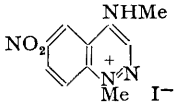
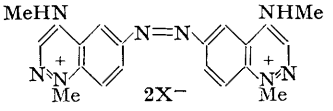
494. *Cinnolines and Other Heterocyclic Types in Relation to the Chemotherapy of Trypanosomiasis. Part V.* Quaternary Salts of 4 : 4′-Bismethylamino-6 : 6′-azocinnoline.*

By J. McIntyre and (the late) J. C. E. Simpson.

The preparation of 4 : 4′-bismethylamino-6 : 6′-azocinnoline and its reaction with methyl iodide are described. Conversion of the crude bismethiodide into the bismethochloride gives two products, the properties of which indicate that they are hydrates of two isomeric dimethochlorides. Both salts show trypanocidal properties against *T. congolense* infections in mice, but differ in the extent of their action, only one of them being curative.

During a study of the action of quaternising agents on 4-amino-6-nitrocinnoline (Atkinson, forthcoming publication), 4-methylamino-6-nitrocinnoline methiodide (I) was prepared. Biological examination of this salt by Dr. E. M. Lourie and Dr. J. M. Walker in the Department of Pharmacology, Oxford, showed that it exerts a curative action against *T. congolense* infections in mice. Consideration of this fact in the light of the hypothesis discussed in Part I of this series suggested that the activity might be a property, not of the salt itself, but of a biscinnolinium derivative such as the azo-salt (II) (cf. Part I, p. 2595), which might be formed from (I) by reduction *in vivo*. The preparation of (II) from 4 : 4′-diphenoxy-6 : 6′-azocinnoline (McIntyre and Simpson, Part IV *) was therefore undertaken.

(I)  (II) 

Treatment of the diphenoxy-compound with methylamine at 135° in the presence of phenol and ammonium chloride (cf. Macey and Simpson, *J.*, 1952, 2602) readily yielded 4 : 4′-bismethylamino-6 : 6′-azocinnoline, which with methyl iodide in the presence of phenol gave a crude bisquaternary iodide in theoretical yield. Conversion of this material into the dimethochloride, however, gave two products which we have designated α- and β-4 : 4′-bismethylamino-6 : 6′-azocinnoline dimethochloride.

The formation of these two salts recalls the behaviour of the diamino-analogue in the same reaction (McIntyre and Simpson, *loc. cit.*); in each case the more soluble α-salt crystallises as a trihydrate, precipitated slowly and incompletely from very dilute hydrochloric acid, whereas the less soluble β-salt forms a hemi- (amino-series) or mono- (methylamino-series) hydrate which is precipitated immediately by very dilute hydrochloric acid. Dr. Lourie and Dr. Walker find that the α-compound cures *T. congolense* infections in mice, the M.T.D. and M.C.D. being 0·5—1·0 and 0·25 mg./20 g., respectively, but that the β-compound, although possessing some trypanocidal action (M.E.D. about 0·25), is

* Part IV, preceding paper.

not curative at the maximum tolerated dose (M.T.D. 1—2 mg./20 g.). The marked difference between the trypanocidal powers of the two compounds is a further analogy between them and their amino-analogues (*loc. cit.*), and indicates that, like the latter, they are hydrates of isomers and not of the same entity.

Experimental

M. p.s are uncorrected.

4 : 4′-*Bismethylamino*-6 : 6′-*azocinnoline*.—Dry methylamine was passed at 90° (bath-temp.) into a mixture of 4 : 4′-diphenoxy-6 : 6′-azocinnoline (5·78 g.), ammonium chloride (1·33 g.), and phenol (100 g.). When the temperature was slowly raised, a clear solution was first formed, followed (at 125°) by the separation of a solid product. After 40 minutes at 135° with continuous passage of methylamine, the mass was cooled and diluted with ether. The solid product was collected, repeatedly digested with ether, and dissolved in acetic acid (500 c.c.). The hot solution was treated with 10N-hydrochloric acid (50 c.c.), whereupon 4 : 4′-*bismethylamino*-6 : 6′-*azocinnoline dihydrochloride* separated (3·67 g., 71%); the salt formed small orange-red needles, m. p. >320°, on recrystallisation from dilute hydrochloric acid (Found : C, 48·9; H, 4·65; N, 26·5; Cl, 16·2. $C_{18}H_{16}N_8,2HCl,H_2O$ requires C, 49·6; H, 4·6; N, 25·7; Cl, 16·3%). The free *base*, obtained by shaking the dihydrochloride with N-sodium hydroxide, was a scarlet solid, m. p. >320°, which was insoluble in water and common organic solvents (Found : C, 60·9; H, 4·4; N, 31·2. $C_{18}H_{16}H_8,\frac{1}{2}H_2O$ requires C, 61·2; H, 4·8; N, 31·7%).

α- *and* β-4 : 4′-*Bismethylamino*-6 : 6′-*azocinnoline Dimethochloride*.—A mixture of the foregoing base (1·92 g.) and phenol (40 g.) was heated on the steam-bath under reflux with methyl iodide (6 c.c.), a further 4 c.c. being added after 1 hour. After a total of 3 hours, the mixture was poured into dry ether, and the crude solid dimethiodide was collected and well washed with ether; it (3·8 g., 100%) had m. p. 274—278° (decomp.), and was soluble in, but not recrystallisable from, water. A stirred solution of the salt (3·8 g.) in hot water (1000 c.c.) containing 10N-hydrochloric acid (2 drops) was boiled under reflux for 1¾ hours with silver chloride (from 500 c.c. of 0·1N-silver nitrate). Evaporation of the filtered solution under reduced pressure to *ca.* 250 c.c. and addition of 10N-hydrochloric acid (3 c.c.) gave crude β-4 : 4′-*bismethylamino*-6 : 6′-*azocinnoline dimethochloride* (1·35 g., 50%), m. p. 281—288° (decomp.), which after recrystallisation from water (35 c.c.) containing 10N-hydrochloric acid (1 drop) formed minute brown-red needles, m. p. 291—294° (decomp.) (Found : C, 52·2; H, 5·4; N, 22·6; Cl, 14·3. $C_{20}H_{22}N_8Cl_2,H_2O$ requires C, 51·8; H, 5·2; N, 24·2; Cl, 15·3%). The filtrate from the crude salt was evaporated further and treated with acetone, whereupon crude α-4 : 4′-*bismethylamino*-6 : 6′-*azocinnoline dimethochloride* (0·7 g., 27%) separated as a brown amorphous solid, m. p. 291—297° (decomp.); after crystallisation from a mixture of 5N-hydrochloric acid and acetone it formed fine brown needles, m. p. 296—300° (decomp.) (Found : C, 48·7; H, 5·2; N, 22·4; Cl, 14·2. $C_{20}H_{22}N_8Cl_2,3H_2O$ requires C, 48·3; H, 5·6; N, 22·4; Cl, 14·2%).

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