119. *Strychnine and Brucine. Part XXV. Reduction of Methylstrychnidinium Salts by Means of Sodium Amalgam in the Presence of Carbon Dioxide.*

By (the late) W. H. Perkin, jun., Robert Robinson, and J. C. Smith.

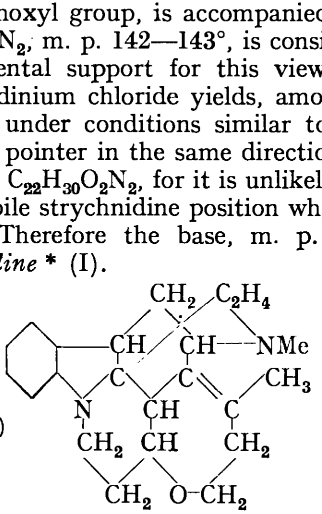
In hot neutral solution sodium amalgam attacks methylstrychninium salts, rupturing two rings, one including N(b) (Emde degradation) and the other being the oxide ring (compare Part XIX; J., 1932, 1240). A parallel series of experiments with methylstrychnidinium methosulphate was instituted and the results are simpler in that the oxide ring is not affected.

This is in harmony with anticipations based on the theory that the ether oxygen is included in the group $\vdots N(a){\cdot}CO{\cdot}CH_2{\cdot}\dot{C}H{\cdot}O{\cdot}C\vdots$, and attention has previously been drawn to a similar contrast in the behaviour of strychnine and strychnidine derivatives, a good example being the formation of *iso*strychnine from strychnine under the influence of basic catalysts and the failure to isomerise strychnidine under similar conditions.

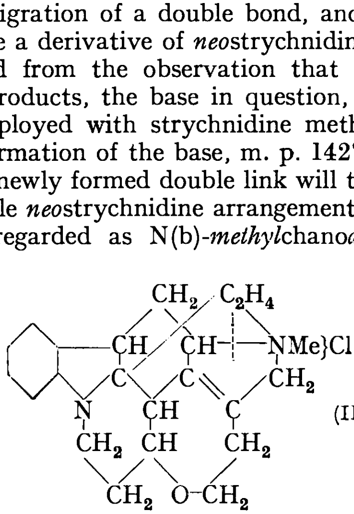
Strychnidine methosulphate, $C_{21}H_{24}ON\vdots N(b)Me\}SO_4Me$, was reduced in boiling aqueous solution with sodium amalgam in the presence of carbon dioxide and a gummy base separated. The residual solution was proved to contain methylstrychnidinium and methyl*neo*strychnidinium salts. The base, worked up by distillation and crystallisation processes, afforded three substances, namely (a) $C_{22}H_{30}O_2N_2$, m. p. 235—236°; (b) $C_{22}H_{28}ON_2$, m. p. 142—143°; and (c) $C_{22}H_{30}ON_2$, m. p. 192—193°. All these substances exhibit colour reactions of the strychnidine type and they are all strong bases. The substance (a) is the hydrate of (b) and, on boiling with phosphoryl chloride, (a) was converted into (b). The base (b) has the composition of a dihydromethylstrychnidine and is therefore, in all probability, a normal product of an Emde degradation in accordance with the scheme: $\vdots N(b)Me{\cdot}C\vdots\}SO_4Me \xrightarrow{H_2} \vdots NMe\ HC\vdots\ MeHSO_4$. In agreement with this hypothesis the base (b) was found to contain one double bond and it has been catalytically reduced to a dihydro-derivative, m. p. 177°. This base has already been obtained by the catalytic reduction of methylstrychnidinium chloride (Part XXIII;

Achmatowicz, *Rocznik Chemji*, 1933, **13**, 25). The formation of the methyldihydrostrychnidine, m. p. 142°, and its dihydro-derivative, m. p. 177°, as well as related strychnine derivatives in several distinct reactions (see the following communication) suggests that we are here concerned with a facile mode of degradation of the strychnine skeleton by a fission at N(b) and there are many reasons for believing that the addition of hydrogen in these reactions takes place at the same points as that of the elements of methyl alcohol in the formation of the methylmethoxydihydro*neo*strychnidine class of derivatives. Moreover it is very probable that the reductive fission, like that involving the introduction of the methoxyl group, is accompanied by the migration of a double bond, and the base, $C_{22}H_{28}ON_2$, m. p. 142—143°, is considered to be a derivative of *neo*strychnidine. Strong experimental support for this view is derived from the observation that methyl*neo*strychnidinium chloride yields, among other products, the base in question, when it is reduced under conditions similar to those employed with strychnidine methosulphate. Another pointer in the same direction is the formation of the base, m. p. 142°, from the hydrate, $C_{22}H_{30}O_2N_2$, for it is unlikely that the newly formed double link will take up the more labile strychnidine position when the stable *neo*strychnidine arrangement is a possibility. Therefore the base, m. p. 142°, is regarded as N(b)-*methyl*chano*dihydro*neo*strychnidine* * (I).

(I.)

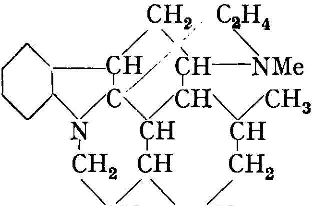


(II.)

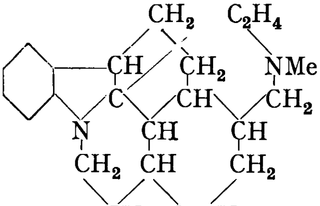


The product (c), $C_{22}H_{30}ON_2$, is a saturated base, m. p. 192—193°, and it is isomeric with the dihydro-derivative, m. p. 177°, of (b). The formulæ (III) and (IV) come into consideration; (III) on our hypothesis being also required for the base, m. p. 177°. The disposition of the methyl group in the heterocyclic seven-membered ring of (III) gives the necessary scope for stereoisomerism and (IV) might result from the fission of the methyl*neo*strychnidinium kation (II) at the point indicated by the dotted line in the formula.

(III.)



(IV.)



Against (III) as a representation for (c) it may be argued that the isomeride, m. p. 177°, is not a product of the reduction of strychnidine methosulphate by means of sodium amalgam; and, conversely, the base (c), m. p. 192—193°, is not obtained as a second product of the catalytic reduction of (b), m. p. 142°. We, therefore, prefer the expression (IV) for (c), keeping (III) for the isomeride, m. p. 177°, and it should be noted that (IV) arises from (II) in an Emde degradation assisted by the relation of the double bond to N(b). Quaternary salts derived from allylamines are known to be especially readily decomposed on reduction: $\colon\mathrm{C}{=}\dot{\mathrm{C}}{-}\dot{\mathrm{C}}\mathrm{H}{-}\mathrm{NR_3}\}\mathrm{Cl} + \mathrm{H_2} \longrightarrow \colon\mathrm{C}{=}\dot{\mathrm{C}}{-}\dot{\mathrm{C}}\mathrm{H_2} + \mathrm{NR_3} + \mathrm{HCl}$. It is for this reason, also, that we have not entertained the hypothesis that fission in the Emde reaction occurs between the groups $-C_2H_4-$ and MeN(b) (compare formula II). In that case the facilitating unsaturation is not suitably arranged and an experimental point which

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* As in Parts XX (Blount and Robinson, J., 1933, 2305) and XXIII (Achmatowicz, *loc. cit.*), the prefix *chano* is employed to denote ring-opening by a real or imaginary process of isomeric change.

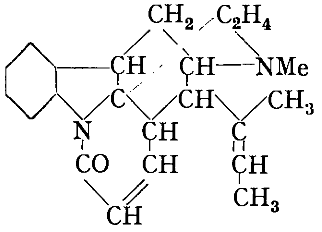
is relevant is the stability of dihydrostrychnidine-(A) methochloride towards sodium amalgam in hot neutral aqueous solution.

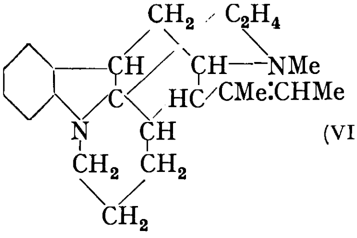
After the separation of (a), (b) and (c) the residual bases were repeatedly electrolytically reduced in dilute sulphuric acid solution. This undoubtedly caused the further production of (a), probably at the expense of (b), and by hydration rather than by reduction. After removal of all of the substance (a), the distilled base had the composition $C_{22}H_{32}ON_2$, and was thus a *methylhexahydrostrychnidine* or a mixture of isomerides. Evidently two of the rings of strychnidine can be opened by vigorous reduction processes. Two of the substances obtained by the distillation of the reduction product of strychnine methosulphate (Part XIX, *loc. cit.*) have been further examined.

The base-K^{11} has been found to contain a very persistent impurity of higher carbon content.

Anhydrotetrahydromethylstrychnine-K^{5} (probably V) on electrolytic reduction furnishes a dihydro-derivative of the related strychnidine (VI). The unusual addition of hydrogen to a double bond under these conditions is doubtless due to the position of the ethylenic link with respect to ⁚N(a)CO·, and this observation confirms the view taken in Part XIX of the course of the reduction of strychnine methosulphate. The double bond is shown in the original position, as in strychnine itself, but the *neo*-position is not excluded.

(V.)





(VI.)

EXPERIMENTAL.

The Base-K^{11} (Part XIX; *loc. cit.*, p. 1253).—Despite the fine appearance of the crystals of this substance, the specimen previously described has been found to be a mixture, and the material is contaminated by a compound of high carbon content, which is extremely difficult to remove. The specimen already described softened from about 211° and melted at 217—218° (Found: C, 79·0; H, 8·2; N, 8·4; Me*N*, 4·3%). After several further crystallisations from methyl alcohol–ethyl acetate, the homogeneous prisms had m. p. 215—217° (Found: C, 78·3, 78·1; H, 8·2, 8·1; N, 8·3; Me*N*, 4·4%).

Further purification by crystallisation alone was not sufficiently effective, and preliminary experiments showed that the impurity was more susceptible to hydrogenation in dilute acetic acid solution in the presence of palladium than was the main product. Accordingly, a specimen, m. p. 218—220° (3·75 g.), was catalytically hydrogenated until 59 c.c. of hydrogen had been absorbed. The recovered base was recrystallised, m. p. 222—224°; it was then thrice crystallised from propyl alcohol, m. p. 227—229° after softening at 223° (Found in material dried at 100° in a vacuum: C, 77·5, 77·9, 77·8; H, 8·2, 8·3, 8·2; N, 8·2%). This specimen was catalytically hydrogenated and slow absorption of hydrogen was observed with the formation of bases of much lower melting point (160—170°), but no pure product could be isolated in this way. The propyl alcohol mother-liquors from the crystallisations mentioned above were concentrated, and the residual bases again submitted to hydrogenation in dilute acetic acid solution in the presence of palladinised charcoal, the temperature being raised to 40° during 20 minutes. The isolated base in its crude form now softened at 217° and melted at 220—222°. Crystallised from propyl alcohol, it had m. p. 225—228°. Two further crystallisations from the same solvent gave m. p. 227—230°. Recrystallised from toluene, m. p. 229—231°, after softening at 225°. Again from the same solvent, m. p. 231—233°, after softening at 227°; after two further crystallisations from toluene, m. p. 232—233°, after softening at 231° (Found in material dried at 130° in a high vacuum: C, 77·2, 77·0; H, 8·3, 8·3; N, 8·1; Me*N*, 4·3%); two final crystallisations from toluene, m. p. 233—234°, after softening at 232° (Found in material dried at 100° in a vacuum: C, 76·3; H, 8·2; N, 8·1%). The crystallisation from toluene produced a slight discoloration of the crystals, and the substance was therefore twice crystallised again from propyl alcohol, affording colourless clear-cut prisms, m. p. 233—234·5° (Found in material dried at 100° in a vacuum: C, 76·0; H, 8·2; N, 8·1%). It appears that at this stage crystallisation effects no change in the melting point, and during the whole series of purifications the crystals were observed to be exceedingly well-shaped prisms. Nevertheless, the value for carbon content appears to be still falling and it may be that the substance rich in carbon has not even yet been completely eliminated. It is difficult to find an empirical formula which accords with the analytical data, but taking into consideration the general course of the purification, and the undoubted presence of a methyl group attached to nitrogen, the most likely composition appears to be $C_{22}H_{28}O_2N_2$, which requires C, 75·0; H, 7·9; N, 7·9%. The substance was obtained by the distillation of the crude product of the reduction of methylstrychninium methosulphate with sodium amalgam, and it may well have been produced by hydrogenation at the N(b) quaternary grouping and also at the double bond.

Dihydroanhydrotetrahydro - N(b) - *methylstrychnidine* - *K*^{5} (VI).—Anhydrotetrahydromethyl-strychnine-K^5 (1·7 g., m. p. 195—200°) was dissolved in 20% sulphuric acid (100 c.c.) and reduced for 20 hours at 10° in the lead cathode chamber of the usual apparatus (0·05 amp./cm.^{2}). The filtered solution was basified with ammonia and the precipitated solid was collected, washed with water, dried, dissolved as far as possible in light petroleum, and the filtered solution concentrated to a small bulk. The separated solid crystallised from methyl alcohol (yield, 0·4 g., m. p. 105—110°) and after two recrystallisations from the same solvent in colourless needles had m. p. 112° (Found: C, 82·0; H, 9·3; N, 8·8. $C_{22}H_{30}N_2$ requires C, 82·0; H, 9·3; N, 8·7%). This *base* was freely soluble in light petroleum or benzene and its solution in dilute hydrochloric acid developed an intense crimson coloration on the addition of ferric chloride.

Strychnidine Methosulphate.—In the preparation of this salt for the purposes of the present investigation, it was necessary to avoid the formation of any strychnidine methyl hydrogen sulphate, and the use of methyl alcohol as a solvent was therefore avoided in the later experiments. The base (25 g.) was dissolved in boiling benzene (400 c.c.), the solution cooled, and methyl sulphate (80 c.c.) added before crystallisation set in. A thick gelatinous mass separated and this was frequently shaken during a period of boiling under reflux for 20 hours. The benzene was decanted from the crude product and extracted several times with water; the gummy methosulphate was then dissolved in these extracts, the solution made up to 400 c.c., and the acid neutralised by means of sodium hydroxide. This solution was kept for some hours, filtered, and then directly reduced by means of sodium amalgam (total 800 g. of 4%) with results similar to those described below. Normally, however, the crude gummy strychnidine methosulphate was crystallised from methyl alcohol until tests showed that the specimen consisted entirely of quaternary salt, and was free from strychnidine salts.

Reduction of Strychnidine Methosulphate by Means of Sodium Amalgam.—The pure methosulphate (27 g.) was dissolved in boiling water (500 c.c.), and the solution stirred by means of a glass tube delivering a rapid stream of carbon dioxide; sodium amalgam (200 g. of 3%) was then introduced, causing the rapid separation of an oily base. After ½ hour a further quantity of amalgam (150 g.) was added, and the process continued, water being added when necessary, until no further separation of oil occurred. On cooling, the oil hardened and could be collected; it was dissolved in alcohol-free ether, the solution washed with water and dried over potassium carbonate, and the solvent removed. The residual pale brown gum distilled completely and almost constantly at 230—237°/2 mm. and then at 222—225°/1 mm. as a colourless oil, hardening to a gum on cooling (Found: C, 79·0, 79·1; H, 8·6, 8·5; N, 8·4. $C_{22}H_{28}ON_2$ requires C, 78·6; H, 8·3; N, 8·3%). A specimen, b. p. 225—229°/1 mm., was prepared from especially pure starting material (Found: C, 78·3; H, 8·2; N, 8·3%). This material is a mixture, but it evidently consists essentially of methyldihydrostrychnidine.

The distilled base was heated at 100° in a well-stoppered pear-shaped glass bottle with a large excess of methyl iodide and anhydrous methyl alcohol for 12 hours. The solution was concentrated and on cooling deposited a mass of soft crystals. This substance is rather sparingly soluble in methyl alcohol and crystallises from this solvent in colourless groups of needles which melt with frothing at about 130° (Found in material dried in a vacuum over sulphuric acid: C, 46·7; H, 6·2; loss at 100°, 22·1. Found in material dried at 100°: C, 57·3; H, 7·1. $C_{22}H_{30}ON_2$,2MeI requires C, 46·3; H, 5·7; 1MeI, 22·8. $C_{22}H_{30}ON_2$,MeI requires C, 57·5; H, 5·8%). (The results do not exclude formulæ based on $C_{22}H_{28}ON_2$.)

In another experiment the methosulphate (80 g.) afforded 38 g. of the crude distilled base. In this case the alkaline aqueous solution was acidified with acetic acid, evaporated to dryness, and the residue thrice extracted with alcohol. On concentration of the filtered solution, a sticky brown residue was obtained consisting almost wholly of quaternary ammonium salts;

this was dissolved in a little boiling methyl alcohol and on cooling furnished a paste of crystals, which were collected and recrystallised from the same solvent as a mass of colourless needles (A), which, after drying at 100°, evolved steam at a higher temperature and had m. p. 275—280° (decomp.) (Found in material dried at 100° in a vacuum : C, 71·7, 71·5; H, 7·3, 7·3. Calc. for $C_{21}H_{24}ON_2$,MeCl : C, 71·3; H, 7·3%). The related methiodide crystallised from methyl alcohol (Found : C, 57·8; H, 5·6. Calc. for $C_{21}H_{24}ON_2$,MeI : C, 57·1; H, 5·8%). This substance is strychnidine methochloride (methiodide), because on heating it yields strychnidine (m. p. and mixed m. p.) and with methyl-alcoholic potash it affords methoxymethyldihydro-*neo*strychnidine, m. p. 125°. The mother-liquor from (A) on concentration deposited a quite different substance in glistening laminæ. This crystallised from water in needles decomposing at 295—300° (Found : C, 56·9; H, 6·0%) and was identified as methyl*neo*strychnidinium iodide by conversion into methoxymethyldihydro*neo*strychnidine, m. p. 124°, and into *neo*strychnidine, m. p. 203°, by way of the methochloride. The m. p.'s of these derivatives were not depressed by admixture with authentic specimens.

Examination of the Gum, b. p. 220—225°/1 *mm.*—In a preliminary experiment a thrice-distilled specimen was dissolved in a little acetone and kept in the ice-chest for about 3 months; it then suddenly deposited a small crop of crystals in the form of opaque flakes. The substance was collected and crystallised from acetone, the melting point being raised to 228—230°, 230—232°, and finally 235° (Found : C, 74·6; H, 8·4; N, 7·8. $C_{22}H_{30}O_2N_2$ requires C, 74·6; H, 8·5; N, 7·9%). This substance is designated *hydroxydihydro*-N(b)-*methyl*chano*dihydro*-neo*strychnidine*-θ. A considerable amount of this substance was obtained in the course of the preparation of methylhexahydrostrychnidine (see below).

In another preliminary experiment the original product was electrolytically reduced at 15° in the usual apparatus, then recovered, dried, dissolved in acetone, and kept in the ice-chest. In this case (see, however, below) the higher-melting product did not separate, but a large separation of a different substance occurred. This had m. p. 133°, raised to 139—140° by subsequent crystallisations (Found : C, 78·8; H, 8·5; N, 8·3. $C_{22}H_{28}ON_2$ requires C, 78·6; H, 8·3; N, 8·3%). This substance is termed N(b)-*methyl*chano*dihydro*neo*strychnidine*-θ.

The effect of the electrolytic reduction is merely to render the crystallisation of this substance more facile; there is no evidence that the crude product (C, 78·3; H, 8·2% after the electrolytic reduction) is hydrogenated in this process. The crude product (150 g., thrice distilled), dissolved in acetone (500 c.c.), cooled to 0°, and seeded with a crystal of methyl*chano*dihydro-*neo*strychnidine-θ, m. p. 140°, afforded a crop of almost colourless needles (22 g., m. p. 125—130°). A week sufficed for the complete separation of the first crop, and on further standing of the mother-liquor for several weeks, crystallisation of nodules commenced. These softened at 170° and melted at 178°, and on recrystallisation (see below) the m. p. could be raised to 192—193° (Found : C, 78·5; H, 8·8; N, 8·2. $C_{22}H_{30}ON_2$ requires C, 78·1; H, 8·9; N, 8·3%). This substance is termed N(b)-*methyldihydro*chano*dihydrostrychnidine*-θ.

Several large specimens of the material mentioned above as separating from the acetone solution of the crude base, and having m. p. 125—130°, were combined and recrystallised from acetone (60 g. of m. p. 133—135°). It was then crystallised from ethyl acetate (150 c.c.), affording a solid of m. p. 125—155° (29 g.) and a mother-liquor (A). The crystals were dissolved in ethyl acetate (100 c.c.) and on long standing in the ice-chest furnished 9·5 g. of a substance, m. p. 152—160°, and a mother-liquor (B). The substance was then crystallised from ethyl alcohol (150 c.c.) as a slowly-separating crust (2·2 g., m. p. 160—190°). The mother-liquor from this crystallisation was mixed with aqueous sodium hydroxide, and the base collected (5·7 g., m. p. 175—180°). A tedious series of crystallisations brought the melting points 160—190° and 175—180° up to 192—193° and the presence of *N*(*b*)-methyldihydro*chano*-dihydrostrychnidine-θ in the first crop of crystals was thus demonstrated. The mixed m. p. with an authentic specimen showed no depression. The mother-liquor (A) was concentrated to 85 c.c. and nucleated with *N*(*b*)-methyl*chano*dihydro*neo*strychnidine-θ, m. p. 140° The crop (7·5 g.) obtained on cooling had m. p. 125—130°, and on recrystallisation from acetone gave 5 g., m. p. 135—137°. Further crystallisations from acetone gave products, m. p. 140—141°, 141—142°, 142°. This substance was shown to be identical with that obtained in the earlier experiments described above. An exhaustive series of fractional crystallisations of the bases obtained from the various mother-liquors was carried out, but gave no evidence of the presence of substances other than the bases, m. p. 142° and 192° respectively.

The second crop of crystals from the original acetone solution was similarly fractionated, alcohol, acetone, ethyl acetate, and amyl alcohol mixed with methyl alcohol being used. Evidence of the presence of some *N*(*b*)-methyl*chano*dihydro*neo*strychnidine-θ, m. p. 142°, was obtained, but the bulk of this second crop was proved to consist of *N*(*b*)-methyldihydro*chano*dihydrostrychnidine-θ, m. p. 192—193°.

Owing to the extremely laborious nature of the crystallisations required, we are unable to give any estimate of the relative proportions of the two main products of the reduction.

Hydroxydihydro-N(b)-*methyl*chano*dihydro*neo*strychnidine*-θ.—This substance is very sparingly soluble in boiling alcohol but on concentration a supersaturated solution is easily produced; transparent needles separate slowly on keeping and these become opaque at 100° (Found : [*] C, 74·5; H, 8·5; N, 8·0%) and then have m. p. 235—237° with a little previous softening. The base is insoluble in boiling water; it exhibits strychnidine-type colour reactions; for example, its solution in very dilute hydrochloric acid becomes immediately pink on the addition of ferric chloride and deep crimson on boiling.

Action of Phosphoryl Chloride on the Base, $C_{22}H_{30}O_2N_2$.—The pure substance (2·1 g., m. p. 235—237°) was heated at 100° with phosphoryl chloride (25 c.c.) for 10 minutes; a gum was formed but a clear colourless solution resulted when the mixture was boiled (sulphuric acid-bath). After 5 minutes the mixture was added to ice-water, and a caseous base isolated. This melted on drying at 100° and was freely soluble in ether. Its concentrated solution in dry acetone was kept in the ice-chest and no crystallisation occurred in 24 hours; on seeding with a crystal of *N*(*b*)-methyl*chano*dihydro*neo*strychnidine-θ, however, a paste of crystals was rapidly formed. The substance was collected (m. p. 135—137°) and thrice crystallised from acetone, m. p. 140—141° (Found : C, 78·5; H, 8·5%) and at the same temperature when mixed with *N*(*b*)-methyl*chano*dihydro*neo*strychnidine-θ, m. p. 142—143°.

N(b)-*Methyl*chano*dihydro*neo*strychnidine*-θ.—This base may well be contaminated with an isomeride, possibly a methyldihydrostrychnidine, because as usually obtained it has m. p. 135—137° and only a prolonged series of crystallisations raises this to 142—143° [Found : C, 78·6, 78·5, 78·5; H, 8·4, 8·5, 8·5; N, 8·3, 8·3; Me*N*, 4·8, 4·9. $C_{21}H_{25}ON(NMe)$ requires Me*N*, 4·4%]. The pure substance is readily soluble in the simple alcohols and in benzene, moderately soluble in ether, and somewhat sparingly soluble in acetone. It crystallises from ether, light petroleum, acetone or methyl alcohol in prismatic needles and it exhibits colour reactions of strychnidine type. The well-crystallised methiodide gave analytical figures corresponding with a mixture of mono- and di-methiodides.

N(b)-*Methyldihydro*chano*dihydrostrychnidine-A*.—Methyl*chano*dihydro*neo*strychnidine-θ (2·0 g., m. p. 137—139°) was dissolved in acetic acid (50 c.c. of 6%) and shaken with hydrogen in the presence of palladinised charcoal (0·2 g. of palladous chloride and 0·7 g. of charcoal) at 20°. The reduction proceeded slowly (at first 1 c.c. H_2/1 min.) and after 21 hours only 61 c.c. of hydrogen had been absorbed (theo., 134 c.c.). The base was isolated (m. p. 130—145°) and crystallised from light petroleum (0·75 g., m. p. 153—167°). Twice recrystallised from acetone, it was obtained in elongated prisms, m. p. 176—177° (Found : C, 78·3; H, 8·9; N, 8·4. Calc. for $C_{22}H_{30}ON_2$: C, 78·1; H, 8·9; N, 8·3%). The melting point was not depressed on admixture with a specimen of *N*(*b*)-methyldihydro*chano*dihydrostrychnidine-A (m. p. 177°) obtained by the catalytic hydrogenation of *N*(*b*)-methylstrychnidinium chloride (Part XXIII; Achmatowicz, *loc. cit.*). We are greatly indebted to Professor Achmatowicz for a specimen of the base prepared by his method. The absorption of hydrogen at a higher temperature was more rapid and could be prolonged beyond the theoretical requirement for two double bonds; however, the dihydro-derivative, m. p. 177°, was again isolated from the product. The other bases obtained had much lower m. p.'s and greater solubility in organic solvents and probably owed their formation to hydrogenation of the aromatic nucleus.

N(b)-*Methyldihydro*chano*dihydrostrychnidine*-θ.—This *base* crystallises from many organic solvents in colourless prismatic needles, m. p. 192—193° (depressed to 158—165° on admixture with the isomeride-A, m. p. 177°) (Found : C, 77·8, 78·1, 77·9; H, 8·9, 8·9, 8·9; N, 8·3, 8·3; Me*N*, 5·0. $C_{21}H_{27}ON{\cdot}NMe$ requires Me*N*, 4·4%). (Many strychnidine derivatives give Me*N*, 1—2%, even when methyl is not attached to nitrogen.) The strong base exhibits the usual strychnidine-type colour reactions and its *methiodide*, very sparingly soluble in boiling acetone, crystallises from hot water in microscopic prisms, m. p. 270° (Found : C, 57·6; H, 6·9. $C_{22}H_{30}ON_2{,}MeI$ requires C, 57·5; H, 6·9%). Catalytic reduction of this base was attempted, but the unchanged substance was recovered along with readily soluble, probably aromatic-nuclear-hydrogenated, compounds; reduction did not occur at the room temperature and only proceeded slowly at 65°.

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[*] The investigation was interrupted for a period of seven years and these and the following analyses of the main products have been made recently in confirmation of the earlier work.

N(b)-*Methylhexahydrostrychnidine*-θ.—After separation of the bases, m. p.'s 235°, 142°, 192°, from the crude distilled product of the original process, a large amount of bases remained in the various mother-liquors and these were collected (over 400 g.). The bases were then submitted to electrolytic reduction in 20% sulphuric acid solution at 30—35° under the usual conditions and recovered. On keeping the acetone solution of the product in the ice-chest, a crystalline crust, m. p. 215—220°, separated and this was purified by crystallisation and found to consist of hydroxydihydro-*N*(*b*)-methyl*chano*dihydro*neo*strychnidine, m. p. 236—237°. The bases were isolated, distilled under 1 mm., again electrolytically reduced, and again isolated and dissolved in acetone. In this way more of the crystalline crust was obtained and the series of operations was repeated six times; no more crystals were then obtained. Two of the reductions were carried out at 12°, two at 18°, two at 30°, and the last at 41°; the duration of the process averaged 16 hours ($C = 5$ amps.). The final product distilled at 230—232°/4 mm. and set to a transparent resin that could not be crystallised (Found: C, 77·7; H, 9·5; N, 8·2. $C_{22}H_{32}ON_2$ requires C, 77·6; H, 9·4; N, 8·2%). This base is probably not homogeneous; it exhibits strychnidine-type reactions and combines readily with methyl iodide to a gummy methiodide. The related methochloride evolved some volatile base on being heated with methyl-alcoholic potash, and the resinous base produced was distilled (b. p. 225—233°/ 3 mm.). This now gave a crystalline *methiodide* very readily and in good yield; it separated from methyl alcohol in minute crossed prisms, m. p. 278—280° (Found: C, 58·3; H, 7·0%).

Reduction of N(b)-*Methyl*neo*strychnidinium Chloride*.—This salt was reduced by sodium amalgam under the conditions already prescribed for strychnidine methosulphate, the only variation being that neutrality was maintained by the addition of a drop of acetic acid when necessary. The separation of a base occurred, but apparently not so readily as in the methylstrychnidinium series. The crude base was isolated by means of pure ether and the gum was extracted with a large volume of boiling light petroleum. Nothing separated from this solution and on evaporation a gum was obtained. This was dissolved in acetone and kept in the ice-chest for a week; soft crystals were then deposited. The mother-liquor was not further examined owing to the paucity of the material, but the crystals were submitted to seven recrystallisations from acetone and then had m. p. 142—143°, alone or mixed with a specimen of the *N*(*b*)-methyl*chano*dihydro*neo*strychnidine-θ, m. p. 142°, described above. The yield was unsatisfactory. No base could be isolated when methyldihydrostrychnidinium-A chloride was treated with sodium amalgam under the conditions used for strychnidine methosulphate.

Oxidation Experiments.—The crude distilled product, b. p. 230—232°/1 mm., from the original reduction was oxidised in several experiments by means of potassium permanganate in acetone solution at 5—10°. The reagent was only slowly attacked and from the manganese dioxide precipitate a brown crystalline *acid* was isolated. This substance darkened at 190° and decomposed at 210—220° (Found: C, 66·6; H, 6·3; N, 7·1. $C_{22}H_{24}O_5N_2$ requires C, 66·7; H, 6·0; N, 7·1%). In another experiment the *acid* isolated gave similar analytical figures (Found: C, 66·4; H, 5·6; N, 6·8. $C_{22}H_{22}O_5N_2$ requires C, 67·0; H, 5·6; N, 7·1%).

The use of *pure* *N*(*b*)-methyl*chano*dihydro*neo*strychnidine-θ gave somewhat different results. Powdered potassium permanganate (13 g.) was gradually added to a solution of the pure base (5 g.) in acetone (300 c.c.) and water (5 c.c.) at 3°. The decomposition of the permanganate occupied 3 days. The liquid was filtered, and the manganese sludge (A) washed with acetone. The solution was evaporated to dryness (gum, 4 g.), and the residue gently heated with very dilute acetic acid; only a small portion dissolved (filtrate B) and the remainder hardened to a pale ochre semi-crystalline mass. This, thrice crystallised from methyl alcohol (norit), formed small colourless prisms, m. p. 235—240° (Found: C, 74·8; H, 7·6; N, 7·9. $C_{22}H_{28}O_2N_2$ requires C, 75·0; H, 7·9; N, 7·9%). This *oxy*-N(b)-*methyl*chano*dihydro*neo*strychnidine*-θ is slightly soluble in boiling water, is a very feeble base, and gives colour reactions of the strychnidine type.

The filtrate (B), on cooling, deposited a crop of crystals, sparingly soluble in ether and readily soluble in methyl alcohol. The *substance* crystallised in colourless prisms from ether, m. p. 180° (Found: C, 72·2; H, 6·9; N, 7·6. $C_{22}H_{26}O_3N_2$ requires C, 72·1; H, 7·1; N, 7·6%). The compound, obtained in very small yield, is a very feeble base of strychnidine type. The number of hydrogen atoms in the molecule remains uncertain.

The precipitate (A) was extracted with boiling water and the filtered solution and washings were concentrated and acidified to Congo-red with sulphuric acid. The pale chocolate precipitate (filtrate C) was collected, dried, dissolved as far as possible in boiling methyl alcohol, and the solution concentrated. The pale brown crystalline acid that separated on keeping was washed and dried (Found: C, 64·2; H, 6·4%). The solution (C) deposited crystals of a very sparingly soluble *acid* (Found : C, 64·3; H, 6·0; N, 7·1. $C_{22}H_{24}O_6N_2$ requires C, 64·1; H, 5·8; N, 6·8%). Possibly this acid is the hydrate of that isolated from the oxidation of the crude reduction product.

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