24. *A Resolution of Mepacrine* [2-*Chloro*-5-(δ-*diethylamino*-α-*methylbutyl*)*amino*-7-*methoxyacridine*].

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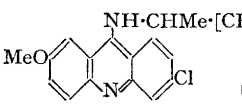
Mepacrine has been resolved in the form of its salt with *d*-4 : 6 : 4′ : 6′-tetranitrodiphenic acid. We obtain $[\alpha]_D$ − 197° and + 205° for the free base in ethyl alcohol, and $[\alpha]_D$ −379° and + 388° for the hydrochloride in water. Previous values are $[\alpha]_D$ − 194·5° and + 197° (Tschelincev and Osetrova, *J. Gen. Chem. Russia*, 1940, **18**, 1978) for the free base in ethyl alcohol, and $[\alpha]_D$ − 357° and + 358·6° (*loc. cit.*) and − 334° and + 355° (Bacher, Buhs, Hetrick, Reiss, and Trenner, *J. Amer. Chem. Soc.*, 1947, **69**, 1534) for the hydrochloride in water.

Mepacrine [2-chloro-5-(δ-diethylamino-α-methylbutyl)amino-7-methoxyacridine (I)] has been resolved by Tschelincev and Osetrova (*loc. cit.*) by the use of what is described as " αα′-bromocamphorsulphonic acid ".



(I.)

We have failed to repeat the resolution by means of any of the available bromocamphorsulphonic acids, possibly owing to our inability to prevent the separation of the mepacrine salts in non-crystalline forms. Bacher, Buhs, Hetrick, Reiss, and Trenner (*loc. cit.*) appear to have overcome this difficulty by the admixture of small quantities of 2-ethoxyethanol (cellosolve) with the solvent (acetone), and have made a complete resolution with *d*-α-bromocamphor-π-sulphonic acid. We have now effected a complete resolution, already reported in brief (*Nature*, **1947**, **159**, 612), into optical antimers having a slightly higher specific rotation than those hitherto reported, by means of *d*-4 : 6 : 4′ : 6′-tetranitrodiphenic acid.

Experimental.

dl-4 : 6 : 4′ : 6′-Tetranitrodiphenic acid was prepared by the nitration of a mixture of 4 : 6′- and 4 : 4′-dinitrodiphenic acids (Christie and Kenner, *J.*, 1922, 619); colourless needles from nitromethane, m. p. 291—293° (decomp.).

The racemic acid was resolved by the method of Christie and Kenner (*loc. cit.*) through the brucine

salt. The *d*-acid was obtained from the less soluble brucine salt as colourless needles, m. p. 227—228°, $[\alpha]_D^{18°}$ + 126° ± 4° (*c*, 0·8 in N/10-sodium hydroxide). Christie and Kenner (*loc. cit.*) give m. p. 226—227°, $[\alpha]_D$ + 115° (aqueous solution of sodium salt).

l-*Mepacrine* d-*Tetranitrodiphenate*.—Boiling solutions of the *d*-acid (1·0 g.) and mepacrine monohydrate (2·0 g.) in ethyl alcohol (20 and 30 c.c. respectively) were mixed. In the course of 4 weeks at room temperature, the initial sticky precipitate changed into clusters of thick yellow transparent needles. This *product* (1·5 g.) was separated, well washed with alcohol and dried in a vacuum at 20°; m. p. 170° (decomp.), $[\alpha]_D^{14°}$ − 162° ± 5° (*c*, 0·08 in 10·4N-acetic acid) (Found: C, 52·9; H, 5·0; N, 11·5; Cl, 4·1. $C_{14}H_6O_{12}N_4,C_{23}H_{30}ON_3Cl,H_2O$ requires C, 52·9; H, 4·5; N, 11·7; Cl, 4·2%).

The preparation of this salt in a state of lower optical purity, but in a much shorter time, was achieved as follows: a mixture of the *d*-acid (0·5 g.), mepacrine monohydrate (1·0 g.), and dioxan (2 c.c.) was warmed until a homogeneous yellow syrup resulted. This was diluted with boiling ethyl alcohol (15 c.c.) and kept for 2 days at room temperature. Small yellow transparent crystals (0·55 g.) separated, $[\alpha]_D^{16°}$ − 126° ± 4° (*c*, 0·32 in 10·4N-acetic acid).

l-*Mepacrine Dihydrochloride*.—*l*-Mepacrine *d*-tetranitrodiphenate (2·2 g.) was decomposed by means of aqueous sodium hydroxide, and the liberated mepacrine was taken up in ether. After removal of the ether, the free base was dissolved in ethyl alcohol (20 c.c.) and the solution made acid to Congo-red by the addition of a 15% solution of hydrogen chloride in alcohol. After 24 hours the crystalline *dl*-mepacrine dihydrochloride was separated and the mother liquor treated with an equal volume of ether. Pure *l*-mepacrine dihydrochloride (0·6 g.) separated in the form of very small yellow needles, m. p. 244—245° (decomp.), $[\alpha]_D^{14°}$ − 379° ± 6° (*c*, 0·1 in water). Tschelincev and Osetrova (*loc. cit.*) give m. p. 243° (decomp.), $[\alpha]_D$ − 357°. Bacher, Buhs, Hetrick, Reiss, and Trenner (*loc. cit.*) obtained $[\alpha]_D^{23°}$ − 334° (*c*, 2 in water).

l-Mepacrine obtained from the hydrochloride, was a yellow transparent oil, $[\alpha]_D^{17°}$ − 197° ± 5° (*c*, 0·4 in ethyl alcohol). Tschelincev and Osetrova (*loc. cit.*) report $[\alpha]_D$ − 194·5° in ethyl alcohol.

d-*Mepacrine Dihydrochloride*.—The alcoholic mother liquor from the initial crystallisation of *l*-mepacrine *d*-tetranitrodiphenate was evaporated, and the residual mixture of partially resolved mepacrine and *d*-acid treated with sodium hydroxide solution and the base isolated by means of ether. Pure *d*-mepacrine dihydrochloride (0·15 g.) was isolated as described for the *l*-salt; small yellow needles, m. p. 244—245° (decomp.), $[\alpha]_D^{10°}$ + 388° ± 7° (*c*, 0·2 in water). Tchelincev and Osetrova (*loc. cit.*) record m. p. 243° (decomp.), $[\alpha]_D$ + 358·6°. Bacher, Buhs, Hetrick, Reiss, and Trenner (*loc. cit.*) obtained $[\alpha]_D^{23°}$ + 355° (*c*, 2 in water).

d-Mepacrine was a yellow transparent oil, $[\alpha]_D^{10°}$ + 205° ± 5° (*c*, 0·2 in ethyl alcohol). Tschelincev and Osetrova (*loc. cit.*) give $[\alpha]_D$ + 197° in ethyl alcohol.

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