

BuOH (80:20 v/v) afforded **3a** in 71% yield and in 51–66% yield when carried out at $50 \pm 2^\circ$, with the balance of the product being a lower boiling ketone.

Autoxidation of Ethyl 2-Cyano-3,3-dipentyl octanoate. Determination of Cyanide and Cyanate Ions.¹¹—The determination was carried out several times and the following procedure is representative. Oxygen was passed into a solution of 3.37 g (0.01 mol) of **2a** and 2.24 g (0.02 mol) of potassium *t*-butoxide in 60 ml of DMSO-*t*-BuOH (80:20 v/v) for 7 hr at $50 \pm 3^\circ$. The mixture was quenched with 50 ml of distilled water and extracted with three small portions of ether and the aqueous portion was adjusted to pH 5–7 with dilute nitric acid. A solution of 2 g (0.012 mol) of silver nitrate in 20 ml of distilled water was added and the white precipitate was collected on a tarred, sintered-glass funnel. It was washed with two small portions of water and treated with five 15-ml portions of dilute (1:5) nitric acid. The remaining silver cyanide was washed with distilled water and dried. The solid weighed 0.33 g (0.0025 mol) which corresponds to 25% cyanide ion; the cyanate ion was taken as the difference from 100%.

The results varied from 25 to 27% cyanide ion in DMSO-*t*-BuOH (80:20 v/v) to 14–18% cyanide ion in DMF. These values represent an approximate product ratio of 80:20 cyanate to cyanide ion on the basis of the determinations with standard solutions. The latter contained 20% cyanide and 80% cyanate ions, in the appropriate solvents, and were subjected to the conditions of the autoxidation and work-up procedure prior to precipitation of the silver salts. The average values for cyanide and cyanate were found to be 23 and 77% in DMSO-*t*-BuOH and 15 and 85% in DMF.

Registry No.—Table I—a, 25593-95-7; b, 25593-96-8; c, 25593-97-9; d, 25593-98-0; e, 25593-99-1; f, 25594-00-7; Table II—g, 13275-31-5; h, 25594-02-9; i, 25565-11-1; j, 25565-12-2; k, 25594-03-0; l, 25594-04-1; m, 25565-13-3; ethyl 2-cyano-3-butyl-2-nonenoate, 25594-05-2; 2-cyano-3-pentyl-2-octenenitrile, 13017-59-9; 2-cyano-3,3-dipentyl octanenitrile, 25594-07-4.

Additions to Bicyclic Olefins. IV.

The Facile Reduction of Labile Epoxides of Bicyclic Olefins by Lithium in Ethylenediamine

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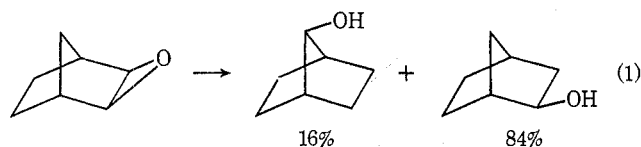
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The reduction of many hindered and unstable bicyclic epoxides with lithium aluminum hydride is very slow and is often accompanied by rearrangement. In contrast, the addition of lithium metal to an ethylenediamine solution of such epoxides at 50° reduces such epoxides rapidly, without rearrangement. In this way, norbornene oxide is readily reduced to essentially pure *exo*-norbornanol in 87% yield. Similarly, badly hindered and labile epoxides, such as 2-methylene-7,7-dimethylnorbornane oxide and *exo*- and *endo*-7,7-dimethylnorbornene oxides, were readily reduced to the corresponding tertiary and secondary alcohols, respectively.

We were interested in studying the stereochemistry of the epoxidation of norbornene, 7,7-dimethylnorbornene, and related olefins.⁴ If the resulting epoxides could be reduced quantitatively to the corresponding known bicyclic alcohols, the stereochemistry of epoxidation could be conveniently established by vapor phase chromatography.

Unfortunately, the usual reduction of epoxides by lithium aluminum hydride is very slow for many of these bicyclic epoxides. Moreover, such reductions are often accompanied by rearrangements. For example, in order to achieve a reasonable rate, Kwart and Takeshita⁵ found it necessary to treat norbornene oxide with lithium aluminum hydride in boiling *N*-ethylmorpholine. They obtained 16% of the rearranged 7-norbornanol in addition to 84% of the expected 2-norbornanol (eq 1). The 7-norbornanol presumably



resulted from electrophilic ring opening of the epoxide ring by lithium aluminum hydride.

Data reported by Hallsworth and Henbest^{6,7} indicated that some steroidal epoxides, which were quite unreactive to lithium aluminum hydride, were easily reduced with a large excess of lithium in ethylamine. However, they obtained some olefin in the reduction of labile steroidal epoxides.

Consequently, a study was begun to determine whether the various norbornyl epoxides would be reduced quantitatively with lithium-ethylamine to the corresponding alcohols without rearrangements or eliminations occurring to complicate the interpretation of the results.

Results and Discussion

We found ethylenediamine (bp 116°) a more convenient medium to use than the much lower boiling ethylamine (bp 16°) for routine laboratory reduction of hindered epoxides.⁸ After some exploratory experiments an exceedingly simple procedure was developed and proved highly satisfactory. This procedure involves dissolving 10 mmol of norbornene oxide in 10 ml of ethylenediamine, adding 30 mg-atoms of lithium wire in 2-mm pieces, and heating at 50° with stirring until a

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(4) H. C. Brown, J. H. Kawakami, and S. Ikegami, *J. Amer. Chem. Soc.*, in press.

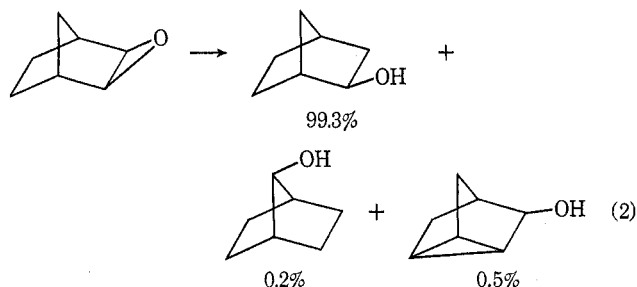
(5) H. Kwart and T. Takeshita, *J. Org. Chem.*, **28**, 670 (1963).

(6) A. S. Hallsworth and H. B. Henbest, *J. Chem. Soc.*, 3571 (1960).

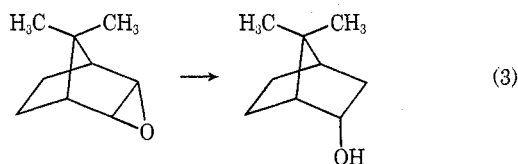
(7) A. S. Hallsworth and H. B. Henbest, *ibid.*, 4604 (1957).

(8) (a) The lithium reduction in ethylenediamine is much less vigorous than in ethylamine. We have encountered side reactions in ethylamine when the reaction conditions were not controlled (see Discussion). (b) Isolation of the alcohol from the epoxide reduction in ethylenediamine is simple because the base is very soluble in water where it exists as the hydrate, and is only slightly soluble in ether, whereas ethylamine is miscible both in water and in ether.

blue color persists. This usually takes approximately 1 hr. The norbornanol was then isolated in 87% yield by the addition of 10 ml of water, followed by extraction with 20 ml of ether or tetrahydrofuran. Analysis by glpc indicated no olefin or epoxide, 99.3% 2-norbornanol, 0.2% 7-norbornanol, and 0.5% nortricyclanol (eq 2). Even the more hindered *endo*-epoxide from

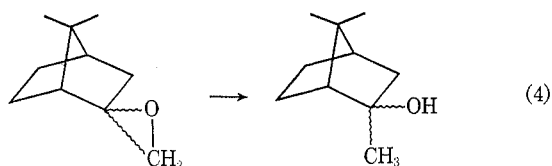


7,7-dimethylnorbornene was readily reduced in 1 hr to 7,7-dimethylnorbornanol in 87% yield (eq 3). In



contrast, the reduction of this epoxide with lithium aluminum hydride in diglyme at 100° for 24 hr yielded 19% unreacted epoxide, 47% 7,7-dimethylnorbornanol, and 44% rearranged alcohols.^{9,10}

The very labile 2-methylene-7,7-dimethylnorbornane oxide underwent isomerization in all of our attempts at a glpc analysis. Its lability is also indicated by the report that the room temperature reduction with lithium aluminum hydride gives chiefly primary alcohol.¹¹ Presumably, the labile epoxide undergoes an electrophilic ring opening prior to reduction by hydride. However, this labile oxide readily underwent reduction by lithium-ethylenediamine to give the tertiary alcohol in 89% yield (eq 4).



This reduction with lithium-ethylenediamine was extended to all of the bicyclic epoxides of interest, as well as to several representative alicyclic and aliphatic epoxides. In all cases the reduction proceeded cleanly and the alcohols were obtained in high yields. The results are summarized in Table I.

Similar results could be obtained using ethylamine, provided that the reaction conditions were rigorously controlled. However, the lithium metal reduction in ethylamine is very vigorous, even at -20°, and is not

(9) This epoxide is stable to our glpc conditions. However, very labile epoxides, such as 2-methylene-7,7-dimethylnorbornane oxide, rearrange on the glpc column.

(10) The reduction of *exo*-norbornene oxide with lithium aluminum hydride yielded various amounts of *endo*-norbornanol depending upon the reaction conditions (see Experimental Section).

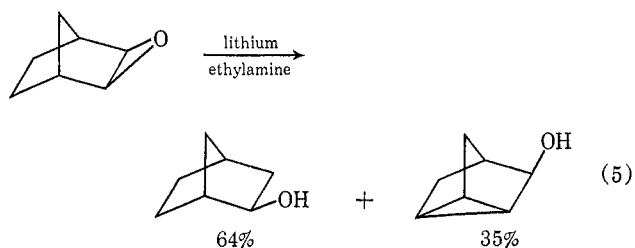
(11) W. Hüchel and D. Volkmann, *Justus Liebigs Ann. Chem.*, **664**, 31 (1963).

TABLE I
LITHIUM-ETHYLENEDIAMINE REDUCTION OF EPOXIDES

Epoxides of olefins	Yield of alcohols, % ^a	Alcohols ^b
Norbornene	87	2-Norbornanol
7,7-Dimethylnorbornene	87	7,7-Dimethyl-2-norbornanol
1-Methyl-2-norbornene	88	60% 1-methyl-2-norbornanol 40% 4-methyl-2-norbornanol
2-Methyl-2-norbornene	100	71% 2-methyl-2-norbornanol 29% 3-methyl-2-norbornanol
1,7,7-Trimethylnorbornene	80	51% 1,7,7-trimethyl-2-norbornanol 49% 1,7,7-trimethyl-3-norbornanol
2-Methylenenorbornane	85	2-Methyl-2-norbornanol
2-Methylene-7,7-dimethylnorbornane	88	2,7,7-Trimethyl-2-norbornanol
1-Methylcyclohexene	93	1-Methylcyclohexanol
1-Butene	82	2-Butanol
2-Methyl-2-butene	82	90% 3-methyl-2-butanol 10% 2-methyl-2-butanol

^a Yield by glpc analysis. ^b Since the epoxides were often mixtures of *exo* and *endo*, the corresponding alcohols were also mixtures of stereoisomers. The stereochemistry of the alcohols always conformed to the stereochemistry of the epoxides, as established by pmr and glpc analysis.

always easy to control. For instance, a drastic change in reaction products is observed if norbornene oxide is added to a mixture of ethylamine and lithium. If the epoxide was added 5 min after a blue color appeared, there was obtained an 87% yield of recovered epoxide, 10% norbornanol, and 3% tricyclanol. If the epoxide was added 1 min after the appearance of the blue color, there was obtained 1% norbornene oxide, 64% norborneol, and 35% nortricyclanol (eq 5). Nortri-



cyclanol probably results from base attack on norbornene oxide, as reported previously by Crandall.¹²

Thus, it appears that the use of ethylenediamine in lithium metal reduction of hindered and labile epoxides has a number of significant advantages over that of ethylamine. In addition, this simple and convenient procedure may also find application in the reduction of many simple aliphatic and alicyclic epoxides. Although the lithium-ethylenediamine reduction is not always selective, it appears that it is widely applicable to bicyclic epoxides and may be very helpful in other instances where the reduction by complex hydrides fails.

Experimental Section

Materials.—Anhydrous ethylenediamine from Fisher Scientific Co. was used without further treatment.

(12) J. K. Crandall, *J. Org. Chem.*, **29**, 2830 (1964).

Gas Chromatography.—The analyses were carried out on the Perkin-Elmer 226 fitted with a 150 ft \times 0.01 in. Gelay column. Authentic samples were utilized to identify the products.¹³

Epoxidation of Olefins.—The olefins were epoxidized with *m*-chloroperbenzoic acid in methylene chloride.⁴

Typical Procedure for the Lithium-Ethylenediamine Reduction of Epoxides.—To a 100-ml three-necked flask fitted with a septum outlet, thermometer, and magnetic stirring bar under nitrogen was added 10 mmol of norbornene oxide and 10 ml of anhydrous ethylenediamine. Then 0.21 g (30 mg-atoms) of lithium wire cut into 2-mm pieces and washed with pentane was added at room temperature with vigorous stirring. The reduction is exothermic above room temperature, but a water bath was necessary to keep the temperature at 50° for 1 hr. Many colors are observed during the reduction, but the reduction is complete when a blue-purple color persists. The reaction mixture was cooled and 10 ml of water was added to destroy excess reagent. Extraction with 20 ml of tetrahydrofuran, drying (MgSO₄), addition of a calibrated internal standard, and analysis by glpc indicated an 87% yield of 99.3% 2-norbornanol, 0.2% 7-norbornanol, and 0.5% nortricyclanol (Ucon LB 550X at 100°) in order of increasing retention time. No 2-norbornanone, norbornene oxide, or norbornene were detected.

Reduction of Norbornene Oxide with LiAlH₄.—To a flame-dried 50-ml round-bottomed flask was added 5 ml of a 1 M LiAlH₄ solution in diglyme, 15 ml of dry and peroxide-free diglyme, and 0.55 g (5 mmol) of norbornene oxide under nitrogen. After 67 hr at 100° there was obtained a 77% yield of 98.1% *exo*- and 1.9% *endo*-norbornanol, and a trace of 7-norbornanol. If the same reduction was run in the presence of air, the amount of *endo*-norbornanol increased to 7% in 24 hr.¹⁴ Although no 7-norbornanol was detected, there was obtained 9% an unknown with a shorter retention time than *exo*-norbornanol (Ucon LB 550X at 100°).

Reduction of 7,7-Dimethylnorbornene Oxide with LiAlH₄.—

(13) H. C. Brown and J. H. Kawakami, *J. Amer. Chem. Soc.*, **92**, 1990 (1970).

(14) S. V. Vitt and N. S. Martinkova, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 524 (1964); *Chem. Abstr.*, **60**, 15696 (1964). These authors observed that when benzhydrol-1-*d* and its potassium salt are heated under nitrogen in diglyme and lithium aluminum hydride, benzhydrol loses some deuterium.

The crude oxide was reduced at 100° in 24 hr with LiAlH₄ in diglyme in the presence of dry air. There was obtained 19% recovered oxide, 18% an unknown (alcohol), 6% 5,5-dimethyl-*exo*-2-norbornanol (?), 2.5% 7,7-dimethyl-2-*exo*-norbornanol, 1% 6,6-dimethyl-2-norbornanol, 47.2% 7,7-dimethyl-2-*endo*-norbornanol, and seven other minor peaks.

Reduction of Norbornene Oxide with Li in Ethylamine.—To a 50-ml flask fitted with a magnetic stirring bar, Dry Ice condenser, and a nitrogen inlet was added 1.1 g (10 mmol) of norbornene oxide and 20 ml of ethylamine *via* a syringe cooled with Dry Ice. The mixture was cooled to -20° and 0.21 g (30 mg-atoms) of Li wire cut in 2-mm pieces was added. The reduction was vigorous. In 5 min a persistent blue color appeared. The Dry Ice condenser was removed and the ethylamine swept out with nitrogen. Water (20 ml) was added; extraction with 20 ml of ether gave on evaporation an 89% yield of 2-norbornanol with only traces of other isomers.

Side Reactions in Reductions with Li in Ethylamine.—After a mixture of 10 ml of ethylamine and 0.21 g (30 mg-atoms) of Li at -20° remained blue for 5 min, a solution of 1.1 g (10 mmol) of norbornene oxide in 30 ml of petroleum ether (35-37°) was added. The blue color dissipated after only 1 mmol of the epoxide solution was added. After stirring the mixture for 15 min at -20°, the work-up indicated an 87% yield of unreacted epoxide, 10% 2-*exo*-norbornanol, and 3% nortricyclanol. In contrast, if the epoxide was added 1 min after the appearance of the blue color, 1% norbornene oxide, 64% 2-norbornanol, and 35% nortricyclanol were obtained.

Reduction of Nonhindered Epoxides.—The lithium-ethylenediamine reductions of nonhindered epoxides such as 1-butene oxide are quite exothermic. The reduction can be controlled with ice cooling.

Registry No.—Norbornene, 498-66-8; 7,7-dimethylnorbornene, 6541-60-2; 1-methyl-2-norbornene, 822-73-1; 2-methyl-2-norbornene, 694-92-8; 1,7,7-trimethylnorbornene, 464-17-5; 2-methylenenorbornene, 497-35-8; 2-methylene-7,7-dimethylnorbornane, 471-84-1; 1-methylcyclohexene, 591-49-1; 1-butene, 106-98-9; 2-methyl-2-butene, 513-35-9.

Synthesis and Properties of Cobalticinium Salts.

I. Synthesis of Monosubstituted Cobalticinium Salts¹

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Procedures for synthesis of methyl (2, 3), carboxy (4, 5), chlorocarbonyl (6), carbalkoxy (7), amino (9), and nitro (10) cobalticinium salts are given. The amino derivative shows extremely low basicity ($pK_b = 15.6 \pm 0.1$) but, in marked contrast to the ferrocene analog, can be diazotized and coupled with phenol to form an azo dye 10, $pK_a = 7.05 \pm 0.03$. The substituted cobalticinium salts show greater resistance toward oxidation than the corresponding ferrocene analogs and are not degraded by concentrated mineral acids or aqueous base. Hydroxy-2,3,4,5-tetraphenylcobalticinium ion, 15, exists in proteolytic equilibrium with the stable π -cyclopentadienyltetraphenylcyclopentadienonecobalt complex, 14, $pK_a = 2.3 \pm 0.1$ in 50% ethanol. Procedure for synthesis of salts of 15 and the acetoxy derivative 16 from 14 are given.

Cobalticinium salts, in contrast to the isoelectronic ferrocene analogs, show strong resistance to oxidation, even by strong oxidizing agents such as fuming nitric acid, potassium permanganate, and ozone.³ Gill and Mann⁴ have found that ferrocene derivatives act as potent haptens, greatly enhancing the ability of synthetic peptides to induce formation of antibodies, but these compounds are degraded by enzymes of the host

organism. They proposed the use of the more stable cobalticinium salts as haptens, as tracers in biological systems, as electron dense markers in electron microscopy and X-ray crystallography, and as carriers of Co⁶⁰ in radiotherapy. We have therefore undertaken a systematic study of the synthesis and chemical properties of cobalticinium salts and their rhodium and iridium analogs.

Results and Discussion

Since electrophilic substitution on the cobalticinium nucleus is yet to be accomplished, substituted derivatives must be prepared directly from substituted cy-

(1) Part II: J. E. Sheats, C. E. Whitten, and W. M. Minihane, paper in preparation.

(2) National Science Foundation Science Faculty Fellow, 1969. Chemistry Department, Rider College, Trenton, N. J. 08602.

(3) E. O. Fischer and G. E. Herberich, *Chem. Ber.*, **94**, 1517 (1961).

(4) T. J. Gill, III, and L. T. Mann, Jr., *J. Immunology*, **96**, 906 (1966).