CXXVIII.—*Strychnine and Brucine. Part VIII. The Action of Hydriodic Acid on Strychnidine. Dihydrostrychnidine (B) and Substances derived therefrom.*

By WILLIAM HENRY PERKIN, jun., and ROBERT ROBINSON.

IN Part VI (J., 1927, 2389) of this investigation it was shown that strychnine, dissolved in dilute acetic acid, is reduced by hydrogen in the presence of palladium with the formation of dihydrostrychnine, $C_{21}H_{24}O_2N_2$.

This substance, on electrolytic reduction, yields dihydrostrychnidine (A), $C_{21}H_{26}ON_2$, m. p. 214°, and hexahydrostrychnine (A), $C_{21}H_{28}O_2N_2$, just as strychnine, under the same conditions, is reduced to strychnidine, $C_{21}H_{24}ON_2$, and tetrahydrostrychnine, $C_{21}H_{26}O_2N_2$ (Tafel, *Annalen*, 1898, **301**, 301). Furthermore dihydrostrychnine (A) and hexahydrostrychnine (A) were obtained by the catalytic reduction of strychnidine and tetrahydrostrychnine, respectively. In describing these changes it was stated in a footnote that a second dihydrostrychnidine, $C_{21}H_{26}ON_2$, m. p. 151°, had been obtained from strychnidine by reduction with hydriodic acid in the presence of phosphorus. This substance, which we have named *dihydrostrychnidine* (*B*), is the principal substance dealt with in the present communication. In investigating the complex changes which dihydrostrychnidine (B) undergoes when it is treated with various reagents, it has been found necessary to carry out comparative experiments with strychnidine, dihydrostrychnidine (A), methoxymethyltetrahydrostrychnidine (J., 1927, 167) and other allied substances, and the description of these experiments is also included.

The conversion of strychnidine into dihydrostrychnidine (B) is brought about by long boiling with fuming hydriodic acid and phosphorus, but the investigation has unfortunately been rendered difficult, and is consequently not so complete as could be desired, by reason of the fact that, in contrast with dihydrostrychnidine (A), dihydrostrychnidine (B) is very readily soluble in the usual organic solvents and therefore difficult to obtain in crystalline condition from the gummy product of the reduction. When, however, the substance is pure, it separates from acetone or ether in thick prisms. It does not yield an acetyl derivative, neither does it combine with hydroxylamine or with benzaldehyde. It is not reduced by boiling with sodium and alcohol, in this respect resembling dihydrostrychnidine (A), which also is not susceptible to further reduction. Dihydrostrychnidine (B) is a strong base, yielding with hydrochloric acid the *monohydrochloride*, $C_{21}H_{26}ON_2,HCl,3H_2O$, but when a solution of the sulphate is mixed with sodium iodide the *dihydriodide*, $C_{21}H_{26}ON_2,2HI$, separates; this is decomposed by boiling methyl alcohol into hydriodic acid and the *monohydriodide*. The behaviour of the base towards methyl sulphate is similar to that of the isomeride (A), since it yields the *monomethosulphate*, $C_{21}H_{26}ON_2,Me_2SO_4$, at the ordinary temperature, but is converted into the dimethosulphate, $C_{21}H_{26}ON_2,2Me_2SO_4$, when its solution in benzene is boiled with methyl sulphate. The conversion of these derivatives into the corresponding methiodides and methochlorides and dimethiodides and dimethochlorides as well as their formation from the base by the direct action of methyl iodide, etc., is described in the experimental section (pp. 975—980).

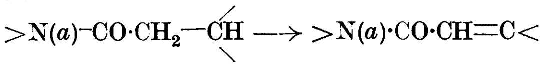
The study of the oxidation of dihydrostrychnidine (B), $C_{21}H_{26}ON_2$, in moist acetone solution by permanganate has yielded interesting results. The main product is a substance, $C_{21}H_{24}O_2N_2$, m. p. 196°, which, for reasons mentioned below, has been named *dihydrostrychnine* (*B*) and is characterised by the fact that its solution in dilute sulphuric acid gives, like strychnine, an intense blue coloration with dichromate. It yields well-defined salts and derivatives, of which the *hydriodide*, $C_{21}H_{24}O_2N_2,HI$, the *methiodide*, $C_{21}H_{24}O_2N_2,MeI$, the *methochloride* and *methobromide* have been prepared and examined. It is also sharply characterised by its conversion into a very sparingly soluble, beautifully crystalline *benzylidene* derivative, $C_{28}H_{28}O_2N_2$, when its solution in alcohol is treated with benzaldehyde and sodium ethoxide. Dihydrostrychnine (B) is readily hydrolysed by sodium ethoxide at 100° and, on acidification with hydrochloric acid, the *hydrochloride* of *dihydrostrychnic acid* (*B*) separates in a crystalline condition. This is decomposed by ammonia with the separation of the free acid, $C_{21}H_{26}O_3N_2$, which melts at 285° with elimination of water and regeneration of dihydrostrychnine (B), a series of changes reminiscent of the conversion of strychnine into strychnic acid and the regeneration of the base from the latter by the action of heat.

This behaviour clearly proves that the oxidation product of dihydrostrychnidine (B) contains the group $>N{-}CO{-}$ and the reactions of the substance (see p. 981) show that it is the group $>N(a){-}CH_2{-}$ and not the group $>N(b){-}CH_2{-}$ that has been transformed (compare J., 1928, 3087, 3090). A substance containing $>N(a){-}CH_2{-}$ and $>N(b){-}CO{-}$ would be expected to show the reactions of the strychnidine type, whereas an isomeride containing $>N(a){-}CO{-}$ and $>N(b){-}CH_2{-}$ would resemble strychnine. Actually the substance $C_{21}H_{24}O_2N_2$, m. p. 196°, shows the characteristic reactions of strychnine and fails to exhibit those characteristic of strychnidine.

Dihydrostrychnine (B) is unchanged by reagents for the carboxyl and hydroxyl groups and it is therefore evident that its condensation with benzaldehyde must involve the change $>N(a)\cdot CO\cdot CH_2{-} \longrightarrow >N(a)\cdot CO\cdot \overset{|}{C}{:}CHPh$, and it is worthy of note that such a process should be so facile. Analogies are forthcoming in the well-known ready formation of the arylidene derivatives of oxindole and in the condensation of derivatives of piperidone with reactive esters such as ethyl oxalate, ethyl cinchoninate, or ethyl nicotinate (Ruzicka, *Helv. Chim. Acta*, 1921, **4**, 472, 482, 486; compare also Späth and Bretschneider, *Ber.*, 1928, **61**, 327).

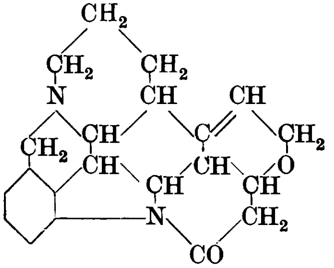
The above interpretation of the nature of dihydrostrychnine (B) and the discovery of its benzylidene derivative suggested that dihydrostrychnine (A) and strychnine itself also might condense with benzaldehyde, and this was found to be indeed the case. A detailed account of these accessible strychnine derivatives, important on account of the new breach in the defences against oxidising agents, is reserved, but we have included a brief description of *benzylidenestrychnine* in this communication. The formation of this substance proves that strychnine contains the group $>N(a)\cdot CO\cdot CH_2{-}$, and this was not previously known with certainty.

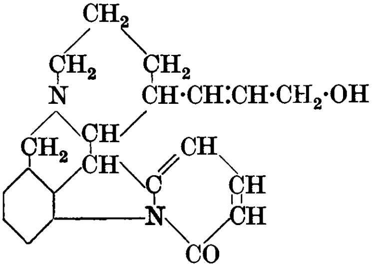
Dihydro*iso*strychnine does not, however, appear to condense with benzaldehyde to form a characteristic derivative analogous to the benzylidenedihydrostrychnines (A) and (B). This would be explicable if the strychnine–*iso*strychnine change involved the transformation



$$>N(a){-}CO\cdot CH_2{-}CH\!\begin{smallmatrix}/\\ \backslash\end{smallmatrix} \longrightarrow >N(a)\cdot CO\cdot CH{=}C<$$

This simple change is difficult to bring into line with the fact that dihydro*iso*strychnine does not absorb hydrogen in the presence of palladium (compare Part VI, *loc. cit.*, p. 2398) and in order to accommodate this observation we have considered the possibility that a further ring-fission occurs, giving a true pyridone which might well offer resistance to catalytic hydrogenation. The scheme given below on the basis of one of the formulæ * recently discussed (J., 1928, 3089) has the advantage that it explains why the strychnine–*iso*strychnine change has no parallel among strychnidine derivatives and it also serves to relate this change to the formation of brucinolone.


Strychnine.


iso*Strychnine.*

The conversion of dihydrostrychnine (A) into dihydro*iso*strychnine can be represented in an entirely similar manner and the assumption that either a saturated or an unsaturated group can break away from the potential pyridone nucleus does not involve any theoretical difficulty. It is analogous to the migrations of saturated alkyl or unsaturated aryl groups in molecular rearrangements. Preliminary experiments on the oxidation of dihydrostrychnidine (A) (Part VI, J., 1927, 2399) with permanganate suggest that this substance behaves similarly to the isomeride (B) only in regard to the composition of the product, since it yields *oxydihydrostrychnidine* (*A*), $C_{21}H_{24}O_2N_2$, m. p. 345°, a substance which has not yet been further investigated but is clearly not identical with dihydrostrychnine (A).

When dihydrostrychnine (B), m. p. 196°, is treated with hydrogen

---

* The point of attachment of the ether oxygen given in the formulæ put forward in this memoir was based on a misapprehension of the facts and requires modification. The heterocyclic ring should be 6-membered and the oxygen should be joined to C 17 and not to C 18, because Leuchs and his collaborators found that the brucinolone, which is the primary product of the decomposition of brucinolic acid, contains the group >N·CO·CH:C<. In subsequent changes the ethylene linkage moves into the $\beta\gamma$-position and then back again into the position indicated; the change is accompanied by another transformation in some other portion of the molecule.—R. C. F., W. H. P., R. R.

peroxide in the presence of methyl-alcoholic potassium hydroxide, it is converted into *dioxydihydrostrychnic acid* (*B*), $C_{21}H_{26}O_6N_2$, which crystallises well from water but has so far been obtained in such minute quantities that further examination has been impossible.

The methochlorides and dimethochlorides of dihydrostrychnidine (B) undergo a very interesting decomposition when they are heated with methyl-alcoholic potassium hydroxide, the main product being *methoxymethyltetrahydrostrychnidine* (*B*), $C_{23}H_{32}O_2N_2$, m. p. 180—181°, a highly characteristic substance which, for this reason, has been investigated in considerable detail.

If the simplest case of this decomposition, namely, the formation of the methoxy-derivative from the monomethochloride of dihydrostrychnidine (B), is considered, it is seen that the change may be represented in the simple manner, $C_{21}H_{26}ON_2,MeCl + MeOK \longrightarrow C_{23}H_{32}O_2N_2 + KCl$, and it will at once be evident that this curious change is reminiscent in many ways of the corresponding conversion of strychnidine methochloride (or the methosulphate) into *methoxymethyldihydrostrychnidine* (J., 1927, 1602) under the same conditions. In both cases it may be assumed that the decomposition takes place essentially according to the scheme

$$>\mathrm{N}\cdot\mathrm{C}\!\begin{smallmatrix}/\\-\\\backslash\end{smallmatrix} \longrightarrow\ >\mathrm{NMe}\quad \mathrm{MeO}\cdot\mathrm{C}\!\begin{smallmatrix}/\\-\\\backslash\end{smallmatrix},$$

rupture of the corresponding strychnidine ring taking place during the process. The strychnidine-type reactions of dihydrostrychnidine methochloride prove that all these changes occur at N(*b*). In accordance with this scheme, methoxymethyltetrahydrostrychnidine (B) contains a methoxy-group and a methyl group attached to nitrogen N(*b*), and the substance which it most closely resembles in properties and possibly also in structure is the isomeric methoxymethyltetrahydrostrychnidine, m. p. 220°, described in Part IV of this investigation (*loc. cit.*, p. 1617). The two substances have these properties in common : they are remarkably sparingly soluble in the usual organic solvents, they may be distilled under reduced pressure without decomposition, and they exhibit no tendency to lose methyl alcohol when boiled with dilute sulphuric acid (compare the behaviour of methoxymethyldihydrostrychnidine, *loc. cit.*, p. 1610). Methoxymethyltetrahydrostrychnidine (B) is not so strongly basic as dihydrostrychnidine (B), since it does not combine with benzyl chloride, but it yields well-characterised salts such, for example, as the *hydriodide*, $C_{23}H_{32}O_2N_2,HI$, and the *methosulphate*, $C_{23}H_{32}O_2N_2,Me_2SO_4$, and combines readily with methyl iodide to yield the *methiodide*, m. p. 235—238° (decomp.), a substance which is decomposed on heating into methyl iodide and the base. When a solution of the base in benzene is boiled with methyl sulphate the *dimethosulphate* is obtained, and from this the *dimethiodide*, $C_{23}H_{32}O_2N_2,2MeI$, m. p. 205—210°, and the *dimethochloride* are obtained.

The oxidation of methoxymethyltetrahydrostrychnidine (B) in acetone solution by means of permanganate has yielded unexpected results. The main product is a base, $C_{23}H_{30}O_3N_2$, m. p. 154°, which contains a MeO but no >NMe group and there can be no doubt that this substance is produced by the conversion of the >NMe group in methoxymethyltetrahydrostrychnidine (B) into >N·CHO, and that the substance of m. p. 154° is *formylmethoxytetrahydrostrychnidine* (*B*).

This view is supported by the fact that, although the substance distils to some extent unchanged under 1 mm., it is largely decomposed in these circumstances with loss of CO and formation of *methoxytetrahydrostrychnidine* (*B*), $C_{22}H_{30}O_2N_2$, m. p. 152°. This substance is also produced when the formyl derivative is boiled with dilute sulphuric acid, elimination of formic acid taking place. Methoxytetrahydrostrychnidine (B) is a secondary base and when treated with methyl iodide yields the hydriodide of methoxymethyltetrahydrostrychnidine (B), as is proved by the fact that a solution of the product in water is decomposed by dilute aqueous ammonia with the separation of this base.

It has been pointed out above that there is some similarity in properties between methoxymethyltetrahydrostrychnidine (B), m. p. 180°, and the isomeric substance, methoxymethyltetrahydrostrychnidine (m. p. 220°) described in Part IV of this series (J., 1927, 1617) and we therefore thought that it would be interesting to find out whether oxidation of the latter isomeride would proceed in the direction just described in the case of the former. Unfortunately, owing perhaps partly to its insolubility in cold acetone, the oxidation of the isomeride, m. p. 220°, takes place with difficulty and leads mainly to gummy products. There were indications that minute quantities of a formyl derivative were produced, but we were unable to obtain this substance in a pure state so as to make a comparison with formylmethoxytetrahydrostrychnidine (B) possible. In some other respects methoxymethyltetrahydrostrychnidine (B) (m. p. 180°) behaves in a different manner from the isomeride (m. p. 220°).

When the hydriodide of the substance, m. p. 180°, is heated in the dry state it loses methyl alcohol and yields the methiodide of dihydrostrychnidine (B), and the same decomposition takes place almost quantitatively when the base is boiled with hydriodic acid (p. 988). This change, which clearly takes place according to the scheme

$$>\mathrm{NMe}\quad \mathrm{MeO{\cdot}C}\!\lessdot + \mathrm{HI} = >\mathrm{N(MeI)C}\!\lessdot + \mathrm{MeOH},$$

is the reverse of that which occurs when dihydrostrychnidine (B) is converted, by the action of alcoholic potash on its methochloride, into methoxymethyltetrahydrostrychnidine (B). When the hydriodide of the isomeride, m. p. 220°, is heated, a change similar to that shown above takes place (compare Part IV, J., 1927, 1618; Part VI, *ibid.*, p. 2410), but the yield is extremely small and preliminary experiments on the action of boiling hydriodic acid on the base seem to show that in this case also the transformation takes place with difficulty and only to a small extent. It is difficult to understand why the two isomerides, m. p. 180° and 220°, should show such very different behaviour in these and some other parallel circumstances.

In describing the action of methyl-alcoholic potash on the methochloride or dimethochloride of dihydrostrychnidine (B) (p. 985), it is shown that the product of this decomposition consists essentially of methoxymethyltetrahydrostrychnidine (B) (m. p. 180°). The mother-liquors which had accumulated from many preparations of this substance contained some dihydrostrychnidine (B) and two new substances, namely, *methyl-ψ-strychnidine (B)** (m. p. 225°) and *dihydrostrychnidine (C)* (m. p. 134°), isomeric with (A) (m. p. 212°) and (B) (m. p. 151°). The formation of dihydrostrychnidine (B) from its methochloride by the action of methyl-alcoholic potash is clearly due simply to the removal of methyl chloride, and this takes place only to a very small extent. A similar change occurs quantitatively when the methochloride of dihydrostrychnidine (C) is heated with methyl-alcoholic potash (see below). Methyl-ψ-strychnidine (B), $C_{22}H_{26}ON_2$ (m. p. 225°) is a sparingly soluble substance yielding a well-crystallised *dimethiodide*, $C_{22}H_{26}ON_2$,2MeI, and a solution of the dimethochloride exhibits a very characteristic behaviour on evaporation, becoming intensely purple. Dihydrostrychnidine (C), $C_{21}H_{26}ON_2$ (m. p. 134°), crystallises from ether in brilliant prisms which Dr. T. V. Barker has kindly examined and measured. On treatment with methyl iodide, it gradually yields a *dimethiodide*, $C_{21}H_{26}ON_2$,2MeI; the *dimethochloride*, obtained from this by the action of silver chloride, is completely decomposed on heating with methyl-alcoholic potash, with regeneration of dihydrostrychnidine (C).

It is evident from the results recorded above that the differences existing between dihydrostrychnidines (A) and (B) either are stereochemical or more probably originate in an isomeric change of

---

* In proposing this name in order to distinguish the new base, we do not imply that there is necessarily any structural relation or analogy with the compound previously termed methyl-ψ-strychnidine.

the ring system under the influence of the drastic treatment to which the base is subjected.

The change might be in the position of a bridge ring, in the shift of a link so that a fused 5-ring : 6-ring system becomes 6-ring : 5-ring, or in a buckling or ring contraction such that, for example, $-CH_2{\cdot}CH_2-$ becomes $-CHMe-$ and a 6-ring becomes a 5-ring. The formation of benzylidenedihydrostrychnine (B) shows that this contraction, if it occurs, does not affect the group $>N(a)-CH_2-CH_2-$. We have no clue to the precise nature of the isomerism, but the behaviour of methoxymethyltetrahydrostrychnidine (B) towards hydriodic acid indicates that the heterocyclic system including $>N(b)-$ is more stable in dihydrostrychnidine (B) than in its isomeride (A).

Pursuing this line of argument, it would appear that the system in dihydrostrychnidine (C) is more stable still, because in this case the ring cannot be opened at all.

These conclusions are not easy to utilise in any definite manner, but they do imply that the strychnine carbon skeleton must be such that it can be modified in two ways so as to reach its most stable arrangement. Such modifications may be collateral or consecutive.

This communication also contains a short account of some new derivatives of strychnidine which are at present under examination.

The preparation of *strychnidine dimethosulphate*,

$$C_{21}H_{24}ON_2,2Me_2SO_4,$$

is described and its conversion into the corresponding *dimethiodide* and *dimethochloride*, and also the preparation of *strychnidine benzylchloride*, $C_{21}H_{24}ON_2,C_7H_7Cl$, and its conversion by the action of methyl-alcoholic potash into *methoxybenzyldihydrostrychnidine*, $C_{29}H_{34}O_2N_2$.

EXPERIMENTAL.

Preparation of Dihydrostrychnidine (B), $C_{21}H_{26}ON_2$.—Carefully purified strychnidine (25 g.) is mixed with hydriodic acid (100 c.c.; *d* 1·94) and amorphous phosphorus (8 g.) in a flask fitted with a wide ground-in condenser, and the mixture is gradually heated on a sand-bath and then boiled for 24 hours, care being taken to avoid stoppage of the condenser tube by phosphonium iodide. The almost colourless liquid, after filtering through asbestos to remove any phosphorus, is mixed with saturated sulphurous acid (100 c.c.), causing the separation of a thick brown paste. On the addition of water (500 c.c.) and thorough shaking, the brown precipitate becomes yellow. When the liquid is now boiled, much of the precipitate dissolves and the whole becomes colourless. After cooling, the clear solution is filtered from an insoluble iodide (8–10 g.; not further examined), made strongly alkaline with caustic potash, and extracted three times with ether; the ethereal solution is well washed several times with water (A; see below), dried over potassium carbonate, and evaporated; a pale yellow gum (13 g.) then remains, which on standing becomes a partly crystalline sticky mass. The separation of pure dihydrostrychnidine (B) from the crude product, owing to its small tendency to crystallise when in this condition, is a tedious process, but may be done in either of the following ways.

(i) The well-dried concentrated solution in pure ether is left in a closed flask in the ice-chest for several days in contact with a few crystals of the substance. A pale yellow crust of prisms gradually forms and this is recrystallised several times from pure dry ether until the substance melts at 145—148°.

(ii) The crude product is digested with a large volume of petroleum (b. p. 60—80°), and the solution is filtered, concentrated, and kept in the ice-chest; the crystalline crust that gradually forms is recrystallised until the pale yellow prisms melt at 145—148°. In view of the fact that the base is almost insoluble in water it is very difficult to understand why, during the washing of the ethereal solution of the crude base with water, about 25% of the substance passes into the washings (A). When these are concentrated by distillation under reduced pressure and then by evaporation on the steam-bath, a syrup separates which sets to a resin on cooling. This is washed and dissolved in pure ether and the solution is dried over potassium carbonate, concentrated, and left in the ice-chest; a crust of colourless glistening prisms then gradually separates which after recrystallisation melts at 146—148° and consists of dihydrostrychnidine (B) (Found : C, 78·3; H, 8·3%. See below).

In either case (i) or (ii), the mother-liquors are evaporated and the viscid syrup is distilled; almost the whole passes over at 225—227°/0·2 mm. and treatment with petroleum then gives a further small quantity of the crystalline base. The distillation and the treatment with petroleum are continued until there is no further crystallisation. It is curious that the final syrup gives analytical numbers agreeing closely with those required for the formula $C_{21}H_{26}ON_2$ (Found : C, 78·2; H, 8·5%) and is converted into the dimethiodide of dihydrostrychnidine (B) (compare p. 977) when a solution in methyl alcohol is boiled with a large excess of methyl iodide.

Dihydrostrychnidine (*B*) crystallises in brilliant colourless prisms which do not melt quite sharply but usually soften at 145° and are molten at 151° (Found : C, 77·9, 78·3; H, 8·1, 8·2; N, 8·8. $C_{21}H_{26}ON_2$ requires C, 78·2; H, 8·1; N, 8·7%). It is unfortunate that the facets of the crystals are not sufficiently well developed to allow of accurate crystallographical measurement. The base is very soluble in alcohol or benzene, less soluble in acetone or ether, and almost insoluble in water. It crystallises well from acetone but appears to suffer some change on long boiling with this solvent; from ether it separates usually in short, hard, glistening prisms but sometimes in groups of striated needles. It is a strong base and a solution in dilute sulphuric acid gives (i) with dichromate at first a faint red colour, deepening on standing or warming to reddish-brown, and (ii) with nitrite an orange colour rapidly becoming brown. The base, dissolved in very dilute hydrochloric acid, gives with ferric chloride no coloration at first, but gradually a pink colour develops which becomes crimson on warming. A solution in dilute acetic acid combines with diazobenzenesulphonic acid to give a yellow solution, becoming intensely crimson on addition of hydrochloric acid.

In order to determine whether dihydrostrychnidine (B) contains a keto-group, its behaviour (i) with hydroxylamine, (ii) towards sodium and alcohol, and (iii) towards electrolytic reduction was investigated.

(i) The base (2 g.), dissolved in alcohol, was mixed with hydroxylamine hydrochloride (5 g.) and sodium acetate (5 g.) and boiled under reflux for 2 hours. The reaction mixture was kept over the week-end, caustic potash then added, and the whole extracted with ether. The washed and dried ethereal solution deposited, on concentration, the unchanged base in prisms (1·5 g., m. p. 145—147°).

(ii) Sodium (20 g.) was rapidly added to a solution of the base (10 g.) in boiling alcohol (350 c.c.). When the whole of the sodium had dissolved, water was added, the base extracted with ether, the ethereal solution well washed, dried over potassium carbonate, and evaporated, and the colourless syrup distilled. The whole passed over at 225—230°/0·4 mm. When it was dissolved in a little ether and left in the ice-chest in contact with a crystal of the original base, a crust of crystals of the unchanged substance, m. p. 145—147°, gradually separated (Found: C, 78·4; H, 8·3%).

(iii) The base, dissolved in 10% sulphuric acid, was placed in the electrolytic apparatus described in Part IV (J., 1927, 1600), and a current of 5 amps. passed for 12 hours. The colourless solution was mixed with caustic soda and extracted with ether, the ethereal solution dried over potassium carbonate and concentrated, and the base distilled. Almost the whole passed over at 225—230°/0·4 mm. as a colourless syrup; a concentrated solution of this in ether, left in the ice-chest, gradually deposited a crust of crystals of the unchanged base, m. p. 145—147°.

In order to determine whether dihydrostrychnidine (B) is capable of yielding an acetyl derivative, the base (2 g.) was digested under reflux on the steam-bath with anhydrous sodium acetate (2 g.) and acetic anhydride (6 c.c.) for 4 hours. The product was mixed with ice and left in the ice-chest over-night, but nothing separated even after addition of an excess of sodium bicarbonate. The whole was made strongly alkaline with potassium hydroxide and extracted with ether : from the dried and concentrated extract the unchanged base separated.

Attempts to condense dihydrostrychnidine (B) with aldehydes were made under the following conditions. The base (1 g.), dissolved in alcohol, was mixed with benzaldehyde (2 c.c.) and a few drops of concentrated sodium ethoxide solution and left over-night. The pasty product was heated in the water-bath for ½ hour, mixed with water, and extracted with ether, and the ethereal solution was well washed, dried over potassium carbonate, and concentrated; the unchanged base then separated in colourless prisms, m. p. 145—147°. The effect of the treatment with benzaldehyde had been merely to remove a trace of colouring matter. Similar results were obtained in experiments in which the benzaldehyde was replaced by piperonal and by salicylaldehyde.

Dihydrostrychnidine (*B*) *hydrochloride*, $C_{21}H_{26}ON_2,HCl,3H_2O$, separates from concentrated aqueous solution in needles and is very soluble in water. The air-dried substance lost 10·2% at 100° and then gave C, 67·3 ; H, 8·0 ; N, 7·6 ; Cl, 9·4 ($C_{21}H_{26}ON_2,HCl,3H_2O$, losing $2H_2O$, requires loss, 9·7%. $C_{21}H_{26}ON_2,HCl,H_2O$ requires C, 67·1 ; H, 8·0 ; N, 7·7 ; Cl, 9·5%). Dried at 100°, the hydrochloride melts at 123° with vigorous decomposition. Addition of ammonia to a dilute solution of the hydrochloride precipitates the base as a caseous mass which melts under water and only slowly crystallises. A concentrated ethereal solution gradually deposits the base in prisms, m. p. 144—147°.

The dihydriodide and monohydriodide. A solution of dihydrostrychnidine (B) in dilute sulphuric acid containing a little sulphurous acid was heated to boiling, and sodium iodide then added in excess; the clear solution obtained, on cooling and rubbing, deposited minute colourless warts, which, after being washed and left on porous porcelain, became sticky on the steam-bath (Found, after drying over sulphuric acid in a vacuum : C, 42·9 ; H, 5·0. $C_{21}H_{26}ON_2,2HI$ requires C, 43·6 ; H, 4·8%). This *dihydriodide* is readily soluble in hot water and sparingly soluble in cold methyl alcohol. After it has been boiled with the latter solvent for some minutes, a mass of soft needles of the *monohydriodide* separates, the boiling with methyl alcohol having removed hydrogen iodide (Found in substance dried at 105°: C, 55·8; H, 6·6. $C_{21}H_{26}ON_2,HI$ requires C, 56·0; H, 6·0%). This hydriodide melts at about 235—240° (efferv.) and is readily soluble in, but does not appear to combine with, chloroform. When it is boiled with water (in which it is sparingly soluble) and silver chloride and the filtered solution is concentrated, the hydrochloride described above separates.

The methosulphate (*a*). When a solution of dihydrostrychnidine (B) (8 g.) in carefully dried benzene (50 c.c.) was mixed at 10° with freshly distilled methyl sulphate (4 c.c.), it clouded immediately and became warm and a jelly separated on the sides of the flask. The benzene layer was at once poured off and the jelly washed with benzene; it then rapidly crystallised. After contact with porous porcelain and drying over sulphuric acid in a vacuum, the colourless mass contained S, 7·6 ($C_{21}H_{26}ON_2,Me_2SO_4$ requires S, 7·2%). This *methosulphate* is very soluble in warm water and on addition of sodium iodide the cloudy liquid deposits a jelly which soon becomes crystalline when warmed on the steam-bath. This *methiodide* (*a*) separates from water, in which it is rather sparingly soluble, in brilliant groups of needles which gradually change to heavy, detached, striated prisms; the mother-liquor, on remaining exposed to the air, deposits the same substance in large crystals. It melts at 340—345° (decomp.),* is almost insoluble in cold acetone, but is moderately readily soluble in hot methyl alcohol, separating in prismatic needles (Found: C, 57·3; H, 6·1; N, 6·1. $C_{21}H_{26}ON_2,MeI$ requires C, 56·9; H, 6·2; N, 6·0%). This methiodide is identical with the substance obtained by the action of methyl-alcoholic potash on dihydrostrychnidine (B) dimethiodide (A) (p. 979) and most of the material was made by that process. It is also identical with the substance obtained by the action of heat on the hydriodide of methoxymethyltetrahydrostrychnidine (B) (p. 988). Its most characteristic property is its behaviour with chloroform, in which the finely powdered substance dissolves completely in the cold; on standing, or much more rapidly on warming, crystallisation sets in with the separation of the sparingly soluble *additive* derivative. This was collected, washed with chloroform, and left on porous porcelain exposed to the air for a few minutes (Found: loss on heating at 100°, 20·2; C, 47·9; H, 5·6. $C_{22}H_{29}ON_2I,CHCl_3$ requires $CHCl_3$, 20·4; C, 47·3; H, 5·2%). This substance gradually loses chloroform on exposure to air and much more rapidly over sulphuric acid in a vacuum; in the latter case after 12 hours the substance contained only 15·7% of chloroform.

---

* The melting points of the methiodides described in this series of papers vary very much with the rapidity of heating and the determinations were always made rapidly in an electrically heated m. p. apparatus (Mason).

The *methochloride* (*a*) was obtained by grinding the methiodide (a) to a paste with warm water and digesting the mass with a large excess of silver chloride and water on the steam-bath for 2 hours. The solution was evaporated to a small bulk and left over sulphuric acid in a vacuum; a hard satiny mass of the methochloride (a) remained, m. p. 335—340° (vig. efferv.) (Found in material dried at 120°: C, 70·2; H, 8·0. $C_{21}H_{26}ON_2,MeCl$ requires C, 70·8; H, 7·8%). *The action of heat.* The dry methochloride, in quantities of 0·5 g., was heated very cautiously in test-tubes until effervescence was complete and a yellowish-brown syrup remained, which set to a resin but did not crystallise. About 5 g. of this resin were distilled under 1 mm., the distillate was dissolved in pure dry ether, and the solution concentrated in a test-tube and left in the ice-chest for several days. The pale yellow prisms which gradually separated had m. p. 145—147° and consisted of dihydrostrychnidine (B), as the analysis and a mixed m. p. showed (Found: C, 78·0; H, 8·1; N, 8·6. Calc. for $C_{21}H_{26}ON_2$: C, 78·2; H, 8·1; N, 8·7%).

Dihydrostrychnidine (*B*) *dimethosulphate* (*A*) was obtained by adding methyl sulphate (5 c.c.) to a solution of the base (2 g.) in warm dry benzene (30 c.c.), shaking the mixture well and keeping it at about 30° for 24 hours. The benzene solution was decanted from the crystalline cake, which was washed with benzene, left in contact with porous porcelain, and dried over sulphuric acid in a vacuum (Found: S, 10·9. $C_{21}H_{26}ON_2,2Me_2SO_4$ requires S, 11·1%). This dimethosulphate is readily soluble in warm water. A rather dilute solution gave, with excess of sodium iodide, no precipitate (but an immediate voluminous crystalline precipitate on the addition of a large quantity of 50% caustic potash). However, the clear solution slowly deposited stars of brilliant prisms, which gradually became yellow unless a little sulphurous acid had been added (Found in material dried at 100°: C, 45·3; H, 5·4; Me as $>NMe$, 4·8. $C_{21}H_{26}ON_2,2MeI$ requires C, 45·6; H, 5·3; 2Me as $2>NMe$, 4·9%). This dimethiodide had m. p. 238—242° (decomp.) and proved to be identical with the substance produced by the direct union of the base and methyl iodide under the conditions explained on p. 977. It is very sparingly soluble in methyl alcohol or benzene but dissolves readily in cold and very readily in hot water. It is very stable and may be warmed on the steam-bath with 20% caustic potash solution for some minutes with very little decomposition. The crystals give no coloration with diazobenzenesulphonic acid and acetic acid and there is no change on the addition of hydrochloric acid. It dissolves with difficulty in chloroform and, on warming, a very sparingly soluble substance separates which has not been analysed but appears to be an additive compound (compare p. 975).

The *dimethochloride* (*A*) was obtained by adding silver chloride to a hot aqueous solution of the dimethiodide (A) and evaporating the filtrate; a syrup remained which became a transparent resin when kept over sulphuric acid in a vacuum. An aqueous solution gives no coloration with a drop of dilute hydrochloric acid and ferric chloride. An aqueous solution does not cloud when boiled with a large excess of caustic potash, and even heating with methyl-alcoholic potash (25%) on the steam-bath only very gradually brings about decomposition. When, however, the temperature is raised to 120°, a rapid change takes place with formation of methoxymethyltetrahydrostrychnidine (B), m. p. 178—180° (p. 985).

The *dimethobromide* (*A*) does not crystallise when sodium bromide is added to a moderately concentrated solution of the dimethochloride, but 50% caustic potash solution gives a cloudy liquid from which a mass of needles soon separates. This dimethobromide is remarkably readily soluble in cold water, but separates from methyl alcohol as a voluminous mass of needles which, dried at 100°, decompose with effervescence at about 345° (Found: C, 53·4; H, 6·5. $C_{21}H_{26}ON_2$,2MeBr requires C, 52·9; H, 6·3%).

The Action of Methyl Iodide on Dihydrostrychnidine (*B*).—It is explained in the introduction that this direct action leads to the formation mainly of the dimethiodide (A), the isomeride (B) being produced in relatively very small quantity. When the base (B) (5 g.), dissolved in a little methyl alcohol, was mixed with methyl iodide (8 c.c.) in the cold, the solution became warm and crystallisation began at once owing to the separation of the monomethiodide (a), m. p. 340—345° (decomp.) (Found: C, 56·8; H, 6·2%. Compare p. 975). When the mixture was heated under reflux on the steam-bath a second reaction occurred, and boiling continued for a considerable time after removal from the bath. Finally the whole was heated for 2 hours, the methyl iodide and some of the methyl alcohol were distilled off, and the product was left for 24 hours in the ice-chest; the crystalline mass was then collected and washed with methyl alcohol. Analysis and the subsequent examination showed that this crude product consists mainly of the dimethiodides (A) and (B), but contains varying quantities of the monomethiodide (a). The product (60 g.) from several experiments was boiled with methyl alcohol, in which it is sparingly soluble, until completely dissolved and the solution was cooled rapidly in running water; a sandy precipitate (40 g.) of the almost pure dimethiodide separated, there was then a distinct pause in the crystallisation, and, after filtration and vigorous shaking, glistening needles (10 g.), which had m. p. 345° (efferv.) and consisted of the almost pure monomethiodide (a), were deposited. These crystals became opaque at 100° (Found : C, 57·2; H, 6·6. Calc. for $C_{21}H_{26}ON_2$,MeI : C, 56·9; H, 6·2%). The mother-liquor contained more of the above substances as well as all the dimethiodide (B) : the separation of these constituents is described on p. 979.

The difficulty of preparing the large amounts of the dimethiodide (A) required for this research was bound up with the difficulty, already commented on (p. 972), of obtaining the requisite quantities of the crystalline dihydrostrychnidine (B). This was, however, got over when it was found that, owing to the facility with which it crystallises, it is possible to obtain the pure dimethiodide in quantity from specimens of the crude base which no longer crystallise. The mother-liquors from the crystalline base were evaporated and the residue was distilled three times; almost the whole then passed over at 220—230° under a pressure of 0·5 mm. The pale yellow syrupy distillate, which set to a resin on cooling and yielded, when dissolved in ether or extracted with petroleum, only a comparatively small quantity of crystalline dihydrostrychnidine (B), nevertheless gave analytical numbers agreeing almost exactly with those required for the formula $C_{21}H_{26}ON_2$ of this base (Found : C, 78·1; H, 8·2. Calc. : C, 78·2; H, 8·1%). As, in spite of careful search, no evidence of the presence of an isomeride could be obtained, it is probable that some slight impurity was present which prevented the separation of the crystalline base : it is known that very small quantities of impurity have this effect. The resin (50 g.), dissolved in as little boiling methyl alcohol as possible, was gradually mixed with methyl iodide (70 c.c.); a good deal of heat was then generated and crystallisation began at once. As soon as the reaction had subsided, the whole was heated under reflux for 4 hours on the steam-bath, the excess of methyl iodide distilled off, a little boiling methyl alcohol added, and the whole left over-night in the ice-chest; the mass of crystals was then collected and washed with methyl alcohol until colourless. After twice crystallising from methyl alcohol, the product (75 g. instead of 110 g.) was the pure dimethiodide (A), m. p. 340—345° (decomp.). Very little more could be got by concentrating the dark brown mother-liquors, the working up of which into methoxymethyltetrahydrostrychnidine (B) is described on p. 986.

Preparation of Dihydrostrychnidine (*B*) *Methiodides* (*a*) *and* (*b*).—Since it was not possible to obtain the large quantities of these substances required for this research from the corresponding methosulphates (compare p. 975), experiments were made in the hope of obtaining them by removing one molecule of methyl iodide from the dimethiodides (A) and (B). In the first experiment, the dimethiodide (A) (5 g.) was digested with mesitylene (50 c.c.) for

½ hour in the manner described in the corresponding conversion of methoxymethyltetrahydrostrychnidine (A) dimethiodide (B) into the monomethiodide (b) (J., 1927, 1621). The substance did not dissolve, and separated from methyl alcohol in colourless needles which became opaque on the steam-bath and decomposed at 340—345°. The analysis (C, 45·8; H, 5·5%) showed that elimination of methyl iodide had not occurred.

After further experiments of a similar kind, it was discovered that the desired result could be easily obtained by treating the crude dimethiodides, obtained as described on p. 977, with methyl-alcoholic potash under the following conditions: The finely powdered mixture of dimethiodides (50 g.) is ground to a fine paste with methyl-alcoholic potash (250 c.c. of 25%), heated just to boiling on the steam-bath, removed, and, after the somewhat vigorous action has subsided, heated with frequent shaking for 3 hours. The substance does not dissolve but changes in appearance, the original pasty liquid depositing a crystalline crust. After remaining for 24 hours in the ice-chest, the solid is collected and washed with methyl alcohol; it then consists essentially of the methiodide (a) containing some unchanged dimethiodide (A). A second treatment with methyl-alcoholic potash does not entirely remove this dimethiodide, but this is easily got rid of by extraction with cold water and may be recovered from the filtrate by distilling off the water under reduced pressure and crystallising the residue from methyl alcohol. The methiodide (a), sparingly soluble in water, is then crystallised from methyl alcohol, separating in colourless needles, m. p. 345° (decomp.), and is identical with the substance already described as resulting from the decomposition of the methosulphate (a) with sodium iodide (p. 975) (Found: C, 57·0; H, 6·3. Calc. for $C_{21}H_{26}ON_2$,MeI: C, 56·9; H, 6·2%).

Dihydrostrychnidine (*B*) *dimethiodide* (*B*) was present only in small quantity in the methyl-alcoholic mother-liquors from which the dimethiodide (A) and the monomethiodide (a) had separated (see p. 977), and its isolation proved to be difficult. The mother-liquor, on concentration, deposited further quantities of the above substances and then a rather sticky mass which, after long contact with porous porcelain and repeated fractional crystallisation from methyl alcohol, ultimately yielded nodules of needles of the dimethiodide (B). This decomposes at 260—265° (efferv.), is very soluble in cold water, and is more soluble in methyl alcohol than the modification (A), from which it also differs in appearance and most other properties (Found: C, 45·7; H, 5·5. $C_{21}H_{26}ON_2$,2MeI requires C, 45·5; H, 5·3%).

Dihydrostrychnidine (*B*) *methiodide* (*b*) may be prepared by digesting the dimethiodide (B) with methyl-alcoholic potash under conditions similar to those described above in the case of the dimethiodide (A), and some was also obtained from the mother-liquors of the methiodide (a) (compare above). It separates from methyl alcohol, in which it is far more soluble than the isomeride (a), as a soft mass of needles which do not become opaque at 100°, shrink at about 250° and gradually melt as the temperature rises (Found : C, 56·2; H, 6·5. $C_{21}H_{26}ON_2$,MeI requires C, 56·9; H, 6·2%). In contrast with the methiodide (a), the substance (b) does not appear to combine with chloroform. It dissolves with difficulty in much chloroform in the cold, much more readily on boiling, and there is no sign of the separation of a sparingly soluble additive compound.

Dihydrostrychnidine (*B*) *methochloride* (*b*) is, in contrast with (a) (p. 976), a well-characterised substance. It was obtained in the usual way by heating the methiodide (b) with water and silver chloride on the steam-bath and evaporating the filtrate to a small bulk; on cooling, balls of needles gradually separated. These were recrystallised from water, from which the substance separated in four-sided, pearly plates containing 2 molecules of water (Found for the air-dried substance : loss at 100°, 9·45. $C_{21}H_{26}ON_2$,MeCl,$2H_2O$ requires $2H_2O$, 8·8%. Found for the dry substance : C, 70·6; H, 8·0. $C_{21}H_{26}ON_2$,MeCl requires C, 70·8; H, 7·7%). This methochloride (b) is relatively sparingly soluble in cold water. The intensely bitter solution gives, with a drop of dilute hydrochloric acid and ferric chloride, a yellow coloration soon becoming pink; on boiling, a crimson colour develops; addition of excess of hydrochloric acid destroys the colour. A solution in dilute sulphuric acid gives, with dichromate, a yellow colour slowly changing to yellowish-crimson, and to crimson on boiling. When this dimethochloride (b) was heated with methyl-alcoholic potash at 120—130° under the conditions given on p. 985, a good yield of methoxymethyltetrahydrostrychnidine (B) (m. p. 178°) was obtained.

The *methobromide* (*b*) was obtained by adding sodium bromide to a hot concentrated aqueous solution of the methochloride and leaving the mixture in the ice-chest for several days. It separated in colourless glistening plates, which became nearly black at 330° and effervesced at 340—345° (Found in substance dried at 110° : C, 63·0; H, 7·3. $C_{21}H_{26}ON_2$,MeBr requires C, 63·3; H, 7·0%).

Dihydrostrychnidine (*B*) *Benzylchloride*.—The base (6 g.), dissolved in toluene (30 c.c.), was mixed with a large excess of benzyl chloride (15 c.c.) and heated with a free flame; a precipitate soon began to separate and there was considerable rise of temperature. After boiling for a few minutes, and cooling, the product was mixed with ether, and the colourless crystalline precipitate was collected, washed with ether, dissolved in warm methyl alcohol, and mixed with much ether; on rubbing, the clear solution deposited a mass of thin plates which were washed with ether and dried at 100° (Found : C, 74·3; H, 7·8; Cl, 7·8. $C_{21}H_{26}ON_2,C_7H_7Cl$ requires C, 74·9; H, 7·5; Cl, 7·8%).

Dihydrostrychnidine (*B*) *benzylchloride* is very soluble in cold water or methyl alcohol but almost insoluble in ether. It melts at about 325° with effervescence and formation of a yellow gum, which is insoluble in water but very soluble in cold dilute acids and appears in part to consist of dihydrostrychnidine (B). A solution in water gives no precipitate with ammonia or dilute aqueous potassium hydroxide.

Oxidation of Dihydrostrychnidine (*B*). *Formation of Dihydrostrychnine* (*B*).—The crystalline base (5 g.), dissolved in acetone (400 c.c.) and water (3 c.c.), was gradually mixed with finely powdered potassium permanganate with frequent shaking, care being taken that the temperature did not exceed 15°. The permanganate was added in quantities of 2 g. each day and, after 13 g. had been added, the whole was heated to boiling and filtered and the manganese precipitate thoroughly extracted with boiling acetone. The extract was dried over potassium carbonate, concentrated to a small bulk, and left in the ice-chest, a crystalline crust gradually forming. This was dissolved in much boiling ether, in which the crystals were rather sparingly soluble, and the solution was concentrated and left in the ice-chest; the new substance then separated as a brilliant crust of nodules of small prisms. Two different specimens were analysed : (i) crystallised from acetone and (ii) from ether [Found : (i) C, 74·9; H, 7·0; N, 8·3. (ii) C, 74·8; H, 7·1. $C_{21}H_{24}O_2N_2$ requires C, 75·0; H, 7·1; N, 8·3%]. *Dihydrostrychnine* (*B*), m. p. about 196°, is somewhat soluble in water, yielding a bitter solution which on concentration deposits the substance in microscopic prisms. It dissolves readily in methyl alcohol or acetone and separates from the latter, often as twin crystals, in glistening prisms. The solution in dilute sulphuric acid (60%) gives with dichromate an intense bluish-purple coloration changing to green and then to brown and, on warming, to brownish-crimson, a reaction reminiscent of the behaviour of strychnine itself. Most specimens of this substance give a pale pink coloration when ferric chloride is added to their solutions in very dilute hydrochloric acid, but when the base is perfectly pure this reaction is negative, even on heating. Similarly the pure base does not couple with diazobenzenesulphonic acid. It is very readily soluble in dilute mineral acids and even in dilute acetic acid and is precipitated by ammonia as a gum which, on warming and rubbing, crystallises. The hydrochloride is rather sparingly soluble and separates well as a voluminous mass of minute needles. When a boiling solution of this salt is mixed with a little sulphurous acid and excess of sodium iodide added, the *hydriodide* separates as a mass of glistening plates. It is sparingly soluble in acetone or methyl alcohol or in boiling water and separates from the last in glistening feathery groups which become opaque at 100°. It melts at 350—355° to a dark brown syrup (Found : C, 53·9 ; H, 5·5. $C_{21}H_{24}O_2N_2$,HI requires C, 54·3 ; H, 5·4%).

The methiodide. A solution of the base in boiling acetone gave, with methyl iodide, an immediate voluminous precipitate; this separated from methyl alcohol, in which it was sparingly soluble, in pale yellow feathery needles which changed partly to pale yellow prisms and, on recrystallisation, became needles again. The crystals darkened gradually above 220° and melted at about 365° (decomp.) (Found : C, 55·6 ; H, 5·8. $C_{21}H_{24}O_2N_2$,MeI requires C, 55·3 ; H, 5·6%). This methiodide is sparingly soluble in cold water and rather readily on boiling and separates as a soft mass of minute needles.

The methochloride. When the methiodide was digested with water and silver chloride, and the filtrate evaporated, the *methochloride* was obtained as a crystalline mass, separating from methyl alcohol in soft needles which became opaque on standing in the air (Found : C, 67·8 ; H, 7·2. $C_{21}H_{24}O_2N_2$,MeCl requires C, 68·3 ; H, 7·0%). This methochloride, m. p. 370—375° (efferv.), is readily soluble in water ; the solution gives no coloration with ferric chloride and a little hydrochloric acid in the cold. A solution in dilute sulphuric acid (60%) gives with dichromate a blue coloration rapidly changing to purple and then to brown.

The *methobromide* separated as a mass of needles when sodium bromide was added to a hot concentrated solution of the methochloride. It is readily soluble in warm water and separates from methyl alcohol, in which it is sparingly soluble, in needles, m. p. about 375° (decomp.) (Found : C, 61·6 ; H, 6·3. $C_{21}H_{24}O_2N_2$,MeBr requires C, 61·3 ; H, 6·3%).

The *benzylidene* derivative was readily formed when a solution of the base (1 g.) in a little boiling alcohol was mixed with benzaldehyde (2 c.c.) and a few drops of concentrated sodium ethoxide and left for 2 days. On vigorous rubbing, crystallisation set in and, after being washed with water, the benzylidene derivative was recrystallised from methyl alcohol, in which it was very sparingly soluble, separating in glistening, pale lemon-yellow flitters, m. p. 270—275° (Found : C, 79·3 ; H, 6·5 ; N, 6·6. $C_{28}H_{28}O_2N_2$ requires C, 79·3 ; H, 6·6 ; N, 6·6%).

When the benzylidene derivative is moistened with hydrochloric acid the hydrochloride separates as a white powder, which is sparingly soluble in cold water but dissolves on boiling; the solution on cooling sets to a jelly. Ferric chloride added to an aqueous solution gives no coloration in the cold but a deep yellow on boiling. The sulphate is more soluble and the solution in 60% sulphuric acid gives, with dichromate, an intense blue colour changing to purple and then to brown. With 10% sulphuric acid this colour reaction is not shown.

Dihydrostrychnine (B) does not appear to yield an oxime, since on adding excess of hydroxylamine hydrochloride and some potassium carbonate to a solution in methyl alcohol and leaving the mixture for 24 hours, the base was recovered on dilution with water and extraction with ether and had m. p. 189—191° (Found: N, 8·0%).

The manganese precipitate (p. 981), from which the dihydrostrychnine (B) had been extracted with acetone, was extracted with boiling water and the brown extract was nearly neutralised with hydrochloric acid, concentrated by distillation under reduced pressure, and acidified; a considerable precipitate of a chocolate-coloured acid then separated which was washed with water and dried in a desiccator. The well-dried acid was extracted for some days in a Soxhlet apparatus with dry ether; from the extract, a small quantity of a pale yellow microcrystalline *acid* separated; this was soluble in boiling water, from which it crystallised rather indefinitely on cooling (Found: C, 60·2; H, 5·9; N, 7·0. $C_{21}H_{24}O_7N_2$ requires C, 60·6; H, 5·8; N, 6·7%). This acid froths and decomposes at about 205°, is readily soluble in dilute ammonia solution and in dilute sulphuric acid. A solution in 60% sulphuric acid gives with dichromate a fine bluish-purple coloration changing to purple and then to brown. Unfortunately, the amount of this acid available was so small that further investigation was impossible.

Hydrolysis of Dihydrostrychnine (*B*).—This substance was boiled with dilute methyl-alcoholic potassium hydroxide for several minutes without any apparent change and was precipitated on the addition of water, but when a solution of 1 g. in a little alcohol was heated in a sealed tube with sodium ethoxide (0·5 g. Na) in a boiling water-bath for 5 hours, complete hydrolysis occurred. The colourless solution was mixed with water and left over sulphuric acid in a vacuum; it then dried to a gum which was very readily and completely soluble in a little water. When this solution was acidified with hydrochloric acid and left over sulphuric acid, groups of feathery crystals containing chlorine gradually separated; these were recrystallised from dilute hydrochloric acid and dried first over sulphuric acid in a vacuum and then for a short time at 100° (Found:

C, 64·2; H, 6·7. $C_{21}H_{26}O_3N_2$,HCl requires C, 64·5; H, 6·9%). This *hydrochloride* of *dihydrostrychnic acid* (*B*) dissolves in concentrated nitric acid to an orange solution; on warming, a pale yellow crystalline substance separates which is readily soluble in hot water. The hydrochloride is very readily soluble in hot water: when ammonia is added to the cold solution there is no precipitate, but when the solution is boiled in a test-tube so that most of the ammonia escapes, a crystalline precipitate of the acid separates, the ammonium salt evidently being dissociated. The precipitate is washed with a little water and dried at 100° (Found: C, 70·7; H, 7·4. $C_{21}H_{26}O_3N_2$ requires C, 71·1; H, 7·3%). *Dihydrostrychnic acid* (*B*) melts at about 285° with effervescence and formation of dihydrostrychnine (B) (see below). A solution in dilute sulphuric acid (50%) gives a reddish-brown colour with dichromate, and addition of ferric chloride to a solution in very dilute hydrochloric acid gives no coloration in the cold but, on boiling, a deep brown-crimson colour develops. *Action of heat.* When a small quantity of the acid was cautiously heated in a test-tube, it effervesced and water was eliminated. The residue was ground and extracted with much boiling ether, and the ethereal solution concentrated to a small bulk and left; a pale yellow substance then separated in minute prisms, m. p. 203°. This substance, which gave an intense blue colour, changing to purple, when its solution in dilute sulphuric acid (50%) was mixed with dichromate, proved to be dihydrostrychnine (B), since a mixture with this substance melted at 201—202°. This method of formation is the only way, so far observed, of raising the melting point of this substance from 196° to 203°.

Action of Perhydrol on Dihydrostrychnine (*B*).—The substance (0·5 g.), dissolved in methyl alcohol (15 c.c.), was mixed with methyl-alcoholic potassium hydroxide (15 c.c.), and perhydrol (1 c.c.) added. After 24 hours, the solution was concentrated to a small bulk, made acid to Congo-red with dilute hydrochloric acid, and left in the ice-chest. The clear solution gradually deposited a colourless crystalline substance which was washed with water and dried at 100° (Found: C, 62·8; H, 6·7; N, 6·7. $C_{21}H_{26}O_6N_2$ requires C, 62·7; H, 6·5; N, 7·0%).

Dioxydihydrostrychnic acid becomes pale brown at 250°, dark brown at 275°, and decomposes at 300—305° to a black mass. It is rather sparingly soluble in cold water but dissolves readily on boiling and separates as a crust of glistening pearly plates. A solution in dilute sulphuric acid (50%) gives with dichromate an orange coloration, deepening on warming; a solution in dilute hydrochloric acid gives no coloration with ferric chloride.

Oxidation of Dihydrostrychnidine (*A*) (Part VI, J., 1927, 2399).

Formation of Oxydihydrostrychnidine (*A*).—Dihydrostrychnidine (A) (8 g.), dissolved in hot acetone (500 c.c.) and water (5 c.c.), was heated to boiling, and finely powdered permanganate added in small quantities at a time with frequent shaking. When 40 g. had been reduced, the liquid was filtered hot and the manganese precipitate extracted twice with boiling acetone. After distillation of some of the acetone on the steam-bath, the concentrated solution began to deposit crystals. When cold these (1·5 g.) were collected, washed with acetone, and crystallised from much boiling alcohol, from which the substance separated as a satiny mass of needles. More of the same substance was obtained by evaporating the acetone mother-liquors to dryness and rubbing the residual gum with methyl alcohol (Found: C, 74·8; H, 7·2; N, 8·4. $C_{21}H_{24}O_2N_2$ requires C, 75·0; H, 7·1; N, 8·3%). *Oxydihydrostrychnidine* (*A*), isomeric with dihydrostrychnine (B) (m. p. 196°; p. 981), melts at about 345° to a black mass and is very sparingly soluble in most of the usual solvents. It dissolves in concentrated sulphuric acid without colour. A solution in 60% sulphuric acid gives with dichromate an immediate intense crimson colour, whereas the isomeride (B) gives a deep blue colour under the same conditions. It may be noted, however, that the final mother-liquors from the purification of the substance (A) contain a substance which also gives a deep blue colour with sulphuric acid and dichromate. Oxydihydrostrychnidine (A) is a feeble base, dissolving with difficulty in dilute hydrochloric acid. It is sparingly soluble in, and does not appear to combine with, methyl iodide, because when heated with a large excess of methyl iodide in a sealed tube in the water-bath for 2 hours it does not dissolve and the recovered substance, after being washed with methyl alcohol, melts at 336—340° and does not contain iodine. When an alcoholic solution of the base is heated in a sealed tube with benzaldehyde and a little sodium ethoxide there is no evidence of the formation of a benzylidene derivative.

In view of the feebly basic character of this substance and its non-identity with dihydrostrychnine (A), it is feasible to regard it as an *epi*dihydrostrychnine derived from dihydrostrychnidine (A) by the transformation of the group $>N(b)\cdot CH_2-$ into $>N(b)\cdot CO-$ (compare J., 1928, 3087, 3090).

Methoxymethyltetrahydrostrychnidine (*B*), $C_{23}H_{32}O_2N_2$, *Methyl-ψ-strychnidine* (*B*), $C_{22}H_{26}ON_2$, *and Dihydrostrychnidine* (*C*), $C_{21}H_{26}ON_2$.—These substances are obtained when dihydrostrychnidine (B) dimethochlorides or monomethochlorides are decomposed by methyl-alcoholic potash. (i) Crude dihydrostrychnidine dimethiodide (50 g.) (p. 977) is converted into the dimethochloride by digestion with water and silver chloride, the solution evaporated to dryness, and the syrup dissolved in boiling methyl alcohol (100 c.c.). Methyl-alcoholic potash (300 c.c. of 25%) is added, and the whole heated on the steam-bath in an open flask for ½ hour. The flask is then transferred to a sand-bath, a thermometer inserted, and the heating continued until the temperature reaches 120°; there is then much frothing and, on removal of the flame, the temperature remains at this point for several minutes. Finally the whole is heated at 140—145° for about 15 minutes until effervescence has ceased. (ii) Dihydrostrychnidine (B) monomethochloride, obtained from the crude monomethiodide (p. 979) (50 g.) by digestion with silver chloride and evaporation to dryness, is digested with methyl-alcoholic potash (300 c.c.) exactly as described above. This process, although rather more tedious from start to finish, appears to proceed more smoothly and to give a purer product in better yield than (i). In either case, the cold product is mixed with crushed ice, water added, and the whole well shaken until the separation of the crude grey mass is complete. This is well washed, dried on porous porcelain, and dissolved in the minimum of boiling methyl alcohol, in which it is rather sparingly soluble, and filtered. The first crop, which separates rapidly on cooling and shaking, is collected and washed with methyl alcohol; the colourless crystalline mass is then usually almost pure *methoxymethyltetrahydrostrychnidine* (*B*), m. p. 177—179°. When the filtrate is concentrated to about a quarter of its volume, a small second crop of the same substance separates, m. p. 165—172°. The mother-liquor is evaporated to dryness, and the residue dissolved in a little boiling acetone; on standing in the ice-chest, a further crop of nearly pure substance, m. p. 172—177°, separates. Finally, the filtrate is boiled for some hours with norite, systematically concentrated, and left in the ice-chest with frequent rubbing until no further separation of a crystalline mass, m. p. 110—130°, consisting of crude *dihydrostrychnidine* (*C*) (p. 995) occurs. The treatment of the final mother-liquors is described on p. 994.

It is very important in carrying out the decompositions (i) and (ii) with methyl-alcoholic potash to be sure that the process is complete, otherwise serious loss may occur. In successful operations the yields of methoxymethyltetrahydrostrychnidine (B) and crude dihydrostrychnidine (C) are in (i) 22—25 g. and 2·3 g. and in (ii) 27 g. and 3—4 g., respectively, or roughly 70—75% of the theoretical. The final mother-liquors are added to the fraction, b. p. 215—220°/1 mm., mentioned below.

Considerable quantities of methoxymethyltetrahydrostrychnidine (B) were obtained from the brown mother-liquors from which dihydrostrychnidine dimethiodide had separated (p. 978). Water was added, the methyl alcohol removed on the steam-bath, and the hot liquid filtered from much tar and heated with excess of silver chloride. The filtrate, evaporated to a syrup, was mixed with a large excess of methyl-alcoholic potash and heated at 120—130° exactly as described above. The gum obtained on addition of water was dissolved in ether, the ethereal solution well washed, dried over potassium carbonate, and evaporated, and the dark brown syrup rapidly fractionated three times. The fraction, b. p. 215—225°/1 mm., when dissolved in methyl alcohol and rubbed, gradually deposited a considerable quantity of crude methoxymethyltetrahydrostrychnidine. The mother-liquor, when evaporated and distilled again, gave a pale yellow syrup, b. p. 220—225°/1 mm., which, dissolved in a little acetone and left for some weeks in the ice-chest, deposited a material (5 g.) which softened at 155° and was not completely melted at 190°. The separation of this into methoxymethyltetrahydrostrychnidine and *methylstrychnidine* (*B*), m. p. 223—225°, is described on p. 994.

Methoxymethyltetrahydrostrychnidine (*B*), like its isomeride (A), m. p. 220° (J., 1927, 1617), is remarkably sparingly soluble in ether or cold methyl alcohol and crystallises from the latter with great facility in colourless glistening needles, m. p. 179—180° (Found: C, 75·3, 75·0; H, 8·7, 8·6; N, 7·6; MeO, 8·0; Me as >NMe, 4·5; Me as combined Me, 8·4. $C_{23}H_{32}O_2N_2$ requires C, 75·0; H, 8·7; N, 7·6; MeO, 8·2; Me as >NMe, 4·1; 2Me as combined Me, 8·2%). It is very sparingly soluble in cold acetone, but dissolves moderately readily on boiling and separates beautifully in glistening triangular prisms; it also separates well from petroleum in glistening plates. When heated rapidly in small quantities in a test-tube, it distils largely unchanged; the distillate separates from methyl alcohol in plates, m. p. 178°. A moist acetone solution decolorises permanganate only slowly in the cold, but more readily on warming (p. 991). A solution in dilute sulphuric acid, on addition of a drop of dichromate, gives in the cold a crimson colour, which becomes very intense on warming. A solution in very dilute hydrochloric acid gives, with ferric chloride, no colour at first; a pink colour then gradually develops and becomes crimson on warming. The base dissolves to a bright red solution in concentrated nitric acid.

When the base was boiled with dilute sulphuric acid (10% by vol.) for 2 hours there was no sign of elimination of methyl alcohol and on addition of ammonia a thick curdy precipitate was produced which soon hardened; this separated from methyl alcohol in plates, m. p. 178°, and proved to be the unchanged base, practically the whole being recovered. In order to determine whether the substance was capable of electrolytic reduction, 1 g., dissolved in dilute sulphuric acid (100 c.c. of 10% by vol.), was placed in the cathode chamber of the apparatus described in Part II of this research (J., 1924, **125**, 1798) and exposed for 14 hours to a current of 5 amps. at 22°. No reduction occurred, since the filtered solution gave, with ammonia, a solid base, m. p. 170—175°, which, after crystallisation from methyl alcohol, had m. p. 178—180°, almost the whole quantity being recovered.

The *hydriodide* was obtained by dissolving the base in a slight excess of dilute sulphuric acid and adding a few drops of concentrated sulphurous acid and then excess of sodium iodide. When the clear solution was warmed on the steam-bath, the crystalline canary-yellow hydriodide largely separated; after being well washed and dried on the steam-bath, this became colourless at 155—160°, softened and decomposed at 175—180°, solidified immediately, effervesced again at 235°, became again solid, and finally decomposed at about 325° to a brown froth (Found in substance dried at 105° : C, 56·0; H, 6·7. $C_{23}H_{32}O_2N_2,HI$ requires C, 55·7; H, 6·6%). It is rather readily soluble in boiling water to a colourless solution and separates, on cooling slowly, in well-developed prisms. The mother-liquor from the canary precipitate gave with ammonia a considerable precipitate of the base.

The hydriodide was heated gradually in a test-tube in a sulphuric acid bath; methyl alcohol was eliminated at 250—260° and after about 10 minutes' heating at 260° decomposition was complete. The brittle grey mass was boiled with water; the filtered solution gradually deposited long, pale pink needles, but sometimes a jelly separated first which soon passed into the needles. The substance was recrystallised from water and dried at 100° (Found : C, 57·5; H, 6·2; N, 5·9. Calc. for $C_{22}H_{29}ON_2I$: C, 56·9; H, 6·3; N, 6·0%). That this substance, which melted at about 345° (decomp.), was a methiodide was shown by the fact that its aqueous solution gave no precipitate with ammonia or caustic potash even on warming, and that it was dihydrostrychnidine (B) methiodide (a) (p. 975) was demonstrated in the following way. The substance yielded the chloroform additive derivative characteristic of this methiodide, and when the methiodide was converted into the methochloride and this decomposed by heating in a test-tube, a yellowish-brown liquid remained which, distilled under 1 mm., dissolved in a little ether, and left in the ice-chest, gradually deposited crystals, m. p. 146—148° (Found : C, 78·0; H, 8·1; N, 8·4. Calc. for $C_{21}H_{26}ON_2$: C, 78·2; H, 8·1; N, 8·7%). That this substance was dihydrostrychnidine (B) was confirmed by the method of mixed melting point.

The same interesting change from methoxymethyltetrahydrostrychnidine (B) to the methiodide of dihydrostrychnidine (B) takes place much more readily and completely when the base (1 g.) is boiled with hydriodic acid (5 c.c.; *d* 1·94) and a little amorphous phosphorus for 2 hours. The solution is diluted with water and filtered, and addition of excess of caustic potash then precipitates a gelatinous mass which separates from boiling water in needles, m. p. 345° (decomp.), and consists of the methiodide (a) of dihydrostrychnidine (B), the yield being almost quantitative.

The methiodide. Methoxymethyltetrahydrostrychnidine (B) (2 g.) is sealed up with methyl iodide (5 c.c.): there is little action in the cold but, on heating in the water-bath, a pale solution is formed which gradually becomes brown owing to the liberation of traces of iodine. After 2 hours there may be no separation, but if a crystal nucleus happens to be formed the whole quickly becomes a mass of crystals. If this is not the case, the methyl iodide is distilled off and the syrup is dissolved in a little hot methyl alcohol and well rubbed; crystallisation then soon sets in. The crystals are collected, washed with methyl alcohol, in which the *methiodide* is sparingly soluble, and dissolved in this medium, from which colourless, glistening, irregular, flat prisms separate; these become chalky at 110° and effervesce at 235—238° to a colourless liquid which crystallises at a higher temperature (Found in material dried at 110—115°: C, 56·5; H, 6·9. $C_{23}H_{32}O_2N_2$,MeI requires C, 56·5; H, 6·9%). This substance is sparingly soluble in cold but readily soluble in hot water, forming a supersaturated solution from which the methiodide separates in long striated prisms on the introduction of a crystal. It dissolves readily in cold chloroform and on leaving or warming there is no separation of an additive derivative.

Action of heat. The methiodide (3·22 g.) lost 0·91 g. of methyl iodide on heating at 250°, or 28·2% (calc. for $C_{23}H_{32}O_2N_2$,MeI losing MeI, 27·8%). The slight sublimate which formed melted at 178° and the residue separated from acetone in prisms, m. p. 178—180°, of pure methoxymethyltetrahydrostrychnidine (B).

The *methochloride*, obtained by digesting the methiodide with water and silver chloride for 2 hours, evaporating the solution to a small bulk, and placing it over sulphuric acid in a vacuum desiccator, separated in soft pearly crusts, which were left on porous porcelain and dried at 100° (Found: C, 68·7; H, 8·5. $C_{23}H_{32}O_2N_2$,MeCl requires C, 68·8; H, 8·4%).

This methochloride begins to decompose at about 150° and effervesces vigorously at 170°; the residue crystallises and consists of methoxymethyltetrahydrostrychnidine (B). It is very soluble in water and the addition of a drop of hydrochloric acid and then ferric chloride gives no coloration in the cold but, on warming, a deep crimson colour develops, fading to brown and then to yellow. A solution in dilute sulphuric acid gives, with dichromate, a yellow colour changing to pink and then to deep crimson. When caustic potash (50%) is added to an aqueous solution of the methochloride the whole sets to a crystalline mass; on warming on the steam-bath, a pale brown syrup floats, crystallises on cooling, and consists of the unchanged methochloride.

The dimethosulphate. The base (7 g.), dissolved in dry benzene (50 c.c.), was mixed with freshly distilled methyl sulphate (20 c.c.) and heated under reflux on the steam-bath; after about 40 minutes, a gum commenced to separate which gradually changed to colourless prisms. After 2 hours, the deposit was collected, washed with benzene, dried on the steam-bath, and immediately analysed because the substance was deliquescent (Found: C, 52·0; H, 7·1. $C_{23}H_{32}O_2N_2,2Me_2SO_4$ requires C, 52·2; H, 7·1%). A solution in dilute sulphuric acid, on addition of dichromate, gives a yellow coloration which becomes deeper on warming. An aqueous solution mixed with ferric chloride and a little hydrochloric acid is coloured merely yellow but on boiling changes to bright green.

The dimethiodide. A solution of the dimethosulphate in hot water, when mixed with sodium iodide, gives a clear solution, which does not crystallise on rubbing and standing for 12 hours. The addition of caustic potash (50%) causes a caseous sticky precipitate to separate which soon hardens, and becomes crystalline on boiling with methyl alcohol. The substance crystallised from methyl alcohol, in which it was very sparingly soluble, in circular nodules which softened at about 205° and melted at 210°, becoming solid again. This dimethiodide is very readily soluble in cold water (Found in material dried at 110°: C, 45·9; H, 6·0. $C_{23}H_{32}O_2N_2,2MeI$ requires C, 46·0; H, 5·8%). The mother-liquors appeared to contain an isomeric dimethiodide, which was not isolated in a pure condition.

When the dimethiodide, m. p. 205—210°, was mixed with methyl-alcoholic potash (25%) and heated on the steam-bath, it did not dissolve but changed in appearance and the pasty liquid deposited a colourless crust. This was collected, washed with a little water, in which the substance was now sparingly soluble, and twice crystallised from methyl alcohol, separating as a soft mass of needles (Found in material dried at 100°: C, 56·2; H, 6·9. Calc. for $C_{23}H_{32}O_2N_2,MeI$: C, 56·5; H, 6·9%). Careful examination showed that this substance, m. p. 233—236° (efferv.), is identical with the methiodide obtained by the direct action of methyl iodide on methoxymethyltetrahydrostrychnidine (B) (see above).

Methoxymethyltetrahydrostrychnidine (B) dissolves in nearly boiling benzyl chloride apparently without combination, since the solution, when diluted with ether, deposits the unchanged base. The same is also true of the isomeride of m. p. 220° (J., 1927, 1617).

Methoxybenzyltetrahydrostrychnidine (*B*).—Dihydrostrychnidine (B) benzylchloride (p. 981) (12 g.) was mixed with methyl-alcoholic potassium hydroxide (200 c.c. of 25%) and gradually heated on a sand-bath until a thermometer placed in the melt registered 150°, the decomposition proceeding very smoothly and without discoloration. On addition of water to the cold mass, a colourless base separated in almost quantitative yield; it was well washed and dissolved in ether, in which it was very soluble. The ethereal solution, dried over potassium carbonate and concentrated, did not deposit crystals when kept in the ice-chest, as so readily happens in the case of methoxymethyltetrahydrostrychnidine (B) (p. 985). When, however, the ether was distilled off and the gum dissolved in methyl alcohol and rubbed, crystallisation rapidly set in and the colourless crystalline substance was now comparatively sparingly soluble in methyl alcohol and separated as a feathery mass of needles, m. p. 126—127° (Found: C, 78·9; H, 8·2; MeO, 6·7. $C_{29}H_{34}O_2N_2$ containing 1 MeO requires C, 78·7; H, 7·8; MeO, 7·0%). It is very soluble in methyl iodide: when the solution is boiled for a few minutes and the methyl iodide evaporated, a gum remains which on warming with water deposits the unchanged base, no combination having occurred under these conditions.

Formylmethoxytetrahydrostrychnidine (*B*) (p. 969).—This substance is obtained when methoxymethyltetrahydrostrychnidine (B), dissolved in moist acetone, is oxidised by permanganate. The base (11 g.), dissolved in acetone (650 c.c.) and water (10 c.c.), was mixed with very finely powdered permanganate (4 g.), the whole being well shaken from time to time and the temperature kept at 12°. After 24 hours, decolorisation was nearly complete and further quantities of the permanganate were gradually added until, when 14 g. had been added, decolorisation became extremely slow. Five such lots were combined and heated for some minutes on the steam-bath, the manganese precipitate was well washed with acetone, and the yellow filtrate and washings were concentrated to a small bulk and left in the ice-chest for several days; the solution then either became a pasty mass of crystals or deposited a hard crust. The crystals were collected, boiled with a little ether to remove a gummy impurity, and fractionally crystallised several times from methyl alcohol to remove the last traces of unchanged methoxymethyltetrahydrostrychnidine (B). The treatment of the large amount of the oxidation product contained in the acetone and methyl alcohol mother-liquors is described on p. 993. *Formylmethoxytetrahydrostrychnidine* (*B*) separates from methyl alcohol in brilliant, colourless, well-developed prisms, which rapidly become opaque when exposed to the air on a watch glass (Found : C, 72·0; H, 7·9; N, 7·3; MeO, 8·0; >NMe, none. $C_{23}H_{30}O_3N_2$ containing 1 MeO requires C, 72·3; H, 7·8; N, 7·3; MeO, 8·1%). It melts at 154°, is very soluble in hot, but much less so in cold, methyl alcohol, and is almost insoluble in boiling water. Dichromate added to a solution of the formyl derivative in dilute sulphuric acid gives a yellow coloration, quickly changing to pink and becoming crimson on warming. A solution in very dilute hydrochloric acid is coloured yellow by ferric chloride, but gradually an intense crimson colour develops which is not destroyed by excess of hydrochloric acid. The base dissolves in concentrated nitric acid to a deep yellow solution. In order to see whether it was capable of hydrolysis, the base was heated with alcoholic sodium ethoxide in a sealed tube in the water-bath for 2 hours. On addition of water the solution became turbid, and when the alcohol was evaporated a syrup separated which crystallised from methyl alcohol, had m. p. 152—154°, and consisted of the unchanged substance. On treatment with benzaldehyde and sodium methoxide in methyl-alcoholic solution, the base is not converted into a benzylidene derivative. The base is readily soluble in, but does not appear to combine with, methyl iodide, since in two experiments in which it was heated (i) with methyl iodide and methyl alcohol in a sealed tube for ½ hour, and (ii) for the same time with methyl iodide alone, practically the whole of it was recovered unchanged.

Action of Dilute Sulphuric Acid on Formylmethoxytetrahydrostrychnidine (*B*). *Formation of Methoxytetrahydrostrychnidine* (*B*).—This interesting decomposition was brought about (1) by boiling formylmethoxytetrahydrostrychnidine (B) with dilute sulphuric acid, and (2) by distilling this substance under reduced pressure (see below). (1) Formylmethoxytetrahydrostrychnidine (B) (1 g.), dissolved in dilute sulphuric acid (20 c.c. of 10% by vol.), was boiled under reflux for an hour, the cold product mixed with excess of potassium hydroxide, and the cloudy solution extracted twice with ether. The ethereal solution was dried over potassium carbonate, concentrated to a small bulk, cooled, and rubbed; crystallisation soon commenced and, after the mixture had been kept for some hours in the ice-chest, the solid was collected, washed with ether, and crystallised from this solvent. The colourless leaflets obtained became opaque on the steam-bath, melted at 150—152°, and were not identical with the original base (m. p. 154°), because a mixture of the two softened at 123° and was nearly melted at 130°

(Found : C, 74·3, 74·4; H, 8·5, 8·4; N,7·8; MeO, 8·0. $C_{22}H_{30}O_2N_2$ containing 1 MeO requires C, 74·6; H, 8·5; N, 7·9; MeO, 8·7%).

Methoxytetrahydrostrychnidine (*B*) dissolves in dilute sulphuric acid (60%) to a pale pink solution which becomes crimson on the addition of dichromate. A solution in very dilute hydrochloric acid gives no immediate coloration with ferric chloride, but a pink colour rapidly develops. A crystal of the base dissolves in concentrated nitric acid to a deep salmon solution. The *nitroso*-derivative separated, when sodium nitrite was added to a well-cooled solution of the base in very dilute hydrochloric acid, as a light yellow, crystalline mass; after addition of sodium acetate, the precipitate was collected, washed, and dried over sulphuric acid in a vacuum desiccator [Found : N, 10·7. $C_{22}H_{29}(NO)O_2N_2$ requires N, 11·0%].

In order to determine whether the methoxy-base was susceptible to electrolytic reduction a solution of 1 g. in 30 c.c. of 15% sulphuric acid was placed in the usual electrolytic reduction apparatus (J., 1924, **125**, 1798) and subjected to a current of 4 amps. for 20 hours. The colourless solution was diluted with water and made alkaline with potassium hydroxide, the milky liquid extracted with ether, and the extract dried over potassium carbonate, concentrated, and kept in the ice-chest; pearly plates separated which melted at 149—151° and consisted of the unchanged base (Found : C, 74·2; H, 8·4%).

Action of methyl iodide. The base dissolved readily in methyl iodide with some rise of temperature, crystals gradually separated, and increased in quantity on heating in a sealed tube in the water-bath. After 2 hours the excess of methyl iodide was distilled off and the crystals were dissolved in boiling methyl alcohol; they separated again as a pale yellow crust, which became opaque on the steam-bath and then melted at about 235° (efferv.), became solid again, and finally decomposed at 320—325° (Found : C, 55·2; H, 6·6. Calc. for $C_{23}H_{32}O_2N_2$,HI : C, 55·7; H, 6·6%). It is explained on p. 969 that this substance is the hydriodide of methoxymethyltetrahydrostrychnidine (B) (compare p. 988). It dissolves readily in warm water and on addition of ammonia colourless crystals immediately separate which crystallise from methyl alcohol in glistening flitters, m. p. 178—180° : there is no depression on admixture with an equal quantity of methoxymethyltetrahydrostrychnidine (B).

Distillation of Crude Formylmethoxytetrahydrostrychnidine (*B*).— Results at first difficult to understand were obtained when the acetone and methyl-alcoholic mother-liquors from a number of preparations of this substance, m. p. 154° (p. 991), were evaporated and distilled. After a good deal of frothing and decomposition, about two-thirds distilled at 225—265°/1 mm., leaving a dark tar, and after two more fractionations most of the substance passed over at 218—223°/1 mm. and set to a pale amber resin (22 g.) on cooling. This was readily soluble in ether : the concentrated cooled solution, from which a mass of crystals began to separate almost immediately, was kept for some days in the ice-chest; the mass then consisted of hard nodules covered with soft needles. By shaking with ether and rapid decantation, the needles were easily separated from the nodules; after recrystallisation they had m. p. 152—154° and consisted of formylmethoxytetrahydrostrychnidine (B) which had escaped decomposition during the distillation. This was proved by analysis (Found : C, 72·1; H, 7·8; N, 7·3. Calc. for $C_{23}H_{30}O_3N_2$: C, 72·3; H, 7·8; N, 7·3%) and by the method of mixed melting point. The nodules had m. p. 130—135° and after many recrystallisations from ether, in which the *substance* was readily soluble, the m. p. rose to 137—138° (Found : C, 74·2; H, 8·2; MeO, 8·2. $C_{22}H_{30}O_2N_2$ containing 1 MeO requires C, 74·6; H, 8·5; MeO, 8·7%). This analysis and the fact that the melting point could not be raised above 137° by recrystallisation seemed to indicate that the substance was a second modification of methoxytetrahydrostrychnidine (B) (m. p. 154°). This view received support from the fact that the nodules, on treatment with methyl iodide, also yielded the hydriodide of methoxymethyltetrahydrostrychnidine (B) (see above). When, however, the nodules were boiled with dilute sulphuric acid and the base was set free with alkali, the crystalline mass no longer separated in nodules but in needles, which melted at 150—152° and at the same temperature when mixed with methoxytetrahydrostrychnidine (B), m. p. 152°. It seems probable, therefore, that the nodules consist of this substance contaminated with small quantities of formylmethoxytetrahydrostrychnidine (B) (m. p. 154°) which resist separation by crystallisation but are converted into methoxytetrahydrostrychnidine (B) (m. p. 152°) by boiling with dilute sulphuric acid.

Methyl-ψ-strychnidine (B) and Dihydrostrychnidine (C).—The final acetone and methyl-alcoholic mother-liquors collected from the purification of a large number of preparations of methoxymethyltetrahydrostrychnidine (B), and from which crude dihydrostrychnidine (C) had separated (compare p. 986), were evaporated and the gummy residue was distilled under reduced pressure, a considerable fraction passing over at 220—225°/1 mm. This was dissolved in acetone and left in the ice-chest in contact with a crystal of methoxymethyltetrahydrostrychnidine (B) for 2 weeks; a thin crust of this base, m. p. 165—175°, then separated. The filtrate, when concentrated and left for some months, deposited about 6 g.

of a substance, m. p. 185—210°; after several crystallisations from alcohol, in which the substance was very sparingly soluble, *methyl-ψ-strychnidine* (*B*) was obtained in brilliant needles, m. p. 222—225° (Found: C, 78·9; H, 8·0; N, 8·3; Me as >NMe, 4·5. $C_{22}H_{26}ON_2$ containing one >NMe requires C, 79·0; H, 7·8; N, 8·4; Me as >NMe, 4·5%).

A solution of methyl-ψ-strychnidine (B) in dilute sulphuric acid (60%) gives an intense crimson colour with dichromate, and addition of ferric chloride to a solution in very dilute hydrochloric acid also produces an immediate crimson colour.

The dimethiodide. The base combines with methyl iodide with some evolution of heat. The mixture was heated in a sealed tube for a few minutes in the water-bath, the excess of methyl iodide distilled off, and the residue dissolved in methyl alcohol. The solution remained for a long time, but, on rubbing, the *methiodide* gradually separated as a crust of minute needles, which melted at about 275° and effervesced vigorously at 280—285°, leaving a pale yellow syrup which crystallised (Found: C, 46·7; H, 5·6. $C_{22}H_{26}ON_2,2MeI$ requires C, 46·6; H, 5·2%). The dimethiodide is somewhat sparingly soluble in cold water, moderately easily soluble in boiling water, and crystallises therefrom in minute needles. In attempting to prepare the dimethochloride, the following curious and characteristic behaviour was observed. When silver chloride was added to a boiling dilute aqueous solution of the methiodide, a pale pink colour developed which, on concentration of the filtered solution on the steam-bath, soon became purplish-pink and then deep purple; when kept over sulphuric acid in a vacuum, the whole dried up to a blackish-purple jelly.

Dihydrostrychnidine (*C*). The mother-liquors from the methyl-ψ-strychnidine (B) yielded, on concentration, a further small quantity of this substance. The filtrate, further concentrated and left in the ice-chest for some weeks, gradually deposited a considerable crop of crystals which proved to be a mixture of dihydrostrychnidine (C) with a little methoxymethyltetrahydrostrychnidine (B) (m. p. 180°). The solid was collected, dissolved together with the substance, m. p. 110—130°, obtained as described on p. 986, in a little acetone, and left in the ice-chest for several days; almost the whole of the substance, m. p. 180°, was deposited as a thin crust; when the mother-liquor was exposed to the air, groups of prisms separated. On repeated fractional crystallisation from ether this crude material yielded brilliant prisms of dihydrostrychnidine (C). These crystals were kindly examined by Dr. T. V. Barker, who reports that no diagrams are necessary, since the habit is simple and constant. The system is monoclinic, $a:b:c = 1{\cdot}037:1:?$; $\beta = 113°48'$, the forms developed being *c* (001) and *m* (110) of equal size and *a* (100) considerably smaller. Following are the results of measurement of two crystals :

	m(110).	*a*(100).	*c*(001).
ϕ	0° 0′	0° 0′	66° 12′
c	46° 31′	90° 0′	90° 0′

Optically an axis emerges through *m*, indicating the axial plane to be normal to *b* (010). The extinction on *m* is about 20° inclined to the vertical edge.

Owing to the fact that the melting point was never quite sharp, two specimens were analysed, namely, (*a*) the prisms from ether and (*b*) the needles from methyl alcohol (see below) [Found : (*a*) C, 78·3; H, 8·3; N, 8·4; Me as >NMe, none. (*b*) C, 78·1; H, 8·2. $C_{21}H_{26}ON_2$ free from >NMe requires C, 78·2; H, 8·1; N, 8·7%]. *Dihydrostrychnidine* (*C*) is readily soluble in ether or acetone but is much less soluble in methyl alcohol, from which it separates, when the solution is rapidly concentrated, in brilliant glistening needles, softening at about 128° and melting at 132—134°. It is a strong base, dissolving readily in dilute acetic acid. A solution in very dilute hydrochloric acid gives no immediate coloration with ferric chloride in the cold, but gradually a yellow colour develops which becomes brownish-pink and, on heating, pale brown. A solution in dilute sulphuric acid (60%) gives with dichromate approximately the same colour changes.

The base was heated with methyl iodide in the steam-bath for a few minutes; no crystallisation took place and on evaporation a gummy substance was obtained which consisted essentially of the monomethiodide. This was readily soluble in water and the solution gave no precipitate with caustic potash. When, however, a solution of the base (1 g.) in methyl iodide (2 c.c.) and methyl alcohol (2 c.c.) was heated in a sealed tube in the steam-bath no change was observed during 3—4 hours; a substance then began to separate in small prisms and the quantity increased slowly during 7 hours. After remaining over-night, the crystals were collected and dissolved in a little boiling water, from which the *dimethiodide* separated as a chalky crust of minute needles, m. p. 265—270°, effervescing to an amber resin (Found in material dried at 100° : C, 44·9; H, 5·2. $C_{21}H_{26}ON_2$,2MeI requires C, 45·5; H, 5·3%).

The dimethochloride, obtained by adding silver chloride to a hot aqueous solution of the dimethiodide and evaporating the filtered liquid, is a non-crystalline brittle mass very soluble in water. When this was heated with methyl-alcoholic potassium hydroxide until the temperature reached 150° (compare p. 985), decomposition took place smoothly and, on addition of ice-water to the cold mass, an ochreous precipitate was obtained which separated from methyl alcohol in glistening plates, m. p. 127—129°, and consisted of dihydrostrychnidine (C), methyl chloride having been eliminated during the process. Identity was established by a mixed m. p. determination, by analysis (Found : C, 78·2; H, 8·3%) and by conversion into the dimethiodide, which was identical with the derivative described above.

In an attempt to reduce dihydrostrychnidine (C) electrolytically, the base (1 g.), dissolved in dilute sulphuric acid (40 c.c. of 10% by volume), was subjected in the usual electrolytic reduction apparatus (J., 1927, 1600) to a current of 5 amps. for 6 hours. The chalky precipitate which separated on addition of caustic potash was collected, dried, and recrystallised from methyl alcohol, separating in needles, m. p. 127—132° (Found : C, 78·0; H, 8·2%). That the substance was unchanged was confirmed by a mixed m. p. determination.

It is conceivable that crude dihydrostrychnidine (B) already contains this isomeride (C) and that the bases are stereoisomerides owing their origin to the new asymmetric carbon atom in a group $^{-}$CHMe^{-} derived from $^{-}CH_2{\cdot}CH_2^{-}$ in strychnidine.

Benzylidenestrychnine.—As explained in the introduction (p. 966), we were led to attempt the condensation of strychnine and some of its simple derivatives with aromatic aldehydes as the result of a theoretical argument based on the properties of dihydrostrychnine (B). We find that strychnine and brucine and many of their derivatives, provided that these retain the group $>N(a){\cdot}CO^{-}$, condense readily with benzaldehyde, anisaldehyde, or piperonal and we are engaged in the detailed investigation of the new bases so obtained.

Owing to the readiness with which it is formed and its good crystallising power, benzylidenestrychnine is a highly characteristic derivative of the alkaloid, but it does not appear to have been previously described. Finely powdered strychnine (34 g.) was added to a boiling mixture of 94% alcohol (300 c.c.) and benzaldehyde (25 c.c.). On the introduction of a solution of potassium hydroxide (5 g.) in water (10 c.c.), the boiling being continued, the strychnine quickly dissolved, giving an orange-yellow solution. The source of heat was then removed and in a few seconds there was a copious separation of glistening yellow leaflets. After cooling, the derivative was collected, washed with alcohol, water, and alcohol, and dried at 100°. The base is very sparingly soluble in boiling alcohol or ethyl acetate, more readily soluble in hot toluene, acetone or pyridine; it may be conveniently crystallised from *iso*amyl alcohol, separating in pale lemon-yellow leaflets, m. p. 235—237° (Found : C, 79·1, 79·9 *; H, 6·2, 6·4; N, 6·4. $C_{28}H_{26}O_2N_2$ requires C, 79·6; H, 6·2; N, 6·6%). *Benzylidenestrychnine* dissolves in concentrated hydrochloric acid to an intensely yellow solution and on dilution with water the colour is largely discharged and the sparingly soluble hydrochloride is precipitated. Its yellow solution in 60% sulphuric acid gives a deep pure blue coloration on the addition of dichromate; this becomes dull green and then brown on keeping. The substance readily forms a methosulphate and other derivatives which will be described subsequently.

In contrast, benzylidenebrucine crystallises with difficulty, but the characteristic *hydrochloride* is readily prepared in the following manner: Caustic potash (4 g.) in water (10 c.c.) is added to a boiling solution of brucine (20 g.) and benzaldehyde (10 c.c.) in alcohol (50 c.c.) contained in a large beaker. After 2 minutes' boiling, the product is cooled, mixed with ether and then with concentrated hydrochloric acid (20 c.c.) diluted with water (200 c.c.). The ether is poured off, fresh ether added, and then a crystal of the hydrochloride from a previous preparation; copious crystallisation of the hydrochloride of benzylidenebrucine occurs. After being washed with dilute hydrochloric acid, this separates from alcoholic hydrogen chloride (2%) in yellow needles which, dried at 100°, appear to contain $\frac{1}{2}H_2O$ (Found : C, 68·3; H, 6·4.

$$C_{30}H_{30}O_4N_2,HCl,\tfrac{1}{2}H_2O$$

requires C, 68·3; H, 6·1%).

We propose to submit this salt and the corresponding, readily soluble base to detailed examination.

Derivatives of Strychnidine.

Strychnidine Methosulphate, $C_{21}H_{24}ON_2,Me_2SO_4$.—The following modification of the method described in Part IV (J., 1927, 1600) gives excellent results and is convenient for the preparation of large quantities of the substance. Strychnidine (50 g.) is finely powdered and stirred in a mortar while a mixture of freshly distilled methyl sulphate (20 c.c.) and methyl alcohol (25 c.c.) is gradually added. Interaction takes place immediately and the whole sets to a hard mass, which is ground, washed with methyl alcohol, and dried at 100°.

Strychnidine Methochloride, $C_{21}H_{24}ON_2,MeCl$.—Strychnidine methiodide (Tafel, *Annalen*, 1898, **301**, 314), dissolved in hot water, was mixed with a large excess of freshly precipitated silver chloride and heated on the steam-bath for 3 hours. The filtrate from the silver salts was evaporated to a small bulk and left in the ice-chest.

---

* Lead chromate tube.

The *methochloride*, which separated as a voluminous mass of needles, was collected, washed with a little water, in which it was very soluble, and left on porous porcelain for 2 days (Found: loss at 100°, 8·2. Found in the dried material: C, 71·7; H, 7·4. $C_{22}H_{27}ON_2Cl,2H_2O$ requires H_2O, 8·8%. $C_{22}H_{27}ON_2Cl$ requires C, 71·3; H, 7·3%). It melts and decomposes at about 370°, leaving a residue containing strychnidine.

When an aqueous solution is dechlorinated by silver hydroxide, and the filtrate concentrated by distillation under reduced pressure and then over sulphuric acid, a colourless crystalline mass—presumably the methohydroxide—remains: this will be examined.

Strychnidine Dimethosulphate, $C_{21}H_{24}ON_2,2Me_2SO_4$.—Strychnidine (25 g.), suspended in dry benzene (200 c.c.), was heated to boiling and the clear solution obtained was cooled and rapidly mixed with methyl sulphate (40 c.c.) before crystallisation set in. When the viscid gelatinous mass of strychnidine methosulphate was heated on the steam-bath, the whole gradually became more limpid and after 20 hours a thick gum had separated below the benzene. The benzene layer was decanted, the gum washed with benzene, the benzene shaken with water, and the aqueous extract used to dissolve the gum. After being filtered from some benzene, the solution of the dimethosulphate was heated to boiling and nearly neutralised with potassium hydroxide, and a large excess of hot concentrated sodium iodide solution added; the clear liquid soon began to deposit a glistening colourless mass of *strychnidine dimethiodide*. This is sparingly soluble in cold water, much more readily on boiling, and separates in long brilliant needles (Found: C, 45·4; H, 5·2. $C_{21}H_{24}ON_2,2MeI$ requires C, 45·7; H, 5·0%).

The dimethochloride, prepared in the usual way from the dimethiodide and silver chloride, was deposited as a gum on evaporation of the aqueous solution. When heated with a large excess of methyl-alcoholic potassium hydroxide (25%) until the temperature rose to 140°, the gum was readily decomposed and on addition of water a grey mass was obtained which separated from methyl alcohol in colourless prisms, m. p. 125°, and was readily identified by analysis and by a mixed melting-point determination as methoxymethyldihydrostrychnidine (J., 1927, 1602). It is remarkable that the specimen obtained was much freer from purple colouring matter than the material prepared from strychnidine monomethosulphate under the same conditions.

Strychnidine Benzylchloride, $C_{21}H_{24}ON_2,C_7H_7Cl$.—A solution of strychnidine (20 g.) in boiling toluene was cooled somewhat, and benzyl chloride (12 c.c.) added: combination began at once with separation of crystals and the whole soon became a paste. The mass was collected, washed with ether, and dissolved in boiling methyl alcohol, and the clear solution mixed with ether. The glistening plates which separated were washed with ether and dried at 100° (Found : C, 75·0; H, 6·9; Cl, 7·8. $C_{28}H_{31}ON_2Cl$ requires C, 75·2; H, 6·9; Cl, 8·0%).

Strychnidine benzylchloride, m. p. 330—335° (efferv.), is very soluble in water. The solution gives no precipitate with alkali, but with dichromate a sparingly soluble, bright yellow chromate is obtained. A solution in dilute sulphuric acid (60%) gives with dichromate the ordinary crimson strychnidine reaction. When the dry substance is heated in small quantities in test-tubes, benzyl chloride is eliminated and strychnidine regenerated, but at the same time small quantities of other substances are produced which are under examination.

When strychnidine benzylchloride (20 g.) is heated with methyl-alcoholic potash (250 c.c. of 25%) until the temperature of the melt reaches 150° and the whole is then cooled and water added, a solid separates in very good yield which is difficult to crystallise and melts at 92—95° (Found : C, 78·5; H, 7·7; MeO, 7·6. $C_{29}H_{34}O_2N_2$ requires C, 78·7; H, 7·7; MeO, 7·1%). This base, which is evidently *methoxybenzyldihydrostrychnidine* (compare Part IV, J., 1927, 1602), will be subjected to a detailed examination.

We are indebted to Mr. R. I. E. Hall, M.A., for the preparation of most of the dihydrostrychnidine (B) required for this investigation and to Mr. F. Hall for carrying out the analyses. We desire also to thank the Government Grant Committee of the Royal Society for repeated grants towards the heavy cost of the work.

THE DYSON PERRINS LABORATORY,
OXFORD.

UNIVERSITY COLLEGE,
LONDON.

[*Received, April 3rd*, 1929.]