[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

THE OPTICAL RESOLUTION OF AMIDONE[1]

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Amidone, 6-dimethylamino-4,4-diphenyl-3-heptanone, possesses one asymmetric carbon atom and thus is capable of existing in a dextro, levo, and racemic form. The isolation of these optical forms is desirable, since they may possess different physiological activity.

The only crystalline salt obtained of Amidone and an optically active acid was the acid *d*-tartrate. The diastereo compound of this salt appears to be the more stable. It is deposited from various solvents under a variety of conditions in small rosettes, m.p. 135.0–138.5°, $[\alpha]_D^{25}$ +10.00°. However, one sample of this salt dissolved in a mixture of ethyl acetate and ether deposited, after a period of three months at room temperature, some long, fine needles as well as the rosettes. Careful isolation and recrystallization of the needles gave a salt, m.p. 149.5–151.0°, $[\alpha]_D^{26}$ −84.43°.

It was found that either the rosettes or needles could be obtained from a saturated acetone solution of the salt, depending on the type of crystal used to seed the solution. Such a separation appears to depend more on the rate of crystallization induced by one form, than on the difference in solubility of the two forms. This phenomenon has been observed previously for other resolutions using tartaric acid by Brode and Wernert (1).

Seeding of a saturated acetone solution of the salt with the needles gave *l*-Amidone-*d*-acid tartrate. The mother liquor was then seeded with the rosettes and the diastereo compound was deposited, leaving the resulting mother liquor rich in *d*-Amidone-*d*-acid tartrate. Recovery of the free base from the *l*-Amidone-*d*-acid tartrate gave *l*-Amidone, m.p. 98.7–99.0°, $[\alpha]_D^{22}$ −29.91°. Recovery of the free base from the enriched *d*-Amidone-*d*-acid tartrate gave enriched *d*-Amidone, m.p. 75.5–96.4°, $[\alpha]_D^{25}$ +17.55°. The melting point obtained for racemic Amidone was 76.9–77.8°. Thus, the racemic compound and the phase diagram of composition plotted against melting point should possess two eutectic points (2). Therefore it should be possible to melt the eutectic mixture away from the pure dextro isomer. This was accomplished by an electrically heated Büchner funnel and the pure *d*-Amidone was obtained, m.p. 98.7–99.0°, $[\alpha]_D^{26}$ +29.51°.

The comparison of the rotatory dispersion of the dextro and levo Amidone and the corresponding hydrochloride salts is given in Figure 1. The observed rotations for the *d*- and *l*-Amidone hydrochlorides for the D line were $[\alpha]_D^{28}$ +127.5° and −127.8° ($c = 2.96$ in water)[3].

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[3] Subsequent to submission of this paper for publication, a note has appeared in *Nature*, **160**, 605 (1947), (Nov. 1, 1947), by Thorp, Walton and Ofner describing a different method of resolution of Amidone. They obtained for the *d*- and *l*-Amidones $[\alpha]_D^{20}$ +28° and −32°; and for the hydrochlorides $[\alpha]_D^{20}$ +143° and −145°

EXPERIMENTAL

Amidone acid tartrate (30.0 g. 0.065 mole) in 400 ml. of acetone was prepared by dissolving 20.0 g. (0.065 mole) of racemic Amidone in 100 ml. of acetone and mixing at room temperature with 10.0 g. (0.067 mole) of *d*-tartaric acid in 300 ml. of acetone. The solution was cooled to 8° in an ice-box and seeded with the needles, m.p. 149.5–151.0°. After 36 hours, 10.3 g. of salt had crystallized, m.p. 142.8–145.0°. Fractionation of this salt from acetone gave 8.7 g. of nice white needles, m.p. 149.5–151.0°, $[\alpha]_D^{26}$ −84.43° ($c = 3.02$ g., $l = 2$ dcm., in distilled water).

The mother liquor, without change in concentration, was seeded with the rosettes, m.p. 135.0–138.5° (*dl*-Amidone-*d*-acid tartrate) and placed in the ice-box at 8° for 48 hours. Rosettes were deposited, 8.7 g., m.p. 130–135°, $[\alpha]_D^{26}$ +26.32° ($c = 3.02$ g., $l = 2$ dcm., in distilled water). The mother liquor from this fraction had a specific rotation of *ca.* 56° (estimated concentration in acetone).

Concentration of this mother liquor and several days standing in the ice-box failed to produce further crystallization. The acetone was removed under vacuum and the free dextro-rich Amidone base recovered, 7.0 g. (11.0 g. of Amidone acid tartrate would yield 7.2 g.), m.p. 75.5–96.4°, $[\alpha]_D^{25}$ +17.55° ($c = 3.02$ g., $l = 2$ dcm., absolute ethanol).

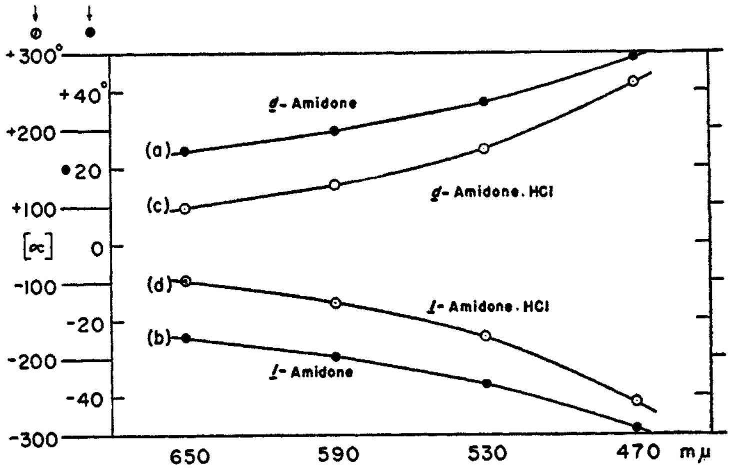

FIG. 1. ROTATORY DISPERSION OF *d*- AND *l*-AMIDONE (●) (a AND b) AND *d*- AND *l*-AMIDONE HYDROCHLORIDE (○) (c AND d)

The pure levo-Amidone was recovered from the *l*-Amidone-*d*-acid tartrate salt (5.85 g. from 8.7 g., 100% yield), m.p. 98.7–99.0°, $[\alpha]_D^{22}$ −29.91°, ($c = 2.66$ g., $l = 2$ dcm., absolute ethanol).

The dextro-rich Amidone is composed of 79.3% of the dextro isomer and 20.7% of the levo isomer.

An electrical heating mantle was built around a seven-centimeter Büchner funnel. The heating element was controlled by a 110-volt, 5-ampere Variac and calibrated for voltage-temperature readings. Five 7.0-cm., No. 1 Whatman filter papers were first placed in the funnel, followed by a 3.0 g. layer of the dextro-rich Amidone and five more filter papers. The funnel was placed on a suction flask, a rubber dam placed on top and the vacuum of a water aspirator applied. The temperature was raised rapidly to 75.5° and then slowly to 94°. The filter press was taken apart and yielded 1.09 g. of solid cake from between the center filter papers. Melting point data indicated the edge of the cake was the pure dextro isomer (m.p. 98.7–99.0°) and the center of the cake still contained some of the levo isomer (m.p. 95.0–99.0°). The specific rotation of this cake was $[\alpha]_D^{26}$ +27.15° in absolute ethanol. Thus, the cake contained 95.6% *d*- and 4.4% *l*-isomer. The reason that the levo isomer was still pressed in the center of the cake was that there was a 12° temperature gradient decreasing from the walls to the center of the funnel. The cake was dissolved in absolute ethanol and seeded with the pure dextro isomer (from the edge of the cake). The pure dextro form was deposited in beautiful prismatic crystals.

These crystals were used to seed the remaining 3.0-g. sample of dextro-rich Amidone dissolved in 6 ml. of absolute ethanol. Pure *d*-Amidone was deposited on standing overnight, 1.5 g., m.p. 98.7–99.0°.

The pure *d*-Amidone-*d*-acid tartrate was formed by mixing equivalents of *d*-Amidone and *d*-tartaric acid in acetone and adding a little ether, m.p. 117.8–118.1°.

SUMMARY

A method for the complete resolution of Amidone through the acid-*d*-tartrate salt is reported.

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REFERENCES

(1) Brode and Wernert, *J. Am. Chem. Soc.*, **55**, 1685 (1933).
(2) Roozeboom, *Z. physik. Chem.*, **28**, 494 (1899).