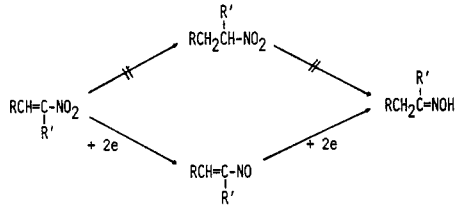
Scheme III



duction leading to oximes has only been studied from a mechanistic point of view.[4] In the present study, we have developed a new electroreductive method which affords the expected products in satisfactory selectivity and yields.

The cathodic reduction of a solution of nitro olefins in aqueous methanol containing sulfuric acid under the conditions of constant current[5] yielded oximes, acetals, and ketones as shown in Scheme II. A variety of aromatic[6] and aliphatic nitro olefins[7] prepared from aldehydes and nitroalkanes were reduced with this electrochemical method. All results are summarized in Tables I and II.[8,12]

Nitro olefins prepared from aromatic aldehydes gave the corresponding oximes as the main products and small amounts of acetals (runs 1 and 4) or ketones (runs 5–8 and 11). In the electroreduction of nitro olefins obtained from aliphatic aldehydes, the nitro olefins corresponding to ketones gave results similar to those for aromatic compounds, whereas the oximes of aldehydes showed a tendency to be changed to the acetals under the reaction conditions.

The intermediary formation of saturated nitro compounds is excluded in our electroreduction, since the formation of (β-nitroethyl)benzene[13] was not observed in the reduction of β-nitrostyrene, and also the electroreduction of (β-nitroethyl)benzene under our reduction conditions did not yield the oxime but gave a complex mixture of unidentified products. The reduction of the double bond may take place after the nitro group is reduced to a nitroso group, though it is not confirmed (Scheme III). It was necessary to keep the reaction medium acidic in our reduction, since in alkaline conditions nitro olefins easily polymerize through a reaction similar to the Michael addition.

Since the transformation of oximes to the carbonyl compounds has been extensively studied,[14] the present electroreductive synthesis of oximes from nitro olefins is useful for the elongation of aldehydes and elongating transformation of aldehydes to ketones.

Experimental Section

Materials. Nitro olefins were prepared according to the reported methods.[6,7]

General Procedures for Reduction of Nitro Olefins. The cathodic reduction was carried out by using a divided cell equipped with a ceramic diaphragm, carbon-rod anode, and platinum cathode.

Into the cathodic chamber was added a solution of nitro olefin (6.00 mmol) and 20% H_2SO_4 (10 mL) in methanol (80 mL), and the anolyte was a methanolic solution (5 mL) of 500 mg of *p*-toluenesulfonic acid. The catholyte was stirred with a magnetic bar and cooled with an ice–water bath to keep temperature at 0–5 °C throughout the reaction. After 4.5 F/mol of electricity was passed with a constant current of 0.1 A, the catholyte was neutralized with aqueous $NaHCO_3$, and the methanol was evaporated. The residue was poured into water, and the mixture was extracted with dichloromethane. After the solution was dried over $MgSO_4$, the solvent was evaporated. The product was purified by silica gel column chromatography (AcOEt–hexane). Yields are shown in Tables I and II.

Registry No. **1**, 102-96-5; **1a**, 7028-48-0; **1b**, 101-48-4; **2**, 7559-36-6; **2a**, 66444-17-5; **3**, 3179-10-0; **3a**, 3353-51-3; **4**, 706-07-0; **4a**, 4410-18-8; **4b**, 42866-89-7; **5**, 705-60-2; **5a**, 13213-36-0; **5b**, 103-79-7; **6**, 17354-63-1; **6a**, 52271-41-7; **6b**, 122-84-9; **7**, 710-20-3; **7a**, 1454-65-5; **7b**, 5586-88-9; **8**, 5438-41-5; **8a**, 52271-42-8; **8b**, 4676-39-5; **9**, 23854-03-7; **9a**, 85629-15-8; **10**, 1202-32-0; **10a**, 5368-18-3; **11**, 1208-78-2; **11a**, 85629-16-9; **11b**, 53917-01-4; **12**, 85629-17-0; **12a**, 13326-89-1; **13**, 4812-25-3; **13a**, 52435-37-7; **13b**, 821-55-6; **14**, 4550-05-4; **14a**, 929-55-5; **14b**, 10022-28-3; **15**, 80922-14-1; **15a**, 82543-06-4; **15b**, 85629-18-1.

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(5) The cathode potential was −1.45 to −1.65 V vs. SCE.

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(8) All the products were identified by the comparison with the authentic samples. Compounds **1a–12a**, **14a**, **5b–8b**, and **14b** have been synthesized as in the following literature. (a) Compound **1a**: Tabei, K.; Hiramura, H.; Amemiya, N. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1085. (b) Compound **2a**: Kling, K. *Bull. Int. Acad. Sci. Cracovie, Cl. Sci.* **1907**, 448. (c) Compound **3a**: Bader, H.; Cross, L. C.; Heibron, I. *J. Chem. Soc.* **1949**, 619. (d) Compound **4a**: Naidan, V. M.; Drumedzei, N. V.; Dombrovskii, A. V. *Zh. Org. Khim.* **1965**, *1*, 1377. (e) Compound **5a**: Dornow, A.; Muller, A. *Chem. Ber.* **1960**, *93*, 32. (f) Compounds **5b**, **10a**, and **11a**: Hass, H. B.; Susie, A. G.; Heider, R. L. *J. Org. Chem.* **1950**, *15*, 8. (g) Compound **6a**: Winstein, S.; Brown, M.; Schreiber, K. C.; Schlesinger, A. H. *J. Am. Chem. Soc.* **1952**, *74*, 1140. (h) Compound **6b**: Rossi, R. A.; Bunnett, J. F. *Ibid.* **1972**, *94*, 683. (i) Compound **7a**: Benigton, F.; Morin, R. D.; Clark, L. C., Jr. *J. Med. Chem.* **1965**, *8*, 100. (j) Compound **7b**: Michael, A.; Jagues, L. *Bull. Soc. Chim. Fr.* **1972**, *5*, 1926. (k) Compound **8a**: Fujisawa, T.; Deguchi, Y. *J. Pharm. Soc. Jpn.* **1954**, *74*, 975. (l) Compound **8b**: Adjangba, S. M.; Billet, D. *Bull. Soc. Chim. Fr.* **1962**, 1970. (m) Compound **9a**: Kotera, K.; Okada, T.; Miyazaki, S. *Tetrahedron*, **1968**, *24*, 5677. (n) Compounds **12a** and **14a**: Yukawa, Y.; Sakai, M.; Suzuki, S. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 2266. (o) Compound **14b**: Corey, E. J.; Beck, A. K. *Chem. Ber.* **1974**, *107*, 367.

(9) The identification of the products **13a**, **15a**, and **15b** was carried out by the comparison of the authentic samples prepared from 2-nonanone[10] and 4-phenylbutyraldehyde.[11]

(10) Commercially available.

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Epoxide Opening by Lithium Aluminum Deuteride. Implications for Isotopic Labeling and Proof of the Proposed Mechanism

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Ring-opening of epoxides by complex metal hydrides has seen widespread application in the synthesis of chiral molecules,[1] including molecules which are chiral by virtue of isotopic labeling. Trevoy and Brown[2] showed in 1949

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(2) Trevoy, L. W.; Brown, W. G. *J. Am. Chem. Soc.* **1949**, *71*, 1675–1678.

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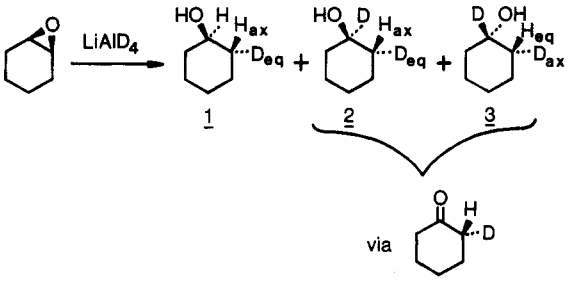
that initial attack on the epoxide is S_N2 in nature. However, Rickborn and his collaborators (using different systems) have found[3] product distributions which suggest that the *overall* mechanism is more complex. In particular, a significant degree (commonly on the order of 10%) of hydroxyl group epimerization has been observed.[3,4] On the basis of mechanistic and intuitive arguments, Rickborn and Quartucci ascribed[3a] this phenomenon to reoxidation by aluminum hydride of a portion of the initially formed alkoxide, followed by reduction of the resulting ketone from the axial face. We report direct experimental evidence from a conformationally unrestrained system, unequivocally confirming Rickborn and Quartucci's mechanistic hypotheses.

Deuterium-substituted cyclohexanol was synthesized by reduction of cyclohexene oxide with lithium aluminum deuteride in refluxing THF. While the 90-MHz proton NMR spectrum of this material showed a hopelessly complex pattern in the region of 1–2 ppm,[5] the corresponding *deuterium* NMR spectrum was readily interpretable. Three product resonances were observed, at 1.21, 1.79, and 3.50 ppm. The relative integrated areas of the three peaks were 0.05, 0.85, and 0.10, respectively. On the basis of published[6] chemical shift values, the following signal assignments were made: 1.21 ppm, C-2 axial ^2H; 1.79 ppm, C-2 equatorial ^2H; 3.50 ppm, C-1 ^2H. Confirmation of these assignments came from the deuterium NMR spectrum of [2,2,6,6-$^2H_4$]cyclohexanol, which showed signals of equal intensity at 1.74 and 1.16 ppm.

The integrated peak areas are of special significance. Since [2-$^2H_1$]cyclohexanone (if formed) will be conformationally labile, carbonyl reduction will lead to equal amounts of **2** and **3**. While the deuterium at C-2 of **2** is



in the equatorial position (hence indistinguishable from the label at C-2 of **1**), the deuterium at C-2 of **3** is axial and easily quantifiable. The 2:1 ratio for C-1/C-2_{ax} proves that the hydroxyl epimerization results from ketone reduction by lithium aluminum deuteride. These results suggest that caution should be observed before using epoxide opening by lithium aluminum deuteride as a means of incorporating a stereospecific isotopic label in a cyclic system.

Experimental Section

Proton and deuterium NMR spectra were run on a JEOL FX-90Q(II) FT NMR spectrometer at a probe temperature of 50 °C. Samples were dissolved in CCl_4, and the spectrometer was locked externally on ^7Li. Chemical shifts are given relative to $CHCl_3$ or C^2HCl_3, added as an internal standard and set to 7.26 ppm. Deuterium spectra were run with broad-banded proton decoupling, and 2040 data points were used over a frequency range of 250 Hz. THF was dried by passage through Woelm alumina (activity super I; ICN).

Reaction of Cyclohexene Oxide with Lithium Aluminum Deuteride. Cyclohexene oxide (3.92 g, 40 mmol) in THF (5 mL) was added over a period of 15 min to a suspension of 462 mg (11 mmol) of lithium aluminum deuteride in 20 mL of THF. Following overnight reflux, excess hydride was decomposed by cautious addition of water (1 mL) in THF (4 mL). At this point the reaction mixture was diluted with ether, and ice-cold 10% H_2SO_4 was added. The aqueous phase was extracted with four aliquots of ether, and the combined organic extracts were washed with brine until the washes were neutral to pH paper. After the mixture was dried (anhydrous $MgSO_4$), volatiles were removed in vacuo, and the residue was purified by distillation [bp 56–57 °C (8 torr)]. The product (3.31 g, 82%) was a colorless semisolid at room temperature and exhibited a single GC peak, with a retention time identical with that of authentic cyclohexanol.

[2,2,6,6-$^2H_4$]Cyclohexanol. [2,2,6,6-$^2H_4$]Cyclohexanone (202 mg, 2.0 mmol; Merck, Sharp & Dohme) was dissolved in 4 mL of anhydrous ether and was treated with an excess (ca. 140 mg, 3.7 mmol) of sodium borohydride in two aliquots. Two drops of ethanol were added to facilitate solution of the borohydride. The reaction mixture was stirred overnight, after which GC analysis showed the reduction to be complete. The reaction mixture was worked up by dilution with water, extraction with ether, drying the ether over anhydrous magnesium sulfate, and removal of solvent in vacuo at 0 °C. The product (234 mg; 90% cyclohexanol and 10% ethanol, by GC) showed deuterium NMR resonances at 1.16 and 1.74 ppm (axial and equatorial C-2 deuterons, respectively).

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Registry No. **1**, 49676-90-6; **2**, 85662-23-3; **3**, 85662-24-4; cyclohexene oxide, 286-20-4; lithium aluminum deuteride, 14128-54-2; [2,2,6,6-$^2H_4$]cyclohexanol, 21273-03-0; [2,2,6,6-$^2H_4$]cyclohexanone, 1006-03-7.

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The Chemistry of Naturally Occurring Polyamines. 6. Efficient Syntheses of N^1- and N^8-Acetylspermidine[1]

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The common polyamines putrescine, spermidine, and spermine are widely distributed in biological systems, not only as free bases but also as alkylated or acylated conjugates with sugars, steroids, phospholipids, fatty acids, and peptides.[2] Many of these more elaborate structures exhibit noteworthy biochemical and pharmacological properties in their own right.[2] Even the simplest spermidine conjugates, terminally acetylated polyamines **2** and **3**, are found in many tissues and in the urine and are thought to be special significance as diagnostic markers in several diseases. Despite broad interest in these metabolites, no regioselective methods for their synthesis have

(1) For Part 5 in this series, see ref 2.

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