Asymmetric Reductions. XIII.[1a] Optically Active Benzyl-*α*-*d* Alcohol and *n*-Butyl-1-*d* Alcohol *via* Reduction by Actively Fermenting Yeast

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Abstract: Benzaldehyde-*α*-*d* and butyraldehyde-1-*d*, in addition to the previously studied trimethylacetaldehyde-1-*d*, have been reduced by actively fermenting yeast to the corresponding optically active dextrorotatory 1-deuterio alcohols. The alcohols have the opposite absolute configuration to those produced by Streitwieser, *et al.*, *via* the chemical reduction of the corresponding 1-deuterioaldehyde using (−)-isobornyloxymagnesium bromide. The rotations of the enzymically produced 1-deuterio alcohols were about 2.2 times greater than those produced by this chemical process, and we presume they are stereochemically pure or nearly so. These results indicate that the responsible enzyme system in yeast exercises its stereospecificity by virtue of a site which stereospecifically binds the aldehyde moiety but is relatively insensitive to the radical, *n*-propyl, *t*-butyl, or phenyl, attached thereto. Benzaldehyde-*α*-*d* has now been reduced by a second optically active chemical reducing agent, namely the Grignard reagent from (+)-1-chloro-2-methylbutane, to give (+)-benzyl-*α*-*d* alcohol with the same configuration and about 19 ± 2% of the optical rotation of that obtained from the yeast reduction.

The classic work of Vennesland, Westheimer, and co-workers[2] on the enzymic reduction of acetaldehyde-1-*d* with alcohol dehydrogenase and diphosphopyridine nucleotide (ADH–DPNH) has shown that the reduction is stereospecific, producing the pure (+) isomer of ethanol-1-*d*. Furthermore, the enzymic reduction of trimethylacetaldehyde-1-*d*[3] by actively fermenting yeast, presumably by the same enzyme system[4] (ADH–DPNH), gives neopentyl-1-*d* alcohol of high stereochemical purity.[5] The configuration of this neopentyl-1-*d* alcohol has been deduced from asymmetric induction experiments using an optically active Grignard reducing reagent[6] and from independent chemical transformations.[5] In order to gather additional data on the steric requirements of these enzymic reductions, we have reduced benzaldehyde-*α*-*d* and butyraldehyde-1-*d* with actively fermenting yeast. In addition, benzaldehyde-*α*-*d* has been reduced by the optically active Grignard reagent from (+)-1-chloro-2-methylbutane. The reduction products, benzyl-*α*-*d* alcohol and butyl-1-*d* alcohol, were of particular interest because their configurations had already been assigned by Streitwieser, *et al.*,[7] and correlated with other optically active compounds by Brewster.[8]

Results

Benzaldehyde-*α*-*d*[9] was reduced by actively fermenting yeast and the product, benzyl-*α*-*d* alcohol, recovered in about 50% yield. After purification both by gas chromatography and by conversion to the acid phthalate and regeneration, the optical rotation was $\alpha^{24}\text{D}$ + 1.43 ± 0.01° (neat, $l = 1$). Since this had 86% of the theoretical deuterium content, the calculated rotation for the product from reduction of benzaldehyde-1-*d* with one deuterium atom per molecule would be $\alpha^{24}\text{D}$ + 1.66 ± 0.01° or $[\alpha]^{24}\text{D}$ + 1.58 ± 0.01° (neat). Care was taken to exclude the possibility of optically active impurities. The product obtained in a control run using nondeuterated aldehyde and purified in the same way had zero rotation within experimental error, thus indicating that optically active trace impurities such as $C_6H_5CH(OH)COCH_3$, which has been reported[10] to be produced in benzaldehyde fermentation, were not present in significant amounts.

The reaction of benzaldehyde-*α*-*d* with the optically active Grignard reagent from (+)-1-chloro-2-methylbutane gave primarily the addition product, but the reduction product was isolated in 20 (run I) and 11% yield (run II). The alcohol from run I was purified by gas chromatography, and conversion to its acid phthalate was followed by regeneration of the purified benzyl-*α*-*d* alcohol. The alcohol from run II was purified only by gas chromatography. The rotations of the benzyl-*α*-*d* alcohol, corrected for one deuterium atom per molecule, were $[\alpha]^{26}\text{D}$ +0.32 ± 0.03° and $[\alpha]^{29}\text{D}$ +0.29 ± 0.02°, respectively, corresponding to an asymmetric reduction of 19 ± 2% based on the reasonable assumption that the enzymically produced benzyl-*α*-*d* alcohol is stereochemically pure.

Butyraldehyde-1-*d*[11] was also reduced by actively fermenting yeast to (+)-butyl-1-*d* alcohol. Since this had 96% of the theoretical deuterium content, the calculated rotation for the material with one deuterium

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[1] (a) We acknowledge with gratitude the support of this investigation by the National Institutes of Health of the U. S. Public Health Service (Research Grant GM 5248) and the National Science Foundation (Research Grant GP 3888). (b) Taken in part from the Ph.D. thesis of V. E. A., Stanford University, 1961.

[2] (a) H. R. Levy, F. A. Loewus, and B. Vennesland, *J. Am. Chem. Soc.*, **79**, 2949 (1957); (b) B. Vennesland and F. H. Westheimer in "The Mechanism of Enzyme Action," W. McElroy and B. Glass, Ed., The Johns Hopkins Press, Baltimore, Md., 1954, p 357.

[3] V. E. Althouse, K. Ueda, and H. S. Mosher, *J. Am. Chem. Soc.*, **82**, 5938 (1960).

[4] J. van Eys and N. O. Kaplan, *ibid.*, **79**, 2782 (1957).

[5] W. A. Sanderson and H. S. Mosher, *ibid.*, **83**, 5033 (1961); and to be published.

[6] V. E. Althouse, E. Kaufmann, P. Loeffler, K. Ueda, and H. S. Mosher, *ibid.*, **83**, 3138 (1961).

[7] A. Streitwieser, Jr., J. R. Wolfe, Jr., and W. D. Schaeffer, *Tetrahedron*, **6**, 338 (1959).

[8] J. H. Brewster, *Tetrahedron Letters*, 23 (1959).

[9] (a) A. Streitwieser, Jr., and J. R. Wolfe, Jr., *J. Am. Chem. Soc.*, **79**, 903 (1957); (b) K. B. Wiberg, *ibid.*, **76**, 5371 (1954); (c) K. B. Wiberg and R. Stewart, *ibid.*, **77**, 1786 (1955).

[10] C. Neuberg and H. Ohle, *Biochem. Z.*, **128**, 610 (1922).

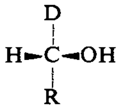
[11] (a) A. Streitwieser, Jr., and W. D. Schaeffer, *J. Am. Chem. Soc.*, **78**, 5597 (1956); (b) D. G. Hill, W. A. Judge, P. S. Skell, S. W. Kantor, and C. R. Hauser, *ibid.*, **74**, 5599 (1952).

atom per molecule is $\alpha^{27}\text{D}$ +0.364 ± 0.005° ($[\alpha]^{27}\text{D}$ +0.45°, neat).

(−)-Propylphenylcarbinol (IV, 85% stereochemically pure)[12] was converted by phosphorus oxychloride and pyridine into (+)-1-chlorophenylbutane (V) and contained an estimated 15% of the olefin, 2-phenyl-1-butene, which was not readily removed but which was not objectionable since it was optically inactive and could be removed in the gas chromatographic purification of the final product. This chloride was reduced with lithium aluminum deuteride[13] to (+)-1-phenylbutane-1-*d* (II), $\alpha^{25.2}\text{D}$ +0.57 ± 0.01° (l = 1.0, neat), which contained an estimated 0.3% impurities by gas–liquid chromatographic analysis but no detectable amount of either the parent alcohol or chloride.

Discussion

Based on the accepted mechanism of the Meerwein–Ponndorf reduction,[14] Streitwieser and co-workers[7] have assigned configuration Ia to (+)-benzyl-α-*d* alcohol and Ib to (+)-butyl-1-*d* alcohol



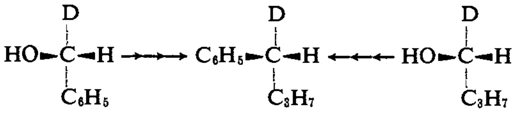
$$\begin{array}{c}\text{D}\\ |\\ \text{H}-\text{C}-\text{OH}\\ |\\ \text{R}\end{array}$$

Ia, R = C_6H_5; *S*-(+)
b, R = $n\text{-}C_3H_7$; *S*-(+)
c, R = $t\text{-}C_4H_9$; *S*
d, R = CH_3; *S*-(−)

These assignments are confirmed by Brewster's analysis[8] and by the present investigations. We have shown that Ic is the configuration of that neopentyl-1-*d* alcohol[15] obtained from the reduction of trimethylacetaldehyde-1-*d* by actively fermenting yeast. Therefore, the 1-deuterio alcohols produced by yeast reduction of the 1-deuterioaldehydes are configurationally related and have the absolute *S* configuration represented by I.

In the three yeast reductions now studied (*n*-butyraldehyde-1-*d*, trimethylacetaldehyde-1-*d*, and benzaldehyde-α-*d*), 1-deuterio alcohols of the same absolute *S* configuration have been produced. Furthermore, the reduction[2a] of acetaldehyde-1-*d* by the crystalline enzyme system, alcohol dehydrogenase–reduced diphosphopyridine nucleotide (ADH–DPNH), has produced (−)-ethyl-1-*d* alcohol, whose absolute configuration has been shown by Lemieux and Howard[16] to be *S*. The implication is that the same enzyme system is operating in each case and that its stereochemistry is defined by a site which binds the aldehyde moeity in a stereospecific manner but is relatively insensitive to the nature of the radical attached to the aldehyde function.

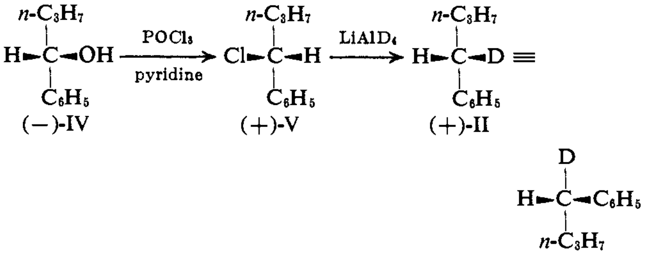
Streitwieser and Wolfe[7] have related Ia and Ib by converting both, *via* reactions whose stereochemistry is known, to the optically active deuterio hydrocarbon (−)-1-phenylbutane-1-*d* (II). They concluded that the absolute configuration of (−)-1-phenylbutane-1-*d* would be the same as (−)-1-phenylethane-1-*d*, whose absolute configuration is known.[13]



$$\begin{array}{c}\text{D}\\ |\\ \text{HO}-\text{C}-\text{H}\\ |\\ C_6H_5\end{array} \longrightarrow \begin{array}{c}\text{D}\\ |\\ C_6H_5-\text{C}-\text{H}\\ |\\ C_3H_7\end{array} \longleftarrow \begin{array}{c}\text{D}\\ |\\ \text{HO}-\text{C}-\text{H}\\ |\\ C_3H_7\end{array}$$

(−)-Ia (−)-II (−)-Ib

We have now confirmed the correctness of this conclusion by the direct synthesis of (+)-1-phenylbutane-1-*d* (II) *via* reactions IV → V → II, the stereochemistry of which is well established.[17,18]



$$\begin{array}{c}n\text{-}C_3H_7\\ |\\ \text{H}-\text{C}-\text{OH}\\ |\\ C_6H_5\end{array} \xrightarrow[\text{pyridine}]{POCl_3} \begin{array}{c}n\text{-}C_3H_7\\ |\\ \text{Cl}-\text{C}-\text{H}\\ |\\ C_6H_5\end{array} \xrightarrow{LiAlD_4} \begin{array}{c}n\text{-}C_3H_7\\ |\\ \text{H}-\text{C}-\text{D}\\ |\\ C_6H_5\end{array} \equiv \begin{array}{c}\text{D}\\ |\\ \text{H}-\text{C}-C_6H_5\\ |\\ n\text{-}C_3H_7\end{array}$$

(−)-IV (+)-V (+)-II

Although the configurational assignments of (−)-benzyl-α-*d* alcohol and (−)-butyl-1-*d* alcohol are thus confirmed, the problem of the maximum rotation of the pure enantiomorphs remains. The fact that both (−)-benzyl-α-*d* alcohol and (−)-butyl-1-*d* alcohol produced by the isobornyloxymagnesium reduction had very nearly the same relative optical purities, as shown by conversion to a common intermediate, in spite of the fact that the steric requirements for thier formation would appear to be quite different, led Streitwieser[7] to reason that these two compounds must approach stereochemical purity. It now appears that the same degree of stereoselectivity in the reduction leading to these two compounds was fortuitous, since we have found that these same alcohols prepared by enzymic reductions have a rotation about 2.2 times higher than those obtained by Streitwieser and Wolfe (Table I). It is reasonable to assume that the enzymically produced butyl-1-*d* and benzyl-α-*d* alcohols are very nearly pure isomers since it has been shown that neopentyl-1-*d* alcohol produced by yeast reduction approaches stereochemical purity.[5]

Since the two 1-deuterio primary alcohols produced by reduction with (−)-isobornyloxymagnesium had about the same optical purity, the ratios of the rotations of the chemically produced alcohols to the enzymically produced alcohols should be the same. From Table I it is seen that this ratio is 0.47 ± 0.01 for the benzyl-α-*d* alcohol and about 0.40 for the *n*-butyl-1-*d* alcohol. If all of the steps for the interrelationships to (+)-1-phenylbutane-1-*d* (II) had been free of racemization, the

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(12) J. Kenyon and S. M. Partridge, *J. Chem. Soc.*, 128 (1936).

(13) E. L. Eliel, *J. Am. Chem. Soc.*, 71, 3970 (1949).

(14) (a) W. von E. Doering and R. W. Young, *ibid.*, 72, 631 (1950); (b) L. M. Jackman, J. A. Mills, and J. S. Shannon, *ibid.*, 72, 4814 (1950).

(15) This neopentyl-1-*d* alcohol does not rotate the plane of visible light significantly,[3] although it gives a levorotatory acid phthalate $[\alpha]^{28}\text{D}$ −1.15° (c 12, acetone). It is, therefore, not possible to designate it either (+) or (−). It has the absolute *S* configuration, based on stereochemical considerations involved in the synthesis[6] and independent chemical transformations.[5]

(16) R. U. Lemieux and J. Howard, *Can. J. Chem.*, 41, 308 (1963).

(17) The reaction of phosphorus oxychloride and alcohols in the presence of pyridine proceeds with inversion (R. L. Burwell, Jr., A. D. Shields, and H. Hart, *J. Am. Chem. Soc.*, 76, 908 (1954)). This is confirmed for this particular system since the reaction of (−)-phenylmethylcarbinol with thionyl chloride in the absence of amines, a reaction which is known to go with retention of configuration, gives (−)-1-chloro-1-phenylethane,[11] while (+)-phenylmethylcarbinol with opposite configuration gives the same (−)-1-chloro-1-phenylethane with phosphorus oxychloride and pyridine.

(18) The reduction of alkyl halides and sulfonic esters with lithium aluminum hydride occurs with inversion in normal cases: (a) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962; (b) D. J. Malter, J. H. Wotiz, and C. A. Hollingsworth, *ibid.*, 78, 1311 (1956); (c) G. K. Helmkamp and B. F. Rickborn, *J. Org. Chem.*, 22, 479 (1957); (d) G. K. Helmkamp, C. D. Joel, and H. Sharman, *ibid.*, 21, 844 (1956).

Table I. Comparison of Rotations of Chemically and Enzymically Produced Deuterated Compounds

Compound	Streitwieser and Wolfe,[a,c] $[\alpha]_D$	Yeast reduction,[a,b] $[\alpha]_D$	Chemical/ enzymic factor
Benzyl-α-*d* alcohol	-0.715 ± 0.002[f]	$+1.58 \pm 0.01$	0.45 ± 0.01
Acid phthalate of benzyl-1-*d* alcohol	$+0.232 \pm 0.005$[d]	-0.49 ± 0.01	0.47 ± 0.01
n-Butyl-1-*d* alcohol	$+0.185 \pm 0.018$	$+0.471 \pm 0.005$[g]	0.40 ± 0.02
1-Phenylbutane-1-*d*	-0.78 ± 0.04	$+0.69 \pm 0.01$	1.13 ± 0.01[e]

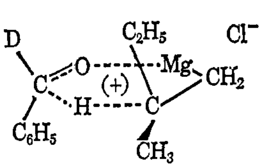
[a] All specific rotation values are at 25°, neat, unless otherwise noted, and are corrected for one deuterium atom per molecule. They are calculated on the basis that the density of the deuterated substances is as calculated from that of the nondeuterated substance, using the formula of A. McLean and R. Adams, *J. Am. Chem. Soc.*, **58**, 804 (1936), *i.e.*, benzyl-α-*d* alcohol, d^{24}_4 1.052; butyl-1-*d* alcohol, $d^{27.5}_4$ 0.8047; 1-phenylbutane-1-*d*, d^{25}_4 0.8265. [b] This paper. [c] See ref 7 and 8a; produced by reduction of the 1-deuterioaldehyde by isobornyloxymagnesium bromide. [d] Calculated from the value of $[\alpha]_D$ −0.645° for a less pure sample, and from $[\alpha]_D$ +0.205° for the acid phthalate derived from this less pure sample; all values corrected for one atom of deuterium per molecule. [e] See ref 11. [f] Rotation at 30°. [g] Rotation at 27.5°.

comparative values for the fourth example in Table I should likewise be about 0.40–0.47. It is reasonable to assume that the reactions used by Streitwieser and Wolfe for the conversion of Ia to II and Ib to II are highly stereoselective and that the stereochemical purity of the (−)-1-phenylbutane-1-*d* (II) is very nearly the same as that of the carbinols (Ia and Ib) from which it was made. On the other hand, there is excellent reason to suppose that the steps involved in the conversion of IV → V → II would be accompanied by considerable racemization.[19]

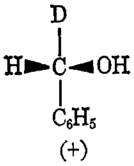
These revised rotations for (+)-benzyl-α-*d* alcohol mean that the optically active derivatives[20] of this alcohol prepared by the Meerwein–Ponndorf method from isobornyloxymagnesium will be partially racemic.

If the assumption is made that there is no racemization in Streitwieser's conversion of Ia → II and that his starting carbinol Ia or Ib is stereochemically pure, the minimum rotation for pure (−)-1-phenylbutane-1-*d* would be $[\alpha]_D$ −1.70° and is higher than that for pure (−)-phenylethane-1-*d*, $[\alpha]^{26}_D$ −0.76°, as would be expected.

The preparation of (+)-benzyl-α-*d* alcohol *via* an asymmetric reduction with (+)-1-chloro-2-methylbutane provides independent confirmation of the configuration assignment. The preferred transition state (VI) for this type of reduction has been fully discussed[3] and should result in the formation of benzyl-α-*d* alcohol with the *S* configuration (Ia). This interpretation is in complete agreement with all of the above considerations concerning the absolute configuration of (+)-benzyl-α-*d* alcohol.



VI



S-Ia

If one assumes that (+)-benzyl-α-*d* alcohol produced by yeast reduction represents a pure optical isomer, then the production of (+)-benzyl-α-*d* alcohol, α^{29}_D +0.29 ± 0.02° (neat), *via* the Grignard reduction represents an asymmetric reduction of 19 ± 2%. This result emphasizes that the difference in steric bulk between the two substituents attached to the carbonyl group is only one of two or more factors involved in determining the stereoselectivity of such asymmetric reductions since the reduction of phenyl *t*-butyl ketone by the same reagent gave approximately the same (17%) asymmetric reduction.

Experimental Section

Benzaldehyde-α-*d*. A mixture of phenylglyoxylic acid,[21] 40 g, 0.27 mole, and 3-aminooxindole hydrochloride,[22] 4 g, 0.02 mole, in a 250-ml distilling flask was treated with six, successive 10-ml portions of deuterium oxide (99.5%). After injecting each portion of D_2O through a serum cap onto the reaction mixture, it was magnetically stirred until homogeneous, and the isotopically diluted deuterium oxide was removed by heating in a bath at 50° and at pressures down to 1 mm. After the last equilibration, the temperature of the flask and contents was slowly raised to 300° at atmospheric pressure while a slow stream of nitrogen was bubbled through the mixture. Benzaldehyde-1-*d* was collected in a flask at 0° and, after removing water with a capillary pipet and drying over anhydrous magnesium sulfate, the product was distilled to give 22 g (78% yield) of a material which analyzed for 96.6 ± 1% deuterium on the aldehydic carbon by nmr,[23] and by mass spectrographic analysis[24] for 98.6 ± 1% deuterium atoms per mole. We have also made the benzaldehyde-1-*d* by the Stephen's reduction of benzonitrile according to the method of Streitwieser and

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(19) The analogous conversion under comparable conditions of methylphenylcarbinol to the corresponding chloride[17] is accompanied by 20% racemization. The lithium aluminum hydride reductions of 2-chloro-2-phenylpropanoic acid and its methyl ester go with 37 and 67% racemization,[18a] respectively, although the primary mechanism in this case may be different. Only a guess can be made at the extent of racemization for the conversions IV → V and V → II, but it is not unreasonable to assume 20% racemization in the first step and 50% racemization in the second. These assumptions would readily reconcile the discrepancy in the rotations of 1-phenylbutane-1-*d* obtained by the two methods.

(20) (a) J. L. Kice, R. H. Engelbrecht, and N. E. Powlowski, *J. Am. Chem. Soc.*, **87**, 4131 (1965); (b) A. Streitwieser, Jr., and J. R. Wolfe, Jr., *J. Org. Chem.*, **28**, 3263 (1963).

(21) T. S. Oakwood and C. A. Weisgerber, *Org. Syn.*, **24**, 16 (1944). Also available from Aldrich Chemical Co.

(22) R. E. Schachot, E. I. Becker, and A. D. McLaren, *J. Org. Chem.*, **16**, 1349 (1951); W. Lagenbeck, R. Hutschenreuter, and R. Jutteman, *Ann.*, **485**, 53 (1931). Isatin is readily converted into its oxime and catalytically reduced over platinum to 3-aminooxindole in over-all yield of 70%. Analysis by nmr shows that exchange of the C-3 hydrogen in 3-aminooxindole is complete in a few minutes in deuterium oxide at room temperature.

(23) The nmr analysis was based upon the ratio of the area of the residual aldehydic proton signal to one-fifth of the area of the aromatic proton signal. These analyses were the average of five integrations using the Varian HR 100 spectrometer. We wish to thank Dr. Lois Durham for these determinations.

(24) Mass spectrographic analyses on benzaldehyde were carried out at 12.0 and 11.5 ev on an Atlas Model CH-4 spectrometer, using the M and M − 1 peaks. At these ionization potentials the M − 1 peak is 5.5 and 4.5%, respectively, of the parent ion peak in contrast to the fragmentation using 70 ev where the M and M − 1 peaks are essentially the same intensity and thus much less useful for analytical purposes: J. D. McCollum and S. Meyerson, *J. Am. Chem. Soc.*, **85**, 1739 (1963). We wish to thank Dr. Carl Djerassi and Dr. Alan Duffield for these determinations.

Wolfe.[9a] In the first experiment, our deuterium incorporation was 0.68 deuterium atom per molecule, probably due to benzoic acid in the benzoyl chloride from which the DCl was generated. With carefully fractionated benzoyl chloride the benzaldehyde-α-*d* had approximately 0.92 deuterium atom per molecule incorporation.

Benzyl-α-*d* Alcohol. Freshly distilled benzaldehyde-α-*d* (0.97 ± 0.01 deuterium atom per molecule, 20 g), dissolved in 10 ml of ethanol, was added over a 2-hr period to a rapidly fermenting mixture of 900 g of glucose, 3.8 l of water, and 216 g of Fleishmanns bakers' yeast. After 5 hr the fermentation slackened and a slurry of 116 g of yeast in 500 ml of water was added. After 12 hr, gas evolution had ceased and the odor of benzaldehyde had disappeared. Fehling's test for unconsumed glucose was faint. The mixture was steam distilled and the first 7 l. of distillate was continuously extracted with ether. The ether extracts were dried over magnesium sulfate, the ether was removed through a fractionating column, and the residue was vacuum distilled to give 10.3 g (50% yield), bp 54° (0.1 mm). This product was purified by preparative chromatography.[25] A sample of the gas chromatographically purified material which had a slight yellow color (2.9 g) was converted to the acid phthalate by heating with phthalic anhydride (5.15 g) in dry pyridine (20 ml) for 4 hr at 100°. The reaction mixture was worked up in the usual way and the crude product (6.4 g, 93% yield, mp 90–98°) was twice recrystallized from 60:40 petroleum ether (bp 60–80°)–benzene to give 5.0 g, mp 103.5–105°, $[\alpha]^{24}$D − 0.42 (*c*14, acetone). This material (5.0 g) was hydrolyzed with 20% sodium hydroxide, the reaction mixture was steam distilled, the distillate was extracted with cyclopentane, and the extracts were dried over magnesium sulfate and distilled to give a colorless benzyl-α-*d* alcohol which on UCON Polar analytical column (5 ft × 0.25 in. at 160°) showed only a trace impurity of cyclopentane; α^{24}D + 1.43 ± 0.01° (l = 1, neat, center-filled tube). This material was analyzed for deuterium by nmr[22] and gave 0.87 ± 0.02 deuterium atom per molecule based on the relative areas of the aromatic and benzylic proton signals. By mass spectrometer[23] at 11.5 ev this gave 0.86 ± 0.01 deuterium atom per molecule, based on the relative intensities of the M and M − 1 peaks, and by duplicate combustion[26] analysis based on the density of the water formed, 0.858 ± 0.004 deuterium atom per molecule.[27]

Benzyl-α-*d* Alcohol by Grignard Reduction. To a solution of 19.3 g (0.10 mole) of freshly distilled benzaldehyde-α-*d* (0.68 deuterium atom per molecule) dissolved in 100 ml of ether was added over a 1.5-hr period 150 ml of 1.285 *N* Grignard reagent prepared from (+)-1-chloro-2-methylbutane, $\alpha^{26.5}$D +1.40° (l = 1, neat). The reaction mixture was refluxed for 1 hr and hydrolyzed with water. The residue (29 g), obtained by evaporation of the ether extracts, was distilled to give 6.9 g, bp 138° (18 mm), and a residue of 21.5 g, α^{25}D +9.0° (l = 1, neat), presumed to be addition product but which underwent dehydration on further heating. The lower boiling fraction contained 4 g (21% yield) of benzyl-α-*d* alcohol by gas chromatographic analysis. It was purified by preparative gas chromatography (UCON Polar column at 195°). This was then distilled under high vacuum in order to remove traces of UCON Polar fluid or decomposition products which might have bled from the column, to give benzyl-α-*d* alcohol, $\alpha^{26.5}$D +0.73 ± 0.03° (l = 1, neat), n^{20}D 1.5350. The infrared spectrum of this sample appeared identical with that of the benzyl-α-*d* alcohol obtained *via* fermentation of the same sample of benzaldehyde-α-*d*. However, it was further purified by conversion to the acid phthalate (90% yield, mp 103.5–104.5°, from which the benzyl-α-*d* alcohol was regenerated by basic hydrolysis to give 1.30 g (92% yield) of benzyl-α-*d* alcohol which was distilled under vacuum to give a product α^{26}D +0.16 ± 0.02° (l = 1, neat), $n^{25.6}$D 1.5350. Assuming the same deuterium content as the starting benzaldehyde-α-*d*, this is equivalent to a rotation of α^{26}D +0.23 ± 0.03°, $[\alpha]^{26}$D +0.32 ± 0.04°, for product containing one deuterium atom per molecule. The much lower rotation after purification *via* the acid phthalate cannot be ascribed to racemization since the same treatment of a sample of (+)-benzyl-α-*d* alcohol from fermentation caused no change. It must be that even in the gas chromatographically purified material a small amount of some positively rotating impurity, possibly the olefin 1-phenyl-3-methyl-1-pentene, was present. The main product of the Grignard reaction was 1-hydroxy-3-methyl-1-phenylpentane-1-*d*, bp 86–86.2° (7 mm), n^{26}D 1.5042, α^{27}D +13.05 ± 0.02° (l = 1, neat).[28] This alcohol dehydrated when an attempt was made to purify it by gas chromatography (Apiezon column, 180°). A strong hydroxyl band (3350 cm^{-1}) in the infrared spectrum disappeared in the product after chromatography. The resulting material, 1-phenyl-3-methyl-1-pentene-1-*d*, was collected, n^{25}D 1.5244, α^{25}D +45.12 ± 0.03° (l = 1, neat). The literature rotation for the nondeuterated compound is α^{15}D +44.8° (neat).[29] The retention time of this olefin on an Apiezon column was 72 min under the same conditions, the retention time of the benzyl-α-*d* alcohol was 21 min, but on the UCON Polar column used for the preparative purification, the retention times overlapped.

To ensure that the benzyl-α-*d* alcohol obtained above was not contaminated by products formed during the gas chromatography on a UCON Polar column (benzyl formate or, possibly, benzylformal), a second batch of benzaldehyde-α-*d* (0.92 deuterium atom per molecule)[23] was reduced by the Grignard reagent from (+)-1-chloro-2-methylbutane and purified by a different route. Benzyl-α-*d* alcohol (obtained in 11% yield) was separated from the reaction mixture by rapid distillation under reduced pressure. It was then purified by gas chromatography on an Apiezon column, followed by gas chromatography on a silicone grease column. The rotation of the resulting product (0.92 deuterium atom per molecule)[23] was α^{29}D +0.14 ± 0.01° (l = 0.5, neat), $[\alpha]^{24}$D 0.29 ± 0.02°. This corresponds to an asymmetric synthesis of 18 ± 2% based on $[\alpha]^{24}$D +1.58 as the rotation for pure (+)-benzyl-α-*d* alcohol.

(+)-1-Butyl-1-*d* Alcohol. Freshly distilled butyraldehyde-1-*d*[11] (6.6 g, 0.09 mole, 0.96 ± 0.02 deuterium atom per molecule)[22] in 10 ml of ethanol was added to a rapidly fermenting mixture of 900 g (5.04 mole) of (+)-glucose, 3.8 l. of water, and 900 g of Fleishmann's bakers' yeast, over a period of 5 min. Gas evolution ceased in 12 hr and the fermentation mixture was steam distilled until 2 l. was collected. This was carefully fractionated through a 30-plate glass helix packed column to remove most of the ethanol and the subsequent fractions below 100° were analyzed by vpc and found to contain 4.8 g of butyl-1-*d* alcohol (71%). This was purified on a preparative gas chromatography column[24] to give butyl-1-*d* alcohol, $\alpha^{27.5}$D +0.349 ± 0.005°[28] (l = 1, neat). Deuterium analysis by nmr showed 0.92 ± 2 deuterium atoms per molecule. Gas chromatographic analysis of this purified sample of (+)-butyl-1-*d* alcohol showed two impurities present to a maximum extent of 0.5%. One was probably isobutyl alcohol and the other water.

(−)-*n*-Propylphenylcarbinol (III). This alcohol was prepared *via* a yeast fermentation[30] from *n*-propiophenone which was purified by preparative gas chromatography.[25] The rotation of the chromatographically pure *n*-propylphenylcarbinol was $\alpha^{26.2}$D −12.18 ± 0.02° (l = 0.5, supercooled liquid). The optical purity of this material, as estimated from the extrapolated curve for the rotation *vs.* temperature of the pure isomer, was 85%.

(+)-1-Chloro-1-phenylbutane (IV). The above (−)-*n*-propylphenylcarbinol (3.2 g, 0.0213 mole) was combined with 8.3 ml (0.105 mole) of dry pyridine and 20 ml of chloroform and cooled to −12°. Into this solution was passed 0.046 mole of hydrogen chloride, generated from 50 ml of benzoyl chloride and 0.42 ml (0.023 mole) of water. The addition was complete in 30 min at which time 2 ml (0.0274 mole) of phosphorus oxychloride was added slowly with stirring to the cold solution (−12°). The addition required 1.75 hr, and the temperature was kept between −11 to −13° throughout. The reaction mixture was then allowed to warm to room temperature and after standing overnight was poured

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(25) Beckman Instruments Megachrom. Four parallel $^5/_8$ in. × 12 ft stainless steel UCON Polar columns at 185° were used.

(26) J. Nemeth, Urbana, Ill.

(27) These multiple analyses were carried out for two reasons. In two previous runs we had experienced difficulty in obtaining concordant results by nmr, by mass spectra, and by an analytical method. This analytical method was based upon the combustion of the sample to water, followed by conversion of the water to hydrogen over zinc: J. Graff and D. Rittenberg, *Anal. Chem.*, **24**, 878 (1952). This latter method was unreliable on small samples in our hands. The mass spectral method gave reproducible results only at the low ionization potentials and in at least one case the nmr analysis gave different results depending upon whether the benzylic proton signal area was compared to that of the aromatic protons or the OH protons. Furthermore, there is a discrepancy between the amount of deuterium in the starting benzaldehyde and the product benzyl alcohol which we wanted to establish with certainty.

(28) P. A. Levene and S. A. Harris, *J. Biol. Chem.*, **111**, 725 (1935).

(29) A. Klages and R. Sautter, *Ber.*, **37**, 652 (1904).

(30) R. McLeod, H. Prosser, L. Fikentscher, J. Lanyi, and H. S. Mosher, *Biochemistry*, **3**, 838 (1964).

onto ice, extracted with chloroform, washed with 85% phosphoric acid, then with water, and dried over magnesium sulfate. On removal of the chloroform at room temperature, 3.5 g (95%) of an oil remained. Infrared and vpc analysis indicated the absence of starting alcohol but showed the presence of an impurity (infrared peak at 5.95 μ) which was undoubtedly 1-phenyl-1-butene from either dehydration of the alcohol or dehydrohalogenation of the product. Attempted purification *via* gas chromatography on a UCON polar on firebrick column at 130° resulted in further decomposition to this dehydrohalogenation product in the preheater (130°) and detector sections of the gas chromatography apparatus. The crude oil was therefore distilled under high vacuum. The rotation of the product when taken immediately after distillation was $\alpha^{24.5}\text{D}$ +37.70 ± 0.02° (l = 0.5, neat) but after 26 hr had fallen to $\alpha^{23}\text{D}$ +33.65 ± 0.02° (l = 0.5, neat).

(+)-**1-Phenylbutane-1-*d* (V).** To a solution of lithium aluminum deuteride[31] (0.4 g, 0.0095 mole) in 30 ml of dry tetrahydrofuran (distilled from lithium aluminum hydride) was added 1.8 g (0.0107 mole) of the above (+)-α-chlorobutylbenzene, $\alpha^{24.5}\text{D}$ +33.65 ± 0.02° (l = 0.5, neat), in 10 ml of dry tetrahydrofuran under a dry nitrogen atmosphere. The addition was complete in 10 min and the reaction mixture was refluxed for 29 hr, then decomposed in the cold with a 50:50 mixture of tetrahydrofuran and water. After extraction with 95% pentane and drying over calcium chloride, the solvent was removed on a glass helix packed column and the residue was purified *via* gas chromatography to give 1-phenylbutane-1-*d*, $\alpha^{25.2}\text{D}$ +0.57 ± 0.01 (l = 1, neat).

Rechromatography of this sample on an analytical column showed none of the parent alcohol or chloride and approximately 0.3% of an unknown, low-boiling impurity. The infrared showed a peak at 4.65 μ (C–D) and deuterium analysis by nmr indicated 0.96 ± 0.02 deuterium atom per molecule.

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[31] Metal Hydrides, Inc., reported to be "95% pure."

The Role of Sulfene Intermediates in the Alcoholysis of Sulfonyl Halides in the Presence of Triethylamine[1]

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Abstract: Evidence for sulfene formation in the reactions of alkanesulfonyl chlorides, methanesulfonyl bromide, and methanesulfonic anhydride with triethylamine has been obtained, consisting of the formation of monodeuterated esters (in the absence of di- and trideuterated esters) when these reactions are carried out in the presence of methanol- and ethanol-*d*. The effect of the leaving group, the structure of the sulfonyl chloride, and the solvent on the deuterium content of the esters indicate competing elimination and substitution reactions between the sulfonyl halide and triethylamine, eventually giving rise to deuterated and undeuterated esters. Products obtained from the isomeric propenesulfonyl chlorides provide further evidence for this competition.

Sulfene intermediacy has received much attention recently, particularly regarding its apparent role in cycloadditions with various electron-rich olefins.[2] In nearly all cases the sulfene intermediate postulated was generated by treatment of an alkanesulfonyl chloride with triethylamine. Staudinger[3] reported that when sulfur dioxide is bubbled through a methanolic solution of diphenyldiazomethane, a high yield of methyl diphenylmethanesulfonate is obtained. They postulated an initial reaction of the diazo compound with sulfur dioxide to give diphenylsulfene which then added methanol. More recently, deMayo and co-workers[4] proposed the addition of alcohol to a sulfene for the photolytically induced transformation of an unsaturated sultone to a sulfonate ester.

From these results it seemed likely that sulfenes generated by the reaction of sulfonyl chlorides with triethylamine should also add alcohol. These reactions in the presence of alcohol-*d* should give rise to *monodeuterated* sulfonate esters. The absence of *polydeuterated* species would preclude deuterium incorporation by simple exchange.

Results

A number of sulfonyl chlorides, methanesulfonyl bromide, and methanesulfonic anhydride were treated with ordinary and deuterated alcohols in the presence of triethylamine. The reactions were carried out in an inert solvent (benzene or hexane) under anhydrous conditions. A benzene solution of the sulfonyl chloride was added over a 20-min period to a mixture of the alcohol (1.2 equiv) and triethylamine (1.3 equiv) dissolved in benzene. The reactions were worked up after stirring for 1.5 hr at room temperature. The sulfonate esters obtained were characterized by comparison of their physical properties with literature values when available and by their infrared and nmr spectra. The nmr spectra were used to determine the position of deuterium incorporated and the product ratios when mixtures were obtained. Mass spectral analysis[5] was used to determine the deuterium distribution (*mono- vs. polydeuteration*). The parent peak and the alkyl fragment obtained upon cleavage of the carbon–sulfur bond were useful in this respect. In all cases, the esters obtained from deuterio alcohols were found to be *monodeuterated* only. These spectra will be discussed in a future publication. The amount of deuteration was determined by combustion analysis.[6]

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[1] Abstracted from the Ph.D Thesis of Robert W. Campbell, Purdue University, 1966.

[2] (a) G. Stork and I. J. Borowitz, *J. Am. Chem. Soc.*, **84**, 313 (1962); (b) G. Opitz and H. Adolph, *Angew. Chem.*, 74, 77 (1962); (c) W. E. Truce, *et al.*, *J. Am. Chem. Soc.*, **84**, 3030 (1962).

[3] H. Staudinger and F. Pfenninger, *Chem. Ber.*, **49**, 1941 (1916).

[4] J. F. King, *et al.*, *Can. J. Chem.*, **41**, 100 (1963).

[5] Mass spectra were measured with a Hitachi RMU-6A instrument.

[6] Analyzed by J. Nemeth, University of Illinois.