358. ind-N-*Methylharmine.*

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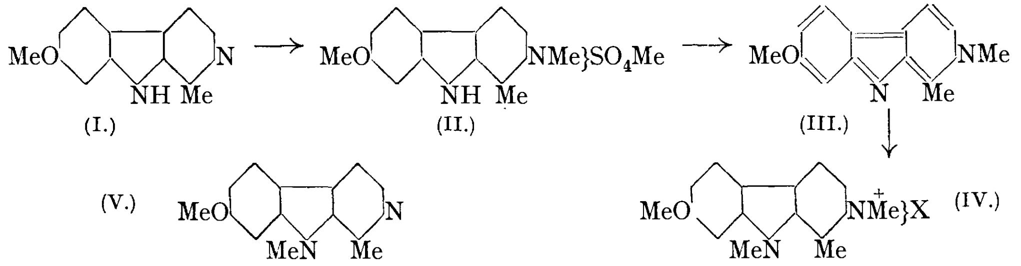
ACCORDING to Kermack, Perkin, and Robinson (J., 1922, **121**, 1872) the alkylation of harmine (I) occurs first at the pyridine nitrogen atom (harmine methosulphate, II) and then at the indole nitrogen.

Thus *py*-methylharmine (III) is of the anhydronium base type (intermediate between quinone, as illustrated, and betaine forms) (compare Armit and Robinson, J., 1925, **127**, 1604) and the action of methylating agents on it gives salts (IV) in which the indole-nitrogen is alkylated. It has been implied that, although the indole-nitrogen is thus alkylated, the kationic charge is taken up by the pyridine nitrogen, but no proof of this point has been offered. It occurred to us that if a chloride containing two methylimino-groups were thermally decomposed with elimination of methyl chloride the methyl would be ejected from the nitrogen atom carrying the kationic charge. Hence dimethylharmine chloride (IV; X = Cl) should yield ind-N-*methylharmine* (V) rather than the methylharmine from which it was generated. On trial this proved to be the case and the new base has been prepared on a considerable scale for the detailed investigation of its pharmacological properties, which has been undertaken by Professor J. A. Gunn. Naturally, when treated with methyl iodide, the *ind-N*-methylharmine yields dimethylharmine iodide (IV, X = I).



(I.) (II.) (III.) (IV.) (V.)

A general statement covering observations in the pyrazole, glyoxaline, benziminazole, and carboline groups is that when successive methylation occurs at different centres by the formation of -onium salts, decomposition of the final product will involve the removal of the methyl group first introduced. This rule applies only when the base corresponding to the first salt-product of methylation is of the anhydronium type and this is true of the groups cited.

EXPERIMENTAL.

Preparation of Harmine.—The crude alkaloids of *Peganum harmala* were available in the form of hydrochlorides, chiefly of harmine and harmaline. As we required only harmine for the present purpose, the harmaline was oxidised as follows. Nitric acid (2·5 c.c., *d* 1·42), dissolved in alcohol (70 c.c.), was added to a solution of the mixed hydrochlorides (10 g.) in 95% alcohol (80 c.c.) and concentrated hydrochloric acid (80 c.c.), and the mixture heated on the steam-bath. When the temperature reached 80° there was vigorous frothing and a rapid rise to 90°; after $\frac{1}{2}$ minute the heating was discontinued and after 20 minutes the harmine hydrochloride crystallised on cooling. The base was recovered by solution of the salt in water (80 c.c.) and addition of ammonia (yield, 6·1 g.; m. p. 257—259°) (75 g. of mixed hydrochlorides, worked up in portions of 15 g., gave 48·5 g. of harmine, m. p. 257—259° without crystallisation).

Harmine Methosulphate (II).—The best conditions of many tried were the following. A mixture of powdered harmine (20 g.), dry benzene (400 c.c.), and pure methyl sulphate (20 c.c.) was heated on the steam-bath for 1 hour. The solid product (32 g., m. p. 203—213°) was crystallised from methyl alcohol (650 c.c.) (yield, 27 g.; m. p. 219—220°). The methosulphate (15·4 g.) gave methylharmine (9·3 g., m. p. 209—210°) on treatment with sodium hydroxide in aqueous solution.

Dimethylharmine Salts.—A mixture of methylharmine (5 g.), dry benzene (50 c.c.), and neutral methyl sulphate (5 c.c.) was heated on the steam-bath for 1 hour (crude crystalline product, 7·8 g.; m. p. 255—260°). The material from two preparations was crystallised from methyl alcohol (900 c.c.); the first two crops had m. p. 268—270° (13·6 g.) and consisted of pure dimethylharmine methosulphate. *Dimethylharmine iodide* was obtained by double decomposition with potassium iodide in hot aqueous solution. The salt crystallised from the hot liquid and, recrystallised from alcohol, formed short, colourless, microscopic needles, m. p. 285° (decomp.) (Found: C, 46·9; H, 5·0; N, 7·1; I, 32·8. $C_{15}H_{17}ON_2I,H_2O$ requires C, 46·9; H, 5·0; N, 7·3; I, 32·9%). Dimethylharmine chloride (Perkin and Robinson, J., 1919, **115**,

949) was previously obtained from the methosulphate by means of an excess of hydrochloric acid; for the present purpose it is best to go through the iodide and treat the latter in the usual manner with silver chloride in hot aqueous solution (yield, theoretical; m. p. 280—282°, decomp.).

ind-N-*Methylharmine* (V).—Dimethylharmine chloride (2 g.) was heated at 290—300°/10 mm. for 20 minutes; after 10 minutes the molten salt decomposed with vigorous effervescence. A filtered acetone solution of the residue was concentrated at room temperature; a mixture of crystals and viscous material resulted. Three preparations afforded 5 g. of the crystals, which, recrystallised from aqueous alcohol, formed flat glistening needles or plates, m. p. 114—118° (air-dried) and 124—125° (dried over phosphoric oxide) (Found in air-dried material: loss at 100°, 13·2, 13·9. Found in anhydrous material: C, 74·5; H, 6·4; N, 12·4; MeO, 13·6; MeN, 9·4. $C_{14}H_{14}ON_2,2H_2O$ requires $2H_2O$, 13·7%. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2; N, 12·4; 1MeO, 11·8; 1MeN, 11·1%).

The determinations of methoxy- and methylimino-groups were successive and it is apparent that the methylimino-group is partly decomposed in the first distillations; the total for MeO and MeN found accords with the theory.

The *hydrochloride* crystallised from dilute hydrochloric acid in slender needles, m. p. 280° (decomp.) (Found in air-dried salt: C, 60·0; H, 6·1; N, 9·9; Cl, 12·5; loss at 110° in a high vacuum, 6·2, 6·5. Found in anhydrous salt: C, 63·9; H, 5·9; N, 10·4; Cl, 13·3. $C_{14}H_{15}ON_2Cl,H_2O$ requires C, 59·9; H, 6·1; N, 10·0; Cl, 12·6; H_2O, 6·4%. $C_{14}H_{15}ON_2Cl$ requires C, 64·0; H, 5·8; N, 10·7; Cl, 13·5%). The aqueous acid solutions have a blue-violet fluorescence and the yellow solution in sulphuric acid exhibits a bright green fluorescence.

The *hydrogen nitrate* crystallised from methyl alcohol in colourless needles, m. p. 242—243° (decomp.) (Found in material dried at 100°: C, 58·4; H, 5·3; N, 14·4. $C_{14}H_{15}O_4N_3$ requires C, 58·1; H, 5·2; N, 14·5%). The salt appears to contain $1H_2O$, but the loss found on heating was lower than the theoretical.

The *picrate* crystallised from acetone or alcohol as a yellow powder of irregular prisms, m. p. 249—250° (decomp.) (Found: C, 52·7; H, 3·8; N, 15·4. $C_{20}H_{17}O_8N_5$ requires C, 52·7; H, 3·7; N, 15·4%), very sparingly soluble in most organic solvents (0·7 g. dissolves in 700 c.c. of hot 95% alcohol).

ind-N-*Methylharmine* combines readily with methyl iodide and methyl sulphate, forming the dimethylharmine iodide and methosulphate respectively. The specimens made in this way were identical with those previously prepared from *py*-*N*-methylharmine, as was proved by a careful comparison.

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