120. *Strychnine and Brucine. Part XXVI. Hofmann Degradation of Methyldihydrostrychnidinium-A Carbonate. Isolation of a Fourth Isomeride of Dihydrostrychnidine.*

By O. ACHMATOWICZ and R. ROBINSON.

ONE of the chief objectives of the present series of investigations has always been the degradation of the molecules of *strychnos* bases by Hofmann's method, but hitherto no true *des*-bases have been obtained by the thermal decomposition of metho-salts or methohydroxides in this series. A long series of trials with the *N*(*b*)-methyl derivatives of strychnine, brucine, strychnidine, brucidine, *neo*strychnine and *neo*strychnidine has been fruitless apart from the formation of the methoxymethyldihydro-types and the reductive fissions (compare preceding communication).

Nevertheless, in Part XV (Achmatowicz, Perkin, and Robinson, J., 1932, 486) theoretical considerations, based on the recognition that both strychnine and *neo*strychnine are of allylamine type, prompted the idea that better success might be the outcome of attempted Hofmann eliminations in the series of the dihydro-bases in which the allylamine structure is no longer present.

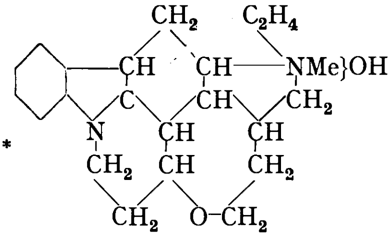
Preliminary experiments in many series have justified this view and the present memoir records the realisation of the project in the case of metho-derivatives of dihydrostrychnidine-A.

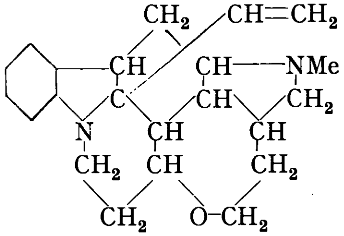
The thermal decompositions of the methohydroxide, methyl hydrogen carbonate (excess of carbon dioxide on methohydroxide), methocarbonate (silver carbonate on the methochloride), dimethohydroxide, dimethyl dihydrogen carbonate, and dimethocarbonate have been studied and similar results obtained in all cases. The use of the methyl hydrogen carbonate was convenient and this example is selected for more detailed description in the experimental section. Of the five products, separated only by laborious fractional crystallisations, the first was recognised as dihydrostrychnidine-A, m. p. 214—215°, and three others could be related to known compounds. These are (2) a *des*-base, $C_{22}H_{28}ON_2$, m. p. 143—144°; (3) a substance, $C_{23}H_{32}O_2N_2$, m. p. 220°; and (4) a substance, $C_{22}H_{30}O_2N_2$, m. p. 158—159°. The *des*-base (2) is identical with the *N*(*b*)-methyl*chano*dihydro(*neo*)strychnidine described in the preceding communication, but the investigation of the two substances was carried out quite independently. This *des*-base, m. p. 143—144°, yields a dihydro-derivative, m. p. 177°, on catalytic reduction, and this substance was also identified by direct comparison and the method of mixed melting points with the base, m. p. 177°, prepared from strychnidine methosulphate by reduction with sodium amalgam and catalytic reduction of the product. If the provisional suggestion that the base $C_{22}H_{28}ON_2$, m. p. 143°, is a derivative of *neo*strychnidine is correct, then the substance is not a *des*-base of the normal type and, in the course of the elimination of water, either a proton is extracted from a ·CH⁝ group in the γ-position to N(b), or there is a shifting of a double bond in the primary product: the first of these alternatives is preferred. The substance (3) was identified as methoxymethyltetrahydrostrychnidine (Part IV; Clemo, Perkin, and Robinson, J., 1927, 1589); and the new substance (4), m. p. 158—159°, has been recognised as the corresponding *hydroxymethyltetrahydrostrychnidine*, because on methylation it yields methoxymethyltetrahydrostrychnidine, m. p. 220°, and by appropriate treatment the methyldihydrostrychnidinium-A salts can be regenerated. For example, this occurs under the influence of hot dilute sulphuric acid or of hydriodic acid. It forms an *O*-acetyl derivative, and dihydrostrychnidine-A is obtained by the thermal decomposition of this substance. The most interesting of the substances separated from the decomposition products of methyldihydrostrychnidinium-A hydrogen carbonate is, however, a second *des*-base-D (designated so for reasons disclosed below), $C_{22}H_{28}ON_2$, m. p. 196—197°. This substance, from its mode of formation and composition, should be unsaturated and an attempt to demonstrate this by reducing it to a dihydro-derivative by means of hydrogen in presence of palladium and in aqueous acetic acid solution gave a remarkable result. Instead of the expected dihydro-derivative, a quaternary acetate was produced; thus the double bond of the *des*-base can add itself to N(b) in a reversed Hofmann or Emde type of reaction. So far as we are aware, a reaction of this kind has not previously been observed. The quaternary acetate was converted into a related *iodide* and *chloride*, and the latter substance on thermal decomposition afforded a new isomeride (D) of dihydrostrychnidine.

The dilute aqueous acid-ferric reaction of the *des*-base-D is *sui generis*, whereas the *des*-base, m. p. 143—144°, gives strychnidine-type reactions. We conclude that the double bond in the *des*-base-D (a) is produced by fission at a MeN(b)-C group different from that affected in the formation of the *des*-base, m. p. 143—144°, and (b) is located in such proximity to N(a) that it can have a large influence on the colour reactions owing to the presence of the aromatic nucleus in association with N(a), and further (c) is situated with respect to N(b) in such a position as to render possible the reconstitution of an *isomeric* dihydrostrychnidine ring-system.

These requirements are accommodated by the formula (I) for dihydrostrychnidine-A (or -D) methohydroxide and (II) for the *des*-base-D. On this hypothesis the isomerism of dihydrostrychnidines-A and -D is dependent on the arrangement of the C_2H_4 group, it being ethylene in the one case and ethylidene in the other. Both arrangements can be set up in practically strainless models. The formation of methyldihydrostrychnidinium-D salts from the *des*-base-D receives only one plausible explanation on the basis of the formula (III) for strychnine. On the assumption of the usual relation between methine and quaternary ammonium hydroxide it is apparent that the *des*-base-D would either be formed from a heterocyclic four-ring in dihydrostrychnidine-A or, alternatively, yield such a four-ring in its transformation to the dihydrostrychnidine-D system. Neither alternative is attractive and the formula (IV) (for methyldihydrostrychnidinium-A hydroxide, after strychnine, III) illustrates this argument, the asterisked carbon atoms denoting the possible sites of unsaturation [in the α- or β-position to N(b)] in the *des*-base-D.

(I.) *





(II.)

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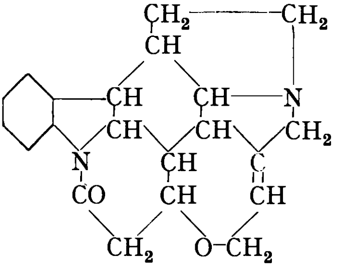
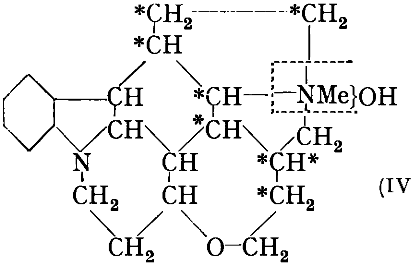
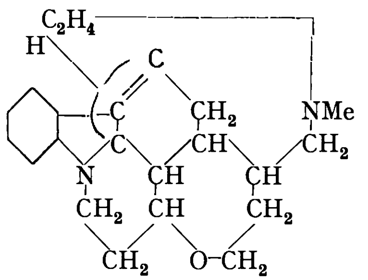
* In this and the preceding and following communications the group C_2H_4 is assumed to be attached to the α-position in the hydro-indole nucleus. The chief reason for this is Leuchs's observation of the ready bromination of diketonucidine. The properties of the *des*-base-D also favour the view adopted provisionally and it should further be noted that Wieland has illustrated his work on vomicine derivatives by means of part formulæ in which a hydroxyl appears on the β-carbon of the hydro-indole nucleus. Nevertheless, it must be clearly stated that the only conclusion on this aspect of the structural problem which we draw from our own observations of the behaviour of strychnine and its derivatives is that the C_2H_4 group is attached to the α- or β-position in the hydro-indole nucleus. Were it otherwise, the formation of aromatic indole derivatives in oxidation processes would surely have been frequently observed.

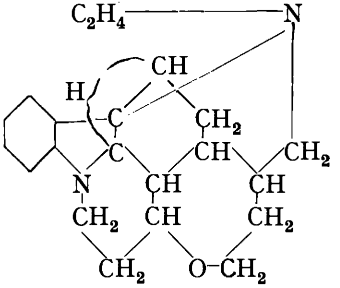
No combination of fission at the dotted lines and a selection of a compatible position for the ethylenic linkage is helpful.


(III.)


(IV.)

On the other hand we now recognise that strychnine is a derivative of γ-phenylpropylamine and it is well known that the Hofmann degradation of bases of this type invariably yields the *iso*propenylbenzenes and not the allylbenzenes. The formulæ (V) and (VI) embody this idea and represent the *des*-base-D and dihydrostrychnidine-D respectively, either (I) or (IV) being used for dihydrostrychnidine-A methohydroxide.


(V.)


(VI.)

Obviously this possibility, also, brings the unsaturated link in the *des*-base-D into relation with N(a) and the aromatic nucleus as the facts require.

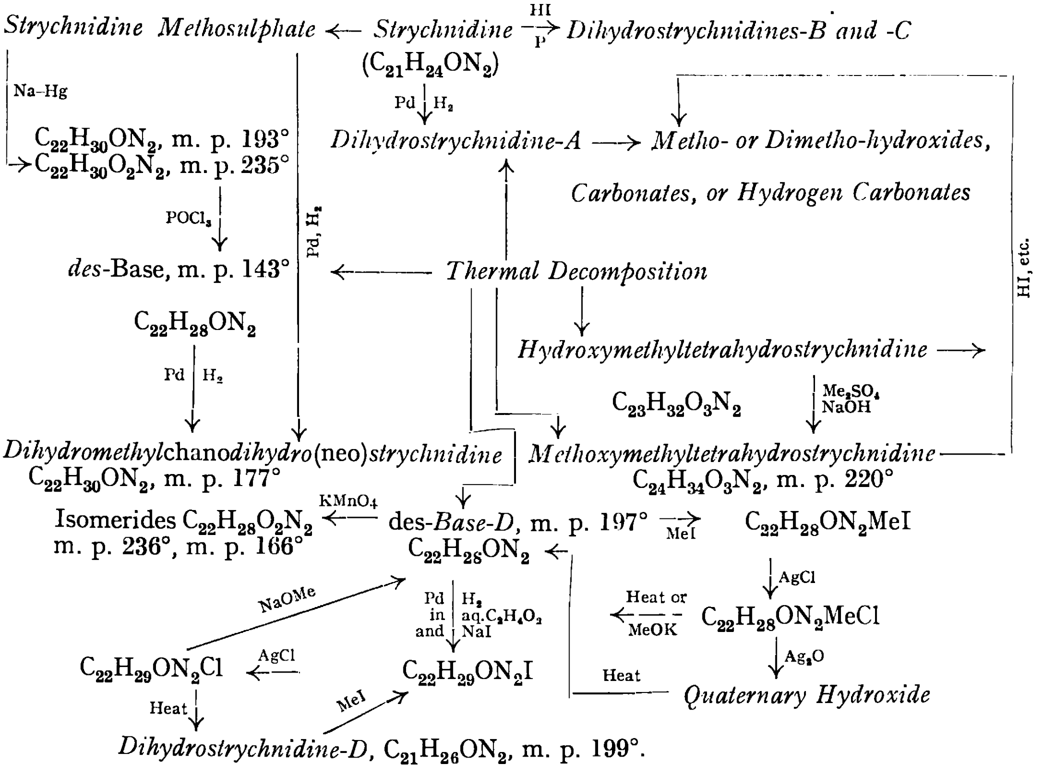
In considering these alternatives it should first be noted that the *des*-base-D, the methyldihydrostrychnidinium-D salts, and dihydrostrychnidine-D are among those strychnine derivatives that give a negative result in the Kuhn–Roth method for estimation of :CMe groups (compare p. 594 for further comments on these results). Hence it seems probable that neither dihydrostrychnidine-A nor dihydrostrychnidine-D contains the group :CMe, and this implies that the C_2H_4 group in strychnine has the ethylene arrangement. Thus the explanation of the formation of dihydrostrychnidine-D which is dependent on the isomerism in the C_2H_4 group is rendered improbable and the formulæ (V) and (VI) are to be preferred. Furthermore, stereochemical considerations favour the attachment of the ethylene group in (V) to the α-position in the indole nucleus; owing to the infraction of Bredt's rule, the alternative cannot be set up on the models with strainless rings.

The behaviour of the isomeric dihydrostrychnidine metho-salts towards methyl-alcoholic potassium hydroxide provides an interesting contrast. (A) gives methoxymethyltetrahydrostrychnidine-A; (B) gives methoxymethyltetrahydrostrychnidine-B and some regenerated dihydrostrychnidine-B; (C) gives no methoxy-compound and no methine, but a quantitative recovery of dihydrostrychnidine-C (compare Part VIII; Perkin and Robinson, J., 1929, 964); (D) gives nothing but the methine, that is, the *des*-base, m. p. 196—197°. Incidentally we may mention that the present communication contains a preliminary description of a fifth *dihydrostrychnidine-E* which has not yet been examined in detail. It was not found feasible to proceed to a second stage of Hofmann degradation using the *des*-base-D. The *methiodide* is a characteristic derivative, but the related methochloride yields the original base, m. p. 196—197°, either by thermal decomposition or by the action of methyl-alcoholic potassium hydroxide. The quaternary hydroxide also loses methyl alcohol, forming the *des*-base-D along with a gummy by-product.

On oxidation with potassium permanganate in acetone solution the *des*-base-D affords two substances, $C_{22}H_{28}O_2N_2$ (or $C_{22}H_{26}O_2N_2$), and it thus exhibits the usual and perplexing behaviour of unsaturated bases of the strychnidine series in merely taking up one oxygen atom.

The annexed table illustrates the relations of some of the substances described in this memoir.

The Isomeric Dihydrostrychnidines.



EXPERIMENTAL.

Derivatives of Dihydrostrychnidine-A.—Large quantities of dihydrostrychnidine-A were prepared by electrolytic reduction of dihydrostrychnine. Methyldihydrostrychnidinium iodide was produced by direct combination of the components and was used for the experiments after being thrice recrystallised from much boiling water. *Methyldihydrostrychnidinium hydrogen carbonate* was prepared by shaking a hot aqueous suspension of methyldihydrostrychnidinium iodide with an excess (20%) of freshly precipitated silver oxide and neutralising the strongly alkaline filtrate with carbon dioxide. The salt is very readily soluble in water and separates from a concentrated solution as a paste of colourless needles (Found in material dried in a vacuum: C, 60·9; H, 8·2. $C_{23}H_{30}O_4N_2,3H_2O$ requires C, 61·1; H, 8·0%). It evolves carbon dioxide on treatment with dilute acids, and on addition of hydriodic acid is converted into methyldihydrostrychnidinium iodide, m. p. 340°. *Methyldihydrostrychnidinium hydroxide*, prepared in a similar way but in an atmosphere protected from carbon dioxide, was obtained as a horny mass freely soluble in water (Found in material dried in a vacuum at 105—110°: C, 74·2; H, 8·8. $C_{22}H_{30}O_2N_2$ requires C, 74·6; H, 8·5%). Its strongly alkaline aqueous solution absorbs carbon dioxide from the air.

The Thermal Decomposition of Methyldihydrostrychnidinium-A Hydrogen Carbonate.—The quaternary derivatives described above give, on thermal decomposition, exactly the same mixture of products. However, the use of the hydrogen carbonate is to be preferred, because the reaction can be conveniently controlled by observation of the rate of evolution of carbon dioxide and in this manner undesirable superheating is avoided. Similar results were also obtained by the action of heat on the quaternary salts produced from methyldihydrostrychnidinium-A iodide or dimethyldihydrostrychnidinium-A di-iodide by means of silver carbonate.

Methyldihydrostrychnidinium hydrogen carbonate (250 g.), dried at 105° and finely powdered, was heated over a flame in test-tubes in batches of 1—2 g. until the evolution of carbon dioxide ceased. The brown glassy decomposition product was dissolved in the minimum of boiling methyl alcohol (3—5 c.c. for each test-tube) and on cooling, crop (1) was deposited. The methyl-alcoholic filtrate was concentrated as far as possible; the residue on rubbing with acetone (150 c.c.) furnished crop (2). The solution was then evaporated to dryness in a vacuum, the residue extracted with light petroleum (1500 c.c., b. p. 80—100°), and the extract filtered from a dark gummy impurity (not examined, 10%) and concentrated to half its volume; after several days crop (3) was deposited. The filtrate was again evaporated to dryness under diminished pressure and the residue was mixed with a little acetone or methyl alcohol; this operation furnished crops (4) and (5), but the crystallisation was very slow and occupied 2 months. The final mother-liquor was distilled and a fraction (b. p. 252—258°/3 mm.) was collected.

Crop (1) was recrystallised from methyl alcohol (norit) and yielded the *des*-base-D, m. p. 196—197° (total yield, 15%), and a small quantity of methoxymethyltetrahydrostrychnidine from the methyl-alcoholic mother-liquor. The methoxy-derivative, obtained at this stage and also isolated from crop (4) (see below) (total yield, 5%), was identified, after being thrice recrystallised from benzene, by m. p., by mixed m. p. (220° in both cases), by analysis (Found : C, 75·2; H, 8·8; MeO, 8·4. Calc. for $C_{23}H_{32}O_2N_2$: C, 75·0; H, 8·7; MeO, 8·3%), and also by conversion into methyldihydrostrychnidinium iodide, m. p. 340°.

Crop (2) was recognised as dihydrostrychnidine-A; it had m. p. 214—216°, alone or mixed with pure dihydrostrychnidine-A, and it yielded the sparingly soluble methyldihydrostrychnidinium iodide, m. p. 340°, on treatment with methyl iodide (total yield, 35%).

Crop (3) consisted of almost pure hydroxymethyltetrahydrostrychnidine hydrate, m. p. 158—159°. It was purified by recrystallisation from ethyl acetate (total yield, 30%).

Crop (4) proved to be a mixture of dihydrostrychnidine-A, methoxymethyltetrahydrostrychnidine (see above), and hydroxymethyltetrahydrostrychnidine hydrate. The mixture was resolved by fractional crystallisation from methyl alcohol, acetone, benzene and ethyl acetate.

Crop (5) gave on fractional crystallisation from methyl alcohol and ethyl acetate a further quantity of hydroxymethyltetrahydrostrychnidine hydrate and also the *des*-base, m. p. 143—144°, the latter (yield, 10%) being purified by repeated crystallisation from methyl alcohol. The *fraction*, 252—258°/3 mm., was separated into dihydrostrychnidine-A and hydroxymethyltetrahydrostrychnidine hydrate.

Anhydromethylstrychnidinium-D Hydroxide (des-*Base-D*, m. p. 196—197°).—The *base* crystallises from methyl alcohol, on slow cooling, in long, fragile, colourless needles (Found : C, 78·4, 78·4; H, 8·6, 8·6; N, 8·1; Me*N*, 5·4. $C_{22}H_{28}ON_2$ requires C, 78·6; H, 8·3; N, 8·3; Me*N*, 4·5%), very sparingly soluble in the simple alcohols, acetone and ethyl acetate; it dissolves readily in chloroform or benzene and separates from the latter solvent in hard quadrilateral plates. With 60% sulphuric acid and a trace of potassium dichromate it gives a pale brown coloration (ferric reaction, see below). The base remained unchanged after being electrolysed in the usual apparatus for 24 hours at 15°; fruitless attempts were also made to reduce it in neutral benzene solution by means of hydrogen in the presence of palladium and charcoal.

The methiodide. The *des*-base-D is not affected by methyl iodide at room temperature or even after warming on a steam-bath for 1 hour. The derivative was prepared by refluxing the base for 5 hours with a large excess of methyl iodide; it is moderately readily soluble in cold water and methyl alcohol, dissolves readily on boiling and separates, on cooling, as a mass of soft colourless needles, m. p. 289—290° (Found in material dried at 104° : C, 57·5; H, 6·6. $C_{23}H_{31}ON_2I$ requires, C, 57·7; H, 6·5%).

The *methochloride*, prepared in the usual way, is very readily soluble in water and separates from a concentrated solution as a crystalline powder which, dried at 105°, has m. p. 308—310°; it possesses the power of retaining water of crystallisation at 105° (Found in material dried at 105° : C, 68·0; H, 8·4. $C_{23}H_{31}ON_2Cl,H_2O$ requires C, 68·2; H, 8·2%). The derivative was decomposed on heating or by digestion with an excess of 20% methyl-alcoholic sodium methoxide and in both cases the *des*-base-D, m. p. 196—197°, alone or after admixture with an authentic specimen, was recovered in good yield.

The hydrogen carbonate was prepared from the above iodide by means of silver oxide, followed by passage of carbon dioxide. It is freely soluble in water and remains on evaporation of the solvent as a brown horny mass, which evolves carbon dioxide on treatment with dilute acids and on addition of hydriodic acid furnishes the methiodide, m. p. 289—290°. The thermal decomposition of the salt afforded the *des*-base-D, m. p. 196—197°, in poor yield along with a gummy by-product which has not yet been examined.

Oxidation of the des-*Base-D.*—Finely powdered and sieved potassium permanganate (5 g.) was added gradually in small quantities to a solution of the base (5 g.) in acetone (1000 c.c.) at the room temperature. When the decolorisation of the reagent was complete (3 days), the manganese precipitate was collected and washed with warm acetone and the combined filtrate and washings were concentrated to a small volume. From the green fluorescent residue two isomeric crystalline oxy-derivatives were isolated by rubbing with methyl alcohol.

The more sparingly soluble oxy-derivative, m. p. 234—236° (yield, 90%), crystallises from much boiling methyl alcohol in minute colourless needles or plates (Found : C, 75·0; H, 7·5. $C_{22}H_{28}O_2N_2$ requires C, 75·0; H, 7·9%). It is very sparingly soluble in cold methyl alcohol or acetone, sparingly soluble even on boiling, but it dissolves readily in chloroform. With 60% sulphuric acid and potassium dichromate it gives a brown coloration with a faint pink tint. It was recovered unchanged after prolonged refluxing with hydroxylamine hydrochloride and sodium acetate in methyl-alcoholic solution; neither could it be induced to combine with benzaldehyde, on standing at the room temperature or on boiling, in methyl-alcoholic solution in the presence of sodium methoxide.

The oxy-derivative, m. p. 162° (yield, about 10%), is very readily soluble in methyl alcohol and separates therefrom in soft colourless needles (Found : C, 75·0; H, 7·9. $C_{22}H_{28}O_2N_2$ requires C, 75·0; H, 7·9%). A solution of the base in 60% sulphuric acid gives with potassium dichromate an intense pink coloration. These substances may be described as the *oxyanhydromethylstrychnidinium-D hydroxides.*

Attempted Catalytic Hydrogenation of the des-*Base-D. Formation of Methyldihydrostrychnidinium-D Acetate.*—The base (3·4 g.) was dissolved in 50% acetic acid (50 c.c.) and hydrogenated in the presence of palladium (0·5 g., free from hydrochloric acid) and charcoal (5 g. in 50 c.c. of water). Absorption of the gas was rapid * and ceased after 75 minutes, 240 c.c. (at N.T.P.) having been taken up (calc. for 2H, 230 c.c.). The filtered solution was basified with ammonia (no precipitate) and the quaternary salt was precipitated by the addition of much solid potassium carbonate and purified by repeated crystallisation from the minimum of boiling water. *Methyldihydrostrychnidinium-D acetate* (yield, 3·2 g.) is very readily soluble in water or methyl alcohol and separates from the former in long, colourless, silky needles, m. p. 307—308° (Found in material dried at 104° : C, 72·5; H, 8·3. $C_{24}H_{32}O_3N_2$ requires C, 72·7; H, 8·1%).

Methyldihydrostrychnidinium-D iodide was prepared by the addition of sodium iodide to an aqueous solution of the above acetate. It is remarkably sparingly soluble in water, hot or cold, and separates in minute, colourless, glistening plates, m. p. 317—318°, containing $1H_2O$ which is not lost at 104° (Found in material dried at 104° : C, 54·3; H, 6·7. $C_{22}H_{29}ON_2I,H_2O$ requires C, 54·8; H, 6·4. Found in material dried at 125—130° : C, 56·9; H, 6·5. $C_{22}H_{29}ON_2I$ requires C, 57·0; H, 6·3%).

Methyldihydrostrychnidinium-D chloride, obtained by the action of silver chloride on an aqueous solution of the iodide, forms colourless needles, m. p. 318—319°, moderately soluble in cold and readily soluble in boiling water. Like the corresponding iodide, it has a tendency to retain water of crystallisation at 104° (Found in material dried at 104° : C, 67·3; H, 8·2. $C_{22}H_{29}ON_2Cl,H_2O$ requires C, 67·6; H, 8·0%).

The Action of Sodium Methoxide on Methyldihydrostrychnidinium-D Chloride.—A suspension of the chloride (2 g.) in methyl-alcoholic sodium methoxide (20 c.c. of 10%) was evaporated to dryness, and the residue heated on a sand-bath until the temperature of the crust reached 110°. On addition of ice a caseous precipitate formed; this was collected, dried at 100° (yield, 2 g.), twice recrystallised from methyl alcohol, and identified with the *des*-base-D by m. p. and by mixed m. p. (196—197° in both cases).

The Thermal Decomposition of Methyldihydrostrychnidinium-D Chloride. Formation of Dihydrostrychnidine-D.—The salt was decomposed by careful heating in a tube immersed in a sulphuric acid bath until the evolution of methyl chloride ceased, and the residual base was repeatedly crystallised from methyl alcohol (norit). *Dihydrostrychnidine-D* (yield, 35%) crystallises in faintly brownish needles, m. p. 197—199° (mixed with the *des*-base-D, m. p.

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* Evidently due to a side-reaction; the product isolated had the original state of oxidation.

150—170°). It is moderately soluble in methyl and ethyl alcohol, sparingly soluble in acetone and ethyl acetate, and readily soluble in chloroform. A solution of the base in 60% sulphuric acid gives a brown coloration on the addition of a drop of aqueous potassium dichromate (Found : C, 78·1; H, 8·3. $C_{21}H_{26}ON_2$ requires C, 78·3; H, 8·1%).

The methiodide. Dihydrostrychnidine-D combines instantly with methyl iodide with evolution of heat and formation of methyldihydrostrychnidinium-D iodide. The identity of the salt thus prepared with that produced by catalytic hydrogenation of the *des*-base-D was established by m. p., mixed m. p. (317—318° in both cases), and by analysis (Found in material dried at 104° : C, 54·5; H, 6·6. Calc. for $C_{22}H_{29}ON_2I,H_2O$: C, 54·8; H, 6·4%).

Hydroxymethyltetrahydrostrychnidine Hydrate.—The base crystallises from ethyl acetate in pale yellowish needles, m. p. 158—159°. It is very sparingly soluble in light petroleum, sparingly soluble also in benzene, moderately readily soluble in ethyl acetate; it dissolves readily in the simple alcohols, acetone or chloroform. When crystallised from methyl alcohol, it separates as a sandy colourless powder; from acetone and light petroleum it is obtained in colourless needles. The aqueous sulphuric acid–dichromate reaction is to a pink coloration which changes to reddish-purple. The base was recovered unchanged after prolonged refluxing with methyl iodide; it is also indifferent towards benzaldehyde in methyl-alcoholic solution in the presence of sodium methoxide (Found in material crystallised from acetone and dried at 100° : C, 71·3; H, 8·8; Me*N*, 4·7. Found in material crystallised from ethyl acetate and dried at 100° : C, 71·4; H, 8·6; N, 7·5; Me*N*, 4·3. Found in material crystallised from light petroleum and dried at 100° : C, 71·4; H, 8·6. $C_{22}H_{30}O_2N_2,H_2O$ requires C, 71·0; H, 8·6; N, 7·5; Me*N*, 4·1. Found in material dried in a high vacuum at 110—115° : C, 74·4; H, 8·6. $C_{22}H_{30}O_2N_2$ requires C, 74·6; H, 8·5%).

The O-*acetyl* derivative was prepared by the addition of anhydrous sodium acetate (1 g.) to a cold solution of hydroxymethyltetrahydrostrychnidine hydrate (3 g.) in acetic anhydride (10 c.c.); reaction occurred immediately with evolution of heat and the derivative crystallised. When the mixture was heated for a few minutes, the yield was considerably diminished and on prolonged heating at 100° no acetyl derivative was produced, a product very soluble in water, presumably methyldihydrostrychnidinium-A acetate, being formed. The crude product was triturated with aqueous sodium hydroxide, dried, and thrice recrystallised from ethyl acetate (total yield, after working up the filtrates, 3 g.). The derivative is very sparingly soluble in cold or boiling methyl alcohol; it dissolves moderately readily in ethyl acetate and separates therefrom in colourless plates (slow cooling) or in needles, m. p. 254—255° (Found : C, 72·6; H, 8·1. $C_{24}H_{32}O_3N_2$ requires C, 72·7; H, 8·1%).

A mixture of this acetyl derivative (1 g.) with methyl-alcoholic potassium hydroxide (10 c.c. of 10%) and water (3 c.c.) was heated for ½ hour on the steam-bath. On dilution with ice-water, hydroxymethyltetrahydrostrychnidine hydrate crystallised. It was dried (yield, 0·8 g.), recrystallised from ethyl acetate, and identified by m. p. and by mixed m. p. (158—159° in both cases).

Methylation of Hydroxymethyltetrahydrostrychnidine. Formation of Methoxymethyltetrahydrostrychnidine.—A suspension of hydroxymethyltetrahydrostrychnidine hydrate (2 g.) in aqueous sodium hydroxide (20 c.c. of 40%) was shaken with methyl sulphate (5 c.c.), which was added gradually. The liquid, which became warm, was diluted with ice-water and the caseous precipitate was collected, dried, washed with methyl alcohol, and recrystallised from benzene (yield, 1·4 g.). The glistening prisms which separated were identified with methoxymethyltetrahydrostrychnidine by m. p., by mixed m. p. (220° in both cases), and by analysis (Found : C, 74·9; H, 8·8; MeO, 8·1. Calc. for $C_{23}H_{32}O_2N_2$: C, 75·0; H, 8·7; MeO, 8·3%).

The Thermal Decomposition of the Acetoxymethyltetrahydrostrychnidine.—When the acetyl derivative (1 g.) was gently heated in a test-tube over a flame, a vigorous effervescence took place and the odour of methyl acetate was noted. The pale-coloured residue crystallised on cooling and after recrystallisation from methyl alcohol proved to be dihydrostrychnidine-A, m. p. 214—216° (yield, 0·7 g.).

The Action of Hot Dilute Sulphuric Acid on Hydroxymethyltetrahydrostrychnidine.—The base is not attacked in 3 hours by boiling 10% sulphuric acid (by vol.). But when a solution of the substance (2 g.) in sulphuric acid (15 c.c. of 50% by vol.) was refluxed for 3 hours, no precipitate was formed on dilution and addition of ammonia. Now, when sodium iodide (3 g.) was added, methyldihydrostrychnidinium-A iodide (1·2 g.) was deposited. This was thrice recrystallised from water (charcoal) and identified by m. p., by mixed m. p. (340° in both cases), by analysis (Found : C, 56·8; H, 6·4. Calc. for $C_{22}H_{29}ON_2I$: C, 56·9; H, 6·3%), and by conversion into the corresponding chloride (usual method), which on thermal decomposition yielded dihydrostrychnidine-A, m. p. 214—216°.

The Action of Hydriodic Acid and Phosphorus on Hydroxymethyltetrahydrostrychnidine Hydrate.—This experiment was carried out in the hope of obtaining the *des*-base, m. p. 143—144°, but the quaternary salt was again produced.

A mixture of the base (3 g.), hydriodic acid (15 c.c., *d* 1·94), and amorphous phosphorus (1 g.) was boiled for 8 hours. The liquid, after filtering through asbestos, was poured into water (200 c.c.) and basified with ammonia. The solution, on concentration to a small volume, deposited two crops of crystals, (A) and (B).

Crop (A) was identified in the usual way with methyldihydrostrychnidinium-A iodide, m. p. 340° (yield, 1·1 g.). Crop (B) was purified by repeated crystallisation from 50% aqueous methyl alcohol. It separated in small aggregates, which were moderately soluble in methyl alcohol and water and melted with vigorous effervescence at 225—228° (yield, 0·7 g.) (Found : C, 56·4; H, 6·6. $C_{22}H_{29}ON_2I$ requires C, 56·8; H, 6·3%). This substance appears to be an *isomeride* of methyldihydrostrychnidinium-A iodide; it has not yet been further examined.

The des-*Base, m. p.* 143—144° [N(b)-*Methyl*chano*dihydro*(neo)*strychnidine*].—The *base* crystallises from methyl alcohol in long, colourless, prismatic needles (Found : C, 78·3; H, 8·3; Me*N*, 4·9. $C_{22}H_{28}ON_2$ requires C, 78·6; H, 8·3; Me*N*, 4·5%). A mixture with N(b)-methyl*chano*dihydro(*neo*)strychnidine, m. p. 142—143° (see preceding communication), had m. p. 142—143°. It is sparingly soluble in cold methyl alcohol and acetone, but dissolves readily in chloroform and benzene. A solution of the base in 60% sulphuric acid gives with a drop of aqueous dichromate a pink coloration, and the same colour is developed in dilute hydrochloric acid on addition of ferric chloride. The *methiodide*, prepared by gently heating a mixture of the components, was readily soluble in water or methyl alcohol and exhibited no tendency to crystallise. On evaporation of the solution it was obtained as a colourless glass (Found in material dried in a vacuum : C, 57·3; H, 7·0. $C_{23}H_{31}ON_2I$ requires C, 57·7; H, 6·5%).

The methochloride (usual method) is a horny mass freely soluble in water; when decomposed by heat or digested with 20% methyl-alcoholic potassium hydroxide, it yields the *des*-base, m. p. 143—144°, in theoretical yield.

The Catalytic Hydrogenation of the des-*Base, m. p.* 143—144°.—A solution of the base (2 g.) in acetic acid (75 c.c. of 30%) was added to a previously reduced catalyst (0·5 g. of palladous chloride, 3 g. of norit, and 200 c.c. of very dilute hydrochloric acid) and stirred in hydrogen. The required volume of the gas (135 c.c.) was absorbed in 4 hours. The filtered liquid was basified with ammonia, and the colourless base (1·8 g.) collected and crystallised from methyl alcohol. It was identified with dihydro-*N*(*b*)-methyl*chano*dihydrostrychnidine (Achmatowicz, *loc. cit.*, and preceding memoir) by m. p., by mixed m. p. (176—177° in both cases), and by analysis (Found : C, 78·0; H, 9·1. Calc. for $C_{22}H_{30}ON_2$: C, 78·1; H, 8·9%).

N(b)-*Ethyldihydrostrychnidinium-A iodide*, prepared by direct combination of the components, forms long colourless needles, m. p. 345—350°. It is very sparingly soluble in cold or boiling water and dissolves moderately readily in boiling methyl alcohol (Found : C, 57·6; H, 6·8. $C_{23}H_{31}ON_2I$ requires C, 57·7; H, 6·5%).

Ethyldihydrostrychnidinium-A hydrogen carbonate, prepared from the iodide by means of silver oxide and carbon dioxide, separates on concentration of the aqueous solution, as a paste of brownish crystals, freely soluble in water (Found in material dried at 100° : C, 67·0; H, 8·1. $C_{24}H_{32}O_4N_2,H_2O$ requires C, 67·2; H, 7·9%).

The Thermal Decomposition of Ethyldihydrostrychnidinium-A Hydrogen Carbonate.—When ethyldihydrostrychnidinium hydrogen carbonate, or the corresponding hydroxide, was decomposed as described in previous cases, ethylene (formed in almost theoretical yield and quantitatively estimated as dibromide), water, carbon dioxide, and traces of formaldehyde (recognised) were evolved and dihydrostrychnidine-A was formed in theoretical yield and was identified in the usual manner.

Dihydrostrychnidine-E.—When the silver salts from the preparation of ethyldihydrostrychnidinium-A hydrogen carbonate (or the hydroxide) were extracted with much boiling water and the pale brown solution was evaporated to dryness, a solid residue containing some metallic silver was obtained. The crude product was insoluble in organic solvents and very sparingly soluble in water; it was decomposed by heat; the product, recrystallised from methyl alcohol, in which it was very sparingly soluble, proved to be an *isomeride* of dihydrostrychnidine-A (Found : C, 78·2; H, 7·8. $C_{21}H_{26}ON_2$ requires C, 78·2; H, 8·1%). The new base has m. p. 254—255° (considerably depressed on admixture with strychnidine) and exhibits colour reactions of strychnidine type. Further examination was precluded by the paucity of the yield.

The Ferric Reaction of Strychnidine and Tetrahydrostrychnine Derivatives.—Strychnidine and tetrahydrostrychnine derivatives exhibit considerable differences of behaviour in this reaction and comparisons were first instituted under the following conditions.

The base (*ca.* 10 mg.) was dissolved in 0·1% hydrochloric acid (5 c.c.), cooled if heat had been applied, and mixed with 0·25% crystallised ferric alum solution (5 c.c.).

Strychnidine group: Strychnidine (colour standard; solution quickly becomes pink, then eosin-red; bluish nuance in thin layers, browner red in thicker layers; coloration very stable, slowly becomes browner on boiling), dihydrostrychnidine-A, strychnidine metho-salts, benzylstrychnidinium chloride, dihydrostrychnidine-A metho-salts, *N*(*b*)-methyl*chano*dihydro*neo*strychnidine-θ, *N*(*b*)-methyltetrahydrostrychnidine-θ (somewhat bluer red than standard), dihydro-*N*(*b*)-methyl*chano*dihydrostrychnidine, hydroxydihydro-*N*(*b*)-methyl*chano*dihydro*neo*strychnidine-θ, dioxyhydroxydihydrostrychnidine (Part VI), *neo*strychnidine, dihydrostrychnidine-B (develops slowly and is weak after 3 hours; good reaction in 1% hydrochloric acid on addition of a drop of aqueous ferric chloride); hydroxy- and methoxy-methyltetrahydrostrychnidines-A (same comment), methoxymethyltetrahydrostrychnidine-B (almost negative; with 1% hydrochloric acid–ferric chloride, slow reaction, good coloration on heating), methoxymethyldihydro*neo*strychnidine (no reaction; good coloration in 1% hydrochloric acid), oxydihydrostrychnidine-B methochloride (quite negative), dihydroanhydrotetrahydro-*N*(*b*)-methylstrychnidine-K[5] (slow appearance of much more orange-red coloration, soon changing to yellow), dihydro*des*methylenetetrahydromethylstrychnidine-K[6] (same comment). In the above results the most striking observations are the large inhibitory effects of the methoxyl groups in the methoxymethyl series of bases and the instability of the colours from the last-mentioned two substances. It is of interest that the ring including :N(a)CH$_2$– in these bases is not fused to the oxide ring. Therefore the somewhat similar behaviour of *iso*strychnidine (Part VI) is significant. Under the standard conditions this base gives only a pale coloration, but with 1% hydrochloric acid–ferric chloride the usual colour is developed; the solution quickly becomes brown and then yellow on boiling. *O*-Acetyl*iso*strychnidine gives no reaction; there is a slow development of colour in 1% hydrochloric acid–ferric chloride on heating (also fades). The *des*-base-D gives slowly a brownish-red solution (suggestion of blue shade at first) and this becomes brownish-yellow on standing. In 1% hydrochloric acid–ferric chloride the reaction approaches that of strychnidine but soon becomes browner and on heating the solution becomes yellowish-brown. Dihydrostrychnidine-D and its methochloride give very rapidly the usual reaction, but this darkens at once; the pink nuance in thin layers persists for some minutes, but after 3 hours the solution is intense brownish-yellow. In 1% hydrochloric acid–ferric chloride the reaction is of more normal type, especially on heating and, though fading to a browner-yellow shade occurs, the coloration is more stable than that due to the *des*-base-D.

Tetrahydrostrychnine group: Under the conditions mentioned above, the reaction of tetrahydrostrychnine derivatives is quite distinctive; they give more opaque, duller, bluer colorations than the strychnidines.

Tetrahydrostrychnine and its *N*(*b*)-metho-salts (reddish-mauve, changing to bluer mauve or dull reddish-violet and violet with blue shade on long standing), hexahydrostrychnine and its methosulphate (slower development of colour and somewhat browner shade than tetrahydrostrychnine; similar colour on keeping), dioxyhydroxyhexahydrostrychnine, methylstrychnine, strychnic acid, and *iso*strychnic acid (weaker colour than normal) were all observed to give reactions of this type.

Negative.—All compounds containing :N(a)·CO· and :NMe(a).

Estimations of :CMe *Groups.*—These were kindly undertaken by Dr. H. Roth of Heidelberg. Dihydrostrychnidine-D and its metho-salts, the *des*-base-D, m. p. 196—197°, and hydroxymethyltetrahydrostrychnidine gave negative results. On the other hand the *des*-base, m. p. 142° (Found: yield of $C_2H_4O_2$, 83·4, 87·0% of the theoretical), and its dihydro-derivative, m. p. 177° (Found: yield of $C_2H_4O_2$, 63·3, 63·7% of the theoretical) (see also the preceding communication), in striking contrast afforded a substantial part of an equivalent of acetic acid when oxidised with chromic acid. These results are of much interest, because they confirm our view that the *des*-base, m. p. 142°, contains a :CMe group and in the case of the dihydro-derivative, m. p. 177°, the positive result with a *saturated* environment of ·CHMe· shows that strychnine should also give a positive result if it did indeed contain the group ·CHMe· in the molecule It was quite to be expected that the unsaturated *des*-base, m. p. 142°, would give a better yield of acetic acid on oxidation than would its dihydro-derivative.

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