CCCCIV.—*Strychnine and Brucine. Part VII. The Constitution of the Alkaloids discussed in Relation to the Hypothesis that Dinitrostrychol is an* iso-*Quinoline Derivative.*

By Reginald Clifford Fawcett, William Henry Perkin, jun., and Robert Robinson.

In Part I (J., 1910, **97**, 305) of this investigation the chemistry of strychnine and brucine was discussed from the point of view that the alkaloids are at one and the same time derivatives of quinoline and carbazole, and when it became apparent that what we believe to have been the logical development of a structural hypothesis based on these premises could not be accepted, we were compelled to reconsider these fundamental assumptions.

The only thing that need be said about the question of the supposed carbazole nucleus in the bases is that there is definite experimental evidence pointing to the reality of its existence and that profound decompositions of strychnine do give rise to indole and carbazole (compare Clemo, Perkin, and Robinson, Part IV, J., 1927, 1589, on the formation of indole and carbazole from methylstrychnine); the same cannot be claimed for the hypothetical quinoline residue, since no known quinoline derivative has yet been obtained by the degradation or decomposition of strychnine.

In common, we suppose, with most other chemists who have studied these problems, we have regarded the formation of dinitrostrycholcarboxylic acid by the nitration and oxidation of strychnine with nitric acid (Tafel, *Annalen*, 1898, **301**, 336) as a proof of the existence of a quinoline ring in the alkaloid, but it is the purpose of this communication to point out that the proof is by no means a rigid one and that an alternative view may be sustained.

Furthermore, our new suggestion that dinitrostrychol is a dinitrodihydroxy*iso*quinoline has been found to be a starting point for the elaboration of new structural formulæ for strychnine and brucine which are capable of symbolising the behaviour of these bases and their derivatives in a satisfactory manner.

It is well known that strychnine contains two nitrogen atoms, of which one, a-N, is directly attached to an aromatic nucleus with a free para-position and also to a carbonyl group, whereas the other, b-N, is not attached to an aromatic nucleus and is the more basic of the two.

Clear indications that, in methylstrychnine, the methyl group is attached to b-N are given in Part IV (*loc. cit.*).

Now it is plain that, if dinitrostrycholcarboxylic acid is a quinoline derivative, the quinoline ring nitrogen atom must be a-N, and the portion of the molecule that includes b-N has been removed by oxidation; methylstrychnine, on this hypothesis, should also be oxidisable to dinitrostrycholcarboxylic acid.

Actually, we find that under the conditions for the production of the acid from strychnine, methylstrychnine gives a different substance (or substances) and the examination of this material, which is not yet complete, has shown that its composition is in fair agreement with the requirements of one of the formulæ

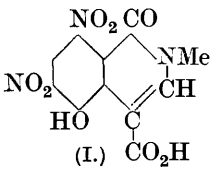
$C_{11}H_7O_8N_3$ (I), $C_{11}H_9O_8N_3$ (II), and $C_{10}H_5O_7N_3,\frac{1}{2}H_2O$ (III).

Direct estimation of the methyl attached to nitrogen gave values which were about 30% of that anticipated from I (containing a single NMe group), but as the methyl iodide was liberated with very great difficulty even at 360° it may well have happened that there was considerable reduction to methane.

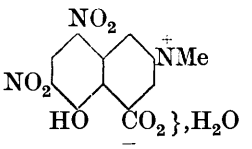
Further distillations gave quite negative results, producing no trace of methyl iodide, so that the presence of NMe in at least a part of the material was qualitatively demonstrated.

The most probable constitutions corresponding to the above formulæ are represented below and we are actively prosecuting this investigation and examining the oxidation products not only of methylstrychnine, but of other *b-N*-substituted strychnines with nitric acid.

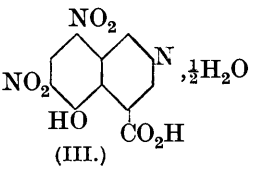
Synthetical work, in relation to the suggested formulæ, is also in progress and we wish to reserve for a short time the experimental development of the subject along the lines suggested by the new conceptions which we advance in this memoir.



(I.)



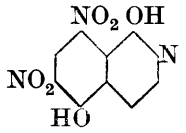
(II.)



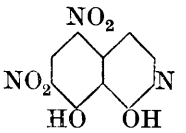
(III.)

For the purposes of the present discussion we are content to start with the fact that methylstrychnine does not yield dinitrostrycholcarboxylic acid on oxidation, and we deduce from this that the b-NMe group is not situated in the portion of the strychnine molecule that is broken up in the oxidation and that consequently the heterocyclic nitrogen of dinitrostrychol was originally the b-N

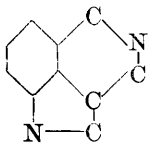
of a strychnine molecule. This is our basic assumption and we think it a sufficiently reasonable one to make it worth while to follow up the consequences. The sequel we believe to be an almost inevitable outcome of this view, but even if the latter proves to be incorrect, several of the suggestions made below can be incorporated in modified strychnine and brucine formulæ and would thus retain some value. If the ring-nitrogen of dinitrostrychol is the b-N of strychnine, then dinitrostrychol must be a dinitrodihydroxy*iso*-quinoline, since b-N cannot be attached to the aromatic nucleus.* In that case a consideration of the fate of the a-N which was attached to the benzene nucleus suggests that the place of a-N is taken by hydroxyl, and on this basis the formulæ (IV) and (V) are feasible as representations of dinitrostrychol.



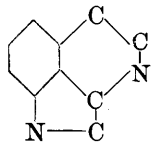
(IV.)



(V.)



(VI.)

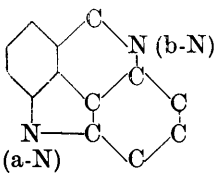


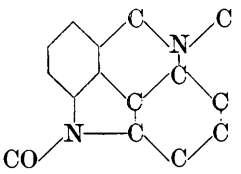
(VII.)

In view of the frequently observed degradation of strychnine to indole derivatives, (IV) and (V) point to the skeletons (VI) and (VII), respectively, as part of the strychnine molecule.

Of these (VI) seems preferable, for it allows the carbazole skeleton to be introduced in a natural manner and we arrive at the conclusion that (VIII) is a ring system of strychnine. This can be expanded to (IX) in view of the tertiary basic character of b-N and the inclusion of a-N in an acid amide grouping.

(VIII.)



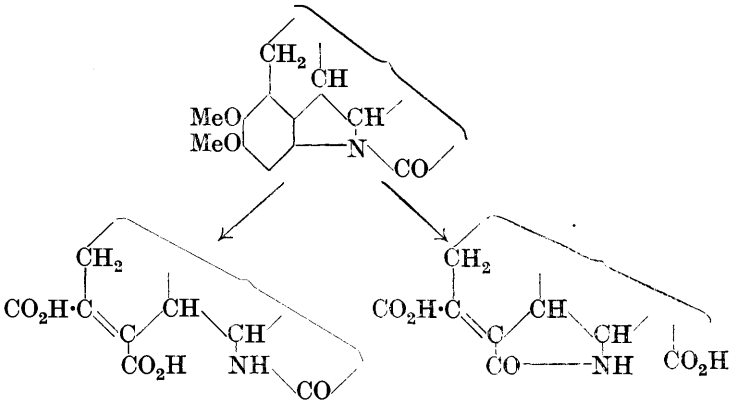


(IX.)

This hypothesis that the benzene nucleus of strychnine bears three substituents must be tested in relation to those degradations in which the benzene nucleus is broken up. No difficulties are encountered in this connexion and, for example, the degradation of brucine to Hanssen's acid, $C_{19}H_{22}O_6N_2$, by way of kakothelin

* Because strychnine, unlike strychnidine, does not exhibit the properties of an alkylated aromatic amine with a free para-position.

(nitrobruciquinone hydrate) can be expressed in full detail, the final result being given by the alternatives.



The degradation can be similarly represented if the methoxy-groups are situated in the alternative position vicinal to the indole nitrogen.

It should be mentioned at this point that the very facile nitration of strychnine to dinitrostrychnine hydrate has always appeared to us to require some special explanation.

Conceivably the formation of a phenol by rupture of the bond between the aromatic nucleus and a-N occurs at an early stage and both dinitrostrychnine hydrate and nitrobrucine hydrate may be nitrophenolic substances.

In order to make further progress it is necessary to consider the important series of degradations of strychnine and brucine that were carried out by Leuchs and his collaborators (Leuchs, *Ber.*, 1908, **41**, 1711; Leuchs and Schneider, *Ber.*, 1908, **41**, 4393; 1909, **42**, 2494; Leuchs and Weber, *ibid.*, p. 3703; Leuchs and Reich, *Ber.*, 1910, **43**, 2417; Leuchs and Brewster, *Ber.*, 1912, **45**, 201; Leuchs and Peirce, *ibid.*, pp. 2653, 3412; Leuchs and Rauch, *Ber.*, 1914, **47**, 370; Leuchs, *ibid.*, p. 536; Leuchs and Schwaebel, *Ber.*, 1914, **47**, 1552; 1915, **48**, 1009; Leuchs and Bendixsohn, *Ber.*, 1919, **52**, 1443; Leuchs and Ritter, *ibid.*, p. 1583; Leuchs, Hellriegel, and Heering, *Ber.*, 1921, **54**, 2177; Leuchs, Grüss, and Heering, *Ber.*, 1922, **54**, 3729; Leuchs and Nitschke, *ibid.*, p. 3738; Leuchs, Gladkorn, and Hellriegel, *Ber.*, 1923, **56**, 2472).

We offer a new interpretation of these results.

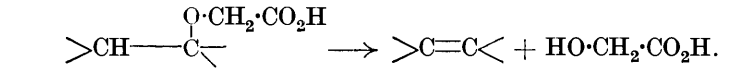
On oxidation with potassium permanganate in acetone solution, brucine, $C_{23}H_{26}O_4N_2$, yields the keto-acid brucinonic acid, $C_{23}H_{24}O_8N_2$, and the secondary alcoholic dihydrobrucinonic acid,

$C_{23}H_{26}O_8N_2$. A stereoisomeride of the latter, namely, brucinolic acid, is obtained by the reduction of brucinonic acid with sodium amalgam.

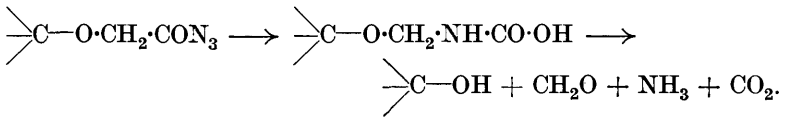
When brucinolic acid is heated with aqueous potassium hydroxide it yields the neutral brucinolone, $C_{21}H_{22}O_5N_2$, and glycollic acid :

$$C_{23}H_{26}O_8N_2 = C_{21}H_{22}O_5N_2 + C_2H_4O_3.$$

There is no evidence that brucinonic acid is other than a monocarboxylic acid, although a second carboxyl appears to be latent in an *N*-CO group; moreover, the formation of *N*-CO linkages in dilute alkaline solution from >NH and $-CO_2H$ seems improbable. Therefore, by far the simplest and most acceptable view of the loss of glycollic acid is that represented by the scheme :

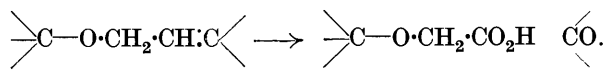


This is supported by the facts that (1) brucinolone contains an ethylene linkage not contained in brucinolic acid, and (2) the acid azide derived from dihydrobrucinonic acid decomposes with formation of formaldehyde (Leuchs and Kanao, *Ber.*, 1924, **57**, 1318) :



We need no more than this to show that strychnine and brucine contain cyclic ether oxygen and since the alkaloids also contain one double bond (compare Part VI, Oxford, Perkin, and Robinson, J., 1927, 2389) the complete nuclear system must be elaborated from (IX) by the inclusion of three more rings.

Further, since the double bond is the point of attack of the oxidising agent, a part of the changes involved in the formation of brucinonic acid must be due to the fission

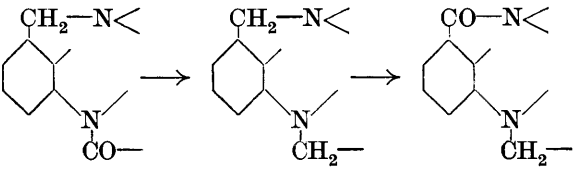


This adds 3O and in some other part of the molecule we must add O and subtract 2H; it is clear that this must be due to the conversion of $-CH_2-N$ (b) into $-CO-N$ (b), because otherwise there is nothing to account for the neutral character of brucinolone.

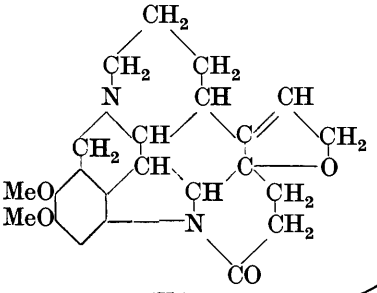
A formula derived from (IX) will include a methylene group which should, on grounds of analogy, be readily oxidised to carbonyl, because it is well known that the carbon atom numbered 1 in the reduced *iso*quinoline ring exhibits a marked susceptibility to oxidising agents.

Furthermore, in the course of experiments on the reduction

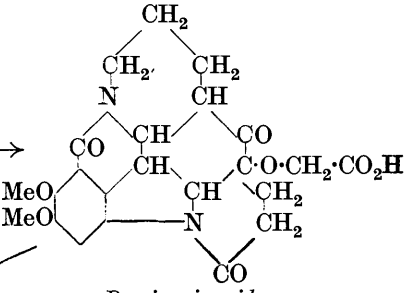
products of strychnine, a substance has been isolated which appears to be a kind of *epi*strychnine, produced in accordance with the scheme :



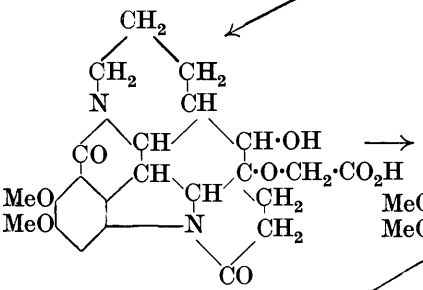
It is hoped that an account of this work will shortly be submitted to the Society.



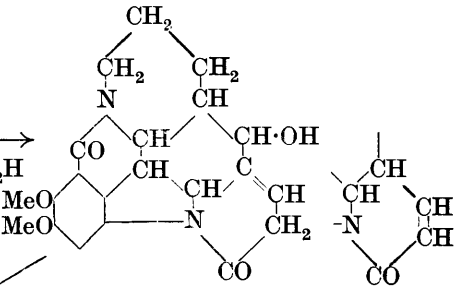
(X.)



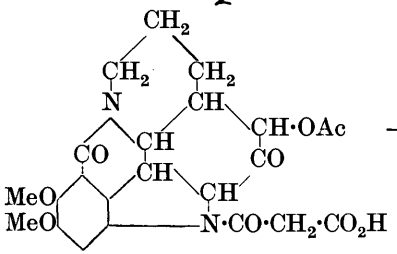
Brucinonic acid.



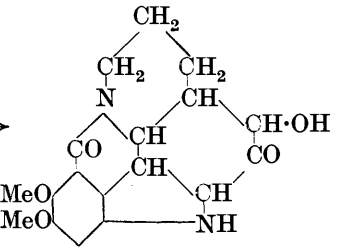
Dihydrobrucinonic and Brucinolic acids.



(*a*) *Brucinolones.* (*b*)

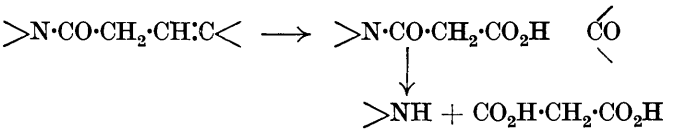


Acetylbrucinolonic acid.



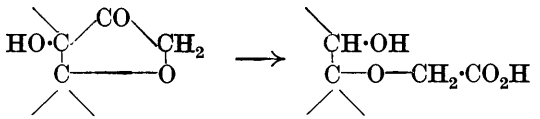
Curbine.

The further degradation of brucinolone to curbine has already been interpreted by Leuchs by means of the scheme :



The elaboration of (IX) so as to accommodate these results can be effected in various ways, and we have considered many alternatives; of these we prefer that, shown below, arising from the postulation of the constitution (X) for brucine.

The formation of dihydrobrucinonic acid by the direct oxidation of brucine is, on every view, a curious result; it may be due to the hydrolytic fission :



Some examples of the application of the expression (X) and the analogous strychnine formula (XI) to the explanation of the chemistry of the reduction products are represented in the annexed scheme.

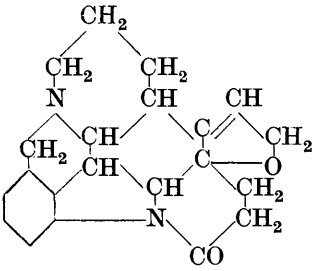
These transformations, described in Part IV (Clemo, Perkin, and Robinson, J., 1927, 1589), take a more normal course at the stage (XII) ⟶ (XIII), when the double bond in (XII) is saturated, the original ring system being reproduced.

Strychnidone (XIV) is here represented as a β-hydroxy-ketone, and the disemicarbazone described in Part IV is then in all probability a semicarbazido-semicarbazone and belongs to a recognised type of αβ-unsaturated ketone derivatives.

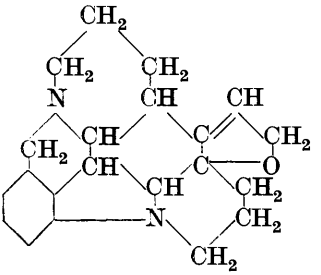
The formulæ for tetrahydrostrychnine and the products of catalytic reduction of strychnine derivatives (compare Part VI, *loc. cit.*) follow automatically, but it must be confessed that we have no very satisfactory explanation of the existence of *iso*-strychnine and dihydro*iso*strychnine to put forward.

The ether oxygen appears to become hydroxylic and it is therefore possible that the formation of *iso*strychnine involves an intramolecular transfer of hydrogen and that the C–O–C group is reduced to $\geqslant$CH HO·C$\leqslant$; perhaps the dihydroindole group provides the necessary hydrogen atoms.

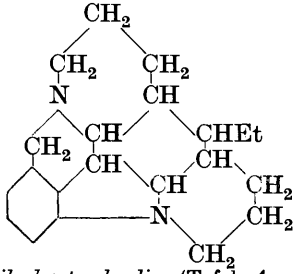
Before considering the permissible modifications of the structures



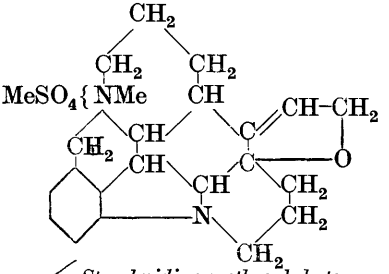
(XI.)



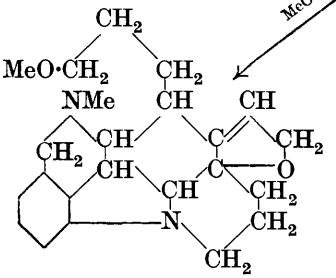
Strychnidine.



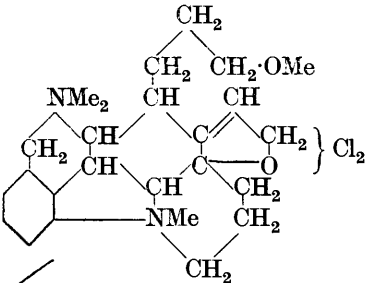
Dihydrostrychnoline (Tafel, *Annalen*, 1898, **301**, 324, 326).



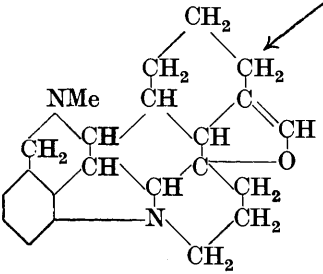
Strychnidine methosulphate.



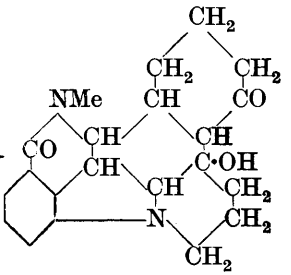
Methoxymethyldihydrostrychnidine.



Dimethochloride (XII).

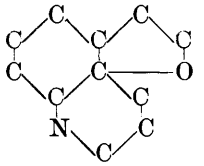


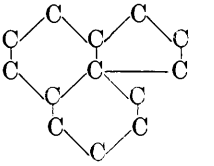
Methyl-ψ-strychnidine (XIII).



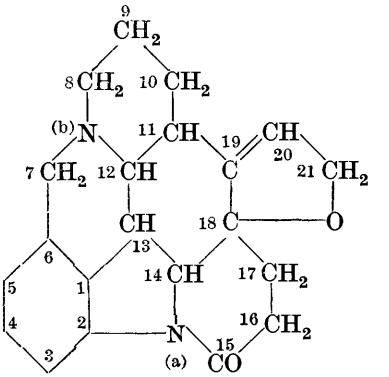
Strychnidone (XIV).

(X) and (XI) it may be noted that the assumed ring system (XV) is a heterocyclic analogue of that (XVI) occurring in cholesterol.

(XV.) 

 (XVI.)

A still more significant coincidence is that the formula (XI) contains three straight chains of seven carbon atoms and all are terminally attached to nitrogen. These chains serve as the basis for the numbering given below and allow us to regard strychnine as the reduction and condensation product of a cyanogenetic glucoside which would, of course, contain the C_6–C–N group.



The chief modifications of the formula (XI) that could be made appear to be the following, and various combinations of these are obviously possible. We have selected a definite formula for purposes of illustration only and the alternatives are not excluded.

(1) Some of the rings may be bridged-rings. For instance, C-10 may be attached, not to C-11, but to C-13 or C-14, preserving in the latter case the three chains of seven carbon atoms. This view is a serious alternative, for it has the advantage that the hydroindole nucleus is blocked and the formation of carbazole involves less stripping off of external groups.

C-20 also might be attached to some other carbon atom, for example, C-10. This spoils the three chains of seven carbon atoms but gives a curbine formula not containing the group –CO·CH(OH)–.

(2) The carbon atoms 8, 9, and 10 may take the *iso*-form $-CH_2\cdot CHMe-$. In certain cases this is also possible for 15, 16, 17.

(3) The ring oxygen may be attached to C-11, givin different but analogous formulæ for the Leuchs series of degradation products. This alternative requires that C-8 should be the point of oxidation, $-N-CH_2- \longrightarrow -N-CO-$. The attachment of the ring oxygen to C-17 we consider to be improbable in view of the alkaline decomposition of brucinolic acid which gives, as the primary product, brucinolone-a containing the group $-N\cdot CO\cdot CH_2\cdot CH{=}\overset{|}{C}-$, and this is further transformed by alkali into brucinolone-b characterised by the group $-N\cdot CO\cdot CH{=}CH-\overset{|}{C}H-$ (Leuchs and co-workers, *loc. cit.*). We are of the opinion that a group $-N\cdot CO\cdot CH_2\cdot \overset{|}{C}H-\overset{|}{C}H-$ would $\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad O\cdot CH_2\cdot CO_2H$ give, in the first instance, the αβ-unsaturated substance on fission in alkaline solution.

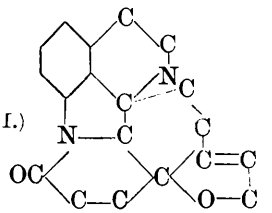
The view which we have put forward in relation to strychnidone (XIV) is also untenable if the ring oxygen is attached to C-17.

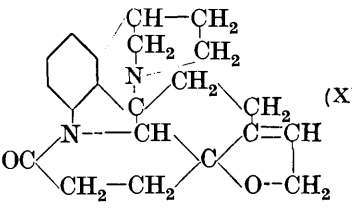
(4) The work of Lions, Perkin, and Robinson (Part III, J., 1925, **127**, 1158) showed that the methoxyls in brucine are situated in the ortho-position to one another and that there can be no free position para to either of the methoxyls. Thus the methoxyls may occupy the positions 4 and 5 as in (X) or positions 3 and 4.

(5) Going back to the alternative (VII), which was temporarily set aside in view of the less bizarre character of the formulæ based on (VI), the inclusion of a carbazole skeleton and the groups necessary to express the Leuchs degradations gives (XVII) or a very similar skeleton. Two carbon atoms must be added; one of them is required to make b-N tertiary, and the other to provide the carboxyl group of dinitrostrycholcarboxylic acid. This leads to the strychnine formula (XVIII) or bridged-ring alternatives.

The decision between structures based on (VI) and those based on (VII) can best be made by a synthesis of dinitrostrychol, which we are attempting at the present time.

(XVII.)





(XVIII.)

Concurrently with the investigations referred to above, we are continuing our study of the reduction products of strychnine and brucine and have been for some time engaged in the careful examination of the crystalline substances formed when the methosulphates

ot strychnine and strychnidine are submitted to the action of sodium amalgam One of the rings can be readily opened in this way and we wish to reserve for a short time the investigation of this interesting decomposition.

THE UNIVERSITIES OF OXFORD AND MANCHESTER, AND
UNIVERSITY COLLEGE, LONDON. [*Received, November 8th*, 1928.]