Nucleophilic Ring Opening of Optically Pure (*R*)-(+)-1,2-Epoxybutane. Synthesis of New (*R*)-2-Butanol Derivatives[1]

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Optically pure (*R*)-(+)-1,2-epoxybutane has been prepared. Treatment of the epoxide with various nucleophiles produces the optically active alcohols resulting from highly selective attack at the 1 position of the epoxide. Reaction of alkyllithium compounds with the epoxide forms some high molecular weight material and conditions are described for minimizing this side reaction. Preparation of four new (*R*)-2-butanol derivatives is reported, including that of (*R*)-(+)-1-methylthio-2-butanol, which previously is unreported even as a racemate. Structure proof of the latter compound by nmr and desulfurization to 2-butanol is described.

Coke and Rice previously have prepared partially resolved (*R*)-(+)-1,2-epoxybutane by Hofmann elimination of the methiodide of (*R*)-(−)-1-dimethylamino-2-butanol.[3] The optically active amino alcohol was prepared from racemic material by recrystallization of the *O,O'*-dibenzoyl (*R*)-tartrate salt. Although the melting point and optical rotation of the salt is unchanged after the first recrystallization, we have found that the optical rotation of the liberated amine increases upon further recrystallizations. As shown in Table I, it is only after five recrystallizations of the salt that the optical rotation of the liberated amine reaches a constant value.[4]

TABLE I

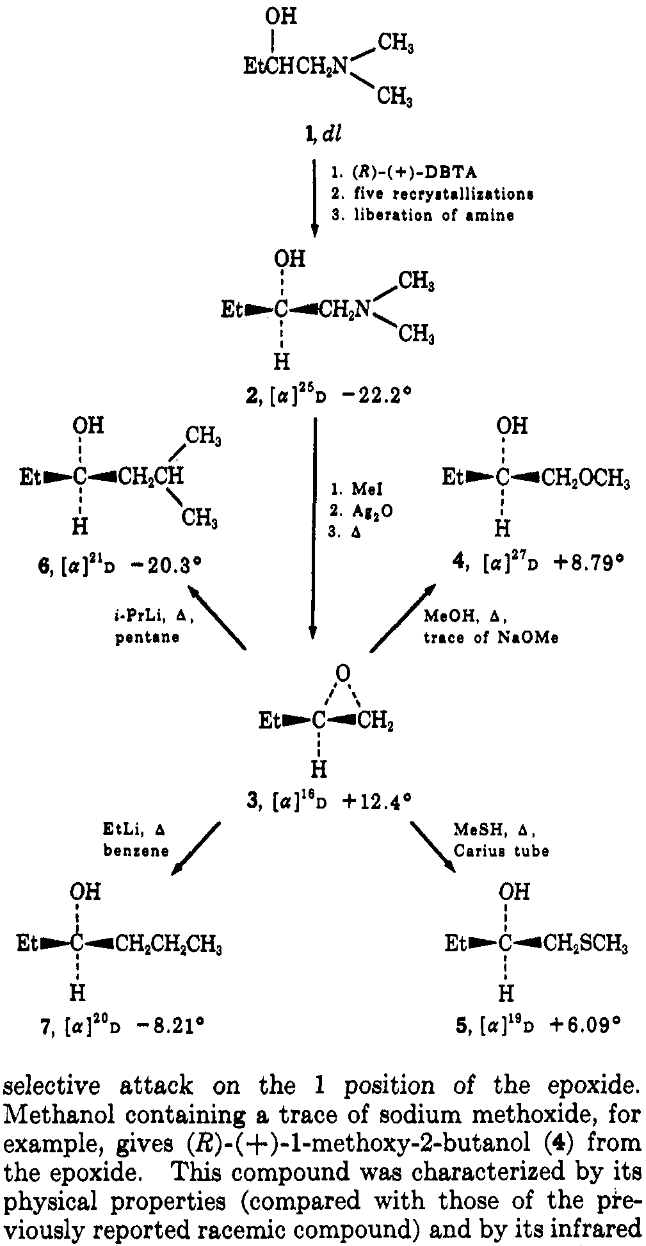
OPTICAL ROTATION OF (*R*)-(−)-1-DIMETHYLAMINO-2-BUTANOL AS A FUNCTION OF THE NUMBER OF RECRYSTALLIZATIONS OF ITS *O,O'*-DIBENZOYL (*R*)-(+)-TARTRATE SALT

Number of salt recrystallization	Ratio of ml of ethanol to g of salt	Recovery of salt, %	$[\alpha]^{25}$D of amino alcohol liberated from salt
1	5.4	76	−18.2
2	6.4	77	−20.8
3	6.4	88	−21.5
4	6.4	87	−22.0
5	6.3	84	−22.2
6	6.4	88	−22.1

Using (*R*)-(−)-1-dimethylamino-2-butanol liberated after five recrystallizations of its precursor [the *O,O'*-dibenzoyl (*R*)-(+)-tartrate salt] we have prepared (*R*)-(+)-1,2-epoxybutane (**3**) with $[\alpha]^{16}$D +12.4°. Levene and coworkers[5] have prepared the epoxide from (−)-1-bromo-2-hydroxybutane of 70% optical purity and obtained a value of $[\alpha]^{25}$D +8.75° for its optical rotation. Since the optical purity of the epoxide prepared by their method should be the same as that of the starting bromo alcohol, the optical rotation of optically pure (*R*)-(+)-1,2-epoxybutane can be calculated to be $[\alpha]^{25}$D +12.5°, which is in good agreement with our epoxide.

The reaction of various nucleophiles with (*R*)-(+)-1,2-epoxybutane was studied. As is shown in Chart I, all reactions studied produce alcohols by highly selective attack on the 1 position of the epoxide. Methanol containing a trace of sodium methoxide, for example, gives (*R*)-(+)-1-methoxy-2-butanol (**4**) from the epoxide. This compound was characterized by its physical properties (compared with those of the previously reported racemic compound) and by its infrared spectrum. It was easily distinguished from 2-methoxy-1-butanol by its boiling point.

CHART I



Formation of high molecular weight material is a serious side reaction when the epoxide is treated with alkyllithium compounds. This material presumably arises by attack of intermediate alkoxides on unreacted epoxide to produce a polyether. As would be expected, this side reaction is minimized when the

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[3] J. L. Coke and W. Y. Rice, Jr., *J. Org. Chem.*, **30**, 3420 (1965).

[4] The value of $[\alpha]^{25}$D given in ref 3 for the optical rotation of (*R*)-(−)-1-dimethylamino-2-butanol is for a sample of that amino alcohol liberated after six recrystallizations of the *O,O'*-dibenzoyl (+)-tartrate. The amino alcohol used in the preparation of (*R*)-(+)-1,2-epoxybutane in ref 3 was liberated after one recrystallization, however.

[5] P. A. Levene and A. Walti, *J. Biol. Chem.*, **94**, 367 (1931); P. A. Levene and H. L. Haller, *ibid.*, **74**, 343 (1927).

epoxide is added to the alkyllithium and epoxide excess is avoided, but yields are relatively low even under these conditions. Ethyllithium, for example, reacts with (*R*)-(+)-1,2-epoxybutane to give a 21% yield of (*R*)-(−)-3-hexanol (**7**), which was characterized by its physical properties and infrared spectrum. The boiling point of **7** easily distinguishes it from 2-ethyl-1-butanol, the isomer possible from reverse opening of the epoxide ring. Similarly, isopropyllithium gives a 19% yield of (*R*)-(−)-5-methyl-3-hexanol (**6**) from the epoxide.

Treatment of the epoxide with methanethiol under autogeneous pressure at 100° gives an 84% yield of (*R*)-(+)-1-methylthio-2-butanol (**5**). Since this compound is unreported previously in either its racemic or optically active forms and since it was synthesized under essentially neutral conditions, it was necessary to fully characterize it. The nmr spectrum of the compound showed a two-proton doublet at τ 7.5 for the methylene on sulfur and an unresolved one-proton pentet at τ 6.0 for the alcohol methine proton. The spectrum was not at all consistent with what would have been expected from 2-methylthio-1-butanol. The structure was confirmed by desulfurization of the compound with W-4 Raney nickel. Vpc analysis of the solution after reaction showed only solvent and 2-butanol. No 1-butanol nor unreacted starting material was detected.

It should be noted that all the compounds prepared from the (*R*)-(+)-1,2-epoxybutane are assigned the absolute configuration shown in Chart I, and that the optical rotations are assumed to be for the optically pure isomers. This presumes that no racemization occurred during epoxide opening. This seems reasonable because no isomeric products involving opening of the epoxide from the more hindered side were detected in any of the final products and because no mechanism is likely for simple racemization of starting material or products under the conditions used.

Experimental Section

All distillations were done through a 2-ft Podbielniak column and the boiling points are corrected. All melting points were taken on a calibrated Kofler hot stage. Infrared spectra were taken on a Perkin-Elmer Model 237B grating Infracord using neat films. Nuclear magnetic resonance spectra were taken on a Varian Model A-60 spectrometer using neat liquids and tetramethylsilane as an internal standard. Optical rotations were taken on a Perkin-Elmer Model 141 polarimeter. Vapor phase chromatography was done on an F & M Model 500 gas chromatograph using a 2-m column of 25% glyceryl–tricyanoethyl ether on Chromosorb P. All distilled compounds were shown to be pure by vapor phase chromatography.

1-Dimethylamino-2-butanol (**1**).—The procedure used was similar to that used by Coke and Rice[3] and Hill.[6] A solution of 100 g (1.39 mol) of 1,2-epoxybutane and 100 g (2.22 mol) of anhydrous dimethylamine was heated in an autoclave under autogeneous pressure at 115° for 72 hr. Unreacted starting material was removed on a steam bath and the residue was distilled to give 154 g (96%) of racemic 1-dimethylamino-2-butanol, bp 143–145° (760 mm), d^{20}_{4} 0.8399 [lit.[7] bp 142–144° (760 mm)].

(*R*)-(−)-**1-Dimethylamino-2-butanol** (**2**).—Racemic **1** was resolved with *O,O′*-dibenzoyl (*R*)-(+)-tartaric acid[8] using the procedure of Coke and Rice.[3] Table I gives the ratio of absolute ethanol to salt and the recovery of salt in the repetitive recrystallizations. Values for the optical rotation of the amine liberated[3] from each salt are given in Table I. The amine used below was that liberated after five recrystallizations of the salt, $[\alpha]^{25}_{D}$ −22.2° (*c* 2.05 g/100 ml, absolute ethanol) [lit.[3] $[\alpha]^{25}_{D}$ −21.9° (*c* 4.18 g/100 ml, absolute ethanol)].

(*R*)-(+)-**1,2-Epoxybutane** (**3**).—The methiodide[8] of **2** was subjected to Hofmann elimination with silver oxide[9] using the procedure of Coke and Rice.[3] The product from 37.5 g of **2** was distilled from anhydrous $MgSO_4$ to give 9.6 g (44%) of **3**, bp 59–62.5° (760 mm) [lit.[10] bp 61–62° (760 mm)], $[\alpha]^{16}_{D}$ +12.4° (*c* 5.98 g/100 ml, dioxane) [lit.[3] $[\alpha]^{25}_{D}$ +8.2° (*c* 4.99 g/100 ml, dioxane)].

(*R*)-(+)-**1-Methoxy-2-butanol** (**4**).—A solution of 3.0 g (0.0417 mol) of **3** in 12 ml of methanol was added slowly under nitrogen to 6 ml of refluxing methanol containing a trace of sodium methoxide. Refluxing was continued for 22.5 hr. The solution was then evaporated under vacuum and the residue was distilled to give 2.7 g (62.5%) of **4**: bp 135–136° (760 mm); n^{20}D 1.4118; d^{20}_{4} 0.9045; $[\alpha]^{27}_{D}$ +8.79° (*c* 2.76 g/100 ml, absolute ethanol); ir (neat) 3410 (broad, OH), 2810 (OCH_3), 1170 (COC), 1110 cm^{-1} (COH) [lit.[11] (of racemic material) bp 133–137° (760 mm); n^{20}_{D} 1.4114].

(*R*)-(+)-**1-Methylthio-2-butanol** (**5**).—Anhydrous methanethiol (2.0 g, 0.0417 mol) and **3** (2.0 g, 0.0278 mol) were sealed in a Carius tube cooled in Dry Ice. The tube was then heated at 100° under autogeneous pressure for 50 hr in a 600-ml autoclave containing 150 ml of MeOH to minimize the pressure difference on the Carius tube. The tube was cooled in Dry Ice, opened, and heated on a steam bath to remove unreacted starting materials. The residue was distilled to give 2.8 g (84%) of **5**: bp 179–180.5° (758 mm); $[\alpha]^{19}_{D}$ +6.09° (*c* 7.26 g/100 ml, absolute ethanol); n^{25}_{D} 1.4782; d^{20}_{4} 0.9821; nmr data given in discussion; ir (neat) 3400 (broad, OH), 1420 (SCH_2), 1315 (SCH_3), 1115 cm^{-1} (COH).

Anal. Calcd for $C_5H_{12}OS$: C, 49.93; H, 10.07. Found: C, 49.96; H, 10.21.

Desulfurization of Racemic 1-Methylthio-2-butanol.—One gram of racemic 1-methylthio-2-butanol (prepared as above, using racemic 1,2-epoxybutane) was refluxed overnight under nitrogen in ethanol containing 15 g of W-4 Raney nickel. The mixture was filtered and the filtrate was concentrated by careful distillation. Vpc analysis of the concentrate showed only ethanol and 2-butanol. No 1-butanol or starting material were detected.

(*R*)-(−)-**5-Methyl-3-hexanol** (**6**).—A solution of 5.67 g (0.079 mol) of **3** in 113 ml of pentane was added slowly and with stirring under nitrogen to 182 ml of 1.64 *M* isopropyllithium in pentane. The solution was refluxed for 48 hr and was then cooled in ice. Water (200 ml) was added slowly with stirring and the layers were separated. The pentane was washed with a small amount of water and the washing was added to the aqueous layer, which was then saturated with NaCl and extracted repeatedly with Et_2O. The ether extracts were combined with the pentane layer and dried over anhydrous Na_2SO_4. Distillation of the mixture gave 1.73 g (19%) of **6**: bp 145–147° (760 mm); $[\alpha]^{21}_{D}$ −20.3° (*c* 5.25 g/100 ml, absolute ethanol); d^{20}_{4} 0.8436; n^{20}_{D} 1.4219; ir (neat) 3350 (broad, OH), 1380 (doublet, *gem*-dimethyl), 1110 cm^{-1} (COH) [lit.[12,13] (of racemic material) bp 146–148° (760 mm); n^{20}_{D} 1.4220].

(*R*)-(−)-**3-Hexanol** (**7**).—A solution of 9.91 g (0.139 mol) of **3** in 100 ml of benzene was added slowly and with stirring under nitrogen to 515 ml of 0.81 *M* ethyllithium in benzene. The solution was refluxed for 68 hr and was then cooled in ice. Water (400 ml) was added slowly with stirring. Isolation and distillation analogous to that given for **6** gave 2.99 g (21%) of **7**: bp 133–136° (760 mm); $[\alpha]^{20}_{D}$ −8.21° (*c* 11.5 g/100 ml, absolute ethanol); ir (neat) identical with that of commercial 3-hexanol [lit.[14] bp (of racemic material) 135° (760 mm)].

Registry No.—**1**, 34487-37-1; **2**, 3760-97-2; **2** *O,O′*-dibenzoyl (*R*)-(+)-tartrate, 39010-59-8; **2** MeI, 3806-20-0; **3**, 3760-95-0; **4**, 39010-62-3; **5**, 39010-63-4; **6**, 39003-07-1; **7**, 13471-42-6; *O,O′*-dibenzoyl (*R*)-(+)-tartaric acid, 2743-38-6.

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