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Stereochemistry of the Primary Carbon. I. Optically Active *n*-Butanol-1-*d*¹

BY ANDREW STREITWIESER, JR.²

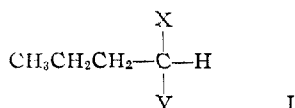
RECEIVED JUNE 1, 1953

The reaction of optically active 2-octyloxy-2-*d*-magnesium bromide with butyraldehyde in ether gave fair yields of *n*-butanol-1-*d* having a small optical rotation. The application of several criteria demonstrate the experimental significance of the optical activity which is due to hydrogen-deuterium asymmetry. 1-Bromobutane-1-*d* was prepared having a small optical activity and its rate of racemization with lithium bromide was measured. This rate corresponded to that for radiochemical exchange.

The study of the stereochemical course of many reactions has proved invaluable in determining their mechanisms, results often being obtained uniquely by this method. The requirement that the functional group being investigated be situated at an asymmetric carbon has led to the extensive use of readily resolvable secondary carbinols and their simple derivatives. However, even in mono-functional aliphatic systems, the mechanistic course of a particular reaction is often quite structure dependent as exemplified by various types of displacement reactions. Knowledge of the differences in the course of reactions of a functional group on a primary, secondary and tertiary carbon atom determined by other methods can be further enriched by application of the stereochemical approach. The recent resolution of a tertiary carbinol³ has already been of value in this direction.⁴

By definition, an ordinary primary compound is debarred from this technique. However, substitution of a deuterium atom for a hydrogen renders the primary carbon asymmetric and hence potentially optically active. That such hydrogen-deuterium asymmetry can effect appreciable optical activity has been demonstrated in theory by Fickett⁵ and experimentally in the systems ethylbenzene- α -*d*,⁶ menthane-3-*d*^{7a} and menthane-2,3-*d*₂.^{7b}

Initiating a general research program on the stereochemistry of primary compounds, our aim was the obtaining of optically active *n*-butanol-1-*d*, since butanol is a typical primary aliphatic alcohol having convenient properties and since the hydroxyl function is readily convertible to other reactive functions. Preparation of this material by a classical resolution did not appear attractive but several alternatives are available. One approach is the resolution of an asymmetric compound, I, where X is either hydroxyl or some group readily convertible stereospecifically to hydroxyl and Y is a group stereospecifically replaceable by deuterium.



(1) Presented in part at the 123rd Meeting of the American Chemical Society, Los Angeles, Calif., 1953.

(2) Atomic Energy Commission Post-doctoral Fellow, 1951-1952.

(3) W. von E. Doering and H. H. Zeiss, *THIS JOURNAL*, **72**, 147 (1950).

(4) W. von E. Doering and A. Streitwieser, *Absts.*, 119th Meeting, American Chemical Society, Boston, Mass., April, 1951, p. 45M.

(5) (a) W. Fickett, *THIS JOURNAL*, **74**, 4204 (1952).

(6) E. L. Eliel, *ibid.*, **71**, 3970 (1949).

(7)(a) E. R. Alexander, *ibid.*, **72**, 3796 (1950); (b) E. R. Alexander and A. G. Pinkus, *ibid.*, **71**, 1786 (1949).

While several such systems were considered, none appeared satisfactory. Another possible method is the introduction of a deuterium atom into butyraldehyde by a stereospecific reduction, either chemically or biochemically. The latter approach is being used successfully⁸ in the preparation of optically active ethanol-1-*d*. Our attention was centered on chemical reduction for its possibly more facile extension to other systems.

The Meerwein-Ponndorf reduction has been shown to be partially stereospecific by Doering and Young⁹ who, in one of their several examples, demonstrated the production of 6-methylheptanol-2 of 6% optical purity from the reaction of 6-methylheptanone-2 with optically pure aluminum 2-butyloxyde. Analogously, reduction of butyraldehyde with aluminum 2-octyloxyde-2-*d* would seem to be a feasible approach to a partially active butanol-1-*d*. However, in the original procedure the reducing alcohol was also used as the solvent and this implies a low yield of product based on deuterium.

A very similar oxidation-reduction reaction is well known¹⁰ between alkoxy magnesium halides and ketones. This reaction is probably mechanistically very similar to the Meerwein-Ponndorf reaction⁹ and should, therefore, also be partially stereospecific. Moreover, since these reactions can be run in ether solution, the use of equimolar quantities of reactants implies a higher yield of product based on deuterium.

Samples of 2-octanol-2-*d* of near optical purity were obtained by reduction of methyl hexyl ketone with lithium aluminum deuteride followed by resolution in the usual manner. When (+)2-octanol-2-*d* was treated with an equivalent amount of ethylmagnesium bromide and allowed to stand with an equimolar quantity of butyraldehyde in ether solution for three days, (-)butanol-1-*d* having a small but definite rotation was obtained in fair yield. The identity of the product was established by comparison of physical constants (Table I) and infrared spectrum (Fig. 1) with butanol-1-*d* prepared unequivocally by reduction of butyraldehyde with lithium aluminum deuteride.

It was, however, necessary to demonstrate conclusively that the small rotation obtained is indeed a property of the butanol-1-*d* isolated and, in particular, to demonstrate the absence of optically active impurities, although the change in sign of

(8) F. A. Loewus, F. H. Westheimer and B. Vennesland, *ibid.*, **75**, 5018 (1953).

(9) W. von E. Doering and R. W. Young, *ibid.*, **72**, 631 (1950).

(10) R. V. Shankland and M. Gomberg, *ibid.*, **52**, 4973 (1930).

TABLE I

Run	2-Octanol-2- <i>d</i> ^a α_D ($l = 0.5$), ^b deg.	Moles ^c	Butyraldehyde, moles ^c	Reaction time, days ^d	Yield, %	1-Butanol-1- <i>d</i> ^e α_D ($l = 4$), ^b deg.	d^{25}_D	n^{25}_D
D ^f	+3.79	0.1	0.1	3.5	29	-0.125 ± 0.01 ^g	1.3948
H	+3.83 ^h	.1	.2	7	45	.00 ± .01
J	+3.87	.1	.2	7	57	- .008 ± .009 ⁱ	0.8151	1.3973
L	-3.87	.1	.1	3	24	+ .105 ± .01 ^j
M	-3.51	.1	.1	3	27	+ .09 ± .01 ^k	.8167	1.3975
N	-3.69	.1	.1	3	29	+ .079 ± .007	.8166	1.3969
O	-3.94 ^h	.1	.1	3	23	+ .002 ± .005 ^l	1.3971
P	-4.01 ^m	.1	.1	3	48	.000 ± .008	.8102
Q	+3.67 ^m	.1	.05	1.7	34	- .182 ± .005	.8102
R-1 ^{n,o}	+3.19 ^m	.1	.1	1	35	- .226 ± .008	.8132	1.3970
R-2 ^{n,o}	+3.19 ^m	.1	.1	2	30	- .142 ± .004	.8097	1.3972

^a Except in runs D and R, ethylmagnesium bromide was used to prepare the octyloxymagnesium halide. ^b Neat. ^c Per 150 cc. of ether solution. ^d All reactions were run at room temperature. ^e Butanol has d^{25}_D , 0.8057; n^{25}_D 1.3971. *n*-Butanol-1-*d* prepared by reduction of butyraldehyde with lithium aluminum deuteride had d^{25}_D , 0.8170; n^{25}_D 1.3971; calculated assuming constancy of molecular volume: d^{25}_D , 0.8167. ^f Methylmagnesium iodide was used as the Grignard source. ^g Fractionation of a portion through a concentric tube column gave product having b.p. 115.9° and α_D -0.05 ± 0.01° ($l = 1$). ^h Control run: non-deuterated reactants used. ⁱ Before fractionation through the concentric tube column had α_D -0.015 ± 0.01° ($l = 4$). ^j Before fractionation through the concentric tube column had α_D +0.14 ± 0.03° ($l = 4$). ^k Before fractionation through the concentric tube column had α_D +0.08 ± 0.03° ($l = 4$). ^l $l = 2$. ^m The 2-octanol-2-*d* was only partially deuterated in the 2-position. See text and Experimental section. ⁿ Half of run R was stopped after one day, the remainder being allowed to stand an additional day. ^o *n*-Propylmagnesium bromide was used as the Grignard source. The 2-octanol-2-*d* was the unreacted material recovered from run Q by shaking the residue after removal of butanol with saturated sodium bisulfite, drying and distilling.

rotation indicates the absence of significant amounts of unreacted 2-octanol-2-*d*. Four general criteria were used, *viz.*, control experiments, reproducibility, purification and kinetic data.

Under the same conditions (Table I) the use of non-deuterated reactants produced butanol with no detectable optical activity (run O). This was considered to be a necessary but not sufficient condition for experimental significance of the observed rotations.

Runs D, L, M and N, all run under approximately the same conditions, resulted in consistent yields (24-29%) of butanol-1-*d* having comparable optical activity. Regardless of the source of the optical activity, reproducible results could, at least, be obtained. Although in all cases a slight deficiency of alkylmagnesium halide was used in converting the octanol to the O-magnesium halide, it should be noted that in several runs methylmagnesium iodide and propylmagnesium bromide were used for this purpose, the latter reagent in particular excluding the possibility that optical activity arose from the reaction of a small amount of unreacted alkylmagnesium halide with butyraldehyde in the asymmetric solvent to give a partially active secondary carbinol since in this case the necessarily racemic heptanol-4 would have resulted.

Runs P, Q and R resulted in butanol having less than one atom of deuterium per molecule, the density of the product formed in run P, for example, corresponding to 0.41 atom of deuterium per molecule. The 2-octanol-2-*d* used in these examples was obtained by reduction of octanone-2

with sodium and deuterioacetic acid in a manner similar to that used by Hauser, *et al.*,¹¹ for the reduction of esters. Apparently the greater lability of the hydrogens alpha to the carbonyl group in the ketone caused extensive exchange with the deuterioacetic acid resulting in dilution of the deuterium actually introduced into the 2-position. The use

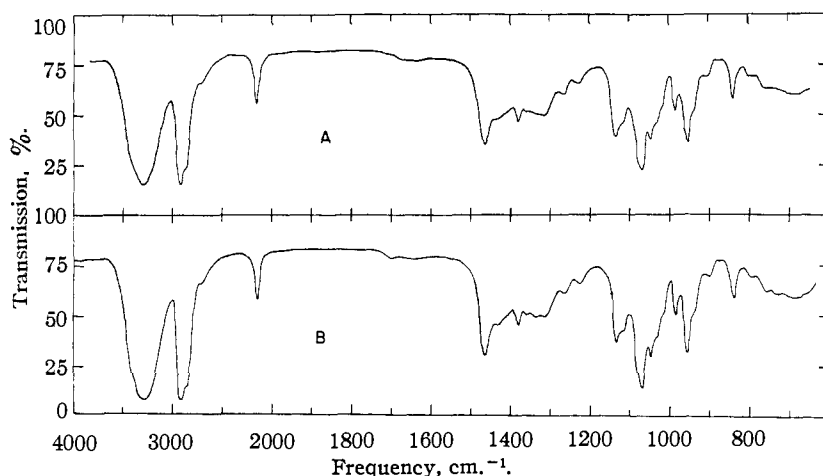


Fig. 1.—Infrared spectra: A, *n*-butanol-1-*d* prepared by reduction of butyraldehyde with lithium aluminum deuteride; B, *n*-butanol-1-*d*, α_D +0.079 ± 0.007° ($l = 4$), from run N.

of this material may therefore be questionable.

Although the reaction time for most of the runs was three days, run R demonstrates that a higher rotation without a sacrifice in yield can be obtained by a shorter reaction time. In this connection it is interesting to note that the oxidation-reduction systems primary alcohol-aldehyde and secondary alcohol-ketone are slower than the secondary alcohol-aldehyde. This is undoubtedly a reflection of the fact that while the first two re-

(11) D. G. Hill, W. A. Judge, P. S. Skell, S. W. Kantor and C. R. Hauser, *THIS JOURNAL*, **74**, 5599 (1952).

actions are thermoneutral, the last is exothermic by some 36 kcal./mole.¹²

In general, butanol-1-*d* was isolated by distillation of the reaction mixture through a Vigreux column followed by redistillation of the butanol fraction through the same column. The control run O shows that this procedure suffices to remove all traces of unreacted octanol. In runs D, J, L and M the product was further distilled through a concentric tube column rated at seventy plates. In none of these cases did this additional purification procedure materially alter the magnitude of the original rotations (Table I). Further purification of the butanol-1-*d* through the preparation of crystalline derivatives is under study.

Reaction of phosphorus tribromide with butanol-1-*d* gave 1-bromobutane-1-*d* of opposite sign of rotation. In the presence of the hydrogen bromide produced in the reaction, the butyl bromide formed would be expected to racemize more or less readily. It was indeed found that the relative magnitude of the optical activity of the product was quite variable (Table II).

TABLE II

Source	CH ₃ CH ₂ CH ₂ CHDOH		CH ₃ CH ₂ CH ₂ CHDBr	
	Butanol-1- <i>d</i> α _D (<i>l</i> = 4, neat), deg.	Yield, %	1-Bromobutane-1- <i>d</i> α _D (<i>l</i> = 2, neat), deg.	
L	+0.09 ± 0.01	48	-0.085 ± 0.01	
L	+ .09 ± .01	40	- .19 ± .02	
N	+ .079 ± .007	48	- .138 ± .007	
R-1	- .226 ± .008	32	+ .067 ± .006	

One demonstration of optical activity as a unique property involves the determination of the rate of some reaction at the asymmetric center by follow-

ing the change in optical rotatory power involved and the comparison of this rate with that obtained by a non-stereochemical method. The equality of the rate of displacement of 2-iodooctane with iodide ion in acetone, obtained by following the racemization when optically active haloalkane was used, with the rate obtained by following the loss of radioactivity of iodide ion, when radioactive iodide ion was used, was one of the early pieces of evidence supporting the hypothesis that each displacement was accompanied by an inversion of configuration.¹³ If one makes the justifiable assumption that the same hypothesis is true also for primary halides the rate of racemization of 1-bromobutane-1-*d* with lithium bromide should be equiv-

alent to the rate of radioactive exchange with lithium radiobromide. The second-order rate constant for displacement of *n*-butyl bromide with lithium radiobromide in 90% aqueous acetone at 25° found by Le Roux and Sugden¹⁴ is 3.3×10^{-5} l. mole⁻¹ sec.⁻¹.

When optically active 1-bromobutane-1-*d* was maintained at 25° with 0.1 *M* lithium bromide in 90% aqueous acetone, it gradually racemized. From the optical rotations of the bromide used (α₀) and that recovered after time *t* (α_{*t*}), a second-order rate constant could be calculated from the equation

$$k = \frac{2.303}{2c_{\text{LiBr}} \times t} \log \frac{\alpha_0}{\alpha_t}$$

where *c*_{LiBr} is the concentration of lithium bromide used. The results of three such experiments are recorded in Table III. The weighted average of the three results is $(3.0 \pm 0.5) \times 10^{-5}$ l. mole⁻¹ sec.⁻¹ in excellent agreement with Sugden's radiochemical results. Figure 2 contains the three observed points with their estimated errors. Through these points has been drawn a line corresponding to Sugden's value of 3.3×10^{-5} . The agreement is in itself good evidence for the significance of the optical rotations. Furthermore, had the optical activity been due to a secondary aliphatic bromide impurity, the slope in Fig. 2 would have been less than or equal to that for isopropyl bromide, a typical secondary bromide, the calculated¹⁵ slope of which is shown as a dashed line. Such slopes are well outside the experimental error and, in fact, if the optical activity were due to secondary bromide, virtually no change in rotation would have been observed under the conditions used.

TABLE III

RACEMIZATION OF OPTICALLY ACTIVE 1-BROMOBUTANE-1-*d* IN 90% AQUEOUS ACETONE, 0.1 *M* IN LITHIUM BROMIDE, AT 25.0 ± 0.1°

1-Bromobutane-1- <i>d</i> used			1-Bromobutane-1- <i>d</i> recovered			
α _D (<i>l</i> = 2), ^a deg.	<i>n</i> _D ^b	Time, hr.	Yield, %	α _D (<i>l</i> = 1), ^a deg.	<i>n</i> _D ^b	Calcd. <i>k</i> × 10 ⁻⁵ , l. mole ⁻¹ sec. ⁻¹
-0.16 ± 0.01	...	25.5	61	-0.085 ± 0.015 ^c	1.4372	3.6 ± 1.1
- .138 ± .007	1.4344	30	70	- .039 ± .007	1.4372	2.6 ± 0.9
+ .067 ± .006	1.4339	50	61	+ .012 ± .004	1.4353	2.9 ± 1.0

^a Neat. ^b *n*_D of *n*-butyl bromide is 1.4368. ^c *l* = 2.

ing the change in optical rotatory power involved and the comparison of this rate with that obtained by a non-stereochemical method. The equality of the rate of displacement of 2-iodooctane with iodide ion in acetone, obtained by following the racemization when optically active haloalkane was used, with the rate obtained by following the loss of radioactivity of iodide ion, when radioactive iodide ion was used, was one of the early pieces of evidence supporting the hypothesis that each displacement was accompanied by an inversion of configuration.¹³ If one makes the justifiable assumption that the same hypothesis is true also for primary halides the rate of racemization of 1-bromobutane-1-*d* with lithium bromide should be equiv-

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Experimental¹⁶

2-Octanol-2-*d*.—To 5.0 g. of lithium aluminum deuteride (Metal Hydrides, Inc., Beverly, Mass.) in 500 cc. of dry ether was added 64 g. of freshly distilled octanone-2. After

(14) L. J. Le Roux and S. Sugden, *ibid.*, 1279 (1939).

(15) From the data of G. A. Elliott and S. Sugden, *ibid.*, 1836 (1939). There is an arithmetic error in this paper. Recalculation using their data demonstrates that the rate constants are actually given as $k \times 10^6$, not $k \times 10^5$ as recorded in their tables.

(16) Two polarimeters were used in this research. The Schmidt and Haensch instrument at M.I.T. could be read to 0.01° and errors are given as at least this quantity. The Rudolf polarimeter at California could be read to 0.001° and the errors are given as <0.01°. Under favorable conditions reproducibility on this instrument was better than 0.004°. Experimental errors are derived as the average deviations of a large number of careful readings. All rotations are given for the homogeneous liquid (neat).

(12) In terms of gas phase free energies of formation taken from N. A. Lange, "Handbook of Chemistry," 8th Ed., Handbook Publishers, Inc., Sandusky, O., p. 1671.

(13) E. D. Hughes, F. Juliusberger, S. Masterman, B. Topley and J. Weiss, *J. Chem., Soc.*, 1525 (1935).

completion of the addition, the viscous solution was refluxed with stirring for several hours. On cooling, concentrated hydrochloric acid was added until the inorganic salts precipitated. The ether solution was poured off and washed successively with dilute hydrochloric acid, water and 10% sodium carbonate, then dried over anhydrous potassium carbonate. After removal of the ether on a steam-bath the residue was distilled through a silvered, vacuum jacketed Vigreux column fitted with a partial takeoff head (used throughout this work), collecting 59.6 g. (91.1%) having b.p. 175–178° and d_{25}^{25} , 0.8220. Octanol-2 has d_{25}^{25} , 0.8149. The calculated value for 2-octanol-2-*d* assuming constancy of molecular volume is d_{25}^{25} , 0.8212. This material was resolved in the usual way.¹⁷

Partially Deuterated Octanol-2.—The procedure was essentially that of Hauser, *et al.*¹¹ To 128 g. (1.0 mole) of freshly distilled octanone-2 in 1 l. of dry ether was added simultaneously, in portions, 46 g. (2.0 g. atom) of sodium in small pieces and 122 g. (2.0 moles) of deuterioacetic acid.¹¹ After stirring for two days the unreacted sodium (2 g.) was removed by filtration through a buchner funnel (no filter paper). The ethereal filtrate was shaken with water to remove the solid sodium acetate and was dried over anhydrous potassium carbonate. The ether was removed on a steam-bath. The residue on distillation through a Vigreux column produced 110 g. (84%) of 2-octanol, b.p. 177–179°, d_{25}^{25} , 0.8241. The residue of this distillation gave a high boiling condensation product which was not further investigated (b.p. 153° at 2.8 mm.). This octanol was resolved¹⁸ and used in runs P, Q and R.

Reduction of Butyraldehyde with 2-Octyloxy-2-*d*-magnesium Halide.—These reductions were all performed in more or less the same way and are typified by the procedure used in run N. To the Grignard reagent prepared from 13.7 g. of ethyl bromide and 3.0 g. of magnesium in 100 cc. of ether still containing traces of water was added 16.5 g. (0.126 mole) of 2-octanol-2-*d* having α_D -3.69° ($l = 0.5$). The resulting solution was filtered through glass wool or a sintered glass funnel into a glass-stoppered graduate. After the careful addition of 9.1 g. (0.126 mole) of freshly distilled butyraldehyde and dry ether to a total volume of 190 cc., the graduate was stoppered and shaken with cooling. Mixing was accompanied by the evolution of heat. After standing at room temperature for three days the mixture was decomposed by the addition of dilute hydrochloric acid. The ether layer was separated and washed successively with dilute hydrochloric acid, water and saturated sodium bicarbonate. After drying over anhydrous sodium sulfate or potassium carbonate ether was removed on a steam-bath. The residue was distilled through the Vigreux column collecting 6.4 cc. of b.p. 95–123°. In some of the runs, this first distillation was conducted *in vacuo*, the low boiling products being collected in a Dry Ice trap. The foreruns always contained water, probably from the thermal dehydration of condensation products. The distillate was dried with potassium carbonate and redistilled, two fractions being collected: 1, b.p. 102–116°, 1.3 cc., α_D $+0.034 \pm 0.007^\circ$ ($l = 2$); 2, b.p. 116–117°, 2.3 cc., α_D $+0.079 \pm 0.007^\circ$ ($l = 4$), d_{25}^{25} , 0.8166. The infrared spectrum was taken on a Perkin-Elmer model 21 spectrometer as a thin film and is recorded in Fig. 1. The spectra of the products from most of the runs were taken. They were all essentially the same except for the partially deuterated butanols. In these cases the C–D band at 2155 cm^{-1} was less intense and a new band appeared at 2370 cm^{-1} , probably due to deuterium in another part of the molecule. There was essentially no change in the remainder of the spectrum.

In runs D, J, L and M the product was redistilled through a concentric tube column (E. L. Wheeler Co., Santa Monica Calif.) rated at 70 plates. The optical rotations before and after this distillation, given in Table I, showed no important differences.

In one run the residue after removal of the butanol fraction was distilled under reduced pressure. The boiling point and refractive index rose continually with no evidence of distinct fractions after those corresponding to octanone and octanol. From a relatively large fraction having b.p. 104–110° at 90 mm., n_D^{20} 1.4161, a dinitrophenylhydrazone was prepared which gave orange silky needles from alcohol, m.p. 56.0–57.5°. The dinitrophenylhydrazone of octan-

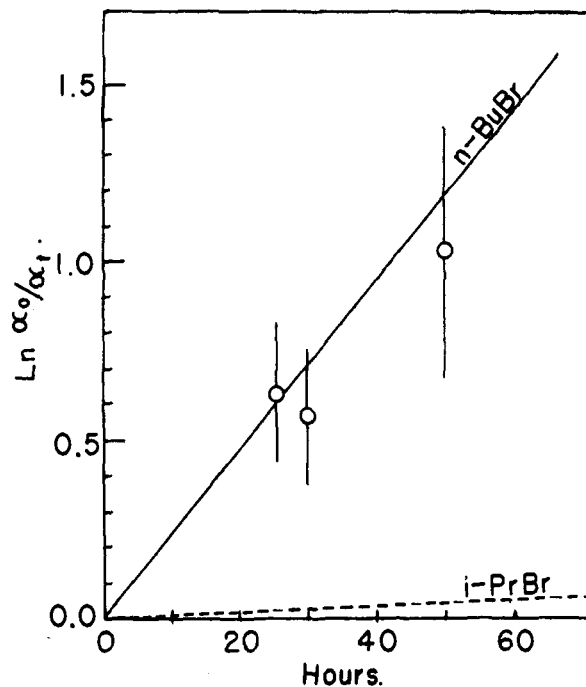


Fig. 2.—Rate of racemization of 1-bromobutane-1-*d* with 0.1 *M* lithium bromide in 90% aqueous acetone at 25°. ϕ , experimental points with estimated uncertainties. The solid line is that calculated for *n*-butyl bromide. The dashed line is that calculated for isopropyl bromide. Both slopes were calculated from the radiochemical data of Sugden, *et al.*^{14,15}

one-2 has m.p. 59.5–60.5°; the mixed m.p. was 58.0–59.0°.

The control experiment (run O) was performed in the same manner using non-deuterated octanol-2 having α_D -3.94° ($l = 0.5$). After a single redistillation of the butanol fraction (b.p. 94–120°) of the first distillation, there was obtained 23% of butanol having b.p. 116–117° and α_D $+0.002 \pm 0.005^\circ$ ($l = 2$). The forerun of this distillation, b.p. 104–115°, had α_D $+0.001 \pm 0.004^\circ$ ($l = 2$).

***n*-Butanol-1-*d*.**—To 1.0 g. of lithium aluminum deuteride in dry ether was added 7.2 g. (0.1 mole) of freshly distilled butyraldehyde. The mixture was decomposed with dilute hydrochloric acid. The ether layer was washed with water, then sodium carbonate and dried over anhydrous potassium carbonate. After removal of ether on a steam-bath, the residue was distilled producing 2.4 g. of butanol-1-*d* (32%) with b.p. 117°, d_{25}^{25} , 0.8170, n_D^{20} 1.3971. The infrared spectrum is reproduced in Fig. 1.

Optically Active 1-Bromobutane-1-*d*.—The preparations are typified by the following: A portion of the butanol-*d* from run N (1.63 g., 0.021 mole) having α_D $+0.079 \pm 0.007^\circ$ ($l = 4$) was cooled in Dry Ice. Phosphorus tribromide (2.0 g., 0.0074 mole) was added. The flask was equipped with reflux condenser and drying tube and then warmed slowly in a water-bath. After the initial exothermic reaction accompanying the thermal mixing of the two layers, the mixture was refluxed for one minute. By this time the copious evolution of hydrogen bromide had more or less subsided. Cold water was added and carrying out the following operations in a centrifuge tube, layers being separated by pipetting after centrifugation, the butyl bromide layer was washed with cold water, then cold 10% sodium carbonate. After drying with sodium sulfate the butyl bromide was drawn off and distilled from a micro-distilling flask yielding 1.44 g. (48%) having b.p. 96–103°, n_D^{20} 1.4340 and α_D $-0.138 \pm 0.007^\circ$ ($l = 2$).

The procedure was checked with ordinary butanol, the infrared spectrum of the product obtained being identical with that of butyl bromide (Eastman Kodak Co.). In the last example in Table II, heating of the mixture was accomplished with a micro-burner. The resulting local superheating apparently caused more extensive racemization.

(17) A. W. Ingersoll in R. Adams, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 400.

Kinetics of Exchange.—These experiments were carried out at widely separated intervals but differed only in minor details. The first example is typical. 1-Bromobutane-1-*d* (1.83 g.) was made up to 100 cc. with 90% aqueous acetone. A 0.2 *M* solution of lithium bromide was prepared by dissolving 4.343 g. (0.0500 mole Mallinckrodt NF Grade, dried at 110°) in 90% aqueous acetone to a volume of 250 cc. After equilibration of each solution in a 25° thermostat overnight, 100 cc. of each solution was mixed and maintained at 25.0 ± 0.1° for 25.5 hours. The mixture was poured into 200 cc. of iced water and extracted with four 50-cc. portions of pentane. After washing with cold water and drying with anhydrous sodium sulfate, the pentane was removed through a Vigreux column. Distillation of the residue from a micro-distilling flask yielded 1.11 g. (61%

recovery), b.p. 94–102°, having $\alpha_D -0.04 \pm 0.01^\circ$ ($l = 1$), $\alpha_D -0.085 \pm 0.015^\circ$ ($l = 2$), $n_D^{20} 1.4368$, corresponding to a second-order rate constant of $(3.6 \pm 1.1) \times 10^{-5}$ l. mole⁻¹ sec.⁻¹. Results of the other runs are given in Table III.

Acknowledgments.—The author wishes to thank Professor John D. Roberts for his interest in this work and for the hospitality of his laboratories during his stay at M.I.T. He is grateful also to Professor Frank H. Westheimer, Dr. Frank Loewus and Dr. B. Vennesland for communications on the progress of their work.⁸

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[CONTRIBUTION FROM THE DEPARTMENTS OF BIOCHEMISTRY AND CHEMISTRY, UNIVERSITY OF CHICAGO]

Enzymatic Synthesis of the Enantiomorphs of Ethanol-1-*d*^{1,2}

BY FRANK A. LOEWUS, F. H. WESTHEIMER AND BIRGIT VENNESLAND

RECEIVED JUNE 5, 1953

With the use of deuterium as a tracer, it has been possible to show that the reduction of acetaldehyde to ethanol, catalyzed by yeast alcohol dehydrogenase, is stereospecific. Thus the enzymatic reduction of CH₃CDO by reduced diphosphopyridine nucleotide (DPNH) yields one pure enantiomorph of CH₃CDHOH, and the enzymatic reduction of CH₃CHO by DPND yields the other enantiomorph, CH₃CHDOH. Although neither stereoisomer was obtained in quantity large enough to permit a polarimetric determination of optical rotation, the stereochemical purity of each isomeric alcohol was demonstrated by observing the specific products of its enzymatic reoxidation. One enantiomorph was further transformed into the other by a stereochemical ("Walden") inversion of its *p*-toluenesulfonyl ester.

Introduction

The mechanism of displacement reactions has been elucidated in large part by observing the stereochemical changes which accompany the reactions of secondary alcohols and of their derivatives.³ In only two instances have the stereochemical changes been observed which accompany the solvolysis of a derivative of a tertiary alcohol.⁴ Prior to the discovery of deuterium, asymmetric primary carbon atoms were of course unknown. Even subsequently the mechanism of reaction of derivatives of primary alcohols has necessarily been determined by inference, since primary alcohols with an asymmetric α -carbon atom (*e.g.*, CH₃CHDOH) were only available as racemic mixtures.

Our previous tracer studies⁵ of the oxidation of ethanol by diphosphopyridine nucleotide (DPN⁺) in the presence of yeast alcohol dehydrogenase had demonstrated that in this reaction, hydrogen (or

deuterium) is transferred directly and reversibly from the α -carbon of the ethanol to DPN⁺ according to equation 1



The transfer was also shown to be sterically specific for the reduced carbon atom of the DPN, and it seemed possible that it might likewise be sterically specific for the ethanol, since those pyridine nucleotide dehydrogenases which react with secondary alcohols (*e.g.*, lactic dehydrogenase, malic dehydrogenase, *etc.*) generally show steric specificity for the substrate.

This paper presents evidence that the enzymatic reduction of acetaldehyde is, in fact, stereospecific. The use of yeast alcohol dehydrogenase (hereafter abbreviated ADH) to prepare both pure enantiomorphs of ethanol-1-*d* is also described. Although these materials have not been obtained in quantity sufficient to allow the polarimetric determination of their specific rotation, the individuality of the two enantiomorphs has been demonstrated by the difference in products obtained on their enzymatic reoxidation. This enzymatic synthesis of the enantiomorphs of ethanol-1-*d*, like the earlier enzymatic synthesis of asymmetric citric acid,⁶ extends the range of utility of Pasteur's biochemical method for the preparation of optically active compounds. Finally, the stereochemical inversion of one of the enantiomorphs of ethanol-1-*d* to the other has been accomplished chemically by way of the *p*-toluenesulfonyl ester of one of the alcohols. The enantiomorphs of ethanol-1-*d* therefore provide a powerful tool for the investigation of the stereochemistry of reactions at a primary carbon atom.

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(1) This investigation was supported in part by a research grant G-3222 from the National Institutes of Health, U. S. Public Health Service, and by the Dr. Wallace and Clara A. Abbott Memorial Fund of the University of Chicago.

(2) Presented in part at the 123rd meeting of the American Chemical Society, March 1953 (Abstracts of Papers 19C) and in part at the meeting of the Federation of American Societies for Experimental Biology (*Federation Proc.*, **12**, 289 (1953)).

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