[CONTRIBUTION FROM THE BANTING-BEST DEPARTMENT OF MEDICAL RESEARCH, BANTING INSTITUTE, UNIVERSITY OF TORONTO]

L(+)Propylene Glycol

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The preparation and the properties of both enantiomers of propylene glycol have been previously described. The levo-rotatory form has been obtained (a) by reduction of ethyl D-lactate with sodium in ethanol and toluene,[1] (b) by desamination of the levo-rotatory 1-aminopropanol-2 hydrochloride with potassium nitrite[2] or silver nitrite,[3,4] (c) by hydrolysis of dextro-rotatory propylene oxide with sodium hydroxide[5] or hydrolysis of levo-rotatory propylene oxide with formic acid and hydrochloric acid[6] and (d) by phytochemical reduction of acetol.[7,8] The dextro-rotatory form of propylene glycol has been obtained by hydrolysis of dextro-rotatory propylene oxide with formic and hydrochloric acid.[5,6] The specific rotations of both enantiomers obtained by the above methods vary greatly. It is obvious that most of these procedures produce mixtures of the dextro- and levo-rotatory propylene glycol, the ratio depending on the optical purity of the starting material and the prevailing experimental conditions.

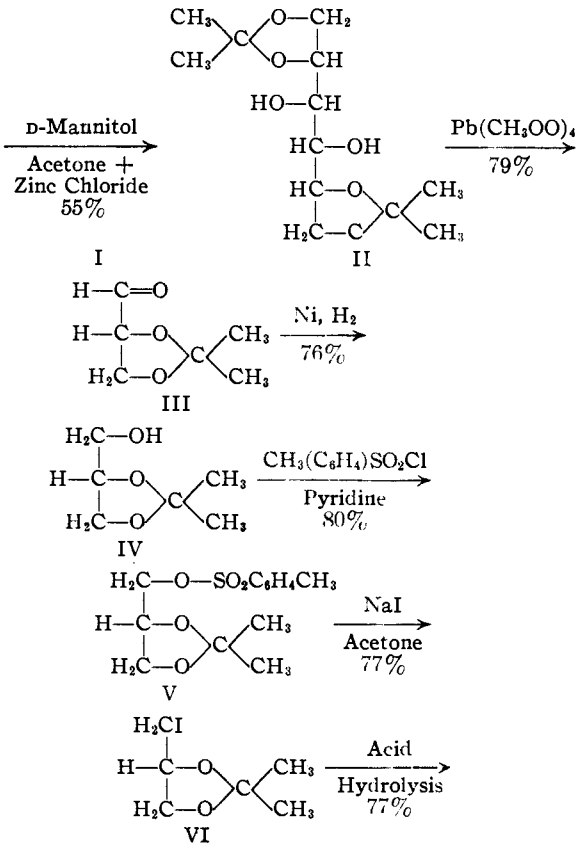
We had at our disposal a method which was expected to yield the pure enantiomers of propylene glycol and to reveal their steric relationship to glyceraldehyde, the accepted compound of reference in stereochemistry. It was decided to prepare by means of this method the dextro-rotatory propylene glycol because this isomer had not yet been obtained in as pure an optical state as the levo-rotatory compound for which an excellent biochemical method of preparation already existed.[7] Incidentally, this choice also permitted the use of the much more readily available D-mannitol as starting material. The sequence of reactions employed in the synthesis of L(+)propylene glycol and the steric interrelationship of the various compounds concerned are outlined in the reaction scheme.

The L(+)propylene glycol, obtained from D-mannitol in seven steps and with an over-all yield of approximately 11% of the theory, was in all respects identical with D(−)propylene glycol prepared by the phytochemical reduction of acetol[7] except that its rotation was opposite in sign. The D(−)propylene glycol can be obtained by the same sequence of reactions starting the synthesis with L-mannitol.

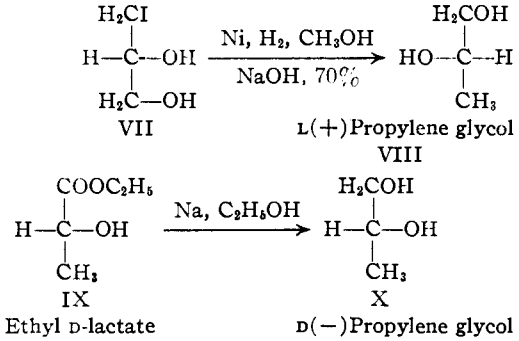
With regard to the steric classification of the dextro-rotatory propylene glycol, it should be noted that the transformation of the acetone D-glyceraldehyde into the dextro-rotatory propylene glycol is accompanied by a reversal in configuration. If one were to oxidize the primary hydroxyl group of the dextro-rotatory propylene glycol the result would be either L-lactic aldehyde or L-lactic acid. Thus the dextro-rotatory propylene glycol belongs to the L-series and the levo-rotatory form to the D-series.[9]

This result is in agreement with the fact that the reduction of ethyl D-lactate IX yields the levo-rotatory D-propylene glycol X.

This optical classification of the propylene glycols seemed to be of interest because recently propylene glycol in the form of its phosphate has been isolated from a natural source, cattle brain, where it constitutes about 5% of the acid soluble phosphorus.[10]



(1) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **67**, 331 (1926).
(2) P. A. Levene and A. Walti, *ibid.*, **68**, 423 (1926).
(3) P. A. Levene and H. L. Haller, *ibid.*, **65**, 49 (1925).
(4) P. Karrer and W. Klarer, *Helv. Chim. Acta*, **8**, 393 (1925).
(5) P. A. Levene and A. Walti, *J. Biol. Chem.*, **73**, 269 (1927).
(6) E. Abderhalden and E. Eichwald, *Ber.*, **51**, 1312 (1918).
(7) E. Färber and F. F. Nord, *Biochem. Z.*, **112**, 313 (1920).
(8) "Organic Syntheses," Coll. Vol. II, p. 545.
(9) The guiding principles in establishing the steric classification of the enantiomeric glycerides and related compounds are outlined in "Preparation and Properties of Optically Active Derivatives of Glycerol" by H. O. L. Fischer and E. Baer, *Chem. Rev.*, **29**, 287 (1941), and *J. Biol. Chem.*, **128**, 475 (1939).
(10) O. Lindberg, *Arkiv. Kemi. Mineral Geol.*, **A23**, 1–45 (1946).



VII L(+)Propylene glycol VIII

IX X

Ethyl D-lactate D(−)Propylene glycol

Experimental Part

α-(*p*-Toluenesulfonyl) D-Acetone Glycerol (V).—To a gently agitated and cooled mixture of 38.0 g. of *p*-toluene sulfonylchloride and 20 ml. of dry pyridine was added 26.4 g. of freshly prepared D(+)acetone glycerol ($[\alpha]_D$ + 13.9°). The reaction mixture was kept in an ice-bath until the reaction had subsided (approximately one hour). After standing forty-eight hours at room temperature a crystalline sludge had formed which was poured with stirring into 500 ml. of ice-water. The supernatant liquid was immediately decanted and the heavy oil, dissolved in ether, washed with sodium carbonate solution. The ether solution was dried with anhydrous sodium sulfate and concentrated *in vacuo* to a thick sirup. The residue (48.4 g.) was dissolved in a mixture of 300 ml. of dry ether and 600 ml. of petroleum ether (b. p. 30–60°), the solution cooled to −70° and the thick sludge filtered with suction on a cooled Büchner funnel. The substance, which liquifies at room temperature, was freed *in vacuo* from adhering solvent. The yield of α-(*p*-toluenesulfonyl) D-acetone glycerol (V) was 46.0 g. (80.2%), $n^{22}D$ 1.5054; d^{24} 1.208. $[\alpha]^{24}D$ −6.7° in substance; $[\alpha]^{24}D$ −4.6° in dry ethanol (*c*, 13).

Anal. Calcd. for $C_{13}H_{18}O_5S$ (286.2): C, 54.51; H, 6.29; acetone, 20.3. Found: C, 54.60; H, 6.28; acetone, 20.6, 20.0.

α-Iodo Acetone L-Propylene Glycol (VI).—A solution of 46.0 g. of α-(*p*-toluenesulfonyl) D-acetone glycerol and 65 g. of sodium iodide in 300 ml. of dry acetone was kept in a pressure bottle at 90° for ten hours. The sodium *p*-toluenesulfonate was collected on a Büchner funnel and thoroughly washed with dry acetone. The combined filtrates were brought to dryness at reduced pressure and the reddish-brown solid extracted with four 100-ml. portions of ether. The ether-extract was washed twice with 30-ml. portions of a dilute sodium thiosulfate solution, dried with anhydrous sodium sulfate and concentrated under diminished pressure (bath to 35°). The fractional vacuum distillation of the residue yielded 30.0 g. (77.4%) of pure α-iodo acetone L-propylene glycol (VI), b. p. (6 mm.) 68–69°; $n^{25}D$ 1.5022; $d^{20.5}$ 1.644; $[\alpha]^{23}D$ + 54.0° in substance; $[\alpha]^{23}D$ + 35.5° in dry ethanol (*c*, 12.7).

Anal. Calcd. for $C_6H_{11}O_2I$ (241.9): I, 52.46; acetone, 23.97. Found: I, 52.63; acetone, 24.3.

α-Iodo L-Propylene Glycol (VII).—A solution of 30.0 g. of α-iodoacetone L-propylene glycol in 75 ml. of 85% ethanol was prepared and after the addition of 2.5 ml. of 5 *N* sulfuric acid kept for twenty hours at room temperature. In order to ensure a complete hydrolysis the solution was diluted with 10 ml. of water and refluxed for a period of five minutes. The cold solution was made neutral to litmus with aqueous baryta and concentrated *in vacuo* to a dry sirup at a bath temperature of 35 to 45°. The residue was extracted with four 75-ml. portions of ether and the combined extracts, after drying with anhydrous sodium sulfate, brought to dryness under reduced pressure. The residue (20.2 g., m. p. 47–49°) was recrystallized from chloroform–petroleum ether (b. p. 30–60°) and yielded 19.3 g. (77%) of analytically pure α-iodo-L-propylene glycol (VII). Platelets, m. p. 48.5–49.5°, $[\alpha]_D$ −5.5° in dry ethanol (*c*, 9.5).

Anal. Calcd. for $C_3H_7O_2I$ (201.9): C, 17.83; H, 3.46; I, 62.85. Found: C, 18.09, 18.07; H, 3.79, 3.74; I, 62.70.

L(+)Propylene Glycol (VIII).—A solution of 19.3 g. of α-iodo-L-propylene glycol (VII) and 15 ml. of 10 *N* sodium hydroxide in 300 ml. of 95% ethanol was shaken with 10 g. of Raney nickel catalyst in a hydrogen atmosphere of slightly positive pressure until the absorption of hydrogen ceased. Within thirty minutes 1906 ml. of dry hydrogen (N.P.T.) or 89% of the theoretical amount had been consumed. The solution was freed from the catalyst, treated with carbon dioxide, filtered and the filtrate evaporated to dryness under diminished pressure and a bath temperature of 35–45°. The residue was dissolved in 60 ml. of dry ethanol and 200 ml. of dry ether and the solution dried with approximately 40 g. of anhydrous sodium sulfate. The ether solution was decanted and concentrated under normal pressure. The rest of the solvent was removed under reduced pressure raising the temperature of the bath to 60°. The remaining mixture of propylene glycol and sodium iodide was gradually heated *in vacuo* to 160° and the colorless distillate purified by fractional distillation either at normal pressure or *in vacuo*. The yield of pure L(+)propylene glycol (VIII) was 4.32 g. (70%), b.p. (765 mm.) 186–188°; b. p. (6 mm.) 76–78°, $n^{23.5}D$ 1.4312, d^{20} 1.04, $[\alpha]^{23}D$ + 15.4° in substance; $[\alpha]^{23}D$ + 20.1° in water (*c*, 7.5), $[\alpha]^{22}D$ + 4.2° in dry ethanol (*c*, 6.6).

Anal. Calcd. for $C_3H_8O_2$(76): C, 47.36; H, 10.52. Found: C, 47.84; H, 10.38.

Summary

Dextro-rotatory propylene glycol was prepared and its L-configuration established by means of the following sequence of reactions: D-acetone glyceraldehyde → D-acetone glycerol → α-(*p*-toluenesulfonyl) D-acetone glycerol → α-iodo acetone L-propylene glycol → α-iodo-L-propylene glycol → L(+)propylene glycol.

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