at 220–240° to rosettes of needles, 245° sintering), $[\alpha]^{20}D$ −31.1 ± 0.2 (*c* 0.8%, H_2O).

Anal. Calcd. for $C_6H_{11}NO_3$: C, 49.64; H, 7.64; N, 9.65. Found: C, 49.44; H, 7.69; N, 9.46.

Synthesis of the Two Diastereoisomers of 5-Hydroxy-D,L-pipecolic Acid. Diethyl 2-(3′-Butenyl)-2-formamidomalonate.[19]—Diethyl aminomalonate was prepared by hydrogenating diethyl isonitrosomalonate at 1500 p.s.i. using 10% palladium–charcoal,[30] b.p. 93–98° (2.5 mm.), 85.5% and formylated in toluene with 90% formic acid[31] to yield diethyl formamidomalonate, b.p. 145–150° (3.25 mm.), m.p. 47–49°, 75% yield. To a solution of one equivalent of sodium ethoxide in 50 ml. of absolute ethanol there was added 17.4 g. of diethyl formamidomalonate. The mixture was heated to gentle boiling under reflux and then 11.6 g. of 3-butenyl bromide (b.p. 98–102°, yield 74% from 3-buten-1-ol[32]) was added slowly. Using essentially the directions of Weisiger, there was obtained, after one recrystallization of the crude product from ethanol, 10.2 g. (46.2%) of colorless crystals, m.p. 94–96°. Two additional recrystallizations from aqueous ethanol yielded the analytical sample, m.p. 96–97° (reported m.p.[18,33] 84°).

Anal. Calcd. for $C_{12}H_{19}O_5N$: C, 56.02; H, 7.44; N, 5.46. Found: C, 55.98; H, 7.59; N, 5.46.

Diethyl 2-(3′,4′-Epoxybutyl)-2-formamidomalonate (IX).—By the use of perbenzoic rather than peracetic acid[19] a simpler procedure and higher yields were made possible. A solution of 5.14 g. (0.02 mole) of diethyl 2-(3′-butenyl)-2-formamidomalonate in chloroform was treated with a chloroform solution of 0.022 mole of perbenzoic acid. After 4 days at 4° titrations indicated that the reaction was 98.3% complete. At this point 50 ml. of water containing several drops of phenolphthalein was added to the chloroform solution of the reaction products. The mixture was treated dropwise with 5 *N* sodium hydroxide solution until the aqueous phase was alkaline. The chloroform solution then was washed with water, dried over sodium sulfate and freed of chloroform at reduced pressure. The residue was 4.8 g. of a pale yellow liquid which crystallized on standing, m.p. 73–78°. Recrystallization of the crude product from acetone–ligroin (66–68°) and benzene–ligroin (66–68°) effected little purification so it was subjected to a four-funnel countercurrent distribution using 20 ml. of benzene to 100 ml. of water–methanol (1:1). Concentration of the combined water–methanol phases at reduced pressure and recrystallization of the residue from benzene–ligroin (66–68°) yielded 2.76 g. (50.6%) of epoxide, m.p. 79–84° (reported[1] 75°). Three recrystallizations from benzene–ligroin (66–68°) yielded the analytical sample, m.p. 78.5–83.0°.

(30) Roche Products Ltd., A. Cohen and J. A. Silk, British Patent 611,600, Nov. 1, 1948; *C. A.*, **43**, 3445 (1949).

(31) "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 590.

(32) R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 1955 (1934).

(33) Dr. Weisiger kindly supplied us with a sample of the compound which was recrystallized from chloroform; it had m.p. 95–96°.

Anal. Calcd. for $C_{12}H_{19}O_6N$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.53; H, 7.18; N, 5.19.

5-Hydroxypipecolic Acid (I).—A solution of 0.1 g. of diethyl 2-(3′,4′-epoxybutyl)-2-formamidomalonate (IX) in 10 ml. of *N* sodium hydroxide solution was allowed to stand at 37° for 3 days. Ten ml. of concentrated hydrochloric acid then was added to the solution. The mixture was boiled under reflux for 5 hr. and then evaporated to dryness at reduced pressure. Two 10-ml. portions of ethanol were added to the residue and evaporated. The residue was dissolved in 10 ml. of water and the resulting solution was adjusted to *p*H 6.5 with ammonia water and filtered from a small amount of an amorphous solid. A two-dimensional paper chromatogram of the solution prepared with 2,4-lutidine–*t*-amyl alcohol and *n*-butyl alcohol–acetone–ammonia indicated the presence of two pairs of diastereoisomeric secondary amino acids and a primary amino acid. One pair with ninhydrin gave a yellow color which exhibited a brick-red fluorescence in the ultraviolet light; these two secondary amino acids presumably were the *cis*- and *trans*-5-hydroxymethylprolines (XI and XII). The other pair gave a violet color with ninhydrin which exhibited a bright red fluorescence in ultraviolet light. Paper chromatographic comparison with natural 5-hydroxypipecolic acid isolated from dates indicated that the amino acids were normal and allo-5-hydroxy-D,L-pipecolic acid (racemes of I and V). The remaining amino acid gave a blue color with ninhydrin, was deaminated with nitrous acid, behaved like serine on paper chromatography and presumably was 5,6-dihydroxy-2-aminocaproic acid. The relative intensities of the colors produced with ninhydrin indicated that the non-cyclic amino acid was much more abundant in the crude product than either of the cyclic amino acids and the 5-hydroxypipecolic acids were the least abundant. The crude product was analyzed on a 150-cm. column of Dowex-50 using 0.15% ninhydrin solution in glacial acetic acid and measuring the absorption at 350 and at 375 mμ. The results of the analysis are shown in Fig. 1. The two smaller peaks, C and D, are those of normal and allo-5-hydroxy-D,L-pipecolic acids, respectively, and the two larger peaks presumably are those of the diastereoisomeric 5-hydroxymethylprolines (XI and XII). In another attempt at synthesis a solution of 0.1 g. of diethyl 2-(3′,4′-epoxybutyl)-2-formamidomalonate (IX) in 5 ml. of a 0.42 *N* solution of anhydrous hydrogen chloride in ether was allowed to stand at room temperature for 3 hr. The ether was then evaporated in a stream of nitrogen. Ten ml. of 0.5 *N* barium hydroxide solution was added to the residue and the mixture boiled under reflux for 3 hr. Ten ml. of concd. hydrochloric acid then was added and the mixture boiled under reflux for 3 hr. Silver sulfate was added and the mixture digested on a hot-plate and filtered. The filtrate was adjusted to *p*H 6 with ammonia water and filtered. A two-dimensional paper chromatogram of the solution of products indicated that the same products were present in approximately the same relative amounts as were present in the previous synthesis.

BETHESDA, MARYLAND

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

Studies on the Stereochemistry of Ephedrine and ψ-Ephedrine*

BY BERNHARD WITKOP AND CALVIN M. FOLTZ

RECEIVED MAY 3, 1956

The epoxides obtained from the quaternary bases of ephedrine, *i.e.*, L-*erythro*-1-phenyl-1-hydroxy-2-methylaminopropane, and of ψ-ephedrine, *i.e.*, L-*threo*-1-phenyl-1-hydroxy-2-methylaminopropane, are D-*threo*-1-phenyl-1,2-epoxypropane (III) and D-*erythro*-1-phenyl-1,2-epoxypropane (IV). The Walden inversion occurring in the epoxide formation at the carbon which loses the trimethylamine group, was proved by catalytic reduction of III and IV. Both epoxides yielded the same D-*glycero*-1-phenyl-2-hydroxypropane (V) characterized as the *p*-toluenesulfonate. Acid-catalyzed hydrolytic ring opening of the epoxides III and IV yielded as major products D-*erythro*-1-phenyl-1,2-propanediol (VI), characterized as the dibenzoate, m.p. 95.5–97°, and D-*threo*-1,2-propanediol VII, m.p. 62°, $[\alpha]D$ −60°, dibenzoate m.p. 89.5–91°.

The Hofmann degradation of the quaternary salts of ephedrine leads to optically active oxides of β-methylstyrene. Although this reaction was discovered in 1902,[1,2] the steps and products of this

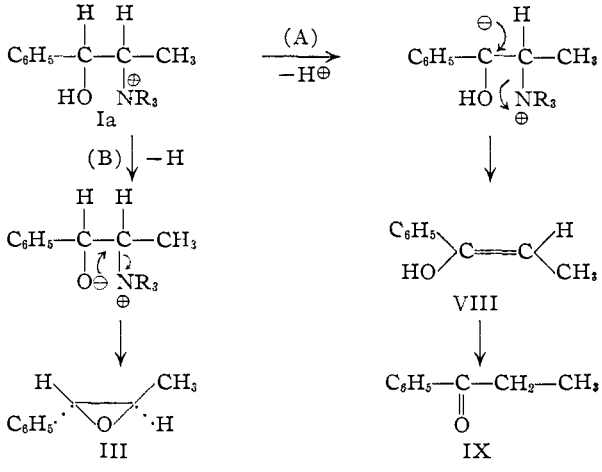
* Presented in part at the 8th Summer Seminar in the Chemistry of Natural Products, Grand Manan Island, New Brunswick, August 6–10, 1956.

(1) E. R. Miller, *Arch. Pharm.*, **240**, 481 (1902); H. Emde, *ibid.*, **244**, 241 (1906); P. Rabe, *Ber.*, **43**, 884, 2622 (1910); **44**, 824 (1911).

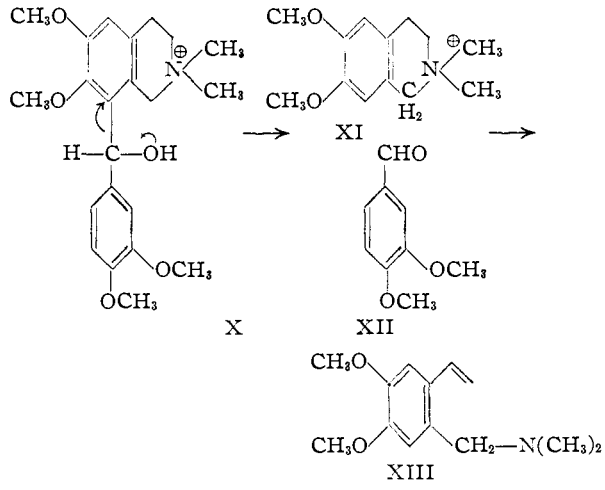
(2) E. Schmidt, *Arch. Pharm.*, **249**, 305 (1911).

sequence have not been formulated correctly.[3] This paper describes the preparation of the pure epoxides, their catalytic reduction to the identical levorotatory benzylmethylcarbinol, their opening to the active phenylpropanediols and the assignment of stereochemical configurations to all of these transformation products and the mechanism of their formation (Chart I).

The bimolecular elimination in onium ions[4] normally proceeds by attack of a strong base on the most available hydrogen atom in β-position to the electron-attracting group. L-Ephedrine (Ia) because of its strongly electron-attracting β-phenyl group has an especially labile hydrogen on a benzyl position and should easily undergo β-elimination (pathway A) which would lead *via* the *trans*-enol VIII to propiophenone (IX). Only minor amounts of propiophenone are found when the quaternary methyl base of ephedrine is distilled with steam. The major product is an optically active β-methylstyrene oxide (III). This indicates the preference for another pathway B.[*] There elimination of trimethylamine occurs by an intramolecular displacement reaction with Walden inversion, similar to the epoxide formation from halohydrins.



The synthesis of epoxides from quaternary derivatives of (phenyl)-ethanolamines is a well known reaction.[5,6] A third type of cleavage is shown by the diastereoisomers of hydroxylaudanosine (X) which undergo reverse aldol cleavage to XI and XII prior to the formation of the normal methine XIII.[7] The quina bases, as tertiary and quaternary bases, undergo elimination commonly by pathway A to form quinotoxines but the formation of epoxides also has been observed.[8] The preparation of narceine from narcotine methochloride[9] follows pathway A. The formation of larger oxide rings in the course of the Hofmann degradation is a phenomenon frequently observed.[10,11]



The mechanism of the internal SN2′ reaction in pathway B requires that no change of configuration occurs at the carbon C(1) carrying the displacing hydroxyl group. The formation of the epoxide and elimination of trimethylamine leads to Walden inversion and *trans* ring-closure at C(2). Ephedrine is LG-*erythro*-1-phenyl-1-hydroxy-2-methylaminopropane. C(1) has been correlated with D(−)-mandelic acid.[12] Written as in Chart I C(1) has the LG-configuration. C(2), the Rosanov[13a] carbon, has been correlated with L(+)-alanine[13b] and has an LS- or LG-configuration.[14] The epoxide from L-ephedrine (I) must therefore be a *trans*-epoxide (III), and, conversely, ψ-ephedrine, which differs from ephedrine only by the opposite DG-configuration at C(1),[15] as a *threo*-compound (II), yields a *cis*-epoxide IV in accordance with the general stereochemical rules established for internal displacement reactions.[16]

The *trans*- and *cis*-epoxides III and IV, which were freed of accompanying propiophenone by reaction with Girard P reagent, like ephedrine and ψ-ephedrine, differ only in the configuration at the benzyl carbon.

This was proved by catalytic reduction of the two epoxides. Hydrogenolytic opening of the oxiran ring[17,18] occurred only at the benzyl ether linkage. The levorotatory liquid benzylmethylcarbinol obtained from both epoxides was converted to the crystalline *p*-toluenesulfonate. Both tolu-

(3) *Cf.* L. Reti, Ephedra Bases, in "The Alkaloids," by R. H. F. Manske and H. L. Holmes, Academic Press, Inc., New York, N. Y., Vol. III, 1953, p. 339.

(4) For a comprehensive review, *cf.* C. N. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 420.

(5) T. V. Braun and W. Teuffert, *Ber.*, **58**, 2210 (1925); **56**, 2178 (1923).

(6) J. Read and I. G. M. Campbell, *J. Chem. Soc.*, 2377 (1930).

(7) R. Robinson and S. Sugasawa, *ibid.*, 789 (1932).

(8) *Cf.* P. Rabe, K. Dussel and R. Teske-Guttmann, *Ann.*, **561**, 159 (1949).

(9) W. Roser, *ibid.*, 247, 167 (1888); P. Rabe, *Ber.* **40**, 3280 1907).

(10) H. W. Bersch, *Angew. Chem.*, **64**, 596 (1952); H. Rapoport and J. B. Lavigne, THIS JOURNAL, **75**, 5329 (1953).

(11) N. R. Easton and V. B. Fish, *ibid.*, **77**, 2547 (1955); J. Weinstock, *J. Org. Chem.*, **21**, 540 (1956).

(12) K. Freudenberg, E. Schöffel and E. Braun, *ibid.*, **54**, 234 (1932).

(13) (a) M. A. Rosanov, THIS JOURNAL, **28**, 114 (1906); (b) K. Freudenberg and F. Nikolai, *Ann.*, **510**, 223 (1934); W. Hückel, *Deut. Apoth. Ztg.*, **95**, 302 (1955); H. K. Müller, *Ann.*, **598**, 70 (1956).

(14) *Cf.* K. Freudenberg, *Monatsh.*, **85**, 537 (1954).

(15) E. Schmidt, *Arch. Pharm.*, 251, 320 (1913); **253**, 52 (1915); H. Emde, *Helv. Chim. Acta*, **12**, 365 (1929).

(16) Some leading references: (a) D. Y. Curtin and E. K. Meislich, THIS JOURNAL, **74**, 5905 (1952); (b) N. H. Cromwell, G. V. Hudson, R. A. Wankel and P. J. Vanderhorst, *ibid.*, **75**, 5387 (1953); (c) S. J. Cristol and W. P. Norris, *ibid.*, **75**, 632 (1953).

(17) *Cf.* P. Tiffeneau and E. Fourneau, *Compt. rend.*, **146**, 697 (1908).

(18) W. F. Whitmore and A. I. Gebhart, THIS JOURNAL, **64**, 912 (1942).

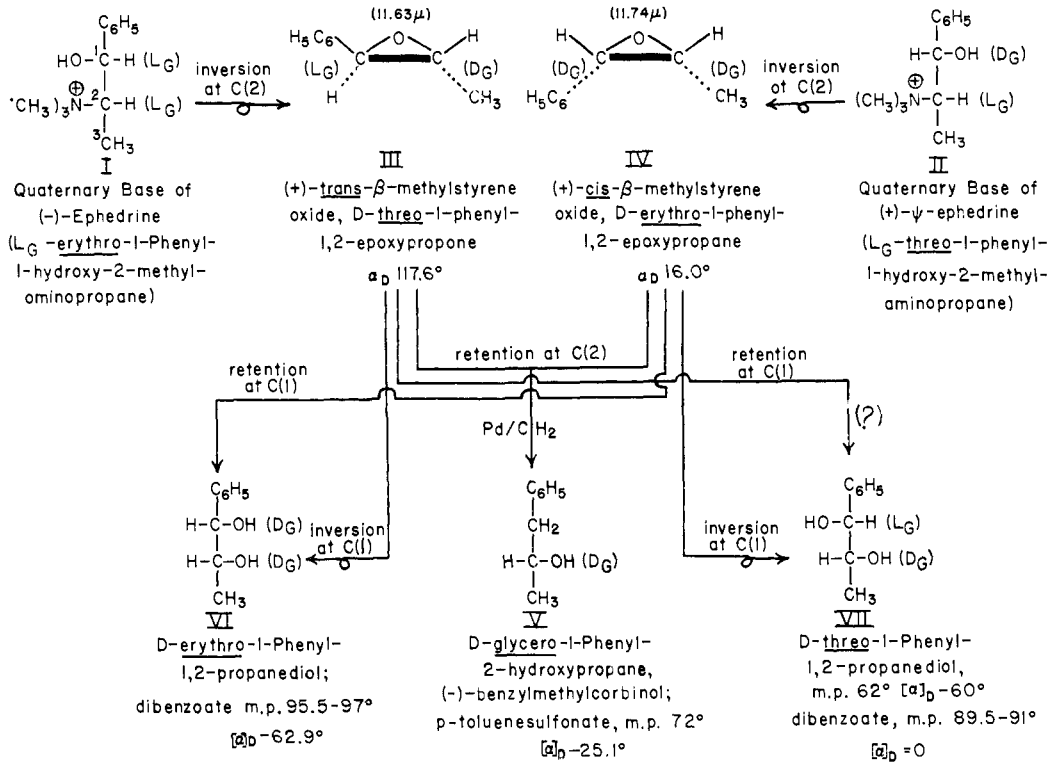
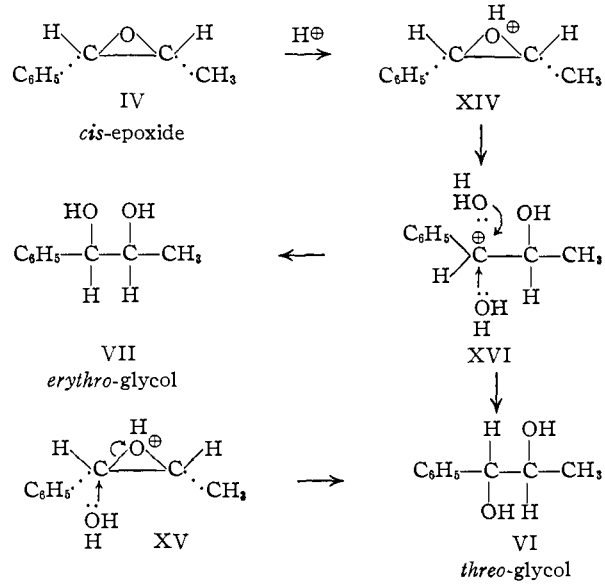


Chart I.—The Conversion of ψ-Ephedrine and Ephedrine into D-*glycero*-1-Phenyl-2-hydroxypropane *via* the (+)-*cis*- and *trans*-β-Methylstyrene Oxides.

enesulfonates from III and IV had the same melting point (72°) and rotation ($[\alpha]_D$ −25.1°) as reported in the literature for D-*glycero*-1-phenyl-2-hydroxypropane (V, Chart I).[19,20] When lithium aluminum hydride was used for the reduction of the epoxides no readily crystallizing *p*-toluenesulfonate could be obtained. This indicates, as has been observed previously,[21] that SN2 ring opening of unsymmetrical epoxides with metal hydrides leads to mixtures of both possible alcohols. With the two pure epoxides III and IV available, the preparation of the pure glycols was attempted. The epoxides which are fairly unreactive toward sodium hydroxide and methoxide[6,22] readily opened up in aqueous medium on addition of a catalytic amount of perchloric acid.[23] The free glycols did not crystallize, not even on prolonged standing.[24] The reason for this behavior became evident on benzoylation. From the *cis*-epoxide IV the immediately crystallizing dibenzoate had m.p. 89.5–91°, $[\alpha]^{20}_D \pm 0°$, the mother liquors of this preparation yielded another dibenzoate, m.p. 95.5–97°, $[\alpha]^{20}_D$ −62.9°, identical with the dibenzoate of the major product of the hydrolysis of the *trans*-epoxide III. Acid-catalyzed opening of the epoxides, therefore, in the case of IV and possibly also in the case of III, leads only to partial inversion at C(1). In addition to the normal nucleophilic attack of H_2O at C(1) with inversion of configuration, there has to be considered quasi-unimolecular ring opening of the oxide-conjugate acid XIV and subsequent rapid reaction of the carbonium ion XV to give both glycols.[25]



Epoxides, with two identical substituents such as optically active *trans*-2,3-epoxybutane or -stilbene oxide and *meso*-2,3-epoxybutane or -stilbene

(19) H. Phillips, *J. Chem. Soc.*, **123**, 44 (1923).
(20) S. Winstein, M. Brown, K. C. Schreiber and A. H. Schlesinger, THIS JOURNAL, **74**, 1140 (1952).
(21) A. Feldstein and C. A. VanderWerf, *ibid.*, **76**, 1626 (1954).
(22) J. Read and I. G. M. Campbell, *J. Chem. Soc.*, 2679 (1930); *Nature*, **125**, 16 (1930).
(23) *Cf.* C. E. Wilson and H. J. Lucas, THIS JOURNAL, **58**, 2396 (1936).
(24) A. McKenzie, E. M. Luis and A. G. Mitchell, *Ber.*, **65**, 798 (1932).
(25) R. G. Kadesch, THIS JOURNAL, **68**, 41 (1946).

have been reported to give good yields of the pure glycols with no sign of crossover from *meso* to *d,l*.[22,23,26]

This dual pathway of acid-catalyzed ring opening *a priori* makes exact assignments of *threo* and *erythro* configurations to the two glycols impossible. The following paper describes the synthesis of the pure racemic glycols and of the oxide of *cis*-β-methylstyrene by unambiguous methods. The synthetic experiments confirm the assignments represented in Chart I.

Experimental[27]

D-*threo*-1-Phenyl-1,2-epoxypropane (III) from *l*-Ephedrine (I).—A solution of 113.4 g. of hydrated, U.S.P., ephedrine alkaloid in 150 ml. of methanol was treated with 88.0 g. of methyl iodide in several portions. The mixture was left for an hour at room temperature and then treated with a solution of sodium methoxide prepared from 14.3 g. of sodium and 400 ml. of methanol. The resulting mixture was treated with 88.0 g. of methyl iodide and allowed to stand overnight. The crystalline methiodide, 143 g., was collected; it softened at 207° and was completely melted at 214°. The salt was dissolved in 300 ml. of water and treated with silver oxide freshly prepared from 99.7 g. of silver nitrate. The mixture was allowed to stand overnight and then filtered. The washings and filtrate were combined and steam distilled. Four liters of distillate was collected. The distillate was saturated with sodium chloride and extracted with ether. The ethereal extracts were washed with hydrochloric acid, saturated sodium chloride solution, combined, dried and evaporated. The residue was 24.7 g. (29.7%) of a straw-colored liquid, $[\alpha]^{20}D$ 36.9° (*c* 1.09 in chloroform). The presence of a ketonic contaminant in this residue was indicated by a small peak at 5.93 μ (pure liquid). A preliminary distillation of 2.89 g. of the crude epoxide through a short Vigreux column yielded 1.40 g. of a colorless liquid, b.p. 85.0–86.0° (17 mm.), $[\alpha]^{20}D$ 47.2° (*c* 1.10 in chloroform); there was only very weak absorption at 5.93 μ. The careful fractional distillation of the remainder of the residue over a high-precision fractionation column resulted in extensive decomposition. After the following fractions had been collected: 1.51 g. of a colorless liquid (fraction I), b.p. 87.0–87.5° (15 mm.), $n^{20}D$ 1.5190, $[\alpha]^{20}D$ 48.2° (*c* 1.10 in chloroform), very weak infrared absorption at 5.86 and 5.93 μ; and 2.09 g. of a colorless liquid (fraction II), b.p. 87.5° (15 mm.), $n^{20}D$ 1.5202, $[\alpha]^{20}D$ 50.0° (*c* 1.17 in chloroform), αD 117.6° (pure liquid); the infrared spectrum showed the following major bands: 3.39m, 6.22w, 6.68m, 6.84m, 7.02m, 7.27m, 7.47w, 7.65w, 8.02w, 8.30w, 8.74w, 9.33m, 9.81m, 10.50m, 11.64s, 12.24w, 13.06s, 13.48s and 14.35s. Both fractions I and II were used in subsequent experiments.

D-*erythro*-1-Phenyl-1,2-epoxypropane (IV) from *d*-ψ-Ephedrine (II).—A solution of 53.8 g. of methyl-ψ-ephedrine methiodide in 275 ml. of water was treated with a slight excess of freshly prepared silver oxide. The mixture was allowed to stand overnight at room temperature and then was filtered. The filter-cake was washed with a small amount of hot water, and the filtrate and washing combined and steam distilled. Two liters of distillate were collected, saturated with sodium chloride and extracted with ether. The ethereal extracts were washed in the same way as described in the ephedrine degradation. The combined ethereal extracts were concentrated to about 500 ml., dried and evaporated. The residue was 13.3 g. of a colorless oil. The presence of a ketonic contaminant in this residue was indicated by a peak of medium intensity at 5.92 μ in the infrared spectrum of the crude epoxide. Nearly complete removal of this contaminant was effected by treatment of 6.10 g. of the crude epoxide in 110 ml. of 10% acetic acid *in* absolute methanol with 8.55 g. of Girard P reagent. The mixture was left standing for 20 hours at room temperature and then poured into 300 ml. of water. The resulting mixture was extracted with ether. The ethereal extracts were washed with water, 5% sodium bicarbonate solution and water, combined, dried and evaporated. Distillation of the epoxide yielded 3.05 g. of a colorless liquid, b.p. 76.0–76.5° (13 mm.), $n^{20}D$ 1.5207. Treatment of another 5 g. of crude epoxide in the same way yielded 2.54 g. of pure product, b.p. 80.0–80.5° (17 mm.), $[\alpha]^{20}D$ 47.5° (*c* 1.17 in chloroform), αD 16° (pure liquid), $n^{20}D$ 1.5206. The total yield of pure oxide was 5.54 g. (24.6%, based on methyl-ψ-ephedrine methiodide). The major bands in the infrared absorption spectrum of thin films of the pure liquid were: 3.39m, 6.23w, 6.68m, 6.90s, 7.07m, 7.23m, 7.38m, 7.64w, 7.97m, 8.32m, 8.72m, 8.92m, 9.49m, 9.74m, 9.93m, 10.48s, 10.96w, 11.74s, 12.65w, 13.13s, 13.49vs and 14.31 vs.

D-*glycero*-1-Phenyl-2-hydroxypropane (V) *p*-Toluenesulfonate. A. By Catalytic Reduction of D-*threo*-1-Phenyl-1,2-epoxypropane (III).—A solution of 0.64 g. of pure *trans*-epoxide III ($[\alpha]^{20}D$ 48.2°) in 15 ml. of absolute methanol was hydrogenated over 0.20 g. of palladium-on-charcoal (10%) at room temperature and atmospheric pressure. After one hour the uptake of hydrogen was complete. The mixture was filtered, and the filtrate freed of methanol at reduced pressure. The residue was 0.46 g. of a pale yellow liquid, $[\lambda]_{max}^{CHCl_3}$ 3.02 μ (broad and strong).

The *p*-toluenesulfonate was prepared by treating a solution of 0.40 g. of the crude alcohol in 2 ml. of pyridine cooled in an ice-bath with 0.56 g. of *p*-toluenesulfonyl chloride. The ester appeared first as a very viscous oil which soon crystallized spontaneously. Recrystallization from acetone–ligroin (66–68°) yielded the analytical sample, m.p. 69.0–70.0°, $[\alpha]^{20}D$ −25.1° (*c* 5.22 in chloroform). Major bands in the infrared absorption spectrum in chloroform: 3.44w, 6.25m, 6.69w, 6.89m, 7.40vs, 7.67w, 7.76w, 8.58vs, 8.84–8.94w, 9.13s, 9.36w, 9.69w, 9.83m, 10.98vs and 11.20vs.

Anal. Calcd. for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25; S, 11.04. Found: C, 66.19; H, 6.35; S, 10.88.

B. By Catalytic Reduction of D-*erythro*-1-Phenyl-1,2-epoxypropane (IV).—A solution of 0.54 g. of the pure *cis*-epoxide IV in 10 ml. of absolute methanol was hydrogenated over 0.2 g. of palladium–charcoal (10%) at room temperature and atmospheric pressure. At the end of 85 minutes the theoretical amount of hydrogen had been consumed. The mixture was filtered and the filtrate freed of methanol at reduced pressure. The residue was 0.39 g. of a straw-colored liquid, $\lambda_{max}^{CHCl_3}$ 2.98 μ (broad and strong).

The *p*-toluenesulfonate was prepared by treating a solution of 0.34 g. of the crude alcohol in 2 ml. of pyridine, cooled in an ice-bath, with 0.48 g. of *p*-toluenesulfonyl chloride. The crude ester was a very viscous oil which was crystallized from acetone–ligroin (66–68°). Recrystallization from acetone–ligroin (66–68°) yielded the analytical sample, m.p. 69.0–70.0°, $[\alpha]^{20}D$ −25.4° (*c* 5.01 in chloroform). The compound was identical with the product obtained under A. Major bands in the infrared absorption spectrum in chloroform: 3.45w, 6.25m, 6.69m, 6.89m, 7.40vs, 7.67m, 7.76m, 8.58vs, 8.84–8.94m, 9.13vs, 9.36 m, 9.69m, 9.83m, 10.98s and 11.20s.

Anal. Calcd. for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25; S, 11.04. Found: C, 65.80; H, 6.30; S, 11.15.

D-*erythro*-1-Phenyl-1,2-propanediol (VI) Dibenzoate from D-*threo*-1-Phenyl-1,2-epoxypropane (III) by Acid-catalyzed Hydrolysis.—To a mixture of 1.41 g. of *trans*-epoxide III and 50 ml. of water which was stirred vigorously was added 4 drops of perchloric acid (60%). After 30 minutes of stirring the mixture became a clear solution. Agitation was continued for an additional two hours. The solution was then saturated with sodium chloride, treated with excess sodium bicarbonate and extracted with ether. The ethereal extracts were washed with saturated sodium chloride solution, dried and evaporated. The residue was 0.66 g. of a colorless, viscous liquid which could not be crystallized despite repeated attempts and prolonged standing. A solution of 0.64 g. of the crude product in 4 ml. of pyridine, cooled in an ice-bath, was benzoylated with 1.18 g. of benzoyl chloride. Crystallization of the crude dibenzoate from methanol yielded 0.64 g. (16.9% based on epoxide) of color-

(26) *Cf.* D. Reulos, *Compt. rend.*, **216**, 774 (1943); **218**, 795 (1944).

ADDENDUM IN PROOF. Retention of configuration in the acid-catalyzed ring opening of stilbene oxides recently has been reported: T. H. Brewster, THIS JOURNAL, **78**, 4061 (1956); D. Y. Curtin, A. Bradley and V. G. Hendrickson, *ibid.*, **78**, 4064 (1956).

(27) All melting points are corrected, all boiling points are uncorrected. The analyses were performed by Dr. W. C. Alford and his associates, Analytical Service Laboratory of the National Institutes of Health.

less crystals, m.p. 92–96°, $[\alpha]^{20}D$ −37.1° (*c* 6.13 in chloroform). Two recrystallizations from methanol gave the analytical sample, m.p. 95.5–97.0°, $[\alpha]^{20}D$ −62.8° (*c* 2.88 in chloroform). Major bands of the infrared absorption spectrum in chloroform solution: 3.46vw, 5.83vs, 6.25w, 6.32vw, 6.72vw, 6.91w, 7.27vw, 7.44vw, 7.64m, 7.88–8.45vs, 9.05s, 9.15s, 9.38m, 9.77w, 10.16 vw and 10.41 vw. The spectrum was identical in every respect with that of the dibenzoate of D,L-*erythro*-1-phenyl-1,2-propanediol (m.p. 103.0–104.5°) described in the following paper.

Anal. Calcd. for $C_{23}H_{20}O_4$: C, 76.65; H, 5.59. Found: C, 76.88; H, 5.58.

D-*threo*-1-Phenyl-1,2-propanediol (VII) Dibenzoate from Acid-catalyzed Hydrolysis of D-*erythro*-1-Phenyl-1,2-epoxypropane (IV).—A mixture of 1.00 g. of pure *cis*-epoxide, 50 ml. of water and 5 drops of perchloric acid (60%) was stirred vigorously at room temperature. After 40 minutes much unchanged starting material remained, so 25 ml. of water and 3 drops of perchloric acid (60%) were added. After another 20 minutes of stirring, the mixture became a clear solution and was stirred for an additional two hours. The solution was then saturated with sodium chloride, treated with excess sodium bicarbonate and extracted with ether. The ethereal extracts were washed with saturated sodium chloride solution, dried and evaporated. The residue was 1.04 g. of a colorless liquid which could not be crystallized. The crude product in 5 ml. of pyridine, cooled in an ice-bath, was benzoylated with 1.91 g. of benzoyl chloride. The product was combined with the crude benzoylation product obtained *via* hydrolysis and benzoylation of 1.5 g. more of *cis*-epoxide in the same way. Crystallization from methanol yielded a first crop of 2.88 g. (42.9% based on epoxide) of colorless crystals, m.p. 85–91°, $[\alpha]^{20}D$ 0.0° (*c* 3.24 in chloroform). Two recrystallizations from methanol yielded the analytical sample, m.p. 89.5–91.0°, $[\alpha]^{20}D$ 0.0° (*c* 6.7 in chloroform). Major bands in the infrared absorption spectrum (chloroform): 3.39vw, 5.81vs, 6.23w, 6.30vw, 6.71vw, 6.89w, 7.25vw, 7.39w, 7.62m, 7.84–8.40vs, 9.02s, 9.12s, 9.37m, 9.76m, 9.99vw and 10.20w.

Anal. Calcd. for $C_{23}H_{20}O_4$: C, 76.65; H, 5.59. Found: C, 76.94; H, 5.62.

D-*threo*-1-Phenyl-1,2-propanediol (VII).—In order to regenerate the glycol 0.50 g. of the dibenzoate (m.p. 89.5–91.0°) in 6 ml. of methanol was treated with 0.16 g. of potassium hydroxide in 3 ml. of water. Slight warming in a water-bath yielded a solution which was allowed to stand at room temperature for 24 hours. Then it was diluted with 15 ml. of water and saturated with sodium chloride. The resulting mixture was extracted with ether, and the ethereal extracts were washed with saturated sodium chloride solution, combined, dried and evaporated. The residue was a viscous oil, $[\alpha]^{20}D$ −64.4° (*c* 0.82 in chloroform), which crystallized after thorough drying and two weeks of standing at room temperature. Recrystallization from ether–ligroin (66–68°) yielded the analytical sample, m.p. 61–62°, $[\alpha]^{20}D$ −60.6° (*c* 0.94 in chloroform). Major bands of the infrared absorption spectrum (chloroform): 2.82m, 2.95w, 3.38w, 3.48w, 6.71w, 6.89m, 7.19m, 7.32m, 7.60w, 7.98–8.43m, 8.95s, 9.03m, 9.36m, 9.67s, 9.86s, 10.97w, 11.57w and 12.06w.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.76; H, 7.97.

D-*erythro*-1-Phenyl-1,2-propanediol (VI) Dibenzoate from the Mother Liquors of the Dibenzoate of the D-*threo*-Glycol VII.—Concentration of the first mother liquor of the D-*threo*-dibenzoate yielded colorless crystals, m.p. 85–96°. Recrystallization from methanol yielded 0.36 g. of crystals, m.p. 90–96° and further recrystallization yielded crystals, m.p. 95.0–97.0°, $[\alpha]^{20}D$ −60.9° (*c* 0.46 in chloroform). Rotation, mixed melting point determination and infrared spectra established the identity with the dibenzoate of the hydrolysis product of the *trans*-epoxide III.

Acknowledgment.—We are greatly indebted to Dr. J. W. Pratt for assistance in nomenclature.

BETHESDA, MARYLAND

CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

The Stereochemistry of the 1-Phenyl-1,2-propanediols and of α-Isoephedrine

BY CALVIN M. FOLTZ AND BERNHARD WITKOP

RECEIVED MAY 3, 1956

cis-β-Methylstyrene (II), obtained by stereospecific reduction of phenylmethylacetylene (I) with Lindlar catalyst, was oxidized by potassium permanganate to D,L-*erythro*-1-phenyl-1,2-propane (V), m.p. 93.5–95°, dibenzoate IV m.p. 103.5–104.5°, and by the silver benzoate iodine complex (Prévost reaction) to the dibenzoate VII of D,L-*threo*-1-phenyl-1,2-propanediol (VI), m.p. 77–78.5°, free glycol m.p. 55–57°. The acid-catalyzed hydrolysis of D,L-*cis*-β-methylstyrene oxide (III), after benzoylation, yielded the dibenzoates VII and IV of the expected *threo*-(VI) as well as of the *erythro*-glycol V, suggestive of normal bimolecular *trans*- as well as of *quasi*- unimolecular racemic opening of the epoxide. The comparison of the infrared spectra of the *rac*-glycols and dibenzoates with the D-*threo* and *erythro*-glycols from ephedrine, ψ-ephedrine and isoephedrine allowed final assignments of configurations.

The structural assignments for the simple disecondary glycols with symmetric substituents, such as *meso*- and *rac*-2,3-butane- or -stilbene are well established.[1,2] The configurations of the two optically inactive diastereoisomers of 1-phenyl-1,2-propanediol[3] are not known.

There are three reasons for this failure of stereochemical assignments in this series: (i) an internally compensated *meso*-form does not exist; (ii) all synthetic procedures[3,4] started out with mixtures of *cis*- and *trans*-propenylbenzene[5] and the intermediate epoxide[6,21] and dibromide[3] were sterically inhomogeneous and invariably led to mixtures of 1-phenyl-1,2-propanediols ("α-form," m.p. 56–57°, "β-form," m.p. 101°); (iii) even with the sterically pure *cis*- or *trans*-β-methylstyrene oxides of known configuration available, acid-catalyzed hydrolysis did not lead to pure *threo*- or *erythro*-glycols but to mixtures.[7]

Pure *cis*-propenylbenzene recently has been prepared by catalytic reduction of 1-phenyl-1-propyne

(1) *Cf.* C. E. Wilson and H. J. Lucas, THIS JOURNAL, **58**, 2396 (1936).

(2) *Cf.* J. Read and I. G. M. Campbell, *J. Chem. Soc.*, 2377 (1930).

(3) Th. Zincke and K. Zahn, *Ber.*, **43**, 849 (1910).

(4) J. Lévy and M. Dvoleitzka-Gombinska, *Bull. soc. chim.*, [4] **49**, 1765 (1931).

(5) A. Klages, *Ber.*, **36**, 621 (1903).

(6) *Cf.* E. Forneau and G. Benoit, *Bull. soc. chim.*, **12**, 985 (1945).

(7) B. Witkop and C. M. Foltz, THIS JOURNAL, **79**, 197 (1957).