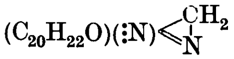
CCX.—*Strychnine and Brucine. Part IV.*

By GEORGE ROGER CLEMO, WILLIAM HENRY PERKIN, junr., and ROBERT ROBINSON.

THE present communication contains the description of part of a general investigation into the reduction products of strychnine, $C_{21}H_{22}O_2N_2$, and is mainly concerned with the examination of strychnidine, $C_{21}H_{24}ON_2$. It also includes a short account of experiments which we have carried out on the decomposition of methylstrychnine under various conditions.

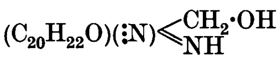
Our knowledge of the reduction products of strychnine is due almost entirely to Tafel, who in 1892 (*Annalen,* **268**, 235, 245) published the results of an important investigation on the reduction of this substance with hydriodic acid in the presence of phosphorus. He showed that strychnine, under these conditions, is converted into deoxystrychnine, $C_{21}H_{26}ON_2$, by the addition of six atoms of hydrogen and elimination of water. This important substance yields, on hydrolysis, deoxystrychnic acid, $C_{21}H_{28}O_2N_2$, which, on treatment with acids, is again converted into deoxystrychnine.

It is clear, therefore, that it still contains the group —CO·N⁝, so characteristic of strychnine, and that it is the second oxygen atom in the molecule which has taken part in the reduction. In a subsequent paper (*Annalen*, 1898, **301**, 285), Tafel describes the reduction of deoxystrychnine (i) to strychnoline, $C_{21}H_{26}N_2$, by treatment with sodium and *iso*amyl alcohol and (ii) to dihydrostrychnoline, $C_{21}H_{28}N_2$, by electrolytic reduction. Tafel also examined the products of the electrolytic reduction of strychnine itself, and showed that this substance is converted, under the conditions he employed, into a mixture of strychnidine, $C_{21}H_{24}ON_2$, and tetrahydrostrychnine, $C_{21}H_{26}O_2N_2$. Since the latter is converted into the former by dehydrating agents, he suggested that the relationship between these substances is probably that represented by the scheme :



$(C_{20}H_{22}O)(\vdots N){<}\begin{array}{l}CH_2\\ |\\ N\end{array}$

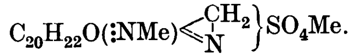
Strychnidine.

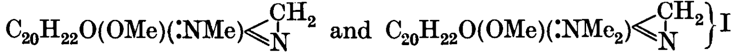


$(C_{20}H_{22}O)(\vdots N){<}\begin{array}{l}CH_2\cdot OH\\ NH\end{array}$

Tetrahydrostrychnine.

In the course of an inquiry into the properties of strychnidine, we have much simplified the preparation of this substance and its separation from tetrahydrostrychnine (p. 1600), and we have thus been able to prepare, in a comparatively simple manner, both of these substances in considerable quantities. The results of an investigation into the properties and decompositions of tetrahydrostrychnine, which are of considerable interest, will form the subject of a later communication. The starting point in the experiments described in the present communication has been strychnidine methosulphate, $C_{21}H_{24}ON_2,Me_2SO_4$, which has been obtained (i) by the direct union of strychnidine with methyl sulphate and (ii) from strychnine methosulphate by electrolytic reduction, and from which a number of simple derivatives such as the methobromide, methochloride, and methiodide have been conveniently prepared.

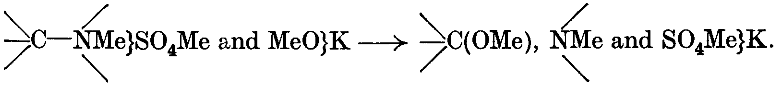
From the fact that these two methods give rise to identical substances, it is evident that the nitrogen atom which is methylated in the course of the formation of strychnidine methosulphate is not that which occurs in the amide group of strychnine. Strychnidine methosulphate is therefore  $C_{20}H_{22}O(\vdots NMe){<}\left.\begin{array}{l}CH_2\\ |\\ N\end{array}\right\}SO_4Me$. When strychnidine methosulphate is digested with methyl-alcoholic potash it is converted into *methoxymethyldihydrostrychnidine*, $C_{23}H_{30}O_2N_2$, m. p. 126°, which crystallises splendidly in prisms, the interesting peculiarities of which have been examined by Dr. T. V. Barker (see p. 1602). This substance, produced from strychnidine by the introduction of a methyl group and addition of methyl alcohol, is a mono-acid base yielding a *hydriodide*, $C_{23}H_{30}O_2N_2,HI$, and a *methiodide*, $C_{23}H_{30}O_2N_2,MeI$, and the latter is converted by silver hydroxide into the *methohydroxide*, $C_{23}H_{30}O_2N_2,MeOH$, m. p. 117°. Like strychnidine, but unlike strychnine, these substances give each an intense crimson coloration when a drop of dichromate is added to its solution in dilute sulphuric acid, and this and other reactions (see below) suggest that the further methylation of methoxymethyldihydrostrychnidine again occurs at that nitrogen atom which is responsible for the basic properties of strychnine. The conclusion appears inevitable that methoxymethyldihydrostrychnidine and its methiodide should be represented by the expressions



$$C_{20}H_{22}O(OMe)(\vdots NMe)\leqslant\begin{matrix}CH_2\\|\\N\end{matrix} \quad\text{and}\quad \left.C_{20}H_{22}O(OMe)(\vdots NMe_2)\leqslant\begin{matrix}CH_2\\|\\N\end{matrix}\right\}I$$

respectively.

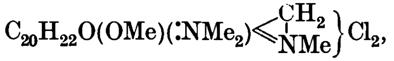
The simplest conceivable formulation of the decomposition of strychnidine methosulphate by means of methyl-alcoholic potassium hydroxide is in accordance with the scheme :



It is, however, by no means certain that the groups $C_{20}H_{22}O$ of strychnidine and of methoxymethyldihydrostrychnidine are identical. Indeed the reconstitution of the quaternary salts with loss of methyl alcohol leads, as shown below, not to methylstrychnidinium salts, but to an isomeric series.

A curious property of methoxymethyldihydrostrychnidine is the fact that, while the direct action of methyl iodide yields the methiodide just mentioned, an entirely different result is obtained when methyl iodide acts on the methyl-alcoholic solution of the base. In these circumstances, two *oxymethoxymethyldihydrostrychnidines*, $C_{23}H_{30}O_3N_2$, namely (A), m. p. 235°, and (B), m. p. 270°, are produced; the former is convertible into the latter in a variety of ways, for example, by merely boiling with xylene. The investigation into the constitutions of these substances and the significance of these curious changes has not yet been completed.

Although methoxymethyldihydrostrychnidine combines with methyl sulphate with difficulty and is only gradually converted into the monomethosulphate under ordinary conditions, it is remarkable that it yields a substance, $C_{23}H_{30}O_2N_2,2Me_2SO_4$, evidently a mixture of two *dimethosulphates* (A) and (B), when its solution in dry benzene is boiled with methyl sulphate for several hours; of these, only the one (A) and its derivatives have so far been obtained in a pure condition. When sodium iodide is added to the aqueous solution of the mixed dimethosulphates, the *dimethiodide* (A), $C_{23}H_{30}O_2N_2,2MeI$, m. p. 297° (decomp.), is precipitated and readily obtained pure. The *dimethochloride* (A), $C_{23}H_{30}O_2N_2,2MeCl,3H_2O$, obtained from the dimethiodide by the action of silver chloride, crystallises from water in glistening prisms and is decomposed by boiling with methyl-alcoholic potash with loss of two molecules of methyl chloride and regeneration of methoxymethyldihydrostrychnidine. It is evident that the dimethochloride must have the formula



$$C_{20}H_{22}O(OMe)(:NMe_2){<}\left.\begin{matrix}CH_2\\ |\\ NMe\end{matrix}\right\}Cl_2,$$

and since, on decomposition as just described, each nitrogen atom loses a methyl group in the form of methyl alcohol and no rings are broken, it is apparent that the heterocyclic ring system of methoxymethyldihydrostrychnidine is one possessing quite unusual stability. When, however, the dry dimethochloride (A) is heated, it loses two molecules of methyl chloride and methyl alcohol and yields *methyl-ψ-strychnidine* (see below). Methoxymethyldihydrostrychnidine, dissolved in dilute methyl-alcoholic potash, is readily oxidised by hydrogen peroxide with the formation of *methoxymethylstrychnidonic acid*, $C_{21}H_{28}O_5N_2$, a gum which is evidently an amino-acid, because, on slow evaporation of its aqueous solution, it is converted into *anhydromethoxymethylstrychnidonic acid*, $C_{21}H_{26}O_4N_2$, which crystallises well from alcohol and melts at 222°.

The further investigation of this interesting substance is in progress.

Ethoxymethyldihydrostrychnidine.—In order to determine whether a process similar to the formation of methoxymethyldihydrostrychnidine would occur if ethyl alcohol were substituted for the methyl alcohol used in the preparation of this substance, strychnidine methosulphate was digested with ethyl-alcoholic potash; a substance was then obtained which melted at about 98° and proved to be ethoxymethyldihydrostrychnidine, $C_{24}H_{32}O_2N_2$. This substance differs from the corresponding methoxy-derivative in the absence of the facility for crystallisation so remarkable in the latter and also in its greater instability on exposure to the air, whereby it rapidly becomes dark purple; it was therefore not further investigated.

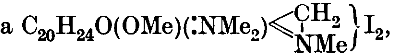
Methyl-ψ-strychnidine, $C_{22}H_{26}ON_2$.—This interesting base is obtained when methoxymethyldihydrostrychnidine dimethochloride (see above) is heated and also by heating methyl*neo*strychnidinium chloride (A) or (B) (see p. 1593). It melts at 203—204° and forms well-defined salts, of which the *hydriodide*, $C_{22}H_{26}ON_2,HI$, is characteristic.

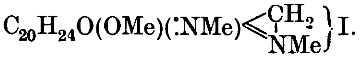
The *methiodide*, $C_{22}H_{26}ON_2,MeI$, produced by the direct combination of the base with methyl iodide, also crystallises well, and is converted by silver chloride into the corresponding *methochloride*, which decomposes on heating into methyl chloride and the base. Methyl-ψ-strychnidine is not changed by electrolytic reduction, but is readily and almost quantitatively oxidised by permanganate to *strychnidone*, $C_{21}H_{24}O_3N_2$, an atom of carbon being lost during the process. This substance crystallises well, melts at 152°, and yields a *monoxime*, $C_{21}H_{25}O_3N_3$, and a *disemicarbazone*, $C_{23}H_{30}O_3N_8$; it is characterised by being remarkably resistant to further oxidation by permanganate. When it is boiled with methyl-alcoholic potash, it is converted into an isomeride, allo-*strychnidone*, m. p. 260—265°, which is no longer capable of combining either with hydroxylamine or with semicarbazide.

*The Methyl*neo*strychnidinium Salts* (A) *and* (B).—When methoxymethyldihydrostrychnidine is boiled with dilute sulphuric acid, methyl alcohol is eliminated and a solution is obtained which evidently contains the quaternary *methyl*neo*strychnidinium sulphates* (A) and (B), and this solution does not give any precipitate on the addition of ammonia or caustic potash. On adding excess of sodium iodide, *methyl*neo*strychnidinium iodide* (A) is precipitated, the isomeride (B) remaining in solution. The iodide (A) crystallises well from water, melts at about 300° (decomp.), and is converted by silver chloride into *methyl*neo*strychnidinium chloride* (A), $C_{22}H_{27}ON_2Cl,3H_2O$, which separates from water in splendid, glistening, prismatic needles, for the description and measurement of which (p. 1612) we are indebted to Dr. T. V. Barker. When this chloride is digested with methyl-alcoholic potash, it adds on methyl alcohol with the formation of methoxymethyldihydrostrychnidine (m. p. 126°), but if the dry chloride is heated it loses hydrogen chloride, and methyl-ψ-strychnidine (m. p. 203°) remains in an almost pure condition. *Methyl*neo*strychnidinium iodide* (B), $C_{22}H_{27}ON_2I$, is obtained when the mother-liquor from the separation of the isomeride (A, see above) containing sodium iodide is mixed with much 50% aqueous potassium hydroxide. This substance separates from acetone as a sandy, crystalline precipitate, m. p. 277° (decomp.), and is converted by silver chloride into *methyl*neo*strychnidinium chloride* (B), $C_{22}H_{27}ON_2Cl,H_2O$, m. p. 255° (decomp.), which, unlike the isomeride (A), exhibits little facility for crystallising. When it is digested with methyl-alcoholic potash, it is converted into methoxymethyldihydrostrychnidine and, on heating in a test-tube, it yields methyl-ψ-strychnidine. This reaction shows that the latter base may be represented by the formula  $C_{20}H_{21}O(:NMe){<}\begin{array}{l}CH_2\\ \vert\\ N\end{array}$, but the elimination of methyl alcohol may not be a simple process involving the formation of a double bond. The difficulty is that methyl-ψ-strychnidine is unchanged by electrolytic reduction, whereas methoxymethyldihydrostrychnidine yields a dihydro-derivative under similar conditions.

Methoxymethyltetrahydrostrychnidine, $C_{23}H_{32}O_2N_2$.—This substance is obtained when methoxymethyldihydrostrychnidine is reduced electrolytically; it melts at 220° and is characterised by the facility with which it crystallises, separating, for example, from xylene in brilliant prisms. Considered as a strong base, it is mono-acid and yields a *hydriodide*, $C_{23}H_{32}O_2N_2$,HI, and a *methiodide* (*a*), $C_{23}H_{32}O_2N_2$,MeI, m. p. 227°, both of which crystallise well. The *methochloride* (*a*), prepared from the methiodide (*a*) with silver chloride, is a readily soluble, waxy, crystalline substance which is decomposed by boiling methyl-alcoholic potash with elimination of methyl chloride and separation of methoxymethyltetrahydrostrychnidine. When this base is boiled with dry benzene and excess of methyl sulphate for 20 hours, it yields a horny mass, which is a mixture of the two dimethosulphates (A) and (B), and the benzene solution gradually deposits crystals of the dimethosulphate (A). The horny mass, dissolved in water, yields on the addition of sodium iodide the *dimethiodide* (A), m. p. 315° (efferv.), the isomeride (B) remaining in solution. From the dimethiodide (A) the *dimethochloride* (A) was prepared with the aid of silver chloride as an indefinite crystalline mass which, when heated, loses two molecules of methyl chloride and methyl alcohol and yields *methyl-ψ-dihydrostrychnidine*, $C_{22}H_{28}ON_2$, m. p. 212° (compare p. 1596).

Methoxymethyltetrahydrostrychnidine dimethiodide (B) is precipitated from the mother-liquors of (A), containing sodium iodide, by the addition of a large excess of caustic potash (50%) and separates from alcohol in prisms. This dimethiodide (B) melts at 165°, and at about 230° loses both molecules of methyl iodide with regeneration of methoxymethyltetrahydrostrychnidine. If, however, the dimethiodide (B) is boiled with mesitylene, only one molecule of methyl iodide escapes, and a *methiodide* (*b*) of methoxymethyltetrahydrostrychnidine separates which has m. p. 325° (decomp.) and is isomeric with the methiodide (*a*) produced by the direct combination of the base with methyl iodide (see above). The methiodide (*b*), on heating at 250°, loses methyl iodide with formation of methoxymethyltetrahydrostrychnidine. The *dimethochloride* (B) obtained from the dimethiodide (B, m. p. 165°) by the action of silver chloride is a horny mass which, when heated in a test-tube, behaves differently from the dimethochloride (A) (see above), since it decomposes simply into methyl chloride and methoxymethyltetrahydrostrychnidine.

The most probable explanation of the isomerism of the dimetho-salts of the series (A) and (B) is that they are stereoisomerides corresponding to the formula  $C_{20}H_{24}O(OMe)(\colon NMe_2)<\left.\begin{matrix}CH_2\\ | \\ NMe\end{matrix}\right\}I_2$, since it is clear that the formation of the di-quaternary salts involves the appearance of a new asymmetric nitrogen atom. The reactions of the methiodides (*a*) and (*b*) show, however, that they are structurally different, and it will be convenient at this stage to mention briefly the methods and arguments which we employ in this and similar cases; some aspects of the matter are also discussed in the following communication (see p. 1633). The presence of an aromatic nucleus bearing the –N•CO– group is the cause of important reactions, many of which were first observed by Tafel. The dichromate reaction (bluish-violet to reddish-violet) in moderately concentrated sulphuric acid solution is characteristic of strychnine; it is not given by strychnidine or its derivatives. On the other hand, these give a crimson coloration when a little potassium dichromate is added to their solutions in dilute sulphuric acid. Closely allied to this is the crimson colour developed in dilute hydrochloric acid solutions of strychnidine derivatives on the addition of ferric chloride. With strychnine, this reaction is completely negative. Finally, strychnidine derivatives, but not strychnine, couple with diazonium salts to give characteristic azo-compounds. In this connexion, we have usually employed diazobenzenesulphonic acid as the reagent, and the alkaline or neutral solutions are then yellow or orange, becoming bluish-red on the addition of a mineral acid. Incidentally it may be mentioned that Tafel's view of the nature of methylstrychnine receives support from the circumstance that this substance couples readily with diazobenzenesulphonic acid. The behaviour of strychnidine derivatives in these reactions is very much influenced by the concentration of acid in the solution, and this again harmonises with the view that we are observing the reactions of a tertiary aromatic amine. Thus in strong hydrochloric acid solution strychnidine does not form azo-compounds and is not affected by ferric chloride. In the latter case, the red colour appears on dilution of the solution, and many strychnidine and brucidine derivatives show a similar behaviour. Tetrahydrostrychnine fails to exhibit these colour reactions at a smaller acid concentration than is necessary to inhibit the strychnidine reactions, whilst, in connexion with other work not described in this communication, strychnidine derivatives have been obtained which only exhibit the ferric chloride reaction in very dilute hydrochloric acid solution and will not couple with diazo-salts in acid solution unless an excess of sodium acetate is introduced. Analogies with the already ascertained behaviour of aromatic amines suggest that when, for example, strychnidine is dissolved in hydrochloric acid of such a strength that the ferric chloride reaction fails, the explanation is that the base is present in the solution as the dihydrochloride. We already know (see above) that the nitrogen atom not joined to the aromatic nucleus is the more basic of the two which are present in the molecule. Important confirmation of this view is derived from the fact that without exception the dimetho-salts of strychnidine derivatives do not couple with diazonium salts and do not give the ferric chloride reaction. Reverting to the question of the constitutions of the methiodides (*a*) and (*b*) of methoxymethyltetrahydrostrychnidine, it is clear that we might expect one of these, that which contains a quaternary ammonium group attached to the benzene ring, to give negative results in the colour tests. Actually, after conversion into methochloride, the methiodide (A) couples easily with diazobenzenesulphonic acid and exhibits a good ferric chloride reaction. The behaviour of the salt is closely similar to that of the parent base. On the other hand, the methochloride from the methiodide (*b*) did not give entirely negative results in the tests, but the colours were developed much more slowly and did not reach the intensity observed in the case of the (*a*) salt. We conclude that the methiodide (*a*) is $C_{20}H_{24}O(OMe)(\vdots NMe_2){<}\left.\begin{matrix}CH_2\\ |\\ N\end{matrix}\right\}I$, whilst the methiodide (*b*), which may not be entirely homogeneous, is



$$C_{20}H_{24}O(OMe)(\vdots NMe){<}\left.\begin{matrix}CH_2\\ |\\ NMe\end{matrix}\right\}I.$$

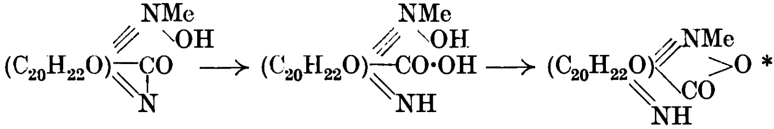
It is shown in the following communication that the corresponding brucidine derivatives behave differently.

Methyl-ψ-dihydrostrychnidine, obtained either from methoxymethyltetrahydrostrychnidine dimethochloride (A) or from methyl*neo*dihydrostrychnidinium chloride (see below) by heating, melts at 212° and yields a *methiodide*, $C_{22}H_{28}ON_2,MeI$, m. p. 335° (decomp.); the corresponding *methochloride* decomposed on heating, yielding a black syrup from which nothing definite could be isolated. Methyl-ψ-dihydrostrychnidine is clearly $C_{20}H_{23}O(\vdots NMe){<}\begin{matrix}CH_2\\ |\\ N\end{matrix}$, but it is not yet certain that it is the dihydro-derivative of methyl-ψ-strychnidine. Further evidence on this point is at present being sought.

*The Methyl*neo*dihydrostrychnidinium Salts*.—As explained in the experimental section, these salts could not be directly obtained from methoxymethyltetrahydrostrychnidine, because this substance, in contrast to the methoxydihydro-base, is not decomposed by boiling with dilute sulphuric acid. The hydriodide of the methoxytetrahydro-base decomposes, however, on heating, yielding methyl alcohol and *methyl*neo*dihydrostrychnidinium iodide*, m. p. 350° (efferv.), the hot aqueous solution of which gives no precipitate with aqueous potassium hydroxide.

On treatment with silver chloride, this yields *methyl*neo*dihydrostrychnidinium chloride*, which, on heating, is decomposed into hydrogen chloride and methyl-ψ-dihydrostrychnidine (m. p. 212°).

Methylstrychnine, $C_{22}H_{26}O_3N_2,4H_2O$.—This substance was first prepared by Tafel (*Ber.*, 1890, **23**, 2732), who obtained it from strychnine methiodide by decomposition with silver sulphate, followed by removal of the sulphuric acid by baryta and concentration of the filtrate; as the result of an extended examination (*Annalen*, 1891, **264**, 62), Tafel concluded that the formation of this substance from strychnine was best represented by the scheme :



Methylstrychninium hydroxide. *Methylstrychnine.*

We have found that methylstrychnine may be obtained directly by simply mixing a solution of strychnine methosulphate with caustic potash, and it has therefore become an easily accessible substance. During an examination of methylstrychnine we observed that it decomposed, on heating under reduced pressure, with elimination of methyl alcohol and formation of a substance, $C_{21}H_{22}O_2N_2$, isomeric with strychnine, for which we suggest the name *normethylstrychnine*. This base has not yet been obtained in a crystalline condition, but it yields a *methiodide*, $C_{21}H_{22}O_2N_2,MeI$, m. p. 315° (decomp.), and a *methochloride*, both of which are crystalline. When methylstrychnine, mixed with methyl-alcoholic potassium hydroxide, is heated gradually to 250°, a considerable quantity of indole is formed, and after this has been removed by steam distillation, the residue, on heating with soda-lime, yields a further amount of indole and also a small quantity of carbazole. Methylstrychnine is decomposed by heating with soda-lime, with the formation of a base, $C_{10}H_{11}N$, b. p. 93°/25 mm., which yields a picrate, m. p. 168°, and appears to be an ethylindole; carbazole is also produced in small quantity during this decomposition. The electrolytic reduction of a solution of methylstrychnine in dilute sulphuric acid is described on p. 1626. After removal of the sulphuric acid by barium carbonate, the crystalline *methylstrychnidinium*

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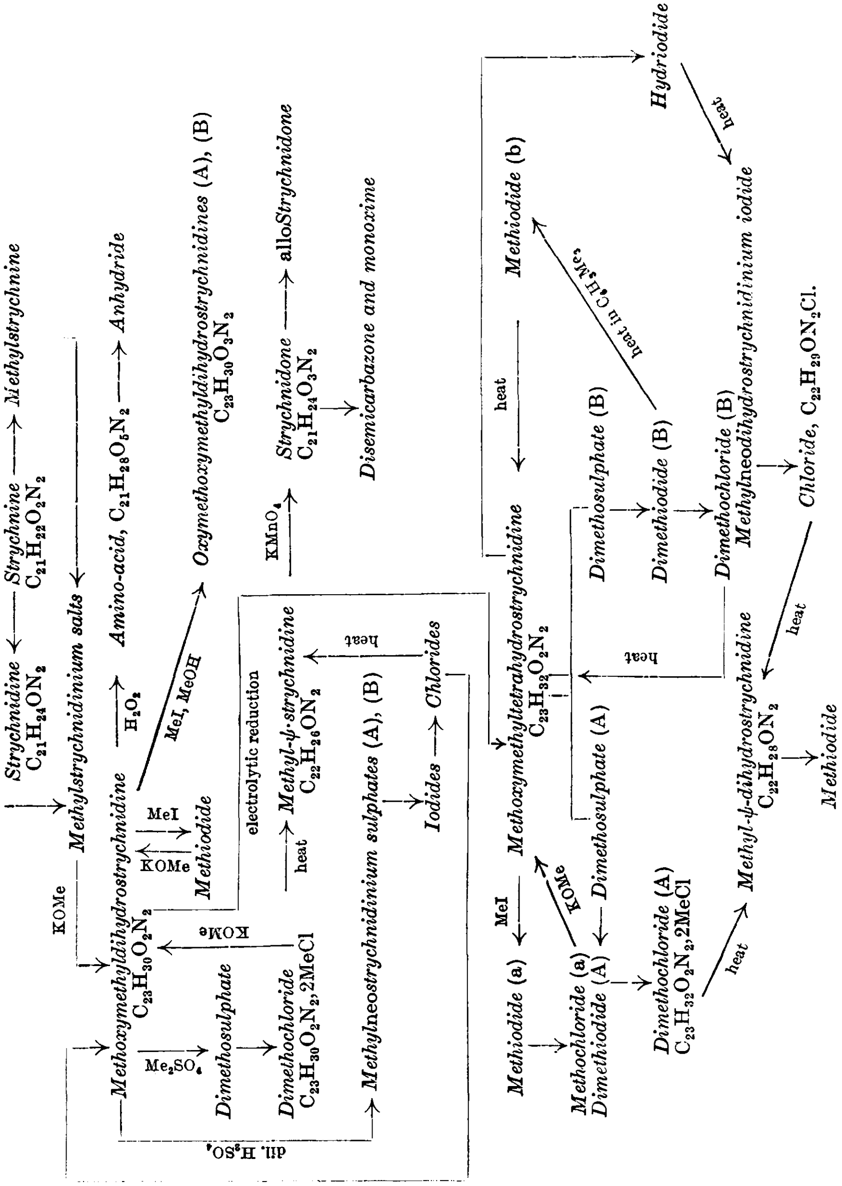
* In accordance with our present-day conceptions regarding the nature of betaines, methylstrychnine is a dipole and it is no longer necessary to assume propinquity of the groups $\cdot CO_2$ and $\mathrm{⫶NMe}$.


Strychnidine
$C_{21}H_{24}ON_2$
Strychnine
$C_{21}H_{22}O_2N_2$
Methylstrychnine
Methylstrychnidinium salts
KOMe
Methoxymethyldihydrostrychnidine
$C_{23}H_{30}O_2N_2$
H_2O_2
Amino-acid, $C_{21}H_{28}O_5N_2$
Anhydride
MeI, MeOH
Oxymethoxymethyldihydrostrychnidines (A), (B)
$C_{23}H_{30}O_3N_2$
MeI
KOMe
Methiodide
Me_2SO_4
Dimethosulphate
Dimethochloride
$C_{23}H_{30}O_2N_2,2MeCl$
KOMe
electrolytic reduction
heat
Methyl-ψ-strychnidine
$C_{22}H_{26}ON_2$
KMnO$_4$
Strychnidone
$C_{21}H_{24}O_3N_2$
alloStrychnidone
Disemicarbazone and monoxime
dil. H_2SO_4
Methylneostrychnidinium sulphates (A), (B)
heat
Iodides
Chlorides
KOMe
Methoxymethyltetrahydrostrychnidine
$C_{23}H_{32}O_2N_2$
heat
Methiodide (b)
Hydriodide
MeI
Methiodide (a)
Methochloride (a)
KOMe
Dimethiodide (A)
Dimethosulphate (A)
Dimethosulphate (B)
Dimethiodide (B)
heat in $C_6H_3Me_3$
heat
Dimethochloride (A)
$C_{23}H_{32}O_2N_2,2MeCl$
heat
Dimethochloride (B)
heat
Methylneodihydrostrychnidinium iodide
Methyl-ψ-dihydrostrychnidine
$C_{22}H_{28}ON_2$
heat
Chloride, $C_{22}H_{29}ON_2Cl$.
Methiodide

hydrogen carbonate, $C_{22}H_{27}ON_2,HCO_3,H_2O$, is obtained, and this is decomposed by boiling methyl-alcoholic potash, yielding methoxymethyldihydrostrychnidine (m. p. 126°). On treatment with acids the carbonate yields the same strychnidine metho-salts as are obtained from strychnidine methosulphate by decomposition with sodium iodide and other salts.

Whilst it is clearly possible to develop arguments bearing on the structure of strychnine and brucine from the new facts brought to light in this and the following investigation, we prefer to postpone such theoretical deductions until further experimental data are available. The annexed table illustrates the more important relationships described in this memoir.

EXPERIMENTAL.

Strychnine Methosulphate, $C_{21}H_{22}O_2N_2,Me_2SO_4$.—Finely powdered strychnine (50 g.) is mixed with methyl alcohol (250 c.c.), and freshly distilled methyl sulphate (50 g.) added with shaking; the base then dissolves completely and the temperature rises about 17°. The *methosulphate*, which soon begins to separate, is collected after 24 hours, washed twice with a little methyl alcohol, and dried on the steam-bath (yield, 60 g.). The substance discolours at 270—280° and decomposes with effervescence at about 282°. It is very soluble in hot water and separates, on cooling, in quadrilateral plates; it also dissolves readily in hot methyl alcohol and crystallises therefrom in groups of glistening needles. The solution in sulphuric acid (60% by vol.) gives with dichromate an intense purple colour, changing to brown (Found: C, 59·7; H, 6·0; N, 6·3. $C_{21}H_{22}O_2N_2,Me_2SO_4$ requires C, 60·0; H, 6·1; N, 6·1%).

Strychnine Methobromide.—When concentrated aqueous solutions of the methosulphate and sodium bromide are mixed, the *methobromide* separates immediately. It is readily soluble in hot water, from which it crystallises as a voluminous mass of glistening needles; it discolours at 300° and melts at about 320° (efferv.) (Found in material dried at 110°: C, 61·3; H, 5·9. $C_{21}H_{22}O_2N_2,MeBr$ requires C, 61·5; H, 5·8%).

The aqueous solution of the methosulphate gives with sodium iodide an immediate precipitate of strychnine methiodide, which separates from much water in glistening, pearly cubes, darkens at 300°, and effervesces at about 320° (compare Stahlschmidt, *Pogg. Ann.*, 1859, **108**, 513; Tafel, *Ber.*, 1890, **23**, 2733).

Strychnidine and Tetrahydrostrychnine.—The following process for the preparation and separation of these substances is a considerable improvement on that recommended by Tafel (*Annalen*, 1898, **301**, 303, 316).

Strychnine (150 g.), dissolved in sulphuric acid (900 g.) and water (600 c.c.), was placed in the cathode chamber of the electrolytic reduction apparatus described in Part II of this research (J., 1924, **125**, 1798) and reduced for 16 hours at 18° by a current of 5 amps. The product was diluted with ice, filtered, made alkaline with a large excess of concentrated caustic soda solution, and the resulting granular precipitate was collected, washed well with water, and dried on the steam-bath. The mixture was then extracted with boiling alcohol (1 litre) and quickly filtered; on cooling, a crystalline precipitate separated (34 g.); from the concentrated mother-liquor, a further 20 g. was obtained.

This colourless crystalline mass, which, after drying at 100° had m. p. 183—185°, was recrystallised from benzene (700 c.c.); the nearly colourless crystals which separated (36 g.) melted at 202° and proved to be pure tetrahydrostrychnine (Found : C, 74·5; H, 7·7. $C_{21}H_{26}O_2N_2$ requires C, 74·5; H, 7·7%). The benzene mother-liquor was evaporated to dryness, and the residue, on crystallisation from alcohol, yielded a voluminous mass of white needles (17 g.), m. p. 244—245°. The residue from the first alcoholic extract, crystallised from alcohol, in which it was sparingly soluble, gave, after the mother-liquors had been worked up, a further quantity (53 g.) of the same substance, m. p. 243—245°. The two portions were mixed and crystallised from alcohol, pure strychnidine, m. p. 246°, being readily obtained.

Strychnidine Hydriodide.—When strychnidine is shaken with dilute sulphuric acid, a crystalline mass of the sulphate results, and, if this is dissolved in hot water and sodium iodide added, a voluminous mass of needles separates. This is collected, washed, dried, and recrystallised from boiling alcohol, in which the *hydriodide* is sparingly soluble, crystallising in stars of glistening needles (Found : C, 56·6; H, 5·6. $C_{21}H_{24}ON_2,HI$ requires C, 56·3; H, 5·6%). This hydriodide is sparingly soluble in boiling water and the solution gives an immediate precipitate with ammonia. It discolours at 275—280°, is nearly black at 290°, and decomposes at about 305° to a black froth.

Strychnidine Methosulphate.—This substance has been prepared in two ways : (i) by direct union and (ii) by the electrolytic reduction of strychnine methosulphate.

(i). Strychnidine (40 g.) is mixed with methyl alcohol (250 c.c.), freshly distilled methyl sulphate (40 g.) added, and the whole shaken and warmed at 40—50°; all passes into solution and suddenly the *methosulphate* commences to separate. After 12 hours, the precipitate is collected, washed with a little methyl alcohol, and recrystallised from this solvent (Found in material dried at

100°: C, 61·2; H, 6·6. $C_{21}H_{24}ON_2,Me_2SO_4$ requires C, 61·8; H, 6·7%).

(ii). Strychnine methosulphate (10 g.), dissolved in sulphuric acid (100 c.c. of 30% by vol.), is reduced in the usual electrolytic cell (p. 1600) by a current of 5 amps. for 16 hours. The clear, almost colourless solution is diluted with water, boiled with excess of barium carbonate, and filtered, and the filtrate and washings are concentrated to a small bulk; the mass of crystals that gradually separates is crystallised from methyl alcohol (Found in material dried at 100°: C, 61·6; H. 6·9; N, 6·4%).

The identity of the methosulphates produced in (i) and (ii) was shown (1) by conversion into identical methobromides and methiodides, and (2) by both yielding methoxymethyldihydrostrychnidine (m. p. 126°) by the action of methyl-alcoholic potash (p. 1602).

The *methobromide* is prepared by mixing a warm, saturated solution of strychnidine methosulphate with sodium bromide; the clear solution slowly deposits a woolly mass of needles, which is washed with water containing a trace of sulphurous acid and dried at 100°. The substance does not melt at 300° (Found: C, 63·9; H, 6·5. $C_{21}H_{24}ON_2,MeBr$ requires C, 63·6; H, 6·5%).

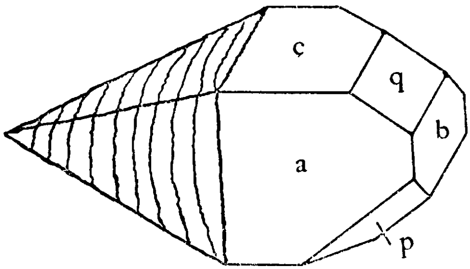
The methiodide separates as a voluminous mass of needles when sodium iodide is added to a hot aqueous solution of the methosulphate; on boiling, a clear solution is obtained from which the methiodide separates as a woolly mass of needles. This substance has already been described by Tafel (*Annalen*, 1898, **301**, 314), who obtained it by direct union of strychnidine with methyl iodide. It decomposes at about 325° to a brown froth.

The Methochloride.—The methiodide just described is readily soluble in boiling water, and on addition of silver chloride and digestion on the steam-bath for an hour decomposition is complete. The filtrate from the silver salts, on evaporation to a small bulk, deposits the very readily soluble *methochloride* in needles. These are collected and dissolved in a very little hot water and the solution is rapidly cooled; it sets to a jelly which gradually changes to colourless needles. The substance, dried at 100°, is a horny mass which begins to darken at 260°, is dark brown at 300°, and decomposes with effervescence at 310° (Found: C, 70·8; H, 7·3. $C_{21}H_{24}ON_2,MeCl$ requires C, 71·1; H, 7·3%). When the dry, powdered methochloride was carefully heated in a test-tube over a free flame, a gas, which burnt with a green-edged flame, was given off and a considerable crystalline sublimate formed. The residual brown syrup crystallised in contact with methyl alcohol, separated from this solvent in needles, melted at 248—250°, and proved to be strychnidine (Found: C, 78·2; H, 7·6%), but, owing to considerable decomposition, the yield was a small one.

Methoxymethyldihydrostrychnidine.

Strychnidine methosulphate (20 g.) is mixed with methyl-alcoholic potash (120 c.c. of 25%) and heated in an open flask in a rapidly boiling water-bath; the clear solution gradually clouds and, after 30 minutes, the well-cooled viscid product gives, on dilution with ice and water (600 c.c.), a caseous precipitate, which is washed well and allowed to dry on porous porcelain at the ordinary temperature. The nearly colourless mass, which melts at about 115—119° and is pure enough for many purposes, is rather readily soluble in boiling methyl alcohol, and separates, on slowly cooling, in highly characteristic, large, glistening, pale purple prisms. For reasons explained on p. 1603, it is advisable to dissolve the substance as rapidly as possible in the methyl alcohol and cool the filtered solution quickly by shaking it in a corked flask in contact with ice and water; after being washed with a little methyl alcohol, the crystalline meal is then only slightly coloured (Found: C, 75·4; H, 8·2; N, 7·5; MeO, 8·2. $C_{23}H_{30}O_2N_2$ requires C, 75·4; H, 8·2; N, 7·6; MeO, 8·4%). *Methoxymethyldihydrostrychnidine* melts at 125—126° and the crystals become pale purple when exposed to the air or more rapidly when heated on a watch-glass on the steam-bath. It is readily soluble in boiling alcohol or benzene, sparingly soluble in cold acetone, ether, or ligroin, and separates well in hard crusts of striated, pale lilac-brown prisms when ligroin is added to a boiling solution in benzene.

FIG. 1.



Crystals which had separated slowly from methyl alcohol were kindly examined by Dr. T. V. Barker, who found them to be monoclinic with the highly characteristic habit shown in Fig. 1. The right-hand termination consists of plane faces, whilst the other gradually tapers to a point in a series of curved surfaces. The crystals are all of one kind, the mirror-image form being no doubt proper to the hitherto unsynthesised enantiomeride. The forms developed are *a*(100), *b*(010), *c*(001), *q*(011) and, not infrequently, *p*(111). The elements $a : b : c = 0·7646 : 1 : 0·6864$, $\beta = 109° 6'$

were computed from the following mean results of measurement of four crystals :

	b (010)	*a* (100)	*c* (001)	*q* (011)	*p* ($\bar{1}$11)
ϕ	Polar.	0° 0′	*70° 54′	70° 54′	*121° 7′
ρ	Face.	90 0	90 0	*57 2	59 29 (+5)

Optically the axial plane is *b*(010) with medium axial angle and positive double refraction.

The salts of methoxymethyldihydrostrychnidine are very readily soluble and a solution of a trace of the base in dilute sulphuric acid gives with a drop of dichromate or concentrated nitric acid an intense crimson coloration, the same coloration being also produced when a solution in dilute hydrochloric acid is warmed with ferric chloride. The solution in glacial acetic acid is not precipitated by water and the base separates on the addition of ammonia as a voluminous mass resembling alumina. *The hydriodide.* When the base, dissolved in a slight excess of dilute sulphuric acid, is mixed with sodium iodide, a yellow to brown coloration rapidly develops, due evidently to oxidation. A nearly pure specimen of the hydriodide was obtained by adding a little sulphurous acid to a solution of the base in dilute sulphuric acid and then precipitating the salt with sodium iodide. The precipitate was rapidly collected and recrystallised from water containing sulphurous acid, separating as a colourless, granular powder. This was collected as rapidly as possible, washed with very dilute sulphurous acid, transferred to porous porcelain, and left over sulphuric acid in a desiccator evacuated to 1 mm. Even then, the substance became slightly yellow, but the salt could now be dried at 100° without further discoloration (Found : C, 56·1; H, 6·2. $C_{23}H_{30}O_2N_2$,HI requires C, 55·9; H, 6·3%). This hydriodide melts at 203° (decomp.).

In the course of a large number of preparations of methoxymethyldihydrostrychnidine, it was always observed that only about 70% of the weight of the crude substance separated during the first crystallisation from methyl alcohol, and still less separated if the boiling with the solvent was prolonged. When the dark purple mother-liquors from several preparations were evaporated to dryness and the residual gum was distilled under reduced pressure, a considerable amount (35 g.) passed over at about 240—260°/2 mm.; from a solution of this in hot methyl alcohol, crystals (5 g.) of methoxymethyldihydrostrychnidine (m. p. 126°) separated. The mother-liquor was again distilled and the fraction 240—250°/1 mm. dissolved in boiling methyl alcohol; on rubbing and keeping for some days, nearly colourless prisms separated (6 g.) which melted at 202—203° after crystallisation and proved to be *methyl-ψ-strychnidine* (Found :

C, 78·8; H, 7·7; N, 8·5. $C_{22}H_{26}ON_2$ requires C, 79·0; H, 7·8; N, 8·4%) (compare p. 1609). On redistilling the mother-liquor of this substance, successive quantities of methoxymethyldihydrostrychnidine (2 g.) and methyl-ψ-strychnidine (2·3 g.) were obtained and also a small quantity of a substance, m. p. 295° (decomp.), which is evidently *oxymethoxymethyldihydrostrychnidine* (Found: C, 72·0; H, 8·0; N, 7·3. $C_{23}H_{30}O_3N_2$ requires C, 72·3; H, 7·8; N, 7·3%) (compare p. 1608). In connexion with the above observations, it was found that methoxymethyldihydrostrychnidine may be distilled without loss of methyl alcohol or other decomposition, and passes over at 235—237°/1 mm. as a colourless syrup, which may set to a resin or become a mass of crystals. The crystals melt, without recrystallisation, at 124—126°, contain C, 75·4; H, 8·2, and show no depression in m. p. after admixture with a specimen crystallised from methyl alcohol.

The distillation of the crude product of the action of methyl-alcoholic potash on strychnidine methosulphate was then investigated, and it was found that this passes over almost without residue at about 240—250°/1 mm. and crystallises at once. This procedure obviates the loss attendant on the crystallisation from methyl alcohol, since the distilled substance is pure enough for most purposes.

Methoxymethyldihydrostrychnidine Methiodide, $C_{23}H_{30}O_2N_2,MeI$.—For reasons explained on p. 1607, this substance must be prepared in the absence of methyl alcohol. The base (10 g.) is heated under reflux with carefully purified methyl iodide (10 c.c.) and the clear solution in about an hour begins to deposit crystals. The mass (12 g.) is collected, washed with methyl iodide, and dried on the steam-bath; m. p. about 275—278° (decomp.) (Found: C, 56·5; H, 6·5; I, 25·4. $C_{23}H_{20}O_2N_2,MeI$ requires C, 56·7; H, 6·5; I, 25·0%). This substance does not appear to undergo change when it is crystallised from methyl alcohol, since the large brown prisms which separate melt at 278° (decomp.). It is sparingly soluble in cold, but readily soluble in hot, water and separates on slow cooling in pink, well-developed, arrow-shaped prisms.

In view of the fact that methoxymethyldihydrobrucidine combines with 2 mols. of methyl iodide at 140° (p. 1629), methoxymethyldihydrostrychnidine (5 g.), dissolved in carefully purified methyl iodide (15 c.c.), was heated in a sealed tube at 130° for 7 hours; the purple solution, on cooling, gradually deposited a crust of purple crystals which, after being washed with methyl iodide, had m. p. 265—270° (decomp.) and consisted of the monomethiodide (Found: C, 57·0; H, 6·4%). When this substance was crystallised from water and the mother-liquor allowed to stand exposed to the air, a crust of nodules gradually separated, which melted at 175°

(decomp.), became solid again, and then melted at about 240—250° (decomp.).

This substance appears to be the methiodide crystallising with 1 mol. H_2O which is not lost at 100° (Found: C, 55·0; H, 6·3. $C_{23}H_{30}O_2N_2,MeI,H_2O$ requires C, 54·7; H, 6·6%). The methyl iodide mother-liquors from the substance m. p. 265—270° (decomp.) gave, on concentration, a little more of the same substance and then a crystalline crust, m. p. 235°, containing a mere trace of iodine (Found: C, 71·6; H, 7·7%), and this substance is evidently identical with the oxymethoxymethyldihydrostrychnidine described on p. 1608.

Methoxymethyldihydrostrychnidine Methohydroxide, $C_{23}H_{30}O_2N_2,MeOH$.—When the methiodide just described is heated on the steam-bath with water and excess of silver chloride, and the filtrate from the silver salts is evaporated, a syrup remains (which was not analysed) which doubtless contains the methochloride. Boiling methyl-alcoholic potash (25%) decomposes this and, on the addition of water, a resin separates. This is dissolved in boiling methyl alcohol, and the solution, after being concentrated and left in the ice-chest, deposits balls of colourless needles, m. p. 113°; on recrystallisation, the substance melts at 116—117° (Found: C, 72·4; H, 8·7; N, 6·8. $C_{24}H_{34}O_3N_2$ requires C, 72·4; H, 8·8; N, 7·0%). The same substance is formed, but less readily, when the methiodide is digested with methyl-alcoholic potash. The *methohydroxide* is very readily soluble in benzene, rather less readily in boiling petroleum, and sparingly even in boiling water. The solution in sulphuric acid (60% by vol.) gives with dichromate an immediate intense crimson colour; in dilute hydrochloric acid, ferric chloride produces an eosin coloration, becoming intense crimson on warming. The solution in dilute nitric acid (30%) is pink, becoming deeper on standing or warming and intense crimson and then green on boiling, and, on addition of ammonia, a yellow, crystalline base separates. When the methohydroxide is heated, it effervesces between 200° and 215°, yielding a brown syrup which sets to a resin on cooling and has not been examined. The methohydroxide dissolves readily in dilute hydrochloric acid and the solution gives, with sodium iodide, a gum, which soon crystallises and separates from methyl alcohol in glistening prisms of the methiodide, m. p. 278° (decomp.) (Found: C, 56·8; H, 6·6. Calc.: C, 56·7; H, 6·5%).

Methoxymethyldihydrostrychnidine Dimethosulphate, $C_{23}H_{30}O_2N_2,2Me_2SO_4$, *the Dimethiodide and the Dimethochloride.*—The methoxydihydrobase does not appear to combine with methyl sulphate when it is mixed with it. Interaction is very slow even when a solution of the base in benzene is digested with methyl sulphate; combination does, however, take place on long boiling, with formation of the dimethosulphate; in spite of careful search, it has not been found possible to isolate the mono-derivative.

The dry base (10 g.), dissolved in specially dried benzene (200 c.c.), was mixed with methyl sulphate (15 c.c.) which had been distilled immediately before the experiment, and the whole was digested in a reflux apparatus, carefully protected from moisture; the original purple solution gradually became paler and, after about 2 hours, a resinous mass began to separate. The heating was continued for 10 hours, the product allowed to remain over-night, and the benzene layer decanted from the pale lilac resin. The clear benzene solution, left in a corked flask, gradually deposited soft, circular nodules, and these were collected, rapidly washed with dry benzene, and dried over sulphuric acid in a vacuum desiccator. Analysis showed that this substance is the *dimethosulphate* (Found: C, 51·6; H, 6·7. $C_{27}H_{42}O_{10}N_2S_2$ requires C, 52·4; H, 6·8%).

The Dimethiodide (A), $C_{23}H_{30}O_2N_2,2MeI$.—A warm aqueous solution of the crude dimethosulphate gave with excess of boiling aqueous sodium iodide a clear solution, and on standing, warty masses gradually separated. After 2 days, the mass was collected, washed with a little water, drained on porous porcelain, and crystallised from methyl alcohol, from which the *dimethiodide* (A) separated in striated, glistening needles, which became opaque on the steam-bath; m. p. about 297° (decomp.) (Found: C, 46·0; H, 5·5; I, 39·4. $C_{25}H_{36}O_2N_2I_2$ requires C, 46·2; H, 5·5; I, 39·3%). This substance is very readily soluble in boiling water and appreciably soluble in the cold and separates as a sandy powder consisting of round, warty masses. The aqueous solution gives no precipitate with ammonia. The yield of the dimethiodide (A) precipitated from the solution of the dimethosulphate by sodium iodide is only 50% of that required by theory and there can be little doubt that the aqueous mother-liquor contains the dimethiodide (B) corresponding with the dimethiodide (B) of methoxymethyltetrahydrostrychnidine (p. 1620). When solid potash was added to these well-cooled mother-liquors, a caseous precipitate separated in large quantity, and on crystallising this from methyl alcohol a small amount of the dimethiodide (A) was obtained as a crust of small prisms. The bulk of the substance remained in the methyl alcohol, but all attempts to isolate the isomeride (B) in a pure state were unsuccessful. This was due partly to the presence of traces of the dimethiodide (A), but mainly to the ready solubility of the isomeride (B) and the small tendency it exhibited to crystallise in definite form.

The *dimethochloride* (A) is obtained when a hot aqueous solution of the dimethiodide (A) is heated on the steam-bath with excess of silver chloride for an hour; the filtrate from the silver salts gives, on evaporation, a solid mass which separates from a little water in large, well-developed, colourless prisms resembling sugar crystals. The air-dried substance loses 6·6% at 100°, and about the same amount when kept over phosphoric anhydride in a vacuum desiccator, the brilliant crystals becoming chalky (Calc. for $C_{25}H_{36}O_2N_2Cl_2,3H_2O$ losing $2H_2O$: H_2O, 6·9%. Found in the substance dried at 100° : C, 62·0; H, 7·6; Cl, 14·3. $C_{25}H_{36}O_2N_2Cl_2,H_2O$ requires C, 61·9; H, 7·8; Cl, 14·6%). The dry crystals give off steam at about 150° and melt at about 255—257° with evolution of gas and formation of methyl-ψ-strychnidine (p. 1609).

A solution in dilute sulphuric acid gives merely a yellow coloration with dichromate. The dimethochloride is very soluble in water or methyl alcohol, and methyl-alcoholic potash gives an immediate precipitate of potassium chloride; on boiling and addition of water, a viscid, curdy precipitate separates which gives an intense crimson colour with dilute sulphuric acid and dichromate, crystallises from methyl alcohol in prisms, m. p. 125—126°, and proves to be methoxymethyldihydrostrychnidine, the yield being nearly a quantitative one.

Oxymethoxymethyldihydrostrychnidines (A) *and* (B).—The isomeride (A, m. p. 235°) is formed in small quantity when methoxymethyldihydrostrychnidine is heated with methyl iodide (see p. 1605), but is produced much more readily and in larger quantity under the following conditions. The base (6 g.) dissolves in methyl alcohol (60 c.c.) and methyl iodide (8 c.c.) in the cold. When the solution is boiled under reflux for 3 hours and then kept for a week, glistening scales (3 g.) separate; after boiling for 3 hours and being concentrated, the mother-liquor deposits a further small quantity. The crystals are washed with methyl alcohol containing a little ammonia to remove traces of iodine, and dried on the steam-bath (Found: C, 72·3; H, 7·9; N, 6·9; MeO, 8·6. $C_{23}H_{30}O_3N_2$ containing 1MeO requires C, 72·3; H, 7·8; N, 7·3; MeO, 8·1%).

Oxymethoxymethyldihydrostrychnidine (A) melts at 235° and dissolves with some difficulty in cold dilute hydrochloric acid. It is readily soluble in glacial acetic acid and is not reprecipitated by water. A solution in dilute sulphuric acid (60% by vol.) gives an intense crimson with dichromate or a drop of concentrated nitric acid; a solution in dilute hydrochloric acid gives no immediate coloration with ferric chloride, but, on warming, a deep crimson colour develops. The substance is apparently not changed when it dissolves in dilute hydrochloric acid, since, if ammonia is added immediately, a gelatinous precipitate separates which becomes chalky on warming and melts at 220—225°. The substance dissolves readily on boiling with alcohol, semicarbazide hydrochloride, and sodium acetate, and on addition of ammonia and warming, a crystalline precipitate separates, m. p. 275° (decomp.), containing N, 7·7%, and is evidently the isomeride (B) (see below). When the dark brown mother-liquor of the substance (A), m. p. 235°, was evaporated to a small bulk and mixed with dilute ammonia, a sticky precipitate separated which soon became crystalline. On warming this with methyl alcohol, most of it dissolved, leaving a sparingly soluble, chalky substance consisting of the isomeride (B); this separated from much methyl alcohol as a rather indefinite, crystalline powder, m. p. about 275° (decomp.) (Found: C, 72·0; H, 7·7; N, 7·1. $C_{23}H_{30}O_3N_2$ requires C, 72·3; H, 7·8; N, 7·3%).

Conversion of Oxymethoxymethyldihydrostrychnidine (A) *into* (B).—This change takes place under the following conditions: (i) When the substance (A) was boiled with a little xylene, gradual change took place and a sandy, crystalline, very sparingly soluble powder was formed, which was washed with xylene; m. p. about 280—285° (decomp.) (Found: C, 73·0; H, 7·9; MeO, 7·8%). The xylene mother-liquor, after being concentrated, slowly developed a hard crust of octahedra, m. p. 285° (decomp.); (ii) when the isomeride (A) was boiled with alcohol for about an hour, the concentrated solution gradually deposited well-defined octahedra, m. p. 280° (decomp.), and the same result was obtained on boiling with acetone, the m. p. of the crystals being about 280° (decomp.). In the last case, analysis gave C, 72·3; H, 8·3; N, 7·3; MeO, 7·8%.

Oxymethoxymethyldihydrostrychnidine (B) was also obtained when methoxymethyldihydrostrychnidine (2 g.) was boiled with nitric acid (5 c.c.), diluted with water (50 c.c.). The pale pink solution became brown, and if, after about 20 minutes, ammonia was added, a sticky precipitate separated which contained some unchanged base. On crystallising it from much alcohol and then from xylene–alcohol, colourless prisms were obtained, m. p. about 285° (decomp.) (Found: C, 72·3; H, 8·1%). The isomeride (B) was also obtained when methoxymethyldihydrostrychnidine (1·5 g.) was boiled with acetic anhydride for 10 minutes, and the solution then kept for some days. The crystalline crust which separated consisted of some unchanged base mixed with the oxy-derivative (B), and there was no sign of the formation of an acetyl derivative; on boiling the mixture with alcohol, the unchanged base dissolved and the isomeride (B) remained in an almost pure condition.

*Methyl-ψ-strychnidine and the Methyl*neo*strychnidinium Salts.*

Methyl-ψ-strychnidine is obtained (i) when the mother-liquors from the crystallisation of crude methoxymethyldihydrostrychnidine are distilled (p. 1603), (ii) when methyl*neo*strychnidinium chloride is heated (p. 1612), and (iii) by the action of heat on methoxymethyldihydrostrychnidine dimethochloride (A), during which this substance loses 2 mols. of methyl chloride and methyl alcohol. The last decomposition is best carried out with small quantities of material, which must be very pure and quite free from inorganic matter; otherwise much tar is produced, the yield of product is small, and the highly coloured mass very difficult to purify. When the dimethochloride (1 g.) is cautiously heated in a wide test-tube over a free flame, a gas is given off which has a very pungent, particularly unpleasant smell and burns with a smoky, green-edged flame, and a considerable crystalline sublimate forms on the sides of the tube. This melts at about 195° and is nearly pure methyl-ψ-strychnidine.

When the effervescence has ceased, the heating is discontinued; the liquid product should then be only slightly coloured and should crystallise completely. Several such tubes are broken up and their contents extracted with much boiling alcohol (in which the product is sparingly soluble), and the solution is digested with norite for an hour and concentrated to a small bulk; the new substance gradually separates in groups of striated, pale ochre needles which become almost colourless after recrystallisation (Found: C, 79·0; H, 7·8; N, 8·6. $C_{22}H_{26}ON_2$ requires C, 79·0; H, 7·8; N, 8·4%).

Methyl-ψ-strychnidine melts at 203—204° and appears to distil under reduced pressure almost without decomposition. It is very sparingly soluble in cold acetone and not readily on boiling; the solution may be concentrated and left for a considerable time without crystallisation setting in, and then groups of needles gradually form. It dissolves very readily in benzene or petroleum and separates very gradually from these in needles. It does not appear to be affected by heating with concentrated sulphuric acid on the steam-bath for ½ hour.

The base is readily soluble in dilute acids. The solution in dilute sulphuric acid is coloured crimson by dichromate, and the same colour develops when the substance is dissolved in concentrated nitric acid. The solution in dilute hydrochloric acid gives, with ferric chloride, a pale pink colour which becomes deep crimson on warming.

The *hydriodide*, $C_{22}H_{26}ON_2,HI$, was prepared by dissolving the base in a slight excess of warm dilute sulphuric acid and then adding warm sodium iodide; on rubbing, the cloudy liquid deposited the hydriodide as a voluminous mass of colourless crystals; these were sparingly soluble in boiling water and the solution gradually deposited crusts, which melted at 265—270° with effervescence, leaving a black mass (Found: C, 56·8; H, 5·9. $C_{22}H_{27}ON_2I$ requires C, 57·1; H, 5·9%).

This hydriodide is sparingly soluble in boiling alcohol and separates therefrom in stars of prismatic needles. The solution in hot water gives with potash an immediate precipitate of the base.

The Methiodide, $C_{22}H_{26}ON_2,MeI$.—When the base (2 g.) was mixed with methyl iodide (5 c.c.), combination took place in the cold with rise of temperature and formation of the methiodide. After warming for a few minutes and cooling in ice, the solid was collected and crystallised from methyl alcohol, from which the substance separated in almost colourless needles. These scarcely darken at 270° and melt at about 312° with effervescence to a dark brown syrup (Found: C, 57·5; H, 6·1. $C_{23}H_{29}ON_2I$ requires C, 57·9; H, 6·1%).

The *methochloride*, prepared in the usual manner by heating the methiodide with water and silver chloride, was obtained, when the solution was concentrated to a small bulk, in long, flat prisms and was very readily soluble. When it was heated in a test-tube, it gave off water and methyl chloride, and a considerable sublimate formed; the residue, on crystallising from methyl alcohol, gave methyl-ψ-strychnidine in almost colourless needles, m. p. 202—203°.

In order to determine whether methyl-ψ-strychnidine could be reduced electrolytically, the base (2·5 g.), dissolved in dilute sulphuric acid (100 c.c. of 20%), was placed in the usual electrolytic cell (p. 1600) and a current of 4 amps. passed for 6 hours. The colourless solution was mixed with excess of ammonia, and the precipitate crystallised from methyl alcohol; colourless needles (2·2 g.) were then obtained which melted at 202° and at the same temperature in admixture with methyl-ψ-strychnidine. Identity was further established by analysis (Found: C, 79·2; H, 7·6. Calc. for $C_{22}H_{26}ON_2$: C, 79·0; H, 7·8%).

*The Methyl*neo*strychnidinium Salts.*—The solution of the methyl*neo*strychnidinium sulphates (A) and (B) from which the other salts were obtained was prepared as follows: Methoxymethyldihydrostrychnidine (p. 1602; 20 g.) was dissolved in dilute sulphuric acid (300 c.c. of 10% by vol.) and heated to boiling in a flask fitted with a long, ground-in condenser. In a short time, methyl alcohol could be detected at the open end of the tube, and when, after 2 hours, all of it had boiled away, a few drops of the liquid no longer gave a precipitate or cloudiness. due to unchanged base, on being basified. The pale brown solution was made just alkaline with ammonia, a little sulphurous acid was added, and then a boiling solution of sodium iodide (25 g.). The clear solution was rapidly filtered and vigorously stirred; *methyl*neo*strychnidinium iodide* (A) then separated either as a heavy, crystalline precipitate or sometimes as a gum which soon crystallised. On standing, a mass of crystals separated from the supernatant liquid. The solid was collected and dissolved in boiling water containing a little sulphurous acid and the solution was rapidly filtered; the iodide (A) then separated, on standing, in characteristic, long needles. After recrystallisation from water (3 g. dissolve in about 75 c.c.), the substance was dried on the steam-bath (Found : C, 56·7 ; H, 6·0 ; I, 26·9. $C_{22}H_{27}ON_2I$ requires C, 57·2 ; H, 5·9 ; I, 27·4%).

This iodide (A) darkens at 295° and decomposes at about 300° to a black mass. It is very sparingly soluble in methyl alcohol. A piece of filter-paper soaked in the aqueous solution gradually becomes yellow and then orange on exposure to air. A hot aqueous solution of the iodide gives no precipitate with caustic potash (30%); even after heating for ½ hour on the steam-bath, the iodide separates unchanged on cooling. Although so sparingly soluble in water, it dissolves readily in cold dilute hydrochloric acid and in large quantities on boiling; the solution deposits, on slowly cooling, stars of prismatic needles of a substance which decomposes at 305° and is not a hydrochloride, as was expected, but consists of the unchanged iodide (Found : C, 57·5 ; H, 6·0%).

*Methyl*neo*strychnidinium Chloride* (A).—The iodide (A) was ground to a paste with warm water and heated on the steam-bath with a large excess of silver chloride for 2 hours with frequent shaking. The colourless filtrate and washings from the silver salts were concentrated to a small bulk by distillation under reduced pressure, and the solution was placed over sulphuric acid in a vacuum desiccator; the chloride then gradually separated in brilliant, colourless, prismatic needles. These, after being recrystallised from very little water and dried on porous porcelain in the air, appeared to contain $3H_2O$, since the loss on heating at 100° was 12·8% (Calc. for $C_{22}H_{27}ON_2Cl,3H_2O$: loss, 12·7%). When exposed over sulphuric acid in a vacuum desiccator, the crystals became opaque and lost the whole of their water of crystallisation, since there was no further loss at 100° (Found : C, 71·5 ; H, 7·3. $C_{22}H_{27}ON_2Cl$ requires C, 71·3 ; H, 7·3%). The chloride (A) melts at about 270° with vigorous effervescence (compare p. 1609) and is very readily soluble in water; the solution, which gives no precipitate either with ammonia or with caustic potash, is intensely bitter. The solution in dilute sulphuric acid gives, with concentrated nitric acid or dichromate, a yellow coloration which changes to crimson on warming; ferric chloride added to a solution in dilute hydrochloric acid gives a pale yellow colour, which changes to crimson on boiling.

The crystals of the chloride (A) have been examined by Dr. T. V. Barker, who reports as follows :

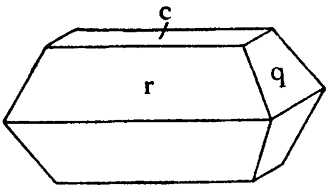
The crystals are orthorhombic (pseudo-tetragonal). The habit is shown in Fig. 2, the list of forms being *c* (001), *r* (010), and *q* (011). The elements $a : b : c = 0·998 : 1 : 1·828$ were calculated from the following mean results of measurement of three crystals.

	c (001).	*q* (011).	*r* (010).
ϕ	Polar.	0° 0′	90° 0′
ρ	Face.	*61 18	*61 21

Optically the crystals are biaxial; birefringence, negative; axial angle, large; dispersion, strong; $\rho < \nu$.

The chloride (A) is very soluble in cold methyl alcohol. When the solution is mixed with methyl-alcoholic potash (25%), an immediate precipitation of potassium chloride occurs; after heating in the water-bath for ½ hour so that much methyl alcohol boils away, the product gives with water a caseous mass which separates from methyl alcohol in prisms, m. p. 125°, and consists of methoxymethyldihydrostrychnidine. The chloride, in quantities of 0·5 g., is cautiously heated in a test-tube over a free flame until effervescence has ceased; the pale yellow, syrupy residue solidifies on cooling, and separates from methyl alcohol in needles, m. p. 202°, which analysis and a mixed m. p. determination prove to be methyl-ψ-strychnidine (p. 1592). This decomposition affords perhaps the most ready method of preparing this substance in a pure condition.

FIG. 2.



*Methyl*neo*strychnidinium Iodide* (B).—The mother-liquors containing sodium iodide from which the iodide (A) originally separated (p. 1611) were concentrated considerably by distillation under reduced pressure, allowed to stand for a couple of days to deposit traces of the iodide (A), and then mixed with aqueous potash (50%) so long as turbidity was produced. After 2 days, the pale salmon, crystalline mass was collected, ground, washed with a little water, and left on porous porcelain to dry. The cake was then dissolved in boiling acetone [in which in this condition it, but not the iodide (A), is rather readily soluble], and the solution was rapidly filtered from the first small crop of crystals and then kept; a copious, colourless, sandy precipitate of the iodide (B) separated which was now very sparingly soluble in cold acetone; further crops were obtained by concentrating the mother-liquor. The iodide (B) begins to darken at 260° and melts and decomposes at about 277° to a black froth (Found : C, 57·3; H, 6·1. $C_{22}H_{27}ON_2I$ requires C, 57·2; H, 5·9%).

This iodide is moderately easily soluble in hot water and separates as a rather indefinite crust on standing; the aqueous solution gives no precipitate with ammonia or caustic potash. It dissolves very readily in warm dilute hydrochloric acid, but exhibits little tendency to crystallise from this solvent.

*Methyl*neo*strychnidinium Chloride* (B).—This was obtained by adding excess of silver chloride to a hot aqueous solution of the iodide (B), heating the mixture on the steam-bath for an hour, and filtering it. The filtrate was concentrated to a small bulk by distillation from the steam-bath under reduced pressure and then left over sulphuric acid in a vacuum desiccator; the pasty mass of minute crystals which gradually formed was left in contact with porous porcelain. The whole residue was dissolved in a very small amount of water, allowed to crystallise again, and transferred to porous porcelain. The colourless residue, dried at 100°, melted at about 255° with effervescence (Found: C, 68·3; H, 7·8. $C_{22}H_{27}ON_2Cl,H_2O$ requires C, 68·0; H, 7·5%). When this chloride is heated with methyl-alcoholic potash under the conditions described in the corresponding case of the chloride (B), a large yield of methoxymethyldihydrostrychnidine, m. p. 125°, is obtained.

In order to determine whether the product of the action of dilute sulphuric acid on methoxymethyldihydrostrychnidine was capable of electrolytic reduction, the solution prepared as explained on p. 1602 was placed in the usual apparatus (p. 1600), and a current of 5 amps. passed for 16 hours at 20°. The solution was then neutralised with ammonia, and a little sulphurous acid added, followed by a large excess of sodium iodide. The bulky precipitate which separated was recrystallised from water and found, by a comparison of properties and an analysis (Found : C, 57·6; H, 6·0. $C_{22}H_{27}ON_2I$ requires C, 57·2; H, 6·0%), to be methyl*neo*strychnidinium iodide (A), showing that reduction had not taken place.

Oxidation of Methyl-ψ-strychnidine. Formation of a Diketone termed Strychnidone.—Methyl-ψ-strychnidine (6 g.), dissolved in warm acetone (400 c.c.), was cooled to 15°, and very finely powdered and sieved permanganate (6 g.) added in small quantities at a time with constant shaking. When decolorisation was complete, the whole was heated on the steam-bath, the manganese precipitate * was

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* When this manganese precipitate is extracted with hot water, a dark brown liquid is obtained containing a small quantity of the potassium salt of an acid which has not been obtained crystalline.

filtered off and well washed with acetone, and the combined acetone filtrate and extracts were evaporated on the steam-bath; the syrupy residue soon crystallised and did so immediately when stirred with methyl alcohol. The whole was dissolved in boiling methyl alcohol; from the solution, brilliant, almost colourless prisms separated, and further crops were obtained by concentrating the mother-liquor, the total yield being 5 g. After a second crystallisation from methyl alcohol, the substance was pure (Found: C, 71·3; H, 6·8; N, 8·0. $C_{21}H_{24}O_3N_2$ requires C, 71·6; H, 6·8; N, 7·9%). *Strychnidone* melts at about 152°, is slightly soluble in boiling water, and very sparingly soluble in cold methyl alcohol.

A solution in dilute sulphuric acid gives, with dichromate, a deep crimson colour; ferric chloride added to a solution in dilute hydrochloric acid gives a pale pink colour which becomes crimson on boiling. The powdered crystals dissolve in concentrated nitric acid to a most intense crimson solution, and the colour is not discharged on dilution. The diketone is remarkably resistant to oxidation, the solution even in boiling acetone decolorising permanganate very slowly.

The Disemicarbazone.—The diketo-derivative (2 g.), dissolved in hot dilute acetic acid, was mixed with a concentrated aqueous solution of semicarbazide hydrochloride (5 g.) and sodium acetate (4 g.) and heated on the steam-bath with gradual addition of potassium carbonate so as nearly to neutralise the acetic acid. After 2 hours, the whole was cooled, filtered from a little gum, and made strongly alkaline with ammonia; a chalky precipitate then separated which was well washed, dried on porous porcelain, and then on the steam-bath (Found: C, 58·1; H, 6·7; N, 24·4. $C_{23}H_{30}O_3N_8$ requires C, 59·1; H, 6·4; N, 24·0%). A further crop of this disemicarbazone (Found: N, 24·2%) slowly separated from the aqueous mother-liquor as a definitely crystalline crust, m. p. about 252° (efferv.).

The Oxime.—The diketo-derivative (2 g.) was dissolved in boiling methyl alcohol, a concentrated aqueous solution of hydroxylamine hydrochloride (4 g.) and sodium acetate (5 g.) added, and the whole heated to boiling; the clear solution then gradually became cloudy. After 3 hours, the product was cooled and mixed with water, ammonia was added until the liquid was alkaline, and the precipitate, which was at first syrupy but soon hardened, was ground with water to a paste, washed, and dried over sulphuric acid in a vacuum desiccator (Found: N, 11·1. $C_{21}H_{25}O_3N_3$ requires N, 11·4%). The oxime was very soluble in methyl alcohol; the solution, after addition of much ether, was washed with water, dried over potassium carbonate, and concentrated; the *oxime* then separated in fluffy masses which had no definite melting point, shrinking at about 150° and effervescing at 170—175° (Found: N, 11·2%). Experiments made with the object of bringing about a Beckmann transformation by means of acetic anhydride or acetyl chloride led to no useful result.

An isomeride of strychnidone was obtained when this substance (6·5 g.), dissolved in the minimum quantity of boiling methyl alcohol, was mixed with methyl-alcoholic potash (25 c.c. of 25%). On heating on the steam-bath, the liquid clouded and a crystalline, chalky precipitate separated. This was collected, washed well with methyl alcohol, and crystallised from much boiling methyl alcohol, from which the substance separated as a colourless, crystalline powder (Found: C, 71·3; H, 7·0; N, 7·7. $C_{21}H_{24}O_3N_2$ requires C, 71·6; H, 6·8; N, 7·9%).

allo-*Strychnidone* shrinks at 245°, gradually becomes brown, and froths at about 260—265°. It dissolves with difficulty in dilute acids and shows the same colour reactions as the original diketo-derivative. It is moderately easily soluble in boiling acetone or xylene and is very stable to permanganate. The same substance appeared to be produced when the original diketo-derivative was left in contact with concentrated sulphuric acid for 2 hours and the brownish-yellow solution, after dilution, was precipitated by ammonia. The decomposing point after recrystallisation was about 265° (Found: C, 71·2; H, 6·9; N, 7·8%). When the methyl-alcoholic solution of the base was boiled with semicarbazide hydrochloride or with hydroxylamine hydrochloride and sodium acetate, under exactly the conditions described above in the case of the isomeride, m. p. 152°, the solution in both cases deposited, on cooling, a mass of crystals of the *allo*-derivative which was identified by the decomposing point, 260°, and by analysis.

Methoxymethylstrychnidonic Acid.—The best conditions for the formation of this substance seem to be the following. Finely powdered methoxymethyldihydrostrychnidine (6 g.), suspended in warm methyl alcohol (50 c.c.), is mixed with methyl-alcoholic potash (10 c.c. of 25%), and perhydrol (20 c.c.) is added all at once. The temperature is kept carefully at 43—44°; a slow effervescence then takes place and a slimy substance separates at first but gradually disappears. After about an hour the effervescence will have ceased. The pale yellow product is left over-night, then mixed with an equal volume of water, and the methyl alcohol removed by distillation under reduced pressure. The filtrate from a small amount of flocculent matter is extracted several times with ether, then with chloroform to remove a gum, which so far has not been investigated, and is again distilled in order to free it from ether and chloroform.

On being acidified with dilute sulphuric acid, the liquid clouds and crude methoxymethylstrychnidonic acid separates as a brown resin. A specimen of the amino-acid in a nearly pure condition was obtained by extracting the crude product with much ether, drying the extract over calcium chloride, distilling off most of the ether, and allowing most of the remainder to evaporate over sulphuric acid; the *amino-acid* then separated as a crust which was not definitely crystalline (Found: C, 64·8; N, 7·5; N, 7·2. $C_{21}H_{28}O_5N_2$ requires C, 65·0; H, 7·2; N, 7·2%).

Anhydromethoxymethylstrychnidonic Acid.—When the crude amino-acid obtained on acidifying the product of the action of perhydrol on methoxymethyldihydrostrychnidine (see above) is warmed with water, almost all dissolves, and on allowing the solution to evaporate at 70—80° it darkens considerably and deposits at first colourless nodules of the anhydro-amino-acid and then a dark tar containing some crystalline matter. The latter is dissolved in a little boiling methyl alcohol and after some days the sparingly soluble anhydro-acid separates as a crust. This is collected and washed with methyl alcohol, the nearly colourless residue mixed with the nodules, and the whole repeatedly crystallised from methyl alcohol (Found: C, 67·6; H, 7·0; N, 7·4; MeO, 8·1. $C_{21}H_{26}O_4N_2$ requires C, 68·1; H, 7·0; N, 7·6; MeO, 8·0%). This anhydro-acid melts at 222° and is sparingly soluble even in boiling methyl alcohol, from which it separates in stars of flat, prismatic needles; on heating in a test-tube, it chars, liberating the odour of indole. It is insoluble in water or cold dilute acids or in dilute caustic soda solution, but dissolves gradually in the last on boiling. The solution in dilute sulphuric acid (60%) gives with dichromate an intense crimson colour, and the solution in warm dilute hydrochloric acid gives with ferric chloride the same coloration. When the anhydro-acid is heated in a sealed tube with methyl iodide and methyl alcohol for a few minutes, a pale yellow solution is obtained which deposits the unchanged anhydro-acid on evaporation.

Ethoxymethyldihydrostrychnidine.—This substance is obtained when powdered strychnidine methosulphate (3 g.) is heated with a saturated solution (25 c.c.) of caustic potash in ethyl alcohol on the steam-bath. The methosulphate gradually dissolves and a cloudy liquid containing drops of oil forms. After 10 minutes, the whole is cooled, water and ice are added, and the chalky precipitate is collected, washed with ice-water, and left on porous porcelain. The substance is very soluble in alcohol; from the solution, after being concentrated and left in the ice-chest, a paste of needles separates which, in contact with porous porcelain, becomes quite colourless but has the tendency, characteristic also of methoxymethyldihydrostrychnidine (compare p. 1602), to become purple on exposure to the air. After being dried at 80°, the substance melts at about 98° (Found: C, 75·9; H, 8·4; N, 7·3. $C_{24}H_{32}O_2N_2$ requires C, 75·8; H, 8·4; N, 7·3%). *Ethoxymethyldihydrostrychnidine* is much more readily soluble in solvents than the corresponding methoxy-derivative and exhibits much less tendency to separate in well-defined crystals. It is very soluble in light petroleum and separates from the concentrated solution, on slow evaporation, in hard, lilac-brown prisms.

Methoxymethyltetrahydrostrychnidine.

The corresponding dihydro-derivative (p. 1602) (10 g.), as obtained directly by the addition of water to the product of the action of methyl-alcoholic potash on strychnidine methosulphate, is dissolved in dilute sulphuric acid (150 c.c. of 20%) and reduced, in the apparatus described on p. 1600, by a current of 5 amps. for 15 hours. The product is diluted and mixed with excess of concentrated caustic potash solution, and the solid is collected, dried on porous porcelain, and warmed with a little alcohol to remove traces of gum. The substance is then twice crystallised from xylene, from which it separates very characteristically in well-developed, glistening, short prisms (Found: C, 75·1; H, 8·6; N, 7·5; MeO, 8·1. $C_{23}H_{32}O_2N_2$ requires C, 75·0; H, 8·7; N, 7·6; MeO, 8·3%). *Methoxymethyltetrahydrostrychnidine* melts at 220° and distils at about 230—235°/1 mm. without any decomposition, since the colourless, crystalline distillate melts at 220—222° either alone or mixed with a specimen of the original substance. It is very sparingly soluble in boiling alcohol, and moderately easily soluble in boiling benzene, from which it crystallises well in plates. It dissolves readily in dilute acids. The solution in dilute sulphuric acid gives with dichromate a pink coloration which rapidly changes to reddish-purple. Acetic anhydride appears to be without action, since, after boiling with the anhydride and a drop of sulphuric acid for several minutes, the base was recovered unchanged on addition of ammonia after the acetic anhydride had been decomposed with water.

The *hydriodide* was prepared by dissolving the base in a slight excess of dilute hydrochloric acid, adding a few drops of sulphuric acid, heating the solution to boiling, and mixing it with a large excess of aqueous sodium iodide; from the milky solution thus produced, a gum separated which soon crystallised. The mass was well washed and dissolved in boiling water, and the solution rubbed with a glass rod; a meal of glistening prisms then separated, m. p. 235° (decomp.) (compare p. 1623) (Found: C, 56·0; H, 6·7. $C_{23}H_{32}O_2N_2$,HI requires C, 55·7; H, 6·7%). This hydriodide is very sparingly soluble in boiling methyl alcohol and separates well, on cooling, in small, colourless needles. Its conversion into methyl-*neo*dihydrostrychnidinium iodide by the action of heat is described on p. 1623.

The Methiodide (*a*), $C_{23}H_{32}O_2N_2,MeI$.—The base, m. p. 220°, does not combine readily with methyl iodide and may indeed be recrystallised from methyl iodide without change. In an experiment in which the base was boiled with methyl alcohol and a large excess of methyl iodide for 12 hours, the clear solution, on being concentrated, deposited a large amount of the unchanged base. When, however, the powdered base (2·5 g.) was heated with methyl iodide (8 c.c.) in a sealed tube in the steam-bath for 5 hours, complete solution gradually took place and, on cooling, a mass of crystals separated, or in some experiments a syrup formed on the surface of the methyl iodide which became crystalline on being rubbed with methyl alcohol. In either case, the crystals were collected, washed with methyl iodide, and recrystallised from a little boiling alcohol, from which the *methiodide* separated, on slowly cooling, as a glistening crust of arrow-shaped prisms (Found: C, 56·0; H, 7·0; I, 24·5. $C_{24}H_{35}O_2N_2I$ requires C, 56·4; H, 6·9; I, 24·9%). This methiodide melts at about 227° with vigorous effervescence. In order to determine the nature of this decomposition, about a gram of the substance was heated in a test-tube at 250°; methyl iodide then condensed on the cold part of the tube. After effervescence had ceased, the nearly colourless gum was dissolved in much boiling methyl alcohol, and the solution concentrated; on cooling, methoxymethyltetrahydrostrychnidine separated in prisms, m. p. 220°. The methiodide is decomposed with great difficulty by methyl-alcoholic potash, since, after boiling for several minutes, most of the unchanged methiodide is recovered on the addition of water. The methyl iodide washings of the crude methiodide gave a syrup on evaporation; a solution of this in boiling methyl alcohol, on standing exposed to air, deposited thick prisms of methoxymethyltetrahydrostrychnidine, showing again the small tendency this base has to combine with methyl iodide.

The Methochloride (*a*).—This was prepared by warming the methiodide with water and excess of silver chloride on the steam-bath for 2 hours and then evaporating the filtrate from the silver salts; the methochloride separated as a waxy, crystalline mass, which was not analysed. When this substance was heated on the steam-bath with excess of methyl-alcoholic potash (20%), decomposition took place immediately with separation of potassium chloride, and, as the product was completely soluble in water, it is probable that the methohydroxide was present at this stage.

If, instead of diluting the mixture with water, the whole is heated at 140° until nearly all the methyl alcohol has evaporated, a crystalline precipitate of methoxymethyltetrahydrostrychnidine is obtained on the addition of water.

The Dimethosulphates, $C_{23}H_{32}O_2N_2,2Me_2SO_4$ (A) *and* (B).—Methoxymethyltetrahydrostrychnidine does not combine readily with methyl sulphate, as is shown by the fact that, if methyl sulphate is added to a boiling concentrated solution of the base in benzene, the unchanged substance crystallises on cooling. Combination takes place readily, however, under the following conditions and with the formation of the dimethosulphates. The base (8 g.), dissolved in specially purified and dried benzene (100 c.c.), is mixed with carefully purified methyl sulphate (20 c.c.) and boiled under reflux with exclusion of moisture; in about 2 hours, the liquid begins to cloud and a gelatinous mass to separate. The boiling is continued for 20 hours, and the hot benzene then decanted from the gummy mass. After several days, the benzene solution deposits a soft, crystalline crust, which is washed with benzene and dried over sulphuric acid in a vacuum desiccator (Found: C, 51·8; H, 6·9. $C_{23}H_{32}O_2N_2,2Me_2SO_4$ requires C, 52·2; H, 7·1%). That this substance is the *dimethosulphate* (A) was confirmed by the fact that the solution in boiling methyl alcohol gave, on the addition of sodium iodide and cooling, the dimethiodide (A), m. p. 315—320° (decomp.). In preparing this substance in quantity, the horny mass of dimethosulphate from which the benzene had been decanted was dissolved in warm water, and the solution was filtered from benzene and mixed with a considerable excess of hot concentrated sodium iodide; the clear solution, on rubbing, immediately began to deposit the *dimethiodide* (A) in flat prisms. After some hours, the crystalline mass was collected, well washed, and dried on porous porcelain and then on the steam-bath (Found: C, 45·8; H, 5·6. $C_{23}H_{32}O_2N_2,2MeI$ requires C, 46·0; H, 5·8%). This dimethiodide (A) does not discolour until 300° and melts and effervesces at about 315° to a reddish-brown froth. It dissolves readily in boiling water and separates on cooling in needles; in boiling methyl alcohol it is very sparingly soluble, but it dissolves in much boiling ethyl alcohol and separates on slow cooling in striated, quadrilateral plates.

The Dimethochloride (A).—A boiling aqueous solution of the dimethiodide (A) was readily decomposed by silver chloride and, on evaporating the filtrate from the silver salts to a small bulk and leaving it over sulphuric acid, a gummy mass was obtained which gradually crystallised but was not analysed. The solution in dilute sulphuric acid gives with dichromate a pink coloration which becomes crimson on warming. The conversion of this dimethochloride (A) into methyl-ψ-dihydrostrychnidine, $C_{22}H_{28}ON_2$, by the action of heat is described on p. 1621.

Methoxymethyltetrahydrostrychnidine Dimethiodide (B), $C_{23}H_{32}O_2N_2,2MeI$.—When the solution of the dimethosulphate, prepared as described on p. 1619, was treated with sodium iodide, less than half the calculated amount of the dimethiodide (A) separated, and very little more was obtained on standing or concentration. On investigating the cause of this, it was found that the addition of caustic potash solution (50%) to the mother-liquor of (A) produced a heavy caseous precipitate. After alkali had been added until there was no further separation, the whole was warmed at 50°; the precipitate then melted and settled on the bottom of the beaker as a viscid gum. The supernatant alkaline solution was decanted, the syrup dissolved in boiling methyl alcohol, and the solution filtered and concentrated; on standing, a thick mass of colourless prisms gradually separated, and more was obtained by concentrating the mother-liquor. This dimethiodide (B) is very readily soluble in boiling methyl alcohol, but sparingly soluble in the cold, and separates in thick, four-sided, twin prisms which effervesce at about 165° owing to the escape of methyl iodide (see below) (Found: C, 46·7; H, 5·9. $C_{25}H_{38}O_2N_2I_2$ requires C, 46·0; H, 5·8%). The final methyl-alcoholic mother-liquors, from which no more of the dimethiodide (B) could be separated, on being concentrated and kept for months in the air, yielded a semi-solid paste; this, in contact with porous porcelain. gradually left a white, crystalline mass, a solution of which in methyl alcohol, when allowed to concentrate in the air, gradually deposited large, glistening prisms, m. p. 225° (vig. efferv.) (Found: C, 56·2; H, 7·0. $C_{23}H_{32}O_2N_2,MeI$ requires C, 56·4; H, 6·8%). Since this substance decomposed on heating into methyl iodide and methoxymethyltetrahydrostrychnidine, it is evident that it was the methiodide of this substance described on p. 1618, and its formation shows that the crude dimethosulphate prepared in benzene solution with a large excess of methyl sulphate contains some monomethosulphate in spite of the fact that a very large excess of methyl sulphate was used and the heating continued for 20 hours (p. 1619).

Methoxymethyltetrahydrostrychnidine Methiodide (*b*).—When the dimethiodide (B) just described is heated in a test-tube in a bath at about 220°, methyl iodide is eliminated and condenses on the cold sides of the tube. In a quantitative experiment, 0·2440 g., heated at 165°, rising to 230° until decomposition was complete, lost 0·1047 g. or 42·8%, whereas $C_{23}H_{32}O_2N_2,2MeI$ losing 2MeI requires a loss of 43·5%. On crystallising the residue from alcohol, colourless leaflets separated which melted at 220° and consisted of methoxymethyltetrahydrostrychnidine (Found: C, 74·9; H, 8·6. Calc. for $C_{23}H_{32}O_2N_2$: C, 75·0; H, 8·7%). The elimination of only 1 mol. of methyl iodide was accomplished under the following conditions. The dimethiodide (B) was gently boiled in a test-tube with carefully dried mesitylene; it then became spongy and granular but did not dissolve. The crystalline deposit was collected, washed with warm mesitylene, and crystallised from a large volume of methyl alcohol, in which it was very sparingly soluble and from which it separated as a sandy, crystalline powder (Found: C, 55·8; H, 6·7. $C_{23}H_{32}O_2N_2$,MeI requires C, 56·4; H, 6·9%). This methiodide (*b*) becomes brown at 300—320°, decomposes with effervescence at about 325° into methyl iodide and methoxymethyltetrahydrostrychnidine, and is readily soluble in boiling water. It is therefore isomeric with the methiodide (*a*) described on p. 1618, which melts at 227°, and it is interesting that both these isomerides lose methyl iodide on heating and yield methoxymethyltetrahydrostrychnidine.

Methoxymethyltetrahydrostrychnidine Dimethochloride (B).—The pure dimethiodide (B), m. p. 165°, was treated with water and silver chloride on the steam-bath in the usual way; the filtrate from the silver salts was evaporated to a small bulk on the steam-bath and then left over sulphuric acid in a vacuum desiccator, but there was no sign of crystallisation and the whole dried to a horny mass. This became brittle on the steam-bath and could be powdered, but the powder rapidly absorbed moisture and became sticky. When the dry substance was heated in a test-tube in a sulphuric acid bath, methyl chloride was eliminated; the effervescence being over, the residue was crystallised from xylene, colourless prisms being thus obtained which melted at 220—222° and consisted of methoxymethyltetrahydrostrychnidine [compare the action of heat on the dimethochloride (A),; see below].

Methyl-ψ-dihydrostrychnidine, $C_{22}H_{28}ON_2$.—This substance is obtained from the dimethochloride (A) of methoxymethyltetrahydrostrychnidine (p. 1619) or from methyl*neo*dihydrostrychnidinium chloride (p. 1623) by heating. The dimethochloride (A), in quantities of not more than 0·5 g., is cautiously heated in test-tubes over a free flame; it soon gives off steam and doubtless also methyl alcohol and then froths at a very high temperature, giving a very unpleasant smelling vapour, which burns with a smoky flame tinged with green, and a small amount of a colourless, crystalline sublimate forms on the sides of the tube. When the effervescence has ceased, the ochre-coloured residue, which crystallises on cooling, is dissolved in much boiling methyl alcohol; the solution, on being concentrated considerably and left in the ice-chest, deposits the new substance in colourless spangles, but the yield is poor even after the mother-liquors have been worked up (Found : C, 78·1 ; H, 8·0 ; N, 8·5. $C_{22}H_{28}ON_2$ requires C, 78·6 ; H, 8·3 ; N, 8·3%).

Methyl-ψ-dihydrostrychnidine melts at 212° and is somewhat soluble in boiling water to a bitter solution which, on cooling, deposits the substance in flitters. It is sparingly soluble in cold methyl alcohol and very sparingly soluble in acetone even on boiling; it separates from the solution, on concentration, in glistening, colourless plates. It is also sparingly soluble in benzene or light petroleum. The solution in acetone does not decolorise permanganate except on the addition of a little water and then only on long standing. The resistance to oxidation was shown in an experiment in which the base (1 g.), dissolved in much boiling acetone and water (3 c.c.), was boiled under reflux, and permanganate (1·5 g.) gradually added. After some hours, decoloration was complete and the acetone filtrate from the manganese precipitate yielded, on being concentrated, 0·7 g. of unchanged substance. A solution of the base in dilute sulphuric acid gives with dichromate a yellow solution which becomes crimson on warming; a solution in dilute hydrochloric acid is coloured yellowish-pink by ferric chloride, the colour changing to crimson on warming. The base dissolves with effervescence in concentrated nitric acid to a reddish-brown solution.

The Methiodide, $C_{22}H_{28}ON_2$,MeI.—When the base, m. p. 212°, was mixed with methyl iodide, there was some rise of temperature. The chalky precipitate produced after the mixture had been heated in a sealed tube for 15 minutes was crystallised from methyl alcohol, in which it was very sparingly soluble and from which it separated in glistening groups of slender needles (Found : C, 57·6; H, 6·3. $C_{23}H_{31}ON_2I$ requires C, 57·7; H, 6·4%). This methiodide is very sparingly soluble in boiling water. It becomes brown at 290° and decomposes with effervescence at about 330—335° to a brown syrup, which crystallises on cooling; this decomposition product was not further investigated.

The *methochloride*, prepared in the usual manner by boiling the methiodide with water and silver chloride, separated from the concentrated aqueous solution, on standing over sulphuric acid, in colourless, very readily soluble needles and was not analysed. It darkens at 260° and effervesces at about 315° to a black syrup. The solution in dilute sulphuric acid gives with permanganate a pink coloration which becomes an intense crimson on standing or warming.

*The Methyl*neo*dihydrostrychnidinium Salts.*

Methoxymethyltetrahydrostrychnidine, unlike the corresponding dihydro-derivative (p. 1610), is not acted on by boiling dilute sulphuric acid: the tetrahydro-base (5 g.) was boiled with sulphuric acid (20% by vol.) for 3 hours, but there was no sign of any elimination of methyl alcohol and on addition of ammonia a caseous precipitate separated which was found to be the unchanged base, practically the whole being recovered. The only way in which the methyl*neo*-dihydrostrychnidinium salts could be prepared was from methoxymethyltetrahydrostrychnidine hydriodide (p. 1617) by the action of heat. The air-dried substance, in quantities of 0·5 g., was spread evenly over the lower surface of large test-tubes and these were heated by a sulphuric acid bath gradually to 230° and kept at this temperature for about 3 minutes; the vapours which came off during the decomposition were apparently water and methyl alcohol. After effervescence had ceased, the residual syrup crystallised, on cooling, as a hard, pale brown crust. This was very sparingly soluble in boiling water, but dissolved very readily in warm dilute hydrochloric acid (compare p. 1611). The solution, after being decolorised with norite, was mixed with excess of ammonia, left for 24 hours, filtered from a small, fluffy, brown precipitate, and concentrated on the steam-bath to a small bulk. The solution of ammonium chloride was decanted from the sparingly soluble, brown crusts which had separated, and the crusts were dissolved in much boiling water. On concentrating the solution considerably, the iodide separated in well-developed, pale brown prisms (Found: C, 57·2; H, 6·4. $C_{22}H_{29}ON_2I$ requires C, 56·9; H, 6·3%).

*Methyl*neo*dihydrostrychnidinium iodide* melts at about 350° with effervescence and is sparingly soluble in alcohol, xylene, or glacial acetic acid. This iodide was rubbed into a paste with hot water and heated on the steam-bath for 2 hours with excess of silver chloride. The filtrate from the silver salts was evaporated to a small bulk and the solution placed over sulphuric acid in a vacuum desiccator; a paste of crystals then formed. In contact with porous porcelain, the mother-liquor was readily absorbed, leaving a hard, colourless mass of *methyl*neo*dihydrostrychnidinium chloride* (Found in material dried at 100°: C, 70·7; H, 8·1. $C_{22}H_{29}ON_2Cl$ requires C, 70·8; H, 7·9%). This chloride is very readily soluble in water. The solution in dilute sulphuric acid gives with dichromate an intense crimson coloration in the cold. The dry substance changes colour at 300° and decomposes at about 345° with effervescence, leaving a brown syrup. In investigating this change, the dry substance (0·5 g.) was very cautiously heated in a large test-tube by a free flame until effervescence had ceased; during this decomposition a very pungent and unpleasant smelling vapour was given off which tinged a flame green. The brown syrup solidified, on cooling, to a very hard crust. A solution of this in much boiling methyl alcohol was decolorised by boiling with norite for an hour and then concentrated; a mass of colourless plates then gradually separated which melted at 210—212° and consisted of methyl-ψ-dihydrostrychnidine, as a comparison of properties and a mixed melting point demonstrated. This is probably the most convenient method of preparing this base, but the yield in this case also is not good.

Methylstrychnine.—This substance may be quickly and conveniently prepared in good yield by the following process. Strychnine (100 g.), finely powdered and passed through a 40-mesh sieve, is stirred in a mortar with the gradual addition of pure methyl sulphate (68 c.c.); the whole soon sets to a solid mass of strychnine methosulphate. This is broken up, left over-night, and dissolved in warm water (300 c.c.), the solution is filtered from unchanged methyl sulphate (about 2 c.c.), and then caustic potash (170 c.c. of 50%) added with shaking. Crystallisation soon sets in and after remaining over-night the crystals are collected and dissolved in boiling water (260 c.c.), and the solution is filtered from unchanged strychnine (about 2 g.) and allowed to cool; the stout, colourless prisms of methylstrychnine, $C_{22}H_{24}O_2N_2,4H_2O$, that separate are collected and dried on the steam-bath. The colourless powder (93 g.) melts and decomposes at about 318—320°. The aqueous mother-liquors are used for the recrystallisation of another batch of crude methylstrychnine.

Normethylstrychnine.—When methylstrychnine, powdered and dried on the steam-bath, is heated in a distilling flask under 1 mm. by a metal bath kept at 200—205°, it gradually melts, there is much effervescence and some sublimation, and the loss is about 15%. The heating is continued for about ½ hour, and the residual resin is then dissolved in a slight excess of dilute hydrochloric acid, ammonia is added until there is a slight precipitation, and the filtered solution is mixed with excess of ammonia and warmed at 50° on the steam-bath. The pale brown, granular precipitate is collected and dissolved in excess of warm oxalic acid; after 2 days, a small amount of a dark crust separates. The filtrate from this is vigorously shaken while dilute ammonia is carefully added so long as a dark-coloured precipitate forms. After being filtered, the solution is shaken with norite and filtered, and excess of ammonia is added to the pale yellow filtrate. A voluminous, pale ochre precipitate separates which becomes granular on warming at 50°, and this is collected, washed, and dried over sulphuric acid in a vacuum desiccator (Found in two different preparations: C, 75·7 and 75·2; H, 6·8 and 6·7; N, 8·2. $C_{21}H_{22}O_2N_2$ requires C, 75·4; H, 6·6; N, 8·4%). This base, which is isomeric with strychnine, has so far not been obtained in a crystalline condition. A solution in dilute sulphuric acid (60% by vol.) gives with dichromate an intense bluish-purple colour, fading to a port wine tint; a solution in dilute hydrochloric acid gives with ferric chloride no coloration in the cold and there is little change on warming.

The Methiodide.—The base was heated in a sealed tube in the steam-bath with a large excess of methyl iodide for 5 hours. Next day, the crust of prisms which had separated on the sides of the tube was scraped off, washed with methyl iodide, and dried on the steam-bath. The old-gold, crystalline mass became opaque at 180°, darkened at 290°, and frothed at about 315° (Found: C, 54·9; H, 5·5. $C_{21}H_{22}O_2N_2$,MeI requires C, 55·4; H, 5·3%). This methiodide of normethylstrychnine was digested with water and silver chloride on the steam-bath, and the pale green filtrate concentrated to a small bulk; a soft, satiny mass separated on standing. This became colourless on porous porcelain and melted at about 285° (Found: C, 68·9; H, 6·6; N, 7·2. $C_{21}H_{22}O_2N_2$,MeCl requires C, 68·7; H, 6·5; N, 7·3%). A solution of this methochloride in dilute sulphuric acid (60% by vol.) gives with dichromate an intense indigo-blue colour, fading to brown. Methylstrychnine (10 g.) mixed with phenol (15 g.) was heated at 240° for an hour; the distillate, on treatment with dilute potash, yielded anisole (1·2 g.), which was recognised by its boiling point and other properties.

Action of Caustic Potash on Methylstrychnine.—Methylstrychnine (10 g.), mixed with methyl-alcoholic potash (60 c.c. of 20%), was heated on the steam-bath for 15 minutes with stirring, powdered potash (30 g.) was then added, and the decomposition continued at 150—200° for 20 minutes with frequent stirring; the temperature was then raised to 250° for 30 minutes. The product from five such operations was steam-distilled, the oil that passed over was extracted with ether, and the extract was dried over potassium carbonate and fractionated. The portion that distilled between 148° and 155°/15 mm., on remaining in the ice-chest, deposited crystals which were collected, drained on porous porcelain, and recrystallised from petroleum. The colourless plates thus obtained in considerable quantity melted at 52° and consisted of indole, as a mixed melting-point determination and a careful comparison of properties conclusively proved. The reddish-brown solution in the steam-distillation flask was cooled, sulphur dioxide passed in, and the precipitate collected, dried, and distilled in quantities of 3 g. with soda-lime under reduced pressure. The distillate, containing oily drops, was extracted with ether, and the extract steam-distilled; a further quantity of indole then passed over. Finally, the residue in the steam-distillation flask was extracted with benzene and distilled, and the fraction, b. p. 240—280°/16 mm., was dissolved in low-boiling petroleum; from the solution a pasty mass of crystals separated which, after recrystallisation, melted at 236°, and this substance was found, by an examination of its colour reactions and other properties and by a mixed m. p. determination, to be carbazole.

Decomposition by soda-lime. Methylstrychnine (2·5 g.) was mixed with soda-lime (10 g.) and heated in a hard glass tube under 20 mm. to about 400°. The distillate from several such operations was steam-distilled, the pale yellow oil extracted with ether, and the extract dried over potassium carbonate and fractionated; an oil passed over at 93°/25 mm. which was insoluble in dilute hydrochloric acid, gave an intense purple colour with *p*-dimethylaminobenzaldehyde, and yielded a picrate, m. p. 168°. The amount obtained was too small to allow of its constitution being determined.

The residue from the steam distillation yielded a small amount of a substance which separated from light petroleum in glistening plates, m. p. 236°, and was recognised as carbazole.

Electrolytic Reduction of Methylstrychnine.—Methylstrychnine (20 g.), dissolved in dilute sulphuric acid (100 c.c. of 60%), was reduced in the usual apparatus (p. 1600) by a current of 5 amps. for 16 hours, the pale pink solution diluted with water and heated on the steam-bath, and barium carbonate added until the sulphuric acid had been removed. The strongly alkaline solution from the barium sulphate was evaporated to dryness; the almost colourless, crystalline methylstrychnidinium hydrogen carbonate that remained was purified by dissolving it in methyl alcohol, in which it was readily soluble, and fractionally precipitating it with ether. The second fraction, after drying on porous porcelain over sulphuric acid in a vacuum desiccator, gave analytical results agreeing approximately with those required for the formula

$$C_{22}H_{27}ON_2,HCO_3,H_2O$$

(Found: C, 65·8; H, 6·9; N, 6·8. Calc.: C, 66·6; H, 7·2; N, 6·8%). When this carbonate was heated at 100° it lost 4·4% (Calc., 4·3%) (Found: C, 69·0; H, 7·4; N, 7·0. $C_{23}H_{28}O_4N_2$ requires C, 69·7; H, 7·1; N, 7·1%). This carbonate is readily soluble in hot water and effervesces with acids; the dry substance also effervesces, when it is heated at 200°, with formation of a colourless syrup. It was readily soluble in hot methyl-alcoholic potash (25%), and after heating in an open flask on the steam-bath for 15 minutes so that considerable concentration had taken place, the milky liquid gave, on dilution with water, a caseous precipitate which separated from methyl alcohol in glistening prisms, m. p. 124—125°, and proved to be methoxymethyldihydrostrychnidine (Found: C, 75·0; H, 8·2. Calc. for $C_{23}H_{30}O_2N_2$: C, 75·4; H, 8·2%). When the carbonate was treated with hydrochloric acid, it yielded a horny methochloride which appeared to be identical with the substance obtained from strychnidine methiodide by treatment with silver chloride (p. 1601).

UNIVERSITIES OF OXFORD AND
MANCHESTER.

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