

### 304. *Strychnine and Brucine. Part XLVII. Oxodihydroneostrychnine and Oxodihydrmethoxymethylidihydroneostrychnine.*

By R. N. CHAKRAVARTI, K. H. PAUSACKER, and SIR ROBERT ROBINSON.

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 methoxymethylidihydroneostrychnidine in methanolic solution it was found that oxidation occurred and the product was termed oxymethoxymethylidihydroneostrychnidine-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 methoxymethylidihydroneostrychnidine 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-C into oxymethylneostrychnidinium salts by boiling it with 20% sulphuric acid. The iodide was analysed, and the related chloride could be converted into the base-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° (A) and m. p. 285° (B) were converted in the known manner in oxymeostrychnidine 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". Methoxymethylidihydroneostrychnine is found to be convertible into *oxodihydrmethoxymethylidihydroneostrychnine* 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  $\alpha$ -amino-ketones are readily oxidised by the reagents mentioned.

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

\* 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.



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.  $C_{23}H_{28}O_4N_2 \cdot 0.5EtOH$  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*-nitrophenylhydrazone 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). Methoxymethylhydroneostrychnine (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.  $C_{23}H_{28}O_4N_2 \cdot 0.5MeOH$  requires C, 68.4; H, 7.3%). Recrystallised from ethanol (gel → 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 methoxymethylhydroneostrychnine immediately decolorise permanganate in very dilute sulphuric acid solution. Oxodihydroneostrychnine 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 Methoxymethylhydroneostrychnine 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 methoxymethylhydroneostrychnine (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 oxodihydroneostrychnine,  $C_{23}H_{28}O_4N_2$ , and methoxymethylhydroneostrychnine,  $C_{23}H_{28}O_4N_2$ , but the substance does not afford a *p*-nitrophenylhydrazone and it gives no precipitate on the addition of *p*-nitrobenzenediazonium chloride to an acid solution. Possibly it is an ether, and the composition  $C_{46}H_{54}O_7N_4$  (Calc. : C, 71.3; H, 7.0; N, 7.2%) is not excluded.

*Oxodihydroneostrychnine.*—A hot solution of neostrychnine (8.35 g.) in 1.5*N*-sulphuric acid (110 c.c.) was cooled to the room temperature and 0.2*N*-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.  $C_{21}H_{22}O_3N_2 \cdot HBr \cdot H_2O$  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.  $C_{21}H_{22}O_3N_2 \cdot MeOH$  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.  $C_{21}H_{22}O_3N_2$  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 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 g., m. p. 110° 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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