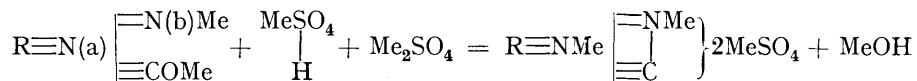


309. *Strychnine and Brucine. Part XXXIV. The Action of Methyl Sulphate on Methoxymethyldihydroneobrucidine and Similar Bases in Boiling Benzene Solution.*

By O. ACHMATOWICZ and ROBERT ROBINSON.

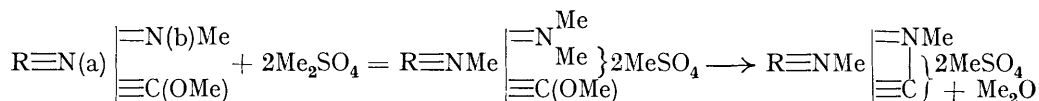
IN Part XXI (*Rocz. Chem.*, 1932, **12**, 862) it was shown that the supposed dimetho-salts-A of methoxymethyldihydrostrychnidine (Part IV, J., 1927, 1589) are actually dimetho-salts of *neostrychnidine*, whereas dimetho-salts-A of methoxymethyltetrahydrostrychnidine are identical with dihydrostrychnidine dimetho-salts. It was conjectured that the formation of these substances from the methoxylated bases was due to the presence of traces of water, methyl hydrogen sulphate participating in accordance with the following scheme :



We have now prepared the dimetho-salts of *neobrucidine* and of dihydrobrucidine and have found the former to be identical with the supposed methoxymethyldihydrobrucidine dimetho-salts-B (Part V; J., 1927, 1627) and the latter with dimetho-salts-B of methoxymethyltetrahydrobrucidine.

However, the plausible hypothesis represented by the above scheme cannot be correct, because on reinvestigation it was found that all the methoxy-bases described in Parts IV and V of this series afford *dimethyl ether* on heating with methyl sulphate in benzene solution (compare the action of methyl iodide on methoxymethyl-dihydrobrucine; Part XVI, J., 1932, 771). Moreover, in all cases the volume of dimethyl ether formed was found to correspond to the yield of dimetho-salts. Thus methoxymethyl-dihydrobrucine (1 mol.) gave dimethyl ether (0.5 mol.) and the yield of *neostrychnidine* dimethosulphate was 50% of that required by the theory. Similar results were obtained with methoxymethyl-tetrahydrobrucine and the analogous brucidine derivative. Even methoxy-benzyl-dihydrobrucine gave an equivalent of dimethyl ether (instead of the expected benzyl methyl ether) along with a theoretical yield of *N(a)*-methyl-*N(b)*-benzyl-*neobrucidinium* dimethosulphate. On the other hand, when methylation was carried out at a higher temperature, benzene being replaced by xylene as solvent, or when the reaction in boiling benzene solution was prolonged, the yield of dimethyl ether increased considerably and a proportional rise of the yield of the corresponding dimethosulphates was observed.

These facts clearly indicate that the action of methyl sulphate on the substances in question involves three reactions, namely, the methylation of *N(b)*, the methylation of both nitrogen atoms and formation of true dimethosulphates of the methoxy-bases; finally a thermal decomposition of the dimethosulphates with ring-closure at *N(b)* and elimination of dimethyl ether.



Light is thrown by this theory on a number of hitherto inexplicable facts:—

(a) The formation of *neobrucidine* by thermal decomposition of so-called methoxymethyl-dihydrobrucine dimethochloride-B is seen to depend on elimination of two molecules of methyl chloride.

(b) The conversion of methoxymethyl-tetrahydrobrucine dimethiodide-A into so-called methoxymethyl-tetrahydrobrucine monomethiodide-B is the result of loss of dimethyl ether and methyl iodide.

(c) The identity of so-called methoxymethyl-dihydrobrucine monometho-salts-B, methyl-*neobrucidinium* salts and methyl-*ψ*-brucidine metho-salts with *neobrucidinium* metho-salts is explained and indeed required by the present hypothesis.

(d) The periodide of so-called methoxymethyl-tetrahydrobrucine dimethiodide-B (Part V, *loc. cit.*, p. 1657) must now be regarded as a periodide of dihydrobrucine dimethiodide: the analysis given in Part V supports this view (Found: I, 55.5, $\text{C}_{25}\text{H}_{36}\text{O}_4\text{N}_2, 2\text{MeI}, \text{I}_2$ requires I, 52.6% and $\text{C}_{23}\text{H}_{30}\text{O}_3\text{N}_2, 2\text{MeI}, \text{I}_2$ requires I, 55.2%). Unfortunately, relatively few iodine estimations were cited in Part V.

The m. p.'s recorded in this communication are in some cases a few degrees higher than those given in Part V, but this is probably a question of a different rate of heating. On this account and also because fusion is accompanied by decomposition, microphotographs are submitted as confirmatory evidence of the identity of salts from different sources.

EXPERIMENTAL.

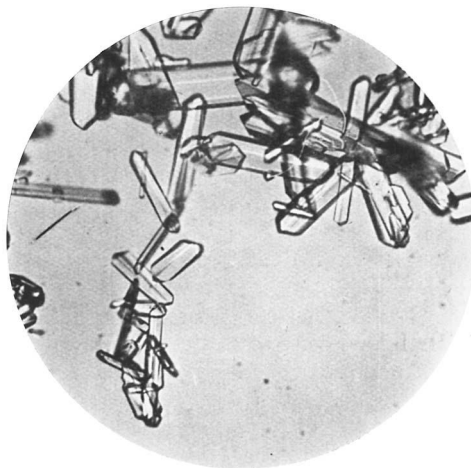
neoBrucidine Dimethiodide.—A mixture of *neobrucidine* (20 g.), benzene (100 c.c.), and methyl sulphate (15 c.c.) was refluxed for 12 hours and the gummy dimethosulphate that separated was dissolved in hot water (75 c.c.), basified with ammonia (no precipitate), and mixed with sodium iodide (20 g.). *neoBrucidine dimethiodide* crystallised completely in 6 hours or in a shorter time if the solution was seeded with so-called methoxymethyl-dihydrobrucine dimethiodide-B. Colourless columns (Fig. 1), m. p. 298° (decomp.), from water (Found: loss at 105° in a high vacuum, 1.5, 1.7. $\text{C}_{23}\text{H}_{28}\text{O}_3\text{N}_2, 2\text{MeI}, 0.5\text{H}_2\text{O}$ requires H_2O , 1.3%. Found in anhydrous material: C, 45.0; H, 5.2; I, 38.6. $\text{C}_{23}\text{H}_{28}\text{O}_3\text{N}_2, 2\text{MeI}$ requires C, 45.2; H, 5.1; I, 38.3%). The salt is sparingly soluble in methanol and it was found to tally with so-called methoxymethyl-dihydrobrucine dimethiodide-B (Fig. 2) prepared by the method described in Part V (*loc. cit.*). The identity of the specimens was proved by mixed m. p. (298°), by conversion into *neobrucidine*

FIG. 1.



neoBrucidine 2MeI obtained from neoBrucidine + Me₂SO₄ + NaI (from H₂O).

FIG. 2.



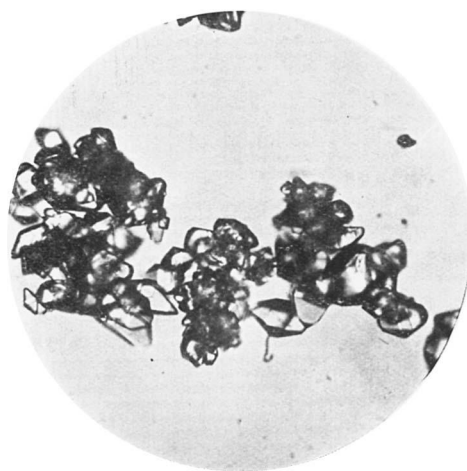
Methoxymethyldihydrobrucidine 2MeI B'' (cryst. from H₂O).

FIG. 3.



Dihydrobrucidine 2MeI obtained from dihydrobrucidine + Me₂SO₄ + NaI (from H₂O).

FIG. 4.



Methoxymethyltetrahydrobrucidine 2MeI B'' (from H₂O).

methiodide, m. p. 298° (see below), and by analysis of so-called methoxymethyl-dihydrobrucidine dimethiodide-B (Found: loss at 105° in a high vacuum, 1.6. Found in anhydrous material: C, 45.0; H, 5.3; I, 38.1. Theo. values as above, but note that $C_{25}H_{34}O_3N_2, 2MeI$ requires C, 45.6; H, 5.6; I, 33.0%). The melting point of *neobrucidine* dimethiodide depends very much on the rapidity and mode of heat ng. When the salt is heated rapidly, it melts and decomposes at 298°; on slow heating, it softens at 265—270° and melts at 298° (decomp.). When the capillary tube with the product is inserted into a bath at 265—270°, the salt effervesces vigorously, becomes spongy, and on further heating decomposes at 298°. In a quantitative experiment, 0.1836 g. heated at 265—270° lost 0.0388 g., or 21.1%, whereas $C_{23}H_{30}O_3N_2, 2MeI$ requires 1MeI, 21.4%. The glassy decomposition product became crystalline on rubbing with methyl alcohol and was recognised as *neobrucidine* methiodide; after crystallisation from methyl alcohol it had m. p. 298°, not depressed on admixture with a specimen prepared directly from the components.

Dihydrobrucidine Methosulphate.—Methyl sulphate (3 c.c.) was added to a solution of dihydrobrucidine (7.6 g.) in methyl alcohol (30 c.c.); heat was evolved, and on cooling the *methosulphate* crystallised (total yield, 9.8 g.). The derivative formed long, colourless, silky needles, m. p. 287—288° (decomp.), freely soluble in water and moderately readily in the simple alcohols and in acetone (Found in material dried at 105°: C, 51.3, 51.4; H, 6.9, 6.8; S, 10.2, 10.4. $C_{23}H_{30}O_3N_2, 2Me_2SO_4$ requires C, 51.1; H, 6.6; S, 10.1%).

Dihydrobrucidine methiodide, prepared in the cold directly from the components or from the methosulphate by double decomposition with sodium iodide, crystallised from methyl alcohol in colourless plates, m. p. 298° (decomp.) (Found in material dried at 105°: C, 55.3; H, 6.4; I, 23.8. $C_{23}H_{30}O_3N_2, MeI$ requires C, 55.0; H, 6.3; I, 24.2%), sparingly soluble in cold water, moderately in the simple alcohols, and readily in the boiling solvents. The identity of this derivative with so-called methoxymethyltetrahydrobrucidine methiodide-B (Part V, *loc. cit.*) was established by mixed m. p. (298°) and by analysis of the latter (Found in material dried at 105°: C, 55.3; H, 6.4; I, 24.0%).

Dihydrobrucidine dimethiodide, prepared from dihydrobrucidine dimethosulphate (Part XI; J., 1930, 1772) by means of sodium iodide, formed colourless needles (from water) or plates (from methyl alcohol), m. p. 286—288° (decomp.) (Fig. 3) (Found: loss at 105° in a high vacuum, 1.2, 1.6. $C_{23}H_{30}O_3N_2, 2MeI, 0.5H_2O$ requires H_2O , 1.3%. Found in anhydrous material: C, 44.9; H, 5.6; I, 37.6. $C_{23}H_{30}O_3N_2, 2MeI$ requires C, 45.0; H, 5.4; I, 38.1%), moderately soluble in water, and sparingly in methyl alcohol, cold or boiling. Its identity with so-called methoxymethyltetrahydrobrucidine dimethiodide-B (Fig. 4) was established by mixed m. p. (286—288°), by conversion of both specimens into the same dimethochloride, m. p. 214°, and by analysis of so-called methoxymethyltetrahydrobrucidine dimethiodide-B (Found: loss at 105° in a high vacuum, 1.5%. Found in anhydrous material: C, 45.2; H, 5.8; I, 37.7%).

N(a)-Methyl-N(b)-benzylneobrucidinium Di-iodide.—A solution of methoxybenzylhydroneobrucidine (5 g.) in dry benzene (50 c.c.) was mixed with methyl sulphate (4 c.c.) and refluxed for 12 hours. The gummy product was dissolved in water (30 c.c.) and basified with ammonia (no precipitate) and the *di-iodide* was precipitated by addition of sodium iodide (5 g.). The crude product was twice crystallised from water, and separated in colourless needles, m. p. 246—248° (decomp.) (Found in material dried at 105°: C, 50.2; H, 5.1; I, 34.0. $C_{23}H_{28}O_3N_2, MeI, C_7H_7I$ requires C, 50.3; H, 5.1; I, 34.3%. $C_{25}H_{34}O_4N_2, MeI, C_7H_7I$ requires I, 32.3%), sparingly soluble in water and moderately readily in the simple alcohols.

N(a)-Methyl-N(b)-benzylneobrucidinium dichloride, prepared in the usual way from the di-iodide, was very readily soluble in water and separated from it in large grayish prisms, containing $7H_2O$; this hydrate melted at 90—92°, decomposed (efferv.) at 156—158°, and decomposed slightly on prolonged heating at 105° (Found in air-dried material: C, 54.0; H, 7.5. $C_{23}H_{28}O_3N_2, MeCl, C_7H_7Cl, 7H_2O$ requires C, 54.3; H, 7.6%). When this salt was heated in a test-tube over a flame, methyl chloride and benzyl chloride were evolved. The glassy residue crystallised in contact with methyl alcohol. It was purified by crystallisation from ethyl alcohol (theoretical yield) and proved to be identical with *neobrucidine*, m. p. 198—199° alone or when mixed with an authentic specimen. When the dichloride was digested with 20% methyl-alcoholic sodium methoxide, methoxybenzyl-dihydroneobrucidine, m. p. 159—160° (yield, 70%), and *neobrucidine* (yield, 25%) were produced.

Estimation of Dimethyl Ether formed on heating the Methoxy-bases with Methyl Sulphate in Benzene or Xylene Solution.—(i) Pure benzene (or xylene) was refluxed for several hours with metallic sodium and distilled over it into a flask protected from moisture; the first 100 c.c. of the distillate were rejected.

(ii) Methyl sulphate was washed with aqueous sodium bicarbonate, dried over anhydrous potassium carbonate, and distilled under diminished pressure. The fraction used in the experiments was free from methyl hydrogen sulphate.

(iii) The methoxy-bases were dissolved in much pure benzene, the solvent was then removed by distillation, and the residue was heated under 10–15 mm. pressure at a temperature 20° higher than the m. p. of the base, in order to remove traces of methyl alcohol. It was established that the methoxy-bases are unchanged under these conditions, except for the formation of small proportions of colouring matters.

Dimethyl ether was collected over 50% aqueous sodium hydroxide. It was recognised as such because it was an inflammable gas soluble in water and in concentrated sulphuric acid; furthermore, on being mixed with air and passed over copper oxide heated to redness, it was oxidised to formaldehyde.

In quantitative estimations of dimethyl ether satisfactory results could be obtained only under certain conditions. In all cases, when a mixture of the initial materials was heated *continuously* for a period even as long as 20 hours, the evolution of dimethyl ether was sluggish and the volume of this gas was less than 10–20% of that required by the theory. When, however, the heating was discontinued after 8–10 hours and the apparatus was left over-night in the cold, then, on further heating, the gas was readily liberated and the required volume was collected in less than an hour. This phenomenon is evidently the result of the gummy nature of the methosulphates, which retain dimethyl ether tenaciously when in this condition; on cooling, the gum becomes visibly porous. It is also noteworthy that evolution of dimethyl ether in two stages occurs with all methoxy-bases and is best demonstrated with methoxy-methyldihydroneobrucidine. When a solution of pure methyl sulphate in dry or moist benzene was refluxed for 20 hours, no dimethyl ether was liberated.

The following table gives the results of the estimations:

	(1).	(2).	(3).	(4).	(5).	(6).
Methoxymethyldihydroneostrychnidine	7.3	40	190	155	385	90
Methoxymethyltetrahydrostrychnidine	7.4	28	182	113	323	72
Methoxymethyldihydroneobrucidine	8.5	60	382		442	99
Methoxymethyltetrahydrobrucidine	8.6	30	204	142	376	84
Methoxybenzyldihydroneobrucidine	10.4	54	390		444	99
Methoxymethyldihydroneostrychnidine (after being heated for 84 hours)	7.3				381	85

(1) Wt. (g.) of the base taken for the experiment; (2) Me₂O, c.c., liberated in 8 hours; (3) Me₂O, c.c., liberated after cooling, keeping for 12 hours, and then heating for an hour; (4) Me₂O, c.c., evolved when benzene was removed and the product was further heated for 5 hours in boiling xylene; (5) total vol. Me₂O formed; (6) % yield of the corresponding dimethosulphate.

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[Received, July 25th, 1935.]