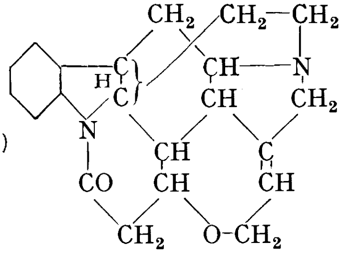
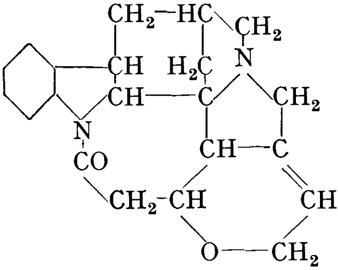
321. *Strychnine and Brucine. Part XXX. Comments on a Memoir of M. Kotake and T. Mitsuwa.*

By Robert Robinson.

Kotake and Mitsuwa (*Sci. Papers Inst. Phys. Chem. Research, Komagome, Hongo,* 1934, **24**, 119) have published a paper on the constitution of strychnine which calls for a reply. These authors accept the main features of the strychnine formula (I) advanced in the present series, but find a few difficulties on stereochemical grounds and make some alternative suggestions.

(I.)





(II.)

In the first place it seems necessary to emphasise that stereochemical restrictions should not be applied to betaines, the dipoles of which are not now assumed to be connected by ordinary valencies. This consideration neutralises the force of the chief argument of Kotake and Mitsuwa, and in regard to the second point mentioned by them it is not agreed, as they claim, that the double bond in (I) makes the formula stereochemically improbable; a satisfactory model can be set up. Little weight can be attached to criticisms on such grounds, unsupported by chemical arguments; on the other hand the formula (II), put forward by Kotake and Mitsuwa, is not acceptable for more serious reasons. A considerable part of it is identical with (I) and naturally this part of the structure serves to illustrate many groups of facts in the same way as (I).

The definite objections to (II) appear to be the following:

(1) On this basis no explanation of the properties and transformations of pseudostrychnine can be devised. This base (Warnat, *Helv. Chim. Acta*, 1931, **14**, 99; Blount and Robinson, J., 1932, 2305) is a hydroxystrychnine capable of reduction to strychnine and it undoubtedly contains the group ⁝N(b)·C(OH)(C⁝)(C⁝), because a derivative, namely, *N*(b)-methyl*chano*-pseudostrychnine, including the groups ⁝N(b)Me CO(C⁝)(C⁝) is a ketone, not an aldehyde, and also because pseudostrychnine itself cannot be oxidised to a lactam.

The N(b) of strychnine is therefore attached to a ·CH(C⁝)(C⁝) group, as in (I), and not to a quaternary carbon, as in (II).

(2) Accepting our view of the methoxylating fission of quaternary salts derived from *strychnos* bases, the formula (II) fails as a basis for an explanation of the course of the oxidation of methoxymethyldihydro*neo*strychnine by means of perbenzoic acid (Briggs and Robinson, this vol., p. 590; Reynolds and Robinson, *ibid.*, p. 592). The results of these investigations are furthermore irreconcilable with the view of the methoxylating fission and of the constitution of the *neo*-series of bases put forward by the Japanese authors [analogous to (A) below].

(3) The formula (II), like the variation of (I) preferred by Professor H. Leuchs, represents strychnine as a dihydroindole capable of direct loss of two hydrogen atoms to give a true aromatic indole. There is no evidence that strychnine, or any of its numerous derivatives with opened ring-structures, undergoes the facile dehydrogenation required by this formulation. It seems certain that the dihydroindole structure is stabilised by double substitution at the α- or β-position of the indole nucleus.

(4) Although the argument will not have universal appeal, some chemists, including the writer, would reject the formula (II) on the sole ground that it does not contain the tryptophan skeleton.

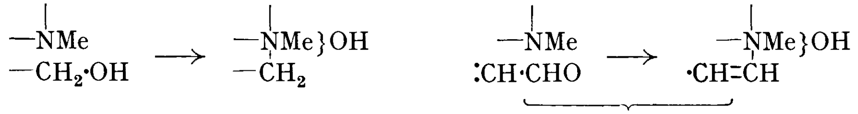
It is encouraging to find that the most recent work in the strychnine group must be cited in the discussion of the relative merits of (I) and (II).

On p. 123 of the memoir of Kotake and Mitsuwa there are some misleading statements. The view is attributed to the writer that the chloride derived from Tafel's base (ethoxymethyldihydro*neo*strychnine in our nomenclature) is produced by direct replacement of ethoxyl by chlorine, $\vdots NMe\ EtO{\cdot}CH_2{}^- \longrightarrow \vdots NMe\ Cl{\cdot}CH_2{\cdot}$! Such a notion must be emphatically disclaimed; the chloride in question is considered to be a quaternary ammonium salt, namely, methyl*neo*strychninium chloride, and was always described as such.

Further, Kotake and Mitsuwa state that their observations on the action of hydrochloric acid on Tafel's base do not agree with ours, but they fail to draw attention to the not irrelevant circumstance that the conditions of the experiments were different.

Achmatowicz, Clemo, Perkin, and Robinson (J., 1932, 771) do not in fact describe the experiment of heating Tafel's base (which is an ethoxy-derivative) with hydrochloric acid at all, but they state that the corresponding methoxy-compound is converted into methyl*neo*strychninium chloride, m. p. 289—290°, by *prolonged heating with concentrated hydrochloric acid on the steam-bath.* Thus we worked with a *methoxy*-base, *concentrated* acid and a *prolonged* reaction. Normally we used 20% sulphuric acid for such processes and worked with an *excess*; *e.g.*, 20 g. of methoxy-base and 300 c.c. of 20% sulphuric acid (*loc. cit.*). The Japanese workers (*loc. cit.*, p. 129) dissolved the *ethoxy*-base in a *little* 6*N*-hydrochloric acid and evaporated the solution on the steam-bath, obtaining crystals, m. p. 265—268°. The process is altogether more gentle than ours, apart from the use of the ethoxyl instead of the methoxyl derivative, which is probably not really significant. (The methyl-Tafel-base of Kotake and Mitsuwa is stated to melt at 117°, whereas pure methoxymethyldihydro*neo*strychnine has m. p. 141—143°. They hydrolysed the base, m. p. 117°, to the salt, m. p. 265°, which goes to show that the behaviour of the methoxy- and the ethoxy-base is identical.)

Apparently, under these milder conditions, Kotake and Mitsuwa have simply hydrolysed the ethoxyl group and the base, m. p. 219°, obtained from the hydrochloride, m. p. 265°, is probably hydroxymethyldihydro*neo*strychnine. It is described as soluble in water to a neutral solution which becomes strongly alkaline on heating. This interesting behaviour is clearly due to the formation of a quaternary ammonium hydroxide :



$$\begin{array}{l}\ \ |\\ -NMe\\ -CH_2{\cdot}OH\end{array} \longrightarrow \begin{array}{l}\ \ |\\ -NMe\}OH\\ -CH_2\end{array} \qquad \begin{array}{l}\quad\ \ |\\ \ \ -NMe\\ \vdots CH{\cdot}CHO\end{array} \longrightarrow \begin{array}{l}\quad\ \ |\\ \ \ -NMe\}OH\\ {\cdot}CH{=}CH\end{array}$$

(A)

The Briggs–Reynolds degradation, mentioned above, excludes the alternative (A).

A point of interest is that Kotake and Mitsuwa attribute the composition $C_{22}H_{25}O_2N_2Cl,H_2O$ to the salt, m. p. 265—268°, and add the statement : Ber. H_2O, 4·43% (Gef. 4·33%), but they do not say at what temperature this drying was conducted, nor do they record any examination of the dried material.

Hydroxymethyldihydro*neo*strychnine hydrochloride is already $C_{22}H_{27}O_3N_2Cl$, and if it loses H_2O it should yield methyl*neo*strychninium chloride, m. p. 289—290°.

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