281. *Strychnine and Brucine. Part XXXIX. Final Stages of the Hofmann Degradation of Dihydrostrychnidine-A. Elimination of Trimethylamine and Isolation of* desaza*Strychnidine-b.*

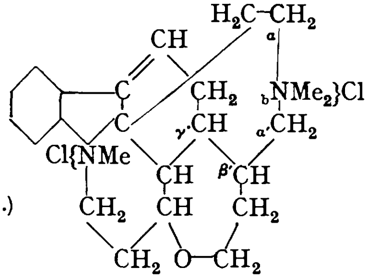
By O. Achmatowicz and C. Dybowski.

The *des*-base-D undergoes Hofmann eliminations only after conversion into dimetho-derivatives. One of the resulting *des*-bases of the second stage is identical with one of those derived from methyl*chano*dihydro*neo*strychnidine; the second is termed dimethyl*des*strychnidine-D. The third stage applied to the latter substance affords the two *desaza*strychnidines-a and -b and trimethylamine.

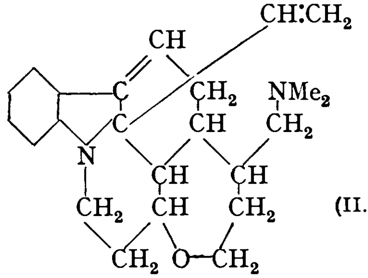
As stated in Part XXVI (Achmatowicz and Robinson, J., 1934, 581) the action of sodium methoxide on the methochloride of the *des*-base-D, as well as the thermal decomposition of the related methocarbonate, gives, as the main product, the *des*-base-D [loss of methyl chloride or methyl carbonate attached to N(b)]. We have now found that a true Hofmann elimination takes place, when instead of the monometho-salts of the *des*-base-D, the dimetho-salts are taken for the above processes.

The *des*-base-D, in common with methyl*des*dihydrobrucidine-a (Achmatowicz, Lewi, and Robinson, J., 1935, 1687), gives, on methylation with methyl iodide at a relatively high temperature, two isomeric dimethiodides, namely, the normal dimethiodide, m. p. 214—216°, and the *allo*-dimethiodide, m. p. 292—294°. The *allo*-dimethiodide is probably a structural isomeride, because the corresponding dimethochloride loses methyl chloride when heated, to yield a base not identical with the *des*-base-D. When the normal dimethiodide was converted into the corresponding dimethochloride and the latter was decomposed with sodium methoxide, the following products were obtained : (i) a base, $C_{22}H_{28}ON_2$, m. p. 193—194°, identified with *des*-base-D ; (ii) a base, $C_{23}H_{30}ON_2$, m. p. 73—74°, identical with dimethyl*desneo*strychnidine ; (iii) a base, $C_{23}H_{30}ON_2$, m. p. 156—157°, termed *N*(*b*)*N*(*b*)-dimethyl*des*strychnidine-D ; and other substances which are under examination.

Dimethyl*des*strychnidine-D contains $\cdot N(b)Me_2$ and two double bonds, as proved by conversion into a dihydro-derivative, m. p. 125—126°, and a tetrahydro-derivative (amorphous ; analysed as the methiodide, m. p. 244—246°). Dimethyl*des*strychnidine-D fails to undergo internal alkylation when hydrogenated in presence of palladised charcoal, as does the *des*-base-D. The formation of dimethyl*des*strychnidine-D is obviously due to fission of either N(b)—C(α) or N(b)—C(α′) in (I). The former alternative is preferred, since (i) fission of N(b)—C(α′) would be expected to lead to a base containing a double bond in the βγ-position (by analogy with the formation of methyl*chano*dihydro*neo*strychnidine from methyldihydrostrychnidinium-A carbonate) and actually a base of such structure was isolated ; it is dimethyl*desneo*strychnidine (see preceding paper) ; (ii) stereoisomerism (with dimethyl*desneo*strychnidine) is excluded, because dimethyl*des*strychnidine-D gives no evidence of the presence of ⁝CMe groups by the Kuhn–Roth method, whereas its dihydro-derivative and the methiodide of the tetrahydro-derivative yield under these conditions one molecule of acetic acid ; (iii) dihydro(dimethyl*des*strychnidine-D) is not identical with dimethyl*des*dihydrostrychnidine-D and dimethyl*des*dihydro*bisneo*strychnidine (comparison of methiodides) described in the preceding paper ; (iv) the methiodide of tetrahydro(dimethyl*des*strychnidine-D) is not identical with the corresponding salt of tetrahydro(dimethyl*desbisneo*strychnidine) and tetrahydro(dimethyl*desneo*strychnidine). We conclude that dimethyl*des*strychnidine-D possesses a different skeleton from that of dimethyl*desneo*strychnidine, and should be represented by the formula (II).



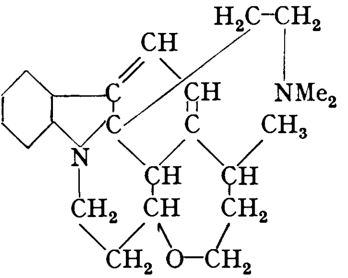
(I.)

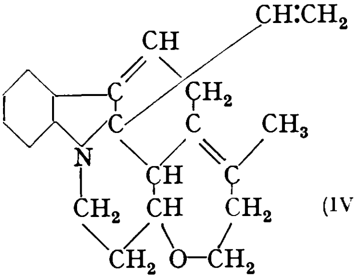


(II.)

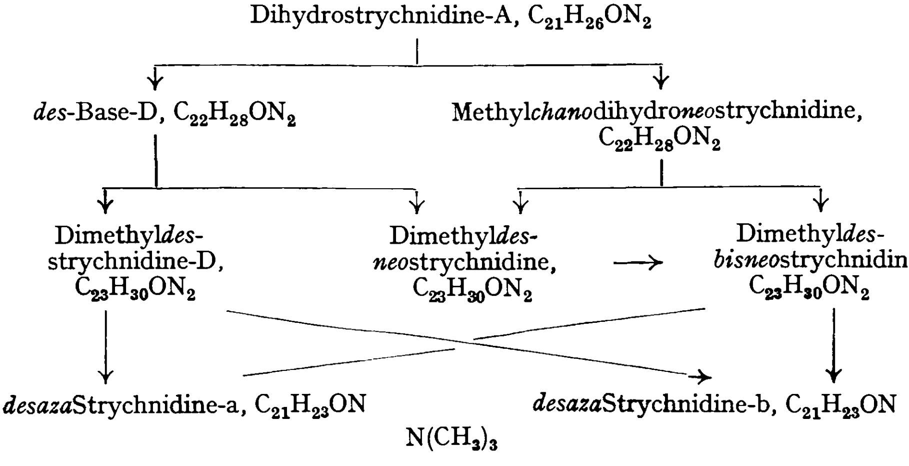
When dimethyl*des*strychnidine-D dimethochloride (or the dimethosulphate) was heated with sodium methoxide at 130°, trimethylamine was evolved and three products were formed. One of them was identified with dimethyl*des*strychnidine-D and the second was recognised as *desaza*strychnidine-b. It had the composition $C_{21}H_{23}ON$, m. p. 109—110°, and gave with methyl iodide a methiodide, m. p. 104—105°, identical with *desaza*strychnidine-b methiodide described in the preceding paper. The third product was *desaza*strychnidine-a, identified as the methiodide, m. p. 154—155°.

*desaza*Strychnidine-b gives with ferric alum solution under standard conditions an eosin-red coloration typical of strychnidine, whence, on the hypothesis advanced in the preceding paper, it must be supposed that the base does not possess a conjugated double bond system. On the other hand, a formula for *desaza*strychnidine-b must explain in a simple manner the formation of this base from dimethyl*des*strychnidine-D dimethochloride and dimethyl*desbisneo*strychnidine dimethochloride. Formula (IV) is in conformity with these requirements [(III) represents dimethyl*desbisneo*strychnidine]. This formula implies that formation of *desaza*strychnidine-b from dimethyl*des*strychnidine-D dimethochloride as well as from dimethyl*desbisneo*strychnidine is associated with wandering of a double bond to the *neo*-position; in the former case it moves from the αβ-position


(III.)


(IV.)

and in the latter from the *bisneo*-position. On this hypothesis the isomerism of *desaza*strychnidine-a and -b is dependent on the different positions of the ethylenic linkages, the skeleton being the same in both substances. However, we have not yet been able to establish this experimentally, as the presumably identical hexahydro-derivatives of *desaza*strychnidines-a and -b and their methiodides fail to crystallise and could not, therefore, be compared. The following table illustrates the relations of the chief substances described in this and the preceding paper:



EXPERIMENTAL.

Methylation of the des-*Base-D.*—A solution of the *des*-base-D (8 g.) in dry benzene (120 c.c. at 40°) was mixed with freshly distilled methyl sulphate (15 c.c.) and refluxed for 20 hours on a water-bath. The semicrystalline, yellow product was dissolved in hot water (30 c.c.), and the solution rendered alkaline with ammonia (no precipitate), cooled, filtered, and mixed with aqueous sodium iodide (10 g. in 15 c.c. of water). The thick yellow oil, which was then precipitated and failed to crystallise, was dissolved in methyl alcohol (15 c.c.) and reprecipitated by addition of ether (150 c.c.). The semi-solid precipitate was crystallised from methyl alcohol and subsequently several times from water, two isomeric dimethiodides being finally obtained, the normal dimethiodide (13·2 g.) and the *allo*-dimethiodide (0·3 g.).

allo-N(b)-*Methyl*des*dihydrostrychnidine dimethiodide* was isolated from the aqueous mother-liquor after separation of the normal dimethiodide; it separated from aqueous solution in stout yellowish prisms, m. p. 274—275° (Found in material dried at 104°: C, 46·2, 46·8; H, 5·8, 5·8; I, 40·8, 40·8. $C_{24}H_{34}ON_2I_2$ requires C, 46·4; H, 5·5; I, 40·9%). The related dimethochloride formed a mass of colourless needles, freely soluble in water. When it was heated in a test-tube over a free flame, methyl chloride was given off and a product not identical with the *des*-base-D was formed. This product is under examination.

The dimethiodide of the des-*base-D.* The normal *dimethiodide* is sparingly soluble in cold water (3 : 100), but dissolves readily on boiling (25 : 100); it is very sparingly soluble in acetone and dissolves moderately readily in the simple alcohols. When crystallised from methyl alcohol, it becomes reddish, but from aqueous solution it separates in colourless plates, m. p. 214—216° (Found in a specimen dried at 104° : C, 46·3, 46·5; H, 5·8, 5·7; I, 40·8. $C_{24}H_{34}ON_2I_2$ requires C, 46·4; H, 5·5; I, 40·9%).

The corresponding dimethochloride, prepared by means of silver chloride, is freely soluble in water, readily soluble in methyl alcohol, and very sparingly in acetone. Crystallised from a mixture of equal volumes of methyl and ethyl alcohol, it separates in minute colourless needles, m. p. 292—294°.

The Action of Methyl-alcoholic Sodium Methoxide on the Dimethochloride of the des-*Base-D. Formation of a New* N(b)N(b)-*Dimethyl*des*strychnidine.*—The dimethochloride of the *des*-base-D (5 g., previously dried at 104°) was mixed with a methyl-alcoholic solution of sodium methoxide (20 c.c. of 25%) and heated in an open flask, first on a rapidly boiling water-bath and subsequently on a sand-bath until the temperature was 115°. The cooled mixture, on dilution with ice-water, gave a grey caseous precipitate, which was washed with water, dried, and thrice crystallised from methyl alcohol. This furnished dimethyl*des*strychnidine-D (2·6 g.); the methyl-alcoholic mother-liquor was examined separately.

N(b)N(b)-*Dimethyl*des*strychnidine-D* forms colourless plates (Fig. 1), m. p. 156—157° (Found : C, 79·1, 79·0; H, 8·7, 8·7; N, 8·2; Me as NMe, 9·2, 9·0; Me as CMe, 1·2. $C_{23}H_{30}ON_2$ requires C, 78·9; H, 8·6; N, 8·0; 2Me as NMe, 8·6; Me as CMe, 4·3%). It is moderately readily soluble in the simple alcohols, sparingly soluble in petroleum, but dissolves readily in chloroform or benzene. A solution of the base (10 mg.) in 0·1% hydrochloric acid (5 c.c.) gives, on addition of 0·25% ferric alum solution (5 c.c.), a pink coloration, changing slowly to eosin-red.

The methiodide. Dimethyl*des*strychnidine-D reacts with methyl iodide at room temperature, forming the *methiodide,* m. p. 244—246° (Found in a specimen dried at 104° : C, 58·5; H, 6·9. $C_{24}H_{33}ON_2I$ requires C, 58·5; H, 6·7%).

Catalytic Hydrogenation of N(b)N(b)-*Dimethyl*des*strychnidine-D in Acid Solution in the Presence of Palladised Charcoal. Formation of a Dihydro-derivative and a Tetrahydro-derivative.*—The hydrogenation of dimethyl*des*strychnidine-D was carried out at room temperature and at 60°, and two different hydrogenation products were obtained.

(i) Dimethyl*des*strychnidine-D (5 g.) was dissolved in 50% acetic acid (25 c.c.) and hydrogenated at 18—19° in the presence of palladised charcoal (0·1 g. of palladous chloride, 1 g. of charcoal previously heated to redness, and 30 c.c. of water). Absorption of the gas ceased after 180 minutes, 355 c.c. (at N.T.P.) having been absorbed (calc. for 2H, 320 c.c.). The dihydro-base was precipitated from the filtered liquid by means of ammonia and dried in a vacuum (5 g.). *Dihydrodimethyl*des*strychnidine-D* crystallises from methyl alcohol in small colourless plates, m. p. 126—127° (Found : C, 78·3, 78·0; H, 9·5, 9·4; Me as CMe, 5·2, 4·8. $C_{23}H_{32}ON_2$ requires C, 78·4; H, 9·2; Me as CMe, 4·3%). It is moderately readily soluble in methyl alcohol or acetone, sparingly soluble in petroleum, and dissolves readily in chloroform or benzene. It readily combines with methyl iodide, yielding a *methiodide*; this derivative is sparingly soluble in methyl alcohol and separates therefrom in colourless needles, m. p. 244—246° (Found in a specimen dried at 104° : C, 58·2; H, 7·6; I, 25·7. $C_{24}H_{35}ON_2I$ requires C, 58·3; H, 7·2; I, 25·7%).

(ii) A solution of dimethyl*des*strychnidine-D (2 g.) in 50% acetic acid (10 c.c.) was hydrogenated at 60° in the presence of palladised charcoal, recovered from the previous experiment. After 4 hours the volume of hydrogen absorbed was 287 c.c. (at N.T.P.; calc. for 4H, 256 c.c.) and absorption ceased. The product, isolated as in the preceding case, was very readily soluble in the usual organic solvents and, as yet, has not been prepared in a crystalline state. When it was treated with methyl iodide at room temperature, a *methiodide* was formed; this salt, recrystallised from methyl alcohol, formed colourless needles, m. p. 278—280° (Found in material dried at 104° : C, 58·3; H, 7·8; I, 25·3; Me as CMe, 2·9, 2·8. $C_{24}H_{37}ON_2I$ requires C, 58·0; H, 7·5; I, 25·6; Me as CMe, 3·0%).

*Examination of the Methyl-alcoholic Mother-liquor remaining after Separation of Dimethyl*des*strychnidine.*—This was evaporated to dryness in a vacuum, and the glassy residue was resolved into the *des*-base-D and dimethyl*desneo*strychnidine by fractional crystallisation first from light petroleum and subsequently from ethyl alcohol and acetone. This very laborious process gave about 0·2 g. of the *des*-base-D, 0·8 g. of dimethyl*desneo*strychnidine, and other crystalline products which are under examination. The *des*-base-D was identified by m. p. and by mixed m. p. (194—195° in both cases). The identity of dimethyl*desneo*strychnidine was established by m. p., by mixed m. p. (73—74° in both cases), by comparison of the microphotographs, and by conversion into dimethyl*desbisneo*strychnidine, m. p. 113—114°, by the method described in the preceding paper.

*Catalytic Hydrogenation of Dimethyl*desneo*strychnidine*.—The base (1 g.) was dissolved in 35% acetic acid (5 c.c.) and hydrogenated at room temperature in presence of palladised charcoal (40 mg. of palladous chloride, 0·4 g. of charcoal, previously heated to redness, and 30 c.c. of water). Absorption of the gas ceased after 55 minutes, 146 c.c. (at N.T.P.) having been taken up (calc. for 4H, 128 c.c.). The reduction product was isolated, as described in similar cases, and, despite numerous efforts, could not be prepared in a crystalline state. When it was treated with methyl iodide, a methiodide, m. p. 263—264° (after recrystallisation from water), was obtained and identified with the methiodide of tetrahydro(dimethyl*desbisneo*strychnidine), described in the preceding paper. The identity was proved by mixed m. p. (no depression) and by analysis (Found in a specimen dried at 104° : C, 58·1; H, 7·8. Calc. for $C_{24}H_{37}ON_2I$: C, 58·0; H, 7·5%).

*Dimethyl*des*strychnidine-D Dimetho-salts.—The dimethiodide.* Dimethyl*des*strychnidine-D (10 g.) was dissolved in benzene (140 c.c. at 40°), mixed with methyl sulphate (25 c.c.), and refluxed for 20 hours on a water-bath. The brown gummy product was dissolved in water (50 c.c.), and the solution basified with ammonia (no precipitate), filtered, and mixed with aqueous sodium iodide (15 g. in 20 c.c. of water). The yellow oily precipitate which was formed crystallised after 12 hours; the crystals were washed with water and thrice recrystallised from this solvent. The *dimethiodide* (15 g.) formed minute colourless needles, m. p. 219—221° (Found in material dried at 90° : C, 47·1, 47·2; H, 6·0, 5·9; I, 39·7. $C_{25}H_{36}ON_2I_2$ requires C, 47·3; H, 5·7; I, 40·0%). It is moderately readily soluble in water and dissolves sparingly in methyl alcohol and acetone. When it is dried at 100° or crystallised from methyl alcohol, it undergoes some decomposition; it becomes red and gives bad analytical figures.

The dimethochloride, prepared by the usual method, separates from a concentrated aqueous solution as a mass of colourless needles, m. p. 212—213° after being dried at 104°.

The Action of Sodium Methoxide on N(b)N(b)*-Dimethyl*des*strychnidine-D Dimethochloride. Elimination of Trimethylamine and Formation of* desaza*Strychnidines-a and -b.*—Dimethyl*des*strychnidine-D dimethochloride (5·3 g., previously dried in a vacuum), dissolved in methyl alcohol (15 c.c.), was mixed with a methyl-alcoholic solution of sodium methoxide (35 c.c. of 25%) and heated on a sand-bath in a flask connected with a condenser. The distillate was collected in 5% hydrochloric acid and the heating was discontinued when the temperature of the melt reached 150°. Evolution of trimethylamine (yield, calc. as hydrochloride, 0·5 g.) began at 105—110° and the gas was identified by conversion into the hydrochloride, m. p. 272—274°, and the platinichloride, m. p. 240—242°. In the early experiments the decomposition product, after being cooled, washed with water, and dried in a vacuum, was resolved into its components (dimethyl*des*strychnidine-D, 1·7 g.; *desaza*strychnidine-a, 0·4 g.; and *desaza*strychnidine-b, 1·1 g.) by extremely tedious crystallisations first from light petroleum and subsequently from methyl alcohol. Later a more convenient, quick method of separation was devised, based on the property of *desaza*strychnidine-*a* and -*b* salts to undergo hydrolysis on dilution with water : The decomposition product was cooled, thoroughly washed with water, and dissolved in the minimum quantity of 25% hydrochloric acid; the acid solution was diluted with water (10 vols.), and the milky mixture exhaustively extracted with benzene (A). The aqueous layer was basified with ammonia and then extracted with benzene (B). The extract (A) was washed with sodium carbonate solution, dried, filtered, and evaporated to dryness in a vacuum. The residue was repeatedly crystallised from ethyl alcohol. This operation gave *desaza*strychnidine-b in crystalline form and *desaza*strychnidine-a as an amorphous semi-solid (in the mother-liquor). The extract (B) was worked up similarly and dimethyl*des*strychnidine-D, which remained after evaporation of the solvent, was crystallised from methyl alcohol. Dimethyl*des*strychnidine was identified by m. p. and by mixed m. p. (156—157° in both cases).

Identification of desaza*strychnidine-a.* The first evidence as to the identity of *desaza*strychnidine-a was obtained by testing the colour reaction. The oily product isolated from the mother-liquor from *desaza*strychnidine-b gave with dilute hydrochloric acid and ferric alum solution (or more quickly with ferric chloride) a reddish-purple coloration. Further evidence was obtained on examining the action of methyl iodide. The product (0·5 g.) was boiled for 4 hours with an excess of methyl iodide. The methiodide which was formed crystallised when rubbed with acetone and after being recrystallised from this solvent had m. p. 154—155°, not depressed by *desaza*strychnidine-a methiodide described in Part XXXVIII.

desaza*Strychnidine-b*. This substance forms colourless elongated plates (Fig. 2), m. p. 109—110° (Found : C, 82·4, 82·5; H, 7·8, 7·7; N, 4·8, 4·8; OMe and Me as NMe, 0. $C_{21}H_{23}ON$ requires C, 82·6; H, 7·5; N, 4·6%). desaza*Strychnidine-b* is very sparingly soluble in light petroleum, moderately readily soluble in the simple alcohols, and dissolves readily in chloroform or benzene. It is sparingly soluble in dilute acids (for example, in 30% acetic acid or 10% hydrochloric acid) and is precipitated in the free state from solutions in more concentrated acids on dilution with water. A solution of the base in 5% hydrochloric acid, on addition of ferric alum or ferric chloride solution, becomes pink and then eosin-red. When the base was hydrogenated in presence of platinum-black, three molecules of hydrogen were taken up, but the reduction product could not be prepared in a crystalline state.

The methiodide. *desaza*Strychnidine-b was recovered unchanged (95%) after being refluxed with methyl iodide for 12 hours on a steam-bath. Methylation took place when the reaction was carried out at 105° in a sealed tube (8 hours). The *methiodide* (yield, 60%) crystallised from water in minute, slightly yellow needles, m. p. 105—106° (Found in a specimen dried in a high vacuum at room temperature : C, 59·3, 59·4; H, 6·0, 6·1; N, 3·3, 3·4. $C_{22}H_{26}ONI$ requires C, 59·1; H, 5·8; N, 3·1%). A mixture of equal quantities of this methiodide and *desaza*strychnidine-b methiodide, described in the preceding paper, had m. p. 104—106°.

Errata.—In Part XXVI (J., 1934, 586) two isomeric oxidation products of the *des*-base-D were described. Now we find that a miscalculation of the analytical figures occurred and that these substances possess different compositions. One of them, namely, oxyanhydromethylstrychnidinium-D hydroxide, m. p. 162° (now raised to 164—165°), has probably the composition $C_{21}H_{26}ON_2$ and not $C_{22}H_{28}O_2N_2$ as previously given (Found now : C, 77·9, 78·1; H, 7·3, 7·7; N, 8·7, 8·7; previous analysis after correction : C, 78·2; H, 7·9. $C_{21}H_{26}ON_2$ requires C, 78·2; H, 8·1%). The composition of the product suggests that it might be a *nor*-base formed by oxidation, $C_{21}H_{25}ON(a)N(b)Me \longrightarrow C_{21}H_{25}ON(a)N(b)H$, and that the other oxidation product is an amine oxide, $C_{21}H_{25}ON(a)N(b)O$. However, this hypothesis has not yet been verified experimentally, although we have established that both products yield well-crystallising methiodides, do not contain active hydrogen (Zerewitinoff), and are indifferent towards reagents for the carbonyl group.

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