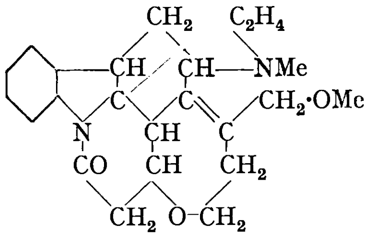
121. *Strychnine and Brucine. Part XXVII. Methoxymethyl*chano*dihydrostrychnone and the Constitution of Strychnidone.*

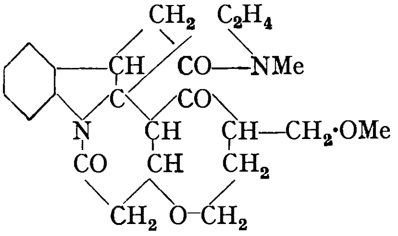
By L. H. Briggs and R. Robinson.

After numerous trials with less suitable oxidising agents, it has been found that perbenzoic acid converts methoxymethyldihydro*neo*strychnine, $C_{23}H_{28}O_3N_2$ (Part XVI; Achmatowicz, Clemo, Perkin, and Robinson, J., 1932, 767), into a dioxy-derivative, $C_{23}H_{28}O_5N_2$, which we designate *methoxymethyl*chano*dihydrostrychnone*. This substance is neutral and hence contains $\colon N(a){\cdot}CO{\cdot}$ and $\colon N(b){\cdot}CO{\cdot}$; it is also a ketone, forming an *oxime* and a p-*nitrophenylhydrazone*.

These facts are readily illustrated by means of the formulæ (I) for methoxymethyldihydro*neo*strychnine and (II) for methoxymethyl*chano*dihydrostrychnone. The formation of a keto-amide in this reaction, in any case, confirms the occurrence of the group $\cdot\dot{C}{=}\dot{C}{-}\dot{C}H{-}N(b)\colon$ in the *neo*strychnine series of bases.

(I.)

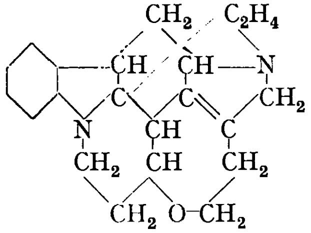


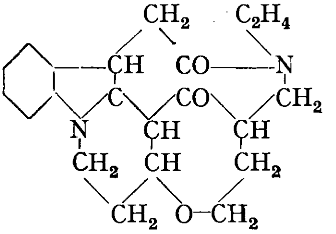


(II.)

These observations suggested to us that strychnidone obtained by the oxidation of *neo*strychnidine (III) (Part IV; Clemo, Perkin, and Robinson, J., 1927, 1589; compare Part XVI, *loc. cit.*) might also be a keto-amide (IV), and the most cogent argument against this hypothesis has now been removed. We confirm the formation of a *monoxime*, but the disemicarbazone previously described (Part IV, *loc. cit.*) should be deleted from the literature, as the specimen analysed was preserved and has now been found to be a mixture containing hydrazodicarbonamide. In this connexion it is of interest to note that the brucine analogue of strychnidone was isolated as an oil which gave a crystalline *brucidone monosemicarbazone* (Part V; Gulland, Perkin, and Robinson, J., 1927, 1627).

(III.)





(IV.)

If strychnidone has the formula (IV), or an analogous one containing $\colon N(b){\cdot}CO{\cdot}$, it should be a weak base (as it is) and its metho-salts should not exhibit strychnidine-type reactions. Actually strychnidone methosulphate could not be obtained analytically pure, but its acid aqueous solution developed no coloration on the addition of ferric chloride or a nitrite.

EXPERIMENTAL.

*Methoxymethyl*chano*dihydrostrychnone*.—Methoxymethyldihydro*neo*strychnine was obtained in 73% yield by the sodium amalgam–methyl alcohol method described in Part XVI (*loc. cit.*). The m. p. was raised to 143—144°. In preliminary trials the use of potassium permanganate in acetone solution had no satisfactory outcome, but the following experiment should be recorded.

Methoxymethyldihydro*neo*strychnine (2·5 g.) was oxidised in dry benzene (160 c.c.) by means of lead tetra-acetate (5·3 g.), and the crude product (0·63 g.) separated from the filtered solution. It crystallised from acetone–methyl alcohol and from methyl alcohol–chloroform in sandy granules, m. p. 210—243° (decomp.), losing 5·7% at 110° in a high vacuum (Found in dried material: C, 70·0; H, 6·8. $C_{23}H_{28}O_4N_2$ requires C, 69·7; H, 7·1%). It appears that this substance is *oxymethoxymethyldihydro*neo*strychnine*. The yield was so unfavourable that the compound could not be further investigated. Ultimately the smooth oxidation by means of perbenzoic acid was adopted.

Perbenzoic acid (6·3 g.; 2 mols.), prepared according to the method of Levin (*J. pr. Chem.*, 1930, **127**, 81), was dissolved in dry ether (175 c.c.) and added in one portion to a solution of methoxymethyldihydro*neo*strychnine (8·75 g., 1 mol.) in boiling anhydrous ether (300 c.c.). Heat was produced and the liquid was cooled. At first some gum was precipitated, but this was soon succeeded by an entirely crystalline mass of needles and prisms; the gum also crystallised on keeping (yield, 92%). The substance was twice crystallised from ethyl acetate–ether and twice from acetone–ether, forming needles, m. p. 198—199° after drying (Found in material dried at 100° in a vacuum: C, 67·0, 67·2; H, 7·1, 6·9; N, 6·8; MeO, 7·6; MeN, 7·2. $C_{23}H_{28}O_5N_2$ requires C, 67·0; H, 6·8; N, 6·8; MeO, 7·5; MeN, 7·0%). The substance, crystallised from ethyl acetate and air-dried, had m. p. 147—150° even after drying in a vacuum, but, after heating to 100° in a vacuum, the m. p. 198—199° was observed.

*Methoxymethyl*chano*dihydrostrychnone* is readily soluble in the simple alcohols, benzene or chloroform, moderately soluble in ethyl acetate or acetone, and appreciably soluble in water; it is very sparingly soluble in ether and light petroleum. Its aqueous solution is neutral and it is not extracted from chloroform or benzene solutions by means of dilute hydrochloric acid. It forms no methosulphate or methiodide. With 60% sulphuric acid and a trace of a dichromate it gives a red coloration, changing to brown. It gives no coloration with Ehrlich's reagent and has the properties neither of an amine-oxide nor of an ethylene oxide. It does not liberate iodine from acidified potassium iodide, nor does it react with sulphurous acid. The substance discolours Tollens's reagent (strychnidone does not) in 5 minutes and a black precipitate is formed in the cold in ½ hour and rapidly on heating. It also reduces Fehling's solution on boiling (strychnidone does not); it is, however, very stable to permanganate under all usual conditions.

Various attempts to oxidise the substance were made, but no crystalline substances other than oxalic acid could be isolated. Dry distillation brought about decomposition and a small amount of an indole derivative was obtained. This gave a dull plum-red coloration with Ehrlich's reagent.

The *oxime* was obtained by boiling a mixture of methoxymethyl*chano*dihydrostrychnone (0·5 g.), methyl alcohol (2 c.c.), hydroxylamine hydrochloride (1 g.), fused sodium acetate (1·25 g.), and water (5 c.c.); on cooling, the clear liquid deposited a gum which partly crystallised (0·38 g. left on porous tile). The crude product was extracted with hot ethyl acetate and the residue, which had become much more sparingly soluble, was crystallised from 60% alcohol and then from 95% alcohol, forming colourless prisms, m. p. 260—261° (decomp.) (Found: C, 64·6; H, 6·7; N, 9·7. $C_{23}H_{29}O_5N_3$ requires C, 64·6; H, 6·8; N, 9·8%).

The p-*nitrophenylhydrazone* was prepared from the components in boiling alcoholic solution; on keeping the concentrated solution in the ice-chest, unchanged *p*-nitrophenylhydrazine separated first and subsequently the new derivative crystallised in long, bright yellow prisms and needles, m. p. about 194°. After one recrystallisation from alcohol and two from acetone the m. p. was raised to 263° with decomposition at 265·5—266° to a red liquid (Found: C, 63·3; H, 6·0; N, 12·7. $C_{29}H_{33}O_6N_5$ requires C, 63·6; H, 6·0; N, 12·8%).

An attempt to prepare a semicarbazone led to the isolation of impure hydrazodicarbonamide, and a re-examination of the supposed " strychnidone disemicarbazone " showed that it also consisted largely of this substance.

Benzylidene derivative. This substance was obtained by the use of a large excess of benzaldehyde in boiling alcoholic solution containing sodium ethoxide; it could not be crystallised in a form recognisable under the microscope, but it separated as a light yellow powder from hot solutions in ethyl alcohol and the best specimens decomposed at 248—256° after shrinking at

235° (Found in material dried at 100° in a vacuum : C, 73·6; H, 6·3; N, 5·2%). The analysis indicates that the anhydro-bis-compound was first formed and that condensation with benzaldehyde occurred subsequently (see below).

*Anhydrobismethoxymethyl*chano*dihydrostrychnone*.—Methoxymethyl*chano*dihydrostrychnone (5 g.), almost completely dissolved in boiling water (60 c.c.), was very slowly treated with a solution of potassium hydroxide (10 g.) in water (40 c.c.); the mixture was then refluxed for 30 minutes. The precipitated gum was well washed and dried (5·03 g.). This substance separated from hot methyl alcohol as an amorphous, colourless powder which decomposed at 268—273° after shrinking at 257° (loss on drying : 5·1, 4·9%) (Found in anhydrous material : C, 68·2; H, 6·5; N, 6·9. $C_{46}H_{54}O_9N_4$ requires C, 68·5; H, 6·7; N, 6·9%). The *substance* is soluble in hot alcohol or cold acetone; it is very sparingly soluble in ethyl acetate, benzene, ether or boiling water. It dissolves in glacial acetic acid or concentrated hydrochloric acid, but is precipitated on dilution of the solutions with water.

In contrast with methoxymethyl*chano*dihydrostrychnone, it is very readily oxidised by permanganate and hence appears to contain an unsaturated linkage. An interesting point is that on boiling with Ehrlich's reagent a reddish-purple coloration is gradually produced, indicating a breakdown to an aromatic indole with a free α- or β-position.

The *benzylidene* derivative of this condensation product was also prepared and its properties were identical with those briefly mentioned above. The bright yellow, amorphous powder shrank at 235° and decomposed at 251—253° (loss on drying, 3·8, 3·7, 3·5%) (Found in anhydrous material : C, 73·3; H, 6·2; N, 5·3; MeO, 6·6; MeN, 5·8. $C_{60}H_{62}O_9N_2$ requires C, 73·3; H, 6·3; N, 5·7; MeO, 6·3; MeN, 5·9%). Thus this substance is formed from $2C_{23}H_{28}O_5N_2$ and $2C_7H_6O$ by the elimination of $3H_2O$.

An oxime of the anhydro-bis-compound could not be prepared and all attempts to reduce the substance were unsuccessful.

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