122. *Strychnine and Brucine. Part XXVIII.* (A) *Methoxymethyl*chano*dihydrostrychnane.* (B) *The Constitution of Anhydrotetrahydromethylstrychnine–K^5.*

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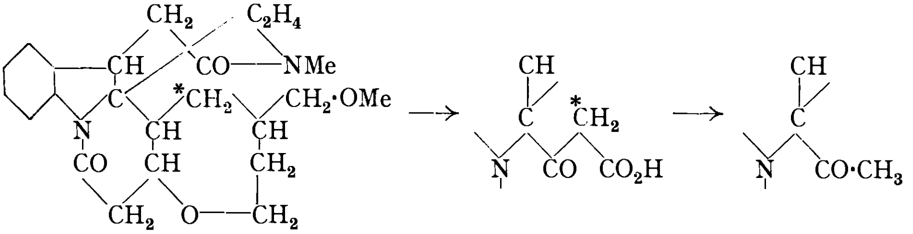
The promising line of investigation opened up by the discovery of the nearly quantitative oxidation of methoxymethyldihydro*neo*strychnine by means of perbenzoic acid (see preceding communication) could be developed in many directions, were it not for the tendency of the product to undergo auto-condensation leading to amorphous derivatives.

We have now found that the ketone can be reduced by Clemmensen's method to *methoxymethyl*chano*dihydrostrychnane,* and this neutral substance is comparatively stable and does not undergo condensation under the influence of hot acid or alkaline solutions. Its resistance to powerful hydrolytic agents is significant and is now mentioned in relation to the preceding communications, although the investigation is still being actively prosecuted. It is now evident that the methoxylation of the $\vdots C{-}\ddot{N}Me(b)\}X$ grouping does not occur with formation of a part structure, $\cdot\dot{C}(OMe)\cdot\dot{C}{=}\dot{C}{-}CH_2\cdot NMe\cdot$, for in this case, methoxymethyl*chano*dihydrostrychnone would have a constitution including the groups $\cdot\dot{C}(OMe)\cdot\dot{C}H\cdot\dot{C}O$; $CHO\cdot\dot{N}Me$. The related " strychnane " would also be a substituted formamide on this hypothesis and would contain the groups, $\cdot\dot{C}(OMe)\cdot\dot{C}H\cdot\dot{C}H_2$; $CHO\cdot\dot{N}Me$. The properties of the substance exclude such a view of its constitution and thus we find a confirmation of the current representation of the mode of formation of substances of the methoxymethyldihydro*neo*strychnidine class. We consider that the " strychnane " has the formula (I) (with the reservation, regarding the position of attachment of the C_2H_4 chain to the indole nucleus, mentioned on p. 582 of a preceding memoir). It should be noted that the methoxylating fission is undoubtedly facilitated by the double bond of the strychnine and strychnidine bases which are of allylamine type. Conversely, the methoxyl group in the products is still under the influence of this double bond in the *neo*-position (allyl methyl ether structure) as shown by its ready hydrolysis under the influence of hot dilute mineral acids in the unsaturated, but not in the saturated, series. Hence, on the basis of any structure at present under discussion, there are really only two possibilities and one of these is now to be recognised as highly improbable. A number of strychnine derivatives have been kindly tested by Dr. H. Roth for methyl attached to carbon by means of the Kuhn–Roth micro-method involving oxidation with chromic acid under drastic conditions and estimation of the acetic acid produced.

Methoxymethyl*chano*dihydrostrychnone in common with other strychnine derivatives gave a negative result (hence C_2H_4 is $-CH_2-CH_2-$ and not $:CHMe$), but methoxymethyl*chano*dihydrostrychnane furnished a molecule of acetic acid.

(I.)



The asterisked methylene in (I) is produced from the carbonyl group of the " strychnone " according to our hypothesis and, as this change is the only one that occurs in the reduction, we propose the above scheme in order to explain the formation of acetic acid. We have not overlooked the possibility that methoxymethyl*chano*dihydrostrychnone may be an aldehyde; some of its properties suggest this, and the formation of acetic acid from the reduction product would then be readily explicable. This hypothesis is hard to reconcile with our views on structure in the strychnine series, but we are continuing experimental investigations with the idea in mind.

A case in which the formation of a simple substance on oxidation has thrown definite light on a structural detail is that of anhydrotetrahydromethylstrychnine-K^5. The alternative formulæ proposed for this base (Part XIX; Perkin, Robinson, and Smith, J., 1932, 1239) contained the group $-\dot{C}:CMeEt$ and the group $-\dot{C}H-CMe:CHMe$, respectively. We have now found that significant amounts of acetaldehyde can be obtained from the base on oxidation with acid permanganate. The second type of grouping is thus indicated and the ethylenic linkage of strychnine remains in its original position in the course of the series of processes resulting in the formation of the base-K^5.

In the reduction of strychnidine methosulphate by means of sodium amalgam, the bond probably moves into the *neo*-position (see Part XXV) and the contrast between the strychnine and strychnidine series may be due to the fact that only in the former case is the oxide ring opened.

EXPERIMENTAL.

*Methoxymethyl*chano*dihydrostrychnane.*—Amalgamated zinc filings (100 g.) (Clemmensen, *Ber.*, 1913, **46**, 1837) were added to a solution of methylmethoxystrychnone (10 g.) in cold concentrated hydrochloric acid (150 c.c.), which was gently refluxed for 29 hours, during which time further quantities of zinc amalgam (2 portions of 50 g. each) and hydrochloric acid (6 portions of 25 c.c. each) were added. The hot filtered solution and washings of the zinc with 15% hydrochloric acid were cooled and extracted four times with chloroform, and the combined extracts (approx. 1000 c.c.) washed once with a small volume of water, dried over magnesium sulphate, and concentrated to 10—15 c.c. On the addition of ether and light petroleum a white crystalline solid (3·5 g.), m. p. 149—151° after marked softening at 95—100°, separated. A specimen from another preparation shrank and softened at 65—70°, m. p. 152—154°; after one recrystallisation from benzene–light petroleum it softened at 65—70° and melted at 154—156°; after four recrystallisations from the same solvents it had m. p. 160—161° without previous softening [Found: C, 69·1; H, 7·5; N, 7·3; MeO, 7·5; MeN, 7·5; *M* (Rast, cryoscopic in camphor), 386. $C_{23}H_{30}O_4N_2$ requires C, 69·4; H, 7·5; N, 7·0; MeO, 7·8; MeN, 7·3%; *M*, 398]. Methoxymethyl*chano*dihydrostrychnone behaved similarly; after two recrystallisations from ethyl acetate–ether it softened at 142—145°, began to soften again at 184°, and was completely molten at 189°; after further recrystallisation it had m. p. 188—190° without previous softening. This behaviour is considered to be due to admixture of the crude products with stereoisomerides. In (I), for example, stereoisomerism may arise from the disposition of the group $\cdot CH_2\cdot OMe$ with respect to the other substituents in the hexamethylene oxide ring.

*Methoxymethyl*chano*dihydrostrychnane* is readily soluble in warm water and the usual organic solvents with the exception of ether and light petroleum. It is readily soluble in 15% hydrochloric acid and only slightly soluble in 20% aqueous sodium hydroxide, but it is completely extracted from acid solutions by chloroform. The addition of a drop of aqueous potassium dichromate to its solution in 60% sulphuric acid gave a reddish-violet coloration, fading rapidly to orange. The ferric reaction in dilute hydrochloric acid solution was negative.

The substance did not appear to form a benzylidene derivative; it was recovered unchanged after being boiled for several minutes with acetic anhydride and pyridine and also after being boiled for 15 minutes with 5% ethyl-alcoholic potassium hydroxide or with 20% aqueous sodium hydroxide. Oxidation with chromic acid (Dr. Roth) gave one molecular equivalent of acetic acid (5·524 mg. gave 0·786 mg. $C_2H_4O_2$. Formation of $1C_2H_4O_2$ requires 0·833 mg. 2·62 Mg. gave 0·366 mg.; required, 0·394 mg.). Strychnine, methylstrychnine, methoxymethyldihydro*neo*strychnine, methoxymethyl*chano*dihydrostrychnone, kakostrychnine, and *iso*dihydrostrychnine gave no acetic acid under the same conditions. It is therefore very improbable that strychnine and brucine can contain a $-CHMe-$ group and the $-C_2H_4-$ in the proposed structural formula must be interpreted as $-CH_2-CH_2-$.

Oxidation of Anhydrotetrahydromethylstrychnine-K^5.—The base-K^5 was purified as described by Perkin, Robinson, and Smith (J., 1932, 1239) and oxidised with acid permanganate; the volatile products were collected and identified in the form of 2 : 4-dinitrophenylhydrazones. Acetaldehyde was the first product of the reaction and it appeared that formaldehyde was formed concurrently but more slowly. As the base was crystallised from alcohol, steps were taken to show that the acetaldehyde was not formed from solvent of crystallisation. Strychnine, under the same conditions, yielded traces of formaldehyde, but no acetaldehyde.

(1) The base-K^5 (0·1 g., m. p. 199—200°) was dissolved in 5% sulphuric acid (50 c.c.), and the solution rapidly distilled while aqueous potassium permanganate (75—80 c.c. of 1·5%) was added in the course of 5 minutes. The oxidation was so rapid that there was not any excess of permanganate in the solution during that time, but the rate of oxidation became markedly slower towards the end of the period and the receiver was changed (25—30 c.c. collected). A further quantity of the permanganate solution (75 c.c.) was added in the course of an hour and the distillate was collected in 3 fractions.

A solution of 2 : 4-dinitrophenylhydrazine sulphate was prepared by shaking 2 : 4-dinitrophenylhydrazine with cold 2*N*-sulphuric acid and then filtering. On mixing with an equal volume of this reagent, the first distillate gave a yellow crystalline precipitate within a minute; no immediate change was observed in the case of the remaining fractions, but a trace of precipitate separated over-night. Even when these fractions were combined and distilled, the first 25—30 c.c. contained so small a quantity of carbonyl compound that it could not be identified.

The solid 2 : 4-dinitrophenylhydrazone from the first distillate was collected after some hours (approx. 20 mg., m. p. 111—113° after softening at 108°) and crystallised thrice from aqueous alcohol, (i) m. p. 133—134° after softening at 127°; (ii) m. p. 151—152° after softening at 146°; (iii) same. Mixed with acetaldehyde-2 : 4-dinitrophenylhydrazone (m. p. 152° after softening at 147°), m. p. 151—152°.

(2) (*a*) The base-K^5 (0·1 g.) was dissolved in 5% sulphuric acid (50 c.c.), and the liquid distilled (20—25 c.c. collected; iodoform reaction negative); water (25 c.c.) was then added to the residue in the flask and the distillation process was twice repeated. The residue was treated as in (1) with exactly similar results.

(*b*) The base-K^5 (m. p. 199—200°) was recrystallised twice from benzene–light petroleum. The m. p. was unchanged and the product was treated as in (1) with the same results.

(3) The base-K^5 was oxidised as before, but the receiver was changed somewhat later and 35—40 c.c. were collected as the first fraction. This gave a 2 : 4-dinitrophenylhydrazone (25—30 mg.), which was recrystallised twice from aqueous alcohol; m. p. 125—127°, unchanged by another recrystallisation; mixed with acetaldehyde-2 : 4-dinitrophenylhydrazone, m. p. 145—147°, mixed with formaldehyde-2 : 4-dinitrophenylhydrazone, m. p. 142—144°, with preliminary softening in both cases. A mixture of formaldehyde- and acetaldehyde-2 : 4-dinitrophenylhydrazones (1 : 1) was recrystallised twice from aqueous alcohol and had m. p. and mixed m. p. almost identical with those mentioned above.

(4) Strychnine (0·1 g.) was oxidised with acid permanganate in the same way. The reaction was much slower and only 2—3 mg. of a 2 : 4-dinitrophenylhydrazone were obtained. A larger quantity (1 g.) was treated in the same way and the product identified by m. p. and mixed m. p. as formaldehyde-2 : 4-dinitrophenylhydrazone.

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