon hardens sufficiently to be pressed between porous tiles in order to remove as much alkali as possible. On boiling with a little ethyl alcohol, it becomes colourless and completely crystalline, without passing into solution to any great extent. The crystals are collected after several hours, washed with alcohol, and dried in a vacuum desiccator (33 g.). This product is essentially the dimethiodide (A), but contains also a little of the dimethiodide (B). In the first experiment, these were separated by fractional crystallisation from methyl alcohol, but later, when the properties of the dimethiodide (A) became known, the following process was found to be much more satisfactory. The mixture is dissolved in a little boiling water, and the solution is cooled, seeded with the dimethiodide (B), and set aside over-night. The remainder of the dimethiodide (B) separates in a practically pure state, and is collected, washed, and dried (5 g.). The filtrate now contains the dimethiodide (A), which is very soluble in water. It is saturated with sulphur dioxide while stirred continuously, and the yellow, crystalline additive compound which is formed is collected, washed with a little sulphurous acid, and dissolved in boiling methyl alcohol. After boiling for about 15 minutes, the solution becomes colourless, and is then concentrated to about 100 c.c. On cooling, the *dimethiodide* (*A*) crystallises in an almost pure condition, m. p. 230° (25 g.). (The yield of the combined dimethiodides A and B is about 81% of that theoretically possible.) One recrystallisation from methyl alcohol gives the pure product in stout prisms, which melt at 230—232° to a colourless froth (see below) (Found : C, 45·1; H, 5·8. $C_{25}H_{36}O_4N_2$,2MeI requires C, 45·5; H, 5·9%). It dissolves readily in cold water, but only very sparingly in methyl or ethyl alcohol. When it is heated at its melting point, a molecule of methyl iodide is liberated smoothly; the glassy residue crystallises from water in the characteristic prisms of the methiodide (B) (see p. 1655).

(ii) A preliminary experiment showed that methoxymethyltetrahydrobrucidine combines with only one molecule of methyl iodide at 100°, even when heated for long periods. When, however, the base (5 g.) and methyl iodide (10 c.c.) are heated in a sealed tube at 140° for 24 hours, and the methyl iodide is distilled off, the

residual solid is the *dimethiodide* (*A*). After two recrystallisations from methyl alcohol, it forms stout prisms, m. p. 230°, which are identical in every way with the substance described above (Found : C, 45·6; H, 6·0; I, 35·4. $C_{25}H_{36}O_4N_2$,2MeI requires I, 35·7%).

The *dimethochloride* (*A*), prepared from the dimethiodide in the usual way by silver chloride, forms a colourless glass which cannot be crystallised. When it is heated gently in a test-tube over a flame, methyl chloride is evolved smoothly; the colourless residue, crystallised from methyl alcohol, forms needles, melting, either alone or when mixed with a specimen of methoxymethyltetrahydrobrucidine, at 133°.

*Methyl*neo*dihydrobrucidinium Salts.*

Methoxymethyltetrahydrobrucidine is not attacked by boiling 10% sulphuric acid under the conditions in which methoxymethyldihydrobrucidine yields methyl*neo*brucidinium sulphate. After the acid solution had been boiled for 2½ hours, ammonia precipitated 98% of the base used. Nor were successful results obtained when methoxymethyltetrahydrobrucidine dihydriodide or dihydrochloride was heated in a test-tube, since a much wider decomposition evidently took place. Ultimately, however, it was found possible to obtain the iodide in the following way.

The iodide. A suspension of methoxymethyltetrahydrobrucidine dihydrochloride (5 g.) in mesitylene (40 c.c.) is heated in an oil-bath at 180°. The solid becomes gummy and evolves hydrogen chloride, which is blown away from time to time in a current of air. After 20 minutes, the light brown gum hardens and is broken up, and the heating is continued for 10 minutes more in order to ensure complete decomposition. Ether is added to the cooled product, and the glassy solid is collected and dried at 100° (3·9 g.). Attempts to crystallise this chloride were unsuccessful (compare below), and it was therefore converted into the iodide. A solution of the chloride in water (25 c.c.) is saturated with sulphur dioxide, and concentrated sodium iodide is added drop by drop until no more oil separates. This additive product solidifies after a short time, and the orange mass thus obtained is boiled with water until the smell of sulphur dioxide has disappeared. On cooling, *methyl*neo*dihydrobrucidinium iodide* (3 g.) separates; it crystallises from water in colourless bipyramids, m. p. 283° (decomp.) (Found : C, 54·9; H, 6·4. $C_{24}H_{33}O_3N_2I$ requires C, 55·0; H, 6·3%). It is rather sparingly soluble in cold water or ethyl alcohol and crystallises in plates from the latter. An aqueous solution is not precipitated by ammonia or dilute alkali solution; concentrated potassium hydroxide solution precipitates the iodide unchanged.

The *chloride*, prepared by heating an aqueous solution of the

iodide with silver chloride and evaporating the filtrate under reduced pressure on the water-bath, is a colourless glass which does not crystallise. An aqueous solution is not precipitated by ammonia or dilute alkali solution. On heating in a test-tube over a flame, charring occurs very readily; the residue dissolves in water to a red solution, which becomes deep red on addition of ammonia, and then bright green on addition of a few drops of potassium hydroxide; much concentrated potassium hydroxide solution precipitates a green oil, which has not been examined. No methyl-ψ-dihydrobrucidine is formed.

Methoxymethyltetrahydrobrucidine Dimethohydrogencarbonates (A) and (B) and their Decomposition by Heat. Methyl-ψ-dihydrobrucidine.

The Dimethohydrogencarbonate (A).—This substance is prepared by shaking a hot aqueous solution of methoxymethyltetrahydrobrucidine dimethiodide (A) with an excess of either silver hydroxide or silver carbonate. In either case, the alkaline filtrate is evaporated as far as possible in an open basin on the water-bath, and then left in a vacuum desiccator over-night. The gummy residue crystallises on being rubbed with acetone containing a little ethyl alcohol, and is recrystallised by the cautious addition of ether to an ethyl-alcoholic solution. The *dimethohydrogencarbonate* (*A*) forms almost colourless, hygroscopic crystals, m. p. 92—94°, or 103—104° when heated in a sealed capillary tube (Found in material dried in a vacuum desiccator: C, 52·5; H, 8·3. $C_{25}H_{36}O_4N_2,2MeHCO_3,5H_2O$ requires C, 51·9; H, 8·1%). It is very soluble in water or ethyl alcohol, and evolves carbon dioxide on treatment with dilute hydrochloric acid. When a small quantity is heated gently in a test-tube over a flame, carbon dioxide is eliminated; the light brown, glassy residue crystallises from methyl alcohol in colourless needles, which, either alone or when mixed with methoxymethyltetrahydrobrucidine, melt at 134°.

The *dimethohydrogencarbonate* (*B*) is prepared from the dimethiodide (B) exactly in the manner described above in the case of the isomeride (A). It is crystallised by the careful addition of ether to a filtered solution in ethyl alcohol, and forms colourless prisms, which are hygroscopic and melt at 109° after drying in a vacuum desiccator (Found: C, 50·3; H, 8·3. $C_{25}H_{36}O_4N_2,2MeHCO_3,6H_2O$ requires C, 50·6; H, 8·1%). It is very soluble in water or ethyl alcohol, and evolves carbon dioxide on treatment with acids.

When it is heated at 135° in an oil-bath, carbon dioxide is evolved. The heating is continued for 30 minutes until the frothing has ceased, and the clear, glassy residue is dissolved in water. As the solution gives no precipitate with ammonia and evolves carbon dioxide on

treatment with acids, it must contain a methohydrogencarbonate. Sodium iodide is therefore added; the precipitate formed crystallises from water in colourless prisms, m. p. 298°, and is identical with methoxymethyltetrahydrobrucidine methiodide (B). The product of the decomposition is therefore the *methohydrogencarbonate* (*B*).

Methyl-ψ-dihydrobrucidine. The dimethohydrogencarbonate (B) (1 g.) is heated gently in a test-tube over a flame. It melts to a froth while gradually losing carbon dioxide, and the methyl alcohol which is evolved may be burnt at the mouth of the tube; when the effervescence has ceased, the light brown residue is quite mobile. After cooling, the tubes are broken and the contents extracted with boiling ethyl alcohol. The filtrate is concentrated to small volume; *methyl-ψ-dihydrobrucidine*, which then separates in moderate yield, recrystallises from ethyl alcohol in colourless tablets, m. p. 220—221° [Found: C, 72·5; H, 8·2; OMe, 15·8. $C_{24}H_{32}O_3N_2$ requires C, 72·7; H, 8·1; $(OMe)_2$, 15·6%]. This substance is soluble in dilute hydrochloric or acetic acid; it is sparingly soluble in ethyl alcohol, moderately easily soluble in acetone, and dissolves readily in benzene. It is extremely stable to oxidation by permanganate in acetone.

The *dihydriodide*, prepared by the addition of sodium iodide to a solution of the base in dilute hydrochloric acid, crystallises from water in small, wart-like granules, which melt at 215—217° to a yellow froth (Found in material dried at 100°: C, 44·0; H, 5·2. $C_{24}H_{32}O_3N_2,2HI$ requires C, 44·2; H, 5·2%). It separates from ethyl alcohol in stout prisms, and is sparingly soluble in this solvent and in water.

Colour Reactions of the Brucidine Derivatives.

The most useful reaction is that with ferric chloride in dilute hydrochloric acid, and a positive result is a deep green or bluish-green coloration, pink in thin layers, becoming red on boiling; when the reaction is negative, no colour is produced even on heating. The following substances give the reaction: brucidine, brucidine methosulphate, tetrahydrobrucine and its methochloride, methoxymethyldihydrobrucidine and its methochloride (B), methoxymethyltetrahydrobrucidine and its methochloride (B), methyl-ψ-brucidine and its methochloride prepared by either method, methyl*neo*brucidinium chloride, methyl-ψ-dihydrobrucidine, and methyl*neo*dihydrobrucidinium chloride. The substances which do not give the reaction are: methoxymethyldihydrobrucidine methosulphate (A) and methochloride (A), methoxymethyltetrahydrobrucidine methochloride (A), methoxymethyldihydrobrucidine dimethochlorides (A) and (B), methoxymethyltetrahydrobrucidine dimethochlorides (A) and (B), dioxymethoxymethyldihydrobrucidine (Y) methochloride, and,

as already mentioned, brucine itself.* Since both strychnidine and brucidine give characteristic but entirely different ferric chloride reactions, the latter must be concerned with the only part of the molecule which is not identical in the two substances, namely, the aromatic nucleus, and this view is confirmed in the case of strychnidine by the observation that those derivatives which give a negative or feeble ferric chloride reaction are the only strychnidine derivatives which do not couple with diazonium salts. It then becomes apparent that the occurrence of the reaction in a particular case is dependent on the condition of the nitrogen atom bound to the aromatic nucleus. When this is salt-forming, the reaction is positive, whilst a negative reaction is due to its inclusion in the group –N–CO– as in brucine, or in a quaternary ammonium salt grouping as in the various dimethochlorides (and dihydrochlorides) described in this and the preceding communications. These views are in complete harmony with experience of simpler aromatic amine derivatives; thus dimethylaniline couples with diazonium salts, whereas *N*-methylacetanilide and phenyltrimethylammonium chloride do not. It is on this basis that we have allocated formulæ to the methochlorides (A) and (B) of methoxymethyldihydrobrucidine and methoxymethyltetrahydrobrucidine respectively (see pp. 1630 and 1633) and have drawn the important inference that the conversion of brucidine into methoxymethyldihydrobrucidine is accompanied by a transposition of the function of the nitrogen atoms in respect of their basic character.

The dichromate test in 60% sulphuric acid is of inferior diagnostic value. It is given by all the brucidine derivatives, but the green colour appears much more slowly in the cases where the ferric chloride reaction is negative.

We are indebted to Mr. R. I. E. Hall, M.A., for preparing the large quantities of material required in these two researches and also to Mr. F. Hall for carrying out, with his usual skill, the whole of the analyses. One of us (W. H. P.) is indebted to the Government Grant Committee of the Royal Society for repeated grants which have covered much of the expense of these investigations.

UNIVERSITIES OF OXFORD AND
MANCHESTER. [*Received, May 24th*, 1927.]

* The brucidine derivatives do not exhibit the reaction in concentrated hydrochloric acid solution. In the cases when the reaction is positive, however, the colour appears on dilution, and this behaviour is clearly due to the formation and hydrolysis of dihydrochlorides.

PRINTED IN GREAT BRITAIN BY RICHARD CLAY & SONS, LIMITED,
BUNGAY, SUFFOLK.

THE CONDENSATION OF CERTAIN ALDEHYDES WITH KETONES OF THE MORPHINE GROUP.

BY

JOHN MASSON GULLAND.

Publication 8

Reprinted from the Journal of the Chemical Society,
March 1928

Reprinted from the Journal of the Chemical Society, 1928.

XCV.—*The Condensation of Certain Aldehydes with Ketones of the Morphine Group.*

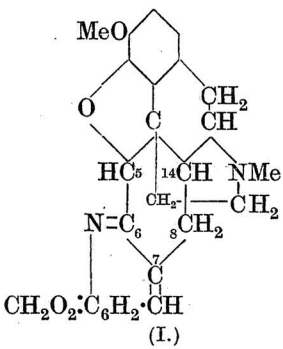
By John Masson Gulland.

The position of the hydroxyl group in hydroxycodeinone and its derivatives (Freund and Speyer, *J. pr. Chem.*, 1916, **94**, 135; Speyer, Selig, and Heil, *Annalen*, 1922, **430**, 1) is an important factor in determining the constitution of thebaine. Gulland and Robinson (*Mem. Manchester Phil. Soc.*, 1925, **69**, No. 10), in showing that the properties of hydroxycodeinone are satisfied only by placing the hydroxyl in position 14, proved that hydroxydihydrocodeinone contains the group $CO{\cdot}CH_2$. One of the steps of this proof consisted in the preparation of dianhydro-6-aminopiperonalhydroxydihydrocodeinone by the condensation of the ketone with 6-aminopiperonal. This quinoline derivative exhibited no fluorescence when dissolved in concentrated sulphuric acid, and thus differed from the simple methylenedioxyquinolines and also from dianhydro-6-aminopiperonalthebainone (Gulland and Robinson, J., 1923, **123**, 998). The absence of this apparently characteristic fluorescence might be considered to weaken the evidence in favour of the presence of a $CO{\cdot}CH_2$ group, but it is now shown that dihydrocodeinone condenses with 6-aminopiperonal, yielding *dianhydro-6-aminopiperonaldihydrocodeinone* (I), which dissolves in concentrated sulphuric acid and in other solvents without exhibiting fluorescence. Dihydrocodeinone undoubtedly contains a $CO{\cdot}CH_2$ group, and it would thus appear that the quinoline bases of this type, in which the attached groups form the larger part of the molecule, do not necessarily yield fluorescent solutions.

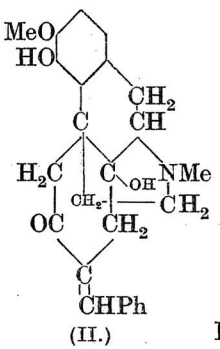
The present communication contains also a brief account of a number of experiments which were carried out in the hope of demonstrating, by the preparation of crystalline benzylidene derivatives, that the phenolic ketones of the morphine series contain a $CH_2{\cdot}CO{\cdot}CH_2$ group (compare Gulland and Robinson, *ibid.*, pp. 980, 998). It may readily be shown that these bases contain one reactive methylene group; for example, *benzylidenehydroxydihydrothebainone* (II) is formed in quantitative yield when hydroxydihydrothebainone (Freund and Speyer, *loc. cit.*) is condensed with benzaldehyde in

alkaline solution. Attempts to show the presence of the second methylene group by the interaction of this benzylidene derivative with 6-aminopiperonal were fruitless, and, as Schöpf has already indicated (*Annalen*, 1927, **452**, 211), this inactivity is comparable with that observed in the case of dehydrocholic acid (Borsche and Frank, *Ber.*, 1924, **57**, 1373) and 3-methyl*cyclo*hexanone (Ruzicka, *Helv. Chim. Acta*, 1926, **9**, 101).

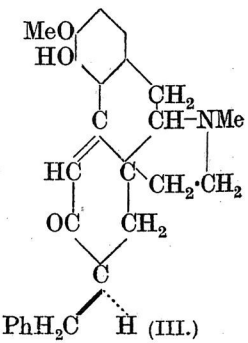
Piperonylidene- and *benzylidene-thebainone* have now been obtained in crystalline condition, and the catalytic reduction of the latter substance yields a mixture of two *benzylthebainones* (III), (A) m. p. 229° and (B) m. p. 179°, which are presumably stereoisomeric about carbon atom 7. These substances are isomeric with, but different from, *benzylidenethebainol*, which is prepared by the condensation of benzaldehyde and thebainol.



(I.)



(II.)



(III.)

EXPERIMENTAL.

Dianhydro-6-aminopiperonaldihydrocodeinone.—A solution of sodium (1 g.) in hot ethyl alcohol (25 c.c.) is mixed with a solution of dihydrocodeinone (2 g.) and 6-aminopiperonal (1·1 g.) in ethyl alcohol (5 c.c.) and boiled gently for several minutes. The product, which separates from the hot solution in yellow leaflets, after being washed, and dried at 100° (2·2 g.), crystallises from benzene in colourless, rectangular leaflets, m. p. 270—271·5° (Found : C, 73·3; H, 5·8. $C_{26}H_{24}O_4N_2$ requires C, 72·9; H, 5·6%). It is very sparingly soluble in hot methyl or ethyl alcohol or in ethyl acetate. The solution in concentrated sulphuric acid is colourless and shows no fluorescence. The substance is a non-phenolic base, which contains a methylenedioxy-group, since it responds to Gadamer's test (*Arch. Pharm.*, 1920, **258**, 148).

The *methiodide*, prepared by boiling the base and an excess of methyl iodide in methyl alcohol under reflux for 20 minutes, evaporating the solvent, rubbing the residual yellow gum with hot

ethyl acetate, and grinding the hardened mass with boiling chloroform (the chloroform contains a small quantity of material which was not examined), is obtained, after crystallising twice from methyl alcohol, in pale yellow tablets which become orange at 200°, gradually soften, and decompose finally at about 260° (Found: C, 56·7; H, 4·9. $C_{26}H_{24}O_4N_2$,MeI requires C, 56·8; H, 4·7%).

Benzylidenehydroxydihydrothebainone.—A solution of benzaldehyde (4 g.) and hydroxydihydrothebainone (2·5 g.) in alcoholic potassium hydroxide (25 c.c. of 4%), after being kept at room temperature for 48 hours, is mixed with water, acidified with hydrochloric acid, and extracted with ether. The residual ether having been removed in a current of air, potassium bicarbonate precipitates a small fraction only of the product, which may be crystallised from benzene–ligroin and then from ethyl alcohol. The remainder of the *benzylidene* derivative separates as an oil when the aqueous filtrate is heated on the water-bath for 30 minutes, and solidifies on cooling. It separates from ethyl alcohol in yellow, coarse, pyramidal crystals, m. p. 188° (Found: C, 74·0; H, 6·7. $C_{25}H_{27}O_5N$ requires C, 74·1; H, 6·7%). The colorations developed with concentrated sulphuric acid, concentrated hydrochloric acid, and alcoholic sodium hydroxide are orange-red, very faint yellow, and orange-yellow, respectively. Attempts to prepare a quinoline derivative by condensing the substance with 6-aminopiperonal were fruitless.

Benzylidenethebainone.—A solution of thebainone (Pschorr, Pfaff, and Herrschmann, *Ber.*, 1905, **38**, 3160) (12 g.) and freshly distilled benzaldehyde (16 g.) in ethyl-alcoholic potassium hydroxide (120 c.c. of 5%) is kept in a closed flask at room temperature for 48 hours. The red colour due to the presence of the sodium salt of thebainone changes to a very intense crimson. The solution is poured into water (600 c.c.), just acidified with dilute hydrochloric acid, extracted twice with benzene to remove the excess of benzaldehyde, and neutralised with potassium bicarbonate solution. The flocculent precipitate slowly becomes crystalline, but readily when seeded. After being washed thoroughly with water to remove all traces of bicarbonate, dried on porous tile and then in a vacuum desiccator, it is crystallised from ethyl alcohol, *benzylidenethebainone* being obtained in canary-yellow needles, m. p. 233° (Found: C, 77·7; H, 6·7. $C_{25}H_{25}O_3N$ requires C, 77·5; H, 6·5%). This substance dissolves readily in benzene and chloroform, is insoluble in light petroleum, forms an intense crimson solution in dilute alkali, is easily soluble in organic acids or in dilute mineral acids, yielding yellow solutions, and develops a brilliant green colour with alcoholic ferric chloride. In concentrated hydrochloric or sulphuric acid a deep red colour is produced which is discharged on dilution with water.

The *methiodide* (compare Gulland and Robinson, *loc. cit.*), prepared by warming a suspension of the base (1 g.) in ethyl alcohol (5 c.c.) and methyl iodide (1 c.c.) until it dissolves, separates, on cooling, in fine yellow needles, and recrystallises from ethyl alcohol in the same form, m. p. 195—197° (decomp.) (Found : C, 59·0; H, 5·3. $C_{25}H_{25}O_3N$,MeI requires C, 59·0; H, 5·3%).

Piperonylidenethebainone is prepared from thebainone (2 g.), piperonal (4 g.), and ethyl-alcoholic potassium hydroxide (20 c.c. of 5%) in the manner described in the case of benzylidenethebainone (yield of yellow, semi-crystalline product, 2·7 g.). It is extremely soluble in the usual organic solvents, except ligroin, but it crystallises from a little ethyl alcohol in yellow, wart-like aggregates of crystals, m. p. 176° after drying at 100° (Found : C, 72·1; H, 5·7. $C_{26}H_{25}O_5N$ requires C, 72·4; H, 5·8%). The solution in concentrated hydrochloric or sulphuric acid is intensely reddish-purple and becomes pale yellow on dilution with water.

Reduction of Benzylidenethebainone. The Isomeric Benzylthebainones (A) *and* (B).—A solution of benzylidenethebainone (6·5 g.) in water (80 c.c.) and acetic acid (5 c.c.), when shaken with palladous chloride solution (15 c.c. of 1%) in an atmosphere of hydrogen, absorbs 1 mol. of the gas in about 20 minutes. Absorption then ceases. The palladium is precipitated and removed, and potassium bicarbonate solution added to the filtrate. The colourless, amorphous precipitate produced is dried on porous tile and dissolved in the minimum of boiling alcohol; on cooling, small colourless needles form on the sides of the vessel, and these are collected (A, 0·3 g.) before the appearance of a mass of felted needles, which fill the body of the liquid. The filtrate, after being concentrated, slowly deposits colourless needles or plates (B, 5 g.).

Benzylthebainone (A) is sparingly soluble in alcohol, and separates from this solvent in colourless needles, m. p. 229° (Found : C, 77·0; H, 6·9. $C_{25}H_{27}O_3N$ requires C, 77·1; H, 6·9%). The sodium salt is orange in colour, and the base exhibits an orange halochromic colour in concentrated hydrochloric acid and a bright red in concentrated sulphuric acid. It was recovered unchanged after an attempt to condense it with 6-aminopiperonal in presence of hot ethyl-alcoholic sodium ethoxide.

The *semicarbazone* is formed when a mixture of the base and an excess of semicarbazide hydrochloride and potassium acetate in dilute acetic acid is kept at room temperature over-night. The product is precipitated by ammonia, and after drying, is obtained as a microcrystalline powder, m. p. 155—160°, by repeated precipitation from benzene by means of ligroin (Found : N, 12·2. $C_{26}H_{30}O_3N_4$ requires N, 12·5%).

Benzylthebainone (B) separates from ethyl alcohol in plates, m. p. 179° (Found : C, 76·8; H, 7·0. $C_{25}H_{27}O_3N$ requires C, 77·1; H, 6·9%), or in needles which lose solvent and become pasty at about 110° (Found : loss at 100°, 5·3. Required for $\frac{1}{2}$EtOH, 5·6%. Found in dried material : C, 77·3; H, 7·1%). Each of these forms may be obtained free from the other by utilising the following facts : (i) The plates separate first and pass into the needle form after remaining for some time in contact with the solvent, and (ii) the needles dissolve more rapidly than the plates when a suspension of the two forms is warmed with ethyl alcohol. Both forms of this substance are more soluble than the isomeride (A), and show the same halochromic colours; the sparingly soluble, orange sodium salt separates in needles when a hot slightly alkaline solution is cooled. The base was recovered unchanged after an attempt to condense it with 6-aminopiperonal.

The *semicarbazone*, prepared as described in the case of the isomeride (A), crystallises from dilute ethyl alcohol in needles, m. p. 140—145° (unaltered by further crystallisation) (Found in material dried at 100°; C, 69·0; H, 6·8. $C_{26}H_{30}O_3N_4$ requires C, 69·9; H, 6·8%).

The *oxime*, prepared in a similar manner, is precipitated by sodium carbonate, collected, and dried on porous tile. It becomes crystalline on boiling with ethyl alcohol, and is then collected and recrystallised from the same solvent, from which it separates in colourless columns, m. p. 152° (Found : N, 6·7. $C_{25}H_{28}O_3N_2$ requires N, 6·9%). This oxime is not reduced when a solution in dilute acetic acid is shaken with palladium and hydrogen (compare Speyer, Selig, and Heil, *loc. cit.*).

Benzylidenethebainol.—The condensation of benzaldehyde (3 g.) with thebainol (2 g.) is carried out in the manner described in the case of benzylidenethebainone. *Benzylidenethebainol* crystallises from ethyl alcohol in faintly yellow needles, m. p. 100—102° (Found in material dried at 100°; C, 77·1; H, 7·2. $C_{25}H_{27}O_3N$ requires C, 77·1; H, 6·9%). The solution in concentrated sulphuric acid is orange-red, in concentrated hydrochloric acid yellow, and these colours are discharged on dilution with water. The solution in alcoholic or hot aqueous sodium hydroxide is orange-yellow.

The author wishes to thank Professor Robinson for the interest which he has taken in this work, and acknowledges his indebtedness to the Chemical Society for a grant which has defrayed a part of the cost of the investigation.

THE DYSON PERRINS LABORATORY,
OXFORD.

[*Received, February 3rd,* 1928.]

PRINTED IN GREAT BRITAIN BY RICHARD CLAY & SONS, LIMITED,
BUNGAY, SUFFOLK.

SYNTHETICAL EXPERIMENTS ON THE APORPHINE ALKALOIDS. PART I. A SYNTHESIS OF 5:6-DIMETHOXY-APORPHINE.

BY

JOHN MASSON GULLAND

AND

ROBERT DOWNS HAWORTH.

Publication 9

Part of the work described in this paper was carried out by me, part by Dr. R.D. Haworth.

Reprinted from the Journal of the Chemical Society, March 1928

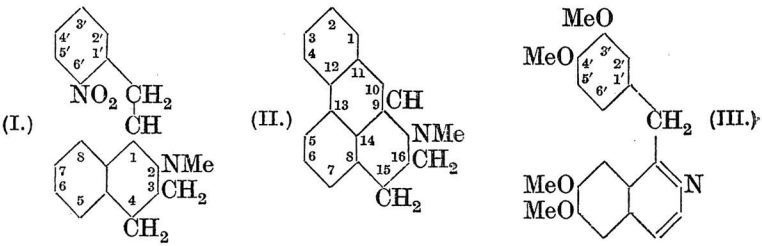
Reprinted from the Journal of the Chemical Society, 1928.

LXXVII.—*Synthetical Experiments on the Aporphine Alkaloids. Part I. A Synthesis of* 5 : 6-*Dimethoxyaporphine.*

By John Masson Gulland and Robert Downs Haworth.

In attempts to synthesise aporphine alkaloids of type (II), the most usual starting points have been the substituted nitro*iso*quinolines of type (I), because these bases on reduction yield the corre-

sponding 2′-amino-derivatives, which may be converted by Pschorr's method (*Ber.*, 1896, **29**, 496) into the aporphine bases.

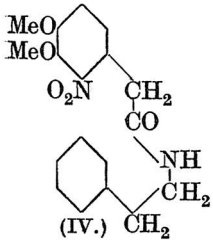


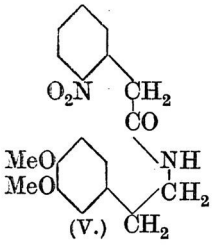
The difficulty of preparing bases of type (I) has, however, until now precluded the synthesis of the naturally occurring alkaloids of type (II), with the exception of glaucine (Gadamer, *Arch. Pharm.*, 1911, **249**, 680) and dicentrine (Haworth, Perkin, and Rankin, J., 1925, **127**, 2018; 1926, 29). Both these alkaloids are exceptional in containing ethereal oxygen atoms in the 2 : 3-positions, and the necessary nitro*iso*quinoline bases are readily prepared by direct nitration of the requisite 1-benzyl*iso*quinoline derivative in which the 3′ : 4′-positions are occupied by methoxy-groups. Thus papaverine (III) readily yields 6′-nitropapaverine, which is convertible into glaucine (Pschorr, *Ber.*, 1904, **37**, 1926; Gadamer, *loc. cit.*). Many alkaloids of the aporphine group contain phenolic or ethereal oxygen in the 3 : 4-positions and in order to prepare bases of this constitution by the method of direct nitration it would be necessary to introduce a nitro-group into the 2′-position of a base of the papaverine type (III)—an operation which has not yet been accomplished.

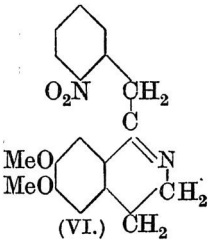
The discovery by Hope and Robinson (J., 1911, **99**, 2114), that cotarnine and the allied pseudo-bases condense with derivatives of *o*-nitrotoluene, provided a new method for the preparation of bases of type (I). Gadamer, Oberlin, and Schoeler (*Arch. Pharm.*, 1925, **263**, 81) have employed this method for the synthesis of aporphine (II), but it has not yet been applied to the synthesis of the naturally occurring alkaloids of the series, partly owing to the inability of some pseudo-bases to condense with *o*-nitrotoluene derivatives and partly on account of the inactivity of the methyl group of 2-nitrohomoveratrole, as opposed to that of the 6-nitro-derivative. Derivatives of dinitrotoluene, however, readily condense with pseudo-bases (Hope and Robinson, *loc. cit.*; Graesser-Thomas, Gulland, and Robinson, J., 1926, 1971; Robinson and West, *ibid.*, p. 1985; Robinson and Shinoda, *ibid.*, p. 1987), but this modification introduces complications which greatly increase the practical difficulties in the preparation of bases of the 1-(2′-aminobenzyl)-2-

methyltetrahydro*iso*quinoline type (compare Robinson and Shinoda, *loc. cit.*).

A review of the literature convinced us that the well-known Bischler–Napieralski synthesis of *iso*quinoline bases had not been sufficiently investigated. From the observations made by Pictet and Kay (J., 1913, **103**, 950) during an attempt to synthesise *apo*morphine dimethyl ether by a modification of this synthesis, it might be concluded that bases of type (I) cannot be prepared by this method. For example, these authors failed to obtain any basic material by the action of phosphorus pentoxide on 2′-nitro-3′ : 4′-dimethoxyphenylaceto-β-phenylethylamide (IV), and Gadamer, Oberlin, and Schoeler (*loc. cit.*) were unable to employ 2′-nitrophenylaceto-β-phenylethylamide in a synthesis of aporphine (II).



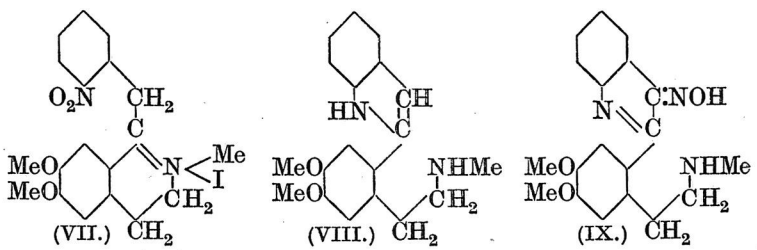




We have now achieved the stage of ring closure at which those attempted syntheses broke down, and as a preliminary case we have examined the action of a number of condensing agents on 2′-*nitrophenylaceto*-β-3 : 4-*dimethoxyphenylethylamide* (V). This amide was selected as being more favourable than the amide (IV), which Pictet and Kay investigated, because the activating influence of the methoxy-groups might be expected to facilitate *iso*quinoline formation. Treatment of the amide (V) with phosphorus pentoxide or phosphorus oxychloride under a variety of conditions did not produce any *iso*quinoline base. It was found, however, that 2′-*nitro*-6 : 7-*dimethoxy*-1-*benzyl*-3 : 4-*dihydro*isoquinoline (VI) was obtained in a yield of 90% by the action of phosphorus pentachloride on a cold chloroform solution of the amide (V). This orange-coloured, crystalline base (VI) yielded a pale yellow, crystalline *hydrochloride*, and the stability of the base is remarkable when it is remembered that 1-benzyl-3 : 4-dihydro*iso*quinoline bases readily undergo atmospheric oxidation (Buck, Haworth, and Perkin, J., 1924, **125**, 2176). The base (VI) readily yielded a sparingly soluble, pale yellow, crystalline *methiodide* (VII), the constitution of which was proved by fission with dilute sodium hydroxide solution in the manner described by Pschorr (*Ber.*, 1904, **37**, 1932). The products of this alkaline fission were *o*-nitrotoluene and 6 : 7-dimethoxy-2-methyl-

3 : 4-dihydro*iso*quinolone (Pyman, J., 1909, **95**, 1272; 1910, **97**, 269), the latter being identified by comparison with an authentic specimen which was presented to us by Dr. H. A. D. Jowett, on behalf of Burroughs Wellcome and Co., to whom we are greatly indebted.

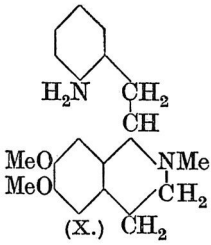
When the methiodide (VII) was reduced with zinc dust and dilute sulphuric acid in *faintly* acid solution, a colourless, crystalline base, $C_{19}H_{22}O_2N_2$, m. p. 132°, was obtained which showed unexpected properties. The base was monoacidic; it formed a crystalline *monohydrochloride* on treatment with an excess of hydrochloric acid, and it was converted into a crystalline, non-basic *monoacetyl* derivative by the action of acetic anhydride. As a result of these and other observations, we have concluded that the substance $C_{19}H_{22}O_2N_2$ is 2-(4′ : 5′-*dimethoxy*-2′-β-*methylaminoethyl*)*phenylindole* (VIII). The presence of the indole nucleus was confirmed



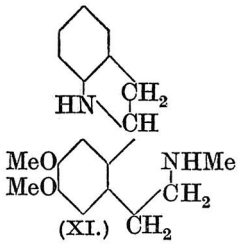
by the positive colour reactions observed on testing with a pine shaving and with *p*-dimethylaminobenzaldehyde. On treatment with nitrous acid, the base, which did not diazotise, yielded a deep red solution, from which a colourless, crystalline compound, $C_{19}H_{21}O_3N_3$, has been isolated. We consider this compound to be the 3-*oximino*-derivative (IX), as it is soluble in sodium hydroxide and dissolves in dilute mineral acids with the production of a red colour, and this view is confirmed by the fact that the compound $C_{19}H_{21}O_3N_3$ does not give the Liebermann nitrosoamine reaction. We are at present unable to explain why the nitrous acid attacks the indole nucleus in preference to the basic methylamino-group.

When the methiodide (VII) was reduced with zinc dust and hydrochloric acid in *strongly* acid solution, a different product was obtained. This new base was an oil which yielded a crystalline *dihydrochloride*, and its *monoacetyl* derivative still possessed strongly basic properties. The base could be diazotised and showed the characteristic reactions of a primary aromatic amine, and there can be no doubt that it is 2′-*amino*-6 : 7-*dimethoxy*-1-*benzyl*-2-*methyltetrahydro*isoquinoline (X). A small quantity of an oily base, isomeric with (X), has been isolated from the mother-liquor of the

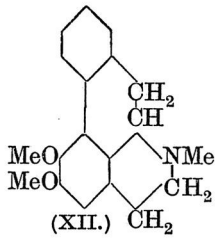
dihydrochloride of the base (X). This isomeric base, which gave a crystalline *dihydrochloride*, did not diazotise; it showed no indole colour reactions, but it yielded an oily *nitrosoamine* which gave the nitroso-reaction. We suggest that this base is 2-(4′ : 5′-*dimethoxy*-2′-β-*methylaminoethyl*)*phenyldihydroindole* (XI).



(X.)



(XI.)



(XII.)

The base (X) was converted into 5 : 6-*dimethoxyaporphine* (XII), either (*a*) by diazotising it in 2*N*-sulphuric acid and adding copper powder, or (*b*) by diazotising it in a mixture of methyl alcohol and 2*N*-sulphuric acid and heating the solution on the water-bath. The yield of 5 : 6-dimethoxyaporphine was poor (10—15% of the theoretical), the chief by-products being the dilaudanosine derivative and the phenolic base, the former predominating in method (*a*) and the latter in method (*b*). 5 : 6-Dimethoxyaporphine is a crystalline base, m. p. 137°, which yields a sparingly soluble crystalline *hydrochloride* and a characteristic *methiodide*. A number of colour reactions are described in the experimental section.

We have obtained several substituted benzyl*iso*quinoline derivatives by the action of phosphorus pentachloride on amides analogous to (V), and we are using this method in the synthesis of the naturally occurring aporphine bases. *dl*-Bulbocapnine methyl ether has already been synthesised, and we hope to publish accounts of this and other researches at an early date.

Experimental.

o-Nitrophenylacetic acid (10 g.; prepared by a slight modification of Reissert's method, *Ber.*, 1897, **30**, 1030, potassium ethoxide being used instead of sodium ethoxide) in chloroform (150 c.c.) was gently refluxed with thionyl chloride (40 c.c.) for 1½ hours. The solvent was then removed by careful distillation under 13 mm. pressure, the liquid being occasionally warmed for a few minutes on the water-bath, with shaking. This procedure is necessary to avoid explosive decomposition of the *o*-nitrophenylacetyl chloride. The residual oil was used without further purification.

2′-*Nitrophenylaceto*-β-3 : 4-*dimethoxyphenylethylamide* (V).—*o*-Nitrophenylacetyl chloride (from 45 g. of acid), dissolved in benzene

(150 c.c.), was gradually added, with cooling and shaking, to β-veratrylethylamine (45 g.) in benzene (100 c.c.), and the slimy, buff-coloured precipitate was decomposed by the gradual addition of 10% sodium hydroxide solution. The amide (V), which separated from the benzene, was collected, combined with a small second crop, obtained by evaporating the benzene layer of the filtrate, and recrystallised from methyl alcohol, giving very pale buff-coloured, slender needles (73 g.), m. p. 112° (Found: C, 62·3; H, 5·9. $C_{18}H_{20}O_5N_2$ requires C, 62·8; H, 5·8%). The *amide* dissolves with sulphonation in concentrated sulphuric acid, giving an orange-coloured solution which is completely miscible with water. No basic material was isolated after the amide had been heated with phosphorus pentoxide or oxychloride in benzene, toluene, or xylene for various times; the products invariably consisted of unchanged amide and a brown, amorphous, non-basic material which could not be obtained in the crystalline condition. After a chloroform solution of the amide had been boiled with phosphorus pentachloride for 2 hours, a large amount of non-basic tar was isolated together with a very small amount of impure basic material.

2′-Nitro-6 : 7-dimethoxy-1-benzyl-3 : 4-dihydroisoquinoline (VI).—The amide (V) (4 g.) was mixed with a solution of phosphorus pentachloride (5 g.) in chloroform (30 c.c.) and kept for 24 hours at room temperature. The solvent was evaporated under reduced pressure from the crystalline material which had separated, the latter was extracted with boiling water and filtered from traces of tar, and the base (VI) was precipitated, by the addition of ammonia to the cooled filtrate, as an amorphous, pink solid which changed to a buff-coloured, crystalline solid after remaining in the liquor for several hours. The crude base crystallised from methyl alcohol in large, stout, orange, rhombic prisms (3·5 g.), m. p. 132°, which developed a deeper colour on heating to 100°, the colour reverting to orange on cooling (Found: C, 66·5; H, 5·7. $C_{18}H_{18}O_4N_2$ requires C, 66·3; H, 5·5%). The *hydrochloride*, pale yellow prisms, m. p. 228° (decomp.), was obtained by evaporating to dryness the pale yellow solution of the base in dilute hydrochloric acid and recrystallising the residue from absolute alcohol (Found: Cl, 9·7. $C_{18}H_{18}O_4N_2$,HCl requires Cl, 9·8%). The base dissolves in acetic anhydride, giving a pale yellow solution, and the absence of a deep green coloration indicates that spontaneous oxidation has not occurred (Buck, Haworth, and Perkin, *loc. cit.*).

2′-Nitro-6 : 7-dimethoxy-1-benzyl-3 : 4-dihydroisoquinoline methiodide (VII) may be prepared quantitatively (*a*) by heating a chloroform solution of the base (VI) and the calculated quantity of methyl iodide in a sealed tube at 100° for 4 hours, and (*b*) more con-

veniently by dissolving the base (VI) in an excess of warm methyl iodide, cooling the solution to room temperature, removing the excess of methyl iodide after 12 hours, and recrystallising the residue from rectified spirit. It forms pale sulphur-yellow needles, m. p. 208°, which are sparingly soluble in water and absolute alcohol (Found: C, 49·0; H, 4·7. $C_{19}H_{21}O_4N_2I$ requires C, 48·7; H, 4·5%). When ammonia was added to an aqueous solution of the methiodide, a deep red solution was obtained from which an ether-soluble, red, amorphous solid was precipitated; this redissolved on addition of water.

Alkaline fission. The methiodide (2 g.) was boiled with 3% sodium hydroxide solution (20 c.c.) for ½ hour, and the product was distilled in steam until the distillate was no longer turbid. From this, ether extracted *o*-nitrotoluene, which was reduced to *o*-toluidine (acetyl and *m*-nitrobenzoyl derivatives, m. p. 110° and 150°, respectively). The non-volatile residue from the steam distillation was evaporated to dryness; from the residual oil, chloroform extracted 6 : 7-dimethoxy-2-methyl-3 : 4-dihydro*iso*quinolone, which crystallised from benzene in colourless prisms, m. p. 124—125° (compare Pyman, *loc. cit.*), and was identified by comparison with an authentic specimen.

2-(4′ : 5′-*Dimethoxy*-2′-β-*methylaminoethyl*)*phenylindole* (VIII).—A solution of the methiodide (VII) (2 g.) in hot methyl alcohol (30 c.c.) was treated with zinc dust (6 g.) and heated on the water-bath while 10% sulphuric acid was added gradually. The methyl alcohol was allowed to evaporate, and the cooled, filtered solution was made alkaline with ammonia and extracted with ether. The extract was dried with sodium sulphate, the solvent removed, and the crystalline residue recrystallised from a little absolute ethyl alcohol. The *indole* derivative (VIII) separated with solvent of crystallisation in colourless, slender prisms (1 g.) which melted at 85°, resolidified, and remelted at 132° (Found: loss at 90°, 12·7. $C_{19}H_{22}O_2N_2,C_2H_5{\cdot}OH$ requires loss, 12·8%. Found in material dried at 90°: C, 73·5; H, 7·4. $C_{19}H_{22}O_2N_2$ requires C, 73·5; H, 7·3%). This substance does not give the carbylamine reaction, but it shows characteristic indole reactions, *e.g.*, a violet coloration in the pine shaving test and a deep pink coloration in dilute hydrochloric acid on treatment with *p*-dimethylaminobenzaldehyde hydrochloride. The *hydrochloride* separated from a concentrated solution of the base (VIII) in ethyl-alcoholic hydrogen chloride in colourless, slender needles, which retained alcohol of crystallisation, melted at about 105°, resolidified, and remelted at a higher but somewhat indefinite temperature (Found in air-dried material: loss at 100°, 9·5; Cl, 9·0. $C_{19}H_{22}O_2N_2,HCl,C_2H_5{\cdot}OH$ requires loss, 11·7;

Cl, 9·0%. Found in material dried at 100°: C, 65·6; H, 6·7. $C_{19}H_{22}O_2N_2$,HCl requires C, 65·8; H, 6·6%). The *monoacetyl* derivative separated as a white solid when an excess of acetic anhydride was allowed to react with a benzene solution of the base (VIII) for 3 days at room temperature. The mixture was shaken with ammonia, the solid collected, and a further quantity obtained by concentration of the benzene layer of the filtrate. The acetyl derivative crystallised from methyl alcohol, in which it was moderately easily soluble, in small prisms, m. p. 138° (Found: C, 71·4; H, 6·8. $C_{21}H_{24}O_3N_2$ requires C, 71·6; H, 6·8%). It is quite devoid of basic properties and resists hydrolysis by dilute aqueous acids and alkalis.

2-(4′ : 5′-*Dimethoxy*-2′-β-*methylaminoethyl*)*phenyl*-3-*oximinoindole* (IX).—When the base (VIII) was dissolved in dilute hydrochloric acid and treated with sodium nitrite, a deep blood-red solution was obtained, the colour of which was not destroyed by boiling. The solution contained no diazonium salt, since no azo-dye was precipitated on adding it to an alkaline solution of β-naphthol. Before the nature of the base (VIII) was established, an attempt was made to bring about the Pschorr reaction, and the *oximino*-derivative (IX) was isolated from the experiment. The hydrochloride (0·2 g.) of the base (VIII), dissolved in 2*N*-sulphuric acid (5 c.c.) and methyl alcohol (5 c.c.), was diazotised below 0° by the gradual addition of the calculated quantity of *N*/20-sodium nitrite (freshly standardised); water (10 c.c.) was added, the solution warmed on the water-bath for 30—40 minutes, cooled, made alkaline with sodium hydroxide, and the slight precipitate extracted twice with ether. The extract was washed with water and dried with potassium carbonate, and the solvent removed; the residual yellow gum deposited colourless needles, m. p. 177—178°, after rubbing with warm ethyl alcohol. A much larger quantity of the oximino-derivative (IX) was obtained by adding solid ammonium chloride to the sodium hydroxide solution, and extracting the colourless solid precipitate with much ether. The extract, which showed a magnificent blue fluorescence, was dried with potassium carbonate, and concentrated until the solution was filled with a mass of colourless needles, m. p. 178° (Found: C, 67·0; H, 6·5. $C_{19}H_{21}O_3N_3$ requires C, 67·2; H, 6·2%). The oximino-compound (IX) is sparingly soluble in ether or ethyl alcohol. It dissolves in dilute hydrochloric acid to a strawberry-coloured solution, and slowly in sodium hydroxide, giving a pale yellow solution, from which it is precipitated by the addition of ammonium chloride. With phenol and concentrated sulphuric acid a yellow coloration was observed, but the characteristic nitroso-reaction was absent.

2'-Amino-6 : 7-dimethoxy-1-benzyl-2-methyltetrahydroisoquinoline (X).—The methiodide (VII) (8 g.), suspended in hot water (80 c.c.) and concentrated hydrochloric acid (160 c.c.), was gradually treated with zinc dust (25 g.) with vigorous shaking. The liquid was filtered, made alkaline with ammonia, cooled, and extracted with ether, the extract dried with sodium sulphate, and the solvent removed. The *base* (X) remained as an oil which could not be crystallised. The *dihydrochloride* was prepared by treating the base with alcoholic hydrogen chloride; it was readily soluble in water, but very sparingly soluble in absolute alcohol, from which it separated in small, colourless prisms, m. p. 243—244° (decomp.) (Found: C, 59·3; H, 6·7. $C_{19}H_{24}O_2N_2,2HCl$ requires C, 59·2; H, 6·7%). A solution of the dihydrochloride, when diazotised, formed a pale orange-coloured solution, which deposited a crimson azo-dye on being poured into an alkaline solution of β-naphthol; the dye dissolved in concentrated sulphuric acid, producing an intense magenta solution. The *monoacetyl* derivative was prepared by the action of the calculated amount of acetic anhydride on an ethereal solution of the base (X). After 2 hours, the acetate which separated was decomposed with ammonia, and the ether removed in a current of air; the acetyl derivative crystallised from methyl alcohol in splendid, colourless prisms, m. p. 153—154° (Found: C, 71·1; H, 7·5. $C_{21}H_{26}O_3N_2$ requires C, 71·1; H, 7·5%). This acetyl derivative is basic; it dissolves in cold dilute hydrochloric acid to a colourless solution, from which it is precipitated by the addition of alkali.

2-(4' : 5'-Dimethoxy-2'-β-methylaminoethyl)phenyldihydroindole (XI).—The *dihydrochloride* of this base gradually separated from the alcoholic hydrogen chloride mother-liquor from which the dihydrochloride of the base (X) had crystallised. It separated from ethyl alcohol, in which it was readily soluble, in colourless prisms which softened slightly at 180° and melted with evolution of gas but no darkening at 186° (Found in material dried at 100°: C, 59·2; H, 6·8. $C_{19}H_{24}O_2N_2,2HCl$ requires C, 59·2; H, 6·7%). The *base* was liberated as an oil by the addition of sodium hydroxide to an aqueous solution of the hydrochloride. It gave no coloration with a pine shaving or with *p*-dimethylaminobenzaldehyde. The addition of sodium nitrite to a solution of the dihydrochloride in dilute sulphuric acid produced a pale yellow solution which did not couple with alkaline β-naphthol. From the solution, basified with ammonia, ether extracted a *nitrosoamine*, a light brown oil which gave the Liebermann nitroso-reaction. The nitroso-group is probably connected to the methylamino-group, as we were unable to isolate a migration product by the action of alcoholic hydrogen chloride.

5 : 6-*Dimethoxyaporphine* (XII).—(*a*) A mechanically stirred solution of the base (X) (from 7·5 g. of dihydrochloride) in 2*N*-sulphuric acid (30 c.c.) was mixed with ice (60 g.) and diazotised by the calculated amount of 2*N*-sodium nitrite (freshly standardised). Copper powder (3 g.) was added to the orange-coloured solution, nitrogen was evolved, and after 6 hours the filtered mixture was reduced with zinc dust (3 g.) and concentrated hydrochloric acid (10 c.c.), and again filtered. The filtrate was made alkaline with ammonia, and thoroughly extracted with ether. Objectionable emulsions, which often made filtration necessary, were produced at this stage, since large quantities of the dilaudanosine derivative separated as a brown amorphous powder. The ethereal extract was washed with sodium hydroxide to remove a small amount of phenolic base, dried with sodium sulphate, and concentrated, and the brown, oily residue mixed with 50% hydrochloric acid (30 c.c.). After 12 hours, the *hydrochloride* of 5 : 6-dimethoxyaporphine (XII) was collected, washed with 50% hydrochloric acid, and recrystallised from hot water (yield 0·7 g.).

(*b*) The dihydrochloride (8 g.) of the base (X) in 2*N*-sulphuric acid (40 c.c.) and methyl alcohol (40 c.c.) was cooled below 0° and treated with the calculated amount of 2*N*-sodium nitrite. The orange-coloured solution was heated on the water-bath for ½ hour, reduced with zinc (4 g.) and concentrated hydrochloric acid (12 c.c.), and filtered, and the pale yellow solution was made alkaline with ammonia and extracted with ether. No dilaudanosine derivative was precipitated, but a large amount of phenolic base was removed by washing the ethereal extract with sodium hydroxide. The ether was dried with sodium sulphate and evaporated, 50% hydrochloric acid (30 c.c.) was added to the residual brown oil, and the hydrochloride (1·2 g.) was isolated as described above in method (*a*). 5 : 6-*Dimethoxyaporphine* (XII) was precipitated by the addition of sodium hydroxide to an aqueous solution of the hydrochloride. The oil, which rapidly hardened, was extracted with ether, the extract dried with sodium sulphate, and the solvent removed until 5 : 6-dimethoxyaporphine began to separate in colourless, large, stout, rhombic prisms, m. p. 136—137° (Found: C, 77·1; H, 7·1. $C_{19}H_{21}O_2N$ requires C, 77·3; H, 7·2%). The base gives a colourless solution in concentrated sulphuric acid, a pinkish-purple coloration with Erdmann's reagent, a deep bluish-purple with Frohde's reagent, and a green coloration, which rapidly turns brown, with Mandelin's reagent. The *hydrochloride* is sparingly soluble in water, from which it separates in colourless, small prisms, m. p. 258° (decomp.) (Found: C, 68·8; H, 6·6; Cl, 10·7. $C_{19}H_{21}O_2N$,HCl requires C, 68·8; H, 6·6; Cl, 10·7%). The *methiodide* was prepared by reflux-

ing the base (XII) for a few minutes with an excess of methyl iodide; the excess of methyl iodide was removed, and the solid residue recrystallised from absolute alcohol, from which the methiodide separated in magnificent, colourless, hexagonal plates, m. p. 223° (Found : C, 55·0; H, 5·5. $C_{20}H_{24}O_2NI$ requires C, 54·9; H, 5·5%).

One of us (R. D. H.) wishes to thank the Research Fund Committee of the Chemical Society for a grant, which has defrayed some of the cost of this investigation.

THE UNIVERSITY OF DURHAM,
ARMSTRONG COLLEGE,
NEWCASTLE-UPON-TYNE.

THE DYSON PERRINS LABORATORY,
OXFORD.

[*Received, December 22nd*, 1927.]

PRINTED IN GREAT BRITAIN BY RICHARD CLAY & SONS, LIMITED,
BUNGAY, SUFFOLK.

THE CONSTITUTION OF THEBENINE.

BY
JOHN MASSON GULLAND
AND
CYRIL JOSEPH VIRDEN.

Publication 10

Part of the work described in this paper was carried out by me, part by Mr. C. J. Virden under my daily direction

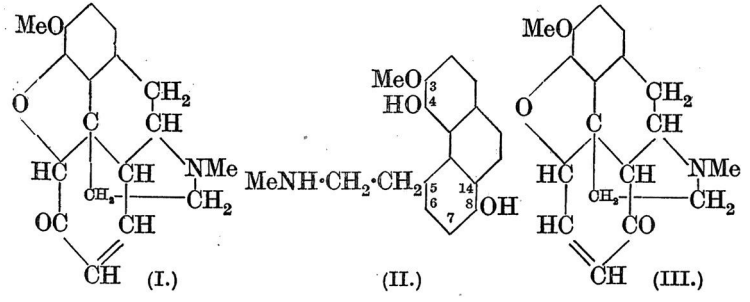
Reprinted from the Journal of the Chemical Society,
April 1928.

Reprinted from the Journal of the Chemical Society, 1928.

CXXII.—*The Constitution of Thebenine.*

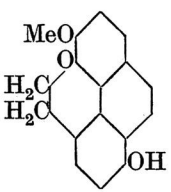
By John Masson Gulland and Cyril Joseph Virden.

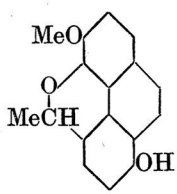
Of the surprising degradations which are found in the chemistry of the morphine alkaloids, perhaps the most remarkable is that in which thebenine (II) is formed (*a*) from thebaine, or (*b*) from codeinone (I), the first product of the hydrolysis of thebaine, or (*c*) from *pseudo*codeinone (III).



In the cases (*a*) and (*b*) the conversion readily takes place on heating for a short time with dilute hydrochloric acid (Freund, *Ber.*, 1897, **30**, 1357; 1899, **32**, 168; Knorr, *ibid.*, 1903, **36**, 3074), whereas in (*c*) boiling acetic anhydride is necessary (Knorr and Hörlein, *ibid.*, 1907, **40**, 2037), and the product contains an aromatic phenanthrene nucleus in which the C–C–N group of the parent substance is present in the form of a side chain. The researches of Pschorr and his collaborators (*Ber.*, 1904, **37**, 2780; 1907, **40**, 2001; *Annalen*, 1910, **373**, 51, 75) have demonstrated conclusively the

positions occupied by the methoxyl and hydroxyl groups of thebenine, but the allocation of the side chain to position 5 is based on less definite evidence. It depends on the fact that the product of the exhaustive methylation of thebenine is thebenol, in which the initial vinyl group has reacted further with one of the phenolic hydroxyls. Pschorr (*loc. cit.*) has shown that it is the hydroxyl in position 4, not that in position 8, which is involved in this ring formation, and he assigned to thebenol the formula (IV). In view of the ease of formation and stability of six-membered oxide rings, we prefer to adopt the formula (V) (compare Cahn, J., 1926, 2562). From stereochemical considerations, therefore, and from the fact that thebenol is converted into pyrene when distilled with zinc dust or reduced by hydriodic acid and phosphorus (Freund, *Ber.*, 1897, **30**, 1357; 1910, **43**, 2128), it seems probable that the side chain of thebenine is in position 5, and the experiments which are described in this paper have shown beyond doubt that this is actually the case.

(IV.) 

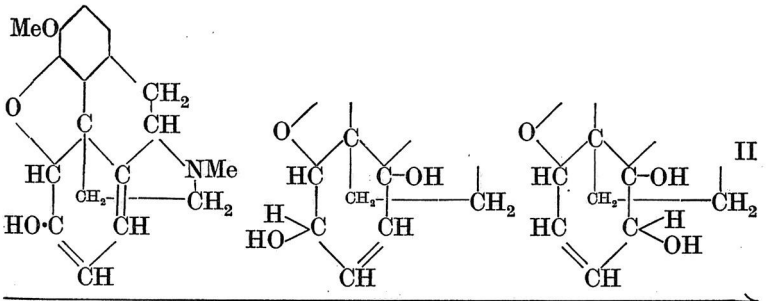


(V.)

Before describing this work in detail, it is necessary to mention two experiments made in order to test the accuracy of a mechanism which has recently been suggested for the thebenine transformation. Schöpf and Borkowsky (*Annalen*, 1927, **458**, 148) explain the formation of thebenine from codeinone by 1 : 4-addition of water (VIa) to the conjugated system produced in an enolic form of codeinone (VI), followed by the codeine–*pseudo*codeine transformation (VIb). The stage (VIa) is the formula which must now be given to the hydroxycodeine * which is obtained by the reduction of 14-hydroxycodeinone (Freund and Speyer, *J. pr. Chem.*, 1916, **94**, 135; Speyer, Selig, and Heil, *Annalen*, 1922, **430**, 1; compare Gulland and Robinson, *Mem. Manchester Phil. Soc.*, 1925, **69**, No. 10), and it seemed interesting to test this theory by direct experiment. We have found that 14-hydroxycodeine is quite unaffected by boiling hydrochloric acid (*d* 1·07, the strength used in the preparation of thebenine), and that prolonged heating with acetic anhydride yields no triacetylthebenine, but a mixture of two *bases*, one crystalline, the other amorphous, which are still under

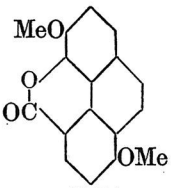
* Assuming that this substance is an unsaturated alcohol.

investigation. A consideration of these facts leads us to believe that Schöpf's theory is improbable.

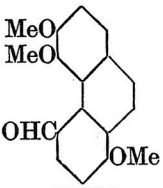


The comparative experiments described in this paper were based in the first instance on the analogous work which has been carried out with *apo*morphine and morphothebaine—the methylation of the phenolic hydroxyl groups, the elimination of the nitrogen atom by exhaustive methylation, the conversion of the resulting vinyl group into methoxyl through the stages of carboxylic acid, hydrazide, azide (Curtius, *Ber.*, 1894, **27**, 778), and the comparison of the methoxyphenanthrene thus obtained with a phenanthrene derivative synthesised by Pschorr's method (*Ber.*, 1896, **29**, 496). Pschorr and his collaborators have converted methebenine, the 8-methyl ether of thebenine, into 3 : 4 : 8-trimethoxy-5-vinylphenanthrene, and have oxidised this to 3 : 4 : 8-trimethoxyphenanthrene-5-carboxylic acid. We have experienced no difficulty in preparing these compounds by the same methods, and the *methyl* ester of the acid readily yielded the corresponding *hydrazide*. A solution of this substance in glacial acetic acid on the addition of sodium nitrite deposited the *azide* as an oil which soon crystallised. When the azide was warmed with ethyl alcohol, nitrogen was evolved, but instead of the expected urethane, a crystalline non-nitrogenous substance, $C_{17}H_{12}O_4$, separated in almost theoretical yield. The same compound was obtained when the azide was heated slowly to 65°, or when methyl or amyl nitrite acted on the hydrazide in alcoholic hydrogen chloride solution. Since this substance contains only two methoxyl groups, and dissolves in methyl-alcoholic potash, although scarcely soluble in methyl alcohol, we regard it as the *lactone* of 4-hydroxy-3 : 8-dimethoxyphenanthrene-5-carboxylic acid (VII), and some confirmation of this view is obtained from its formation in the acid hydrolysis of 3 : 4 : 8-trimethoxy-5-cyanophenanthrene (see below), and from the facility with which the same methoxyl is hydrolysed when

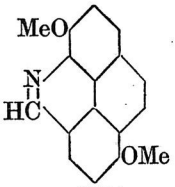
methebenol is produced by the crystallisation from acetic acid of the trimethoxyvinylphenanthrene mentioned above.



(VII.)



(VIII.)

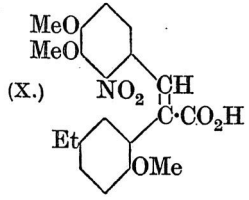


(IX.)

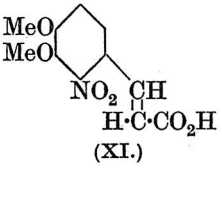
The chief product of the oxidation of 3 : 4 : 8-trimethoxyvinylphenanthrene is a non-acidic substance, $C_{18}H_{16}O_4$, which Pschorr termed "oxymethebenol," but which we have shown by the preparation of an *oxime* and a *semicarbazone* to be 5-*aldehydo*-3 : 4 : 8-*trimethoxyphenanthrene* (VIII). The poor yield (20—30%) of trimethoxyphenanthrenecarboxylic acid led us to try to prepare it from this aldehyde by oxidation, but in this we were unsuccessful in spite of a number of attempts. An indirect method of oxidation was therefore attempted; the oxime of (VIII) yielded 3 : 4 : 8-*trimethoxy*-5-*cyanophenanthrene* on dehydration by boiling with acetic anhydride and sodium acetate, but this compound appeared to be stable to boiling alcoholic potash, and was converted into (VII) either by boiling with a mixture of hydrochloric and acetic acids, or by hydrolysing the corresponding imino-ester hydrochloride. A by-product of the dehydration of the oxime was a base, $C_{17}H_{13}O_2N$, the properties of which were so reminiscent of those of thebenidine (Vongerichten, *Ber.*, 1901, **34**, 767) that we consider the substance to be 3 : 8-*dimethoxythebenidine* (IX), or the isomeride in which the CH and N are transposed. This transposition is analogous to the rearrangement which takes place when *iso*quinoline is produced by the dehydration of cinnamaldoxime (Bamberger and Goldschmidt, *Ber.*, 1894, **27**, 1954).

The experiments described above indicated that the conversion of methebenine into 3 : 4 : 5 : 8-tetramethoxyphenanthrene was impracticable, and we decided therefore to modify the original scheme. 3 : 4 : 8-Trimethoxy-5-vinylphenanthrene was reduced catalytically to 3 : 4 : 8-*trimethoxy*-5-*ethylphenanthrene*, which proved to be identical with a specimen prepared synthetically. The materials required for this synthesis were 2-nitroveratraldehyde (Pschorr and Sumuleanu, *Ber.*, 1899, **32**, 3405; Pisovschi, *ibid.*, 1910, **43**, 2137) and 6-methoxy-3-ethylphenylacetic acid, and the starting point for the preparation of this acid was *p*-ethylanisole, obtained by the reduction of *p*-methoxyacetophenone by Clemmensen's method (*Ber.*, 1914, **47**, 51). This was converted into

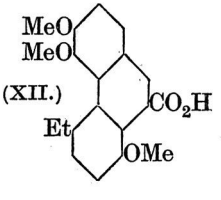
6-*methoxy*-3-*ethylbenzaldehyde* by the modification of Gattermann's aldehyde synthesis which has been introduced by Adams and Levine (*J. Amer. Chem. Soc.*, 1923, **45**, 2373; 1924, **46**, 1518), and the aldehyde yielded 6-*methoxy*-3-*ethylphenylacetic acid* in good yield through the intermediate stages of *azlactone* and 6-*methoxy*-3-*ethylphenylpyruvic acid*. The condensation of 2-nitroveratraldehyde with sodium 6-methoxy-3-ethylphenylacetate by heating at 100° with acetic anhydride results in a mixture of trans-α-(6′-*methoxy*-3′-*ethylphenyl*)-2-*nitro*-3 : 4-*dimethoxycinnamic acid* (X) and trans-2-*nitro*-3 : 4-*dimethoxycinnamic acid* (XI). Some derivatives of the second acid (XI) are described in the experimental part of this paper. On reduction with ferrous sulphate and ammonia, the acid (X) yielded trans-α-(6′-*methoxy*-3′-*ethylphenyl*)-2-*amino*-3 : 4-*dimethoxycinnamic acid*, and an aqueous methyl-alcoholic solution of the diazonium sulphate of this amino-acid deposited 3 : 4 : 8-*trimethoxy*-5-*ethylphenanthrene*-9-*carboxylic acid* (XII) on boiling or on addition of copper powder. This acid (XII) lost carbon dioxide when its solution in glacial acetic acid was heated at 230°, and the resulting 3 : 4 : 8-*trimethoxy*-5-*ethylphenanthrene* was identical with the preparation obtained from thebaine.



(X.)



(XI.)



(XII.)

EXPERIMENTAL.

The Action of Hydrochloric Acid and Acetic Anhydride on 14-*Hydroxycodeine*.—This base, prepared according to Speyer, Selig, and Heil (*loc. cit.*), was recovered unchanged when ammonia was added to a solution in hydrochloric acid (*d* 1·07) which had been boiled under reflux for 2 hours. It was therefore refluxed with ten times its weight of acetic anhydride for 8 hours; the addition of water to the solution obtained precipitated no non-basic material. Ammonia was added, the precipitate was taken up in chloroform, washed with water, and dried with sodium sulphate, and the solvent was evaporated. When the resinous residue was rubbed with hot alcohol, part dissolved (see below) and part separated in colourless needles, which were collected and recrystallised from ethyl alcohol; m. p. 304° (Found: C, 68·0; H, 5·9%). These figures are in agreement with a number of possibilities, and the substance is still under examination. It is readily

soluble in dilute acetic or hydrochloric acid, and is very sparingly soluble in cold alcohol.

The alcoholic mother-liquor (see above) was evaporated to dryness, and the residue was dissolved in ether, dried, and freed from solvent by distillation. It was a pale yellow oil which dissolved in dilute acetic and hydrochloric acids, and was readily soluble in the usual solvents except ligroin; from this it separated as an oil when a hot solution was cooled. The picrate, hydrochloride, hydriodide, and perchlorate were amorphous.

3 : 4 : 8-*Trimethoxy*-5-*vinylphenanthrene*.—In preparing the stages intermediate between this substance and thebaine, we have followed closely the details given by Freund and Holthoff (*Ber.*, 1899, **32**, 168) and Pschorr and Massaciu (*Ber.*, 1904, **37**, 2780), but throughout the series of reactions we have been able to improve the yields. Pschorr's method of preparing trimethoxyvinylphenanthrene proved unsatisfactory, and the following process was found more suitable. Dimethylmethebenine methosulphate (m. p. 283—285°; Pschorr and Massaciu give m. p. 268—270°) (12 g.) and *sodium* hydroxide solution (200 c.c. of 20%) were boiled gently under reflux for 12 hours; during the reaction the vinylphenanthrene separated in small, colourless needles (yield, 76%), m. p. 121° (Pschorr gives 122·5° corr.).

3 : 4 : 8-Trimethoxyphenanthrene-5-carboxylic acid (m. p. 236—237°) was obtained as described by Pschorr, Loewen, and Rettberg (*Annalen*, 1910, **373**, 51; m. p. 224—226°) by the oxidation by permanganate of 3 : 4 : 8-trimethoxy-5-vinylphenanthrene in acetone solution. The *methyl* ester separated when a solution of the acid in methyl-alcoholic hydrogen chloride was boiled for 18 hours and allowed to cool. After recrystallisation from methyl alcohol, it melted at 149—151°.

The *hydrazide* was prepared by boiling under reflux for 18 hours a mixture of equal weights of the ester, hydrazine hydrate, and ethyl alcohol. It separated on cooling, and crystallised from ethyl alcohol in colourless needles, m. p. 177° (Found : N, 8·4. $C_{18}H_{18}O_4N_2$ requires N, 8·6%).

The *azide* was obtained by the gradual addition of sodium nitrite solution (1·5 c.c. of 5*N*) to a cooled solution of the hydrazide (0·5 g.) in glacial acetic acid (5 c.c.). It separated as an oil which crystallised rapidly, and was collected, washed, and dried on porous tile. The azide decomposed smoothly at 65° when heated slowly (see below), but exploded at 80° if suddenly immersed in a bath at that temperature.

5-*Aldehydo*-3 : 4 : 8-*trimethoxyphenanthrene* (VIII).—The acetone filtrate from the preparation of the trimethoxyphenanthrene-

carboxylic acid was evaporated to dryness, and the residual oil, which crystallised on rubbing, was recrystallised first from ethyl alcohol and then from benzene–ligroin. The aldehyde formed colourless plates, m. p. 151°, which were readily soluble in benzene (Found: C, 72·9; H, 5·5. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%).

The *semicarbazone* separated in colourless needles when an aqueous-alcoholic solution of the aldehyde and an excess of semicarbazide hydrochloride and sodium acetate were heated on the water-bath for 2 hours. It was sparingly soluble in the usual solvents, but was recrystallised from nitrobenzene; m. p. 243—246° (decomp.) (Found: N, 11·8. $C_{19}H_{19}O_4N_3$ requires N, 11·6%).

The *oxime* was prepared by boiling under reflux for 2 hours a mixture of the aldehyde, a slight excess of hydroxylamine hydrochloride and potassium acetate, and aqueous alcohol; water precipitated the crude product as an oil which soon crystallised. After drying in a vacuum desiccator, the oxime was crystallised repeatedly from benzene, and dried in a vacuum desiccator, being obtained in dull yellow, lozenge-shaped leaflets, which softened at 110°, became pasty at 140—142°, and were molten at 153° (Found: loss at 100°, 11·5. $C_{18}H_{17}O_4N,\frac{1}{2}C_6H_6$ requires loss, 12·2%. Found in material dried at 100°: N, 4·9. $C_{18}H_{17}O_4N$ requires N, 5·0%). It dissolved readily in warm 2*N*-sodium hydroxide; on cooling, the *sodium* salt separated in cream-coloured leaflets, which redissolved on addition of water.

3 : 4 : 8-*Trimethoxy*-5-*cyanophenanthrene*.—The oxime described above (4 g.), anhydrous sodium acetate (4 g.), and acetic anhydride (20 c.c.) were boiled under reflux for 6½ hours. After the product had been cooled and mixed with water, the crystalline *nitrile* was collected, washed, pressed on tile (3·5 g.), and crystallised twice from methyl alcohol, forming pale brown needles, m. p. 145—146° (Found: C, 73·8; H, 5·4. $C_{18}H_{15}O_3N$ requires C, 73·7; H, 5·1%). The nitrile dissolved readily in benzene, forming a solution which exhibited a blue fluorescence, but was sparingly soluble in ether. It crystallised unchanged when a solution in aqueous methyl-alcoholic potash which had been boiled on the water-bath for 5 hours was cooled.

The orange-coloured acid mother-liquor from the preparation of the nitrile contained a small quantity of a base, probably 3 : 8-*dimethoxythebenidine* (IX), which was precipitated by ammonia as a yellow, flocculent mass. This substance was extracted by chloroform, and, after being dried by anhydrous sodium sulphate, it separated as orange-yellow leaflets during the concentration of the solvent. When recrystallised from methyl alcohol, it formed orange leaflets, m. p. 229—230° (Found in material dried at 100°: C, 77·1;

H, 5·1; N, 5·2. $C_{17}H_{13}O_2N$ requires C, 77·6; H, 4·9; N, 5·3%). The properties of this base closely resemble those of thebenidine (Vongerichten, *loc. cit.*). It formed an orange-yellow solution in dilute hydrochloric acid, from which it was precipitated unchanged by alkali, and the colour of the acid solution was almost completely discharged on reduction by tin. The base did not appear to react with nitrous acid. It exhibited pronounced fluorescence in different solvents: in very dilute hydrochloric acid, green; in concentrated sulphuric acid, an intense emerald-green; in chloroform, blue.

The *picrate* separated from a methyl-alcoholic solution of the base and picric acid in wart-like nodules; after recrystallisation from methyl alcohol (bright green fluorescence), it formed orange needles, m. p. 255° (decomp.).

Lactone of 4-Hydroxy-3 : 8-dimethoxyphenanthrene-5-carboxylic Acid (VII).—This substance was obtained from derivatives of 3 : 4 : 8-trimethoxyphenanthrene-5-carboxylic acid in the following ways: (i) A small quantity of the azide was heated gently to 65° and maintained at that temperature until the evolution of gas ceased.

(ii) Methyl nitrite was passed into an ice-cold solution of the hydrazide (2 g.) in alcoholic hydrogen chloride (70 c.c. of 0·3*N*), or alternatively amyl nitrite (0·2 c.c.) was added to an ice-cold solution of the hydrazide (0·1 g.) in alcoholic hydrogen chloride (5 c.c. of 0·5*N*). In either case, on standing overnight, the lactone separated in practically theoretical yield.

(iii) The nitrile (1 g.) was heated on a sand-bath for 6 hours with concentrated hydrochloric acid (15 c.c.) and glacial acetic acid (15 c.c.). The lactone, part of which separated during the reaction, was completely precipitated by the addition of water.

(iv) An ice-cold solution of the nitrile (1 g.) in dry benzene (100 c.c.) and methyl alcohol (2 c.c.) was saturated with dry hydrogen chloride. Next day the light brown needles of the imino-ester hydrochloride (1 g.) were collected, washed with benzene, and dissolved in 50 c.c. of water. When the solution was warmed on the water-bath, the lactone separated in crystalline condition.

The *lactone*, prepared by any of the methods just described, crystallised from glacial acetic acid, in which it was very sparingly soluble when cold, in faintly yellow needles, m. p. 246—247° (Found: C, 72·9; H, 4·3; *M* in camphor by Rast's method, 267. $C_{17}H_{12}O_4$ requires C, 72·9; H, 4·3%; *M*, 280). It was very sparingly soluble in boiling methyl alcohol and insoluble in boiling sodium hydroxide solution, but dissolved readily in hot methyl-alcoholic potash and did not separate on cooling. On addition of water, a clear solution was obtained which immediately began to deposit the unchanged

lactone in an amorphous condition; presumably the potassium salt of the phenolic acid is hydrolysed in aqueous solution. In estimating methoxyl by Zeisel's method, it was necessary to prolong the reaction for a number of hours at 150—160° [Found: OMe, 20·9. $C_{15}H_6O_2(OMe)_2$ requires OMe, 22·1%]. The demethylated substance, presumably the *lactone* of 3 : 4 : 8-trihydroxyphenanthrene-5-carboxylic acid, crystallised from the hydriodic acid, and after being collected and washed with sodium thiosulphate solution, crystallised from ethyl alcohol in colourless needles; it decomposed from 305° onwards, and formed a yellow solution in sodium hydroxide, but was insoluble in bicarbonate solution.

p-*Ethylanisole.*—*p*-Methoxyacetophenone (25 g.) (Gattermann, *Ber.*, 1890, **23**, 1202) was heated on the water-bath for several hours with amalgamated zinc (100 g.) and concentrated hydrochloric acid (Clemmensen, *loc. cit.*), and after being decanted from the excess of zinc the mixture was steam-distilled. Ethylanisole passed over and was taken up in ether, dried with potassium carbonate, and distilled, being obtained as a colourless oil, b. p. 199—200° (Moschner, *Ber.*, 1901, **34**, 1257, gives b. p. 199—200°, and Klages, *ibid.*, 1903, **36**, 3584, b. p. 196—197°). The yield was 40% of that theoretically possible, and there remained a considerable non-volatile residue (compare Steinkopf and Wolfram, *Annalen*, 1923, **430**, 113). Attempts to improve the yield by modifying the conditions were unsuccessful, and the method of Gilman and Hoyle (*J. Amer. Chem. Soc.*, 1922, **44**, 2621) using magnesium, bromoanisole, and ethyl sulphate proved unsatisfactory.

6-*Methoxy*-3-*ethylbenzaldehyde.*—The aldehydo-group was introduced into *p*-ethylanisole by the method of Adams and Levine (*loc. cit.*). A mixture of *p*-ethylanisole (50 g.), zinc cyanide (95 g.), and dry benzene (350 c.c.) was stirred mechanically in a flask fitted with an inlet for dry hydrogen chloride, an efficient stirrer passing through a mercury seal, and an outlet tube connected through a reflux condenser with a Woulff's bottle containing sulphuric acid. The stirred mixture was saturated with hydrogen chloride (24 hours), aluminium chloride (80 g.) added, and the flask warmed at 50° for 12 hours while the mixture was again saturated with hydrogen chloride. The stirring was then stopped, and next day the upper of the two layers into which the mixture had separated was poured off, and the dark-coloured lower one was hydrolysed by boiling hydrochloric acid (150 c.c. of 3*N*) and submitted to steam distillation. The residual benzene distilled rapidly, and then 6-methoxy-3-ethylbenzaldehyde passed over slowly, and was taken up in ether. The crude oil left by distillation of the ether was converted into the

bisulphite compound, which separated from the hot sodium bisulphite solution on cooling and was then hydrolysed by hot hydrochloric acid. The resulting oil was extracted with ether, washed with water, and dried, and the removal of the ether left the aldehyde (yield 55%), which was converted directly into the azlactone.

6-Methoxy-3-ethylbenzaldehyde is an oil, b. p. 261—262°, which was analysed in the form of its *semicarbazone*. The aldehyde (1 g.), semicarbazide hydrochloride (3 g.), and sodium acetate (4 g.) in aqueous alcohol were heated on the water-bath for 2 hours. The semicarbazone, which separated on cooling, crystallised from ethyl alcohol in colourless needles, m. p. 226—227° (Found : N, 19·2. $C_{11}H_{15}O_2N_3$ requires N, 19·0%).

5-*Keto*-2-*phenyl*-4-(6′-*methoxy*-3′-*ethylbenzylidene*)-4 : 5-*dihydro-oxazole*, $MeO{\cdot}C_6H_3Et{\cdot}CH{:}C\begin{array}{l}N{:}CPh\\CO\end{array}O$.—This azlactone was obtained by heating together on a water-bath for 30 minutes 6-methoxy-3-ethylbenzaldehyde (10 g.), hippuric acid (12 g.), fused sodium acetate (12 g.), and acetic anhydride (20 c.c.). The yellow solid produced was washed with cold alcohol and repeatedly with boiling water. Further treatment was unnecessary for the next stage, but the azlactone crystallised from acetic acid, ethyl acetate, or ethyl alcohol in bright yellow needles, m. p. 159° (Found : N, 4·5. $C_{19}H_{17}O_3N$ requires N, 4·6%).

6-*Methoxy*-3-*ethylphenylpyruvic acid*,

$$MeO{\cdot}C_6H_3Et{\cdot}CH_2{\cdot}CO{\cdot}CO_2H,$$

was prepared from the azlactone (10 g.) by boiling with sodium hydroxide solution (50 c.c. of 10%) for 12 hours. The *sodium* salt of the acid, which separated in colourless plates, m. p. 184°, when the dark liquid was allowed to remain for some hours, was recrystallised from water (Found : loss at 100° after drying in a vacuum desiccator, 3·4. $C_{12}H_{13}O_4Na,\frac{1}{2}H_2O$ requires loss, 3·6%. Found in dried material : Na, 9·2. $C_{12}H_{13}O_4Na$ requires Na, 9·4%). The *acid* was obtained as an oil, which slowly crystallised in needles, by acidifying an aqueous solution of the salt, and the alkaline liquor from which the salt had separated after the hydrolysis of the azlactone yielded a further quantity of the acid when acidified by sulphur dioxide (Haworth, Perkin, and Rankin, J., 1924, **125**, 1686). The total yield was 70% of that theoretically possible.

6-Methoxy-3-ethylphenylpyruvic acid dissolved readily in ethyl alcohol, ether, acetone, or acetic acid, but was somewhat less soluble in methyl alcohol, and crystallised from this solvent in yellow prisms, m. p. 185°, which liquefied on being kept for a short time. Satisfactory analyses of the acid could not be obtained, and it was

therefore analysed in the form of 3-*hydroxy*-2-(6′-*methoxy*-3′-*ethylbenzyl*)*quinoxaline*, $MeO{\cdot}C_6H_3Et{\cdot}CH_2{\cdot}C\begin{matrix}N\text{——}C_6H_4\\ C(OH){:}N\end{matrix}$, which separated when a hot alcoholic solution of the acid and *o*-phenylenediamine was cooled. This substance crystallised from ethyl alcohol in very small, colourless needles, m. p. 184—185° (Found: N, 9·4. $C_{18}H_{18}O_2N_2$ requires N, 9·5%).

6-*Methoxy*-3-*ethylphenylacetic Acid*, $MeO{\cdot}C_6H_3Et{\cdot}CH_2{\cdot}CO_2H$.—An ice-cold solution of sodium 6-methoxy-3-ethylphenylpyruvate in 2*N*-sodium hydroxide was oxidised by a slight excess of 30% hydrogen peroxide diluted with four volumes of water. Next day the phenylacetic *acid* (85% yield) was precipitated in shining leaflets by dilute sulphuric acid, and was collected, dried, and recrystallised from light petroleum (b. p. 60—80°); it formed colourless leaflets, m. p. 68—69°, which readily dissolved in ethyl alcohol, ether, and benzene (Found in material dried at 100°: C, 67·9; H, 7·6. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·2%). The *sodium* salt was prepared by evaporating to dryness a solution of the acid in the requisite amount of sodium carbonate solution. It was very readily soluble in water.

The Condensation of 2-*Nitroveratraldehyde with* 6-*Methoxy*-3-*ethylphenylacetic Acid.* trans-α-(6′-*Methoxy*-3′-*ethylphenyl*)-2-*nitro*-3 : 4-*dimethoxycinnamic Acid* (X) *and* trans-2-*Nitro*-3 : 4-*dimethoxycinnamic Acid* (XI).—A mixture of sodium 6-methoxy-3-ethylphenylacetate (7 g.), 2-nitroveratraldehyde (14 g.), and acetic anhydride (80 c.c.) was heated under reflux at 100° for 72 hours. Water was then added to destroy the acetic anhydride, and the residual oil was taken up in ether. The ether was repeatedly extracted with sodium carbonate solution, and when the mixed extracts were fractionally precipitated by hydrochloric acid the *acid* (X) separated first; it was recrystallised from ethyl alcohol.

trans-α(6′-*Methoxy*-3′-*ethylphenyl*)-2-*nitro*-3 : 4-*dimethoxycinnamic acid* formed pale lemon-yellow prisms, m. p. 193—194° (Found: C, 62·6; H, 5·5. $C_{20}H_{21}O_7N$ requires C, 62·0; H, 5·4%). The acid dissolved readily in hot dilute ammonia, but on cooling, the *ammonium* salt separated in pale yellow, silky needles.

Both this acid (X) and the acid (XI) (below) have the *trans*-configuration, since on reduction they yield the corresponding amino-acids, and not the carbostyril derivatives (compare Stoermer, *Annalen*, 1915, **409**, 13).

In the fractional precipitation by acid (see above), the partly neutralised solution was decanted from the first oily precipitate when crystals began to separate. The crystals are the acid (XI), and complete precipitation yielded this acid in a comparatively pure

condition; on recrystallisation from ethyl alcohol, trans-2-*nitro*-3 : 4-*dimethoxycinnamic acid* formed colourless needles, which softened at 217° and melted at 229° (Found: C, 52·5; H, 4·4. $C_{11}H_{11}O_6N$ requires C, 52·2; H, 4·3%). This acid was identical in every way with a specimen prepared by the following method. 2-Nitroveratraldehyde (4 g.), malonic acid (6·3 g.), piperidine (0·5 c.c.), and pyridine (20 c.c.) were heated together on the water-bath for 1 hour, and the mixture was then poured into water and acidified by hydrochloric acid. The precipitated acid was collected, washed, purified by solution in sodium carbonate and reprecipitation, and crystallised from ethyl alcohol, from which it separated in pale yellow needles, m. p. 229° after softening at 217°.

2-*Amino*-3 : 4-*dimethoxycinnamic Acid* (as XI, but with NH_2 instead of NO_2).—A hot ammoniacal solution of the nitro-acid was added to a reducing mixture prepared from the theoretical quantity of ferrous sulphate ($7H_2O$)* and an excess of ammonia. After heating on the water-bath for 20 minutes, the solution was filtered, and the amino-acid precipitated by acetic acid (yield, 65%). This acid crystallised from ethyl alcohol in colourless needles, m. p. 173—178° (decomp.) (Found: N, 6·4. $C_{11}H_{13}O_4N$ requires N, 6·3%). The *hydrochloride* was sparingly soluble, and crystallised from water in colourless leaflets which charred on heating. The *acetyl* derivative was prepared by heating the acid with acetic anhydride on the water-bath for 15 minutes, precipitated with water, and crystallised from ethyl alcohol. It formed colourless needles, m. p. 253° (decomp.), which were soluble in sodium bicarbonate.

7 : 8-*Dimethoxycarbostyril*.—The amino-acid or its acetyl derivative (1 g.) was heated on the water-bath for 15 minutes with acetic anhydride (10 c.c.) and one drop of concentrated sulphuric acid. Water and an excess of sodium bicarbonate were then added; the *carbostyril*, which separated in plates, crystallised from ethyl alcohol in the same form, m. p. 166—168° (Found: N, 6·8. $C_{11}H_{11}O_3N$ requires N, 6·8%). It dissolved in dilute alkali and acid.

trans-α-(6′-*Methoxy*-3′-*ethylphenyl*)-2-*amino*-3 : 4-*dimethoxycinnamic Acid* (as X, but with NH_2 instead of NO_2).—An ammoniacal solution of the corresponding nitro-acid (X) (4·2 g.) was added to a hot reducing mixture prepared by adding ammonia (*d* 0·880; 50 c.c.) in water (35 c.c.) to ferrous sulphate (27·2 g.) in hot water (100 c.c.). After heating on the water-bath for 30 minutes, the

* Experiments on a number of reductions of this type have shown that the use of the theoretical amount of ferrous sulphate is essential. An excess of ferrous hydroxide, if present, passes through the filter, and forms ultimately the insoluble basic acetate.

mixture was filtered and the amino-acid obtained in almost theoretical yield by acidifying the filtrate with acetic acid. It was purified further by solution in hydrochloric acid and precipitation by means of sodium acetate, and after being collected, washed, and dried, was crystallised from benzene; it formed lemon-yellow, flat prisms, m. p. 151—152° (Found: C, 67·2; H, 6·4. $C_{20}H_{23}O_5N$ requires C, 67·2; H, 6·4%), which were very soluble in alcohol but insoluble in light petroleum.

3 : 4 : 8-*Trimethoxy-5-ethylphenanthrene-9-carboxylic Acid* (XII).—The calculated quantity of sodium nitrite solution (freshly standardised; approximately *N*) was added slowly to an ice-cold solution of α-(6′-methoxy-3′-ethylphenyl)-2-amino-3 : 4-dimethoxycinnamic acid (1 g.) in methyl alcohol (16 c.c.) and sulphuric acid (10 c.c. of 2*N*). The clear red solution, diluted with ice-water (30 c.c.), was divided into two parts. (i) On heating, nitrogen was evolved, and the acid (XII) separated as a gum, which crystallised from ethyl alcohol in colourless needles, m. p. 207°. (ii) Copper bronze powder was added to the second part; when the evolution of nitrogen ceased, the solution was made alkaline with sodium carbonate and filtered, and the acid (XII) precipitated by sulphuric acid. The yield in either case was about 35%, and the acid crystallised from benzene in needles, m. p. 207°, which were sparingly soluble in acetic acid (Found: C, 70·1; H, 5·8. $C_{20}H_{20}O_5$ requires C, 70·6; H, 5·9%).

3 : 4 : 8-*Trimethoxy-5-ethylphenanthrene* was obtained either by the reduction of 3 : 4 : 8-trimethoxy-5-vinylphenanthrene (from thebaine), or by the elimination of the carboxyl group of the acid (XII).

(i) A methyl-alcoholic solution of trimethoxyvinylphenanthrene (1 g.) absorbed a volume of hydrogen equivalent to one molecule when shaken in an atmosphere of the gas in presence of palladinised charcoal (6 g.), prepared as described by Oxford, Perkin, and Robinson (J., 1927, 2389). The filtered solution was evaporated to dryness; the residue crystallised from ethyl alcohol in colourless needles, m. p. 112—113° (Found: C, 77·0; H, 7·0. $C_{19}H_{20}O_3$ requires C, 77·0; H, 6·7%). A cold acetone solution of this substance resisted oxidation by potassium permanganate to a marked extent.

(ii) The acid (XII) (0·6 g.) in glacial acetic acid (30 c.c.) was heated in a sealed tube at 230° for 44 hours. The product was poured into an excess of dilute ammonia and extracted with ether. The extract, after being washed with water and dried with potassium carbonate, was distilled, yielding a dark-coloured oil which was extracted repeatedly with cold methyl alcohol in order to free the product from a black, insoluble residue. The methyl-alcoholic

solution was concentrated (charcoal), and on cooling deposited yellow columns, m. p. 165—166°; the examination of this substance is described below. The methyl-alcoholic mother-liquor was concentrated to a very small volume; 3 : 4 : 8-*trimethoxy-5-ethylphenanthrene* then separated, and after recrystallisation from ethyl alcohol (charcoal) melted at 112—113° (Found : C, 77·0; H, 7·1%). There was no depression of the melting point of a mixture of this substance with the preparation described in (i).

The substance, m. p. 165—166°, was recrystallised from ethyl alcohol, and the m. p. remained constant (Found : C, 73·9; H, 5·6%). The properties of this substance were those of a lactone; it dissolved immediately in hot dilute alcoholic sodium hydroxide, and the solution remained clear on dilution with water. Acidification with dilute sulphuric acid precipitated a yellow amorphous acid which became crystalline on standing. It was recrystallised from alcohol, from which it separated in minute prisms, m. p. 155—157° after softening at 140°. This substance dissolved in sodium carbonate, and the melting point of a mixture of it with the original compound, m. p. 165°, was depressed. The amount of material was insufficient for further examination, but it is suggested tentatively that the substance, m. p. 165°, is the *lactone* of 8-hydroxy-3 : 4-dimethoxy-5-ethylphenanthrene-9-carboxylic acid ($C_{19}H_{16}O_4$ requires C, 74·0; H, 5·2%).

One of us (C. J. V.) wishes to thank the Goldsmiths' Company for a Senior Studentship and the Department of Scientific and Industrial Research for a grant which have enabled him to take part in this research. The authors acknowledge their indebtedness to the Chemical Society for grants which have defrayed part of the cost of this investigation.

THE DYSON PERRINS LABORATORY,
OXFORD.

[*Received, February 11th*, 1928.]

PRINTED IN GREAT BRITAIN BY RICHARD CLAY & SONS, LIMITED,
BUNGAY, SUFFOLK.

SYNTHETICAL EXPERIMENTS ON THE APORPHINE GROUP. PART II. A SYNTHESIS OF BULBOCAPNINE METHYL ETHER.

BY
JOHN MASSON GULLAND
AND
ROBERT DOWNS HAWORTH.

Publication 11

Dr. R. D. Haworth carried out the experiments described in this paper.

Reprinted from the Journal of the Chemical Society,
May 1928

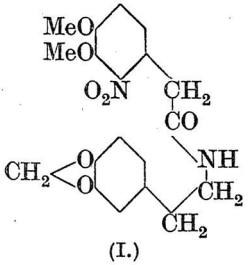
Reprinted from the Journal of the Chemical Society, 1928.

CXLIII.—*Synthetical Experiments on the Aporphine Group. Part II. A Synthesis of Bulbocapnine Methyl Ether.*

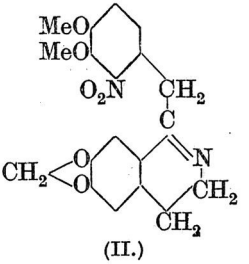
By John Masson Gulland and Robert Downs Haworth.

The synthesis of 5 : 6-dimethoxyaporphine described in Part I (this vol., p. 581) depended on the discovery of experimental conditions which allowed the Bischler–Napieralski synthesis to be utilised in the preparation of 1′-nitrobenzyl-3 : 4-dihydro*iso*quinoline bases. The present communication contains an account of an extension of the method to the synthesis of bulbocapnine methyl ether (V).

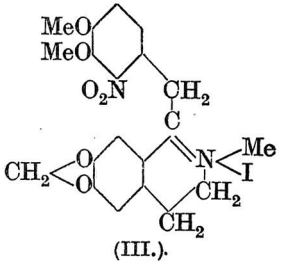
2′-*Nitro*-3′ : 4′-*dimethoxyphenylaceto*-β-3 : 4-*methylenedioxyphenylethylamide* (I) was prepared by condensing β-piperonylethylamine and 2-nitro-3 : 4-dimethoxyphenylacetyl chloride (Kay and Pictet, J., 1913, **103**, 952). By treating a cold chloroform solution of the amide (I) with phosphorus pentachloride, a good yield of 2′-*nitro*-3′ : 4′-*dimethoxy*-6 : 7-*methylenedioxy*-1-*benzyl*-3 : 4-*dihydro*isoquinoline (II) was obtained. This pale yellow crystalline base, which yielded a sparingly soluble, almost colourless, crystalline *hydrochloride*, did not undergo atmospheric oxidation. When heated in a sealed tube at 100° with methyl iodide, the base (II) was converted into the *methiodide* (III); this yielded oxyhydrastinine and 2-nitrohomoveratrole on heating with dilute alkali.



(I.)



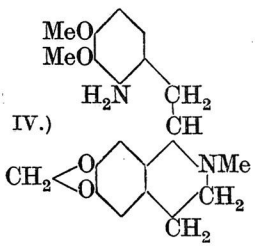
(II.)



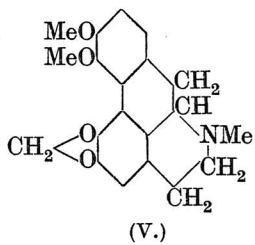
(III.)

The methiodide (III), in strongly acid solution, was reduced with zinc dust to 2′-*amino*-3′ : 4′-*dimethoxy*-6 : 7-*methylenedioxy*-1-*benzyl*-2-*methyltetrahydro*isoquinoline (IV), which, although itself an oil, yielded a crystalline *dihydrochloride*. The addition of sodium nitrite to a solution of the base (IV) in dilute hydrochloric acid yielded a diazo-solution, which coupled with alkaline β-naphthol. These facts support the constitution assigned to the base (IV) and exclude the possibility of indole formation, which was observed in Part I of this series (pp. 584, 587).

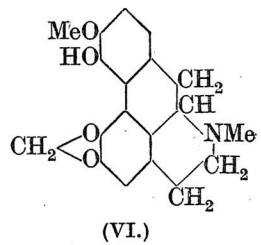
The phenanthrene ring-closure was effected by diazotising the base (IV) in a mixture of methyl alcohol and 2*N*-sulphuric acid, but considerable difficulty was experienced in the isolation of the *dl*-bulbocapnine methyl ether from the reaction mixture. Previously it had been possible to isolate the aporphine bases in the form of their sparingly soluble hydrochlorides, but the solubility of the hydrochloride of *dl*-bulbocapnine methyl ether precluded the use of this method. Eventually the alkaloid was isolated in the form of a crystalline *hydriodide*, from which *dl*-bulbocapnine methyl ether (V) was liberated by the action of sodium hydroxide.



IV.)



(V.)



(VI.)

The synthetical base crystallised from ether in well-defined rhombs, m. p. 135°, which were identical with a specimen of *dl*-bulbocapnine methyl ether, prepared from natural *d*-bulbocapnine as described by Gadamer (*Arch. Pharm.*, 1911, **249**, 508). Its colour reactions and *methiodide* also were indistinguishable from those of *dl*-bulbocapnine methyl ether prepared from naturally occurring *d*-bulbocapnine.

As Gadamer (*loc. cit.*, p. 509) has resolved *dl*-bulbocapnine methyl ether into its optically active modifications, this synthesis of the *dl*-form completes the synthesis of *d*-bulbocapnine methyl ether. The structure of *d*-bulbocapnine is therefore now limited to one of the two formulæ which are obtained by replacing one of the methoxyl groups in structure (V) by the hydroxyl group. Gadamer (*loc. cit.*) has selected formula (VI) as the more probable constitution of bulbocapnine, and we are engaged in an attempt to synthesise this base.

EXPERIMENTAL.

2-Nitro-3 : 4-dimethoxyphenylacetyl Chloride.—2-Nitroveratraldehyde was prepared as described by Pisovschi (*Ber.*, 1910, **43**, 2137), and was converted into 2-nitro-3 : 4-dimethoxyphenylacetic acid by the method of Kay and Pictet (*loc. cit.*). No attempt was made to purify the intermediate products, and the following description indicates briefly the modifications which were adopted in the preparation of large quantities of the acid. 2-Nitroveratraldehyde was subjected to the action of alcoholic potassium hydroxide as

described by Kay and Pictet, and the mixture was poured into water and extracted thoroughly with benzene. After being washed with sodium bisulphite solution, the extract was dried with sodium sulphate, and the benzene removed. The residual 2-nitro-3 : 4-dimethoxybenzyl alcohol, which solidified on cooling, was converted into the corresponding chloride by the action of phosphorus pentachloride in benzene solution; the benzene and phosphorus oxychloride were removed under diminished pressure, and the crude chloride which remained was converted into the corresponding cyanide as described by Kay and Pictet. The excess of alcohol was removed by distillation, water was added, and the cyanide extracted with benzene; the extract was dried with sodium sulphate and the benzene removed. The residual oil was sufficiently pure for conversion into 2-nitro-3 : 4-dimethoxyphenylacetic acid, more especially as the separation of the imino-ether hydrochloride provided a convenient purification.

2-Nitro-3 : 4-dimethoxyphenylacetic acid (5 g.), chloroform (20 c.c.), and thionyl chloride (3 c.c.) were warmed for 1 hour on the water-bath. The solvent was removed in a vacuum, and the residual 2-nitro-3 : 4-dimethoxyphenylacetyl chloride, which solidified on cooling, was employed without further purification for the following experiments.

2′-*Nitro*-3′ : 4′-*dimethoxyphenylaceto*-β-3 : 4-*methylenedioxyphenylethylamide* (I).—2-Nitro-3 : 4-dimethoxyphenylacetyl chloride (from 6 g. of acid) in benzene (30 c.c.) was gradually added to a cooled solution of β-piperonylethylamine (5 g.) in benzene (20 c.c.), which was constantly shaken, and the buff-coloured precipitate which separated was decomposed by the addition of 10% sodium hydroxide solution. The amide (I), which rapidly separated from the benzene, was collected, combined with a small second crop obtained by concentrating the benzene layer of the filtrate, and crystallised from ethyl alcohol; it formed colourless needles (8 g.), m. p. 158° (Found : C, 58·9; H, 5·4. $C_{19}H_{20}O_7N_2$ requires C, 58·8; H, 5·2%). This amide is sparingly soluble in light petroleum, ether, benzene, and cold methyl or ethyl alcohol, but readily soluble in chloroform.

2′-*Nitro*-3′ : 4′-*dimethoxy*-6 : 7-*methylenedioxy*-1-*benzyl*-3 : 4-*dihydro*-iso*quinoline* (II).—Phosphorus pentachloride (6 g.) was added to a cooled solution of the amide (I) (5 g.) in chloroform (50 c.c.), and the mixture kept at room temperature for 36 hours, a pale yellow solid gradually separating. The chloroform and phosphorus oxychloride were removed under diminished pressure, the solid residue was extracted with much hot water and filtered off while hot from a small amount of tar, and the filtrate was made alkaline with ammonia. The dihydro*iso*quinoline (II) separated as a cream-coloured, amorph-

ous powder, which rapidly became crystalline. On recrystallisation from ethyl alcohol it formed pale yellow prisms (3·8 g.), m. p. 164° (Found: C, 61·6; H, 4·9. $C_{19}H_{18}O_6N_2$ requires C, 61·6; H, 4·9%). This base is sparingly soluble in light petroleum, ether, and cold methyl or ethyl alcohol and readily soluble in chloroform. The sparingly soluble *sulphate* and *nitrate* separate when the base is dissolved in dilute sulphuric and nitric acids respectively. When a solution of the base in hot dilute hydrochloric acid was cooled, the *hydrochloride* separated in very pale yellow plates, m. p. 230° (decomp.) (Found: C, 56·0; H, 4·8. $C_{19}H_{18}O_6N_2$,HCl requires C, 56·1; H, 4·7%).

*2'-Nitro-3':4'-dimethoxy-6:7-methylenedioxy-1-benzyl-3:4-dihydro*iso*quinoline Methiodide* (III).—The base (II) (3·2 g.) and methyl iodide (10 c.c.) were heated at 100° in a sealed tube for 1 hour and the excess of methyl iodide was then removed by distillation. The residue crystallised from rectified spirit in bright yellow needles, m. p. 215° (decomp.) (Found: C, 47·1; H, 4·2. $C_{20}H_{21}O_6N_2I$ requires C, 46·9; H, 4·1%). The methiodide (III) is sparingly soluble in water, methyl and ethyl alcohol. The methiodide (2 g.) and 5% sodium hydroxide solution (20 c.c.) were heated on a water-bath for 2 hours, and the colourless solution was subjected to steam distillation. The distillate was extracted with ether, the extract dried with sodium sulphate, and the solvent removed, leaving 2-nitrohomoveratrole as an oil. This was oxidised by a hot dilute solution of potassium permanganate to 2-nitroveratric acid, m. p. 201°, which was identified by comparison with a specimen prepared by the method of Pschorr and Sumuleanu (*Ber.*, 1899, **32**, 3409). The non-volatile portion was evaporated to dryness, and the solid residue extracted with chloroform. The residue from the dried, evaporated extract crystallised from aqueous alcohol in colourless needles, m. p. 98°. These were identified as oxyhydrastinine by comparison with a specimen of the latter prepared by the action of potassium hydroxide on hydrastinine (Freund and Will, *Ber.*, 1887, **20**, 2400; Freund, *Ber.*, 1889, **22**, 457).

*2'-Amino-3':4'-dimethoxy-6:7-methylenedioxy-1-benzyl-2-methyl-tetrahydro*iso*quinoline* (IV).—A suspension of the methiodide (III) (3·5 g.) in water (35 c.c.) and concentrated hydrochloric acid (70 c.c.) was heated on the water-bath and shaken vigorously while zinc dust (11 g.) was gradually added. A colourless crystalline salt gradually separated as the reduction proceeded. The hot solution was filtered, the residue thoroughly extracted with hot water, and the combined filtrate and washings made alkaline with ammonia and extracted with ether. The ethereal extract was dried with sodium sulphate, the ether removed, and the residual oil, which did not

crystallise, was dissolved in alcohol containing hydrogen chloride. The dihydrochloride of the base (IV), which rapidly separated, was collected (2·3 g.) and washed with alcohol. The *dihydrochloride* crystallised from alcohol, in which it is sparingly soluble, in colourless, glistening prisms, m. p. 231° (decomp.) (Found in material dried at 110° : C, 56·2; H, 6·0. $C_{20}H_{24}O_4N_2,2HCl$ requires C, 55·9; H, 6·1%). The bright yellow solution obtained on addition of sodium nitrite to the dihydrochloride in water gave, on treatment with alkaline β-naphthol, a crimson azo-dye, which formed a deep magenta-coloured solution in concentrated sulphuric acid.

dl-*Bulbocapnine Methyl Ether* (V).—An ice-cold solution of the dihydrochloride (5·5 g.) of the base (IV) in sulphuric acid (27 c.c. of 2*N*) and methyl alcohol (27 c.c.) was diazotised by the gradual addition of the calculated amount of 2*N*-sodium nitrite (freshly standardised). The bright yellow solution was heated on the water-bath for 40 minutes, and the deep-red solution obtained was reduced with zinc dust (3 g.) and concentrated hydrochloric acid (9 c.c.). The hot liquid was filtered, the residue washed thoroughly with boiling water, and the combined filtrate and washings were decomposed with ammonia and extracted with much ether; at this stage a considerable quantity of the amorphous dilaudanosine derivative separated. The pale yellow ethereal extract was washed with sodium hydroxide solution and dried with sodium sulphate, and the ether removed. The residual oil was dissolved in dilute hydrochloric acid, and a concentrated solution of potassium iodide added; the hydriodide separated as a gum. The clear supernatant liquid was decanted, and the gum dissolved in hot alcohol; on cooling, dl-*bulbocapnine methyl ether hydriodide* (1·2 g.) separated in almost colourless prisms, which darken at 240° and melt with decomposition at 250° (Found : C, 51·5; H, 4·9. $C_{20}H_{21}O_4N,HI$ requires C, 51·4; H, 4·7%). *dl*-Bulbocapnine methyl ether was obtained as a gum by decomposing a hot aqueous solution of the hydriodide with sodium hydroxide. This was extracted with ether, the extract dried with sodium sulphate, and the ether allowed to evaporate slowly. dl-*Bulbocapnine methyl ether* separated in large, very pale yellow rhombs, m. p. 135°, and no alteration was observed in the melting point of a mixture of the synthetical base and a specimen of *dl*-bulbocapnine methyl ether prepared from *d*-bulbocapnine as described by Gadamer (*loc. cit.*). The synthetical base and the specimen obtained from natural sources gave identical colour reactions. They dissolved in concentrated sulphuric acid to form colourless solutions which rapidly became orange-red; they yielded deep red solutions with Erdmann's reagent, deep greenish-blue colorations with Frohde's reagent, and with Mandelin's reagent a

red coloration was first produced, which rapidly became violet, then purple and finally blue. dl-*Bulbocapnine methyl ether methiodide* was prepared by heating the base with an excess of methyl iodide for 1 hour. The excess of methyl iodide was removed by distillation; the residue crystallised from methyl alcohol in long, colourless needles, m. p. 243° (Found : C, 52·5; H, 5·2. $C_{21}H_{24}O_4NI$ requires C, 52·4; H, 5·0%). The methiodide obtained from *dl*-bulbocapnine methyl ether of natural origin was prepared in a similar manner, and no alteration was observed in the melting point of a mixture of the methiodides obtained from the two sources.

Our thanks are due to Mr. D. G. P. Paterson, B.Sc., for help in some of the preparative work, and to the Research Fund Committee of the Chemical Society for grants.

THE UNIVERSITY OF DURHAM,
ARMSTRONG COLLEGE,
NEWCASTLE-ON-TYNE.

THE DYSON PERRINS LABORATORY,
OXFORD.

[*Received, February 15th*, 1928.]

PRINTED IN GREAT BRITAIN BY RICHARD CLAY & SONS, LIMITED,
BUNGAY, SUFFOLK.

THE ISOMERIC 2-AMINO-*a*-ARYLCINNAMIC ACIDS.

BY

JOHN MASSON GULLAND

AND

CYRIL JOSEPH VIRDEN.

Publication 12

Part of the work described in this paper was carried out by me, part by Mr. C. J. Virden under my daily direction.

Reprinted from the Journal of the Chemical Society, June 1928.

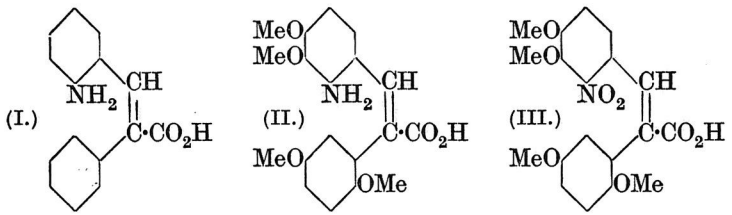
Reprinted from the Journal of the Chemical Society, 1928.

CXCV.—*The Isomeric 2-Amino-α-arylcinnamic Acids.*

By John Masson Gulland and Cyril Joseph Virden.

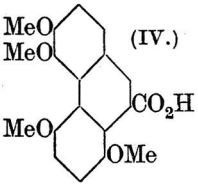
Pschorr (*Ber.*, 1896, **29**, 496) observed that 2-amino-α-phenylcinnamic acid (I) exists in two interconvertible isomeric forms, one yellow, the other colourless. Stoermer and Prigge (*Annalen*, 1915, **409**, 23) confirmed this observation, but did not examine the isomerides more closely, and other workers who have prepared 2-amino-α-arylcinnamic acids make no mention of such isomerism. During an investigation into the constitution of thebenine (this vol., p. 921), we had occasion to prepare 2-amino-3 : 4 : 2′ : 5′-tetramethoxy-α-phenylcinnamic acid (II), and found that it occurs in

two forms, one yellow, the other colourless. This communication is an account of the experiments which have been carried out up to the present time in order to elucidate the nature of this isomerism.

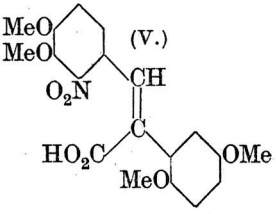


The synthesis of the amino-acids (II) follows the usual stages. 2 : 5-Dimethoxybenzaldehyde, prepared by introducing the aldehydo-group into *p*-dimethoxybenzene, condenses with hippuric acid, yielding the azlactone, *5-keto-2-phenyl-4-(2′ : 5′-dimethoxybenzylidene)-4 : 5-dihydro-oxazole*, which is converted into *α-benzamido-2 : 5-dimethoxycinnamic acid* by heating for a short time with dilute hydrochloric acid or sodium hydroxide. Prolonged alkaline hydrolysis of the azlactone yields 2 : 5-*dimethoxyphenylpyruvic acid*, which is oxidised by hydrogen peroxide to 2 : 5-dimethoxyphenylacetic acid. When the sodium salt of this acid is condensed with 2-nitroveratraldehyde (Pisovschi, *Ber.*, 1910, **43**, 2137), trans-*2-nitro-3 : 4 : 2′ : 5′-tetramethoxy-α-phenylcinnamic acid* (III) is formed, together with a small amount of 2-nitro-3 : 4-dimethoxycinnamic acid (this vol., p. 931). The reduction of the acid (III) with ferrous sulphate and ammonia yields a mixture of two *2-amino-3 : 4 : 2′ : 5′-tetramethoxy-α-phenylcinnamic acids* (II), A, m. p. 219°, which is colourless, and B, m. p. 167°, which is yellow; the marked difference of solubility in alcohol provides an easy method of separation. These acids are interconvertible : the addition of an excess of sodium acetate to a solution of either in dilute hydrochloric acid precipitates the acid B, and either acid, uncontaminated by the other, may readily be obtained at will when an ammoniacal solution of A or B is treated with acetic acid under conditions which are described in the experimental section. Both these acids must have the *trans*-configuration for the following reasons. In the first place, both yield *3 : 4 : 5 : 8-tetramethoxyphenanthrene-9-carboxylic acid* (IV) when a methyl-alcoholic solution of the diazonium sulphate is boiled. When the acid (IV) is heated with glacial acetic acid in a sealed tube, it loses carbon dioxide and forms *3 : 4 : 5 : 8-tetramethoxyphenanthrene*. Secondly, the corresponding *cis*-amino-acid exists only in alkaline solution. Thus, *trans*-2-nitro-3 : 4 : 2′ : 5′-tetramethoxy-α-phenylcinnamic acid (III) is partly converted into

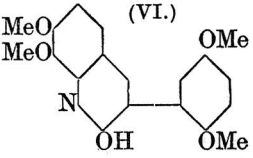
cis-2-*nitro*-3 : 4 : 2′ : 5′-*tetramethoxy*-α-*phenylcinnamic acid* (V) when an aqueous solution of its sodium salt is exposed to ultra-violet light, and the reduction of the barium salt of this acid (V) with ferrous sulphate yields a solution from which hydrochloric acid precipitates 7 : 8 : 2′ : 5′-*tetramethoxy*-3-*phenylcarbostyril* (VI) (compare Stoermer, *loc. cit.*, p. 18). The same carbostyril derivative is formed from the amino-acids (II), either by exposing an alcoholic solution of B to ultra-violet light, or by heating A or B with acetic anhydride and a trace of sulphuric acid.



(IV.)



(V.)



(VI.)

The difference in colour of alcoholic solutions of the acids A (almost colourless) and B (bright yellow) indicates that the isomerism is not due merely to dimorphism, and the molecular weights of the acids confirm this deduction. The acid B, m. p. 167°, proved to be unimolecular in camphor (Rast, *Ber.*, 1922, **55**, 1051), as was to be expected from its lower melting point and the close resemblance of its properties to those of other 2-amino-α-arylcinnamic acids. The acid A, m. p. 219°, on the other hand, was bimolecular, and therefore it became important to determine the molecular weights in other solvents, and to ascertain the effect of adding a small amount of one form to a saturated solution of the other (compare Sidgwick, J., 1915, **107**, 672). The sparing solubility of the acid A restricted the choice of solvent: in benzene, for example, it is practically insoluble. In azobenzene, the acids A and B were associated, but at comparable concentrations the observed values for the molecular weights of A were approximately twice those of B. In acetic acid, the acids A and B were readily soluble and both appeared to be unimolecular; the values for A were consistently low, but it should be noted that this acid retains moisture, which cannot be eliminated without causing decomposition.

In acid or alkaline solutions the unimolecular form of the 2-amino-α-arylcinnamic acids predominates. (The properties of the hydrochloride and chloroplatinate of Pschorr's colourless amino-acid, *loc. cit.*, are also those of the corresponding derivatives of the yellow form, and we consider that these are all salts of the unimolecular yellow form.) In neutral solvents, on the other hand, the bi-

molecular is the stable form, and we have observed that in benzene or azobenzene the acid B changes into the acid A in a comparatively short time.

The precise nature of the bimolecular form of these acids can be elucidated only by the further study of this and other cases of the isomerism. Since the analytical data for Pschorr's acid indicate that it is anhydrous, it is not possible on the basis of the available evidence to decide whether the water of crystallisation of the acid A is essential for the production of the bimolecular form, or whether the A type is composed intrinsically of two molecules of the B type, and we wish therefore to record the facts, and to postpone the discussion of the theoretical question until a later publication.

EXPERIMENTAL.

2 : 5-*Dimethoxybenzaldehyde.*—After several unsatisfactory attempts to introduce the aldehydo-group into quinol by the method of Tiemann and Müller (*Ber.*, 1881, **14**, 1986), the modification of the Gattermann aldehyde synthesis recommended by Adams and Levine (*J. Amer. Chem. Soc.*, 1923, **45**, 2373; 1924, **46**, 1518) was found to be satisfactory. The conditions which have already been detailed (this vol., p. 929) were closely adhered to, and the pure aldehyde was obtained in a yield of 70% of that theoretically possible.

5-*Keto*-2-*phenyl*-4-(2′ : 5′-*dimethoxybenzylidene*)-4 : 5-*dihydro-oxazole.*—This azlactone is obtained by heating together on a boiling water-bath 2 : 5-dimethoxybenzaldehyde (10 g.), hippuric acid (12 g.), fused sodium acetate (12 g.), and acetic anhydride (20 c.c.). The orange product is washed with cold alcohol and repeatedly boiled with water (yield, 75%); further treatment is unnecessary for the next stage. The *azlactone* crystallises from acetic acid, ethyl acetate, or ethyl alcohol, from which it separates in orange needles, m. p. 170—172° (Found: N, 4·4. $C_{19}H_{15}O_4N$ requires N, 4·5%).

α-*Benzamido*-2 : 5-*dimethoxycinnamic Acid*,

$$C_6H_3(OMe)_2\cdot CH{:}C(NHBz)\cdot CO_2H.$$

—When the azlactone is boiled for a short time with alcoholic hydrochloric acid or with dilute sodium hydroxide, a clear solution is obtained which deposits this *acid* on cooling or acidification, respectively. It separates from alcohol in colourless needles, m. p. 195—196° (Found in material dried at 100°: N, 4·5. $C_{18}H_{17}O_5N$ requires N, 4·3%). The azlactone is regenerated by boiling with acetic anhydride.

2 : 5-*Dimethoxyphenylpyruvic acid*, $C_6H_3(MeO)_2\cdot CH_2\cdot CO\cdot CO_2H$, is

obtained in 76% yield when the azlactone is hydrolysed by boiling 10% sodium hydroxide solution for 12 hours, and the product is separated from benzoic acid by the sulphur dioxide method of Haworth, Perkin, and Rankin (J., 1924, **125**, 1686). It separates from glacial acetic acid in cream-coloured octahedra, m. p. 166—170° (decomp.), which are rather readily soluble in methyl alcohol or acetone, but sparingly soluble in benzene (Found: C, 58·8; H, 5·5. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·3%).

3-*Hydroxy*-2′ : 5′-*dimethoxy*-2-*benzylquinoxaline*.—2 : 5-Dimethoxyphenylpyruvic acid (2 g.) and *o*-phenylenediamine (1 g.) in ethyl alcohol (5 c.c.) are heated on the water-bath for a few minutes. On cooling, the clear solution deposits colourless needles, which after recrystallisation from ethyl alcohol melt at 179—180°, and retain half a molecule of alcohol when dried in a vacuum desiccator (Found: loss at 120°, 7·1; N, 8·8. $C_{17}H_{16}O_3N_2,\frac{1}{2}EtOH$ requires loss, 7·2; N, 8·8%).

2 : 5-Dimethoxyphenylacetic acid, $(MeO)_2C_6H_3\cdot CH_2\cdot CO_2H$, is obtained (yield, 80%) when a solution of 2 : 5-dimethoxyphenylpyruvic acid (5 g.) in ice-cold sodium hydroxide (35 c.c. of 2*N*) is oxidised by perhydrol (5·5 c.c. made up to 20 c.c.). Next day the pure acid is precipitated in colourless needles by dilute sulphuric acid. It crystallises from benzene in plates, m. p. 123°, which dissolve readily in alcohol, ether, and acetone (Found: C, 60·8; H, 6·0. Calc.: C, 61·2; H, 6·1%). Wolkow and Baumann (*Z. physiol. Chem.*, 1892, **15**, 214) give m. p. 124·5°. The *sodium* salt is prepared by evaporating to dryness a solution of the acid in the calculated amount of aqueous sodium carbonate.

Condensation of 2-*Nitroveratraldehyde with* 2 : 5-*Dimethoxyphenylacetic Acid*. trans-2-*Nitro*-3 : 4 : 2′ : 5′-*tetramethoxy*-α-*phenylcinnamic Acid* (III) *and* trans-2-*Nitro*-3 : 4-*dimethoxycinnamic Acid*.—A mixture of sodium 2 : 5-dimethoxyphenylacetate (10 g.), 2-nitroveratraldehyde (Pisovschi, *Ber.*, 1910, **43**, 2137) (30 g.), and acetic anhydride (200 g.) is heated at 100° for 60 hours. Water is then added to destroy the acetic anhydride, and the residual oil is repeatedly extracted with small quantities of boiling dilute sodium carbonate solution. On cooling, the combined extracts deposit long silky needles of sodium *trans*-2-nitro-3 : 4 : 2′ : 5′-tetramethoxy-α-phenylcinnamate. These are ground with concentrated hydrochloric acid; the *acid* obtained, after being washed and dried (13·5 g.), crystallises from ethyl alcohol in bright yellow, hexagonal plates, m. p. 204—205° (Found: C, 58·9; H, 4·9. $C_{19}H_{19}O_8N$ requires C, 58·6; H, 4·9%).

Acidification with concentrated hydrochloric acid of the alkaline mother-liquor from which the sodium salt has separated (above)

precipitates *trans*-2-nitro-3 : 4-dimethoxycinnamic acid (1·5 g.), which crystallises from ethyl alcohol in colourless needles, m. p. 229° with softening from 216°. There is no depression in the melting point of a mixture of this acid with the cinnamic acid obtained by the condensation of 2-nitroveratraldehyde and malonic acid (compare this vol., p. 932). The amount of this acid which is produced in the condensation described above increases rapidly with rise in temperature, and in earlier experiments it was observed that when the reaction took place at 140° equal weights of the two acids were produced.

The Isomeric trans-2-*Amino*-3 : 4 : 2′ : 5′-*tetramethoxy*-α-*phenylcinnamic Acids, A and B* (II).—A hot solution of *trans*-2-nitro-3 : 4 : 2′ : 5′-tetramethoxy-α-phenylcinnamic acid (13·0 g.) in dilute ammonia (100 c.c.) is added carefully (frothing) to a hot reducing mixture previously prepared by the addition of ammonia (*d* 0·880; 120 c.c.) to a solution of ferrous sulphate (83·6 g.) in hot water (150 c.c.); the mixture is heated on the water-bath for 30 minutes. After the ferrosoferric oxide has been thoroughly washed with dilute ammonia, the combined filtrate and washings are cooled and just acidified with glacial acetic acid. The product separates as a gummy mass which rapidly crystallises; on recrystallisation from ethyl alcohol, the acid A (7·5 g.) separates in colourless needles. From the alcoholic mother-liquor, when evaporated to small bulk and cooled, the acid B is obtained as yellow needles (0·5 g.). The quantity of this acid increases, and the amount of A decreases correspondingly, if an excess of acetic acid is used in precipitating the product of the reduction.

The *acid B* is purified by dissolving it in cold, dilute hydrochloric acid (charcoal) and precipitating it by the addition of sodium acetate solution. After being washed with water and dried on porous tile, it crystallises from ethyl alcohol in yellow needles, m. p. 167° (Found in material heated at 100° : C, 62·6, 62·3; H, 5·6, 5·7; N, 3·8; OMe, 33·2. $C_{19}H_{21}O_6N$ requires C, 63·5; H, 5·9; N, 3·9; 4OMe, 34·5%). The somewhat low percentage of carbon indicates the retention of traces of moisture, which are lost only by heating to 140° (Loss at 140° : 0·6, 0·7%. Found in material dried at 140° : C, 63·5; H, 6·0%). The acid forms a yellow solution in dilute hydrochloric acid and a colourless solution in dilute sodium hydroxide or carbonate or ammonia, and is precipitated from these by the addition of sodium acetate or acetic acid respectively. It dissolves rather readily in methyl or ethyl alcohol, forming a bright yellow solution, but is sparingly soluble in cold benzene. It was converted into an uncrystallisable gum when a 0·1% aqueous solution was boiled under reflux for 12 hours.

When an ethyl-alcoholic solution of the acid B in a silica flask is exposed to ultra-violet light for several days, 7 : 8 : 2′ : 5′-*tetramethoxy-3-phenylcarbostyril* (VI) separates quantitatively as colourless needles, m. p. 189° (Found: C, 64·3; H, 5·7. $C_{19}H_{19}O_5N$ requires C, 64·6; H, 5·4%). The same substance is obtained by heating for 30 minutes on the water-bath a solution of the acid (0·5 g.) in acetic anhydride (5 c.c.) containing one drop of concentrated sulphuric acid, pouring the mixture into water, and crystallising the precipitate from alcohol. It is insoluble in sodium carbonate, but dissolves in concentrated sodium hydroxide or concentrated hydrochloric acid.

The *acid A*, when obtained as described above, softens at 180° and melts at 198°. In attempting to purify it in the first instance, it was dissolved in sodium bicarbonate and precipitated by the slow addition of glacial acetic acid and scratching. On this occasion only was the acid A reprecipitated in this way; in all subsequent cases, the acid B separated. Further investigation showed that the acid A is obtained in a pure condition when a solution of the crude acid, m. p. 198°, in dilute ammonia is just neutralised with the requisite quantity of acetic acid (previously determined by titration); no separation takes place until the vessel is scratched; the acid A is then precipitated as a colourless, crystalline powder. On recrystallisation from ethyl alcohol it forms colourless needles, m. p. 219°, which retain water of crystallisation at 140° (Found: C, 62·1, 62·3, 62·4; H, 6·2, 6·4, 6·2. $C_{19}H_{21}O_6N,\frac{1}{2}H_2O$ requires C, 62·0; H, 6·0%). It dissolves sparingly in hot ethyl alcohol, forming a faintly yellow solution from which it crystallises on cooling, and it is insoluble in benzene (mean f. p. of benzene, 0·061°; after addition of the acid A, 0·059°). Its solution in dilute hydrochloric acid is yellow, and in sodium hydroxide or carbonate or ammonia colourless; the addition of sodium acetate or acetic acid, respectively, precipitates the acid B. On the other hand, by neutralising a solution of either acid, A or B, in dilute ammonia by the sudden addition, with vigorous mechanical stirring, of the calculated amount of acetic acid (previously determined), a clear, colourless solution is obtained which deposits the acid A on scratching. This difference in the precipitation of the two acids is presumably due to the formation of a neutral, supersaturated solution, and explains the production of both acids in the reduction of the nitro-acid and careful precipitation by acetic acid. The acid A crystallised unchanged when a 0·1% aqueous solution which had been boiled under reflux for 12 hours was concentrated. When heated with acetic anhydride and sulphuric acid as described in the case of the acid B, it is converted quantitatively into 7 : 8 : 2′ : 5′-tetramethoxy-3-phenylcarbostyril (VI).

Molecular weights of the acids A and B. For $C_{19}H_{21}O_6N$, $M = 359$.

Acid.	Solvent.	% Concentration.	*M*.	Remarks.
B	Camphor.	10·0	357	Rast's method.
A		5·6	723	
		11·2	732	
B	Acetic acid.	0·6	328	
A		0·4—2·8	254	Mean of 6 results between 249 and 258.
B	Azobenzene.	2·0	623	
		5·2	839	
		8·8	1100	
A		1·4	1211	

Transformation of the Acid B into the Acid A in Azobenzene.—The azobenzene was distilled, crystallised from ethyl alcohol, and dried at 100°, and the samples of the acids were dissolved in the solvent by warming to about 80°, except where otherwise stated. The freezing point of a freshly prepared solution of the acid A, saturated at about 80°, was 0·211° below that of azobenzene, but it is probable that the solution was supersaturated, since the depression fell to 0·06° in the course of 1½ hours. The addition (without warming) of some of the acid B to the fresh solution of A increased the depression to 0·436°. The depression of a freshly prepared 8·8% solution of the acid B was 0·666°, and after ½ hour this had decreased to 0·229°. On addition of some of the acid A (without warming), the freezing point continued to rise (0·198°), and after ½ hour the depression was 0·088°. On dissolving the azobenzene in benzene, the whole of the amino-acid was recovered in the insoluble, bimolecular form.

cis-2-*Nitro*-3 : 4 : 2′ : 5′-*tetramethoxy*-α-*phenylcinnamic Acid* (V) *and its Reduction.*—A concentrated aqueous solution of sodium *trans*-2-nitro-3 : 4 : 2′ : 5′-tetramethoxy-α-phenylcinnamate in a quartz flask is exposed to ultra-violet light for 8 days. (Subsequent experiments showed that the yield of *cis*-acid is not increased by more prolonged exposure.) The solution is then just acidified with acetic acid, and the unchanged *trans*-acid (4·75 g.) which separates is removed. The addition of concentrated hydrochloric acid now precipitates the *cis*-acid (0·15 g.) in an impure condition. The combined yields of *cis*-acid from two experiments are recrystallised from ethyl alcohol, from which the *cis*-acid separates in pale yellow needles, m. p. 186° (Found : C, 58·4; H, 4·9. $C_{19}H_{21}O_8N$ requires C, 58·6; H, 4·9%).

The alkaline reduction of this acid yields a solution of the corresponding *cis*-2-amino-3 : 4 : 2′ : 5′-tetramethoxy-α-phenylcinnamic acid, which passes into 7 : 8 : 2′ : 5′-tetramethoxy-3-phenylcarbostyril (VI) on acidification. A solution of the *cis*-nitro-acid (0·08 g.)

in a little dilute ammonia is added to a hot reducing mixture, prepared from barium hydroxide (0·55 g.) in hot water (10 c.c.) and ferrous sulphate (0·53 g.) in hot water (8 c.c.). During the reaction a stream of nitrogen is passed through the vessel in order to prevent atmospheric oxidation of the ferrous hydroxide. The mixture is heated on the water-bath for 15 minutes and filtered, and the cooled filtrate is acidified by hydrochloric acid. The carbostyril which separates crystallises from ethyl alcohol in colourless needles, m. p. 189°; there is no depression of the melting point of a mixture of this preparation with the material obtained from the *trans*-amino-acid.

3 : 4 : 5 : 8-*Tetramethoxyphenanthrene*-9-*carboxylic Acid* (IV).—An ice-cold solution of *trans*-2-amino-3 : 4 : 2′ : 5′-tetramethoxy-α-phenylcinnamic acid (4 g.) in methyl alcohol (60 c.c.) and sulphuric acid (40 c.c. of 2*N*) is diazotised, and the clear red solution is diluted with water and heated at 60° until the evolution of nitrogen ceases; the *acid* is then precipitated as a gum, which becomes crystalline on being rubbed with alcohol (yield, about 50%). The acid crystallises from ethyl alcohol in colourless needles of constant m. p. 190—198° (Found: C, 66·2; H, 5·2. $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·3%).

3 : 4 : 5 : 8-*Tetramethoxyphenanthrene*.—The preceding acid (1 g.) in glacial acetic acid (40 c.c.) is heated in a sealed tube at 240° for 40 hours. The dark solution is poured into water, made alkaline with ammonia, and extracted with ether. The extract is washed and dried, the solvent evaporated, and the residual oil crystallised repeatedly from methyl alcohol, from which 3 : 4 : 5 : 8-*tetramethoxyphenanthrene* separates in light brown needles, m. p. 118—120° (Found: C, 71·9; H, 5·9. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·0%).

The *picrate*, prepared in alcoholic solution, separates from ethyl alcohol in dark chocolate needles, m. p. 158° (Found: N, 7·9. $C_{24}H_{21}O_{11}N_3$ requires N, 7·9%).

The authors wish to thank Dr. N. V. Sidgwick for his most helpful criticism, and acknowledge with gratitude their indebtedness to the Chemical Society for grants which have defrayed part of the cost of this investigation. One of the authors (C. J. V.) thanks the Goldsmiths' Company for a Senior Studentship, and the Department of Scientific and Industrial Research for a grant, which have enabled him to take part in this research.

THE DYSON PERRINS LABORATORY,
OXFORD.

[*Received, April 14th*, 1928.]

PRINTED IN GREAT BRITAIN BY RICHARD CLAY & SONS, LIMITED, BUNGAY, SUFFOLK.

SYNTHETICAL EXPERIMENTS ON THE APORPHINE ALKALOIDS. PART III. A SYNTHESIS OF CORYTUBERINE DIMETHYL ETHER.

BY

JOHN MASSON GULLAND

AND

ROBERT DOWNS HAWORTH.

Publication 13

Dr. R. D. Haworth carried out the experiments described in this paper.

Reprinted from the Journal of the Chemical Society, July 1928

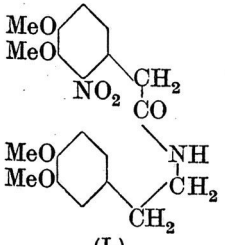
Reprinted from the Journal of the Chemical Society, 1928.

CCXXXVII.—*Synthetical Experiments on the Aporphine Alkaloids. Part III. A Synthesis of Corytuberine Dimethyl Ether.*

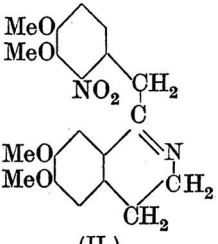
By John Masson Gulland and Robert Downs Haworth.

The method described in Parts I and II of this series (this vol., pp. 581, 1132) has now been applied to the synthesis of 3 : 4 : 5 : 6-tetramethoxyaporphine (IV), the *d*-form of which is identical with corytuberine dimethyl ether (corydine and *iso*corydine monomethyl ether).

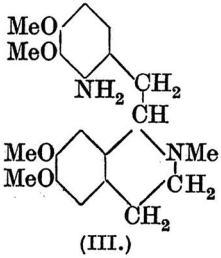
2′-*Nitro*-3′ : 4′-*dimethoxyphenylaceto*-β-3 : 4-*dimethoxyphenylethylamide* (I) was prepared from 2-nitro-3 : 4-dimethoxyphenylacetyl chloride and β-veratrylethylamine, and converted into 2′-*nitro*-6 : 7 : 3′ : 4′-*tetramethoxy*-1-*benzyl*-3 : 4-*dihydro*isoquinoline (II) by the action of phosphorus pentachloride. This pale yellow, crystalline base, which forms a crystalline *hydrochloride*, was converted into its *methiodide*, and the latter was reduced with zinc dust and hydrochloric acid to 2′-*amino*-6 : 7 : 3′ : 4′-*tetramethoxy*-1-*benzyl*-2-*methyltetrahydro*isoquinoline (III). This oily base, which yields a crystalline *dihydrochloride*, diazotises readily and the diazonium salts couple with β-naphthol in alkaline solution.



(I.)



(II.)



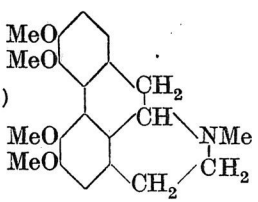
(III.)

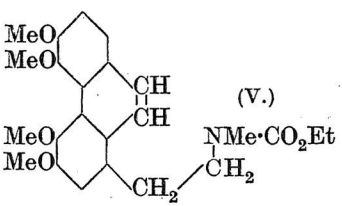
The base (III) was diazotised in a mixture of methyl alcohol and sulphuric acid and converted into 3 : 4 : 5 : 6-*tetramethoxyaporphine* (IV) by warming. This *dl*-base is a pale yellow oil from which a crystalline *methiodide* has been prepared. The *dl*-base (IV) was resolved by means of *d*-tartaric acid, and 1-*corytuberine dimethyl ether* d-*bitartrate* was thus obtained in crystalline

condition. *d*-Corytuberine dimethyl ether *l*-bitartrate was then prepared by liberating the base from the mother-liquors and combining it with *l*-tartaric acid. The *d*- and *l*-bases were obtained from the bitartrates in the form of oils. These gave the colour reactions described by Gadamer (*Arch. Pharm.*, 1911, **249**, 547) for the oily corytuberine dimethyl ether, which he prepared by methylating naturally occurring *d*-corytuberine.

As we do not possess a sample of the natural product, direct comparison has not been possible, but the melting points, solubilities, and rotation values of the *l*-bitartrate and the methochloride of the synthetical *d*-base are in close agreement with those which Gadamer (*loc. cit.*) records for the corresponding derivatives of the *d*-base obtained from natural sources. Further, the optically inactive carbethoxycorytuberine dimethyl ether (V), prepared by the action of sodium hydroxide and ethyl chloroformate on the synthetical *d*- or *dl*-base, appears to be identical with the product obtained by Osada (*Arch. Pharm.*, 1924, **262**, 501) in a similar manner from the *d*-base of natural origin.

(IV.)





(V.)

This synthesis confirms the structure which Gadamer (*loc. cit.*) suggested for corytuberine dimethyl ether (corydine and *iso*corydine monomethyl ether), and we hope to determine by analogous syntheses the positions of the phenolic hydroxyl groups in these alkaloids.

EXPERIMENTAL.

2′-Nitro-3′ : 4′-dimethoxyphenylaceto-β-3 : 4-dimethoxyphenylethylamide (I).—A benzene solution of 2-nitro-3 : 4-dimethoxyphenylacetyl chloride (prepared from 5 g. of acid as described in this vol., p. 1134) and β-veratrylethylamine (3·7 g.) was cooled and shaken with a slight excess of 15% sodium hydroxide solution. The benzene layer was washed with dilute hydrochloric acid and dried with sodium sulphate, and the solvent removed. The residual oil was dissolved in a little methyl alcohol (in which it is very soluble) and mixed with ether, the alcohol was removed by washing with water, and the ether was dried and allowed to evaporate slowly; the *amide* separated in almost colourless nodules, m. p. 64—65°, containing solvent of crystallisation which is lost at 100° (Found in material dried at 110°: C, 60·2; H, 6·2. $C_{20}H_{24}O_7N_2$ requires

C, 59·6; H, 5·7%). This amide is very soluble in the usual organic solvents with the exception of light petroleum.

2′-Nitro-6 : 7 : 3′ : 4′-tetramethoxy-1-benzyl-3 : 4-dihydroisoquinoline (II).—A solution of the amide (I) (5 g.), chloroform (50 c.c.), and phosphorus pentachloride (6 g.) was allowed to remain at room temperature for 36 hours. The solvent was removed in a vacuum from the buff-coloured solid, the residue was dissolved in hot water, and the filtered solution made alkaline with ammonia. The solid base, collected after 3 hours, crystallised from ethyl alcohol in pale yellow prisms (3·9 g.), m. p. 159—160° (Found: C, 61·9; H, 5·9. $C_{20}H_{22}O_6N_2$ requires C, 62·2; H, 5·7%). This *base* is almost insoluble in light petroleum, sparingly soluble in ether and cold alcohol, but readily soluble in benzene and chloroform. It dissolves in hot dilute hydrochloric acid, and on cooling, the *hydrochloride* separates in very pale yellow needles, m. p. 227° (decomp.). The *methiodide* was prepared by allowing the base to react with an excess of methyl iodide at room temperature for 12 hours. The excess of methyl iodide was then removed, and the residue crystallised from ethyl alcohol, in which it was readily soluble. It forms rosettes of yellow needles, which contain solvent of crystallisation and melt at 105—107°, resolidify, and decompose gradually between 180° and 190° (Found in material dried at 100°: C, 47·7; H, 5·0. $C_{21}H_{25}O_6N_2I$ requires C, 47·7; H, 4·7%).

2′-Amino-6 : 7 : 3′ : 4′-tetramethoxy-1-benzyl-2-methyltetrahydroisoquinoline (III).—A hot solution of the methiodide (2·3 g.) in water (25 c.c.) and concentrated hydrochloric acid (25 c.c.) was reduced by the gradual addition of zinc dust (7·5 g.). The liquid having been filtered and made alkaline with ammonia, the base was extracted with ether and dried, and the solvent removed. The residual oil was dissolved in chloroform and saturated with dry hydrogen chloride; the *dihydrochloride* of the base (III) separated in colourless needles (1·7 g.), m. p. 188—190° (Found in material dried at 100°: C, 56·8; H, 6·7. $C_{21}H_{28}O_4N_2,2HCl$ requires C, 56·6; H, 6·7%). The dihydrochloride was hygroscopic and dissolved readily in ethyl alcohol. The addition of sodium nitrite to an aqueous solution of the dihydrochloride produced a bright yellow solution which coupled with alkaline β-naphthol, yielding a vermilion azo-dye which became deep port-wine in colour when dissolved in concentrated sulphuric acid.

dl-*Corytuberine dimethyl ether* (IV).—The dihydrochloride of the base (III) (2 g.), dissolved in methyl alcohol (10 c.c.) and sulphuric acid (10 c.c. of 2*N*), was diazotised by the gradual addition of the calculated amount of 2*N*-sodium nitrite. The bright yellow liquid became deep red after boiling for ½ hour; zinc dust (1 g.) and con-

centrated hydrochloric acid (3 c.c.) were then added, and the boiling was continued for 15 minutes. The mixture was filtered, and the residue extracted with boiling water. The combined filtrate and washings were rendered alkaline with ammonia and extracted with ether, the extract was washed with sodium hydroxide solution and dried, and the ether was removed. *dl*-Corytuberine dimethyl ether (0·3 g.) remained as a pale yellow oil which did not crystallise. The *hydrochloride* was very soluble in water and alcohol, and the *hydriodide* separated as a gum when potassium iodide was added to an aqueous solution of the hydrochloride. The *methiodide*, which was obtained by heating the *dl*-base with an excess of methyl iodide, crystallised from ethyl alcohol in colourless prisms which darken slightly at about 220° and decompose at 248° (Found: C, 52·9; H, 5·5. $C_{22}H_{28}O_4NI$ requires C, 53·1; H, 5·6%).

Resolution of dl-*Corytuberine Dimethyl Ether*.—When *dl*-corytuberine dimethyl ether (1 g.) in absolute ethyl alcohol (15 c.c.) was mixed with an absolute-ethyl-alcoholic solution of *d*-tartaric acid (3 c.c. of 2*N*), a gum separated. This dissolved on boiling, and the colourless crystals of l-*corytuberine dimethyl ether* d-*bitartrate* which rapidly separated were collected by filtering the boiling solution and recrystallised from rectified spirit, forming colourless needles, m. p. 219—221° (decomp.) (Found in material dried at 100°: C, 59·2; H, 6·3. $C_{25}H_{31}O_{10}N$ requires C, 59·4; H, 6·1%). In aqueous solution: $l = 1$, $c = 1·005$, $\alpha_D = -1·49°$, whence $[\alpha]_D = -148·2°$. On cooling, the hot filtrate deposited a gum; the clear supernatant liquid was decanted and evaporated to dryness and the base was liberated by the action of sodium hydroxide solution and extracted with ether. The ethereal extract was dried, the solvent removed, and the residual oil was dissolved in absolute ethyl alcohol (15 c.c.) and mixed with an absolute-ethyl-alcoholic solution of *l*-tartaric acid (3 c.c. of 2*N*). *d*-Corytuberine dimethyl ether *l*-bitartrate separated; it crystallised from rectified spirit in colourless needles, m. p. 219—222° (decomp.). Gadamer (*loc. cit.*) gives 219—224° (decomp.) (Found: C, 59·3; H, 6·3. Calc. for $C_{25}H_{31}O_{10}N$: C, 59·4; H, 6·1%). In aqueous solution, $l = 1$, $c = 1·017$, $\alpha_D = +1·53°$, whence $[\alpha]_D = +149·7°$. Gadamer (*loc. cit.*) gives $[\alpha]_D = +150°$.

The *d*- and the *l*-base were liberated as oils from the bitartrates by the action of sodium hydroxide solution. With concentrated sulphuric acid, concentrated nitric acid, Erdmann's reagent, Fröhde's reagent, Mandelin's reagent, and a solution of selenic acid in concentrated sulphuric acid, the *d*- or the *l*-base gave colour reactions which were in agreement with those described by Gadamer (*loc. cit.*) for *d*-corytuberine dimethyl ether.

d-Corytuberine dimethyl ether methochloride was prepared by refluxing the *d*-base with an excess of methyl iodide for 1 hour, removing the excess of methyl iodide, digesting the residual methiodide with an aqueous suspension of silver chloride for 2 hours, filtering the solution, and evaporating the filtrate to dryness. When ether was added gradually to a solution of the gummy residue in a little absolute ethyl alcohol, the methochloride separated in slender needles, m. p. 243° (decomp.). Gadamer gives m. p. 234—237° (decomp.). In aqueous solution: $l = 1$, $c = 1{\cdot}112$, $\alpha_D = +2{\cdot}17°$, whence $[\alpha]_D = +196°$. Gadamer gives 197·6°.

Carbethoxycorytuberine dimethyl ether (V), m. p. 93°, was prepared from the synthetical *d*- or *dl*-base by the process described by Osada (*loc. cit.*) and appeared to be identical with that obtained from natural sources.

Our thanks are due to the Research Fund Committee of the Chemical Society for grants.

THE UNIVERSITY OF DURHAM,
ARMSTRONG COLLEGE,
NEWCASTLE-ON-TYNE.

THE DYSON PERRINS LABORATORY,
OXFORD.

[*Received, May 15th*, 1928.]

PRINTED IN GREAT BRITAIN BY RICHARD CLAY & SONS, LIMITED,
BUNGAY, SUFFOLK.

SYNTHETICAL EXPERIMENTS ON THE APORPHINE ALKALOIDS. PART IV. A SYNTHESIS OF MORPHOTHEBAINE DIMETHYL ETHER.

BY

JOHN MASSON GULLAND

AND

ROBERT DOWNS HAWORTH.

Publication 14

The work described in this paper was carried out by me.

Reprinted from the Journal of the Chemical Society, August 1928

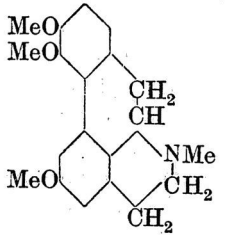
Reprinted from the Journal of the Chemical Society, 1928.

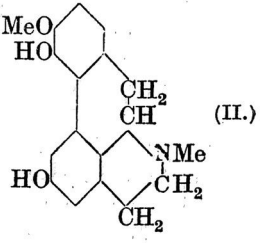
CCLXXIII.—*Synthetical Experiments on the Aporphine Alkaloids. Part IV. A Synthesis of Morphothebaine Dimethyl Ether.*

By John Masson Gulland and Robert Downs Haworth.

The method for the preparation of bases of the aporphine group which was described in Part I of this series (this vol., p. 581) has now been extended to the synthesis of 3 : 4 : 6-*trimethoxyaporphine* (I). The lævo-form of this base is identical with morphothebaine dimethyl ether (Klee, *Arch. Pharm.*, 1914, **252**, 242), and thus the structure for morphothebaine (II) advanced by Pschorr and Halle (*Ber.*, 1907, **40**, 2004) is substantiated. Morphothebaine is produced when hot concentrated hydrochloric acid acts on thebaine, and as a phenanthreno*iso*quinoline base, it forms one of the connecting links between the morphine and aporphine groups of alkaloids.

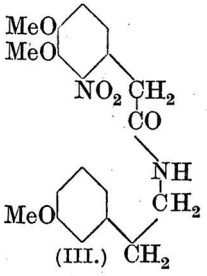
(I.)



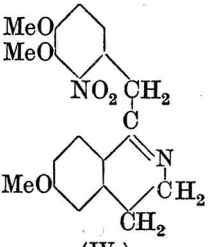


(II.)

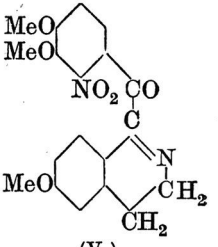
2′-*Nitro*-3′ : 4′-*dimethoxyphenylaceto*-β-3-*methoxyphenylethylamide* (III), prepared by the interaction of 2-nitro-3 : 4-dimethoxyphenylacetyl chloride and 3-methoxy-β-phenylethylamine (Helfer, *Helv. Chim. Acta*, 1924, **7**, 945), was converted into 2′-*nitro*-6 : 3′ : 4′-*trimethoxy*-1-*benzyl*-3 : 4-*dihydro*isoquinoline (IV) by the action of phosphorus pentachloride. This pale yellow crystalline base, which forms a sparingly soluble *hydrochloride*, *sulphate*, and *methiodide*,



(III.)



(IV.)



(V.)

is remarkably stable to atmospheric oxidation, but a small quantity of feebly basic 2′-*nitro*-6 : 3′ : 4′-*trimethoxy*-1-*benzoyl*-3 : 4-*dihydro*-

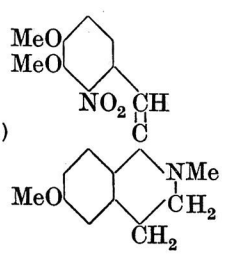
iso*quinoline* (V) was actually isolated from the mother-liquor of the preparation of the base (IV), and was converted into the amorphous, alkali-soluble *oxime*.

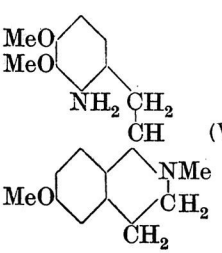
The methiodide of the base (IV), which was abnormal in that it did not appear to undergo alkaline scission but yielded only the crystalline anhydro-base, 2′-*nitro*-6 : 3′ : 4′-*trimethoxy*-1-*benzylidene*-2-*methyltetrahydro*iso*quinoline* (VI), was reduced with zinc dust and hydrochloric acid to 2′-*amino*-6 : 3′ : 4′-*trimethoxy*-1-*benzyl*-2-*methyltetrahydro*iso*quinoline* (VII), an oily base which yielded a crystalline *dihydrochloride* and diazotised readily. The base (VII) was diazotised in a mixture of methyl alcohol and sulphuric acid, and converted by heating into 3 : 4 : 6-*trimethoxyaporphine* (I), an oil from which a crystalline *hydriodide* has been prepared.

This *dl*-base (I) was resolved by means of *d*-tartaric acid, and *l*-morphothebaine dimethyl ether hydrogen *d*-tartrate obtained in crystalline condition. It appeared from its crystalline form, melting point, and rotation, and by a mixed melting-point determination, to be identical with the salt prepared from morphothebaine in the manner described by Klee (*loc. cit.*). The *l*-base was obtained from the hydrogen tartrate as an uncrystallisable oil, which showed the same colour reactions and rotation as a specimen of natural morphothebaine dimethyl ether. Further, the *methiodides* of the two preparations appeared from a comparison of their crystalline form, melting point, and rotations to be similar in every respect, and there can be no doubt that the synthetical and natural products are identical.

d-*Morphothebaine dimethyl ether hydrogen* l-*tartrate* was obtained from the mother-liquor of the resolution by liberating the crude *d*-base and allowing it to combine with *l*-tartaric acid. The *d*-base is an oil which has not crystallised.

(VI.)





(VII.)

EXPERIMENTAL.

2′-*Nitro*-3′ : 4′-*dimethoxyphenylaceto*-β-3-*methoxyphenylethylamide* (III).—2-Nitro-3 : 4-dimethoxyphenylacetyl chloride (from 10 g. of acid) in benzene (50 c.c.) was added gradually to a solution of

3-methoxy-β-phenylethylamine (7 g.) in benzene (50 c.c.). After a short time, the dull yellow precipitate which had separated was mixed with 8% sodium hydroxide solution, and the benzene layer was washed with water and dried. When the solvent had been removed, the residual brown oil solidified; it was then crystallised from methyl alcohol, from which the *amide* separated in colourless needles, m. p. 107—108° (Found: C, 60·7; H, 5·9. $C_{19}H_{22}O_6N_2$ requires C, 61·0; H, 5·9%).

2′-Nitro-6 : 3′ : 4′-trimethoxy-1-benzyl-3 : 4-dihydroisoquinoline (IV).—A solution of the amide (III) (10 g.) and phosphorus pentachloride (12 g.) in chloroform (80 c.c.) was kept at room temperature for 36 hours. After the solvent and phosphorus oxychloride had been removed from the mass of felted needles by distillation under reduced pressure, the residue was dissolved in boiling water, and the solution was filtered and cooled. The sparingly soluble *hydrochloride* of the base (IV) which separated was collected (see below for examination of the mother-liquor), suspended in hot water, and decomposed by ammonia. The *base* (IV) thus liberated crystallised from methyl alcohol in faintly yellow, blunt-ended prisms, m. p. 121—123° (7·5 g.) (Found: C, 64·2; H, 5·5. $C_{19}H_{20}O_5N_2$ requires C, 64·0; H, 5·6%).

The *hydrochloride* separated in colourless needles, m. p. 217—218° (decomp.), when a solution of the base in hot dilute hydrochloric acid was cooled (Found: Cl, 9·0. $C_{19}H_{20}O_5N_2$,HCl requires Cl, 9·0%). It is moderately easily soluble in water and ethyl alcohol, but very sparingly soluble in dilute hydrochloric acid. The *sulphate*, prepared by dissolving the base in dilute sulphuric acid, forms colourless needles, m. p. 237° (decomp.).

The *methiodide* was obtained in a yield exceeding 90% when a mixture of the base and an excess of methyl iodide was heated under reflux on the water-bath for 30 minutes, and the excess of methyl iodide removed. It crystallised from ethyl alcohol in yellow needles, m. p. 220° (decomp.), which were sparingly soluble in water (Found: C, 48·4; H, 4·9. $C_{20}H_{23}O_5N_2I$ requires C, 48·2; H, 4·6%). This substance appeared to be unusually stable to alkaline fission, and attempts to decompose it with sodium hydroxide of various concentrations led only to *2′-nitro-6 : 3′ : 4′-trimethoxy-1-benzylidene-2-methyltetrahydroisoquinoline* (VI), which separated as a red oil and was extracted with benzene. When the solution was dried and the solvent removed, the base (VI) solidified; after twice crystallising from benzene–ligroin, it was obtained in prisms, m. p. 108—109°, which appeared as red diamond-shaped tablets or as yellow prisms, according to the angle from which they were observed (Found in material dried at 100°: C, 64·9; H, 6·0. $C_{20}H_{22}O_5N_2$ requires

C, 64·9; H, 5·9%). By adding sodium iodide to a solution of the base (VI) in dilute hydrochloric acid, the methiodide of the base (IV) was regenerated as an oil which crystallised when rubbed with ethyl alcohol.

2'-Nitro-6 : 3' : 4'-trimethoxy-1-benzoyl-3 : 4-dihydroisoquinoline (V).—The acid mother-liquor from which the hydrochloride of the base (IV) had separated (see above) was rendered alkaline with ammonia; the precipitate obtained, when crystallised twice from methyl alcohol, formed faintly yellow prisms, m. p. 164° (decomp.) (Found: C, 61·5; H, 4·9; N, 7·5. $C_{19}H_{18}O_6N_2$ requires C, 61·6; H, 4·9; N, 7·5%). This substance is insoluble in alkali, but dissolves in warm dilute hydrochloric acid and is reprecipitated by sodium acetate. A consideration of its properties leads us to assign to it the constitution (V), and in this connexion it is noteworthy that the colour of a solution of the compound in boiling acetic anhydride is yellow, whereas the non-nitrated 1-benzoyl-3 : 4-dihydro*iso*quinolines develop a characteristic green coloration under the same conditions (Buck, Haworth, and Perkin, J., 1924, **125**, 2176). The *oxime*, prepared by the action of hydroxylamine hydrochloride and pyridine at 100°, is amorphous and dissolves readily in dilute sodium hydroxide solution.

2'-Amino-6 : 3' : 4'-trimethoxy-1-benzyl-2-methyltetrahydroisoquinoline (VII).—The methiodide (8 g.) of the base (IV), suspended in water (80 c.c.) and concentrated hydrochloric acid (150 c.c.), was heated on the water-bath and reduced by the gradual addition of zinc dust (31 g.). The clear, colourless solution was then cooled, and on several occasions a zinc chloride double salt separated in characteristic, colourless, fan-shaped aggregates of needles. After the addition of an excess of sodium hydroxide solution, the base was isolated by repeated extraction with ether; this extract, when washed with water, dried, and distilled, yielded a pale yellow, uncrystallisable oil. This was converted into its *dihydrochloride* by treating an absolute alcoholic solution with dry hydrogen chloride and evaporating the solution to dryness under reduced pressure. The residual oil crystallised from dry chloroform in colourless needles which softened and shrank at 135°, melted at 155°, and retained solvent when dried in a vacuum desiccator (Found in material dried in a vacuum desiccator: Cl, 32·0. $C_{20}H_{26}O_3N_2,2HCl,CHCl_3$ requires Cl, 33·2%). This substance diazotises readily, and the diazonium salts couple with β-naphthol in alkaline solution, yielding a scarlet dye which develops a reddish-purple colour with concentrated sulphuric acid.

dl-*3 : 4 : 6-Trimethoxyaporphine* (I).—A solution of the hydrochloride of the base (VII) (5 g.) in 2*N*-sulphuric acid (30 c.c.) was

boiled in order to free it from chloroform, cooled in ice, and diazotised by the calculated amount of 2*N*-sodium nitrite. After the addition of methyl alcohol (30 c.c.), the orange solution was boiled under reflux for 30 minutes, mixed with concentrated hydrochloric acid (6 c.c.), reduced by zinc dust (2 g.), cooled, filtered, and made alkaline with 30% sodium hydroxide solution. The base (I) was isolated as a pale yellow oil by repeated extraction with ether, followed by the removal of the solvent, and was converted into the *hydriodide* by the addition of sodium iodide to a solution in dilute hydrochloric acid. This salt separated as a gum, but crystallised when rubbed with ethyl alcohol after the mother-liquor had been decanted, and when recrystallised from the same solvent formed almost colourless needles, m. p. 227° (decomp.) (Found in material dried at 100°: C, 53·2; H, 5·2. $C_{20}H_{23}O_3N$,HI requires C, 53·0; H, 5·3%). It is sparingly soluble in water and separates as a granular, non-crystalline mass when a hot solution is cooled.

Resolution of dl-3 : 4 : 6-*Trimethoxyaporphine*. 1-*Morphothebaine Dimethyl Ether*.—The oily *dl*-base (I) was liberated from the hydriodide by sodium carbonate and extracted with ether, and the solvent evaporated. The residue, dissolved in a little 95% ethyl alcohol, was mixed with an alcoholic solution of an equimolecular amount of *d*-tartaric acid; in a few moments, the colourless *l*-morphothebaine dimethyl ether hydrogen *d*-tartrate separated. It crystallised from ethyl alcohol in stellate aggregates of shining needles, m. p. 208—209° (decomp.) (Found in material dried at 100°: C, 60·3; H, 6·3. Calc. for $C_{24}H_{29}O_9N$: C, 60·6; H, 6·1%). In aqueous solution, $c = 1{\cdot}123$, $l = 1$, $\alpha_D = -0{\cdot}84°$, whence $[\alpha]_D = -74{\cdot}8°$. *l*-Morphothebaine was liberated as a colourless oil from the hydrogen tartrate (0·1684 g.) and carefully extracted by successive small quantities of chloroform, and the mixed extracts were dried with a little sodium sulphate and made up to 20 c.c.; $l = 1$, $\alpha_D = -1{\cdot}00°$, whence $[\alpha]_D = -173{\cdot}5°$. The colour reactions with Erdmann's and Fröhde's reagents were indistinguishable from those given by the natural *l*-base (see below). The *methiodide* separated in crystalline condition when a solution of the base and methyl iodide in ethyl acetate was warmed for a few minutes on the water-bath; it crystallised from ethyl alcohol in colourless needles which became pasty at 190° and melted at 195° (Found in material dried at 100°: C, 54·0; H, 5·6. $C_{21}H_{26}O_3NI$ requires C, 54·0; H, 5·6%). In aqueous solution, $c = 0{\cdot}448$, $l = 1$, $\alpha_D = -0{\cdot}39°$, whence $[\alpha]_D = -87{\cdot}1°$.

Natural l-*Morphothebaine Dimethyl Ether*.—For comparison, a specimen of natural morphothebaine dimethyl ether was prepared by methylating morphothebaine with diazomethane as described

by Klee (*loc. cit.*). The oil obtained in this way was converted into the hydrogen *d*-tartrate, which crystallised from 95% ethyl alcohol in stellate clusters of shining needles, m. p. 208—209° (decomp.) (Klee gives 205°), and there was no depression of the melting point of a mixture of this material with the synthetical product. In aqueous solution, $c = 1{\cdot}040$, $l = 1$, $\alpha_D = -0{\cdot}78°$, whence $[\alpha]_D = -75{\cdot}0°$ (Klee gives $-74{\cdot}3°$). The oily base, which was liberated by sodium carbonate solution from the hydrogen *d*-tartrate (0·2150 g.), was extracted with chloroform (20 c.c.) as described in the case of the synthetical substance; $l = 1$, $\alpha_D = -1{\cdot}27°$, whence $[\alpha]_D = -172{\cdot}7°$ (Klee gives $-184{\cdot}8°$). With Erdmann's reagent an olive-green colour was immediately developed which changed to a dirty violet-blue and then became red on dilution, and with Fröhde's reagent a deep bluish-green colour was produced which finally became dull violet. The methiodide, prepared as described for the synthetical material, crystallised in needles which became pasty at 190° and melted at 195°, and this melting point was not altered on admixture with the synthetical preparation. In aqueous solution, $c = 0{\cdot}533$, $l = 1$, $\alpha_D = -0{\cdot}47°$, whence $[\alpha]_D = -88{\cdot}2°$.

d-*Morphothebaine Dimethyl Ether.*—The alcoholic mother-liquor from which the *l*-morphothebaine dimethyl ether hydrogen *d*-tartrate had separated (see above) was concentrated, mixed with ammonia, and extracted with ether. The extracts were washed with water, dried, and distilled, and the residue was converted into d-*morphothebaine dimethyl ether hydrogen* l-*tartrate* by mixing an alcoholic solution with an alcoholic solution of the requisite amount of *l*-tartaric acid. This salt separated when the vessel was rubbed, and crystallised from ethyl alcohol in stellate clusters of shining needles, m. p. 208—209° (decomp.) (Found in material dried at 100°: C, 60·6; H, 6·3. $C_{24}H_{29}O_9N$ requires C, 60·6; H, 6·1%). In aqueous solution, $c = 0{\cdot}821$, $l = 1$, $\alpha_D = +0{\cdot}62°$, whence $[\alpha]_D = +75{\cdot}5°$. The colourless oily d-*base*, liberated from the hydrogen *l*-tartrate (0·1231 g.), was dissolved in chloroform (20 c.c.); $l = 1$, $\alpha_D = +0{\cdot}76°$, whence $[\alpha]_D = +174{\cdot}2°$.

The authors wish to thank the Research Fund Committee of the Chemical Society for grants which have defrayed part of the cost of this investigation.

THE UNIVERSITY OF DURHAM,
ARMSTRONG COLLEGE,
NEWCASTLE-ON-TYNE.

THE DYSON PERRINS LABORATORY,
OXFORD.

[*Received, June 11th*, 1928.]

PRINTED IN GREAT BRITAIN BY RICHARD CLAY & SONS, LIMITED,
BUNGAY, SUFFOLK.