58. *Strychnine and Brucine. Part XV.* neo*Strychnidine and its Derivatives.*

By Osman Achmatowicz, (the late) William Henry Perkin, jun., and Robert Robinson.

In Part IV of this investigation (Clemo, Perkin, and Robinson, J., 1927, 1589) it was shown that strychnidine metho-salts, when digested with methyl-alcoholic potash, do not undergo the usual Hofmann elimination but yield a methoxymethyldihydrostrychnidine, m. p. 126°, and the essential change was represented by the scheme :

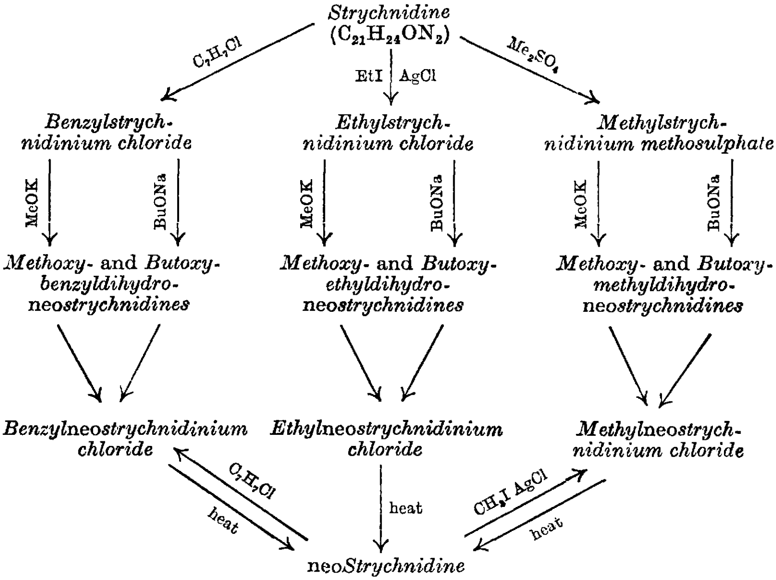
$$\vdots C{\cdot}\dot{\underset{\cdot}{N}}Me\}SO_4Me \text{ and } MeO\}K \longrightarrow \vdots C(OMe),\dot{\underset{\cdot}{N}}Me \text{ and } SO_4Me\}K$$

It was pointed out (*loc. cit.*, p. 1591) that this was probably not the only change involved, because the reconstitution of the quaternary salt, on boiling methoxymethyldihydrostrychnidine with dilute sulphuric acid, leads to the formation of methyl*neo*strychnidinium salts, isomeric and not identical with the corresponding methylstrychnidinium salts.

In pursuing the study of this series we were at first inclined to the view that this account of the decomposition was inaccurate and that the elements of water and not of methyl alcohol were eliminated, but further work cleared up the ambiguity, due to the small differences in the theoretically required analytical figures for the two possibilities, and we are now able to state definitely that the original hypothesis has been entirely justified.

Nevertheless, an important correction, not of the experimental results of Part IV, but of their interpretation, must be made in one particular. The substance previously termed methyl-ψ-strychnidine, which was obtained by heating methyl*neo*strychnidinium chloride, is in reality an isomeride of strychnidine and we propose the name neo*strychnidine* for this base.

The first experimental method that gave clear indications that "methyl-ψ-strychnidine" does not contain the methyl group was the preparation of the substance from benzylstrychnidinium chloride and from ethylstrychnidinium chloride. The annexed table summarises the transformations that have been realised.



Very strong confirmatory evidence was afforded by the observation that *neo*strychnidine may be reduced by hydrogen in the presence of palladium to dihydrostrychnidine (A), which is the product of the catalytic hydrogenation of strychnidine. This experiment also makes it certain that the cause of the isomerism of strychnidine and *neo*strychnidine resides in the unsaturated group, which evidently does not occupy the same position in the two bases.

*neo*Strychnidine and methyl sulphate furnish the methyl*neo*strychnidinium salt and this is decomposed by methyl-alcoholic potash with formation of the substance previously called methoxymethyldihydrostrychnidine. This compound is, however, clearly a *neo*strychnidine derivative and should be known henceforth as methoxymethyldihydro*neo*strychnidine. A similar correction in the nomenclature of the tetrahydro-series is hardly necessary, since the distinction between strychnidine and *neo*strychnidine derivatives disappears on saturation of the ethylenic linkage.

Here the appropriate corrections are that methyl-ψ-dihydrostrychnidine is the known dihydrostrychnidine (A) and the methyl*neo*dihydrostrychnidinium salts should be called methyldihydrostrychnidinium (A) salts. Attention has already been drawn to these points (Part VI; Oxford, Perkin, and Robinson, J., 1927, 1420).

The very striking divergence of behaviour between methoxymethyldihydro*neo*strychnidine and methoxymethyltetrahydrostrychnidine on treatment with boiling dilute sulphuric acid has already been the subject of comment (Bakerian Lecture, Royal Society, 1930), since the more reduced base is perfectly stable under these conditions.

The suggestion was made that methoxymethyl*neo*dihydrostrychnidine contains the group C=C—C(OMe), and that the reactivity of the methoxyl group is due to the activating influence of the double bond, as in an allyl or a benzyl ether. It is therefore of interest to note that the decomposition of benzyltrimethylammonium chloride by means of methyl-alcoholic potassium hydroxide proceeds smoothly with the formation of benzyl methyl ether. The unsaturated group is not essential for the reaction and phenyltrimethylammonium chloride and potassium butoxide furnished butyl methyl ether; however, phenylbenzyldimethylammonium chloride and potassium methoxide gave benzyl methyl ether. Hence the formation of a benzyl ether was favoured and this accords well with the hypothesis regarding the position of the double linking in *neo*strychnidine and its derivatives.

We assume that the double bond in strychnidine moves only one step to reach *neo*strychnidine and the change might be represented by one of the alternatives :—

(A) $\mathrm{C{=}C{-}CH{-}C{-}N \longrightarrow CH{-}C{=}C{-}C{-}N}$

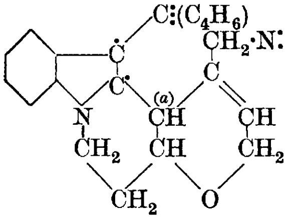
(B) 

$\mathrm{\begin{matrix}C\\CH\end{matrix}\!>\!C{-}C{-}N \longrightarrow \begin{matrix}CH\\C\end{matrix}\!>\!C{-}C{-}N}$

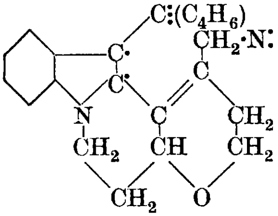
Of these we prefer (B), because (A) offers no explanation of the failure of methylstrychnidinium hydroxide to undergo a Hofmann elimination for which, since the ring is to break in any case, all the circumstances would appear to be favourable.

The scheme (B) also allows of the course of the permanganate oxidation of strychnine (Leuchs) receiving a natural explanation.

We therefore suggest that strychnidine and *neo*strychnidine may be represented by the annexed formulæ, which embody arguments put forward previously and also take cognisance of the identification of dinitrostrycholcarboxylic acid as an indole derivative (Part XII; J., 1931, 773). It is conceivable that a carbon atom of the C_4H_6 group may be interpolated at (*a*), making the oxide ring seven-membered.



Strychnidine.



*neo*Strychnidine.

The oxidation of *neo*strychnidine to the diketone strychnidone (Part IV; *loc. cit.*, p. 1614) by means of potassium permanganate is in good accord with this suggestion. The process consists merely in the disruption of the double bond by addition of two oxygen atoms and the resulting large ring offers no difficulties at the present time in view of the existence of cryptopine, trimethylbrazilone, and the many poly-ring-membered substances prepared by Ruzicka.

One of the most remarkable properties of methoxymethyldihydro*neo*strychnidine (Part IV; *loc. cit.*) is its conversion into isomeric oxymethoxymethyldihydro*neo*strychnidines when it is heated in methyl-alcoholic solution with methyl iodide; we now find that this is not an isolated phenomenon and *methoxybenzyldihydro*neo*strychnidine* behaves similarly, taking up an oxygen atom under similar conditions.

The oxidation of methoxymethyldihydro*neo*strychnidine by means of potassium permanganate has also been studied and the product appears to be oxymethoxymethyldihydro*neo*strychnidine (B), although if that is the case the melting point has been raised from 285° to 305°.

Attempts to prepare the tetrahydrostrychnine analogue of *neo*strychnidine were not successful, although a compound which is doubtless *tetrahydro*neo*strychnine methiodide* was obtained.

The corresponding methochloride did not decompose smoothly when heated.

Experimental.

Strychnidine Benzylochlorides (*A*) *and* (*B*).—These salts have been previously obtained by the combination of the components and by the electrolytic reduction of strychnine benzylochloride; the following modified method gives improved results.

Strychnidine was triturated with a slight excess (3%) of benzyl chloride and when the reaction was complete the product was crystallised from water. The isomeride (A) (yield, 90%), which is sparingly soluble in cold water and only moderately readily soluble in hot water (1 g. in 50 c.c.), separated in colourless needles, m. p. 325—330° with evolution of benzyl chloride (Found: C, 75·0; H, 6·9. Calc. for $C_{28}H_{31}ON_2Cl$: C, 75·2; H, 6·9%). The isomeride (B), which is very readily soluble in water, separated as a sandy powder, m. p. 300—302° (decomp.) (yield, 5—7%).

Benzylstrychnidinium hydroxide was prepared by the action of silver oxide (5% excess) on a hot aqueous solution of the chloride. The filtrate from silver chloride was concentrated under diminished pressure on the steam-bath; the hydroxide separated, on cooling, in long colourless needles which, after recrystallisation from water, had m. p. 306—307° and contained H_2O not lost at 104° (Found: C, 75·3; H, 7·5. $C_{28}H_{32}O_2N_2,H_2O$ requires C, 75·3; H, 7·6%). The very strong base absorbs carbon dioxide from the air and on decomposition by heat it gives *neo*strychnidine (yield, 8—10%) and other substances. The *neo*strychnidine has m. p. 201—203° and affords a methiodide, m. p. 312° (Found: C, 57·4; H, 5·9%).

*Methoxybenzyldihydro*neo*strychnidine*,
$C_{19}H_{24}ON(a)[N(b){\cdot}CH_2Ph](MeO)(C{:}C)$.
—A mixture of strychnidine benzylochloride (A) (20 g.) and methyl-alcoholic potassium hydroxide (150 c.c. of 10%) was heated in an open flask until the temperature of the melt reached 140°; the bases were then collected by means of ether and distilled.

The fraction, b. p. 257—260°/1 mm., could be crystallised from methyl alcohol and afforded *neo*strychnidine (yield, 20—30%), m. p. 203—204° (Found: C, 78·7; H, 7·6. Calc. for $C_{21}H_{24}ON_2$: C, 78·7; H, 7·5%). The substance was identified by comparison (undepressed mixed melting point) with an authentic specimen. A solution of the *crude* reaction product, in ether, deposited about 0·8 g. of a substance which after crystallisation was identified as *neo*strychnidine.

The pale brown distillate at 268—271°/1 mm. (55—60%) was easily soluble in most organic solvents but could not be crystallised. It consisted of *methoxybenzyldihydro*neo*strychnidine* (Found: C, 78·7; H, 7·5. $C_{29}H_{34}O_2N_2$ requires C, 78·7; H, 7·7%). The base shows the strychnidine-type reaction with 60% sulphuric acid and a dichromate.

Methoxybenzyltetrahydrostrychnidine,
$C_{19}H_{24}ON(a)[N(b){\cdot}CH_2Ph](MeO)(CH{\cdot}CH)$.
—The last-mentioned substance (10 g.) was dissolved in sulphuric acid (150 c.c. of 20%) and reduced in the apparatus described in Part II (J., 1924, **125**, 1798) by means of a current of 5 amps. during

16 hours at 12—15°. The base was set free by means of ammonia, dried, and crystallised from ethyl alcohol, forming colourless rhombs, m. p. 106—107° (Found : C, 79·0; H, 8·4. $C_{29}H_{36}O_2N_2$ requires C, 78·4; H, 8·1%). The substance is sparingly soluble in methyl alcohol and moderately readily soluble in benzene; it is stable towards permanganate and is not changed by boiling 20% sulphuric acid. It exhibits strychnidine-type colour reactions.

*Oxymethoxybenzyldihydro*neo*strychnidines (A) and (B)*.—Methoxybenzyldihydro*neo*strychnidine does not combine readily with methyl iodide at room temperature, and in a solvent oxidation occurs. The base (5 g.) was dissolved in acetone containing a few drops of methyl iodide and kept for 2 days; the crystalline deposit was then fractionated from acetone. The *isomeride* (*A*), which is very sparingly soluble in acetone, separated in large transparent cubes which became opaque on exposure to the air and melted at 249° (Found : C, 75·8; H, 7·7. $C_{29}H_{34}O_3N_2$ requires C, 75·9; H, 7·5%). The *isomeride* (*B*), which is moderately readily soluble in acetone, crystallised in minute needles, m. p. 267° (Found : C, 76·0; H, 7·5%). Neither of these substances can be acetylated or converted into a semicarbazone or an oxime.

*Action of Hot Dilute Sulphuric Acid on Methoxybenzyldihydro*neo*strychnidine*.—A solution of the base (20 g.) in sulphuric acid (300 c.c. of 20%) was boiled for 3 hours (the formation of methyl alcohol and traces of benzyl alcohol was established in a separate experiment), and the cooled solution rendered alkaline. The base that separated was collected (3 g.) and crystallised from methyl alcohol (norite) and identified by analysis (Found : C, 78·9; H, 7·5. Calc. : C, 78·7; H, 7·5%) and by m. p. (198—200°) and mixed m. p. (200—202°) as *neo*strychnidine. It is possible, although not very probable, that this product of the reaction was present in the base employed.

Sodium iodide (20 g. in 25 c.c. of water containing a little sulphur dioxide) was added to the alkaline filtrate from the *neo*strychnidine; *benzyl*neo*strychnidinium iodide* (yield, 64%) then separated as a lilac-coloured solid mass. The salt crystallised from methyl alcohol in silky needles, m. p. 186—188°, decomp. 238—240° (Found in material dried at 100° : C, 61·0; H, 6·3. $C_{28}H_{31}ON_2I,CH_4O$ requires C, 61·1; H, 6·1%). The salt also crystallised from much acetone or from water and then had m. p. 238—240° (decomp.) (Found : C, 62·4; H, 5·9. $C_{28}H_{31}ON_2I$ requires C, 62·5; H, 5·8%). It is possible that the gummy product obtained by concentration of the alkaline mother-liquor consisted of an isomeric salt; it was very readily soluble in water in comparison with the substance described. When an aqueous solution of the iodide was heated with silver chloride, *benzyl*neo*strychnidinium chloride* was obtained : it crystallised from water in large brilliant prisms, m. p. 230—232°, and after re-solidification (*neo*strychnidine) at 199—201° (Found in material dried at 100° : C, 71·2 ; H, 7·5. $C_{28}H_{31}ON_2Cl,1\frac{1}{2}H_2O$ requires C, 71·0 ; H, 7·2%).

*Action of Heat on Benzyl*neo*strychnidinium Chloride.*—When the salt (0·5—1·0 g.) was cautiously heated in a wide test-tube over a free flame, benzyl chloride was evolved and *neo*strychnidine (85—90%) was produced.

The base (green-fluorescent impurity) was crystallised from methyl alcohol and had m. p. 203—204° (Found : C, 78·8 ; H, 7·5 ; N, 8·5. Calc. for $C_{21}H_{24}ON_2$: C, 78·7 ; H, 7·5 ; N, 8·7%). When the original methoxybenzyldihydro*neo*strychnidine was not sufficiently pure, a by-product was found (5—10%) in the methyl-alcoholic mother-liquors from the *neo*strychnidine. Once separated, however, the substance does not redissolve in methyl alcohol and it is also insoluble in benzene and acetone. It dissolves in hot pyridine and from this solution it is precipitated by the addition of boiling alcohol as a mass of colourless, slender, microscopic needles, m. p. 239—240° (Found : C, 74·7 ; H, 7·1. $C_{21}H_{24}O_2N_2$ requires C, 75·0 ; H, 7·1%). This substance does not yield an acetyl derivative, nor could it be induced to condense with semicarbazide, hydroxylamine, or benzaldehyde. It possesses basic properties and is designated *oxy*neo*strychnidine.*

Strychnidine Ethiodide.—This salt was prepared by direct union of strychnidine and ethyl iodide ; it is very sparingly soluble in boiling methyl alcohol and even in water (1000 c.c. at 99° dissolve 5·0 g.), from which it separates in needles, m. p. 335° (Found : C, 58·3 ; H, 6·1. $C_{23}H_{29}ON_2I$ requires C, 57·9 ; H, 6·1%). The ethochloride (usual method) separated from concentrated aqueous solution as a paste of crystals which, dried at 100°, melted at 300—302°.

*Methoxyethyldihydro*neo*strychnidine,*

$$C_{19}H_{24}ON(a)[N(b)Et](MeO)(C\!:\!C).$$

—Strychnidine ethochloride (20 g.) was digested with methyl-alcoholic potassium hydroxide (120 c.c. of 20%) until the temperature reached 110° ; the cooled melt was then mixed with water and the bases were separated by fractional crystallisation from methyl alcohol. In this way *neo*strychnidine (10—15%) and *methoxyethyldihydro*neo*strychnidine* (60%) were isolated ; the latter is sparingly soluble in the cold solvent and much more readily soluble on boiling. It crystallised in large plates, m. p. 102—103° (Found : C, 75·6 ; H, 8·3. $C_{24}H_{32}O_2N_2$ requires C, 75·8 ; H, 8·4%).

The crystals, like those of most substances of this type, become pale purple on keeping. The *methiodide*, produced at 100° from the pure components, separated from methyl alcohol as a colourless crystalline powder, m. p. 258—260° (Found: C, 57·9; H, 6·9. $C_{25}H_{35}O_2N_2I$ requires C, 57·5; H, 6·7%).

Methoxyethyltetrahydrostrychnidine,
$C_{19}H_{24}ON(a)[N(b)Et](OMe)(CH{\cdot}CH)$.
—This substance was obtained by the electrolytic reduction of methoxyethyldihydro*neo*strychnidine at a lead cathode under the conditions already mentioned above in connexion with the benzyl derivative. The product (yield, 82%) crystallised from benzene or ethyl alcohol in colourless microscopic prisms, m. p. 175—176° (Found: C, 75·3; H, 8·6. $C_{24}H_{34}O_2N_2$ requires C, 75·3; H, 8·9%). The base is stable towards permanganate and towards boiling 20% sulphuric acid.

*Ethyl*neo*strychnidinium Salts*.—Methoxyethyldihydro*neo*strychnidine was subjected to the action of 20% sulphuric acid exactly as described above for the benzyl derivative (methyl alcohol was again recognised as a product) and the resulting quaternary sulphates were converted into iodides. A relatively soluble, possibly isomeric, salt in the mother-liquor was not fully examined. The main product (yield, 72%) crystallised from methyl alcohol, in which it was sparingly soluble, in colourless needles, m. p. 285—286° (decomp.) (Found: C, 58·1; H, 6·0. $C_{23}H_{29}ON_2I$ requires C, 58·0; H, 6·0%).

The *ethochloride* is readily soluble in water and crystallises from methyl alcohol in microscopic prisms, m. p. 285—286° (decomp.) (Found: C, 72·2; H, 7·5. $C_{23}H_{29}ON_2Cl$ requires C, 71·9; H, 7·5%). It decomposed smoothly when heated into ethyl chloride (recognised) and *neo*strychnidine, which after crystallisation had m. p. 203—204°, alone or mixed with the specimen from benzyl*neo*strychnidinium chloride (Found: C, 78·5; H, 7·2%) (yield, 85%).

When ethyl*neo*strychnidinium chloride (2·0 g.) was digested with methyl-alcoholic potassium hydroxide (15 c.c. of 20%), it afforded methoxyethyldihydro*neo*strychnidine, m. p. 102°.

*Preparation of the Alkyl*neo*strychnidinium Salts by Way of the Butoxyalkyldihydro*neo*strychnidines*.—The methyl-, ethyl-, and benzyl-strychnidinium salts (20 g.) were heated for 2 hours at 100° with a *n*-butyl-alcoholic solution of sodium *n*-butoxide (from 10 g. of sodium and 250 c.c. of butyl alcohol). The crude product contained about 15% of *neo*strychnidine, and this was isolated after the treatment with dilute sulphuric acid. It was, however, detected in the crude product itself by means of the formation of the methiodide, m. p. 310—312°, which was compared with an authentic specimen.

None of the products could be crystallised and the butoxy-bases were accordingly directly converted into the quaternary sulphates (production of butyl alcohol) and other salts by the usual methods.

Benzyl*neo*strychnidinium iodide was crystallised from methyl alcohol and was identified with the specimen previously obtained by analysis (Found : C, 61·0 ; H, 5·8%), by m. p. and mixed m. p. (186—188°). The chloride derived from this specimen was decomposed by heat and the resulting *neo*strychnidine (Found : C, 78·9 ; H, 7·4%) had m. p. 202—203° ; benzyl chloride was also produced.

Ethyl*neo*strychnidinium iodide, obtained from the butoxy-derivative, had m. p. 285—286° (undepressed by admixture with the specimen obtained as described above) ; it was also converted into the chloride and then into methoxyethyldihydro*neo*strychnidine, m. p. 102—103°, and *neo*strychnidine, m. p. 202—203° (with loss of ethyl chloride).

Methyl*neo*strychnidinium iodide from the butoxy-derivative was proved to be identical with specimens of " methyl-ψ-strychnidine methiodide " and " methyl*neo*strychnidinium iodide (A) " (compare Part IV, *loc. cit.*) by a close comparison of properties. The salt had m. p. 312° (alone or in mixture) and the chloride, m. p. 275—280°, and *neo*strychnidine, m. p. 202—203°, were obtained from it. The chloride was also converted into methoxymethyldihydro*neo*strychnidine, m. p. 124—125°.

The formation of methyl chloride by the thermal decomposition of methyl*neo*strychnidinium chloride (40 g.) was controlled by passing the evolved gas through aqueous silver nitrate (no precipitate) and then into a solution of sodium iodide in acetone. Sodium chloride (about 5 g.) was precipitated and the methyl iodide formed was recognised by using it for the formation of methylstrychnidinium iodide.

*Direct Formation of Alkyl*neo*strychnidinium Salts.*—*neo*Strychnidine does not combine easily with benzyl chloride at room temperature ; the reaction was completed in 1 hour on the steam-bath.

Benzyl*neo*strychnidinium chloride, so obtained, and crystallised from water (Found in material dried at 100° : C, 70·6 ; H, 7·0%), had m. p. 230—232°, alone or mixed with the salts obtained as above from the methoxy- and butoxy-bases. It also yielded the iodide, m. p. 186—188° after crystallisation from methyl alcohol (Found : C, 61·0 ; H, 6·4%) (see above). Similarly the methiodide was prepared and from it the methochloride. Both salts were identical with those previously examined.

In the direct formation of alkyl*neo*strychnidinium salts, only the sparingly soluble forms were encountered.

Finally, crystallographic measurements were kindly undertaken by (the late) Dr. T. V. Barker, who reported as follows :—" I have measured two crystals of two substances * labelled methyl-ψ-strychnidine MeCl, m. p. 270°, and find them identical in every way with the substance described in Part IV, page 1612, under the name of methyl*neo*strychnidinium chloride."

Reduction of neo*Strychnidine.*—After electrolytic reduction for 30 hours under the usual conditions, 80% of the base was recovered unchanged. At 100°, however, the base (5 g.) in sulphuric acid (150 c.c. of 20%) was reduced in 14 hours and dihydrostrychnidine (A) was isolated in a yield of 90%. The substance crystallised from methyl alcohol in prisms, m. p. 215—216° (Found : C, 78·2; H, 7·9. Calc. for $C_{21}H_{26}ON_2$: C, 78·3; H, 7·9%). It is very interesting that strychnidine itself could not be reduced under the same conditions and the base was recovered unchanged.

The reduction of *neo*strychnidine was also carried out under the following conditions : A solution of the base (1·2 g.) in dilute acetic acid (75 c.c. of 10%) was added to previously reduced catalyst (from 0·2 g. of palladous chloride, 2·0 g. of norite, and 200 c.c. of very dilute hydrochloric acid) and stirred in hydrogen. The absorption of the gas was slow and the required volume (103 c.c.) was taken up in 12 hours. The filtered liquid was basified with ammonia, and the colourless base (0·9 g.) collected; it crystallised from methyl alcohol in leaflets, m. p. 214—215° (undepressed by admixture with the product of electrolytic reduction of *neo*strychnidine or of the catalytic reduction of strychnidine; Part VI, *loc. cit.*).

*Oxidation of Methoxymethyldihydro*neo*strychnidine by Means of Potassium Permanganate.*—A solution of potassium permanganate (4 g.) in water (300 c.c.) was gradually added to one of the base (7 g.) in pure acetone (500 c.c.) at 2—4° : the permanganate was at once decolorised. The liquid was filtered, and the manganese dioxide washed with acetone. On neutralisation of the combined filtrate and washings with carbon dioxide a crystalline precipitate (0·8 g.) separated.

This was almost insoluble in most organic solvents but could be crystallised from a large volume of acetone in plates, m. p. 167—168° (Found in material dried at 105° : C, 70·5; H, 8·3; N, 6·5; MeO, 7·0. $C_{23}H_{30}O_3N_2,C_3H_6O$ requires C, 70·9; H, 8·2; N, 6·5; 1MeO, 7·0%). The acetone is not lost at 104° and may therefore be combined (perhaps as in berberine-acetone); when the derivative was heated in a sealed tube for 10 hours with methyl iodide at 100°, it gave an *oxymethoxymethyldihydro*neo*strychnidine*, m. p. 305—306° (Found : C, 72·2; H, 7·6; N, 7·5; MeO, 8·3. $C_{23}H_{30}O_3N_2$ requires C, 72·3; H, 7·8; N, 7·3; 1MeO, 8·1%).

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* Wrongly so labelled, of course; the specimens were made from *neo*-strychnidine.

A further quantity (2·4 g.) of the same substance, m. p. 305—306°, was obtained when the aqueous filtrate was evaporated to dryness under reduced pressure and the solid residue was washed with acetone (the acetone washings were examined separately). Oxymethoxymethyldihydro*neo*strychnidine is very sparingly soluble in most organic solvents, but dissolves readily in pyridine and may be precipitated by addition of methyl or ethyl alcohol and this method was used for the purification of the base. The derivative remains unchanged after prolonged boiling with anhydrous sodium acetate and acetic anhydride; it also fails to combine with hydroxylamine or semicarbazide.

The acetone washings were mixed with anhydrous sodium sulphate and evaporated to dryness and the solid residue was powdered and extracted with ether for several days in a Soxhlet apparatus. The extract obtained in the first 24 hours was gummy and has not been further examined. Continued extraction (about 3 days) yielded a crystalline product, readily soluble in methyl or ethyl alcohol, moderately readily soluble in acetone, but insoluble in ether. It crystallised from aqueous methyl alcohol (50%) in colourless plates, m. p. 186—188° (Found: C, 68·4; H, 7·6; N, 7·2. $C_{22}H_{28}O_4N_2$ requires C, 68·7; H, 7·3; N, 7·3%). Owing to the small yield (about 10%) the substance could not be further investigated.

*Oxymethyl*neo*strychnidinium Salts*.—The oxymethoxymethyldihydro*neo*strychnidine, m. p. 305—306° (5 g.), was dissolved in sulphuric acid (100 c.c. of 20%); on boiling, methyl alcohol was produced. After refluxing for 2 hours, the liquid was cooled and basified with ammonia (no precipitate), and sodium iodide (5 g. in 10 c.c. of water) added. The precipitate (5·2 g.) crystallised from methyl alcohol in minute colourless needles, m. p. 238—240° (decomp.) (Found: C, 55·4; H, 5·8. $C_{23}H_{27}O_2N_2I$ requires C, 55·2; H, 5·6%).

The related chloride was a glass, but when it was digested with methyl-alcoholic potash on the steam-bath for 1 hour oxymethoxymethyldihydro*neo*strychnidine, m. p. 305—306°, was recovered.

As already stated in the introduction, it is probable that the latter substance is the isomeride (B) described in Part IV. When the isomeride (A) was employed in the present process, it gave the same iodide as that derived from the product, m. p. 305—306°. This was proved by m. p. and mixed m. p. of the iodide (238—240°), by analysis (Found: C, 55·5; H, 5·8%), and by conversion into the chloride and then into the oxymethoxymethyldihydro*neo*strychnidine, m. p. 305—306°.

The thermal decomposition of the chloride mentioned in this section yielded an unworkable gum. These transformations are of interest in that it becomes clear from them that the oxygen absorbed so easily by methoxymethyldihydro*neo*strychnidine takes up a stable form of combination and cannot, for example, be attached as in an ethylene oxide or amine oxide. Moreover it does not affect the quaternary salt-forming power of N (b).

Derivatives of Tetrahydrostrychnine.—Methosulphate. A suspension of tetrahydrostrychnine (20 g.) in methyl alcohol (100 c.c.) was mixed with a slight excess of freshly distilled methyl sulphate and heated on the steam-bath for 5 minutes. On cooling, the pale brown solution deposited long colourless needles, which were collected (the total yield, after the mother-liquor had been worked up, was 90%), washed, and recrystallised from methyl alcohol. The derivative is very soluble in water, moderately readily soluble in cold methyl alcohol, and readily on boiling. It melts and decomposes at 266—268° and, like other tetrahydrostrychnine salts, described below, gives with sulphuric acid (60%) and dichromate a brown coloration (Found: C, 59·3; H, 7·2. $C_{21}H_{26}O_2N_2,Me_2SO_4$ requires C, 58·5; H, 6·9%).

Methiodide. When boiling aqueous solutions of the methosulphate (20 g. in 1000 c.c.) and of sodium iodide (7 g. in 50 c.c.) were mixed and allowed to cool, *tetrahydrostrychnine methiodide* was precipitated as a voluminous mass of minute colourless needles. It was recrystallised from water and after having been dried at 100° melted at 312—314° (decomp.) (Found: C, 55·2; H, 6·0. $C_{21}H_{26}O_2N_2,MeI$ requires C, 55·0; H, 6·0%). The salt is sparingly soluble in water and moderately readily soluble in methyl alcohol.

The same methiodide was obtained directly from tetrahydrostrychnine and methyl iodide. It was identified with the specimen obtained from tetrahydrostrychnine methosulphate by m. p. (312—314° alone or mixed) and by conversion into the methochloride, m. p. 270—272°.

Methochloride. This derivative was obtained by heating tetrahydrostrychnine methiodide with water and excess of silver chloride on the steam-bath for 2 hours. The aqueous filtrate from the silver salts, on concentration to a small bulk, deposited a crystalline, lilac, waxy mass, very easily soluble in water. The *methochloride* thus obtained contains water of crystallisation, which may be completely removed at 100°. The anhydrous salt was recrystallised from methyl alcohol, in which it is readily soluble, and formed microscopic needles, m. p. 270—272° (Found: C, 67·8. $C_{21}H_{26}O_2N_2,MeCl$ requires C, 68·0%).

Benzylochloride. This was obtained in good yield when tetrahydrostrychnine was stirred with a slight excess of benzyl chloride. It is moderately readily soluble in cold water or methyl alcohol, but dissolves readily on boiling and separates as a woolly mass of slightly yellow needles, m. p. 202—204°. The salt crystallises with $5H_2O$, only partly lost at 100° (Found: loss at 100°, 13·8; calc. for $4\frac{1}{2}H_2O$, 13·0%. Found in material dried at 100°: C, 70·5; H, 7·1. $C_{21}H_{26}O_2N_2,C_7H_7Cl,\frac{1}{2}H_2O$ requires C, 70·8; H, 7·2%).

The Action of Methyl Alcoholic Potassium Hydroxide on Quaternary Salts derived from Tetrahydrostrychnine.—Tetrahydrostrychnine methosulphate (20 g.) was mixed with methyl-alcoholic potassium hydroxide (120 c.c. of 20%) and heated in an open flask in a rapidly boiling water-bath. The clear solution gradually clouded and after 2 hours the slightly yellow semi-solid residue was washed with hot water until the reaction was neutral. The product solidified on cooling to a greenish-grey sticky mass, freely soluble in most organic solvents and difficult to obtain in a crystalline condition (on one occasion, when it was dissolved in methyl alcohol, filtered, and rapidly cooled in ice, a small quantity of methoxymethyldihydro*neo*strychnidine, m. p. 124—126°, was obtained). The colour reaction of the product with sulphuric acid and dichromate was not as clear as that obtained with pure tetrahydrostrychnine or strychnidine derivatives; addition of a drop of dichromate produced a brown coloration with a pink tint, which indicated that a mixture of tetrahydrostrychnine and strychnine derivatives was present. An attempt to purify the substance by fractionation under reduced pressure also gave an unsatisfactory result; the product distilled over a wide range (230—280°) and could not be separated into definite fractions (however, from the fraction, b. p. 240—250°/1 mm., on recrystallisation from methyl alcohol, a small quantity of methoxymethyldihydro*neo*strychnidine, m. p. 124—126°, was obtained).

The composition of the product in question was subsequently established by electrolytic reduction and by treatment with dilute sulphuric acid. The experiments then showed that it consisted of methoxymethyldihydro*neo*strychnidine (about 40%), methoxymethylhexahydrostrychnine (about 15%), and probably of small proportions of *neo*strychnidine and tetrahydro*neo*strychnine.

The same results were obtained when tetrahydrostrychnine methochloride was subjected to the action of methyl-alcoholic potassium hydroxide.

Tetrahydrostrychnine benzylochloride under exactly the same conditions gave almost entirely methoxybenzylhexahydrostrychnine, as is shown below.

Unfortunately, neither methoxybenzylhexahydrostrychnine nor its dihydro-derivative (electrolytic reduction product) could be crystallised or purified by distillation under diminished pressure.

The crude product of the action of methyl-alcoholic potassium hydroxide on tetrahydrostrychnine methosulphate (20 g.) was dissolved in 20% sulphuric acid (300 c.c.) and reduced at a lead cathode under the usual conditions for 20 hours at 15—17°. On working up, a product sparingly soluble in methyl alcohol was isolated. This, crystallised from benzene, had m. p. 220—222° and was identified with methoxymethyltetrahydrostrychnidine (yield, 8 g.) (compare Part IV; *loc. cit.*). The base in the methyl-alcoholic mother-liquor is doubtless a hexahydrostrychnine derivative, but it could not be purified.

Action of Dilute Sulphuric Acid on Presumed Methoxymethylhexahydrostrychnine.—The crude product (20 g.) from the action of methyl-alcoholic potash on tetrahydrostrychnine methosulphate was refluxed for 3 hours with 20% sulphuric acid (300 c.c.); the formation of methyl alcohol was detected. Addition of ammonia precipitated a mixture of bases (5 g.), from which no definite substances could be isolated. The alkaline filtrate was mixed with sodium iodide (15 g. in 50 c.c. of water), precipitating a brown oil which solidified in contact with methyl alcohol (yield, 10 g.) and was identified as methyl*neo*strychnidinium iodide, m. p. 310° (Found: C, 57·2; H, 6·1. Calc. for $C_{22}H_{27}ON_2I$: C, 57·1; H, 5·8%). The methochloride, methoxymethyldihydro*neo*strychnidine, and *neo*strychnidine were all prepared by the known methods from the methiodide, and all these derivatives exhibited the correct properties. The mother-liquor from several preparations of this methiodide was evaporated to dryness and the dark oily residue was again dissolved in boiling water and the solution filtered, and again concentrated, giving an oil (A) and a supernatant liquor which deposited pale yellow prismatic needles on cooling. Further extraction of the oil (A) provided more of the same substance. It is very readily soluble in methyl alcohol or hot water and usually separates from hot aqueous solutions as an almost colourless oil which rapidly crystallises in well-developed plates, m. p. 242—243° (Found in material dried at 104°: C, 55·1; H, 5·9. $C_{22}H_{29}O_2N_2I$ requires C, 55·0; H, 6·0%). This substance is doubtless *tetrahydro*neo*strychnine methiodide*). The related *methochloride* is very readily soluble in water and forms a low-melting waxy mass of crystals containing water of crystallisation. Dried at 104° and crystallised from methyl alcohol, it had m. p. 265—267° and was very hygroscopic (Found in material dried at 104°: C, 68·0; H, 7·6. $C_{22}H_{29}O_2N_2Cl$ requires C, 68·0; H, 7·5%).

The action of methyl-alcoholic potash on this methochloride gave uncrystallisable gums, and thermal decomposition afforded *neo*strychnidine in 60% yield. The base was identified by m. p. and mixed m. p. (202—203°) and by analysis (Found: C, 77·5; H, 7·5%). The mother-liquor from the *neo*strychnidine undoubtedly contained tetrahydro*neo*strychnine, but this could not be fully purified and the best sample had m. p. 162—169° and gave tetrahydrostrychnine-like colour reactions.

Similarly, *tetrahydro*neo*strychnine benzyloiodide* was prepared; it formed a hard crust of pale yellow plates, m. p. 205—207° (Found: C, 60·2; H, 6·0. $C_{28}H_{33}O_2N_2I$ requires C, 60·4; H, 5·9%), and was best isolated from the methyl-alcoholic mother-liquors after the separation of oily material containing benzyl*neo*strychnidinium iodide. The related benzylochloride was amorphous and on thermal decomposition furnished *neo*strychnidine (m. p. 202—203°) in 50% yield.

Decomposition of Benzyltrimethylammonium Chloride by Means of Methyl-alcoholic Potassium Hydroxide.—The quaternary salt was prepared by leading trimethylamine into a methyl-alcoholic solution of benzyl chloride maintained at 0°. It separated as colourless crystals, m. p. 235° (Found: C, 65·0; H, 8·9. Calc. for $C_{10}H_{16}NCl$: C, 64·7; H, 8·6%).

A mixture of the quaternary chloride (20 g.) and methyl-alcoholic potassium hydroxide (120 c.c. of 20%) was distilled until the temperature reached 110°. On working up the product, benzyl methyl ether (9·5 g.), b. p. 167—169° (Found: C, 78·9; H, 8·6. Calc. for $C_8H_{10}O$: C, 78·7; H, 8·2%), was obtained.

Phenyltrimethylammonium iodide (40 g.) and butyl-alcoholic sodium butoxide (10 g. of sodium in 250 c.c.) were refluxed for 2 hours. *n*-Butyl methyl ether (6 g.), b. p. 69—71° (Found: C, 67·8; H, 13·4. Calc. for $C_5H_{12}O$: C, 68·2; H, 13·6%), was isolated from the product and dimethylaniline (14 g.) was recovered.

A mixture of phenylbenzyldimethylammonium chloride (30 g.) and methyl-alcoholic potassium hydroxide (150 c.c. of 20%) was heated until the temperature reached 110°. Benzyl methyl ether (10 g., b. p. 167—169°) and dimethylaniline (12 g.) were isolated from the product.

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