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Stereochemistry of the Primary Carbon. XI. Ethanolysis of Optically Active Benzyl-*α*-*d* *p*-Toluenesulfonate[1]

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The reaction of optically active benzyl-*α*-*d* tosylate with alcoholic sodium ethoxide apparently goes with complete inversion of configuration. The preparation of ethyl benzyl-*α*-*d* ether by the reaction of the alcohol with silver oxide and ethyl iodide or with potassium *t*-butoxide and ethyl iodide involves some racemization. Solvolysis of benzyl-*α*-*d* tosylate in absolute ethanol goes with complete inversion of configuration; ethanolysis and hydrolysis in 80% aqueous ethanol involve at most a few per cent. of racemization.

As part of a study of the stereochemistry of ethanolysis and acetolysis of some primary and secondary sulfonates, the simple benzyl system was of interest because it combines the low steric hindrance to displacement of a primary system with a carbonium ion stability similar to that of secondary carbonium ions.[3] In this paper we report the results of our study of the stereochemistry of ethanolysis of optically active benzyl-*α*-*d* tosylate which was made possible by the recent preparation of optically active benzyl-*α*-*d* alcohol.[4]

The benzyl-*α*-*d* alcohol used throughout this study had $\alpha^{30}\text{D}$ $-3.006 \pm 0.004°$ (l 4).[5] Preparation of the tosylate by reaction of the alcohol with tosyl chloride and alkali hydroxide[6] or sodium hydride[7] was undesirable because of the possibility of racemization in these reactions. However, the procedure used by Edgell and Parts[8] for the preparation of methyl tosylate was adapted to our preparation. This procedure, the reaction of benzyl-*α*-*d* alcohol with tosyl chloride in pyridine at $-40°$, gave 50% yields of once recrystallized benzyl-*α*-*d* tosylate often contaminated with some unreacted tosyl chloride. Because of the instability of the benzyl tosylate no attempts at further purification were made. The results to follow demonstrate that no racemization of the tosylate occurred during this preparation and that the presence of some tosyl chloride could be tolerated.

Several procedures have been used for the stereospecific conversion of alcohols to ethers. Mislow[9] has demonstrated that in some cases the reaction of an alcohol with silver oxide and ethyl bromide or iodide involves no racemization. Applied to benzyl-*α*-*d* alcohol this procedure gave ether having a lower rotation than that from other preparations. The presence in the crude product of this reaction of an ionizable iodide which may have been benzyl iodide indicates the possibility of racemizing side reactions. From the results summarized in Table I we estimate that about 14% racemization occurred in this preparation. Hence this procedure cannot be used for the stereospecific preparation of ethers without circumspection. The highest rotation for the ether was obtained by the reaction of benzyl-*α*-*d* tosylate with alcoholic sodium ethoxide. The reaction with ethoxide ion is undoubtedly a direct displacement; since the competing solvolysis has been shown also to involve little or no racemization (*vide infra*), this rotation, $[\alpha]\text{D} + 0.098 \pm 0.004°$, is taken to be of the same relative optical purity as the starting alcohol and of opposite configuration. The reaction of benzyl-*α*-*d* alcohol in *t*-butyl alcohol solution with potassium *t*-butoxide and ethyl iodide gave the ethyl ether with a slightly lower rotation.[10]

Final purification of these ethers included reaction with lithium aluminum hydride which generated a few per cent. of benzyl alcohol undoubtedly by reduction of peroxide formed by air oxidation. Indeed, the product from the potassium *t*-butoxide reaction was found after a year of storage to be somewhat decomposed and to have lost several per cent. of its optical activity undoubtedly because of reactions induced by air oxidation.

The solvolysis of benzyl-*α*-*d* tosylate about 0.15 *M* in absolute ethanol for 5-6 half-lives at 25° gave a product which was found to contain chlorine. It seems likely that ethanolysis of the contaminating tosyl chloride produces chloride ion which reacts with benzyl-*α*-*d* tosylate chloride at a rate comparable to ethanolysis of the tosylate. In both runs the optical activity of the mixture and the chlorine analysis was used to estimate the rotation of benzyl-*α*-*d* chloride as $[\alpha]_{\text{D}}$ $0.51 \pm 0.07°$ and $0.67 \pm 0.02°$, respectively. Since this product is undoubtedly of inverted configuration, alcohol and chloride of the same sign of rotation have the same configuration. Indeed, alcohol, acetate, bromide, chloride and ethyl ether of the same sign of rotation have the same configuration. The relative rotations of various benzyl derivatives are summarized in Table II. It is interesting to note that the rotations of the bromide and chloride are of comparable magnitude.

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[7] J. Kochi and G. S. Hammond, THIS JOURNAL, **75**, 3443 (1953).

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[9] K. Mislow, *ibid.*, **73**, 4043 (1951).

[10] The rotation with the mercury green line is actually higher than that of the "standard." However, the dispersion ratio, $\alpha_{5461}/\alpha_{\text{D}} = 1.32$, for this case is much higher than that of any other preparation. We consider the rotation with the sodium D line to be more accurate and that the 5461 Å. rotation in this case is suspect.

TABLE I

OPTICAL ACTIVITY OF PREPARATIONS OF BENZYL-α-*d* ETHYL ETHER

Reaction	Temp., °C.	Benzyl-α-*d* ethyl ether		
		α_D[a] (l 1)	α_{5461}[a] (l 1)	α_{5461}/α_D
ROH + *t*-BuOK + EtI	Room	−0.086 ± 0.001°	−0.113 ± 0.002°	1.32 ± 0.03
ROH + EtI + Ag_2O	Reflux	− .081 ± .002	− .092 ± .002	1.14 ± .03
ROTs + NaOEt, EtOH	Room	+ .093 ± .004	+ .108 ± .005	1.17 ± .06
ROTs, EtOH	25	+ .095 ± .002	+ .109 ± .007	1.15 ± .06
ROTs, 80% EtOH	25	+ .086 ± .004	+ .095 ± .010	1.10 ± .11

TABLE II

RELATIVE ROTATIONS AND CONFIGURATIONS OF SOME BENZYL-α-*d* DERIVATIVES

C_6H_5CHDX X	α_D (l1)	$[\alpha]_D$[a]
OH	−0.752°	−0.715°[b]
$OCOCH_3$	− .182	− .170[c]
OC_2H_5	− .093	− .098[d]
Cl		− .6[d,e]
Br	− .9	− .6[c]
$OCOC_6H_4COOH$-*o*		+ .22[d,f]

[a] Signs of rotations for same relative configuration. [b] Ref. 5. [c] Ref. 4. [d] This paper. [e] In benzyl-α-*d* ethyl ether. [f] In acetone.

The ethanolysis product was purified by reaction with lithium aluminum hydride to remove the benzyl chloride then by a treatment with phthalic anhydride and pyridine to remove alcohol; comparison of the rotations with those of the "standard" ether at the sodium D line and mercury 5641 Å. line showed the ethanolysis to involve 102 ± 5% and 100 ± 7% net inversion of configuration, respectively. The contamination by benzyl-α-*d* chloride was not expected to affect these results since this compound solvolyzes less than 1/1000 as fast as the tosylate.[11]

Benzyl-α-*d* tosylate was allowed to solvolyze in 80% aqueous ethanol for about 7 half-lives at 25°. No benzyl chloride was formed in this reaction undoubtedly because displacement by chloride ion does not compete with this faster solvolysis. The ethyl ether produced in the solvolysis showed 93 ± 6% and 87 ± 10% inversion at the sodium D and mercury 5461 Å. lines, respectively. The few per cent. of racemization is apparently real although the amount found is hardly greater than the estimated experimental error. The benzyl-α-*d* alcohol simultaneously produced in the solvolysis was isolated as the hydrogen phthalate and the rotation was compared with that of hydrogen phthalate prepared directly from the alcohol. The hydrolysis went with 96 ± 5% and 101 ± 4% inversion at the sodium D and mercury 5461 Å. lines, respectively. Hence there is no evidence for racemization in the hydrolysis reaction.

The complete inversion found in the present solvolysis in ethanol may be compared with the complete inversion also found for ethanolysis of secondary alkyl sulfonates.[12] The slightly greater racemization found for ethanolysis of benzyl tosylate compared to 2-butyl brosylate in 80% aqueous ethanol, if real, indicates that the benzyl cation is somewhat more stable than a secondary alkyl carbonium ion. The addition of an α-alkyl group to the benzylic system causes a large increase in the amount of racemization; α-phenethyl tosylate solvolyzes with 17% net inversion in ethanol,[9,13] whereas the chloride gives about 27% net inversion.[9,14] The addition of a second alkyl group apparently causes still more racemization (methanolysis of phenylmethylethylcarbinyl hydrogen phthalate gives about 10% net inversion of configuration[15]). Addition of an α-aryl group apparently results in complete racemization (methanolysis of optically active phenyl-*p*-tolylcarbinyl hydrogen phthalate gives a racemic methyl ether; however, the optical stability of the product to the reaction conditions was not determined[16]). The stereochemistry of a range of structural types may now be summarized as in Table III. The results seem to depend almost wholly on carbonium ion stability and little or not at all on the nature (*i.e.*, primary, secondary or tertiary) of the reacting center.

TABLE III

STEREOCHEMISTRY OF ETHANOLYSIS, $PhCR_1R_2X$

R_1	R_2	Net % inversion
H	H	100[a]
R	H	17–27[b]
R	R	~10[c]
Ar	H	~ 0[c]
Ar	R	~ 0[d]
Ar	Ar	~ 0[d]

[a] For X = OTs; probably also true for X = halogen or esters. [b] For X = OTs and Cl, respectively. [c] For X = hydrogen phthalate in methanol. [d] Assumed.

Experimental

Benzyl-α-*d* Alcohol and Benzyl-α-*d* *p*-Toluenesulfonate.—The preparation of the optically active compounds used in this research has been described previously.[5]

Ethyl Benzyl-α-*d* Ether. Silver Oxide Method.—A mixture of 10 ml. (0.1 mole) of benzyl-α-*d* alcohol, α^{30}_D −3.006° (l 4), 24 g. (0.10 mole) of freshly prepared dry silver oxide[17] and 100 ml. (1.34 moles) of ethyl iodide was stirred for 3 days with daily additions of a further total of 48 g. of silver oxide and 200 ml. of ethyl iodide. After refluxing for 48 hours the mixture was filtered and distilled to yield a crude product which was contaminated with about 3% of benzyl-α-*d* alcohol (infrared spectrum). The alcohol was removed by treatment with pyridine and phthalic anhydride. Distillation gave 5.4 ml. of colorless liquid, b.p. 83–84° (24 mm.), which turned a light tan color on standing for several days. This product was treated with 5 g. of lithium aluminum hydride in ether at room temperature and was recovered in the usual manner to yield 4.5 ml. of benzyl-α-*d* ethyl ether contaminated with a small amount of benzyl alcohol. This

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(12) A. Streitwieser, Jr., and A. C. Waiss, Jr., unpublished results.

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(17) H. Rapoport, *J. Org. Chem.*, **13**, 714 (1948).

material had α^{25}_{D} −0.322 ± 0.009° (*l* 4) and α^{25}_{5461} −0.382 ± 0.005° (*l* 4). After a second treatment with pyridine and phthalic anhydride, 3.1 ml. of ether was recovered, b. 81–85° (25 mm.), having α^{30}_{D} −0.161 ± 0.004° and α^{30}_{5461} −0.183 ± 0.004° (*l* 2) and $n^{25.5}_{\mathrm{D}}$ 1.4900. The infrared spectrum was identical to that of benzyl-*α*-*d* ethyl ether prepared by other methods.

A similar reaction of ordinary benzyl alcohol and ethyl iodide with silver oxide which has been stirred in the dark for a month resulted in the codistillation of a small amount of iodine with the product (identified by odor and color). The iodine was removed by washing the distillate with aqueous sodium thiosulfate. Redistillation of the colorless organic material gave a colorless product which gave a yellow-white precipitate with alcoholic silver nitrate which turned to a light tan color on standing. This experiment indicates the presence of an ionizable iodide, possibly benzyl-*α*-*d* iodide.

Potassium *t*-Butoxide Method.—This method was conceived on the presumption that benzyl alcohol is a significantly stronger acid than *t*-butyl alcohol. To a solution of potassium *t*-butoxide prepared under nitrogen from 350 ml. of dry *t*-butyl alcohol and 8 g. (0.2 g. atom) of potassium was added 10 ml. (0.1 mole) of benzyl-*α*-*d* alcohol and 27 ml. (0.35 mole) of ethyl iodide. After a few minutes the solution became milky due to the precipitation of potassium iodide. After stirring for 24 hours and dilution with water, the mixture was extracted with ether. Distillation of the washed and dried extract gave 10.5 ml. of benzyl-*α*-*d* ethyl ether contaminated with about 2% of benzyl-*α*-*d* alcohol. After treatment with pyridine and phthalic anhydride, 7.5 ml. of benzyl-*α*-*d* ethyl ether was recovered, b. 83.5–84.5° (23–23 mm.), having α^{26}_{D} −0.344 ± 0.003°, α^{26}_{5461} −0.452 ± 0.008° (*l* 4) and $n^{25.5}_{\mathrm{D}}$ 1.4909. The infrared spectrum was identical with that of benzyl-*α*-*d* ethyl ether of other preparations. After storage for a year the rotations had dropped about 7% and the infrared spectrum showed additional bands.

Sodium Ethoxide Displacement.—To a solution of sodium ethoxide prepared from 23 g. (1.0 g. atom) of sodium and 400 ml. of dry ethanol was added 12.4 g. (0.047 mole) of optically active benzyl-*α*-*d* tosylate at room temperature. After stirring for 19 hours an additional 3 g. (0.01 mole) of benzyl-*α*-*d* tosylate obtained as a second crop of the above preparation was added and the reaction mixture was stirred for an additional 5 hours. The mixture was diluted with water and extracted with ether. Distillation of the washed and dried ether extract gave 3.6 ml. of benzyl-*α*-*d* ethyl ether, α^{25}_{D} 0.179 ± 0.004°, α^{25}_{5461} 0.249 ± 0.004° (*l* 2). After treatment of this material with lithium aluminum hydride and then pyridine and phthalic anhydride, 1.0 ml. was recovered having α^{29}_{D} 0.139 ± 0.006°, α^{28}_{5461} 0.163 ± 0.007 (*l* 1.5), $n^{25.5}_{\mathrm{D}}$ 1.4900. The infrared spectrum was identical with that of benzyl-*α*-*d* ethyl ether prepared by other methods.

Solvolysis of Benzyl-*α*-*d* Tosylate in Anhydrous Ethanol.—Two runs were made. In the first run, 13.6 g. (0.52 mole) of optically active benzyl-*α*-*d* tosylate was dissolved in 350 ml. of dry ethanol previously thermostated at 25°. After the solution was maintained at 25° for 18 hours (about 5 half-lives) it was poured into 1.5 l. of water and the resulting mixture was extracted with ether. Distillation of the washed and dried extract gave 3.7 ml. of colorless liquid, b. 85–86.5° (24–25 mm.), α^{21}_{D} 0.256 ± 0.005°, α^{21}_{5461} 0.308 ± 0.013° (*l* 2). Redistillation of the product gave two fractions each having α^{28}_{D} 0.126 ± 0.004° (*l* 1). Elementary analysis showed 1.78% chlorine. The combined product was treated with 5 g. of lithium aluminum hydride; 3.2 ml. of colorless liquid was recovered, b. 84–87° (26–27 mm.), α^{25}_{D} 0.175 ± 0.004°, α^{25}_{5461} 0.215 ± 0.005° (*l* 2). The infrared spectrum showed the presence of about 2% of benzyl alcohol which was not present prior to the lithium aluminum hydride treatment. This alcohol presumably arose from reduction of peroxide which formed in the benzyl-*α*-*d* ethyl ether by air oxidation. The product was heated on a steam-bath for 6–7 hours with 10 ml. of dry pyridine, 7.5 g. of recrystallized phthalic anhydride and 10 ml. of dry benzene. This reaction mixture was poured into aqueous sodium carbonate and the resulting mixture was extracted with ether. Distillation gave the purified solvolysis product.

The solvolysis was repeated as above with a second batch of benzyl-*α*-*d* tosylate for 25.8 hours (about 6 half-lives). There was obtained 3.6 ml. of product, b. 81.5–82° (24 mm.), α^{25}_{D} 0.365 ± 0.004° (*l* 2). Elementary analysis showed 3.67% chlorine. This product was treated with lithium aluminum hydride and then pyridine and phthalic anhydride as above. The products of the two solvolyses were combined and redistilled to yield 3.1 ml. of colorless liquid, b. 87–88° (27 mm.), α^{27}_{D} 0.189 ± 0.004°, α^{27}_{5461} 0.217 ± 0.013° (*l* 2), $n^{25.5}_{\mathrm{D}}$ 1.4899; the infrared spectrum was identical with that of benzyl-*α*-*d* ethyl ether synthesized by other methods.

Solvolysis of Benzyl-*α*-*d* Tosylate in 80% Aqueous Ethanol.—To a solution of 23 g. (0.089 mole) of optically active benzyl-*α*-*d* tosylate in 1 l. of dry ethanol was added 250 ml. of distilled water. The solution was maintained at 25° for 4 hours (about 7 half-lives). The solution was neutralized with sodium hydroxide and distilled to half of its original volume. The residue was diluted with water and the resulting mixture was extracted with ether. Distillation of the washed and dried ether extract left a residue which was heated on a steam-bath for 7 hours with 22.5 g. of recrystallized phthalic anhydride, 30 ml. of dry pyridine and 25 ml. of dry benzene. The mixture was poured into aqueous sodium carbonate and extracted with ether. Distillation of the washed and dried ether extract gave 2.5 ml. of benzyl-*α*-*d* ethyl ether, b. 81–82° (23 mm.), α^{25}_{D} 0.168 ± 0.005°, α^{26}_{5461} 0.204 ± 0.009° (*l* 2). The infrared spectrum was identical with that of benzyl-*α*-*d* ethyl ether prepared by other methods. This product was treated with lithium aluminum hydride; the recovered ether had α^{27}_{D} 0.130 ± 0.003° (*l* 1.5). Since this product contained a small amount of alcohol, it was treated with pyridine and phthalic anhydride as described above; the recovered product had α^{26}_{D} 0.086 ± 0.004°, α^{27}_{5461} 0.095 ± 0.010° (*l* 1), $n^{25.5}_{\mathrm{D}}$ 1.4891.

The aqueous carbonate solution was acidified to *p*H 2 with hydrochloric acid. The crystalline benzyl-*α*-*d* hydrogen phthalate which formed on standing was filtered and recrystallized to constant rotation from benzene giving product having $[\alpha]^{29}_{\mathrm{D}}$ −0.209 ± 0.009°, $[\alpha]^{29}_{5461}$ −0.275 ± 0.008° (*c* 16.4, acetone). Benzyl-*α*-*d* hydrogen phthalate prepared directly from the alcohol used to prepare the tosylate was recrystallized from benzene to constant rotation and had $[\alpha]^{28}_{\mathrm{D}}$ 0.219 ± 0.005°, $[\alpha]^{28}_{5461}$ 0.271 ± 0.006° (*c* 19.8, acetone).

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