279. *Strychnine and Brucine. Part XXXVII. Conversion of Dihydrostrychnidine-D into Dihydrostrychnidine-A.*

By O. Achmatowicz and Robert Robinson.

In Part XXVI (J., 1934, 581) the production of two *des*-bases by thermal decomposition of methyldihydrostrychnidinium-A carbonate was recorded. One of these gave a dihydro-derivative on catalytic hydrogenation, but the other (*des*-base-D), in acetic acid as solvent, was converted into a quaternary ammonium salt by a reversal of the Hofmann and Emde fission. It is now found that methyldihydrostrychnidinium-A acetate is a by-product of this process and the implications are discussed.

The relations of some of the substances mentioned in this communication are shown in the scheme on p. 1468.

Further study of the catalytic reduction of the *des*-base-D has shown that the main product, methyldihydrostrychnidinium-D acetate, is accompanied by a smaller but substantial amount of the isomeride-A. This proves that the *des*-base-D is in reversible relation with two different dihydrostrychnidine systems. Three explanations suggest themselves :

(1) Dihydrostrychnidines-A and -D may be stereoisomerides. This view appears from the models to be a possible one on the basis of some of the strychnine structures at present under discussion. For example, in (III) the two five-membered rings may be fused in the *cis*- or *trans*-position and the other rings can be added equally conveniently in both cases. Similar stereoisomerism may be recognised on the basis of (I), but it is not so with (II) and (IV). The quite different behaviour of the isomeric dihydrostrychnidine metho-salts on decomposition (cf. Part XXVI, *loc. cit.*) tells against the hypothesis of stereoisomerism. Although the argument is not conclusive, it is most probable that the isomerism of the A and D series is structural.

Strychnine $C_{21}H_{22}O_2N_2$ [N(a)·CO; N(b), tert.-basic; C=C] $\xrightarrow{\text{electr. red.}}$ Strychnidine $C_{21}H_{24}ON_2$ [N(a)·CH_2·; :C=C:] $\xrightarrow{\text{Pd, H}_2}$ Dihydrostrychnidine-A $C_{21}H_{26}ON_2$ (:CH—CH:)

$\longrightarrow$ Metho-salts or dimetho-salts (carbonate, hydrogen carbonate)

$\xrightarrow{\text{heat}}$ $C_{22}H_{28}ON_2$ {Methyl*chano*dihydro(*neo*)strychnidine, m. p. 143°; Anhydromethylstrychnidinium-D hydroxide (*des*-base-D), m. p. 193°}

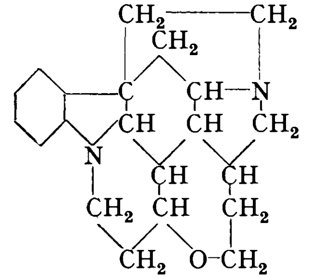
$\downarrow$ Pd, H_2, AcOH

{Methyldihydrostrychnidinium-D acetate $\longrightarrow$ chloride $\xrightarrow{\text{heat}}$ Dihydrostrychnidine-D

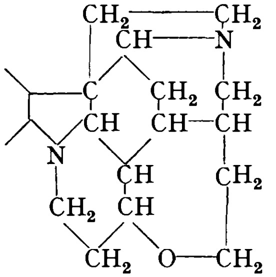
Methyldihydrostrychnidinium-A acetate $\downarrow$ Chloride $\xrightarrow{\text{heat}}$ Dihydrostrychnidine-A

(2) The simplest way to conceive such structural isomerism is that *des*-base-D contains a double bond, either end of which may be attached to N(b) when the quaternary ammonium salt is reconstituted. Such a double bond under the present heading is assumed to be in the normal position between carbon atoms originally αβ to N(b) in dihydrostrychnidine. If this idea correctly interprets the results, then the *des*-base-D does not contain $-CH=CH_2$ in its molecule because neither of the dihydrostrychnidines-A and -D gives evidence of the presence of a side-chain methyl group. The ethylene linkage must be centrally situated.

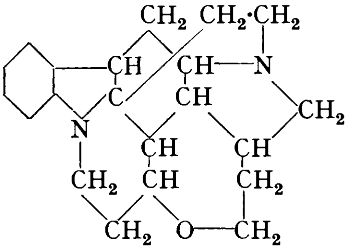
(I.)



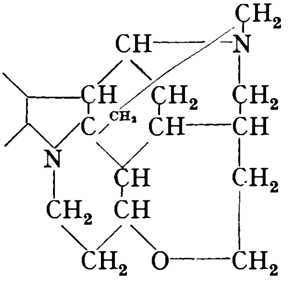
(I, D.)



(II.)

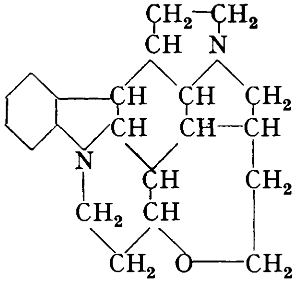


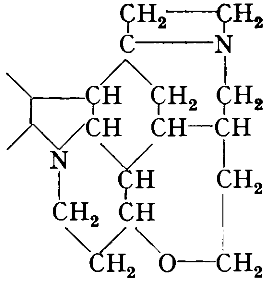
(II, D.)



Such a view can be applied to (I) and (II), but not to (III) because in this case dihydrostrychnidine-D would be a derivative of trimethyleneimine, which is a highly improbable assumption.

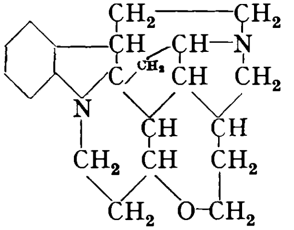
(III.)

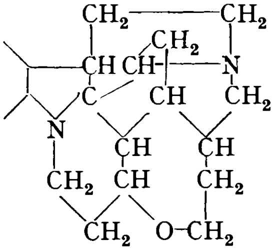




(III, D.)

(IV.)



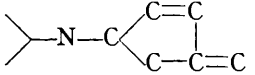


(IV, D.)

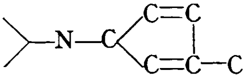
The formula (IV), which has been mentioned as an alternative to (I) and (II) (Openshaw and Robinson, J., 1937, 941), does not contain a ready-formed carbazole nucleus (such would, however, be easily formed by rearrangement in vigorous decomposition processes) but has otherwise much to recommend it. It is the only formula which serves to explain in a natural manner all the three following fundamental facts: the monobromination of diketonucidine (Leuchs), the ready formation of β-indolylethylamine from strychnine (Clemo, Kotake), and the blocked hydroaromatic nature of the hydroindole nucleus (this series of papers). The expressions (I, D), (II, D) and (IV, D) can be set up on the models and the curious appearance on paper is therefore irrelevant to the discussion. The changes from (I) and (II) to (I, D) and (II, D) respectively appear to be quite natural on the models and all four formulæ are strainless. The formulæ (IV) and (IV, D) are also free from strain but give a closer-packed assemblage.

On the basis of (IV) the *des*-base-D would be a derivative of allylaniline and this might be sufficient to explain its peculiar ferric reaction.

In the later stages of the Hofmann degradation of methyl*chano*dihydro*neo*strychnidine (see the two following communications) the primary product and its transposition product would contain the groups



and



respectively and this would serve to explain the peculiar reaction of the *bisneo*-derivative. However, in the penultimate stage of the Hofmann degradation of dihydrostrychnidine-D the group produced is not an ethylidene but a vinyl group (no acetic acid is obtained on oxidation until the unsaturated group is reduced; one molecule is then obtained). Hence it is unlikely that the *des*-base-D contains the fragment $Ar{\cdot}CH{\cdot}CH_2{\cdot}CH_2{\cdot}NMe{\cdot}$, which by analogy should give $Ar{\cdot}\dot{C}{=}CHMe$ on degradation. This consideration tells against (IV) but does not apply to (I), (II), or (III).

(3) Even if the *des*-base-D is produced by the mechanism $Ar{\cdot}\dot{C}H{\cdot}\dot{C}H{\cdot}\dot{C}H{-}\ddot{N}Me\}OH \longrightarrow Ar{\cdot}\dot{C}{:}\dot{C}H{\cdot}\dot{C}H_2\ \ \ddot{N}Me + H_2O$, there is no sound theoretical reason for supposing the decomposition to be irreversible. No analogy for this reverse transformation is known to the authors, but this is probably due to the difficulty of finding suitable test-cases. Indeed few if any good analogies exist in any circumstances for the reverse Emde reaction which

we have observed. It is accordingly a possibility not to be ignored that our original view (Part XXVI, *loc. cit.*) of the nature of the *des*-base-D may be correct in spite of the fact that its formation from methyldihydrostrychnidinium-A salts is now known to be reversible.

Summarising the above, the hypothesis of stereoisomeric A and D series can be used with structures (I) and (III), the hypothesis of ring-system slip in which N(b) moves to an adjacent carbon atom can be applied to structures (I), (II), and (IV), and our original hypothesis that *des*-base-D is a styrene derivative (γ-phenylpropylammonium type of fission) can be illustrated by structures (II) and (III) and more easily by (II). We wish to withdraw a former stereochemical objection to the formulation of a *des*-base-D (styrene type) on the basis of (III). It has been consistently maintained in this series of papers that strychnine is a blocked hydroindole derivative (that is, disubstituted in the α- or β-position) and this view is confirmed by the results of the Hofmann degradation described in the following memoirs. The final products contain three double bonds and in spite of the stringent conditions of the thermal decompositions, no true aromatic indole derivative (and incidentally no new benzene ring) is formed at any stage. In this connection we do not rely so much on the fact that *desaza*strychnidine takes up three molecules of hydrogen, because the products have not been crystallised; it is more pertinent that the substance itself exhibits a strychnidine reaction and so cannot be an aromatic indole derivative.

For these and other reasons already advanced, we do not favour the formula (III). The final decision between (I), (II), and (IV) cannot yet be made with certainty.

In the following communications the original hypothesis has been retained *only for the sake of simplicity of representation*, but it is not regarded as proven and readers will have no difficulty in making the changes in the formulæ necessary for conformity with any of the alternatives mentioned above.

EXPERIMENTAL.

The Action of Hydrogen on des-*Base-D in Acid Solution in the Presence of Palladised Charcoal or Platinum-black.*—The "hydrogenation" of *des*-base-D was carried out under various conditions and in all cases similar results were obtained. When the absorption of hydrogen ceased at 17—19°, the mixture was heated to 85—90°, but no further absorption took place. The yields and conditions are summarised in the following table:

					Yield, g.			
Amount of *des*-base-D, g.	Catalyst.	Solvent.	C.c. of hydrogen absorbed (at N.T.P.).	Calc. for 2H, c.c.	Methyl-dihydro-strych-nidinium-D iodide.	Methyl-dihydro-strych-nidinium-A iodide.	Total.	Theo., g.
7·4	Pd	50% $C_2H_4O_2$	270	493	7·28	2·47	9·75	10·2
8·6	Pt	,,	160	573	6·9	3·8	10·7	11·6
9·0	Pd	10% HCl	345	600	8·7	3·2	11·9	12·5
6·2	Pt	,,	118	713	5·8	2·4	8·2	8·5

In all cases absorption of hydrogen was rapid (about 5 c.c. per minute), but the volume absorbed was far less than that required by the theory for saturation of one double bond. This suggests that hydrogen is absorbed by the catalyst, which evidently becomes more active after addition of the substance. The yield of the products seems to be independent of the nature of the acid and the catalyst.

The quaternary salts were usually isolated as iodides, but when the reaction was carried out in 10% hydrochloric acid, methyldihydrostrychnidinium-D chloride crystallised shortly after hydrogen ceased to be taken up.

The following is a description of one of the experiments: *des*-Base-D (9 g.) was dissolved in dilute hydrochloric acid (130 c.c. of 10%) and shaken in hydrogen in presence of palladised charcoal (from 0·8 g. of palladous chloride and 8 g. of charcoal) at room temperature. Absorption ceased after 85 minutes, 355 c.c. (at N.T.P) of hydrogen being taken up (calc. for 2H, 600 c.c.). The temperature was then raised to 90°, but no absorption took place. The hot liquid (when it was allowed to cool, methyldihydrostrychnidinium-D chloride separated in long silky needles) was filtered, basified with ammonia (no precipitate), concentrated in a vacuum to one-third volume, and mixed with sodium iodide (10 g. in 10 c.c. of water). The colourless precipitate, consisting of a mixture of the isomeric iodides D and A, was collected and repeatedly crystallised from water. All the concentrations of the mother-liquors were carried out under reduced pressure; otherwise the yield of both products was diminished and they became coloured. The isomeride D formed the first crops (total yield, 8·7 g.), whereas methyldihydrostrychnidinium-A iodide was isolated from the mother-liquors (total yield, 3·2 g.).

Identification of Methyldihydrostrychnidinium-A Iodide.—The identity of methyldihydrostrychnidinium-A iodide formed in these experiments was proved in the following way: The salt had m. p. 345—350°, undepressed by admixture with an authentic specimen (Found in material dried at 104°: C, 57·1; H, 6·5. Calc. for $C_{22}H_{29}ON_2I$: C, 56·9; H, 6·3%). The corresponding chloride, on dry distillation at 300—320°/1 mm., gave dihydrostrychnidine-A, m. p. 214—216° (yield, 85%); the m. p. was not depressed after admixture with pure dihydrostrychnidine-A. The chloride, on being treated with sodium methoxide at 135—140°, yielded methoxymethyltetrahydrostrychnidine, m. p. 220—222°, along with a small quantity of *des*-base-D, m. p. 196°.

Pure methyldihydrostrychnidinium-D iodide has a higher m. p. than that given in Part XXVI (the specimen previously obtained was evidently contaminated with the isomeride-A). The salt melts with effervescence at 325—327°. Its solubility in water is 0·08 : 100 at 18° and 0·45 : 100 at 100°. The other properties were as described in Part XXVI (Found in material dried at 104°: C, 54·7; H, 6·6. Calc. for $C_{22}H_{29}ON_2I,H_2O$: C, 54·8; H, 6·4. Found in material dried at 130°: C, 56·8; H, 6·7. Calc. for $C_{22}H_{29}ON_2I$: C, 57·0; H, 6·3%).

Methyldihydrostrychnidinium-D chloride has m. p. 330—332° (*loc. cit.*; 318—319°). The salt on decomposition with sodium methoxide at 130° furnished *des*-base-D (yield, 95%). It does not contain a *C*-Me group (Kuhn–Roth test).

Improved Method for the Preparation of Dihydrostrychnidine-D.—The thermal decompositions of various substances described in previous papers of this series were carried out in open test-tubes with small quantities of material, and the yield of the decomposition products was often poor and the products were coloured, undoubtedly owing to the action of air. Better results are obtained when the decomposition is carried out under 1 mm. pressure. Methyldihydrostrychnidinium-D chloride (10 g.), previously dried at 104° in a high vacuum, was gradually heated to 350°/1 mm. After effervescence had ceased, the residual syrup crystallised, on cooling, as a hard, pale brown crust (part of the dihydrostrychnidine-D and a small quantity of the unchanged chloride were collected in the receiver). The base was extracted with boiling benzene (150 c.c.) and, on concentration of the extract to a small volume, separated in well-developed, pale brown plates. These were twice recrystallised from benzene and then had m. p. 199—201°; a specimen recrystallised from methyl alcohol had m. p. 198—200° (Part XXVI; m. p. 197—199°) (total yield, 7·9 g.) (Found: C, 78·3; H, 8·1; NMe, 0·0; CMe, negligible. Calc. for $C_{21}H_{26}ON_2$: C, 78·3; H, 8·1%).

Attempt to effect the Internal Alkylation of des-*Base-D by Means of Hydrochloric Acid.*—This experiment was carried out under the conditions which Willstätter (*Annalen*, 1901, **317**, 307) used for the conversion of dimethylamino*cyclo*heptene into dihydrotropidine methochloride. *des*-Base-D was dissolved in 30% hydrochloric acid and the solution was saturated with hydrogen chloride at − 10°, kept for 5 days in the cold, cooled to − 15°, and basified with sodium hydroxide below − 10°. The alkaline liquid was extracted with benzene, and all the *des*-base-D recovered unchanged.

The Action of Palladised Charcoal on des-*Base-D in Acid Solution in the Absence of Hydrogen.*—When the *des*-base-D, dissolved in 10% hydrochloric acid or 50% acetic acid, was shaken with palladised charcoal, it was completely converted in 30 minutes into an amorphous substance (or a mixture), which had basic properties, contained halogen, and was characterised by sparing solubility in organic solvents except methyl and ethyl alcohols. This substance is under examination.

Dihydrobrucidine-D.—This *base* was prepared by thermal decomposition of methyldihydrobrucidinium-d chloride, the decomposition being carried out exactly as in the case of methyldihydrostrychnidinium-D chloride (350°/1 mm.). The base was moderately readily soluble in the simple alcohols, acetone, and ethyl acetate and readily in benzene and chloroform. It crystallised from methyl alcohol in minute, pale rose-coloured needles, m. p. 197—199°, and became red on standing in the air (Found in a specimen dried in a high vacuum: C, 72·1, 72·2; H, 8·0, 7·8. $C_{23}H_{32}O_3N_2$ requires C, 72·3; H, 7·8%). The base combined readily with methyl iodide, yielding a salt identical with methyldihydrobrucidinium-d iodide described in Part XXXV.

We take this opportunity to state that methyldihydrobrucidinium-c iodide described in Part XXXV is probably identical with dihydrobrucidine methiodide.

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