

the guanidino group⁶ exhibited heterogeneity at about pH 5 and remained monodispersed at pH 6.5. The appearance of heterogeneity in both of these albumin derivatives was found to be reversible.⁷

Further work is being done on this problem in the intermediate pH range of 4 to 11.

In view of these heterogeneity effects, some of which also have been observed by Reichmann and Charlwood,⁸ it would seem questionable as to whether one could make an unambiguous statement about the configuration of albumin at low and high pH . It is, therefore, not yet possible to decide whether the anomalous reactivity of serum albumin at low and high pH can be attributed either to expansion of the molecule² or to reversible formation and breakage of internal hydrogen bonds.⁹ It may be that both effects are present.

(6) W. L. Hughes, Jr., H. A. Saroff and A. L. Carney, *THIS JOURNAL*, **71**, 2476 (1949).

(7) The sedimentation studies on the guanidinated albumin were made several years ago by H. A. Saroff while at the Department of Physical Chemistry, Harvard Medical School.

(8) M. E. Reichmann and P. A. Charlwood, *Can. J. Chem.*, **32**, 1092 (1954).

(9) M. Laskowski, Jr., and H. A. Scheraga, *THIS JOURNAL*, **76**, 6305 (1954).

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A Mechanical Resolution of *dl*-Methadone Base

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The potent analgesic *l*-methadone has been separated from its much less active optical antipode by a number of workers. Crystallization of the diastereoisomeric acid *d*-tartrates from acetone¹ and *n*-propyl alcohol² leads to the preferential deposition of *l*-methadone *d*-tartrate. A cleaner separation is obtained with *d*- α -bromocamphor- π -sulfonic acid which forms a water-insoluble salt with *d*-methadone and a water-soluble one with the *l*-form.³

This note reports a successful resolution of *dl*-methadone by slow crystallization of the base from a concentrated petroleum ether solution seeded with two crystals of the pure *d*-base and two crystals of the pure *l*-base, both obtained in the conventional manner by preliminary resolution through the acid *d*-tartrates. Nearly 50% of the original *dl*-mixture was recovered in the form of four crystals (one weighed 11 g.), far from physically perfect, but of optical purity equal to that of the seeds from which they were grown.

Experimental

The apparatus consisted of a cylindrical glass jar 90 mm. in diameter with straight sides 80 mm. high fitted with a metal

(1) W. R. Brode and M. W. Hill, *J. Org. Chem.*, **13**, 191 (1948).

(2) A. A. Larsen, B. F. Tullar, B. Elpern and J. S. Buck, *THIS JOURNAL*, **70**, 4194 (1948).

(3) E. E. Howe and M. Sletzing, *ibid.*, **71**, 2935 (1949).

screw cap (neither lined nor gasketed) in the center of which a round hole was cut to accommodate a no. 4 rubber stopper. A glass tube (8 mm. inside diameter), extending through the stopper, was equipped with a silicone lubricated rubber seal which served as a bearing for the stirrer. The stirrer was made of a 5-mm. glass rod bent at a point just below the end of the bearing tube so that the resulting radius of eccentricity of the rotating stirrer was approximately half the radius of the cylindrical container.

Fifty-six grams of *dl*-methadone base was dissolved in 225 cc. of boiling petroleum ether (b.p. 63–68°, Skellysolve B) and filtered by gravity into the open cylindrical jar. The solution was concentrated on the steam-bath to a volume of 145 cc. The metal cap with the stirrer inserted was then screwed to the top of the jar which was placed in an oven held at 40°. During the cooling process stirring at 240–250 r.p.m. was accomplished by means of a constant speed stirring motor placed above the oven and attached to the stirrer shaft extending through the oven vent. (A temperature-controlled water-bath probably could be substituted for the oven, with the result that observational conditions of the experiment would be greatly improved.)

When temperature equilibrium was attained, the cap was removed and two seeds each of pure *d*- and *l*-methadone base were placed in alternating order around the perimeter of the container bottom, so that seeds of like sign were directly opposite each other. The seeds used were approximately 2–3 mm. across and were taken, still wet with solvent, directly out of the petroleum ether (Skellysolve B) solution from which they had been freshly crystallized. The screw cap was replaced and stirring was resumed at the same rate as before and was continued at 40° for 125 hours. During this time approximately one-fourth of the solvent evaporated through the threads of the screw cap and two large and two smaller crystals grew from the original seeds. The two crystals of *l*-methadone weighed 8.8 g. ($[\alpha]^{25D} -35.7^\circ$, c 4, Skellysolve B) and 4.2 g. ($[\alpha]^{25D} -36.2^\circ$, c 4, Skellysolve B). The two crystals of *d*-methadone weighed 11.2 g. and 1.9 g. (combined $[\alpha]^{25D} +36.0^\circ$, c 4, Skellysolve B). The total of 26.1 g. of resolved material represents a 46% yield, but 29.0 g. of *dl*-methadone was obtained from the residual solution to give a nearly quantitative recovery of product.

The optical purity of the resolved material was further tested by grinding together the two crystals of like sign and measuring the rotation of a solution in absolute ethanol: *l*-form, $[\alpha]^{27D} -26.8^\circ$ (c 4.10, l 2 dcm.); *d*-form, $[\alpha]^{27D} +26.5^\circ$ (c 4.00, l 2 dcm.).

Brode and Hill¹ reported the values $[\alpha]^{22D} -29.91^\circ$ (c 2.66, l 2 dcm., absolute ethanol) for *l*-methadone base and $[\alpha]^{25D} +29.51^\circ$ (ethanol) for the *d*-form. Larsen and co-workers² reported the values $[\alpha]^{25D} -26^\circ$ and $+26^\circ$ (c 1.5, U.S.P. ethanol) for *l*- and *d*-methadone, respectively. Walton, Ofner and Thorp⁴ reported the values $[\alpha]^{22D} -32^\circ$ (alcohol) and $[\alpha]^{20D} +28^\circ$ (alcohol) for the two optical isomers of methadone.

(4) E. Walton, P. Ofner and R. H. Thorp, *J. Chem. Soc.*, 648 (1949).

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Substituted Malonitriles of the Type Aryl CH₂CX(CN)₂

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Recent work in this Laboratory has made available a series of monosubstituted malonitriles of the type Aryl CH₂CH(CN)₂.¹ This paper reports some of the results of a study of these compounds.

In agreement with the observations of Hessler,² benzylmalonitrile (I) and in general Aryl CH₂-CH(CN)₂ were soluble in aqueous sodium hydroxide, and when precipitated promptly by the addition of a mineral acid were recovered unchanged.

(1) J. C. Westfahl and T. L. Gresham, *THIS JOURNAL*, **76**, 1076 (1954).

(2) J. C. Hessler, *Am. Chem. J.*, **22**, 181 (1899)