CCCXX.—*Strychnine and Brucine. Part VI. The Catalytic Hydrogenation of Strychnine and Some Derivatives.*

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The motive of this investigation was our desire to gain further knowledge of the function of the characteristic groups and of the nitrogen and oxygen atoms in the molecule of strychnine, and we directed our attention in the first place to the question of the unsaturated centres. The results show clearly that strychnine contains one double bond. According to Skita and Franck (*Ber.*, 1911, **44**, 2863), the reduction of strychnine in dilute acetic acid solution by means of hydrogen in presence of palladium (from 1% palladous chloride in presence of gum arabic) yields a dihydrostrychnine, m. p. 209—210°, but the volume of hydrogen stated to have been absorbed is only about half of that theoretically required. Owing to an erroneous calculation of the latter, Skita and Franck considered that the correct amount had been absorbed. Repetition of the experiment under the conditions employed by these authors gave negative results, but under other conditions we obtained *dihydrostrychnine*, $C_{21}H_{24}O_2N_2$, which crystallised well from aqueous methyl alcohol with $2H_2O$, and when anhydrous had m. p. 220—222°. Skita and Franck make no mention of the water of crystallisation, and they state, further, that the catalytic reduction of strychnine under 3 atm. pressure at 70° yields tetrahydrostrychnine, identical with the substance obtained by the electrolytic reduction of strychnine. It is certain, at least, that our dihydrostrychnine could not be an intermediate product in the latter process. Just as strychnine, $C_{21}H_{22}O_2N_2$, by electrolytic reduction yields strychnidine, $C_{21}H_{24}ON_2$, and tetrahydrostrychnine, $C_{21}H_{26}O_2N_2$, by conversion of $\cdot CO \cdot N\colon$ into $\cdot CH_2 \cdot N\colon$ and $\cdot CH_2(OH) + NH\colon$, respectively (Tafel, *Annalen*, 1898, **301**, 301), so, in the same manner, dihydrostrychnine yields *dihydrostrychnidine* (A),* $C_{21}H_{26}ON_2$, m. p. 212—214°, and *hexahydrostrychnine*, $C_{21}H_{28}O_2N_2$, m. p. 197—199°. Furthermore, catalytic reduction of strychnidine gave dihydrostrychnidine (A) and catalytic reduction of tetra-

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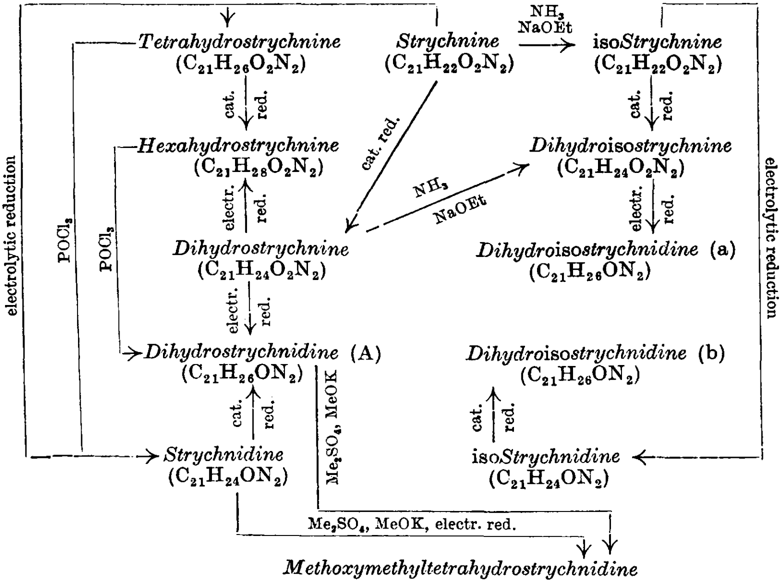
* Two dihydrostrychnidines, $C_{21}H_{26}ON_2$, have been prepared during the course of our investigations, and we propose to designate by (A) the substance described in the present communication, m. p. 212—214°. The isomeric dihydrostrychnidine (B) melts at 151° and is obtained from strychnidine by reduction with hydriodic acid and phosphorus. An account of the interesting properties of this substance will form the subject of a communication to be published in the near future.

hydrostrychnine gave hexahydrostrychnine, identical with the bases already mentioned. The dehydration of tetrahydrostrychnine to strychnidine is also paralleled by the similar conversion of hexahydrostrychnine into dihydrostrychnidine (A). The further reduction of these substances by hydrogen in presence of catalysts could not be accomplished, and dihydrostrychnine is characterised by its stability towards oxidising agents. It seems certain that the strychnine molecule contains only one double bond, and Tafel's view of the relation of strychnine to strychnidine and tetrahydrostrychnine is amply confirmed. Although, therefore, dihydrostrychnine contains the ·CO·N⁚ group, we have not found it possible to demonstrate this by the preparation of dihydrostrychnic acid, and it is evident that the reduction has stabilised the lactam ring. At one point, we have made a contact with the investigation described in Part IV (this vol., p. 1617), since *dihydrostrychnidine* (A) *methosulphate* yields methoxymethyltetrahydrostrychnidine, m. p. 220°, when it is heated with methyl-alcoholic potassium hydroxide. Methoxymethyltetrahydrostrychnidine was previously obtained by electrolytic reduction of methoxymethyldihydrostrychnidine, m. p. 126° (*loc. cit.*), the product of the action of methyl-alcoholic potash on strychnidine methosulphate. It is evident that the double bond which resists electrolytic reduction in strychnidine may be readily saturated when methoxymethyldihydrostrychnidine is submitted to the same treatment.

The examination of dihydrostrychnine has led us to consider further the important problem of the relation of strychnine to *iso*strychnine. On catalytic reduction *iso*strychnine yields *dihydro*iso*strychnine*, $C_{21}H_{24}O_2N_2,3H_2O$, m. p. 249—251°, and the same substance was more readily obtained from dihydrostrychnine by the action of warm alcoholic sodium ethoxide. This proves that the strychnine–*iso*strychnine isomerism in no way depends on a shift of the double bond, as had previously been assumed, and that the process involved in the conversion of strychnine into *iso*strychnine does not even require the presence of the double bond. All attempts to prepare acetyl and other similar derivatives of strychnine, strychnidine, dihydrostrychnine, and dihydrostrychnidine (A) have failed, but both *iso*strychnine and dihydro*iso*strychnine yield monoacetyl derivatives. There is no evidence of the presence of imino-groups, and since the *acetyl*iso*strychnine* and *acetyldihydro*iso*strychnine* are strong bases, they must be *O*-acetyl derivatives. Hence the interesting fact emerges that the change of strychnine to *iso*strychnine and of dihydrostrychnine into dihydro*iso*strychnine involves the appearance of a hydroxyl group. On the assumption, therefore, that *iso*strychnine contains the group ·CO·N⁚ (see below), we know that the other groups in the molecule include a tertiary basic nitrogen atom, one double bond, and a hydroxyl group. It is of fundamental importance that *iso*strychnine contains only one double bond because oxygen can only occur as C⁚O, C·O·C, or C·OH, and if a substance containing a carbonyl or an ether group isomerises with the production of an alcohol the process must be accompanied by the formation of a new double bond or a new ring. Experiment excludes the former alternative and we must therefore accept the latter. On the hypothesis that strychnine contains an ether group, it becomes necessary to assume the occurrence of some such process as the slipping of a bond in pentamethylene oxide with formation of a hydroxy*cyclo*pentane. This does not commend itself as a probable explanation: there are few analogous reactions and we cannot imagine that such a change would be brought about by the agency of sodium ethoxide in warm alcoholic solution. On the hypothesis that strychnine contains a carbonyl group, however, we can readily explain the appearance of a hydroxyl group in *iso*strychnine as due to an intramolecular condensation, ⁚CO + CH⋮ ⟶ ⁚C(OH)·C⋮. It is interesting that no parallel to the strychnine–*iso*strychnine transformation exists in the strychnidine and tetrahydrostrychnine series (see p. 2407), and this suggests that the ·CO·N⁚ group is directly concerned. If it should be proved in the future that strychnine is a ketone, then an acceptable explanation of the change of strychnine to *iso*strychnine is that expressed in the scheme

⁚CO + C̈H·CO·N⁚ ⟶ ⁚C(OH)·C̈·CO·N⁚

These considerations have necessitated the further examination of the reactions of *iso*strychnine. As stated above, it yields an *O*-acetyl derivative, but we have been unable to confirm the statement of Oliveri-Mandalà and Comella (*Gazzetta*, 1923, **53**, 627) that the base gives a crystalline semicarbazone, m. p. 215° (decomp.). In addition we were unable to obtain a phenylhydrazone of *iso*strychnine or a semicarbazone of dihydro*iso*strychnine. The argument presented above, and indeed any theory implying that the hydroxyl group of *iso*strychnine is derived by modification of the function of the cryptic oxygen atom of strychnine (*i.e.*, that oxygen atom not included in the ·CO·N⁚ group), can only be sustained if *iso*strychnine contains the ·CO·N⁚ group of strychnine. In favour of this view we may marshal the facts that *iso*strychnine is a monoacid base, that it exhibits colour reactions of the strychnine type, that it yields *iso*strychnic acid on hydrolysis (Pictet and Bacovescu, *Ber.*, 1905, **38**, 2787; compare p. 2395), although the reverse change has not been accomplished, and that *iso*strychnic acid exhibits colour reactions of the strychnidine type; nothing is known that is not in agreement with the suggestion that *iso*strychnine contains this group. We have sought further confirmation by studying the electrolytic reduction of *iso*strychnine and of dihydro*iso*strychnine, and have obtained new bases of the strychnidine type, *viz.*, iso*strychnidine*, $C_{21}H_{24}ON_2,1{\cdot}5H_2O$, and *dihydro*iso*strychnidine*, $C_{21}H_{26}ON_2,0{\cdot}5H_2O$, respectively. The latter must be designated *dihydro*iso*strychnidine (a)*, since an isomeride, *dihydro*iso*strychnidine (b)*, is obtained by the catalytic reduction of *iso*strychnidine. These bases exhibit many of the characteristics of strychnidine, and their preparation affords strong support to the view that *iso*strychnine contains the cyclic amide grouping.



The following miscellaneous observations are included in this communication. Some further work on the coupling of strychnine derivatives with diazonium salts has been carried out. Reduction of *sulphobenzeneazostrychnidine* gives *aminostrychnidine*, $C_{21}H_{25}ON_3$, and the striking colour reactions of this base establish beyond question that it is p-*aminostrychnidine*, the amino-group being in the para-relation to the nitrogen atom attached to the benzene nucleus in strychnine. It is, for example, convertible into an analogue of toluylene-blue and then into the eurhodine analogous to toluylene-red.

The Schotten–Baumann benzoylation of strychnic acid was expected to attack the :NH group that this substance is supposed to contain, and although we have isolated a definite product of the correct composition, yet its behaviour suggests that it is the mixed *anhydride* of benzoic and strychnic acids rather than *N*-benzoylstrychnic acid.

In the course of abortive attempts to convert strychnidine and tetrahydrostrychnine into members of the *iso*strychnine series, it was found that on being heated with water in an autoclave at 170—185° each of these bases was partly converted into an oxidation product.

The scheme on page 2392 summarises the relationships of some of the substances discussed above. A more detailed examination of certain of the new bases now described is in progress, and the work is being extended to the brucine series.

EXPERIMENTAL.

Dihydrostrychnine.—All the catalytic reductions described in this communication were carried out in a flask fitted with an efficient stirrer with gas-tight packing. Norite (50 g., previously heated to redness) was added to a solution of palladous chloride (4 g.) in water (400 c.c.) containing a few drops of concentrated hydrochloric acid, and the mixture stirred in hydrogen until no further absorption took place. A solution of strychnine (57 g.) in 50% acetic acid (200 c.c.) was then introduced and agitation continued for 3—4 hours, during which 3,600 c.c. of hydrogen were absorbed (calc. for one double bond: 3,820 c.c.). The filtered liquid was basified with ammonia, whereupon practically pure *dihydrostrychnine* was precipitated in a crystalline condition (yield, 93%). The recovered catalyst may be reactivated by exposure to the air for a day and can be used at least 4 times, but in any one experiment 1 g. of palladous chloride is unable to catalyse satisfactorily the reduction of more than 17 g. of strychnine.

Dihydrostrychnine crystallises from 50% aqueous methyl alcohol in long, silky, colourless needles (Found: C, 68·3, 67·9; H, 7·5, 7·4; N, 7·1; loss at 100°, 9·3; loss at 130°, 9·8. $C_{21}H_{24}O_2N_2,2H_2O$ requires C, 67·7; H, 7·5; N, 7·5; $2H_2O$, 9·7%). The anhydrous base melts without decomposition at 220—222° (Found: C, 75·1; H, 7·1. $C_{21}H_{24}O_2N_2$ requires C, 75·0; H, 7·2%). It dissolves in about 190 parts of boiling water and is sparingly soluble in cold water; it is readily soluble in cold ethyl and methyl alcohols, moderately readily soluble in cold benzene, and sparingly soluble in cold ethyl acetate and in boiling acetone, from which it separates in minute, compact prisms. The substance has a bitter taste similar to that of strychnine. The faintly acid solutions of dihydrostrychnine develop no coloration on the addition of ferric chloride, and the base does not couple with diazobenzenesulphonic acid. With 60% sulphuric acid (by vol.) and potassium dichromate it gives an intense reddish-purple colour, slowly fading to a brownish-red. Attempts to obtain a semicarbazone of the base were fruitless, and failure also attended an attempt to acetylate it by means of anhydrous sodium acetate and acetic anhydride, the dihydrostrychnine being recovered unchanged and identified by analysis (Found : C, 68·0; H, 7·6; N, 7·5%), by m. p., and by mixed m. p. (220° in each case).

If the base contained the ·CH(OH)· group it should yield a ketone under the conditions used to change codeine into codeinone (Ach and Knorr, *Ber.*, 1903, **36**, 3070). Dihydrostrychnine (5 g.) was dissolved in a cold mixture of concentrated sulphuric acid (3·5 c.c.) and water (31 c.c.); addition of finely powdered potassium dichromate (3 g.) with stirring produced an orange-coloured precipitate, and when the mixture was heated for 20 minutes on the steam-bath a deep brownish-red solution was obtained, from which 4 g. of pure dihydrostrychnine could then be recovered.

Oxidation of the base with potassium permanganate was attempted under the conditions prescribed by Leuchs and Schwabel (*Ber.*, 1913, **46**, 3695) for the oxidation of strychnine. Dihydrostrychnine dihydrate (15 g.), dissolved in chloroform (120 c.c.) and acetone (600 c.c.), was stirred with a little finely powdered potassium permanganate for 1 hour. Oxidation did not occur and the mixture was boiled for 3 hours with gradual addition of potassium permanganate (30 g.), and then for 1 hour longer. The permanganate was destroyed, but 12 g. of dihydrostrychnine were recovered, and the working up of the manganese precipitate gave only a minute amount of a brown syrup that was not further investigated.

Further catalytic hydrogenation of dihydrostrychnine was attempted at 100°, 0·6 g. of palladous chloride being used for 3 g. of the base. No absorption of hydrogen occurred, and the whole of the base was recovered unchanged. Attempts to convert dihydrostrychnine into dihydrostrychnic acid (*e.g.*, by the method used by Tafel, *Annalen*, 1891, **264**, 50, for the conversion of strychnine into strychnic acid free from *iso*strychnic acid) gave either dihydro*iso*strychnine (see below) or an amorphous base melting over a wide range, but in no case was any satisfactory acid product isolated. It may be mentioned here that the catalytic reduction of strychnic acid in dilute acetic acid solution gave dihydrostrychnine in good yield, but in all probability the strychnic acid was first converted into strychnine and then reduced.

Dihydrostrychnine Methosulphate.—A mixture of dihydrostrychnine (10 g.), methyl sulphate (6 c.c.), and benzene (120 c.c.) was boiled for 5 minutes, then cooled; the resulting solid crystallised from alcohol in fine, colourless rods, m. p. 322° (decomp.) with previous darkening from 300° (Found : C, 59·1; H, 6·4. $C_{23}H_{30}O_6N_2S$ requires C, 59·7; H, 6·5%). This derivative is readily soluble in water, but very sparingly soluble in cold alcohol or boiling ethyl acetate or acetone. When it was reduced in aqueous solution by 4% sodium amalgam (under conditions similar to those employed for strychnine methosulphate in experiments that will shortly be reported), no oily base separated and the brownish-red solution was not further investigated. The related *methiodide* was obtained in a similar manner by direct combination of the components. It is moderately readily soluble in water, very sparingly soluble in alcohol, and crystallises from a mixture of these solvents in stellar aggregates of colourless rods, that suffer slight discoloration between 300° and 330° (Found : C, 53·8; H, 5·6. $C_{22}H_{27}O_2N_2I,H_2O$ requires C, 53·2; H, 5·8%).

iso*Strychnine and* iso*Strychnic Acid.*—An attempt to repeat the preparation of the semicarbazone described by Oliveri-Mandalà and Comella (*loc. cit.*) did not succeed, and *iso*strychnine was recovered unchanged (Found : C, 65·5; H, 7·2. Calc. for

$$C_{21}H_{22}O_2N_2,3H_2O :$$

C, 65·0; H, 7·2%). No other result was obtained when the sodium hydroxide prescribed by the above-mentioned authors was replaced by a large excess of sodium acetate. When the base (1 g.), together with phenylhydrazine (0·4 g.) and 6% acetic acid (3·5 c.c.), was heated for 3 hours on the steam-bath, the recoverable crystalline base was found to be unchanged *iso*strychnine, m. p. 220°, alone or mixed with an authentic specimen.

The colour reaction of *iso*strychnine with 60% sulphuric acid and potassium dichromate differs somewhat from that of strychnine. It is a not very intense pure violet coloration, fading in a few seconds to a very pale brown. The conversion of *iso*strychnine into *iso*strychnic acid can be accomplished according to Pictet and Bacovescu (*loc. cit.*) by the action of boiling alcoholic sodium ethoxide (concentration not stated) during 6 hours. We find, however, that the yield is very small under their conditions. A mixture of *iso*strychnine trihydrate (4·5 g.) and alcoholic sodium ethoxide (from 0·7 g. of sodium and 7·5 c.c. of alcohol) was heated on the steam-bath for 6¼ hours, giving a deep brownish-red solution that exhibited a green fluorescence. After dilution with water (85 c.c.) and keeping for some hours in the ice-chest, nothing separated and the solution was exactly neutralised with acetic acid. The slimy, red precipitate consisted chiefly of an insoluble pigment and was extracted with hot water (charcoal); ultimately, colourless, slender needles of *iso*strychnic acid (0·5 g.), m. p. 231° (decomp.), were isolated. The yield was increased to 40% when the hydrolysis was carried out for 11 hours at 60°. This material does not lose weight when heated at 140° for several hours (Found : C, 68·3; H, 7·1. Calc. for $C_{21}H_{26}O_4N_2$: C, 68·1; H, 7·0). We have found that *iso*strychnic acid cannot be reduced by hydrogen in presence of palladinised charcoal in dilute acetic acid solution. It is usually regarded as $C_{21}H_{24}O_3N_2,H_2O$, but the facts suggest that the molecule of water may be constitutionally bound, *e.g.*, by addition to the ethylene linkage. The acid is unchanged by boiling dilute hydrochloric acid and under no conditions has it been reconverted into *iso*strychnine. The colour reactions indicate that the N–CO link has been broken, since they are of the strychnidine type. With ferric chloride in dilute hydrochloric acid solution a red colour develops slowly in the cold, but, on warming, the solution becomes intensely blood-red. Coupling with diazobenzenesulphonic acid occurs in cold dilute acetic acid solution to an azo-compound exhibiting the usual properties. Unlike strychnic acid (see below), *iso*strychnic acid could not be converted into a benzoyl derivative by the Schotten–Baumann method.

O-*Acetyl*iso*strychnine*.—Oliveri-Mandalà and Comella (*loc. cit.*) found that *iso*strychnine, but not strychnine, reacts with magnesium ethyl bromide, yielding a molecular proportion of ethane. They attributed this to interaction of the Grignard reagent with an imino-group in the base; it seems more probable to us that the liberation of ethane is due to the presence of a hydroxyl group in the *iso*strychnine molecule, and we can recall no evidence indicating that the substance is a secondary base.

A mixture of *iso*strychnine (2 g.), fused sodium acetate (1 g.), and acetic anhydride (6 c.c.) was heated on the steam-bath for 4 hours and considerable darkening occurred. The cooled mass was added to water, and the excess of acetic acid neutralised by sodium bicarbonate. The product was isolated by means of chloroform and crystallised repeatedly from light petroleum, a process which greatly diminishes the final yield. The *acetyl* derivative crystallises in groups of minute, colourless needles, m. p. 133—134° (Found : C, 73·3; H. 6·4. $C_{23}H_{24}O_3N_2$ requires C, 73·4; H, 6·4%); it is readily soluble in most organic solvents and dissolves at once in very dilute acetic acid, the addition of sodium hydroxide then producing a turbidity which soon clears, doubtless as the result of hydrolysis.

*Preparation of Dihydro*iso*strychnine*.—(A) *By the catalytic reduction of* iso*strychnine*. Norite (12 g.) was palladinised (0·5 g. of palladous chloride in 250 c.c. of water) as already described, and a solution of *iso*strychnine trihydrate (4·9 g.) in a few c.c. of dilute acetic acid was then introduced. The theoretical volume of hydrogen (340 c.c.) was absorbed in 5 hours; absorption then ceased suddenly. The filtered liquid was basified with dilute aqueous sodium hydroxide, a colourless oil being precipitated which solidified after being kept for a long time. The *dihydro*iso*strychnine* was crystallised from benzene–light petroleum and then several times from water; fern-like bunches of coarse, colourless needles, m. p. 244—246°, were thus obtained (Found: C, 64·7; H, 7·5. $C_{21}H_{24}O_2N_2,3H_2O$ requires C, 64·6; H, 7·7; $3H_2O$, 13·8%).

(B) *By isomeric change of dihydrostrychnine.* Strychnine has been converted into *iso*strychnine in two ways: (1) by heating with water at 170—175° (Pictet and Bacovescu, *loc. cit.*; compare also Leuchs and Nitschke, *Ber.*, 1922, **55**, 3171, and Oliveri-Mandalà and Comella, *loc. cit.*); (2) by heating with methyl-alcoholic ammonia under various conditions (Leuchs and Nitschke, *loc. cit.*). A third method (3) is indicated by the observation of Tafel (*Annalen*, 1891, **264**, 50) that strychnine yields *iso*strychnic acid as well as strychnic acid when it is heated with alcoholic sodium ethoxide at temperatures above 70°. The three processes have been applied to the transformation of dihydrostrychnine.

(1) Dihydrostrychnine (1 g.) and water (25 c.c.) were heated in a sealed tube at 165—185° for 5 hours. Very little decomposition occurred (distinction from strychnine), and the aqueous solution was separated from the gummy residue and kept in the ice-chest. The gum solidified and was found to consist of unchanged material, whilst the solution deposited amorphous material which could be crystallised from water in slender, colourless needles, m. p. 237—238°. This product is slightly impure dihydro*iso*strychnine, as was proved by comparison with specimens prepared by other methods.

(2) This method gave quite good results on a small scale, but an attempt to reproduce the conditions on a larger scale in an autoclave failed completely. A sealed tube containing dihydrostrychnine dihydrate (1·2 g.) and 25 c.c. of methyl-alcoholic ammonia (saturated at 15°) was heated at 120—140° (but not higher) for 48 hours. The tube was opened and the pale yellow liquid evaporated in a vacuum; the residue crystallised from water in colourless needles, m. p. 240—245° (Found: C, 64·8; H, 7·8%).

(3) This is the most satisfactory method of preparation, but the yield is greatly diminished if the operation is carried out on a larger scale. Dihydrostrychnine dihydrate (5 g., finely powdered) was added to an alcoholic solution (20 c.c.) of sodium ethoxide (0·5 g. of sodium), and the mixture heated on the steam-bath

until complete solution had been effected. The deep purplish-red liquid was boiled for 2 minutes, then cooled and maintained at 44—46° for 6 hours. A yellow solid soon began to separate and eventually the liquid became filled with the crystals, forming a thick paste. After being cooled and kept in the ice-chest, the solid was collected, washed with a little alcohol, and dried (2 g., or 40%). Nothing further could be obtained from the alcoholic filtrate, which gave an amorphous precipitate on dilution with water. The base crystallised from water in bunches of colourless needles, m. p. 248—250° (Found: C, 65·1; H, 7·5; loss at 120°, 13·5%). The anhydrous base crystallised from benzene–light petroleum in needles, m. p. 249—251° (Found: C, 74·6; H, 7·2. $C_{21}H_{24}O_2N_2$ requires C, 75·0; H, 7·2%).

The following mixtures had melting points that were higher than those of the lower-melting specimens in each case, the m. p.'s of the specimens being those already quoted above: (A) with (B2), (A) with (B3), (B2) with (B3).

Dihydro*iso*strychnine dissolves in 90—100 parts of boiling water and is sparingly soluble in cold water, cold ethyl alcohol, boiling benzene or acetone; it is moderately readily soluble in boiling ethyl acetate, and readily soluble in chloroform, cold methyl alcohol, and hot ethyl alcohol. It gives no ferric chloride reaction, and addition of potassium dichromate to its solution in 60% sulphuric acid produces an intense purple coloration, persisting for a minute and then fading to a light reddish-brown. Attempts to prepare a semicarbazone were quite unsuccessful, and it was found that the further catalytic hydrogenation of the base at 70° could not be accomplished. There was some evidence, in that a weak Liebermann reaction was observed, that the base gives a nitrosoamine, but the isolated product (Found: N, 6·6%) was the unchanged base. Probably the crude material contained a trace of an ester of nitrous acid resulting from the interaction of the acid with the alcoholic hydroxyl group of the base. The *methosulphate* is a readily soluble gum, but the *methiodide* crystallises from alcohol containing a little water in groups of thick, colourless rods, m. p. 320° (decomp.) with darkening from 310° (Found: N, 6·2. $C_{22}H_{27}O_2N_2I$ requires N, 5·9%). It is sparingly soluble in hot alcohol and readily soluble in cold water.

O-*Acetyldihydro*iso*strychnine*.—A mixture of dihydro*iso*strychnine (1 g.), fused sodium acetate (0·5 g.), and acetic anhydride (3·5 c.c.) was heated on the steam-bath for 3 hours. The product was decomposed by water, the acid neutralised by sodium bicarbonate, and the base extracted by chloroform. After removal of the solvent in a vacuum, the residue crystallised from light petroleum, containing a little benzene, in rods which were recrystallised several times from light petroleum without material alteration of the m. p. The slender, colourless needles thus obtained had m. p. 202—204° (Found: C, 72·9; H, 7·1. $C_{23}H_{26}O_3N_2$ requires C, 73·0; H, 6·9%), and m. p. 190—195° when mixed with dihydro*iso*strychnine. O-*Acetyldihydro*iso*strychnine* is immediately soluble in dilute acetic acid, and on the progressive addition of sodium hydroxide a turbidity appears and then disappears; on keeping, this solution deposits dihydro*iso*strychnine in needles.

Preparation of Dihydrostrychnidine (A).—(I) *By catalytic hydrogenation of strychnidine.* The reduction of strychnidine could not be accomplished at the ordinary temperature, and under the following conditions it gave good results on a small scale only. A violently agitated mixture of norite (4 g., previously heated to redness) and palladous chloride (0·4 g.) dissolved in very dilute hydrochloric acid (100 c.c.) was allowed to absorb hydrogen, and when no further change occurred a solution of strychnidine (3 g.) in 67% acetic acid (30 c.c.) was introduced and the flask immersed in water at 65° (renewed when it cooled to 50°). After 3½ hours the volume of hydrogen absorbed was 190 c.c. (theory, 210 c.c.) and absorption ceased. The base was precipitated from the filtered liquid by means of sodium hydroxide, and the grey granules were collected and dried in a vacuum (yield, 50%; m. p. 200—209°). The substance, crystallised from methyl alcohol and then from light petroleum, formed small, well-defined, colourless tablets, m. p. 212—214° (Found: C, 78·3; H, 7·9. $C_{21}H_{26}ON_2$ requires C, 78·3; H, 8·1%). When crystallised from methyl alcohol the base forms large, glistening, colourless leaflets (Found: C, 78·6; H, 8·0%). *Dihydrostrychnidine* (A) is not appreciably soluble in boiling water, but it is readily soluble in cold ethyl alcohol, benzene, or carbon tetrachloride; it is moderately readily soluble in hot ethyl acetate, and sparingly soluble in boiling acetone and light petroleum. Unlike strychnidine, it gives only a faint coloration when ferric chloride is added to its solution in an excess of dilute hydrochloric acid; a rose-red coloration develops on warming. If only a trace of hydrochloric acid is present, an intense coloration develops a few seconds after the addition of ferric chloride. As explained in Parts IV and V (this vol., pp. 1595, 1662), this behaviour is closely connected with the strength of the substances as di-acid bases, and is a clear indication that the nitrogen atom joined to the aromatic nucleus is a much stronger basic centre in dihydrostrychnidine (A) than it is in strychnidine. The base is stable to potassium permanganate in cold acetone solution containing a few drops of water, but it is rapidly oxidised if much water is added. It is unaffected by acetic anhydride and dry sodium acetate at 100°. The base is unacted upon by magnesium phenyl bromide in boiling benzene or by magnesium methyl iodide. It was also recovered unchanged after vigorous treatment with sodium and boiling *iso*amyl alcohol.

(II) *By electrolytic reduction of dihydrostrychnine.* Dihydrostrychnine dihydrate (22 g.), dissolved in a mixture of concentrated sulphuric acid (83 c.c.) and water (100 c.c.), was reduced at a lead cathode (compare Tafel, *Annalen*, 1898, **301**, 302) by a current of 6 amps. at 3·8 volts (current density, 0·09 amp./cm.^{2}). At the end of 3 hours, the liquid in the cathode cell gave no appreciable ferric chloride reaction; at the end of 9 hours both the ferric chloride and Otto reactions were positive; after 18 hours the Otto reaction was very faint; and after 2 hours more it had disappeared. Tafel (*loc. cit.*) found that strychnine was completely reduced (using similar conditions, but with a rather smaller current density and a rotating cathode) in 8 hours, so that dihydrostrychnine is apparently less easily reduced by this method than strychnine is. The liquid was diluted with 3 times its volume of water, and the base precipitated by the cautious addition, with cooling, of potassium hydroxide. The crude product was collected and dried (14 g.). After crystallisation from methyl alcohol and then from light petroleum, pure dihydrostrychnidine (A) was obtained, m. p. 212—214°, unchanged by admixture with a specimen obtained as in (I). The above method is the one that should be adopted for the preparation of the base in quantity.

Dihydrostrychnidine (A) *methosulphate* was obtained under conditions similar to those used for dihydrostrychnine methosulphate (p. 2394). It crystallises from alcohol–light petroleum in rosettes of colourless, pointed needles, m. p. 250° (decomp.) (Found: C, 61·3; H, 7·5; N, 5·8. $C_{23}H_{32}O_5N_2S$ requires C, 61·6; H, 7·2; N, 6·2%). The derivative is readily soluble in water and alcohol and sparingly soluble in most other organic solvents. The salt (2 g.) was heated at 105—115° for 8 hours (reflux) with 40% methyl-alcoholic potassium hydroxide (22 c.c.). On addition of water, fine, colourless leaflets separated. Complete purification was effected by two crystallisations from methyl alcohol, and the massive, colourless, hexagonal tablets, m. p. 219—220°, were found to consist of methoxymethyltetrahydrostrychnidine (Part IV, this vol., p. 1617). The m. p. was not depressed on admixture with a specimen obtained by the electrolytic reduction of methoxymethyldihydrostrychnidine.

The methiodide. Dihydrostrychnidine (A) (5 g.) was suspended in methyl alcohol (50 c.c.), and methyl iodide (12 c.c.) added; the base then dissolved completely with little rise of temperature, crystallisation soon commenced, and a sandy precipitate separated. The mixture was boiled for ½ hour and left over-night; the *methiodide* was then collected, washed with methyl alcohol, and dried at 100°. When rapidly heated, it decomposed at about 340—350° to a brown syrup. It is sparingly soluble in boiling water or methyl alcohol and separates from water in striated, arrow-shaped prisms (Found: C, 57·0; H, 6·4. $C_{22}H_{29}ON_2I$ requires C, 56·8; H, 6·5%).

The *methochloride* was obtained by digesting the methiodide with much water and silver chloride for 2 hours and evaporating the filtered solution to a small bulk; a colourless syrup remained which, kept over sulphuric acid in a vacuum desiccator, crystallised to a mass of needles. After contact with porous porcelain, the colourless mass was recrystallised from a few drops of water, and dried over sulphuric acid. It did not then lose weight at 100° (Found: C, 70·7; H, 8·0. $C_{22}H_{29}ON_2Cl$ requires C, 70·8; H, 7·9%). This substance decomposes at about 345° and the aqueous solution gives with hydrochloric acid and ferric chloride a pale pink colour, which gradually becomes deep pink on warming. The solution in dilute sulphuric acid (60%) is coloured intensely brownish-crimson by dichromate. The methochloride (0·5 g.) was heated cautiously in a test-tube over a free flame until decomposition at the high temperature was just complete; the residue crystallised from methyl alcohol (norite) in leaflets, m. p. 212—213°, of dihydrostrychnidine (A). When the methochloride was heated with methyl-alcoholic potassium hydroxide (25%) on the sand-bath until the temperature of the melt reached 125°, the resulting product gave on addition of water a grey mass, which was well washed and left in contact with porous porcelain. This separated from xylene (norite) in leaflets, m. p. 220—222°, and proved to be methoxymethyltetrahydrostrychnidine.

As stated in the Addendum at the end of this paper, these and other properties prove that dihydrostrychnidine (A) methiodide and methochloride are identical with methyl*neo*dihydrostrychnidinium iodide and chloride (Part IV, this vol., p. 1623).

The dimethosulphate and dimethiodide. A solution of dihydrostrychnidine (A) (7 g.) in carefully purified boiling benzene (50 c.c.) was cooled, and freshly distilled methyl sulphate (20 c.c.) added; the solution became warm, clouded, and the monomethosulphate separated as a voluminous crystalline precipitate. On heating on the steam-bath under reflux, the crystals gradually gave place to a gelatinous mass. After the mixture had been boiled for 15 hours and cooled in ice-water, the benzene layer was decanted and the viscid dimethosulphate, which showed no sign of crystallising, was dissolved in water. The solution was filtered from benzene, neutralised with potash, and heated to boiling, and a large excess of hot sodium iodide solution added. The clear solution soon began to deposit brilliant, arrow-shaped plates of the *dimethiodide*, which were collected, washed, and dried at 100°; m. p. about 285—290° (decomp.) (Found: C, 46·0; H, 5·5. $C_{23}H_{32}ON_2I_2$ requires C, 45·6; H, 5·3%). A further small crop of crystals was obtained on concentrating the mother-liquor; the filtrate gave, on addition of 50% potassium hydroxide solution, only a slight turbidity (compare Part IV, this vol., p. 1594).

The same dimethiodide was obtained when dihydrostrychnidine (A) was heated in a sealed tube with a large excess of methyl iodide alone (compare the preparation of the monomethiodide above) for several hours in the steam-bath, since the old-gold plates which separated had m. p. 285—290° (decomp.) and gave C, 45·2; H, 5·5%. This dimethiodide is very sparingly soluble in boiling methyl alcohol, but dissolves readily in cold and very readily in hot water.

The *dimethochloride*, prepared from the dimethiodide and silver chloride in the usual way, is a hygroscopic syrup.

After this had been heated on the sand-bath with methyl-alcoholic potassium hydroxide (25%) in an open flask until the temperature of the melt was 130°, the cold product gave with water a grey precipitate of methoxymethyltetrahydrostrychnidine and *methyldihydrostrychnidine* (A) in about equal proportions. Owing to the small quantity of material available, the separation of these two substances proved to be difficult. The mixture was dissolved in boiling benzene and the solution was digested with norite and concentrated to a very small bulk. On standing in ice, crude methoxymethyltetrahydrostrychnidine separated. After crystallisation from xylene, it melted at m. p. 220—222°, alone or when mixed with a specimen of the methoxy-derivative obtained as described in Part IV (this vol., p. 1617). The benzene filtrate was evaporated, and the colourless syrup boiled with methyl alcohol; a mass of crystals, m. p. 155—190°, then separated. This crude substance was rubbed with a very little benzene, the small quantity of very sparingly soluble residue, m. p. 220—222°, was filtered off, and the syrup was again treated with methyl alcohol after the benzene had been evaporated. This process was repeated and the substance was then crystallised from methyl alcohol and finally from acetone (Found, in two different preparations: C, 79·0, 78·9; H, 8·5, 8·4. $C_{22}H_{28}ON_2$ requires C, 78·6; H, 8·3%).

Methyldihydrostrychnidine (A) melts not quite sharply at 178—180° and is characterised by being remarkably sparingly soluble in boiling methyl alcohol or acetone and unusually readily soluble in benzene. It separates from methyl alcohol or acetone in flat needles. A solution in dilute hydrochloric acid gives, on treatment with ferric chloride, an immediate crimson colour, changing to pale brown on warming. The base has unexpectedly little tendency to combine with methyl iodide. When a concentrated solution in benzene was boiled with methyl iodide for several minutes and evaporated, the residue obtained consisted essentially of the unchanged base and separated from methyl alcohol in needles, m. p. 175—177° (Found: C, 78·3; H, 8·2%). The base is readily soluble, without rise of temperature, in methyl iodide and even after 10 minutes' boiling a good deal of uncombined base remains.

Hexahydrostrychnine (*Dihydrotetrahydrostrychnine*).—(A) *Catalytic reduction of tetrahydrostrychnine.* This was carried out as in the cases described already, and the quantities were: palladous chloride (0·8 g.), water (300 c.c.), norite (12 g.), tetrahydrostrychnine (6 g.), 50% acetic acid (60 c.c.). Absorption at the ordinary temperature was very slow (20 c.c. in 1 hour), but at 50—70° the theoretical volume of hydrogen was absorbed in 4 hours. The filtered liquid was made strongly alkaline with potassium hydroxide (cooling necessary), and the slightly pink, granular solid was collected and dried in a vacuum (yield, 60%). The *hexahydrostrychnine* crystallises from ethyl acetate, containing a little light petroleum, in large, rectangular tablets, mostly with facets at the corners, and faintly pink as the result of superficial oxidation. The m. p. of this substance, 197—199°, is thus close to that of tetrahydrostrychnine (200—202°), but a mixture of the two gave a very large depression (Found: C, 74·4; H, 8·2. $C_{21}H_{28}O_2N_2$ requires C, 74·1; H, 8·3%). This base is sparingly soluble in light petroleum and appreciably soluble in boiling water; it is moderately readily soluble in cold ethyl acetate and in boiling benzene, acetone, or carbon tetrachloride, and readily soluble in cold ethyl alcohol or boiling methyl alcohol. Like tetrahydrostrychnine, hexahydrostrychnine gives no coloration with ferric chloride if too much hydrochloric acid is present in the solution, but in the presence of only a trace of acid a brownish-red coloration slowly develops.

(B) *By electrolytic reduction of dihydrostrychnine.* The alkaline solution from which crude dihydrostrychnidine was precipitated (see p. 2400) was exhaustively extracted with chloroform, the red extract separated and dried over sodium sulphate (norite), and the solvent removed, finally in a vacuum at 40°. The residual gum solidified in contact with light petroleum, and this material (5 g. from 22 g. of dihydrostrychnine), after three crystallisations from ethyl acetate containing light petroleum, was obtained in large, faintly brown, irregular tablets, m. p. 197—199°, alone or mixed with the specimen prepared as described under (A) above.

Evidence was obtained that hexahydrostrychnine yields a nitrosoamine, but the substance could not be fully purified. Similarly, the *diacetyl* derivative, prepared in the usual manner (compare *O*-acetyldihydro*iso*strychnine), was obtained only as a very pale yellow, hygroscopic syrup (Found : N, 6·8. $C_{25}H_{32}O_4N_2$ requires N, 6·6%). It is of interest to note that this substance gives no coloration with ferric chloride, thus indicating the neutralised character of the nitrogen atom attached to the aromatic nucleus. The dehydration of hexahydrostrychnine with formation of dihydrostrychnidine (A), analogous to the conversion of tetrahydrostrychnine into strychnidine, can be accomplished by boiling the substance with ten times its weight of phosphoryl chloride for 4 minutes. The crude base, isolated in the usual way, has m. p. 200—210°, and yields pure dihydrostrychnidine (A), m. p. 212—214°, after one crystallisation from light petroleum.

iso*Strychnidine*.—The electrolytic reduction of *iso*strychnine was effected in the usual apparatus. *iso*Strychnine trihydrate (13 g.), dissolved in a cold mixture of concentrated sulphuric acid (50 c.c.) and water (70 c.c.), was placed in the cathode cell and submitted to a current of 4·4 amps. at 4 volts (current density, 0·065 amp./cm.^{2}) for 20 hours, after which the Otto reaction could no longer be obtained. The base precipitated by means of potassium hydroxide from the diluted solution (with cooling) weighed 9 g., and was repeatedly extracted with much boiling water. On cooling, the solutions deposited tufts of slender, very pale brown needles, m. p. 155—157°, with sintering at 107—118°. The behaviour on heating was not altered by subsequent recrystallisation from water (Found : loss at 105°, 6·9; at 130°, 7·4. Found in anhydrous material: C, 78·7; H, 7·6. $C_{21}H_{24}ON_2,1{\cdot}5H_2O$ requires H_2O, 7·8. $C_{21}H_{24}ON_2$ requires C, 78·8; H, 7·5%). iso*Strychnidine* which had been heated at 110° for an hour was crystallised thrice from light petroleum and formed very light, feathery groups of colourless needles, m. p. 163—168° (slight decomp.) [Found : (A) C, 77·6; H, 7·9%]. Again, the alkaline mother-liquors from the crude *iso*strychnidine were worked up by extraction with chloroform in the usual manner, with the object of determining whether any *iso*tetrahydrostrychnine was formed in the reduction, but the only definite product isolated was one that crystallised from light petroleum in colourless needles, m. p. 165—167°, alone or mixed with the specimen of m. p. 163—168° mentioned above (Found : C, 76·5; H, 7·5. $C_{21}H_{24}ON_2,0{\cdot}5H_2O$ requires C, 76·6; H, 7·7%). The analysis (A) (above) requires a still smaller proportion of associated water (0·25 mol.). *iso*Strychnidine is easily decomposed on heating, *e.g.*, it is discoloured at 110° after 1 hour, and a possible explanation of our results is that the low m. p. of the product crystallised from water is the result of decomposition occurring during the sintering period, when solvent of crystallisation is being removed. Crystallisation from light petroleum seems to give less fully hydrated modifications, which may melt at higher temperatures as the result of their superior stability. Confirmation of this view was obtained by crystallising a specimen, m. p. 163—168°, from water, whereupon the m. p. fell to 155—157°. *iso*Strychnidine is readily soluble in cold methyl and ethyl alcohols, ethyl acetate, acetone, or chloroform, and in boiling benzene, from which a small proportion crystallises on cooling in elongated, rectangular plates. It is sparingly soluble in light petroleum. In the presence of an excess of dilute hydrochloric acid, it gives no coloration with ferric chloride when cold, and a very pale colour on warming. If only a trace of hydrochloric acid is present, an intense rose-red colour develops in a few seconds. The *methosulphate* crystallises from a mixture of alcohol and light petroleum in minute, elongated, rectangular, nearly colourless prisms, m. p. 200—205° (decomp.) (Found: N, 5·9. $C_{23}H_{30}O_5N_2S$ requires N, 6·3%). When heated with methyl-alcoholic potassium hydroxide, it yielded a resinous base that could not be crystallised and was not further investigated.

*Dihydro*iso*strychnidine* (a).—This base was obtained by the electrolytic reduction of dihydro*iso*strychnine. A solution of this (10·1 g.) in a mixture of concentrated sulphuric acid (50 c.c.) and water (80 c.c.) was submitted to a current of 4 amps. (3·7—4·1 volts), the current density at the lead cathode being 0·07 amp./cm.^{2}. The anode cell contained 20% sulphuric acid. At the end of 21 hours the Otto reaction was no longer exhibited, and the *dihydro*iso*strychnidine* (a) was isolated as a pale yellow, gelatinous precipitate (8 g.), which, crystallised from acetone and then twice from benzene, formed pale yellow bunches of needles, m. p. 191—192°. A final crystallisation from light petroleum (b. p. 80—100°) did not alter the m. p. (Found: C, 76·5, 75·9; H, 8·6, 8·1; *M*, in camphor by micro-Rast, 301. $C_{21}H_{26}ON_2,0{\cdot}5H_2O$ requires C, 76·1; H, 8·2%; *M*, 331). On being heated at 110° for 8 hours, the substance lost only 1·0% (theory, 2·7%), and this suggested the possibility that it might be an ether derived from two molecules of the hypothetical hexahydro*iso*strychnine. The molecular-weight determination disposes of this view and makes it necessary to assume that the compound is $2C_{21}H_{26}ON_2,H_2O$, giving $C_{21}H_{26}ON_2$ and $C_{21}H_{26}ON_2,H_2O$ in fused camphor solution. Naturally any water set free would be evaporated at the temperature of fused camphor, and so would not affect the result. The original alkaline mother-liquor, from which this base was collected, was extracted with chloroform, and the gum remaining after removal of the solvent was purified by solution in ethyl acetate and precipitation with light petroleum, followed by two similar processes, using benzene and light petroleum. The product, m. p. 170—190°, then crystallised from water in tiny, colourless leaflets, m. p. 191—192° (Found: C, 75·6; H, 8·1%). This substance was readily soluble in hot water, and was unaltered by further crystallisation. It thus appeared to differ from the specimen first described, but a mixture of the two specimens had m. p. 191—192°. The base from the first precipitate was boiled with 1000 parts of water, which dissolved only 5% of its weight. On evaporation of the solution, nearly colourless leaflets, m. p. 190°, alone or mixed with the original material, were obtained. In all such cases it is very difficult to determine whether we are observing the behaviour of a mixture of isomerides, or whether it is merely an example of the large influence occasionally exerted by traces of impurity on the solubility properties. The base is readily soluble in methyl alcohol, ethyl acetate, or boiling benzene, it is moderately readily soluble in boiling acetone, and sparingly soluble in boiling light petroleum. It exhibited the usual ferric chloride reaction, and was partly recovered unchanged after boiling with phosphoryl chloride and after treatment with nitrous acid.

*Dihydro*iso*strychnidine* (b).—Unlike strychnidine, *iso*strychnidine may be catalytically reduced at the ordinary temperature. The quantities employed were: palladous chloride (0·5 g.), dissolved in water (200 c.c.) and a little hydrochloric acid, norite (7 g.), *iso*strychnidine (2·4 g.), dissolved in a little dilute acetic acid. The volume of hydrogen absorbed in 3 hours was 200 c.c. (theory, 160 c.c.). The filtered liquid was basified with sodium hydroxide, and the gelatinous precipitate collected and boiled with water (800 c.c.). On cooling, the filtered solution deposited copiously small, colourless plates, and these crystallised from water in tufts of slender, colourless needles, m. p. 150°. Further extraction of the crude product yielded nothing. The *dihydro*iso*strychnidine* (b) was twice recrystallised from light petroleum (b. p. 60—80°), giving spongy clusters of colourless needles, m. p. 151—153° after sintering at 140° (Found: C, 73·9; H, 8·2. $C_{21}H_{26}ON_2,H_2O$ requires C, 74·1; H, 8·3%). This material, evidently a monohydrate, lost 3·6% at 110—120° in 4 hours (theory, 5·3%), but some discoloration occurred. The solubilities, except in water, were similar to those of dihydro*iso*strychnidine (a) and the new base gives a rose-red colour on the addition of ferric chloride, even in an excess of dilute hydrochloric acid. Our examination of the isomeric dihydro*iso*strychnidines is not complete and we have not yet sufficient data to enable us to advance any suggestions as to the structural or stereochemical differences that may exist between them. Attempts to obtain one or other of these compounds from dihydrostrychnidine (A) were fruitless. Dihydrostrychnidine (A) is quite unchanged when it is heated with water at 180—185° for 6½ hours or with methyl-alcoholic ammonia at 120—145° for 48 hours.

Dioxyhydroxydihydrostrychnidine.—Strychnidine was unaffected by heating with methyl-alcoholic ammonia at 130—140° for 48 hours and also by treatment with alcoholic sodium ethoxide under various conditions. When heated with water, it yielded the oxidation product here described, but no *iso*strychnidine. Strychnidine (10 g.) was heated with water (300 c.c.) (and some air) at 170—185° for 5½ hours in a phosphor-bronze autoclave; 5 g. of the base were recovered unchanged, and the aqueous solution was concentrated to one-fourth of its original volume, filtered, and kept in the ice-chest. An abundant crystallisation occurred and the *dioxyhydroxydihydrostrychnidine* was recrystallised several times from water; flat, pointed, colourless needles, m. p. 260° (decomp., darkening from 250°) (Found: loss at 105°, 15·3; N, 6·4. Found in anhydrous material: C, 68·6; H, 7·0. $C_{21}H_{26}O_4N_2,4H_2O$ requires H_2O, 16·3; N, 6·3. $C_{21}H_{26}O_4N_2$ requires C, 68·1; H, 7·0%). The anhydrous substance is hygroscopic and recovers almost the whole of its water of crystallisation on exposure to the air for a week. The base is much more readily soluble in water than any other strychnine derivative (except the salts) described in this memoir; it is also readily soluble in the simple alcohols and in boiling benzene or chloroform, but very sparingly soluble in hot ethyl acetate or light petroleum. The ferric chloride reaction is exhibited well in the presence of a large excess of hydrochloric acid.

Dioxyhydroxyhexahydrostrychnine.—When tetrahydrostrychnine was heated with methyl-alcoholic ammonia at 130—140° for 48 hours, it was recovered entirely unchanged. Tetrahydrostrychnine (11 g.) was heated with water (300 c.c.) in a phosphor-bronze autoclave at 170—185° for 6½ hours. The brownish-yellow liquid was filtered from a little black material, concentrated somewhat, again filtered from a tar, and kept in the ice-chest. Bunches of coarse needles (3 g., m. p. 197—203°) separated, and several recrystallisations from water yielded bunches of large, fibrous, colourless needles, m. p. 201—203° (with effervescence a few degrees higher) (Found: loss at 105°, 9·3. Found in anhydrous material: C, 64·9; H, 6·9;

N, 7·1. $C_{21}H_{28}O_5N_2,2H_2O$ requires H_2O, 8·5. $C_{21}H_{28}O_5N_2$ requires C, 65·0; H, 7·3; N, 7·3%). Neither in the case of this base nor in that of the corresponding compound from strychnidine (see the preceding section) is the formula with two hydrogen atoms less excluded by the analyses. The substance is readily soluble in methyl alcohol, sparingly soluble in cold ethyl alcohol, and very sparingly soluble in boiling benzene, chloroform, ethyl acetate, or acetone. It is moderately readily soluble in cold water, but less soluble than the similar strychnidine derivative. With ferric chloride in presence of much dilute hydrochloric acid, it gives only a faint brown coloration; in presence of a trace of hydrochloric acid, an intense brownish-red colour develops rapidly.

p-*Aminostrychnidine.*—The various derivatives of strychnidine all couple with diazobenzenesulphonic acid in acid solution, giving in the course of time equally intensely-coloured solutions, but the speed of the reaction varies greatly from case to case. In acid solution strychnidine couples much more rapidly than dihydrostrychnidine (A), but in neutral solution the velocities are not very different. We interpret this as due to the increased basic strength of the dihydrostrychnidine (A), and it therefore seems probable that the double bond of strychnidine is not far distant in the molecule from the nitrogen atom that is bound to the aromatic nucleus. *Sulphobenzeneazostrychnidine* is a crimson powder, insoluble in organic solvents. The finely powdered substance (2·6 g.) was added to a solution of hydrated stannous chloride (6·5 g.) in concentrated hydrochloric acid (16 c.c.), and the mixture boiled for a few minutes. It was then cooled, rendered strongly alkaline with sodium hydroxide, and extracted with chloroform. The extracts were dried and evaporated until crystallisation began; much light petroleum was then added. The nearly colourless precipitate crystallised from benzene in microscopic prisms which decompose above 330° (Found: N, 12·4. $C_{21}H_{25}ON_3$ requires N, 12·5%). *Aminostrychnidine* is moderately readily soluble in chloroform, sparingly soluble in hot benzene, and practically insoluble in boiling ethyl acetate or light petroleum. This amine gives, with ferric chloride in hydrochloric acid solution, an eosin-red coloration, quickly fading to yellow; addition of sodium nitrite to an acid solution produces the same colour change, but if the solution is used at once it can be shown to contain a diazonium salt. The product of coupling with β-naphthol and H-acid is violet, and with J-acid red. Diazotised sulphanilic acid and aminostrychnidine give a purple coloration, probably not due to a normal azo-compound since it is discharged by the addition of sodium hydroxide. The most interesting colour reactions of aminostrychnidine are, however, the following, which show that strychnidine has free *m*- and *p*-positions with respect to the nitrogen atom. When ferric chloride is added to a solution of the base in dilute hydrochloric acid containing hydrogen sulphide, a brownish-reddish-purple colour is produced and the solution exhibits an intense brown fluorescence. Addition of ferric chloride to an acid solution containing dimethylaniline gives a royal-blue colour, doubtless owing to the formation of an indamine of the type of Bindschedler's green. If *m*-tolylenediamine is employed in place of the dimethylaniline, a deep blue coloration is developed, and on warming, the solution becomes intense bluish-eosin-red, and on dilution exhibits a striking greenish-yellow fluorescence.

Sulphobenzeneazomethylstrychnine.—Methylstrychnine (0·75 g.) was dissolved in very dilute acetic acid (200 c.c.) and diazobenzenesulphonic acid (0·85 g., 2·2 mols.) added with stirring. A red oil quickly formed and solidified; this was collected and crystallised from much hot alcohol as a dull brick-red powder (Found: N, 9·7%, showing that only one sulphobenzeneazo-group has been introduced). The *substance* is insoluble in organic solvents with the exception of the simple alcohols; it is moderately soluble in cold water, but a change occurs on boiling, the colour deepens and the solid that separates on cooling is readily soluble in cold acetone.

Strychnic Benzoic Anhydride.—Benzoyl chloride (5 c.c.) was gradually added to a well-agitated solution of strychnic acid (4 g.) in 3% aqueous sodium hydroxide (100 c.c.). The light brown precipitate was collected and crystallised from xylene–light petroleum (b. p. 80—100°) in golden-yellow clusters of minute rods, m. p. 215—218° (Found: C, 73·6, 73·7; H, 6·2, 6·4; N, 6·2, 6·3. $C_{28}H_{28}O_4N_2$ requires C, 73·7; H, 6·2; N, 6·1%). A product requiring less purification, and otherwise identical, is obtained from strychnic acid (6 g.), sodium bicarbonate (14 g.), water (200 c.c.), and benzoyl chloride (8 c.c.). This substance is insoluble in dilute aqueous sodium hydroxide and is *slowly* hydrolysed on boiling the solution; it is also hydrolysed on boiling with water. It is, however, *immediately* hydrolysed by dissolution in cold dilute aqueous acids, even acetic acid, and addition of sodium hydroxide then precipitates strychnine. The behaviour of this compound seems inconsistent with any theory of its nature other than that which we have advanced—the formation of mixed anhydrides in the Schotten–Baumann process has frequently been observed in other cases.

Addendum made on October 3rd, 1927. After the present paper had been set up in proof, the discovery was made that dihydrostrychnidine (A), m. p. 212—214°, is identical with the substance described in Part IV (this vol., p. 1622) as methyl-ψ-dihydrostrychnidine, $C_{22}H_{28}ON_2$, m. p. 212°. The latter was obtained in very poor yield by the action of heat on the dimethochloride (A) of methoxymethyltetrahydrostrychnidine and it was thought that its formation was due to the following change: $C_{23}H_{32}O_2N_2,2MeCl = C_{22}H_{28}ON_2 + 2MeCl + MeOH$.

It is now clear that a more drastic decomposition must take place and that a $>CH_2$ group also is lost at the high temperature necessary for the change. The identity of the substance thus produced with dihydrostrychnidine (A) was proved by a close comparison of the properties, and also by the m. p. (212—214°) of a mixture, of the two preparations. Moreover the analysis given in Part IV, p. 1622 (Found: C, 78·1; H, 8·0; N, 8·5) agrees rather better with the formula $C_{21}H_{26}ON_2$ (Calc.: C, 78·2; H, 8·1; N, 8·7%) than with the formula $C_{22}H_{28}ON_2$ (Calc.: C, 78·6; H, 8·3; N, 8·3%) suggested at the time, and the same applies to the analyses of the derivatives.

It is also clear that the substance described as methyl*neo*dihydrostrychnidinium iodide (*loc. cit.*, p. 1623), obtained from methoxymethyltetrahydrostrychnidine hydriodide by the action of heat, is in reality dihydrostrychnidine (A) methiodide, and a similar correction must be applied to the corresponding chloride. It is therefore necessary in Part IV, pp. 1596, 1597, 1621, 1622 and 1623, to replace the names methyl-ψ-dihydrostrychnidine by dihydrostrychnidine (A) and methyl*neo*dihydrostrychnidinium iodide (chloride) by dihydrostrychnidine (A) methiodide (methochloride). It is also probable that the substance, m. p. 220—221°, described as methyl-ψ-dihydrobrucidine in Part V of this investigation (this vol., p. 1661) is in reality dihydrobrucidine (A), but the proof of this cannot be supplied until this substance has been obtained by a process similar to that employed in the preparation of dihydrostrychnidine (A). Experiments with this object in view are in progress.

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