

resin. The column was eluted with 50 ml. of water, and the eluate evaporated.

The colorless crystalline residue was recrystallized from 70% ethanol, giving 50 mg. (50%) of the desired product, m.p. 283–285° (cap.) with decomposition. For analysis and n.m.r. spectrum (see Fig. 1), the material was again recrystallized, giving 25 mg., m.p. 284–285° dec. (cap.).

*Anal.* Calcd. for  $C_8H_{12}O_4$ : C, 48.64; H, 8.16. Found: C, 48.68; H, 8.09.

*meso*(15/24) Diastereomer of (*trans/trans*) 1,2,4,5-Cyclohexanetetrol Tetrabenzoate, M.p. 267°, IX. (A). From Diene.—To a solution of 45.6 g. of iodine in 400 ml. of anhydrous benzene was added a slurry of 82 g. of dry silver benzoate<sup>34</sup> in 250 ml. of benzene. The mixture was stirred 30 min., then 3.6 g. of 1,4-cyclohexadiene<sup>19</sup> was added and the resulting mixture boiled 1 hr. under reflux (anhydrous conditions), then allowed to stand overnight.

The yellow precipitate was removed by filtration, and the filtrate washed successively with water, sodium bicarbonate solution, sodium thiosulfate solution, and again with water. After drying, the benzene solution was evaporated. The oily residue was taken up in 120 ml. of boiling absolute ethanol, and the solution cooled. After 12 hr., the crystals were collected, giving 0.8 g. of crude product, m.p. 236–250°.

This material was taken up in 30 ml. of chloroform (filter), and absolute ethanol (15 ml.) was added. After 12 hr., the colorless needles which separated were collected, giving 420 mg. (3%) of the desired product, m.p. 266–267° (reported<sup>9</sup> m.p. 265°).

*Anal.*<sup>36</sup> Calcd. for  $C_{34}H_{28}O_8$ : C, 72.33; H, 5.00. Found: C, 71.14; H, 5.09.

The original ethanolic filtrate was reserved for preparation of the m.p. 208° isomer.

The 100-Mc. n.m.r. spectrum showed well defined strong patterns centered at  $\delta = 7.6$  and 8.0 due to the twenty aromatic protons. The *ortho* protons were responsible for the signals at  $\delta = 8.0$ , while the *meta* and *para* protons produced the signals around  $\delta = 7.6$ . The four O-C-H proton signals were centered around  $\delta = 5.7$  and the symmetrical pattern was 28 c.p.s. wide. Two of the methylene protons produced a doublet of spacing 13 c.p.s., with fine structure indicative of a tripling with a 3 c.p.s. splitting. This pattern was centered around  $\delta = 2.9$ . The other two methylene protons produced a poorly defined pattern of signals 55 c.p.s. wide around  $\delta = 2.0$ . Except for the

(36) The 1.19% low carbon value is possibly due to persistence of some iodocyclohexanetriol tribenzoate in the repeatedly recrystallized product. Any such impurity is eliminated during preparation of the free tetrol, which gave an excellent microanalysis for carbon and hydrogen.

enhanced chemical shifts and a difference in clarity, this tetrabenzoate spectrum (not shown) was very similar to that of the corresponding free tetrol (Fig. 1-D).

(B) From Enediol Dibenzoate.—To a mixture of finely pulverized, dry silver benzoate<sup>34</sup> (9.2 g., 0.04 mole) and 5.1 g. of iodine (0.02 mole) in 100 ml. of dry benzene was added a solution of 3.2 g. (0.01 mole) of the enediol dibenzoate (m.p. 99–100°) in 20 ml. of benzene. After stirring 0.5 hr., the mixture was boiled under reflux for 4 hr., then kept at 20° for 65 hr., and filtered. The filtrate was successively washed with water, sodium bicarbonate solution, sodium thiosulfate solution, and again with water. After drying, the benzene solution was evaporated. The residual oil was taken up in 38 ml. of absolute ethanol (charcoal). After 12 hr., the white powdery crystals were collected, giving 40 mg. of crude product, m.p. 253–257°. A second crop of 20 mg. was obtained, m.p. 248–254°.

The product (60 mg.) was taken up in 3.0 ml. of chloroform (charcoal) and 4.0 ml. of absolute ethanol added. After 12 hr. at 20° there was obtained 50 mg. (0.9%) of the desired pure product, m.p. 266–266.5°.

The original ethanolic mother liquors were reserved for preparation of the m.p. 208° isomer.

A mixture m.p. with the tetrabenzoate<sup>36</sup> (m.p. 259–260°) of racemic (13/24) *ortho* cyclohexanetetrol (“dihydrocondurol-B”) was depressed, and infrared spectra confirmed non-identity of the two samples. (If the 1,4-diene starting material used contained a large amount of 1,3 impurity or if the unconjugated diene rearranged into conjugated diene during the reaction, the isolated product might conceivably be the *ortho* tetrol tetrabenzoate.)

**Infrared Spectra.**—The infrared spectrum was recorded for each new compound prepared, using potassium bromide pellets. The cyclohexanetetrols showed the expected strong O—H stretching absorption. The tetraacetates showed strong ester carbonyl absorption, and an absence of O—H absorption. One tetrol monoacetate was examined (see above). The tetrabenzoates, in addition to carbonyl absorption, showed the “C-H rock” characteristic of monosubstituted benzenes at about 710  $cm^{-1}$ .

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## The Absolute Configuration of *threo*-2-Amino-1,2-diphenylethanol. A Correction of the Literature

GLORIA G. LYLE AND WILLIAM LACROIX

Department of Chemistry, University of New Hampshire, Durham, New Hampshire

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The absolute configurations of the *threo*-2-amino-1,2-diphenylethanols have been corrected as D-(+) and L(-) or by the Cahn, Ingold, Prelog system as 1*R*:2*R*-(+) and 1*S*:2*S*-(-).

The stereochemistry of the epimeric 2-amino-1,2-diphenylethanols (I) was established by Weijlard *et al.*,<sup>1</sup> in 1950, and these authors confirmed the earlier assignment that the *threo*-racemate was the lower-melting and the *erythro*-racemate the higher-melting form. By converting one of the optically active *erythro* isomers of established absolute configuration into one of the *threo* isomers, an absolute configurational assignment was made to the *threo* forms. Since the method of interconversion was shown to involve epi-

(1) J. Weijlard, K. Pfister, 3rd, E. F. Swanezy, C. A. Robinson, and M. Tishler, *J. Am. Chem. Soc.*, **73**, 1216 (1951).

merization of the hydroxyl asymmetric center, the *D-threo* isomer was assigned the levo rotation.

In 1955, Pratesi, *et al.*,<sup>2</sup> supported this configurational assignment but later<sup>3</sup> offered evidence contradicting both their earlier conclusion and that of the Merck group.<sup>1</sup> Watson and Youngson<sup>4</sup> in 1954 gave unequivocal evidence for the absolute configuration of the

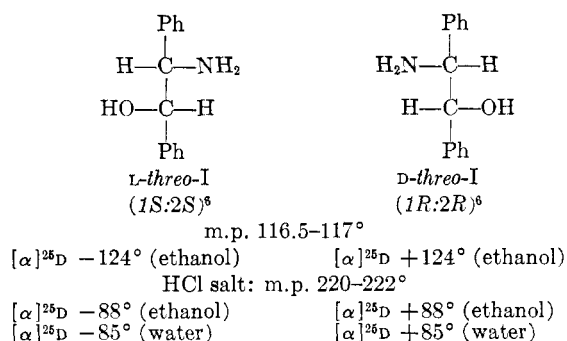
(2) P. Pratesi, A. LaManna, and L. Fontanella, *Farmaco* (Pavia), *Ed. Sci.* **10**, 673 (1955).

(3) P. Pratesi, A. LaManna, and G. Vitali, *Farmaco* (Pavia), *Ed. Sci.* **15**, 387 (1960).

(4) M. B. Watson and G. W. Youngson, *Chem. Ind.* (London), 658 (1954).

*erythro* isomers, but the configuration of the *threo* isomers remained in doubt. Since these compounds were necessary for studies of optical rotatory dispersion of some  $\alpha$ -aminocarbonols to establish stereochemical correlations, it seemed desirable to resolve the conflict.

In order to obtain the pure epimeric compounds, the procedure of the Merck group<sup>1</sup> was followed since other methods gave only the *erythro* isomers or mixtures. In every step of the reaction the yields, melting points, and rotations were as reported with the exception of the final step. Treatment of the N-formyl derivative prepared from D-(-)-*erythro*-2-amino-1,2-diphenylethanol with thionyl chloride gave the crystalline *threo* isomer (I), m.p. 116.5–117°, and its hydrochloride, m.p. 220–222°. The product of the reaction was reported to be dextrorotatory, but both the base and hydrochloride had specific rotations in ethanol which were opposite in sign to those reported in the literature.<sup>1</sup> In contrast to their publication, a check of the laboratory research notebooks by the Merck group revealed agreement with our finding.<sup>5</sup> This configurational assignment of I agrees with the latest paper of the Italian workers.<sup>3</sup> The absolute configuration, specific rotation, and melting point are indicated with the Fischer projection formulas.



The optical rotatory dispersion curves of the levorotatory *threo* and *erythro* isomers were compared with those of the ephedrine which have been reported.<sup>7</sup> In both cases the *threo* bases in alcoholic solution gave much more intense Cotton effect curves with relatively large rotations at the first extrema as compared with the *erythro* isomers (Fig. 1). The presence of two aromatic rings considerably enhanced the rotations, but the difference in the R.D. curves of the *threo* and *erythro* isomers followed the same pattern as in the case of the ephedrine. The R.D. curves thus add confirmation of the assignment of the *threo* configuration to the lower-melting isomers of I. This offers additional evidence that optical rotatory dispersion is a practical physical method for differentiating between diastereomeric  $\alpha$ -amino alcohols.

### Experimental

The optical rotatory dispersion data were obtained from a Rudolph recording spectropolarimeter model 260/655/580-C14 using a 1-cm. path length and temperatures of 27–30°.

(5) Personal communication from Dr. K. Pfister. In preparation of the manuscript, the reaction sequences were inadvertently interchanged at the N-formyl stage, thus also interchanging the products of thionyl chloride inversion.

(6) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

(7) G. G. Lyle, *J. Org. Chem.*, **25**, 1779 (1960).

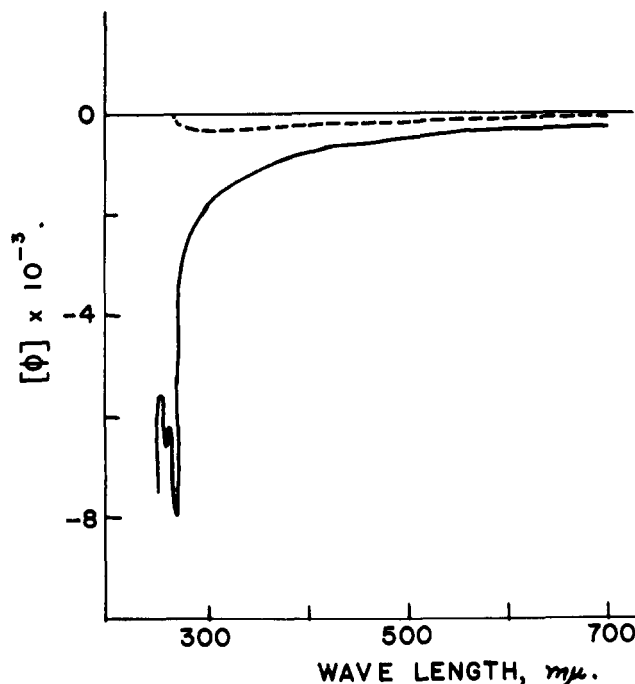


Fig. 1.—Optical rotatory dispersion curves of *threo*-2-amino-1,2-diphenylethanol (—) and the *erythro* isomer (---) in ethanol.

*L-threo*-2-Amino-1,2-diphenylethanol (I).—A mixture of 427 mg. of the hydrochloride of D-(-)-*erythro*-2-amino-1,2-diphenylethanol, m.p. 209.5–210°,  $[\alpha]_{25}^{\text{D}} - 50.7^\circ$  (water, *c*, 0.56), and 1.5 ml. of formamide was heated at 150° in an oil bath for 15 min. On cooling, 7.5 ml. of water was added and the precipitated formyl derivative was separated by filtration. After the product was washed free of chloride ion (silver nitrate test), it was dried, yielding 320 mg., m.p. 208–209°, lit.,<sup>1</sup> m.p. 203–204°, and was rearranged without further purification.

Thionyl chloride (0.65 ml.) was cooled to 5° in an ice-salt bath and 300 mg. of the formyl derivative prepared above was added. The mixture was allowed to stand at 5° for 10 min. and then warmed to room temperature. Approximately 8 g. of ice was added, and the mixture was heated under reflux for 3 hr. and treated with charcoal. After removing the charcoal by filtration, the filtrate was neutralized with 40% sodium hydroxide solution (pH approximately 8), and the solid product was collected and washed with water yielding 128 mg., m.p. 114–118°. Conversion of the product to the hydrochloride in anhydrous ether gave 113 mg. of *threo*-I hydrochloride, m.p. 221–223°, which, on recrystallization, melted at 220–222°,  $[\alpha]_{25}^{\text{D}} - 88.3^\circ$  (ethanol, *c*, 0.555); lit.,<sup>1</sup> m.p. 220–221°,  $[\alpha]_{\text{D}} + 84.7^\circ$  (water, *c*, 0.01).

The hydrochloride (84 mg.) was dissolved in water and any insoluble material was separated by centrifuging. On neutralization of the supernatant liquid with sodium hydroxide solution, 48 mg. of *L-threo*-2-amino-1,2-diphenylethanol (I) was obtained, m.p. 116.5–117°,  $[\alpha]_{25}^{\text{D}} - 96.7^\circ$  (ethanol, *c*, 0.60); lit.,<sup>1</sup> m.p. 116–116.5°,  $[\alpha]_{\text{D}} + 124^\circ$  (ethanol, *c*, 1.18).

**Optical Rotatory Dispersion Data.** D-*erythro*-2-Amino-1,2-diphenylethanol.—R.D. (Fig. 1) in ethanol (*c*, 0.527):  $[\phi]_{595} - 4.0^\circ$ ,  $[\phi]_{589} - 12.1^\circ$ ,  $[\phi]_{290} - 142^\circ$ ,  $[\phi]_{265} 0^\circ$ .

D-*erythro*-2-Amino-1,2-diphenylethanol Hydrochloride.—R.D. in ethanol (*c*, 0.217, 0.0542):  $[\phi]_{595} - 196^\circ$ ,  $[\phi]_{589} - 230^\circ$ ,  $[\phi]_{265} - 6910^\circ$ ,  $[\phi]_{250} - 6450^\circ$ ,  $[\phi]_{236} - 10,000^\circ$ .

*L-threo*-2-Amino-1,2-diphenylethanol.—R.D. (Fig. 1) in ethanol (*c*, 0.6, 0.02):  $[\phi]_{595} - 171^\circ$ ,  $[\phi]_{589} - 206^\circ$ ,  $[\phi]_{265} - 8420^\circ$ ,  $[\phi]_{264} - 6610^\circ$ ,  $[\phi]_{261} - 7360^\circ$ ,  $[\phi]_{256} - 5330^\circ$ ,  $[\phi]_{252} - 7040^\circ$ .

*L-threo*-2-Amino-1,2-diphenylethanol Hydrochloride.—R.D. in ethanol (*c*, 0.555, 0.0189):  $[\phi]_{595} - 176^\circ$ ,  $[\phi]_{589} - 221^\circ$ ,  $[\phi]_{235} - 10,000^\circ$ .

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