137. *Strychnine and Brucine. Part XLI. Re-examination of the Action of Bromine on Diketonucidine and its Bearing on the Structure of the Alkaloids.*

By H. L. Holmes and (Sir) Robert Robinson.

We have been able to reproduce the descriptive results of Leuchs (*Ber.*, **1932**, **65**, 1237) in connexion with the action of bromine on diketonucidine in aqueous solution and the subsequent isolation of the perchlorate of a base. The product in our experiments was found to be diketonucidine perchlorate. The argument from this reaction is accordingly reversed and examination of other reasons for the belief that the β-position of the hydroindole nucleus bears a hydrogen atom throws serious doubt on the validity of this conclusion.

It is probable that the base $C_{17}H_{20}O_3N_2Br_2$, obtained from cacotheline by the action of bromine, is 3 : 3-dibromo-2-hydroxynucine, and its product of hydrolysis, $C_{17}H_{22}O_5N_2$, is regarded as 2-keto-3-hydroxynucine hydrate. The balance of evidence now points unmistakably to a particular constitutional formula for strychnine (II).

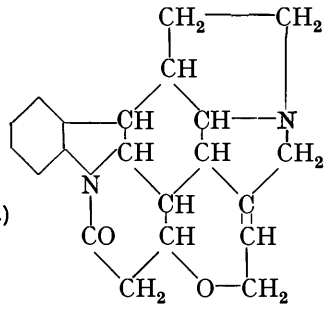
An interpretation of the chemistry of the alkaloids and the course of the known degradations of strychnine and brucine, including the permanganate-oxidation series of Leuchs, was first given definite shape in full formulæ in which N(a) formed part of a tetrahydroquinoline nucleus (Bakerian Lecture of 1930, *Proc. Roy. Soc.*, 1931, *A*, **130**, 431). Shortly afterwards the recognition that dinitrostrycholcarboxylic acid is 5 : 7-dinitroindole-2 : 3-dicarboxylic acid led to a recasting of the proposed constitutions, but the essential features of the earlier views were retained.

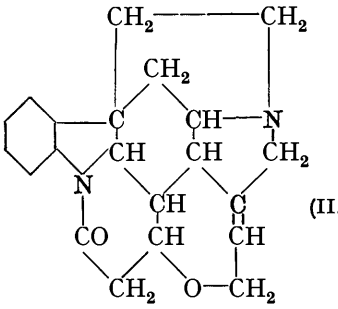
The first structure formulated at this stage was (I), and K. N. Menon submitted a thesis to the University of London on this basis in 1931. Further considerations showing that strychnine cannot bear hydrogen atoms in both the 2- and the 3-position of the indole nucleus and must be a 2 : 3-trisubstituted dihydroindole derivative resulted in the modification to (II) (Menon and Robinson, J., 1932, 781). A few months later Leuchs (*Ber.*, **1932**, **65**, 1230) adopted the formula (I) and stated that it " differed little from that proposed by the English chemists." The structure (I) is indeed identical with that developed in this series of papers with the exception of a slight modification which we had considered and rejected for what appeared, and still appear, to be good reasons.

A very strong argument against (II) was provided by the observation of Leuchs (*loc. cit.*) that diketonucidine (III on the basis of II) could be readily monobrominated, pre-

sumably in the α-position to the keto-carbonyl group. Hence it was considered necessary to contemplate the alternative (IV) (Blount and Robinson, J., 1932, 2308).

(I.)

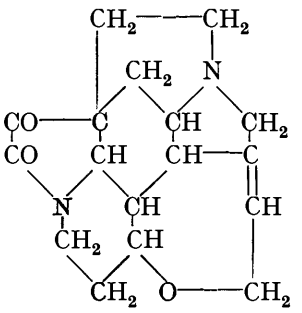


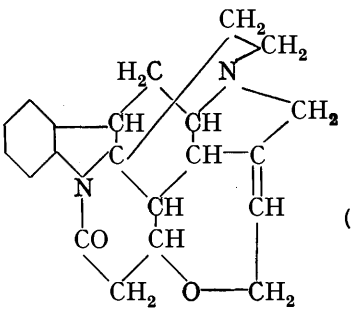


(II.)

The formula (IV) (or an expression including both II and IV) was employed in later papers, the only reason for doing so being the failure of (II) to explain the bromination of diketonucidine. A clear statement to this effect was made in Part XXVI (Achmatowicz and Robinson, J., 1934, 583). Strong evidence that the ethanamine chain is attached to the β-position of the indole nucleus was provided by the discovery that degradation of strychnine and some of its derivatives by hot alkali affords tryptamine in significant

(III.)





(IV.)

amount (Kotake, *Proc. Imp. Acad. Tokyo*, 1936, **12**, 99; Clemo, J., 1936, 1695), and, this structural feature being accepted, location of a hydrogen atom in the β-position would imply that the upper methylene of the carbazole skeleton of (II) is attached to the α-position. This third possibility (Openshaw and Robinson, J., 1937, 941) did not commend itself on general grounds, but it seemed necessary in order to reconcile the formation of tryptamine with the monobromination of diketonucidine.

As all the other evidence of a hydrogen atom in the β-position is inconclusive and capable of different explanations, we thought it desirable to examine bromodiketonucidine hydrate perchlorate more closely and expecially to study the function of the halogen; if, for example, the bromo-derivative were an α-bromo-ketone, it should be reducible by hydrogen iodide.

The bromination experiment described by Leuchs (*loc.cit.*) is a simple one and in our repetitions the various superficial changes which he recorded were always observed. The product had about the same rotatory power as the supposed bromodiketonucidine hydrate perchlorate of Leuchs, but it was diketonucidine perchlorate and bromination had not occurred in the manner stated. Nevertheless diketonucidine does take up a molecular proportion of bromine and the solution then becomes neutral and bromination ceases; diketonucidine perchlorate, on the other hand, does not react with bromine under the same conditions.

The salt isolated by Leuchs gave analytical results (no bromine estimation) for a bromodiketonucidine hydrate perchlorate, and it crystallised in " right-angled tablets." We have not obtained this substance and we suggest it may have been an unstable N(a)Br derivative [because N(a)·CO is hydrolysed when a hydrate is formed] which slowly passes in aqueous solution into diketonucidine perchlorate and perhaps a bromate. It is possible

that the specimen analysed by Leuchs was not the same as that used for the determination of rotatory power and that the latter was, as in our experiment, diketonucidine perchlorate. This salt crystallises in irregular hexagonal plates, prismatic needles, or prisms.

Conceivably a small part of the base is oxidised or brominated by several molecules of bromine (or dehydrogenated and later combined with bromine, which is an equivalent process) and the hydrogen bromide so liberated stabilises the rest of the diketonucidine, which could then be isolated as the perchlorate. Such far-reaching bromination or oxidation might be anticipated in the case of a base which can form a dibromide and a perbromide and contains so many alicyclic structures.

Other explanations of the disappearance of a molecular proportion of bromine have not been excluded. Thus the formation of bromide and bromate is possible so long as the solution has an alkaline reaction. In any case the experiment now provides no positive evidence bearing on the structural problem and the negative result, so far as it goes, supports the view that the β-position of the dihydroindole nucleus is disubstituted.

In addition to the bromination of diketonucidine, Leuchs (*loc. cit.*) has cited the nature of the transformation products of diketonucic acid hydrate, $C_{17}H_{20}O_8N_2$ (Leuchs and Hoffmann, *Ber.*, 1929, **62**, 1253; 1930, **63**, 442), in support of the hypothesis that the β-position of the indole nucleus bears a hydrogen atom. This is obtained from Hanssen's acid, $C_{19}H_{22}O_6N_2$ (Hanssen, *Ber.*, 1887, **20**, 451; H. Leuchs, Mildbrand, and W. R. Leuchs, *Ber.*, 1922, **55**, 2403), by permanganate oxidation to $C_{17}H_{22}O_6N_2$ (:C:CH·CO_2H ⟶ :CO + $C_2H_2O_4$), followed by the action of bromine in hydrobromic acid, which by lactamisation and oxidation affords an aldehydo-acid, $C_{17}H_{20}O_7N_2$. The oxidation to a dicarboxylic acid, $C_{17}H_{20}O_8N_2$, is effected by means of mercuric oxide. The order of these stages can be varied and $C_{19}H_{22}O_6N_2$ may be treated successively with bromine, mercuric oxide and permanganate.

Furthermore, $C_{17}H_{22}O_6N_2$ is Wieland's acid obtainable directly from brucine by oxidation with chromic acid (Wieland and Münster, *Annalen*, 1939, **469**, 216). This acid is a ketonic dicarboxylic acid and if the action of bromine involves opening of a double bond (·O·CH_2·CH:C: ⟶ ·O·CH_2·CHO CO:) it should produce a diketo-aldehydo-acid (one carboxyl lactamising). Only two carbonyl groups can be diagnosed and the second carbonyl group, apparently produced in this fission of bromine in all similar reactions, is inert towards semicarbazide. On the basis of the above hypothesis (cf. Bakerian Lecture, *loc. cit.*) this is a curious circumstance, because the inactive carbonyl would have the same situation as the active keto-carbonyl of strychninonic acid. The latter may, it is true, be activated by its inclusion in the system N(b)·CO·CO. N(b)·$\dot{C}H_2$ is not oxidised to N(b)·CO in the bromine fission, because it is apparent from the isolation of many of the products as hydrobromides that N(b) retains its basic character. It may be that this view of the bromine fission at the double bond is incorrect, and that the oxidation occurs at the ether linkage, accompanied by addition of the elements of water to the double bond, possibly in the *neo*-position.

The point made by Leuchs is that $C_{17}H_{20}O_8N_2$ is reducible to $C_{17}H_{22}O_8N_2$ in which a keto-group cannot be recognised (presumably :CO ⟶ ·CH·OH) and which, when heated with hydrobromic acid, affords an unsaturated acid, $C_{17}H_{20}O_7N_2$. It is suggested by Leuchs that the reaction proves the occurrence of hydrogen in the β-position of the indole structure (position 4 of nucine), because the double bond must be located between carbon atoms 3 and 4 of nucine. The unsaturated acid has not been submitted to further close study and, in view of the possibility of intramolecular migration and the many dubieties, its formation is susceptible of alternative explanations. The formulation of the curious yellow dianhydride of $C_{17}H_{20}O_8N_2$ prepared by Leuchs is difficult on the basis of the straightforward view of the constitution of the acid, and it seems that we are dealing with a degradation that presents its own problem.

A further series relevant to the present discussion is that derived from the base $C_{17}H_{20}O_3N_2Br_2$, which is a by-product of the action of bromine on cacotheline (Leuchs, Mildbrand, and Leuchs, *loc. cit.*). We would suggest that this is 3 : 3-dibromo-2-hydroxynucine, [N(a) being numbered 1] or the ring-chain tautomeric aldehyde, but probably the

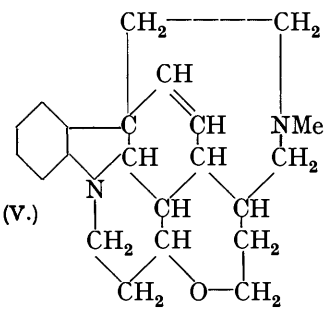
former in view of the ease with which chloral condenses with amides. The substance, $C_{17}H_{22}O_5N_2$, obtained from it by the action of barium hydroxide might be the related α-keto-aldehyde, but as it is neutral in reaction a carboxyl group is probably present and the most likely formulation is that of a 2-keto-3-hydroxynucine hydrate [$-CBr_2\cdot CHO \longrightarrow -CH(OH)\cdot CO_2H$]. The amide ring opened might be either the pyrrolidine or piperidone ring of a 2-ketonucine. The oxidation of $C_{17}H_{22}O_5N_2$ to $C_{17}H_{22}O_6N_2$ (Wieland's acid) then involves $-CH(OH)- \longrightarrow -CO-$ and $:N\cdot CO\cdot \longrightarrow :NH\cdot CO_2H$, a more natural view than that put forward by Leuchs and Hoffmann (*Ber.*, 1930, **63**, 439).

The anhydride of the diacetyl derivative (Leuchs and Hoffmann, *Ber.*, 1929, **62**, 2309) previously described as 2 : 3-diacetoxy-Δ^3-nucenine is probably 2 : 3-diacetoxy-Δ^2-nucenine. This again is a natural explanation involving $\cdot CO\cdot NH\ CO_2H\cdot CH(OH) \longrightarrow -CO\cdot\dot{N}\cdot C(OAc)=C(OAc)$. According to Leuchs the substance $C_{17}H_{22}O_5N_2$ contains neither carbonyl nor carboxyl groups (*Ber.*, 1929, **62**, 1934), but the absence of the latter was inferred as the result of an experiment in which the hydrobromide of the substance was treated with boiling 10% methyl-alcoholic hydrogen chloride and the salt did not pass into solution. In an earlier paper the neutrality of $C_{17}H_{22}O_5N_2$ was noted and it was pointed out that this suggests the presence of a carboxyl group. The anhydro-diacetyl derivative has an alkaline reaction.

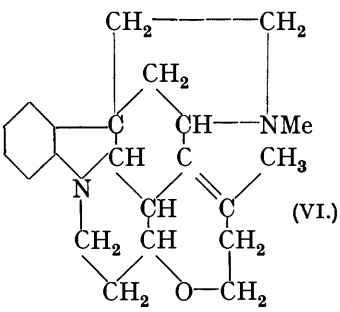
The reduction products of $C_{17}H_{20}O_3N_2Br_2$ offer no difficulties. One or two bromine atoms may be replaced by hydrogen; $C_{17}H_{22}O_3N_2$ (2-hydroxynucine) may be oxidised to $C_{17}H_{22}O_4N_2$, which is the lactam of the acetic acid corresponding to Wieland's acid ($\cdot CH_2\cdot CO_2H$ instead of $\cdot CO\cdot CO_2H$ and $\cdot CO_2H\{-NH_2 \longrightarrow -CO\cdot NH$). Clemmensen reduction of $C_{17}H_{20}O_3N_2Br_2$ gives $C_{17}H_{22}O_2N_2$, which is nucine (Leuchs and Hoffmann, *loc. cit.*). The constitutions mentioned above have already been propounded by Leuchs and Wegener (*Ber.*, 1930, **63**, 2216) for $C_{17}H_{22}O_2N_2$, $C_{17}H_{22}O_3N_2$ and $C_{17}H_{22}O_4N_2$, but $C_{17}H_{20}O_3N_2Br_2$ has been regarded as 3 : 4-dibromo-2-hydroxynucine and $C_{17}H_{22}O_5N_2$ as the corresponding 2 : 3 : 4-trihydroxynucine. The assumed neutralisation of the basic function of N(b) by three hydroxyl groups is not in accord with experience of other polyhydroxy-bases. Our new interpretations appear consistent with the facts, and do not require substitution of the 4-position of nucine by bromine or hydroxyl.

Finally the bromination of diketodihydronucidine is also mentioned by Leuchs (*loc. cit.*), but experimental details are not available. Under conditions similar to those used for the attempted bromination of diketonucidine we find that the unchanged base may be recovered as perchlorate.

A large part of the perplexity and ambiguity in regard to the constitutions of the *strychnos* bases is thus resolved. There is no longer any sound objection to the structure (II) for strychnine and in spite of the supposed difficulty of the β-hydrogen this expression



(V.)



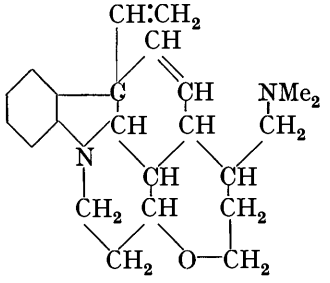
(VI.)

has always seemed the most natural. In planning a synthetic investigation attention was focused on this formula and it has been given prominence over alternatives in various lectures (cf. XIXth Earl Grey Memorial Lecture, King's College, Newcastle-upon-Tyne, 1937).

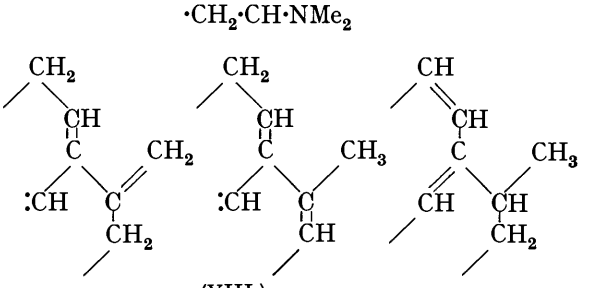
The only part of the theory which is affected by the definite adoption of formula (II) for strychnine is that connected with the Hoffmann ring-fissions in derivatives of dihydro-

strychnidine-A. The formula (V) can now be allotted to the *des*-base-D (J., 1934, 581) and dihydrostrychnidine-D is either (ID) (printed on p. 1468, J., 1938) or, less probably a stereoisomeride of dihydrostrychnidine-A.

The *des*-base, m. p. 143°, termed methyl*chano*dihydro*neo*strychnidine, is probably (VI). The second stage of the Hoffmann process applied to (V) (Achmatowicz and Dybowski, J., 1938, 1483) gives dimethyl*des*strychnidine-D (VII), this substance having been recognised as containing a vinyl group. This *des*-base is not obtained from (VI). The structure of the *des*-base from (VI) not obtained from (V), namely, dimethyl*desbisneo*strychnidine (Achmatowicz, J., 1938, 1472), cannot yet be deduced, but it may correspond to one of the part formulæ (VIII).



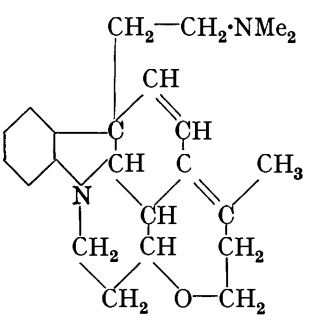
(VII.)

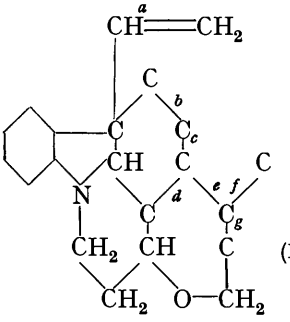


(VIII.)

The common *des*-base from (V) and (VI), termed dimethyl*desneo*strychnidine, is probably (IX). The positions available for the three double bonds of the isomeric *des-aza*strychnidines are indicated in (X) and are *a*, *b*, *e*; *a*, *b*, *d*; *a*, *c*, *f*; *a*, *c*, *g*.

(IX.)





(X.)

Experimental.

Strychnidine.—The previous descriptions of the preparation by Tafel's method (cf. J., 1924, **125**, 1798; 1927, 1600) require supplement in a few details. The strychnine sulphate solution, made up as stated, was placed in the cathode chambers of six cells in series, and the temperature kept below 12° (not 18° as recorded). The crude mixture of bases was extracted with boiling alcohol (800 c.c.), and the residue crystallised from the same solvent (1500 c.c. in five portions). The yield was that formerly reported, and the strychnidine had m. p. 244—245°.

Diketonucidine (Leuchs and Kröhnke, *Ber.*, 1930, **63**, 1045; Leuchs and Schulte-Overberg, *Ber.*, 1931, **64**, 1007).—The base employed had m. p. 267—269° (clear liquid at 273°) and $[\alpha]_D^{20°}$ + 56·2°/*d*. Leuchs and collaborators give $[\alpha]_D^{13°}$ + 56°/*d* and $[\alpha]_D$ + 55°/*d*. The perchlorate crystallised in six-sided plates and had $[\alpha]_D^{20°}$ + 95°/*d* (Leuchs and Schulte-Overberg give $[\alpha]_D^{24°}$ + 94°/*d*). Leuchs and Kröhnke's statement that this salt crystallises in four-sided plates and prisms is of interest, because the brominated hydrate perchlorate was also stated to crystallise in right-angled tablets. We have not observed this habit of crystallisation.

Action of Bromine on Diketonucidine.—The experiment was conducted as described by Leuchs (*loc. cit.*). A solution of diketonucidine (0·6 g.) in water (24 c.c.) was stirred at 5°, and 10 c.c. of bromine water (made from 12 c.c. of 0·4N and 24 c.c. of water) added at the rate of about 7 drops in a minute. Yellow plates separated and later disappeared, giving a colourless solution

with a small amount of suspended solid. After the addition of 2 c.c. (20% excess over 1 mol.) more of the bromine water, a clear colourless solution resulted and this was concentrated at room temperature under diminished pressure to about 4 c.c. Aqueous perchloric acid (2 c.c. of 2N) was added and nodules began to separate in about an hour's time. After 12 hours the salt was collected (0·45 g., and 0·25 g. more on further concentration). This material was found to be free from oxidising or ionisable bromine; it reacted with dilute sodium iodide and sulphuric acid on gentle heating at the same slow rate as diketonucidine perchlorate. The salt was recrystallised four times by solution in water and concentration at room temperature. It then had $[\alpha]_D + 97°/d$ (Found in material dried at room temperature over phosphoric oxide under 1 mm. pressure : C, 48·3; H, 5·6; Cl, 8·8; loss at 100°/1 mm., 4·0. $C_{17}H_{20}O_3N_2,HClO_4$, H_2O requires C, 48·8; H, 5·5; Cl, 8·5; H_2O, 4·5%).

This salt (0·2 g.) was dissolved in water (25 c.c.), and the solution rendered ammoniacal and extracted with chloroform. The residue from the separated and dried extract was crystallised from alcoholic solution by concentration at room temperature (0·12 g. of the base) (Found : C, 67·6; H, 6·5; Br, 0·0. Calc. for $C_{17}H_{20}O_3N_2$: C, 68·0; H, 6·7%). Material dried at 100°/10 mm. had $[\alpha]_D^{2°} + 57·3°/d$ in water. When diketonucidine perchlorate was treated with bromine under conditions similar to those used for the base, bromine was not absorbed and the unchanged salt was recovered.

Dihydrostrychnidine-A.—Improved results were obtained when strychnidine (9·9 g.) was hydrogenated in acetic acid solution (50 c.c., distilled over potassium permanganate) at 17°/762 mm. in the presence of Adams's platinic oxide catalyst (0·1 g.). Hydrogen (830 c.c.; theoretical, 822 c.c.) was absorbed in 6 hours. The product (9·2 g.) had m. p. 208—209° after one crystallisation, m. p. 213—215° and 215—216° after two and three crystallisations.

Diketodihydronucidine was obtained by the method of Leuchs and Kröhnke (*loc. cit.*) in 12·6% yield and had the recorded properties. The base (0·45 g.), dissolved in water (18 c.c.) at 5°, was treated with bromine water (9·0 c.c. of 0·4N) as in the previously described experiment. A considerable yellow flocculent precipitate made its appearance and later passed very slowly into a colourless solution. After 7·5 c.c. of the bromine water had been added, the solution was neutral and when the rest was added the yellow colour of the bromine was persistent. The solution was concentrated at room temperature in a vacuum to 3 c.c. and mixed with perchloric acid (1·5 c.c. of 2N). The perchlorate slowly separated as pinkish crystals, and was recrystallised in the same manner, being obtained as thin plates having $[\alpha]_D^{20°} + 135·4°/d$ (Leuchs and Kröhnke, *loc. cit.*, give $[\alpha]_D^{15°} + 136°/d$ for diketodihydronucidine perchlorate). The yield after two crystallisations was 0·32 g. exclusive of further material obtained from the mother-liquors (Found : Cl, 9·0. $C_{17}H_{22}O_3N_2,HClO_4$ requires Cl, 8·8%). Estimation of carbon and hydrogen failed as the result of explosive decomposition; the salt was not analysed by Leuchs and Kröhnke.

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