ether, the m. p. was 147–148°; $[\alpha]_{546.1}^{26.5}$ +258° (*c*, 4.018; *l*, 2; $CHCl_3$). *Anal.* Calcd. for $C_{25}H_{32}O_{17}Br_2$: Br, 20.92. Found: Br, 20.87.

Di-(2,3,4-triacetyl-β-*d*-methylglucosidyl) Carbonate (IV).—Four grams of silver oxide, 10 g. of Drierite, and 75 cc. of absolute methanol were placed in a 200-cc. round-bottom, three-neck flask equipped with a calcium chloride drying tube, sealed glass stirrer, and dropping funnel. The flask was wrapped with black paper. The mixture was stirred for one hour to dry the reactants. Five grams of III in 25 cc. of dry, alcohol-free chloroform (see ref. 2 for purifying the chloroform) were added through the dropping funnel over a one-hour period to the well-stirred reaction mixture. Stirring was continued overnight at room temperature. The mixture was filtered and the solution crystallized upon evaporation. After recrystallization from methanol, the m. p. was 191–192°; yield 3.8 g. (87%); $[\alpha]_{546.1}^{26}$ −75.0°. *Anal.* Calcd. for $C_{27}H_{38}O_{19}$: C, 48.64; H, 5.75. Found: C, 48.59; H, 5.75.

Di-(1,2,3,4,2′,3′,4′-heptaacetyl-β-gentiobiosyl) Carbonate (V).—Ten grams of silver oxide, 20 g. of Drierite, 9.2 g. of I, and 65 cc. of dry, alcohol-free chloroform were stirred for one hour in the reaction flask described in the preparation of IV. Ten grams of III in chloroform was added with stirring during one hour. After twenty-two hours of stirring, the reaction mixture was filtered through a layer of kieselguhr and the residue washed well with chloroform. The combined filtrate and washings were concentrated to a sirup when the solvent was removed by a current of dry air. The sirup was dissolved in methanol and crystallization began at once. The yield of V was 6.9 g. (40% based on III); m. p. 220–222°; after two recrystallizations from methanol, m. p. was 237–238° $[\alpha]_{546.1}^{23}$ −28.8° (*c*, 2.31; *l*, 1; $CHCl_3$). *Anal.* Calcd. for $C_{53}H_{70}O_{37}$: C, 48.97; H, 5.43. Found: C, 48.78; H, 5.30.

Conversion of V to β-*d*-Gentiobiose Octaacetate (VII).—Four grams of V was dissolved in a mixture of 20 cc. of chloroform and 15 cc. of methanol. Five cubic centimeters of sodium methylate solution (1 g. of sodium in 200 cc. of methanol) was added and the reaction solution was stirred at room temperature for one hour. The β-*d*-gentiobiose (VI) which precipitated was separated and dried over phosphorus pentoxide *in vacuo;* yield 1.6 g. (76%). This was mixed with 1 g. of fused sodium acetate and 10 cc. of acetic anhydride. After heating on the steam-bath for two hours, the product was precipitated in ice water, yielding 1.3 g. of VII (53%). Twice recrystallized the material had a m. p. of 195–196° and a mixed m. p. with a sample of VII prepared by another method[2] showed no depression of m. p.

Summary

1. Some new crystalline sugar derivatives have been prepared and characterized: di-(1,2,3,4-tetraacetyl-β-*d*-glucosyl) carbonate, di-(1-bromo-2,3,4-triacetyl-β-*d*-glucosyl) carbonate, di-(1,2,3,4,2′,3′,4′-heptaacetyl-β-gentiobiosyl) carbonate and di-(2,3,4-triacetyl-β-*d*-methyl glucosidyl) carbonate.

2. Evidence is presented to substantiate the structures assigned to these new compounds.

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

Optically Active Phenylurethan Anesthetics[1]

BY MAYNARD S. RAASCH[2] AND WALLACE R. BRODE

Asymmetric local anesthetics which have been prepared in their enantiomorphic forms and physiologically tested include cocaine and pseudococaine,[3] eucaine and isoeucaine,[4] tutocaine,[5] and stovaine.[6] The present work provides examples of the phenylurethan type.

Diothane (*dl*-1-piperidinopropane-2,3-diol dicarbanilate hydrochloride)[7,8] was prepared in optically active forms by first resolving the intermediate *dl*-1-piperidinopropane-2,3-diol with *l*-menthoxyacetic acid. This gave the *levo* form of the amino alcohol which melted at 20°. Since the *dl*-form melts at 83°, it was possible to obtain the *dextro* form very nearly pure by isolating the crude *dextro* form from the resolution mother liquors and filtering the racemate from it at 25°. This unusual fractional filtration procedure provides a means for obtaining both enantiomorphic forms pure with the use of only one resolving agent.

The active piperidinopropanediols were allowed to react with phenyl isocyanate to form the dicarbanilate and then with hydrogen chloride to form the optically active diothanes. The products were readily recrystallized from methyl ethyl ketone with which they formed a solvate containing one molecule of the ketone to one of the active diothane. Recrystallization from other

(1) Presented before the Organic Division at the Atlantic City meeting of the American Chemical Society, September, 1941.

(2) Wm. S. Merrell Fellow, 1939–1941.

(3) Gottlieb, *Arch. Exptl. Path. Therap.*, **97**, 113 (1923).

(4) King, *J. Chem. Soc.*, **125**, 41 (1924).

(5) Waser, "Synthese der organischen Arzneimittel," Ferdinand Enke, Stuttgart, 1928, p. 82.

(6) Fourneau and Ribas, *Bull. soc. pharmacol.*, **35**, 273 (1928).

(7) Rider, THIS JOURNAL, **52**, 2115 (1930); *J. Pharmacol.*, **47**, 255 (1933).

(8) Rider and Cook, THIS JOURNAL, **59**, 1741 (1937); *J. Pharmacol.*, **64**, 1 (1938).

solvents, including other methyl ketones, was difficult or unsuccessful. It is interesting that methyl ethyl ketone has this specific action and that the hydrochlorides of the corresponding optically active monocarbanilates of piperidinopropanediol do not become solvated.

The resolution of 1-diethylamino-2-propanol was effected with camphoric acid and the active forms were converted to local anesthetics by reaction first with phenyl isocyanate and then with hydrogen chloride to give the optically active forms of 1-diethylamino-2-propanol carbanilate hydrochloride. The racemic form has been described previously.[9]

Physiological Activity.[10]—No difference in the anesthetic activity of 1% aqueous solutions of dextro, levo and racemic diothanes, freed of methyl ethyl ketone, was found when the compounds were tested on rabbit's cornea. The intravenous toxicity, however, indicated that the *levo* form was less toxic, the values being 18 mg. per kg. of body weight for *dextro* diothane, 25 mg. per kg. for the *levo* form and 18 mg. per kg. for the racemic form.

No difference in the toxicity of the *dextro* and *levo* diothane methyl ethyl ketonates was observed, but the *levo* form showed a slightly better anesthetic activity on rabbit's cornea. The anesthesia lasts 40–45 minutes.

In the case of *dextro*, *levo* and racemic diethylamino-2-propanol carbanilate hydrochlorides, no difference in activity was found. The duration of anesthesia on rabbit's cornea was only about 16 minutes, which would make detection of any difference difficult. Piperidinopropanediol monocarbanilate hydrochloride is likewise a weak anesthetic.

Experimental[11]

Resolution of *dl*-1-Piperidinopropane-2,3-diol.—One hundred and fifty-three grams of *dl*-piperidinopropanediol, supplied by the Wm. S. Merrell Co., dissolved in 460 ml. of warm acetone was mixed with 205 g. of *l*-menthoxyacetic acid[12] in 300 ml. of acetone. After crystallization started the mixture was allowed to stand for two hours and then filtered. The crystals were rinsed with a little acetone; yield, 176 g. of impure *l*B*l*A; theory for *l*B*l*A, 179 g. The salt was twice recrystallized from acetone, giving 135 g. of the pure salt; m. p. 106°; yield, 75%; $[\alpha]^{24}D$ −67.0° (*c*, 2.8; absolute alcohol) (*c* = g. per 100 ml.).

The salt was dissolved in a little water and 15 ml. of sulfuric acid in 100 ml. of water was added. The liberated *l*-menthoxyacetic acid was extracted with ether. The aqueous layer was made strongly basic with sodium hydroxide and the *levo* piperidinopropanediol was extracted with chloroform. After removing the chloroform the viscous residue was distilled; b. p. 137° (12 mm.); m. p. 20°; $[\alpha]^{20}D$ −13.1° (*c*, 4; absolute alcohol); yield, 46 g. or 60%, based on the original piperidinopropanediol.

Anal. Calcd. for $C_8H_{17}O_2N$: neut. equiv., 159.2. Found: neut. equiv. with methyl red, 159.5.

The acetone was removed from the mother liquor of the resolution and from the residue the impure *dextro* piperidinopropanediol was recovered. This was carefully freed of solvent under reduced pressure, inoculated with the racemate and cooled in ice until the entire mass crystallized. After this the amine was allowed to come to room temperature. In this way, the *dl*-amine (m. p. 83°) crystallizes out and may be filtered from the *d*-amine by suction. The filtrate was distilled; b. p. 137° (12 mm.); $[\alpha]^{20}D$ +13.1° (*c*, 4; absolute alcohol); yield, 30 g. If the rotation comes out too low, the process of crystallizing out the racemic form should be repeated.

When equal amounts of the liquid *d*- and *l*-piperidinopropanediols are mixed, a solid racemic form results, indicating compound formation.

With *d*-camphorsulfonic acid, *dl*-piperidinopropanediol forms a partially racemic salt, *dl*B*d*A; m. p. 123°; $[\alpha]^{22}D$ +13.2° (*c*, 4; water). Crystalline salts were formed with menthyl acid phthalate and camphoroxalic acid,[13] but resolution with these was not studied. The latter acid apparently has never been used as a resolving agent.

***d*- and *l*-Diothane Methyl Ethyl Ketonates.**—Twenty grams of *levo* piperidinopropanediol was dissolved in 85 ml. of dry benzene and placed in a three-necked flask equipped with thermometer, mercury seal stirrer and dropping funnel. Thirty grams of phenyl isocyanate was added to the stirred liquid over a period of two hours. The temperature was kept below 30° and the mixture was allowed to stand overnight. Dry hydrogen chloride was passed in precipitating the *l*-diothane as a sticky mass. These reactions are quantitative. The sticky material was dissolved in methyl ethyl ketone from which it crystallized almost immediately as a solvate. After two recrystallizations from methyl ethyl ketone the product melted at 96–98°; $[\alpha]^{24}D$ −14.3° (*c*, 4; water).

Anal. Calcd. for $C_{22}H_{27}O_4N_3 \cdot CH_3COC_2H_5 \cdot HCl$: Cl, 7.01. Found: Cl, 7.02.

d-Diothane methyl ethyl ketonate was prepared in the same manner as the *l*-form; m. p. 98–99°; $[\alpha]^{24}D$ +14.5°; Cl, 7.01.

The methyl ethyl ketonates were very stable but by heating them above their melting points, the ketone was distilled off and identified as the semicarbazone. These solvates are sparingly soluble in methyl ketone but very soluble in other methyl ketones.

Some of the sticky *d*-diothane was crystallized with great

(9) Cook and Rider, THIS JOURNAL, **58**, 1079 (1936).

(10) The pharmacological tests were carried out by the Wm. S. Merrell Co.

(11) Melting and boiling points reported are not corrected.

(12) Frankland and O'Sullivan, *J. Chem. Soc.*, **99**, 2329 (1911); Rule and Rod, *ibid.*, 1932 (1931); Holmes and Adams, THIS JOURNAL, **56**, 2093 (1934).

(13) Tingle and Tingle, *Am. Chem. J.*, **21**, 247 (1899); **19**, 398 (1897).

difficulty from acetone and from ethyl acetate, but in both cases an indefinite amount of solvent was retained.

***d*- and *l*-Piperidinopropanediol Monocarbanilate Hydrochlorides.**—Two grams of *d*-piperidinopropanediol and 1.5 g. of phenyl isocyanate (mole ratio, 1:1) were mixed in benzene solution and allowed to stand overnight. Hydrogen chloride was then passed in and the crystalline hydrochloride precipitated in quantitative yield (3.9 g.). The product was dissolved in methanol and reprecipitated with acetone as glistening plates; m. p. 187–188°; $[\alpha]^{30}D$ +15.7° (*c*, 4; methanol); $[\alpha]D$ 18.3° (*c*, 4; water).

Anal. Calcd. for $C_{15}H_{22}O_3N_2 \cdot HCl$: Cl, 11.23. Found: Cl, 11.20.

Values found for the *levo* form were: m. p. 187–188°; $[\alpha]^{21}D$ −15.6° (*c*, 4; methanol); Cl, 11.17.

The racemic form has been reported previously.[5]

Resolution of 1-Diethylamino-2-propanol.—Two hundred and twenty-eight grams of *d*-camphoric acid, 150 g. of *dl*-1-diethylamino-2-propanol (b. p. 157°), supplied by the Wm. S. Merrell Co., and 500 ml. of acetone were warmed together until solution was complete. The mixture was cooled in ice for two hours after crystallization started. The crystals were filtered off and rinsed with small portions of acetone; yield, 68 g. of *d*B*d*A. The salt was pure after two recrystallizations from acetone; yield, 57 g.; m. p. 126–127°; $[\alpha]^{24}D$ +41.8° (*c*, 3.4; absolute alcohol).

The *dextro* amine was liberated from the salt with aqueous sodium hydroxide, extracted with ether, dried over sodium sulfate, and distilled; b. p. 156.5–157°; $[\alpha]^{26}D$ +46.7° (*c*, 4; absolute alcohol); yield, 40 g. or 53%.

The *l*-1-diethylamino-2-propanol recovered from the resolution mother liquor had a specific rotation of −25.6° in absolute alcohol. To obtain the pure *levo* amine, the Ingersoll[14] principle was used. Fifty-four grams of the recovered *levo* amine was allowed to react with 82.5 g. of *dl*-camphoric acid in acetone. The crystals which formed after a day were filtered off and recrystallized four times from acetone; yield, 20 g. of *l*B*l*A; m. p. 125–126°; $[\alpha]^{24}D$ −41.5° in absolute alcohol. Thirty-one grams of the amine recovered from the mother liquor of this resolution was combined with 35.5 g. of *dl*-camphoric acid and 11.8 g. of *l*-camphoric acid which was recovered from the *l*B*l*A. The salt formed was recrystallized four times from acetone, giving an additional 19 g. of *l*B*l*A. Repetition of the process on 19 g. of the recovered amine, 14 g. of *l*-camphoric acid and 15 g. of *dl*-camphoric acid gave only 7 g. of pure salt. The total amount of *l*B*l*A was 46 g.

The *levo*-1-diethylamino-2-propanol recovered separately from each batch of *l*B*l*A was combined, dried and distilled. The yield was 16 g.; b. p. 157°; $[\alpha]^{24}D$ −46.2 (*c*, 4; absolute alcohol).

The *dl*-camphoric acid used was prepared from synthetic camphor by the procedure used by Noyes[15] on *d*-camphor.

***d*- and *l*-1-Diethylamino-2-propanol Carbanilate Hydrochlorides.**—Twenty grams of *dextro*-1-diethylamino-2-propanol and 18.1 g. of phenyl isocyanate were allowed to react together by the procedure described for the diothanes. After the reaction was complete, dry hydrogen chloride precipitated the hydrochloride in crystalline form; yield, 39.5 g. or 90%. This was recrystallized from acetone containing 5% of water; m. p. 165°; $[\alpha]^{24}D$ +10.3° (*c*, 4; absolute alcohol).

Anal. Calcd. for $C_{14}H_{22}O_2N_2 \cdot HCl$: Cl, 12.36. Found: Cl, 12.26.

The *levo* form was prepared in the same manner; m. p. 165°; $[\alpha]^{24}D$ −10.2° in absolute alcohol; Cl, 12.38.

Summary

1. 1-Piperidinopropane-2,3-diol has been resolved with *l*-menthoxyacetic acid.

2. *Dextro* and *levo* diothane methyl ethyl ketonates have been synthesized.

3. The antipodal forms of 1-piperdinopropane-2,3-diol monocarbanilate hydrochloride have been prepared.

4. The complete resolution of 1-diethylamino-2-propanol has been effected with *d*-camphoric acid.

5. The antimeric forms of 1-diethylamino-2-propanol carbanilate hydrochloride have been prepared.

6. The comparative local anesthetic action of the enantiomorphic pairs of carbanilates has been determined.

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(14) Ingersoll and co-workers, THIS JOURNAL, **54**, 274, 4712 (1932); **55**, 411 (1933); **56**, 2123 (1934).

(15) Noyes, *Am. Chem. J.*, **16**, 501 (1894).