165. *Strychnine and Brucine. Part XIX. Reduction of Strychnine Methosulphate by Means of Sodium Amalgam in the Presence of Carbon Dioxide.*

By (the late) WILLIAM HENRY PERKIN, jun., ROBERT ROBINSON, and JOHN CHARLES SMITH.

THE attempt to apply the method of exhaustive methylation to the problem of the degradation of strychnine and strychnidine derivatives has not met with unqualified success because, although one of the rings may be readily broken, there is a remarkably strong tendency for the system to be reconstituted at a later stage. Thus methylstrychninium and methylstrychnidinium salts are converted by alcoholic potash into methoxydihydro*neo*strychnine and methoxydihydro*neo*strychnidine, respectively, and the action of hot dilute acids on these bases affords the methyl*neo*strychninium and methyl*neo*strychnidinium salts in which the original structure recurs.

In order to avoid this difficulty we have had recourse to Emde's method of degradation of quaternary ammonium salts (*Annalen*, 1912, **391**, 88) by reduction with sodium amalgam in neutral, acid, or weakly alkaline solution. One of us has already employed this device in the investigation of cryptopine and protopine with gratifying results (J., 1916, **109**, 815; 1919, **115**, 713) and a preliminary study of its applicability in the case of the *Strychnos* bases has been made. The present communication deals with some methylstrychnine derivatives and later we hope to submit the results of a parallel investigation in the methylstrychnidine series. The first important point to be noticed is that strychnine methosulphate gives a gummy base; dihydrostrychnine methosulphate appears to be unchanged by the reducing agent (compare Part VI, J., 1927, 2395).

We are greatly indebted to Mr. G. Davies, M.Sc., for carefully confirming these facts in regard to the behaviour of methyldihydrostrychnine.

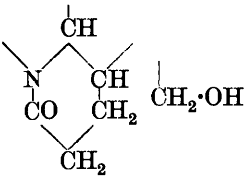
This is strongly in favour of the view, frequently advanced and advocated in this series of papers, that strychnine contains the group C:C·C·N(b), the ethenoid link represented being saturated in the formation of dihydrostrychnine. Bases of allylamine type, when converted into quaternary ammonium salts, are readily attacked by sodium amalgam, often in cases such that the related saturated salts are quite stable under the same conditions of experiment. Thus benzyltrimethylammonium chloride furnishes toluene, and not methane, on reduction; phenyldimethylallylammonium chloride gives propylene and dimethylaniline, whereas phenyldimethyl-β-hydroxyethylammonium chloride yields benzene and hydroxyethyldimethylamine (Emmert, *Ber.*, 1912, **45**, 430) and there are many other instances that could be cited.

The product of the reduction is an amorphous base, $C_{22}H_{28}O_2N_2$, which is essentially a methyltetrahydrostrychnine and possibly a mixture of stereoisomerides. The crude material contains certain crystalline by-products, the examination of which is not complete.

Clues to the nature of the main product are that it contains NMe and that on distillation it loses water with formation of a substance, $C_{22}H_{26}ON_2$, again an amorphous base, mixed with crystalline by-products. Furthermore, all these substances—main products or by-products—exhibit the strychnine-type of colour reactions and therefore the original group N(a)·CO remains unchanged throughout.

The oxygen lost on distillation of $C_{22}H_{28}O_2N_2$ is accordingly that present in the cyclic ether group of the alkaloid. Electrolytic reduction of $C_{22}H_{28}O_2N_2$ gives a base, $C_{22}H_{30}ON_2$, which is *not* decomposed on distillation. This contrast would be inexplicable if the cyclic ether oxygen, when transformed into a hydroxyl group, did not remain in its original position relative to N(a)·CO.

If the group (I) were reduced to (II), the stability of the electrolytically reduced base [which shows strychnidine-type reactions and must contain N(a)·CH_2] would be inexplicable, but the production of (III) would afford a ready explanation of the phenomenon. In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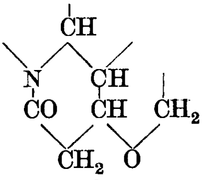
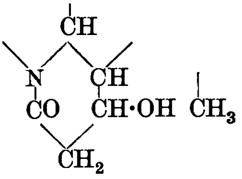
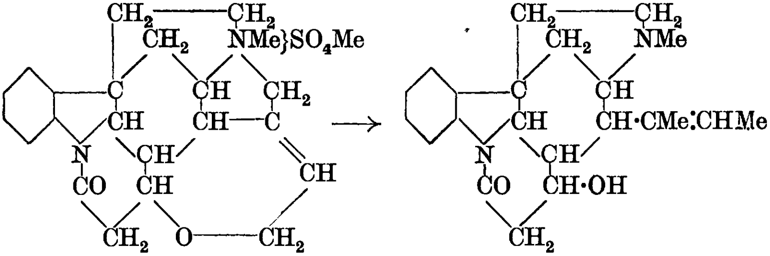

(I.)


(III.)

this case the loss of water suffered by $C_{22}H_{28}O_2N_2$ on distillation is the result of the occurrence of the hydroxyl group in the β-position to carbonyl; clearly the base $C_{22}H_{30}ON_2$ no longer exhibits this constitutional feature. The main product, $C_{22}H_{28}O_2N_2$, is probably derived from the methylstrychninium salt by fission of the quaternary ammonium and cyclic ether structures and on the basis of the formula advanced in Part XVIII (this vol., p. 780) it would be represented in the following manner:

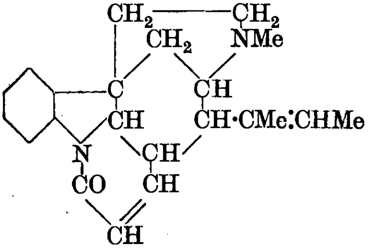


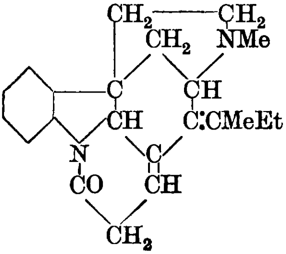
In conformity with this view the product $C_{22}H_{28}O_2N_2$ absorbs hydrogen in the presence of palladium and on distillation of the reduced base water is eliminated and the product will absorb more hydrogen in the presence of the catalyst.

The crude material obtained by distillation of $C_{22}H_{28}O_2N_2$ has approximately the composition $C_{22}H_{26}ON_2$ and the individual substances that have been separated from this are all tertiary bases containing NMe and N(a)·CO.

One of these, m. p. 200—201°, has the formula $C_{22}H_{26}ON_2$ and, as required by the theory, may be catalytically reduced to a base $C_{22}H_{28}ON_2$ and with greater difficulty to $C_{22}H_{30}ON_2$.

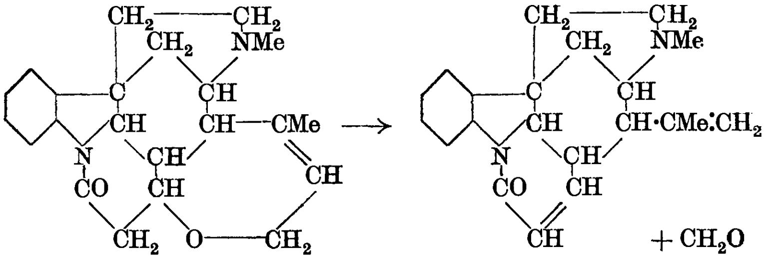
It appears that the original ethylenic linkage of strychnine might retain its original position or move to that occupied in *neo*strychnine, whilst the new ethylenic bond produced by dehydration of the alcohol, $C_{22}H_{28}O_2N_2$, might also occupy one of at least two positions. Consequently (on the basis of the strychnine formula already quoted) there are at least four possible formulæ for the substance $C_{22}H_{26}ON_2$. Two are represented below, and the other two can be derived by combining the double bond positions in the other two possible ways.





We have no information bearing on the problem of the order of saturation of the ethenoid groups in the process of catalytic hydrogenation.

A second pure constituent of the crude distilled $C_{22}H_{28}O_2N_2$ is a base $C_{21}H_{24}ON_2$, m. p. 172°. This substance contains NMe, and therefore a carbon atom of the strychnine skeleton has been extruded and as this carbon is eliminated together with an oxygen atom we conclude that some simple molecule such as carbon monoxide or formaldehyde has been formed in the decomposition. The following scheme represents our present view of the nature of the process; we start with the assumption that the crude $C_{22}H_{28}O_2N_2$ contains some $C_{22}H_{26}O_2N_2$:



In agreement with this suggestion the new base, *desmethylene-anhydrotetrahydromethylstrychnine*, is catalytically reduced to a dihydro-derivative and then absorbs more hydrogen. The analytical results for the tetrahydro-derivative were not, however, so sharp as could be desired.

Again the group N(a)·CO was diagnosed by the method of electrolytic reduction, the product being a base $C_{21}H_{28}N_2$. This shows the behaviour of a strychnidine analogue and it will be noticed that one of the double bonds has been reduced in addition to the lactam grouping. The formula given above is obviously only one of several isomeric possibilities depending on the position of the double bonds.

A third crystalline substance isolated from the distillation product of $C_{22}H_{28}O_2N_2$ is a well-defined base, m. p. 218°, with previous softening. It has the composition $C_{22}H_{28}ON_2$ or $C_{23}H_{28}ON_2$ and has not yet been completely investigated. It contains NMe and N(a)·CO and does not give a benzylidene, acetyl or nitroso-derivative.

When all crystalline products have been separated from the bases obtained by distilling crude $C_{22}H_{28}O_2N_2$, there remains a gummy base, $C_{22}H_{26}ON_2$, which gives a *methiodide* and an especially characteristic *methochloride*. The action of hot aqueous potassium hydroxide on this appears to bring about the formation of a *methine*, $C_{23}H_{28}ON_2$. In this base three of the seven rings of strychnine are broken, and if it were more readily accessible further investigation would be of much interest.

EXPERIMENTAL.

Strychnine Methosulphate.—In methyl-alcoholic solution the components invariably yielded a relatively large proportion of strychnine methyl hydrogen sulphate, but when finely powdered strychnine (200 g.) was ground with freshly distilled methyl sulphate (136 c.c.) the mass soon solidified; it was broken up, and employed for the reduction after some 12 hours.

Reduction of Strychnine Methosulphate with Sodium Amalgam.—The methosulphate (from 200 g. of strychnine) was dissolved in boiling water (1800 c.c.) in a large dish, sodium amalgam (1000 g. of 3%) added, and the liquid stirred by a rapid stream of carbon dioxide; a grey oil soon separated. After ½ hour, a further equal quantity of sodium amalgam was added, and stirring continued until no more oil was produced. The oil hardened on cooling and was then collected, ground, washed with water, dried in the air, and dissolved in alcohol-free ether. The extract was dried with potassium carbonate, concentrated to about 350 c.c., and kept in the ice-chest; a small crystalline crust (A) was then deposited. The clear solution was evaporated, leaving a golden-yellow syrup (80 g.). In various experiments the yield was approximately 50%. This product is designated K (Found: C, 75·4, 75·3; H, 7·3, 7·4; N, 8·0, 7·9. $C_{22}H_{26}O_2N_2$ requires C, 75·4; H, 7·4; N, 8·0. $C_{22}H_{28}O_2N_2$ requires C, 75·0; H, 7·9; N, 7·9%). The constituent, $C_{22}H_{28}O_2N_2$, is termed *tetrahydromethylstrychnine*-K.

The investigation was resumed after some years and the method then adopted was as follows.

Strychnine methosulphate was prepared from the base (20 g.) and methyl sulphate (2 mols.) in boiling benzene solution (*ca.* 1000 c.c.); the product, crystallised from methyl alcohol, was free from strychnine salts: even the crude substance had m. p. 280° (lit., 282°).

A solution of the methosulphate (100 g.) in water (700 c.c.) was heated to 90° and stirred by means of a rapid current of carbon dioxide. Sodium amalgam (300 g. of 4%) was added and, as before, a grey semi-solid product rose to the surface; this was immediately removed. At intervals of 15 minutes two further equal quantities of the amalgam were introduced. The product was washed, dissolved in dilute hydrochloric acid (1000 c.c.), and the solution repeatedly filtered until clear; it was then diluted with water and crushed ice (1000 g.) and basified with dilute aqueous ammonia. After being washed, and dried over calcium chloride, the light yellow powder (35—45 g.) had m. p. 65—150° and was easily soluble in the usual organic solvents except light petroleum (Found: C, 75·1; H, 7·9%).

The evidence from numerous analyses of K is that it consists essentially of one or more substances $C_{22}H_{28}O_2N_2$, possibly mixed with some $C_{22}H_{26}O_2N_2$ or other substances in smaller relative amount. The colour developed on the addition of dichromate to a solution of K in 50% sulphuric acid is intense purple and the material exhibits no reactions of the strychnidine type. It is slowly oxidised by permanganate in acetone solution.

The dried powder (20 g.), dissolved in acetic acid (20 c.c.) and water (250 c.c.), absorbed 1250 c.c. of hydrogen in 18 hours at 12° in the presence of palladium (from 3 g. of palladous chloride) and charcoal (15 g.). Theoretically, 20 g. of a substance $C_{22}H_{28}O_2N_2$ require 1274 c.c. of hydrogen for the saturation of one double bond. The product, like K, was amorphous and, on distillation under 1 mm., decomposition did not set in until the temperature reached 320°. At 365° frothing occurred and the whole product (12·1 g.) was then found to absorb 540 c.c. of hydrogen in the presence of palladised charcoal (theory, 830 c.c.). We conclude from this experiment that when hydrogenated K is distilled, the product is unsaturated, and it will be noted that the decomposition by distillation was incomplete, a circumstance accounting for the fact that only two-thirds of the required volume of hydrogen was absorbed.

Examination of the Crystalline Crust (*A*).—Some specimens of K were worked up with the object of increasing the yield of the crystals, the ether being more carefully dried, the solution concentrated until a nearly 30% solution of bases was obtained, and the liquid kept at − 5° for several days. The crystals separated in circular warty aggregates and the liquid was often filled with soft colourless needles (m. p. 168—175°). This material (25 g.) was crystallised from ether, in which it was very sparingly soluble, and then from methyl alcohol. The melting point was thus raised to 177—180°, 193° with previous softening, and ultimately to 200° (K^1) (Found: C, 78·5; H, 7·7; N, 8·3%).

A second portion of the solid (A) (30 g.) was powdered and extracted with boiling ether, leaving an extremely sparingly soluble residue of flakes containing inorganic contamination. The solution on concentration gave successive crops: (a) needles (2 g.), m. p. about 275°, (b) prismatic needles (2 g.), m. p. 287°, (c) needles (3 g.), m. p. 270—275°, (d) soft needles (5 g.), m. p. 177—185°. The last fraction was recrystallised from methyl alcohol and its m. p. was raised to 198—200° (evidently K^1). The fraction (a) was recrystallised from much methyl alcohol and obtained as a crystalline crust, m. p. 290°, identical in all respects with strychnine. This was confirmed by the preparation of the methiodide, pale amber needles (Found: C, 55·3; H, 5·3. Calc. for $C_{22}H_{25}O_2N_2I$: C, 55·4; H, 5·2%), which was directly compared with an authentic specimen. It was not certain that the strychnine isolated in this way was a real product of the reduction, and special experiments were therefore made in which the strychnine methosulphate solution was carefully freed from any strychnine by rendering it alkaline, keeping it in the ice-chest, and filtering it from traces of the base that might be deposited. In this case the most sparingly soluble constituent of the crust (A) was obtained as a colourless crust, deposited from methyl alcohol; after several recrystallisations this had m. p. 277° (K^2) (Found: C, 75·1; H, 6·7. $C_{21}H_{22}O_2N_2$ requires C, 75·4; H, 6·6%). A second substance separated in needles after the separation of K^2 without further concentration. It had m. p. 267° (K^3) (Found: C, 73·1; H, 7·2%). K^2 and K^3 are apparently not identical with each other or with strychnine, but further investigation of these substances is necessary. A large number of fractions, m. p. above 200°, having accumulated, they were all combined (30 g.) and fractionally crystallised from ethyl alcohol. Crop I, m. p. 258° (5 g.), was unfortunately lost. Crop II was a crust of gritty prismatic needles, m. p. 232—245° (*ca.* 12 g.) (Found: C, 73·8; H, 6·6%). Crop III, m. p. 232—245° (6 g.), and IV, m. p. 230—240° (2 g.), were also needles (Found: C, 73·9; H, 6·9%), whereas V, obtained by slow evaporation in the air, was a hard crust (5·5 g.).

Crop III furnished a methiodide which crystallised from methyl alcohol in prismatic needles, m. p. 295—297° (decomp.) (Found: C, 57·0; H, 5·7%). It is probable that these fractions consisted of mixtures of K^2, K^3, strychnine, and perhaps other substances.

The more readily soluble constituent (K^1) of the crust (A) did not readily combine with methyl iodide in boiling methyl-alcoholic solution and could thus be purified. A specimen of the fraction, m. p. 175—180° (15 g.), was mixed with methyl iodide (30 c.c.) and methyl alcohol (100 c.c.) and the solution refluxed for ½ hour. After distillation of methyl iodide and a part of the methyl alcohol, the cooled solution deposited crystals, m. p. 190—195° (7 g.). Recrystallisation gave needles, m. p. 198—200°, identical with K^1. The methiodide (K^4, MeI) in the methyl-alcoholic mother-liquor was obtained from the first and last of five fractions (the intermediate fractions had much lower melting points) and after recrystallisation from methyl alcohol was obtained in brilliant colourless prisms, which became pink at 210° and frothed vigorously at 235—237° (Found: C, 56·7; H, 6·1%).

It must be emphasised that the above constituents of K are only by-products which it has been possible to examine owing to the very large scale of our operations. The main product is the uncrystallisable gum, essentially $C_{22}H_{28}O_2N_2$.

Electrolytic Reduction of K.—The gum (80 g.), dissolved in 20% sulphuric acid (700 c.c.), was reduced for 20 hours at 18° by a current of 4—5 amps. The product was isolated by means of ether from a strongly alkaline solution, and the crude syrup (66 g.) distilled in a high vacuum, b. p. 240—243°/1 mm. on a second fractionation (Found : C, 78·4, 78·3; H, 8·9, 8·8. $C_{22}H_{30}ON_2$ requires C, 78·1; H, 8·9%). This substance gives strychnidine-type reactions : for example, an intense crimson on the addition of a bichromate to its solution in 50% sulphuric acid. It evidently bears the relation to the main constituent of K that strychnidine does to strychnine. The substance may be designated *tetrahydromethylstrychnidine-K*. It does not readily yield a crystalline methiodide, but it is a strong base. Qualitatively the presence of a hydroxyl group was proved by treatment with a large excess of benzoyl chloride. The resulting deep green oil was treated with dilute hydrochloric acid and the mixture repeatedly washed with ether; the oil was then recovered from the aqueous solution and on hydrolysis with aqueous potassium hydroxide it afforded a considerable relative amount of benzoic acid.

Distillation of K.—This process has been frequently carried out and a number of different products of the reaction have been isolated. The experiment leading to the separation of the two bases which have been most carefully characterised was as follows :

Crude K (50 g.) was heated under 1 mm. pressure with a small flame for ½ hour; effervescence then occurred and steam was evolved. The oil was thereafter distilled rapidly until frothing set in, heating with a small flame then being resumed for 15 minutes. These periods of distillation and heating for decomposition were alternated until the whole had been distilled. It is necessary to arrange the apparatus in such a way that a volatile sublimate does not choke the side tubes; therefore these were wide, and not more than 3 inches long, and the side tube of the receiving flask was fitted into a tower containing spun glass. The distillate, a pale brown resin, was twice redistilled; b. p. 245°/0·3 mm., remarkably constant (Found : C, 79·5; H, 8·0. $C_{22}H_{26}ON_2$ requires C, 79·0; H, 7·8%). When the resin from 5 such operations (190 g.) was ground with light petroleum (b. p. 60—80°), much dissolved and a considerable amount of crystalline material separated; the liquid was boiled until all the resin had disappeared and was then filtered hot, and the residue washed with light petroleum. This material (35 g.) had m. p. 155—165°. The light petroleum mother-liquor was again distilled, finally at 1 mm., and the recovered resin (105 g.) again treated with light petroleum (yield of solid, 15 g.). Again the mother-liquor was distilled (resin, 75 g.) and the product now afforded a solid (10 g.) and a distilled resin (55 g.), which was converted into a well-crystallised methiodide (K^9,MeI; see below). The solid bases crystallised from methyl alcohol in needles and short thick prisms (the latter, separated mechanically, had m. p. 198—200°), and this mixture was separated by means of ether, in which the prisms (Y) were almost insoluble. The ethereal solution after concentration deposited a voluminous mass of soft needles, m. p. 158—162°; on recrystallisation from alcohol the m. p. was raised to 168—169°. This apparently homogeneous product is still a mixture and although a rough separation can be effected by means of ether, the process is wasteful.

A better method depends on fractional basification of an acid solution with ammonia. The mixed bases (2·0 g., m. p. 164—166°) were dissolved in the minimum of dilute hydrochloric acid, and the solution was diluted to 150 c.c., heated to boiling, and vigorously stirred. *N*/10-Ammonia solution was then gradually added drop by drop until a crystalline precipitate was obtained. The base was so divided into fractions (a) 0·15 g., m. p. 184—195°, (b) 0·3 g., m. p. 177—179°, (c) 0·7 g., m. p. 168—170°, (d) 0·35 g., m. p. 169—171°, (e) 0·3 g., m. p. 169—170°. In working up 10 g. of the bases in a similar fashion, 7 fractions, averaging 1·2 g., were obtained and the volume of *N*/10-ammonia required to yield each fraction was 50 c.c. The first two fractions and in general all specimens fusing above 175° gave on recrystallisation from ethyl alcohol the base K^5, m. p. 200—201°; the later fractions of lower m. p., also crystallised from alcohol, afforded K^6, m. p. 172—173° (see below).

The mixture of needles and prisms (see above) crystallised from methyl alcohol contained about 30% of K^5 and 70% of K^6. It is impossible, however, to give even an approximate estimate of the amount of K^5 and K^6 in the crude distilled K.

In some of the earlier experiments the whole product was dissolved in light petroleum (instead of being washed hot as above) and the crystals that separated on keeping (25 g. from 90 g. of the distilled K) were dissolved in pure ether and the solution kept in the ice-chest. The first fraction separated in plates (the second fraction of soft needles gave results similar to those already described) and on repeated crystallisation from ether was obtained in pale yellow prisms (0·4 g.), m. p. 182—184° (Found: C, 74·6; H, 7·8%). In a second, entirely fresh experiment the same substance (0·3 g., m. p. 184°) was obtained (Found: C, 74·8; H, 7·8; N, 8·0. $C_{22}H_{28}O_2N_2$ requires C, 75·0; H, 7·9; N, 7·9%). This substance (K^7) appears to be a *hydrate*, since it combines with methyl iodide at 100° in a sealed tube with formation, by dehydration, of a *methiodide* which crystallises from methyl alcohol in short prisms, m. p. 250° (decomp.) (Found : C, 57·6, 57·8; H, 6·0, 6·1. $C_{23}H_{29}ON_2I$ requires C, 58·0; H, 6·1%). The Otto reaction of K^7 in 60% sulphuric acid is red, rapidly fading, whereas K^5 and K^6 give a more normal strychnine-type reaction.

Starting from strychnine (1200 g.) and working as described up to the crystallisation from light petroleum and then crystallising the product twice from ether and once from methyl alcohol, we obtained 110 g., m. p. 158—170°. This material was repeatedly extracted with ether and five successive crops of the usual K^5K^6 mixtures were isolated. These (total weight, 79 g.), tested by the ammonia precipitation method, contained 30—35% of K^5. The ethereal mother-liquors on concentration deposited two crops of similar character and then some colourless needles, m. p. 155—158°, which seem to consist of a new substance (K^8) (Found : C, 79·5; H, 8·1; N, 8·1. $C_{23}H_{28}ON_2$ requires C, 79·3; H, 8·0; N, 8·0%). The Otto reaction of this substance was of strychnine type and no coloration was developed on addition of ferric chloride to a solution in very dilute hydrochloric acid. No specimen of this base is available, so our suggestions in regard to it are provisional.

Finally, it has already been mentioned that the product of distillation of K that could not be crystallised and remained in the light petroleum mother-liquors was converted into a methiodide. The syrup (20 g.) (Found : C, 77·9; H, 7·8; N, 8·5%) was dissolved in methyl alcohol and methyl iodide (20 c.c.) and heated on the steam-bath. The liquid boiled without further application of heat, but the reaction was completed by refluxing for 1 hour. On removal of the solvent by distillation there was a crystalline residue, which, after being washed with methyl alcohol, crystallised from this solvent in groups of colourless needles, m. p. 265—270° (slow decomp.) (Found : C, 58·4; H, 6·2. $C_{23}H_{29}ON_2I$ requires C, 58·0; H, 6·3%). This *methiodide* (K^9,MeI) is sparingly soluble in boiling water and crystallises from this solvent in long colourless needles of constant m. p. 265—270°. The related *methochloride*, prepared in the usual manner, is a very characteristic salt, crystallising with great facility from water in long quadrilateral tablets, m. p. 255° (vigorous effervescence, leaving a pale brown syrup) (Found in material dried at 100° : C, 72·4; H, 7·4. $C_{23}H_{29}ON_2Cl$ requires C, 71·8; H, 7·5%). The glistening crystals become opaque at 100° or on boiling with methyl alcohol and the clear solution deposits prisms and needles. The solution in sulphuric acid (60% by vol.) gives a deep bluish-purple coloration with a trace of a dichromate. The methochloride evolved methyl chloride when heated; the residual syrup (K^9) was dissolved in dilute hydrochloric acid (norite), precipitated with ammonia, dried, and distilled under 1 mm. (Found : C, 79·2 ; H, 7·9 ; N, 8·6. $C_{22}H_{26}ON_2$ requires C, 79·0 ; H, 7·8 ; N, 8·4%). It seems that K^9, which is the main product of the distillation of K, has the composition of a methyltetrahydrostrychnine, but all attempts to crystallise this substance have been fruitless.

When a concentrated solution of K^9 methochloride was mixed with 50% aqueous potassium hydroxide a voluminous crystalline precipitate, probably consisting of the methohydroxide, was thrown down and, on heating on the steam-bath, this was converted into an oil having a curious coppery lustre and solidifying on cooling. The solid was collected, dissolved in methyl alcohol, and mixed with ether, the alcohol removed by washing with water, and the ethereal solution dried over potassium carbonate and evaporated. The residual gum solidified when rubbed ; traces of oil were removed by washing with ether and draining on porous porcelain, and the colourless crystals were carefully dried over sulphuric acid ; m. p. 70—75° (Found : C, 79·5 ; H, 8·1. $C_{23}H_{28}ON_2$ requires C, 79·3 ; H, 8·0%). This substance (K^{10}) appears to be a methine derived from K^9. It gives a bluish-purple Otto reaction, and no coloration with ferric chloride in dilute acid aqueous solution.

The prisms (Y, above), crystallised from ethyl alcohol and from methyl alcohol–ethyl acetate, were obtained in characteristic prisms, m. p. 218° with previous softening. This substance (K^{11}) is further described below; there was little loss in obtaining it from the fraction of distilled K that was most sparingly soluble in ether (later experiments in which K^7 was not encountered).

Note on the Determination of Molecular Weights of Bases by Means of Sparingly Soluble Chloroaurates.—The chloroaurate derived from K^5 ($C_{22}H_{26}ON_2$; *M*, 334), prepared in hydrochloric acid of various concentrations and dried at 20° and 40° or even 100°, had m. p. 183—184° (decomp.) and gave Au, 28·87—28·90% (four specimens). The apparent molecular weight of the base was therefore 343. After the salt had been heated at 130°/0·2 mm. over phosphoric oxide for 2 hours, it gave Au, 29·36% (*M*, 332). Evidently $K^5,HAuCl_4$ contains $\frac{1}{2}H_2O$.

Hydration of chloroaurates appears to be a rather common phenomenon ; *e.g.*, Fischer (*Ber.*, 1902, **35**, 1593) found that betaine chloroaurate occurred with $1\frac{1}{2}H_2O$. In order to avoid this inconvenience we have adopted a direct method, suggested to us by Dr. B. Lambert, which is applicable to sparingly soluble chloroaurates. The base (0·04 g. may be used) was converted into the chloroaurate by means of a slight excess of the reagent in a solution cooled to 0° and the whole precipitate was collected and ignited;

very consistent results were obtained. All the weighings were made on a micro-balance.

Anhydrotetrahydromethylstrychnine-K^5.—This base crystallises in prisms with almost flat ends, m. p. 200—201° [Found : C, 79·1; H, 7·9; N, 8·7; Me(N), 4·6; *M*, by direct chloroaurate method, 333. $C_{22}H_{26}ON_2$ requires C, 79·0; H, 7·8; N, 8·4; Me, 4·5%; *M*, 334]. It is sparingly soluble in hot light petroleum or ether and in cold acetone, methyl or ethyl alcohol and readily soluble in cold benzene or chloroform. The Otto reaction is an intense purple and the strychnidine-type reactions, for example, with ferric chloride, are not exhibited. The base is immediately oxidised by potassium permanganate in acetone solution.

A solution of the base-K^5 (0·9 g.) in alcoholic sodium ethoxide (2 g. of sodium in 60 c.c. of alcohol) was kept for 15 hours at 70°. The recovered base was recrystallised from alcohol and proved to be unchanged (m. p. 192—197°; mixed m. p. 197—199°). Neither somerisation nor hydrolysis occurred under the above conditions.

Dihydroanhydrotetrahydromethylstrychnine-K^5.—A solution of the base-K^5 (1·0 g.) in 20% acetic acid (25 c.c.) was mixed with palladised charcoal (0·1 g. of palladous chloride and 1 g. of charcoal) and shaken with hydrogen at 19° for 40 minutes, 69 c.c. (at N.T.P.) of hydrogen being absorbed (calc. for saturation of one double bond, 67 c.c.). The reduced *base* (0·85 g.), crystallised from methyl alcohol–light petroleum and then from methyl alcohol, formed brilliant, hexagonal prisms, m. p. 160° (mixed with dihydro-K^6, m. p. 160—162°, the m. p. was depressed by 20°) (Found : C, 78·7; H, 8·3. $C_{22}H_{28}ON_2$ requires C, 78·6; H, 8·3%). This base is easily soluble in most organic solvents except light petroleum and cold methyl alcohol. It gives no reaction with 60% sulphuric acid and a dichromate, but a solution in concentrated sulphuric acid develops, on addition of potassium dichromate, a transient purple colour, changing to red-brown, orange-brown, and brownish-green. The base gives no colour reaction with Ehrlich's reagent or with ferric chloride in weakly acidic solutions; it appears to be stable to permanganate in cold acetone solution.

Tetrahydroanhydrotetrahydromethylstrychnine-K^5.—The base-K^5 (1·0 g.) was reduced as above, with twice the relative proportion of catalyst, for 3 hours at 18°, 81 c.c. of hydrogen (at N.T.P.) being absorbed, and then at 70—75° for 2 hours. The total volume of the gas absorbed was 136 c.c. and further shaking at 75° produced no change. The product (0·7 g.), crystallised from benzene–light petroleum, had m. p. 156—161°; recrystallised from methyl alcohol, it formed prisms, m. p. 163—164° (depressed about 20° by admixture with $C_{22}H_{28}ON_2$-K^5, m. p. 160°) (Found : C, 77·9; H, 8·9.

$C_{22}H_{30}ON_2$ requires C, 78·1; H, 8·9%). The crystals of this base were characteristically shaped with one end pointed, like miniature stakes.

When a trace of solid potassium dichromate was rapidly ground into a solution of the base in concentrated sulphuric acid a reddish-violet coloration was produced; this soon changed to orange-brown and brownish-yellow. The base is more readily soluble in most organic solvents than the dihydro-derivative of K^5. It is stable to permanganate in acetone solution and gives no colour with ferric chloride in weakly acidic solution.

Desmethyleneanhydrotetrahydromethylstrychnine - K^6. —This base crystallised from alcohol in monoclinic prisms, m. p. 172—173° (not raised by recrystallisation) [Found: C, 78·9; H, 7·5; N, 8·8; Me(N), 5·2; *M*, by direct chloroaurate method, 321. $C_{21}H_{24}ON_2$ requires C, 78·7; H, 7·5; N, 8·8; Me, 4·9%; *M*, 320].

It is moderately readily soluble in cold methyl or ethyl alcohol, ether or hot light petroleum and easily soluble in cold acetone, benzene, or chloroform. Its acid solutions develop no colour on the addition of ferric chloride, but with dichromate and sulphuric acid (60%) an intense blue coloration, fading rapidly to purple and then to pale green, is obtained. Permanganate is immediately reduced in acetone solution. The base does not yield a benzylidene or acetyl or nitroso-derivative.

The *methiodide* was prepared from a specimen, m. p. 168°, by dissolution in an excess of methyl iodide and separated after 24 hours. The crust of prisms was collected, ground, washed with methyl iodide, and recrystallised from methyl alcohol, forming colourless prisms, m. p. 250—252° (efferv.) (Found: C, 57·5; H, 6·0. $C_{22}H_{27}ON_2I$ requires C, 57·2; H, 5·9%).

A warm aqueous solution gives no precipitate on addition of ammonia or potassium hydroxide. When heated to 280°, the salt, or the related gummy methochloride, decomposed with regeneration of the base-K^6, m. p. 168° (Found: C, 78·9; H, 7·8%). The base-K^6 (0·5 g.) was unchanged by heating at 70° with a solution of sodium ethoxide (from 1 g. of sodium and 15 c.c. of alcohol) for 16 hours.

Dihydrodesmethyleneanhydrotetrahydromethylstrychnine - K^6. — A solution of K^6 (2·5 g., m. p. 172—173°) in acetic acid (50 c.c. of 20%) was shaken with hydrogen at 14° in the presence of palladised charcoal (from 0·2 g. of palladous chloride and 1·0 g. of charcoal). Absorption of the gas was rapid at first, but very slow after 50 minutes, 183 c.c. (at N.T.P.) having been taken up (calc. for saturation of one double bond, 175 c.c.). The product was dried at 100° (yield, 2·3 g.; m. p. 153—158°), twice crystallised from methyl alcohol–light petroleum, and finally obtained in long flat-ended prisms, m. p. 160—162° (Found: C, 78·4; H, 8·3; N, 8·7. $C_{21}H_{26}ON_2$ requires C, 78·2; H, 8·1; N, 8·7%). This *base* is sparingly soluble in cold light petroleum, but dissolves freely in most other common organic solvents. It gives no reactions of strychnidine-type and the Otto reaction is very difficult to observe. A solution in 60% sulphuric acid, treated with a very small trace of a dichromate, develops a bright purplish-red colour which rapidly fades to yellow. If more than a trace of the reagent is used, the colour is so rapidly destroyed that it cannot be observed.

The more complete catalytic reduction of K^6 has been investigated, but the results are not so clear as was the case with K^5. When rather more than twice the relative proportion of catalyst was used, the theoretical volume of hydrogen was absorbed at 14° in 15 minutes; the reduction was continued at 70—75° for 2½ hours and the total volume of gas then absorbed exceeded that required for saturation of 2 double bonds (150 c.c. instead of 140 c.c.). The air-dried product (0·8 g.) was crystallised from benzene–light petroleum and gave 0·3 g., m. p. 153—158°; recrystallised, m. p. 157—160° (mixed with dihydro-K^6, m. p. 160—162°, the m. p. was 158—160°) (Found: C, 77·9; H, 8·2. Calc. for $C_{21}H_{26}ON_2$: C, 78·2; H, 8·1%). Evidently a large fraction of the material is the dihydro-derivative of K^6.

The mother-liquor on concentration afforded 0·3 g. of crystals, m. p. 112—115° (Found in material heated at 90°: C, 78·3; H, 9·1. $C_{22}H_{28}ON_2$ requires C, 77·8; H, 8·6%). It was thought that hydrocarbons, particularly benzene, might still be adherent, so the base was crystallised from light petroleum and the prisms heated for 3 hours at 100°/2 mm. over phosphoric oxide. This specimen developed a pink colour and melted sharply at 114° to a yellow liquid (Found: C, 78·7; H, 8·7%). Paucity of material forced us to abandon the investigation of this base, but the results point to persistent hydrocarbon contamination or to gradual dehydration on heating.

Dihydrodesmethylenetetrahydromethylstrychnidine-K^6.—The base-K^6 (2·0 g.), dissolved in 20% sulphuric acid (100 c.c.), was reduced at a lead cathode at 15° for 19 hours with a current density of 0·05 amp./cm.². The base deposited from the solution after basification in the presence of ice was collected, dissolved in 2*N*-sulphuric acid, and reprecipitated with ammonia. It was then taken up in benzene, the extract dried and evaporated, and the syrupy residue dissolved in a little cold methyl alcohol. The reduced *base* crystallised slowly in slightly dark aggregates (0·35 g.), m. p. 97—99° (Found: C, 80·6; H, 9·2; N, 9·0. $C_{21}H_{28}N_2$ requires C, 81·8; H, 9·2; N, 9·1%).

Recrystallised from methyl alcohol–light petroleum, the base was obtained in long, colourless, monoclinic prisms, often forming parallel clusters, m. p. 98—100° (Found : C, 81·3; H, 9·0; N, 9·1%). A specimen made from crude K^6, m. p. 166—167°, in a similar fashion to the above was distilled under 1 mm. (b. p. could not be determined) (Found : C, 82·0; H, 9·0; N, 8·8%). The base gives strychnidine-type colour reactions and is easily soluble in benzene and light petroleum and rather sparingly soluble in the simple alcohols.

The *methiodide*, prepared from reduced base-K^6, m. p. 167°, separated from water as a hard crust, m. p. *ca.* 170° and decomp. 190—200° (Found : C, 59·0; H, 7·1. $C_{22}H_{31}N_2I$ requires C, 58·7; H, 6·9%). The related methochloride gives strychnidine-type colour reactions and hence the quaternary ammonium group in these salts includes N(b).

The Base-K^{11}.—This substance is very sparingly soluble in ether and in order to purify it the crude material was well ground and extracted several times with the solvent. The residue crystallised from a large volume of methyl alcohol or from methyl alcohol–ethyl acetate in splendid monoclinic prisms, very well-shaped and homogeneous in appearance under the microscope. All specimens in spite of their fine appearance soften from about 211° and melt at 217—218° [Found : C, 78·7, 79·0, 79·1; H, 8·3, 8·2, 8·1; N, 8·4, 8·5; Me(N), 4·25; *M*, by chloroaurate method, 343. $C_{22}H_{28}ON_2$ requires C, 78·6; H, 8·3; N, 8·3; Me, 4·5%; *M*, 345, assuming $\frac{1}{2}H_2O$ in the chloroaurate. $C_{23}H_{28}ON_2$ requires C, 79·3; H, 8·0; N, 8·0; Me, 4·4%; *M*, 348]. Owing to the fact that the chloroaurate is a little too soluble in water, the direct method could not be used in this case; the assumption of $\frac{1}{2}H_2O$ is a probable one in view of the similar behaviour of the chloroaurate of K^5 which has been already mentioned.

Micro-analyses often give a high value for the content of carbon and we consider that the most likely formula is $C_{22}H_{28}ON_2$.

Addition of a trace of a dichromate to a solution of this substance in 60% sulphuric acid produces a bluish-purple coloration which rapidly fades to dull yellow; strychnidine-type reactions were not observed.

The base does not form a benzylidene, acetyl, or nitroso-derivative. It is not readily hydrolysed to an amino-acid by means of alcoholic sodium ethoxide.

Methiodide. The base reacted very slowly with methyl iodide in the cold and was heated with a large excess of the reagent and some methyl alcohol at 100° in a sealed tube. The *salt* then formed crystallised from methyl alcohol in pale brown, circular warts,

m. p. 250° (vigorous efferv.) (Found : C, 57·3 ; H, 6·4. $C_{23}H_{31}ON_2I$ requires C, 57·7 ; H, 6·4%). The substance is readily soluble in water and the related methochloride exhibits the same Otto reaction as the parent base.

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