Stereochemistry of the Primary Carbon. XV. Preparation of Optically Active Ethanol-1-*d* by Asymmetric Induction and Its Absolute Configuration[1,2]

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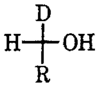
Ethanol-1-*d* of partial optical purity has been prepared by reduction of acetaldehyde with isobornyloxymagnesium-2-*d* bromide. The (−) alcohol was shown to have the *S* configuration by displacement of its *p*-nitrobenzenesulfonate ester with methyl acetoacetate followed by hydrolysis and reduction to (*R*)-(+)-pentane-2-*d*. (*S*)-(−)-Pentane-2-*d* was prepared by reduction of the methanesulfonate of (*R*)-(−)-2-pentanol with lithium aluminum deuteride.

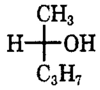
The enantiomers of ethanol-1-*d* were first prepared by Loewus, Westheimer, and Vennesland[3] by reduction of acetaldehyde-1-*d* with reduced diphosphopyridine nucleotide. The optical purity of the enantiomers was ingeniously established and, later, enough of one enantiomer was isolated for measurement of its optical rotation as [α]D −0.28 ± 0.03°.[4] During this same period we had prepared optically active butanol-1-*d* by the partially asymmetric reduction of butyraldehyde with the magnesium halide salt of an optically active secondary deuterio alcohol.[5] From the presumed mechanism of this reduction we concluded[6] that (+)-butanol-1-*d* has the *S* configuration (Ia).



$$\begin{array}{ccc} & \mathrm{D} & \\ \mathrm{H} & + & \mathrm{OH} \\ & \mathrm{R} & \end{array}$$

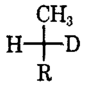
(*S*) I

a, R = C_3H_7-(+)
b, R = CH_3-(−)
c, R = CH_2COCH_3-(−)



$$\begin{array}{ccc} & \mathrm{CH_3} & \\ \mathrm{H} & + & \mathrm{OH} \\ & \mathrm{C_3H_7} & \end{array}$$

(*S*)-(+) II



$$\begin{array}{ccc} & \mathrm{CH_3} & \\ \mathrm{H} & + & \mathrm{D} \\ & \mathrm{R} & \end{array}$$

(*S*) III

a, R = C_3H_7-(−)
b, R = C_2H_5-(−)
c, R = CH_2COCH_3-(−)

Among the secondary alcohols, methylalkylcarbinols of the same sign of rotation correspond generally to the same configuration.[7] It was originally assumed that this same correspondence might extend to the series of primary deuterioalcohols[4] but Brewster concluded instead, on the basis of his semiempirical theory of optical activity, that ethanol-1-*d* and butanol-1-*d* of the same sign of rotation have opposite configurations.[8] In this paper we report the confirmation of Brewster's conclusion by the conversion of ethanol-1-*d* to pentane-2-*d* in agreement with the independent establishments of the absolute configuration of ethanol-1-*d* by Lemieux and Howard[9] and by Weber, Seibl, and Arigoni.[10] In a subsequent paper,[11] this configuration is related to that of butanol-1-*d* by its conversion also to pentane-2-*d*.

A convenient preparation of optically active butanol-1-*d* was shown previously[12] to result from the reduction of butyraldehyde by the Grignard salt of the mixed deuterated isoborneol and borneol prepared by reduction of natural (+)-camphor with lithium aluminum deuteride. This method gives a partially deuterated alcohol having a rotation that corresponds to [α]D +0.17° for fully deuterated butanol-1-*d*. This level of optical activity can be obtained reproducibly although the product may have varying deuterium content.[13]

When this procedure is applied to acetaldehyde, extensive condensation occurs perhaps because the alkoxymagnesium halide functions as a Lewis acid or base catalyst. Nevertheless, the use of a large excess of acetaldehyde added at intervals during the reaction did afford after purification by glpc a fair yield of optically active ethanol containing 0.37 atom of deuterium and having a rotation corrected to fully deuterated ethanol-1-*d* of [α]D −0.123 ± 0.025°. Based on the enzymatically prepared alcohol our product is 44 ± 9% optically pure. The low deuterium level of the product indicates further oxidation–reduction during the long reaction period. Because of the extensive condensation, the reaction with acetaldehyde was not as satisfactory as our earlier reactions with butyraldehyde[12] and probably does not represent a kinetically controlled chemical reaction or optical purity.

It is significant that the sign of rotation of this product is opposite that of butanol-1-*d* prepared by the same method. If our thoughts concerning the mechanism of the asymmetric reduction are correct, both alcohols should have the same configuration.

The ethanol-1-*d* was converted to the crystalline *p*-nitrobenzenesulfonate which was treated with methyl acetoacetate and sodium methoxide followed by hydrolysis and decarboxylation to 2-pentanone-4-*d* having [α]D +0.25 ± 0.03.[14] Since this sequence involves one displacement reaction on the optical center, the net result is a single inversion of configuration. Clemmensen reduction of the ketone gave pentane-2-*d*, [α]D +0.19 ± 0.06°,[14] based on the optical purity of ethanol-1-*d*, optically pure pentane-2-*d* should have [α]D +0.43 ± 0.16°.

2-Pentanol ([α]D −1.769°, 16.1% optically pure)[15] was converted to the methanesulfonate and reduced with lithium aluminum deuteride to give pentane-2-*d*, [α]D −0.067 ± 0.004°; the corresponding rotation from optically pure 2-pentanol is −0.42 ± 0.03°.

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[1] This research was supported in part by a grant from the Petroleum Research Fund of the American Chemical Society.

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[4] H. R. Levy, F. A. Loewus, and B. Vennesland, *ibid.*, **79**, 2949 (1957).

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

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[8] J. H. Brewster, *Tetrahedron Letters*, No. 20, 23 (1959).

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

[10] H. Weber, J. Seibl, and D. Arigoni, *Helv. Chim. Acta*, **49**, 741 (1966).

[11] Paper XVII: A. Streitwieser, Jr., I. Schwager, L. Verbit, and H. Rabitz, *J. Org. Chem.*, **32**, 1532 (1967).

[12] A. Streitwieser, Jr., and W. D. Schaeffer, *J. Am. Chem. Soc.*, **79**, 6233 (1957).

[13] Preparations by Dr. H. Koch.

[14] Corrected to one deuterium atom per molecule from partially deuterated material.

[15] R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).

Helmkamp and Rickborn[16] have established rigorously that the comparable reduction of the 2-butyl ester occurs with inversion of configuration and 20% racemization. Thus, optically pure pentane-2-*d* has $[\alpha]_D$ $-0.5°$. From the known[17] *S* configuration of (+)-2-pentanol (II), (−)-pentane-2-*d* has the same configuration (IIIa). (−)-Butane-2-*d* has been shown previously[18] to have also the *S* configuration (IIIb). Within the rather wide limits of experimental error in the measurement of the magnitudes of the rotations, complete self-consistency is obtained for these magnitudes as well as for the signs of rotation of pentane-2-*d* derived from 2-pentanol and from ethanol-1-*d*. Correspondingly, (−)-2-pentanone-4-*d* has the *S* configuration (Ic).

Pentane-2-*d* has also been prepared by the reduction of 1-pentene with diisopinocampheyldeuterioborane.[11] The configuration, sign, and magnitude of the rotation for optical purity of pentane-2-*d* from the various preparations agree completely; the optical rotatory dispersion curve of this preparation is the same as that of the hydrocarbon prepared from ethanol-1-*d*.

Experimental Section

(−)-Ethanol-1-*d*.—Reduction of 122 g of (+)-camphor with 10 g of lithium aluminum deuteride gave 114 g (0.735 mole) of a mixture, 85% in (−)-deuterioisoborneol ($[\alpha]^{25}_D$ $-25.8°$), which had only a trace of carbonyl absorption in the infrared. This material was converted into the alkoxymagnesium salt by addition to the Grignard reagent prepared from 101 g (0.735 mole) of *n*-butyl bromide and 24.3 g (0.735 g-atom) of magnesium. Benzene (750 cc) was added and the ether was distilled off. After cooling in an ice bath a total of 140 cc of freshly distilled acetaldehyde in benzene was added at intervals over a period of 2 days. The mixture was acidified with dilute HCl and the separated benzene layer was washed several times with water. The combined aqueous solutions were made basic with potassium carbonate, washed with pentane, and distilled. The material boiling up to 99° was redistilled twice through a small column collecting 22 cc of a fraction, bp 77–79°. The distillate was gas chromatographed on a Carbowax column at 60° yielding 12 cc (28% yield based on deuterioisoborneol) of pure ethanol-1-*d*, α_D $-0.072 \pm 0.003°$ (*l* 2), $-0.145 \pm 0.023°$ (*l* 4), $-0.057 \pm 0.033°$ (*l* 1.5). Deuterium content by nmr was 37 ± 3 atom % D. Note that this procedure assumes that all of the deuterium is present as CH_3CHDOH; it seems a reasonable assumption that any contribution by CH_3CD_2OH is small.

(+)-2-Pentanone-4-*d*.—Five milliliters of the (−)-ethanol-1-*d* above was treated in an ice–salt bath with 21 g of *p*-nitrobenzenesulfonyl chloride and 20 cc of pyridine in methylene chloride. The mixture was acidified and extracted with ether. After washing and drying, the solvent was evaporated and the residue was crystallized from 20% benzene in hexane to yield 15.4 g (79%) of ethyl-1-*d* *p*-nitrobenzenesulfonate, mp 89–90° (lit.[19] mp 91°).

This material (15.3 g, 0.067 mole) was added to a mixture prepared from 35.6 cc (0.335 mole) of freshly distilled methyl acetoacetate and 1.54 g of sodium in 250 ml of absolute methanol. After stirring at 60° for 36 hr, 1 cc of acetic acid was added to the now neutral mixture and the methanol was distilled through a small column. The solid residue was washed several times with ether and the ether was distilled from the combined washings. Vacuum distillation of the residue gave 30.4 cc of product bp 35–40° (0.5–0.6 mm) which was shown by gc to be a mixture of unreacted methyl acetoacetate and monoalkylated ester together with a small amount of dialkylated ester. This mixture was saponified with 5% sodium hydroxide, acidified, and warmed with stirring for several hours. The reaction mixture was made basic with potassium carbonate and extracted continuously with ether. The dried extract was distilled through a small column giving 2.3 cc of crude 2-pentanone-4-*d* which was purified by gc on a SE-30 column yielding 0.9 cc, α_D $+0.075 \pm 0.015°$ (*l* 1). Repetition of this experiment gave an additional 0.5 cc. From the combined final distillation residues and gc purification there was obtained an additional 1.9 cc of 2-pentanone-4-*d*, α_D $+0.073 \pm 0.009°$ (*l* 1), $+0.109 \pm 0.008°$ (*l* 1.5). Total yield from the two preparations was 3.3 cc of pure (single peak on gc) ketone (23% yield based on ethyl-1-*d* nitrosylate).

(+)-Pentane-2-*d* from Ethanol-1-*d*.—The above ketone was refluxed with 10 g of amalgamated zinc and aqueous hydrochloric acid for 34 hr. From the Dry Ice trap above the reflux concenser there was obtained 1.6 cc (50% yield) of pentane-2-*d*, α_D $+0.045 \pm 0.015°$ (*l* 1). This material was identified by gc and showed no more than 5% of an impurity having the same retention time as an authentic *cis–trans* mixture of 2-pentene. The ORD curve for this sample was the same as that of pentane-2-*d* prepared from 1-pentanol-2-*d*.[11,20]

Pentane-2-*d* from 2-Pentanol.[21]—The 2-pentanol used had $[\alpha]^{24}_D$ $-1.769 \pm 0.005°$ (16.1% of optical purity). A mixture of 11.2 g of this alcohol and 14.6 g of freshly distilled methanesulfonyl chloride in 70 ml of methylene chloride was treated with 15 ml of pyridine at $< -5°$. After stirring for 1 hr in the cold, the mixture was stored in the refrigerator for 24 hr and poured into dilute sulfuric acid. The washed and dried organic layer was evaporated at room temperature and the residue was pumped at 5 mm for several hours to yield 17.2 g (81%) of an almost colorless oil of 2-pentyl methanesulfonate, α^{25}_D $-2.917 \pm 0.005°$ (*l* 1).

This product was added dropwise to a solution of 4.5 g of lithium aluminum deuteride in 70 ml of dry diglyme maintained at 75°. The pentane-2-*d* was distilled as formed through a small Vigreux column into a Dry Ice–isopropyl alcohol trap protected by a drying tube. The yield was 5.9 g (80%) of product having α^{23}_D $-0.083 \pm .004°$ (*l* 2). Gas chromatography showed <1%, of an impurity which was probably pentene; purification by gc gave pure pentane-2-*d*, α^{24}_D $-0.040 \pm 0.010°$ (*l* 1), 96 ± 5 atom % D (density of combustion water).

Registry No.—Ib, 6189-38-4; (+)-2-pentanone-4-*d*, 10035-82-2; IIIa, 10035-83-3.

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[16] G. K. Helmkamp and B. F. Rickborn, *J. Org. Chem.*, **22**, 479 (1957).

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[19] F. Bell, *J. Chem. Soc.*, 2776 (1928).

[20] We are indebted to Dr. L. Verbit for this determination.

[21] Preparation by I. Schwager.