304. Strychnine and Brucine. Part XLVII. Oxodihydroneostrychnine and Oxodihydromethoxymethyldihydroneostrychnine.

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It is shown that bases of the *neo*-series are characterised by facile oxidation to oxo-derivatives formed by addition of one atom of oxygen. The carbon-nitrogen skeleton of strychnine is found unaltered in reduction products of these substances.

In the course of attempts to prepare the methiodide of methoxymethyldihydroneostrychnidine in methanolic solution it was found that oxidation occurred and the product was termed oxymethoxymethyldihydroneostrychnidine-A, m. p. 235°. It was convertible into an isomeride-B, m. p. 280° (285°), in various ways, for example by boiling with xylene or acetone (Clemo, Perkin, and Robinson, J., 1927, 1608). No semicarbazone could be prepared, and the base was unchanged by boiling acetic anhydride. It was recognised that the methyl iodide was a source of a trace of catalytic iodine, and the brucidine analogue was obtained by the use of methanol and a crystal of iodine (Gulland, Perkin, and Robinson, J., 1927, 1643).

In a later paper (Achmatowicz, Perkin, and Robinson, J., 1932, 495), the oxidation of methoxymethyldihydroneostrychnidine by means of potassium permanganate in acetone solution was studied. The product was an acetone compound of the oxymethoxydihydroneostrychnidine-C, m.p. 305—306°. The opinion was expressed that (C) is (B) in purer form.

An interesting observation was the conversion of the isomeride- \hat{C} into oxymethyl*neo*strychnidinium salts by boiling it with 20% sulphuric acid. The iodide was analysed, and the related chloride could be converted into the base- \hat{C} by the action of methanolic potassium hydroxide. This was regarded as a proof that the oxygen taken up is not present in a labile group such as an ethylene oxide.

Our further observations suggest that these so-called isomerides are either very labile isomerides or owe their differing melting points to the presence of tenaciously held solvent.

Material of m. p. 285°, corresponding to isomeride-B, afforded a p-nitrophenylhydrazone which could not, however, be fully purified by crystallisation. It gave the characteristic colour reaction of its class with aqueous alcoholic sodium hydroxide.

The bases of m. p. $210-224^{\circ}$ (A) and m. p. 285° (B) were converted in the known manner in **oxyneostrychnidine** methiodide; the same product was obtained in each case and it tallied with the description (*loc. cit.*) of the salt from isomeride-C. On treatment with methanolic potassium hydroxide the latter base was produced.

An indication that the skeleton was unaltered by the oxidation was afforded by reduction of isomeride-B under Clemmensen's conditions with formation of methoxymethyltetrahydrostrychnidine. These results suggest that the oxidation product is an aldehyde or ketone, and we propose the replacement of the prefix "oxy" by "oxodihydro". Methoxymethyldihydroneostrychnine is found to be convertible into oxodihydromethoxymethyldihydroneostrychnine either by leaving a methanolic solution containing a trace of iodine to evaporate in the air, or by boiling with methanol and methyl iodide. The use of ethanol led to the formation of an uncrystallisable gum. The new base holds firmly $\frac{1}{2}$ MeOH or $\frac{1}{2}$ EtOH. Although it certainly forms a p-nitrophenylhydrazone, this derivative showed no tendency to crystallise. The base was also oxidised by means of ferric chloride in N-hydrochloric acid. The crystalline product appears to have the composition $C_{46}H_{56}O_7N_4$, that is, two molecules of the base take up one atom of oxygen. A low value was obtained for the molecular weight in fused camphor, but this is probably due to fission of the molecule under the conditions of the experiment. A very satisfactory oxidation of neostrychnine occurs when its acid solution is treated with bromine water in the cold. The hydrobromide of oxodihydroneostrychnine * crystallises in high yield. The free base exhibits interesting properties and transformations which will be described in detail in a subsequent communication. It is mentioned here because the composition change is the same as that observed in other cases and because this substance is the most characteristic of the oxodihydroneo-bases which we have encountered.

Although this and the other oxodihydro-bases reduce ammoniacal silver solutions with ease and slowly reduce Fehling's solution, it does not follow that they are aldehydes. It is well known that many α -amino-ketones are readily oxidised by the reagents mentioned.

The aldehyde hypothesis seems to be inconsistent with the reduction of oxodihydromethoxy-

* The use of *neo* in this name may be superfluous because dihydroneostrychnine is dihydrostrychnine. But this depends on the validity of our views and the *neo* is retained in order to show the origin of the base. methylneostrychnidine to methoxymethyltetrahydrostrychnidine and with the formation of oxodihydromethoxymethylstrychnidine-C from oxodihydromethylstrychnidinum salts by the action of such a vigorous reagent as methyl alcoholic potassium hydroxide.

The only rational explanations of the formation of these oxodihydroneo-bases that we can devise are as follows :

$$(a) : N(b)-C=CH- \longrightarrow :N(b)-CH-CO-$$

$$(b) : N(b)-CH_{2}- \longrightarrow :N(b)-CH-CO-$$

$$(c) : N(b)-CH=C \longrightarrow :N(b)-CH-CO-$$

Added May 9th, 1947.-It now seems probable that oxodihydroneostrychnidine is not analogous to the other oxo-compounds mentioned herein, and the discussion is therefore postponed.

Added November 9th, 1947.-It has been established that the salt first formed is a neostrychnine dibromide (one bromidion) which changes to oxodihydroallostrychnine hydrobromide in warm aqueous solution. The free base is an aldehyde produced in accordance with hypothesis (c). A statement of these relations was made to the Organic Chemistry Section of the International Congress of Chemistry (London, 1947).

EXPERIMENTAL.

Oxodihydromethoxymethyldihydroneostrychnidine.—This substance was obtained by the known method (*loc. cit.*, 1927) and had variable m. ps. ranging from 210° to 224° (lit. 235°) in different runs. After addition of methanol to a solution in pyridine, the crystals that separated had m. p. 285° and the same value was reached by refluxing the initial product with ethanol or acetone. Only a small quantity of dark material remained in the filtrate.

Oxidation of methoxymethyldihydroneostrychnidine (7 g.) by means of potassium permanganate in acetone solution (*loc. cit.*, 1932) gave 0.5 g. of the variety, m. p. 305°. This separated on concentration of the acetone solution, and the bulk of the product was obtained on removal of the solvent as an uncrystallisable oil. It is very difficult to determine whether the varieties, m. p. 285° and m. p. 305°, are identical or not. The mixed m. p. was 288-294°, and when a pyridine solution of the base, m. p. 285°, was mixed with methanol containing a few crystals of the base, m. p. 305°, the separated crystals had m. p. 304—306°. On the other hand the variety, m. p. 285°, can be recrystallised without change of m. p. and no change of m. p. was observed on refluxing it with acetone, alone or in presence of a little sodium hydroxide. Conversion of any of the supposed isomerides into oxymethyl*neo*strychnidine methiodide (*loc. cit.*) gave one and the same salt, m. p. 232—234° (lit., 238—240°) showing undepressed mixed m. ps. The quaternary chloride from the variety, m. p. 285°, was treated with methanolic potassium hydroxide in the known manner and afforded a base, m. p. 298—300°, m. p. 300—302° on admixture with the

variety, m. p. 305°.

A mixture of the variety, m. p. 285° (0.1 g.), p-nitrophenylhydrazine (0.04 g.), and acetic acid (2 c.c.) was heated on the steam-bath for $\frac{1}{2}$ hour. Addition of aqueous ammonia precipitated a light yellow amorphous solid which was purified by solution in hot ethanol and addition of water; it could not be crystallised (Found : C, 67.9; H, 7.0. $C_{29}H_{35}O_4N_5$ requires C, 67.3; H, 6.8%). The substance softened at 120° and decomposed at 185—186° but these figures have little significance. Its alcoholic solution at 120 and decomposed at 160-160 but these figures have never significance. Its alcohole solution developed an intense red coloration on the addition of a drop of 10% aqueous sodium hydroxide, the reaction characteristic of p-nitrophenylhydrazones. Its acid solution developed a carmine coloration (strychnidine reaction) on addition of ferric chloride. The variety, m. p. 305°, gave a similar p-nitrophenylhydrazone exhibiting these reactions.

A mixture of the variety, m. p. 285° (2.0 g.), concentrated hydrochloric acid (5 c.c.), water (4 c.c.), and amalgamated zinc (5 g., prepared according to "Organic Reactions," 1, 163) was refluxed for 12 hours with the addition of further concentrated hydrochloric acid (1 c.c.) each hour. The diluted solution was basified with sodium hydroxide and the product obtained as a white solid (18g., m. p. 220-221°). The substance was crystallised from benzene and from pyridine-methanol and identified as methoxymethyltetrahydrostrychnidine by observation of the m. p. 220-221°, undepressed on admixture with an authentic specimen.

Oxodihydromethoxymethyldihydroneostrychnine.—Methoxymethyldihydroneostrychnine was prepared from methylstrychnine by the method of Achmatowicz, Clemo, Perkin, and Robinson (J., 1932, 769), and a consistent yield of about 75% was secured by a modification of procedure of isolation. After the removal of methanol and addition of water the alkaline solution was mixed with crushed ice and gradually acidified by acetic acid in a funnel with shaking with ether. In this way the formation of gummy by-product was avoided.

(A). Methoxymethyldihydro*neo*strychnine (5 g.) was dissolved in hot methanol (300 c.c.) and a small crystal of iodine added. The solution was allowed to evaporate in the air for a week. Gum was separated from the sparingly soluble crystalline crust by treatment with hot methanol, the solid was collected, and the filtrate allowed to evaporate again. By repetition of this process the yield was 1.8 g. The substance separated from pyridine-methanol as a jelly which became crystalline on warming. It is sparingly soluble in ethanol, and when the solutions were quickly cooled a gel was also formed; on slow cooling, however, the substance separated as radiating cluster of fine needles, which shrank at 225°,

m. p. 275—277° on slow heating. If heated rapidly the m. p. ranges from 230° to 240° (Found in material dried over sulphuric acid: C, 68.6; H, 7.1; N, 6.7; MeO, 11.3. $C_{23}H_{28}O_4N_2,0.5E$ tOH requires C, 68.7; H, 7.4; N, 6.7%; 1 MeO + 0.5 EtO, Calc. as MeO, 11.1%). When ethanol was employed in this preparation no crystallisable product was obtained. The base dissolves slowly but completely in N-hydrochloric acid and is precipitated by the addition of sodium acetate. It forms a p-nitrophenyl-hydrazone and a 2: 4-dinitrophenylsemicarbazone, but neither of these derivatives could be crystallised. The former gave an intense orange-red coloration, blue-tinged in thin layers, on the addition of potassium hydroxide to its alcoholic solution.

(B). Methoxymethyldihydroneostrychnine (4 g.) was refluxed with methyl iodide (5 c.c.) and methanol (40 c.c.) for 3 hours and then shaken in contact with air for 10 days. The separated crystals (0.6 g.) were deposited from pyridine solution by the addition of methanol as a jelly which crystallised on keeping. This specimen softened at 222°, m. p. 275—277° (Found : C, 68·5; H, 6·9. $C_{23}H_{28}O_4N_2,0.5MeOH$ requires C, 68·4; H, 7·3%). Recrystallised from ethanol (gel \longrightarrow crystals) it was obtained in needles, softening at 240°, m. p. 275—277°, and mixed with the product from (A) it softened at 235°, m. p. 275—277°. It is quite possible that the half molecule of solvent is in combination in the form $-\dot{C}(OR)-O-\dot{C}(OH)$ — and that the variations of softening points are due to incomplete exchange of R by R'. When iodine (0·2 g.) was used in place of methyl iodide in this procedure, the yield was 1·0 g. The *p*-nitrophenylhydrazone shrank at 130°, m. p. 155—157° (decomp.). Strychnine and methoxymethyldihydroneostrychnine is very slowly attacked under these conditions.

Reduction according to Clemmensen afforded a base, m. p. 261-262°, readily soluble in methanol, but the investigation of this substance has not yet been completed.

Oxidation of Methoxymethyldihydroneostrychnine by Means of Ferric Chloride.—A cold solution of ferric chloride (3.3 g., anhydrous) in water (15 c.c.) was added to one of methoxymethyldihydroneostrychnine (3.8 g.) in N-hydrochloric acid (35 c.c.). After an hour the red solution was basified with ammonia, precipitating the base along with ferrous hydroxide. The whole was shaken with ethyl acetate (about 50 c.c.), filtered, and the ester layer separated and evaporated (2.6 g. of crystalline residue). The substance is very sparingly soluble in hot methanol or ethanol, readily soluble in dilute hydrochloric acid. It crystallises from chloroform on the addition of ether in small, flat needles, m. p. 190° [Found : C, 70.9; H, 7.1; N, 7.3; M (Rast in camphor), 467. $C_{46}H_{56}O_7N_4$ requires C, 71.1; H, 7.2; N, 7.2%; M, 776]. The composition suggests a compound of oxodihydromethoxymethyl-dihydroneostrychnine, $C_{23}H_{28}O_4N_2$, and methoxymethyldihydroneostrychnine, $C_{23}H_{28}O_3N_2$, but the substance does not afford a p-nitrophenylhydrazone and it gives no precipitate on the addition of p-nitrophenylhydrazone and it gives no precipitate on the addition of p-nitrophenylhydrazone and it gives no precipitate on the addition $C_{46}H_{54}O_7N_4$ (Calc : C, 71.3; H, 7.0; N,7.2%) is not excluded. Oxodihydroneostrychnine.—A hot solution of neostrychnine (8.35 g.) in 1.5N-sulphuric acid (110 c.c.)

Oxodihydroneostrychnine.—A hot solution of neostrychnine (8.35 g.) in 1.5N-sulphuric acid (110 c.c.) was cooled to the room temperature and 0.2N-bromine water (250 c.c.) added in 4 to 5 portions with shaking, so that the yellow perbromide that separated was quickly decomposed. The white crystalline precipitate was collected after 15 minutes, washed with a little water, and dried in a vacuum desiccator (9.8 g.). The salt is a hydrobromide free from sulphate. Although very sparingly soluble in cold water, it dissolves readily on heating and forms supersaturated solutions. Crystallisation is best effected from concentrated solutions and seeding is necessary. The colourless, well-shaped prisms become deep red with shrinkage at 170° and gradually decompose on further heating (Found : C, 55-2, 56·0; H, 5·6, 5·7; Br, 17·3, 18·7. C₂₁H₂₂O₃N₂,HBr,H₂O requires C, 56·1; H, 5·6; Br, 17·8%). The free base was obtained as a chalky precipitate on addition of ammonia to a cold solution of the hydrobromide. It was collected, washed, and dried in a vacuum (7·5 g., m. p. 80—140°). This product was dissolved in methanol (80 c.c.) and the solution concentrated to 15—20 c.c. when it separated in stellate clusters of transparent prisms (6 g.), m. p. 128° (decomp.) (Found: C, 69·1; H, 6·9; N, 7·4. C₂₁H₂₂O₃N₂,MBCH requires C, 69·1; H, 6·8; N, 7·3%). The solvent is lost slowly at 100°, more rapidly at near 120° (loss, 7·6. Calc.: 8·3%). The solvent-free base has m. p. 190° and is hygroscopic (Found : C, 71·6; H, 6·4; N, 7·9. C₂₁H₂₂O₃N₂ requires C, 72·0; H, 6·3; N, 8·0%). It is of interest that oxodihydroneostrychnine can also be obtained, although in poor yield, by aerial or solution of an exetury bing in given by a endance of accentrychnine in gravery disclose of accentrychnine in grave

It is of interest that oxodihydroneostrychnine can also be obtained, although in poor yield, by aerial oxidation of neostrychnine in methanol containing iodine. A mixture of neostrychnine (3 g.), methanol (120 c.c.), and iodine (0.2 g.) was shaken for 9 days under air. Some neostrychnine remained undissolved (1.8 g., m. p. 224—225°) and the filtrate was evaporated and the residue extracted with dilute sulphuric acid. Ammonia precipitated a white solid $(0.5 \text{ g.}, \text{ m. p. } 110^\circ$ with frothing) and this was converted into the semicarbazone hydrochloride in the usual manner. The salt, when slowly heated, darkened at 240° and decomposed at 255°, and the behaviour was unchanged on admixture with the derivative prepared from oxodihydroneostrychnine. The base is sparingly soluble in the simple alcohols but has a tendency to form supersaturated solutions. It is readily soluble in chloroform and can easily be crystallised by addition of ether to a concentrated solution. It is fairly soluble in dilute hydrochloric acid. A silver mirror is formed with ammoniacal silver nitrate after heating on the steam-bath for 10 minutes, and the base also reduces silver oxide in boiling alcoholic suspension, forming a mirror. It slowly reduces Fehling's solution on heating. The Otto reaction (60% sulphuric acid) is a transient violet coloration changing to deep red and finally brown. The p-nitrophenylhydrazone is a yellow solid, the alcoholic solution of which becomes deep red on the addition of aqueous sodium hydroxide. Crystalline derivatives showing the presence of a carbonyl group have been prepared and analysed, but a description of these is reserved for a future communication.

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