99. *Strychnine and Brucine. Part XVI.* neo*Strychnine.*

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The ring-fission of alkylstrychnidinium salts under the influence of potassium alkoxide occurs in accordance with the scheme

$$\mathrm{X\{{:}NR{\cdot}C\vdots + KOR' \longrightarrow {:}NR \qquad R'O{\cdot}C\vdots + KX}$$

(Part IV; J., 1927, 1617), but at the same time the ethylenic linkage moves to a new position (compare Part XV; this vol., p. 486).

Thus strychnidine methosulphate and potassium methoxide furnished methoxymethyldihydro*neo*strychnidine, and from this, by the action of hot dilute sulphuric acid, methyl*neo*strychnidinium sulphate could be obtained. The corresponding chloride lost methyl chloride when heated and yielded *neo*strychnidine.

The latter base and strychnidine are related by the fact that they yield the same dihydrostrychnidine (A) on catalytic hydrogenation.

All these reactions can be paralleled in the strychnine series and in this way neo*strychnine* has been obtained. On catalytic hydrogenation it yields the dihydrostrychnine obtainable from strychnine and on electrolytic reduction it affords *neo*strychnidine and *tetrahydro*neo*strychnine*. Thus the double bonds in *neo*strychnine and *neo*strychnidine are situated in like positions and from this we may justly conclude that the movement of the unsaturated linkage is not influenced by the lactam carbonyl of strychnine.

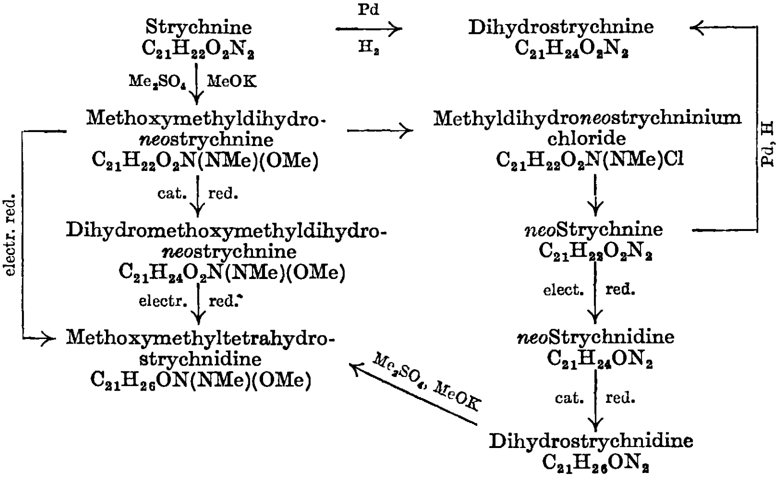
The change is therefore not of the form

$$\mathrm{{:}N(\mathit{a}){\cdot}CO{\cdot}CH_2{\cdot}C{=}C{:} \longrightarrow {:}N(\mathit{a}){\cdot}CO{\cdot}CH{=}C{-}CH{:}}$$

and this is confirmed by the fact that *neo*strychnine condenses with benzaldehyde with formation of *benzylidene*neo*strychnine*, the reactive methylene being doubtless that of the group $\mathrm{{:}N(\mathit{a}){\cdot}CO{\cdot}CH_2}$.

Although *neo*strychnidine doubtless contains the indole skeleton, its properties are not consistent with the view that this substance contains a true aromatic indole nucleus and thus the alteration of the position of the double bond has apparently occurred at some point in the molecule relatively remote from the benzene nucleus and N(*a*). This deduction is in harmony with the requirements of formulæ on the general lines of those suggested in recent parts of this series (compare also Bakerian Lecture, Royal Society, 1930).

Further experiments on the derivatives of *neo*strychnine are in progress and some of the relations established in the present communication are summarised below.



EXPERIMENTAL.

Benzylstrychninium chloride, prepared by direct union of the base and benzyl chloride, is moderately readily soluble in water and separates from concentrated solutions in needles, m. p. 303—305° (Found: C, 72·6; H, 6·5. Calc. for $C_{28}H_{29}O_2N_2Cl$: C, 73·0; H, 6·3%). When potassium hydroxide (15 c.c. of 50% solution) was gradually added to a hot aqueous solution of the salt (10 g.), and the mixture cooled, benzylstrychnine crystallised as a voluminous mass of colourless needles. After recrystallisation the base had m. p. 270° (Found: loss at 104°, 27·8; C, 76·0; H, 7·1. Calc. for $C_{28}H_{30}O_3N_2,9\frac{1}{2}H_2O$: H_2O, 27·9; C, 76·0; H, 6·8%). It is moderately readily soluble in water, sparingly soluble in methyl alcohol, and apparently insoluble in cold dilute mineral acids (probably owing to the formation of a sparingly soluble salt on the surface of the crystals). A solution in 60% sulphuric acid becomes deep violet on the addition of a trace of potassium dichromate.

When the base (1—2 g.) was carefully heated over a free flame (or distilled under 1 mm. pressure), benzyl alcohol was evolved and the residue consisted of strychnine (m. p. 267—268° after crystallisation, and undepressed mixed melting point).

Garzarolli (*Monatsh.*, 1889, **10**, 1) prepared benzylstrychninium chloride in alcoholic solution. The product so obtained is not quite pure and has m. p. 262—263° when anhydrous.

Benzylstrychnine, crystallising with $9H_2O$, has been described by Tafel and Moufang (*Annalen*, 1899, **304**, 53), who treated benzylstrychninium iodide successively with silver sulphate and barium hydroxide. The process given above has the advantage of convenience.

*Ethoxymethyldihydro*neo*strychnine.*—In the course of his investigations of methylstrychnine Tafel (*Annalen*, 1891, **264**, 64) obtained a compound, $C_{24}H_{30}O_3N_2$, by heating methylstrychnine with alcoholic sodium ethoxide. We have made improvements in the method of preparation of this substance.

A solution of strychnine methosulphate (20 g.) in alcoholic sodium ethoxide (6 g. of sodium in 150 c.c.) was distilled from the steam-bath until all the alcohol was removed (2—3 hours). The pale brown, fluorescent residue was dissolved in water (200 c.c.) and cooled in ice, and dilute acetic acid (5% excess) added. The supernatant liquid (A) was decanted, and the gummy product (B) extracted with much ether. [It is essential to extract the substance as soon as precipitated; any delay causes the formation of substances (C) insoluble in ether and difficult to purify. It is also advisable not to wash away the small amount of acetic acid remaining in the crude material after the solution is decanted : if the acetic acid is completely removed, the substance left after distillation of the ether is gummy and crystallises only after prolonged boiling with water.]

The ethereal extract (B) was dried over sodium sulphate and filtered, and the solvent evaporated; the dark liquid residue crystallised on cooling or when brought into contact with ethyl alcohol. The substance, recrystallised from methyl alcohol containing ammonia, formed long, colourless, silky needles, m. p. 158—159° (Found: C, 72·8; H, 7·7. Calc. for $C_{24}H_{30}O_3N_2$: C, 73·1; H, 7·6%). A further small quantity of the same substance was obtained when the solution (A) was saturated with sodium chloride and extracted with ether. The yield of the pure base is 40—70%.

The gummy product (C), which is always formed and is insoluble in ether, could not be obtained crystalline. It was therefore dissolved in acetone, the filtered solution mixed with methyl iodide, and the crystalline precipitate, which soon began to separate, recrystallised from much water (charcoal); long colourless needles, m. p. 325°, were obtained. The substance was identified with methyl*neo*strychninium iodide (see below).

The same ethoxymethyldihydro*neo*strychnine was obtained when strychnine methosulphate was replaced by methylstrychnine and the resulting product was worked up by the above-described modification of Tafel's method.

*Methoxymethyldihydro*neo*strychnine.*—A mixture of finely powdered methylstrychnine (20 g.) in methyl-alcoholic sodium methoxide (6 g. of sodium in 150 c.c.) was slowly heated in an open flask until the methylstrychnine had dissolved (about 2 hours). The brown product, which showed a green fluorescence, when worked up in the way described in the preceding experiment, gave *methoxymethyldihydro*neo*strychnine*. The base is readily soluble in chloroform, sparingly soluble in cold methyl or ethyl alcohol, but dissolves readily on boiling and separates on cooling in long, colourless, silky needles, m. p. 141—143° (Found: C, 72·3; H, 7·3. $C_{23}H_{28}O_3N_2$ requires C, 72·6; H, 7·4%). A solution in dilute sulphuric acid (60%) gives a violet coloration on addition of a drop of aqueous potassium dichromate. It is noteworthy that methoxymethyldihydro*neo*strychnine (and the ethoxy-derivative) does not exhibit the property of becoming purple which methoxymethyldihydrostrychnidine exhibits on exposure to the air.

*neo*Strychnine remained in the fraction insoluble in ether and was isolated in the form of its methiodide, m. p. 325°.

The same result was obtained when methylstrychnine was replaced by strychnine methosulphate and the yield was about 60% in both cases.

A method of preparation which is convenient and gives a clear product is the following.

A suspension of powdered anhydrous methylstrychnine (15 g.) in dry methyl alcohol (100 c.c.) was refluxed for 24 hours with 4% sodium amalgam (200 g.). The resulting pale yellow solution was concentrated under diminished pressure, and the residue taken up in water (60 c.c.), cooled, and acidified with hydrochloric acid. The gummy precipitate dissolved in excess of the acid and the base (10 g.) was then reprecipitated by means of sodium hydroxide. Doubtless the solution initially contained methoxymethyldihydro*neo*strychnic acid and lactam formation was catalysed by hydrogen ions.

The base obtained in this way crystallised from methyl alcohol in colourless prisms, m. p. 143° (Found: C, 72·4; H, 7·4%).

*Dihydromethoxymethyldihydro*neo*strychnine.*—A mixture of methoxymethyldihydro*neo*strychnine (5·0 g.), glacial acetic acid (30 c.c.), aqueous palladous chloride (5 c.c. of 2%), and aqueous gum arabic solution (55 c.c.) was stirred with hydrogen for 4 hours. The filtered solution (charcoal) was concentrated under diminished pressure, the residue treated with ammonia, and the solid collected (5·0 g.). The product crystallised from methyl alcohol in stout colourless prisms (4·2 g.), m. p. 174° (Found: C, 72·1; H, 7·9. $C_{23}H_{30}O_3N_2$ requires C, 72·3; H, 7·8%). This *base* could not be converted into the metho-salts of dihydrostrychnine by the action of boiling dilute sulphuric acid, a stability parallel to that exhibited by methoxymethyltetrahydrostrychnidine under like conditions.

Methoxymethyltetrahydrostrychnidine.—This substance was obtained when either methoxymethyldihydro*neo*strychnine or its dihydro-derivative was reduced at a lead cathode. Methoxymethyldihydro*neo*strychnine (5 g.), dissolved in 20% sulphuric acid (120 c.c.), was reduced for 20 hours (5 amps.). The product crystallised from benzene in glistening plates, m. p. 220—222° (Found: C, 75·1; H, 8·6. Calc. for $C_{23}H_{32}O_2N_2$: C, 75·0; H, 8·7%), alone or mixed with an authentic specimen (Part IV; J., 1927, 1617).

Dihydromethoxymethyldihydro*neo*strychnine (3 g.) in 20% sulphuric acid (80 c.c.) was submitted to a current of 3 amps. for 15 hours. The product, crystallised from acetone, had m. p. 221° (Found: C, 74·8; H, 8·7%), alone or mixed with an authentic specimen.

*The Methyl*neo*strychninium Salts.*—Methoxymethyldihydro*neo*strychnine (20 g.) (or the related ethoxy-compound) was heated with 20% sulphuric acid (300 c.c.) until methyl alcohol (or ethyl alcohol) was no longer produced; the solution was then cooled, neutralised with ammonia, and mixed with an aqueous solution of sodium iodide (25 g.). The precipitated iodide (yield, 80%) was sparingly soluble in the usual organic solvents and in hot water it gave an approximately 1% solution, from which the salt separated on cooling in long, colourless, fragile needles, m. p. 325° (decomp.) (Found: C, 55·5; H, 5·5. $C_{22}H_{25}O_2N_2I$ requires C, 55·5; H, 5·3%).

*Methyl*neo*strychninium iodide* was also obtained by heating methoxymethyldihydro*neo*strychnine (4·0 g.) with methyl iodide (6 c.c.) and methyl alcohol (6 c.c.) in a sealed tube at 100° for 15 hours. The considerable pressure developed was attributed to the formation of methyl ether:

$$\text{:NMe} \qquad \text{MeO·C:} + \text{MeI} \longrightarrow \text{I}\{\text{:NMe·C:} + \text{Me}_2\text{O}$$

The crystalline precipitate (3·7 g.) in the tube, recrystallised from boiling water, formed long colourless prisms, m. p. 325° (Found: C, 56·3; H, 5·3%). The substance was proved to be identical in every way with the methiodide of *neo*strychnine prepared from methyl iodide and the base in methyl-alcoholic or acetone solution. A careful direct comparison of the salt prepared by the latter method and that first mentioned in this section was also made and the substances are identical in every way and yield the same methochloride.

*Methyl*neo*strychninium chloride* has been prepared from the iodide by means of silver chloride or directly from methoxymethyldihydro*neo*strychnine by prolonged heating with concentrated hydrochloric acid on the steam-bath. The salt is readily soluble in water, moderately readily soluble in methyl alcohol, and crystallises therefrom in brilliant plates, m. p. 289—290°. The transparent crystals become opaque on exposure to air, but in spite of this efflorescence they retain $1CH_4O$ which is not lost on short heating at 100° (Found : C, 66·4 ; H, 6·9. $C_{22}H_{25}O_2N_2Cl,CH_4O$ requires C, 66·3 ; H, 6·9%).

neo*Strychnine*.—This base was obtained by carefully heating methyl*neo*strychninium chloride until the evolution of gas ceased. The faintly fluorescent residue was taken up in hot chloroform, and the solution mixed with boiling methyl alcohol ; on cooling, the base separated in microscopic plates, m. p. 224—226°. Two recrystallisations from acetone raised the m. p. to 228—229° (Found : C, 75·1 ; H, 6·5%).

The base was also obtained by heating the dry hydrochloride of methoxymethyldihydro*neo*strychnine (prepared by passing hydrogen chloride into an ethereal solution) at 285°/1 mm. for about 5 minutes. The product crystallised from ethyl alcohol in faintly brown plates, m. p. 225° (Found : C, 75·7 ; H, 6·7, N, 8·4. $C_{21}H_{22}O_2N_2$ requires C, 75·4 ; H, 6·6 ; N, 8·4%).

neo*Strychnine* is very sparingly soluble in cold or hot methyl or ethyl alcohol, in benzene, or ethyl acetate ; it is moderately readily soluble in hot acetone and readily soluble in chloroform. It is a moderately strong base, but owing to the formation of sparingly soluble salts it appears to dissolve in aqueous acids with some difficulty.

The colour reaction with 60% sulphuric acid and potassium dichromate is the same as that of strychnine.

Attempts to prepare *neo*strychnic acid gave indications of the formation of the substance, which was not, however, isolated in a pure condition. Similarly the formation of *iso-neo*strychnine was attempted under the following conditions :—

1.	*neo*Strychnine (5 g.) Water (75 c.c.)	48 hours at 135—140°	no change
2.	,, ,,	,, 175—185°	,,
3.	,, ,,	,, 210—215°	75% unchanged and indefinite gum
4.	*neo*Strychnine (5 g.) MeOH–NH_3 (sat. at 15°) (75 c.c.)	60 hours at 100°	no change
5.	,, ,,	,, 135—140°	,,
6.	,, ,,	,, 175—185°	unchanged base and trace of a gum
7.	,, ,,	,, 210—220°	60% unchanged and indefinite gum
8.	*neo*Strychnine (5 g.) EtONa (0·2 g. in 50 c.c.)	24 hours at 46—48°	no change
9.	,, ,,	48 hours at 70—75°	50% unchanged and indefinite gum
10.	,, ,,	1 hour at 100° and subsequently at 46—48° for 6 hours.	complete change with the formation of a gum (basic and acidic)

In no case could any crystalline product other than *neo*strychnine be isolated.

Dr. M. H. MacKeith (University Department of Pharmacology) has kindly examined the physiological properties of *neo*strychnine and *neo*strychnidine and reports as follows :—

" I have had the opportunity of testing certain of these substances for their pharmacological activity. *neo*Strychnine and *neo*strychnidine both possess the convulsant action typical of strychnine itself. The minimum lethal dose of *neo*strychnine is about 250 mg. per kilogram weight of frog, *i.e.*, it has an activity about one-fiftieth that of strychnine and approximately equal to that of brucine or of strychnidine. *neo*Strychnidine is about twice as powerful in this respect as *neo*strychnine."

This report is of much interest because it shows that the characteristic action of strychnine is not so closely connected with the cyclic amide grouping as has usually been supposed.

neo*Strychnine* N-*Oxide*.—A mixture of *neo*strychnine (2 g.) and aqueous hydrogen peroxide (20 c.c. of 5%) was heated on the steam-bath until a clear solution was obtained (about 1 hour). The *amine-oxide* separated on cooling in well-shaped colourless plates, which were recrystallised from water; it then melted at 179—180° and contained $3H_2O$ not lost at 120° (Found: C, 62·1; H, 6·6. $C_{21}H_{22}O_3N_2,3H_2O$ requires C, 62·1; H, 6·6%). An aqueous solution of the oxide was saturated with sulphur dioxide and kept for 12 hours; *neo*strychnine was recovered on basification with ammonia.

The formation of methyl*neo*strychninium iodide from *neo*strychnine and methyl iodide has already been mentioned. This salt furnished the chloride, agreeing with the substance previously described, and the action of boiling methyl-alcoholic sodium methoxide on the latter salt regenerated methoxymethyldihydro*neo*strychnine, identical in all respects with the derivative obtained from strychnine. It is certain, therefore, that the movement of the double bond (as in the strychnidine case) occurs when methylstrychnine is treated with hot alcoholic sodium methoxide and not at a subsequent stage.

*Benzylidene*neo*strychnine*.—Finely powdered *neo*strychnine (1·5 g.) was mixed with benzaldehyde (1 c.c.) and alcohol (15 c.c.), and potassium hydroxide (0·3 g. in 1 c.c. of water) added to the boiling solution. After 10 minutes the liquid was cooled and kept in the ice-chest. A lemon-yellow crystalline precipitate gradually formed; this was collected, washed with water, alcohol and ether, and dried at 100°; m. p. 158—159° (Found: C, 79·1; H, 7·2. $C_{27}H_{26}O_2N_2$ requires C, 79·6; H, 7·5%). The derivative is sparingly soluble in most organic solvents.

The Catalytic Reduction of neoStrychnine. Formation of Dihydrostrychnine.—*neo*Strychnine is much more difficult to hydrogenate than strychnine and an attempt to reduce the base at the ordinary temperature did not succeed. After 20 hours the volume of hydrogen absorbed was only 20% of that required and but a small amount of dihydrostrychnine could be isolated. An almost theoretical yield (97%) was, however, obtained when a solution of *neo*strychnine (2 g.) in 50% acetic acid (75 c.c.) was added to an activated mixture of palladous chloride (0·2 g.), norite (1 g.), and water (about 200 c.c.) and agitated in hydrogen at 50°. After 3½ hours, absorption ceased and the volume of hydrogen absorbed (130 c.c.) was 99% of the theoretical. The base, precipitated by addition of aqueous ammonia to the filtered liquid, was washed, dried, and recrystallised from aqueous methyl alcohol (50%). The long silky needles obtained melted at 130—135°, and at 220—222° when anhydrous and when anhydrous and mixed with authentic anhydrous dihydrostrychnine (Found in material dried in the air: C, 67·3; H, 7·4. Calc. for $C_{21}H_{24}O_2N_2,2H_2O$: C, 67·7; H, 7·5%).

The Electrolytic Reduction of neo*Strychnine.*—The base (10 g.), dissolved in dilute sulphuric acid (200 c.c. of 40%), was subjected in the cathode chamber of the usual apparatus to a current of 5 amps. until the Otto reaction was negative (21 hours). After the reduction, the liquid was diluted with ice-cold water, filtered, and rendered alkaline with ammonia. The caseous precipitate was collected (7 g.), washed with water and dried; the alkaline filtrate and the washings were examined separately (A).

neo*Strychnidine.* The dry precipitate was finely powdered, extracted with boiling alcohol (50 c.c.), and the solution quickly filtered. The minute colourless needles which separated on cooling melted at 200—202° and consisted of *neo*strychnidine. The bulk of the base remained in the residue from the alcoholic extract and after being recrystallised from methyl alcohol melted at 204—205°, alone or when mixed with pure *neo*strychnidine (Found: C, 78·9; H, 7·6. Calc. for $C_{21}H_{24}ON_2$: C, 78·7; H, 7·5%). The yield of the base amounted to 4·2 g.

*Tetrahydro*neo*strychnine.* The mother-liquor from the alcoholic extract was evaporated to dryness, and the gummy residue recrystallised from benzene. *Tetrahydro*neo*strychnine* separated on cooling as a hard crystalline crust, m. p. 167—168° (Found: C, 74·2; H, 7·7. $C_{21}H_{26}O_2N_2$ requires C, 74·5; H, 7·7%). The base is readily soluble in methyl or ethyl alcohol and sparingly soluble in benzene or ethyl acetate. Evidence was obtained that tetrahydro*neo*strychnine yields a nitrosoamine, but the derivative could not be purified. The total yield of the base was 1·2 g.

Hexahydrostrychnine. The alkaline filtrate (A) and the washings were mixed with potassium carbonate and extracted with chloroform. The extract was dried over calcium chloride and filtered, and the solvent removed. The dark gummy residue was taken up in hot benzene, and the solution cooled; almost pure hexahydrostrychnine then separated. It was twice recrystallised from benzene, giving colourless tablets, m. p. 197—199° (Found : C, 74·3; H, 8·2. Calc. for $C_{21}H_{28}O_2N_2$: C, 74·1; H, 8·2%).

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