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Stereochemistry of Some Lithium Aluminum Deuteride Reductions

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Evidence is presented that the reduction of sulfonates and halides with lithium aluminum hydride involves inversion of configuration.

The lithium aluminum hydride reduction of esters of sulfonic acids or of alkyl halides follows the general reactivity sequence primary > secondary > tertiary. Consequently, observation of the stereochemistry of such a reduction is limited because only a tertiary compound can give rise to an optically active product. However, if lithium aluminum deuteride is used, replacement of secondary functional groups leads to a product which may be asymmetric by virtue of a —CHD— group. The optical activity of deutero compounds of this type has been well established by the preparation of α-deuteroethylbenzene,[1] 1-butanol-1-*d*,[2] menthane-2-*d*,[3] and butane-2-*d*.[4]

The configuration of levorotatory butane-2-*d*, IV, prepared by the route shown in Fig. 1, was assumed to be D[4] by analogy with the epoxide ring-openings observed by Trevoy and Brown.[5] One inversion during deuteride reduction of D-2,3-epoxybutane, I, should yield D-erythro-3-butanol-2-*d*.[6] Subsequent reduction of the functional group *via* L-*threo*-3-bromobutane-2-*d*, III, should not affect the adjacent —CHD— center of asymmetry.

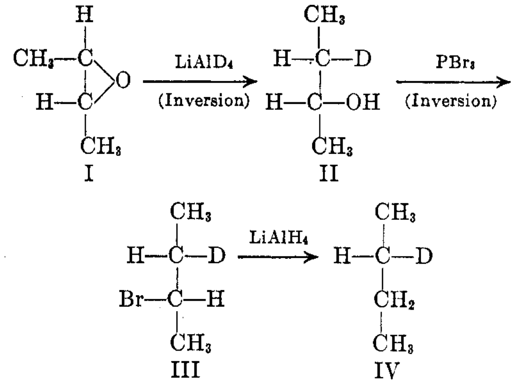

FIG. 1. REDUCTION OF D(+)-2,3-EPOXYBUTANE

The same epoxide, I, was also used as a convenient starting material for the preparation of D-2-bromobutane, VI, and L-2-methanesulfonoxybutane, VII, *via* L-2-butanol, V (Fig. 2), all with known configuration.

Reduction of the D-bromide, VI, with lithium aluminum deuteride yielded a dextrorotatory isomer, L-butane-2-*d*, IX, formed with one inversion. The inversion of configuration provides evidence that the mechanism involved a bimolecular nucleophilic displacement, and that the reaction would be closely related to the reduction of primary alkyl halides, for which second order kinetics have been observed.[7] A similar reduction of the L-ester, VII, yielded levorotatory, hence D, butane-2-*d*, VIII, with one inversion.

In order further to substantiate the route of the reductions, dideutero compounds were prepared

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(1) E. L. Eliel, *J. Am. Chem. Soc.*, **71**, 3972 (1949).

(2) A. Streitwieser, *J. Am. Chem. Soc.*, **75**, 5014 (1953).

(3) E. R. Alexander, *J. Am. Chem. Soc.*, **72**, 3796 (1950).

(4) G. K. Helmkamp, C. D. Joel, and H. Sharman, *J. Org. Chem.*, **21**, 844 (1956).

(5) L. W. Trevoy and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 1675 (1949).

(6) The deutero alcohols and bromides are named with the deuterium atom in the 2-position. The family is determined by the configuration about the 3-position according to the method described in *Report of the Committee on Carbohydrate Nomenclature, Chem. Eng. News*, **26**, 1623 (1948).

(7) D. J. Malter, J. H. Wotiz, and C. A. Hollingsworth, *J. Am. Chem. Soc.*, **78**, 1311 (1956).

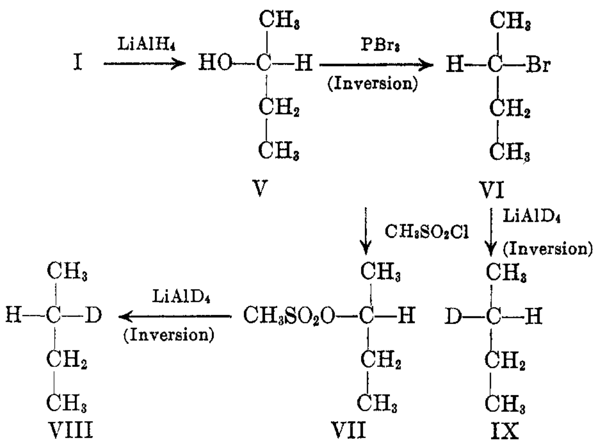

Fig. 2. Preparation and Deuteride Reduction of D-2-Bromobutane and L-2-Methanesulfonoxybutane

from D-*erythro*-3-methanesulfonoxybutane-2-*d*, X, and L-*threo*-3-bromobutane-2-*d*, III (Fig. 3).

The *erythro* ester, X, led to an active levorotatory isomer, L-butane-2,3-d_2, XI, and the *threo* bromide, III, led to an isomer with little optical activity, *meso*-butane-2,3-d_2, XII. Each of these configuration assignments is consistent from the standpoint that the reductions were accompanied by one inversion.

TABLE I

Physical Constants of Deuterobutanes

Isomer	Source	α_D^{25a}	$[\alpha]_D^{25}$	d_4^{25} Calcd.[b]	d_4^{25} Found[c]	Mole Fraction C_4H_{10} Impurity
D-2-*d*[d]	Bromide III	−0.32°	−0.56°	0.5836	0.5829	0.084
D-2-*d*	Ester VII	−0.27°	−0.47°	0.5836	0.5840	0.051
L-2-*d*	Bromide VI	+0.29°	+0.50°	0.5836	0.5838	0.012
L-2,3-d_2	EsterX	−0.59°	−1.01°	0.5935	0.5941	0.038[e]
meso-d_2	Bromide III	−0.02°	−0.03°	0.5935	0.5933	0.043[e]
Butane	Bromide VI	0.00°	0.00°	. . .	0.5737	. . .

[a] Homogeneous liquid; l = 9.85 cm.; reproducibility ±0.01°. [b] Calculated from the density of butane, assuming constancy of molar volumes, according to the method of McLean and Adams.[8] [c] Method of Coffin and Maas.[10] [d] Ref. 2. [e] Mole fraction of C_4H_9D impurity.

Pertinent physical constants of these deuterobutanes are given in Table I. The densities of the various compounds agreed fairly well with calculated values,[8] but in each instance the product formed by reduction of the ester had a slightly higher density than that from the bromide, indicating the possibility of contamination of the former by starting material or alkene, or of the latter by C_4H_{10}. Further distillation, or extraction with sulfuric acid, water, or phosphoric acid, caused no significant change in density. In all instances sufficient alkene was present to show an infrared absorption peak at 960 cm.$^{-1}$ at one atmosphere pressure; however, no butene peaks appeared during partition chromatography in a system capable of detecting 0.5% butene. The mass spectrometric method of Stevenson and Wagner[9] was employed to determine the extent of C_4H_{10} impurities in C_4H_9D, and of C_4H_9D in C_4H_8D (Table II). In the latter instance, the assumption was made that negligible amounts of C_4H_{10} were present.

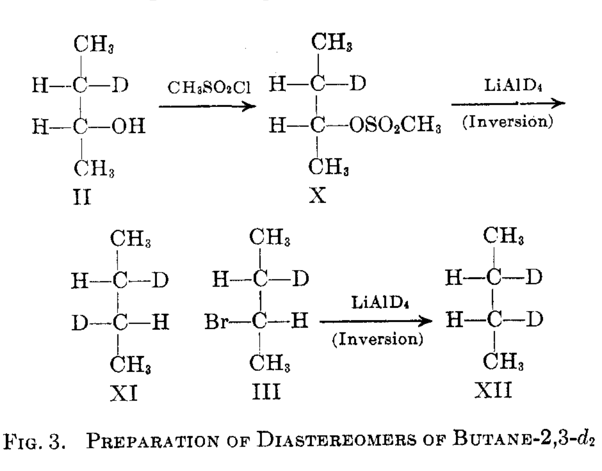

Fig. 3. Preparation of Diastereomers of Butane-2,3-d_2

The L- and *meso*-dideuterobutanes exhibited distinctly different spectra in the 850–1150 cm.$^{-1}$ region (Fig. 4).

The observed rotation of the various deuterobutanes was used as an indication of the extent of racemization taking place during reduction. The isomer with the highest specific rotation, D-butane-2-*d*, IV, contained 8.4% of butane as an impurity; consequently, the specific rotation of a pure isomer cannot be less than −0.61°. During reduction of the ester, VII, at least 20% racemization took place because the specific rotation of the product was 80% of the best value. This could have occurred during synthesis and isolation of the ester or during the reduction reaction. The latter was considered the major cause because successive ester syntheses yielded products with the same optical properties, even though distillations were carried out at different pressures. The L-butane-2-*d*, IX, is at least 17% racemic, but in this instance the racemization probably occurred both during the

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[8] A. McLean and R. Adams, *J. Am. Chem. Soc.*, **58**, 804 (1935).

[9] D. P. Stevenson and C. D. Wagner, *J. Am. Chem. Soc.*, **72**, 5616 (1950).

[10] C. C. Coffin and O. Maas, *J. Am. Chem. Soc.*, **50**, 1427 (1928).

TABLE II

MASS SPECTRAL DATA FOR DEUTERO BUTANES

Compound	m/q	Specific Intensity $V^- = 9$	Specific Intensity $V^- = 10$
Butane	57	0.0071	0.0509
	58	0.343	0.807
D-Butane-2-*d*, IV	58	0.0307	0.0798
	59	0.307	0.646
D-Butane-2-*d*, VIII	58	0.0222	0.0758
	59	0.308	0.736
L-Butane-2-*d*, IX	58	0.0120	0.0483
	59	0.324	0.692
L-Butane-2,3-d_2, XI	59	0.0194	0.0557
	60	0.270	0.611
meso-Butane-2,3-d_2, XII	59	0.0275	0.0830
	60	0.282	0.603

conversion of L-2-butanol to D-2-bromobutane and the reduction of this halide. In contrast to the ester synthesis, successive halide syntheses yielded 2-bromobutane with specific rotations which varied as widely as 5°.

In attempting to interpret the magnitude of optical rotation of the dideutero compounds, it was necessary to assume that the rotatory contributions of the two centers of asymmetry should be additive. This is reasonable since there is no verified instance in which compounds such as $CHD_2CD_2CH(OH)CH_2CH_3$[11] or $HOCH_2CH(OH)CHDOD$[12] exhibit any measurable optical rotation; *i.e.*, a carbon atom which is asymmetric by virtue of an alkyl group *vs.* a deutero alkyl group does not contribute significant optical rotatory power to an organic molecule. Consequently, for L-butane-2,3-d_2, each asymmetric carbon atom should contribute independently of the other. The configuration of carbon atom C-2 is determined when the epoxide ring is opened with lithium aluminum deuteride, and its contribution should be −0.56°. The C-3 atom, with a configuration determined during reduction of the ester, should contribute −0.47°. The sum of these, −1.03°, was very near the observed value, −1.01°, and again the total racemization during ester reduction was of the order of 20%. By the same process, the calculated value of $[\alpha]_D^{25}$ for *meso*-butane-2,3-d_2 was −0.06° compared with the observed −0.03°.

Although we have concluded that reduction of 2-methanesulfonoxybutane proceeds primarily by a nucleophilic displacement, the 20% racemization may be associated with a competitive S_N1-like reaction with a carbonium intermediate. This would compare with the cyclocholesteryl cation intermediate proposed by Corey *et al.*[13] to explain the retention of configuration during reduction of cholesteryl tosylate with lithium aluminum deuteride.

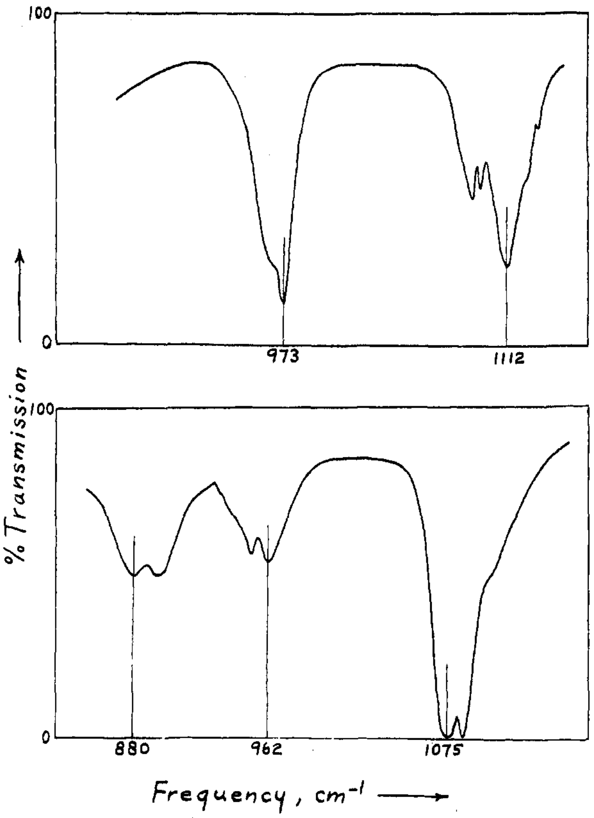

FIG. 4. INFRARED ABSORPTION IN THE 850-1150 CM.$^{-1}$ REGION: UPPER CURVE, *meso*-BUTANE-2,3-d_2, 816 MM.; LOWER CURVE, L-BUTANE-2,3-d_2, 858 MM.

EXPERIMENTAL[14]

D(+)-*2,3-Epoxybutane*, D(−)-*erythro-3-butanol-2-d*, L(+), *threo-3-bromobutane-2-d*, D(−)-*butane-2-d*, L(−)-*2-butanol-and* D(+)-*2-bromobutane*. These compounds were products from previously reported syntheses.[4]

L(−)-*2-Methanesulfonoxybutane*. Using the procedure of Roberts *et al.* for the *p*-toluenesulfonate,[15] 5.0 g. L-2-butanol, 2.1 g. sodium hydride, and 7.1 g. methanesulfonyl chloride yielded 4.7 g. (50%) of the ester: b.p. 61.4–61.5° (0.50 mm.); n_D^{25} 1.4232; d_4^{25} 1.1053; α_D^{25} −19.18°; $[\alpha]_D^{25}$ −17.35°.

Anal. Calcd. for $C_5H_{12}O_3S$: C, 39.45; H, 7.95. Found: C, 39.22; H, 8.04.

D(−)-*erythro-2-Methanesulfonoxybutane-2-d*. By the same procedure, 10 g. D-*erythro*-3-butanol-2-*d*, 4.2 g. sodium hydride, and 14.3 g. methanesulfonyl chloride yielded 12.7 g. (62%) of the deutero ester: b.p. 66.8–67.0° (1.35 mm.); n_D^{25} 1.4232; d_4^{25} 1.1127; α_D^{25} −19.00°; $[\alpha]_D^{25}$ −17.07°.

Anal. Calcd. for $C_5H_{11}DO_3S$: C, 39.19; H + D, 8.55; H as reported in microanalyses, 7.97. Found: C, 39.17; H, 8.01.

Reduction of halides and esters. The reductions were carried out with a slurry of equal parts by weight of lithium aluminum deuteride and lithium deuteride in tetrahydrofuran or diethyl ether.[16] Isolation and purification tech-

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(11) F. C. McGrew and R. Adams, *J. Am. Chem. Soc.*, **59**, 1497 (1937).

(12) H. Erlenmeyer, H. O. L. Fischer, and E. Baer, *Helv. Chim. Acta*, **20**, 1012 (1937).

(13) E. J. Corey, M. G. Howell, A. Boston, R. L. Young, and R. A. Sneen, *J. Am. Chem. Soc.*, **78**, 5036 (1956).

(14) Microanalyses by F. Geiger, 312 Yale St., Ontario, Calif.

(15) J. D. Roberts, W. Bennett, R. E. McMahan, and E. W. Holroyd, *J. Am. Chem. Soc.*, **74**, 4283 (1952).

(16) J. E. Johnson, R. H. Blizzard, and H. W. Carhart, *J. Am. Chem. Soc.*, **70**, 3664 (1948).

niques were identical with those reported previously.[4] In a typical example, L(+)-butane-2-*d* was prepared by adding 8.0 g. (0.058 mole) D(+)-2-bromobutane to 1.0 g. (0.024 mole) lithium aluminum deuteride and 0.9 g. (0.10 mole) lithium deuteride in 50 ml. tetrahydrofuran at reflux temperature. The product was passed through two scrubbers containing 85% phosphoric acid, dried over sodium hydroxide pellets, and distilled: b.p. −2 to −1° (740 mm.) (lit.[17] $-1^1/_2$ to $^1/_2$°, for DL-butane-2-*d*); yield, 2.8 g., 82%. Additional physical constants are given in Table I.

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[17] C. D. Wagner and D. P. Stevenson, *J. Am. Chem. Soc.*, **72**, 5785 (1950).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Certain Acylations of Ferrocene and Some Condensations Involving the α-Hydrogen of Acetylferrocene[1]

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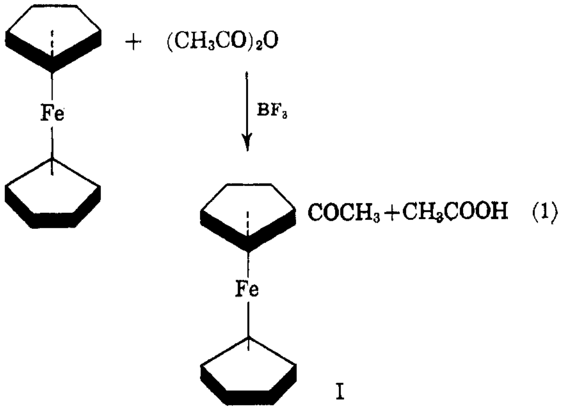
The boron fluoride method of acylation of ferrocene was developed, and some base-catalyzed aldol and Claisen type condensations involving the α-hydrogen of acetylferrocene were effected. The β-diketone from acetylferrocene and methyl benzoate was cyclized with hydrazine, and the β-keto ester from this ketone and ethyl carbonate was cyclized with phenylhydrazine. Attempts to effect boron fluoride catalyzed condensations involving the α-hydrogen of acetylferrocene were unsuccessful.

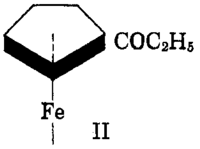
Earlier workers have shown that the Friedel-Crafts type of acetylation of ferrocene (dicyclopentadienyliron) to form acetylferrocene (I) may be effected with acetyl chloride by aluminum chloride,[2] and with acetic anhydride by hydrogen fluoride,[3] stannic chloride,[4] or boron fluoride.[2] The reaction may be illustrated with the last reagent (Equation 1).



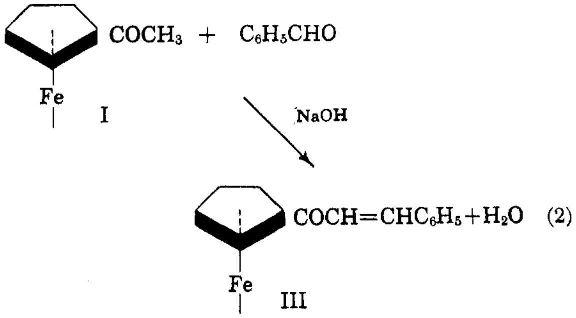
In the present investigation a study was made of the boron fluoride method of acylation of ferrocene,[5] and of some condensations involving the α-hydrogen of acetylferrocene (I).

The details of the earlier boron fluoride procedure for the acetylation of ferrocene have not been available.[2] Our procedure involved simply the saturation of a methylene chloride solution of ferrocene and acetic anhydride with the gaseous reagent at 0° (or the use of a boron fluoride-ethyl acetate complex), and the decomposition of the reaction mixture with aqueous sodium acetate. The yields of acetylferrocene (I) were 88–90%. This method appears preferable to those employing the other reagents listed above.

Similarly ferrocene was propionylated with propionic anhydride to form propionylferrocene (II) which was isolated in good yield as its oxime.



Several condensations involving the α-hydrogen of acetylferrocene (I) were realized satisfactorily with bases. Thus, the aldol type of condensation (accompanied by dehydration) was effected with this ketone and benzaldehyde by means of dilute sodium hydroxide to form α,β-unsaturated ketone III in 70% yield (Equation 2).



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[1] Supported by the Office of Ordnance Research, U. S. Army.

[2] See P. L. Pauson, *Quart. Revs.* (*London*), **9**, 392 (1955).

[3] V. Weinmayr, *J. Am. Chem. Soc.*, **77**, 3009 (1955).

[4] A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya, and O. A. Nesmeyanova, *Doklady Akad. Nauk U.S.S.R.*, **97**, 459 (1954).

[5] We are indebted to Linde Air Products Co., Tonawanda, N. Y. (Dr. R. L. Pruett) for a generous sample of this compound.