separation of IIIa from thermal decomposition products and from IIa was necessary. Accordingly, radiation-induced oxidation of cholesterol is of some preparative utility. Yields of 5.8–7.4% of 1,2-^{3}H-IIIa free from other detectable sterols have been attained from 1,2-^{3}H-cholesterol by irradiation with ^{60}Co γ radiation for 8 hr.

Experimental Section[15]

Radiation Conditions.—Samples (2 and 5 g) in glass beakers of crystalline cholesterol (purified to a high degree by multiple recrystallizations from methanol and in which no autoxidation component could be detected) were exposed in air to four radiation conditions. Samples were exposed to ^{60}Co γ rays in a Gammacell 200 (Atomic Energy of Canada Ltd., Ottawa) providing 2.7×10^5 rad/hr. After 15 min the 7β-hydroperoxide IIIa was readily detected. Other samples were exposed to a 254-nm germicidal ultraviolet light for 1 hr at a distance of 10 cm, after which time IIIa was readily detected. Samples were exposed to daylight and air on the laboratory bench for 6 days, at which time IIIa was readily detected. Samples were heated at 100° in an electric oven. After 42 hr IIIa was readily detected.

Sample Preparation.—Irradiated samples were dissolved (2 g/40 ml, 5 g/100 ml) in the dark at 40° under N_2 in diethyl ether–methanol (1:1). Chilling to 5° yielded crystalline cholesterol which was filtered off for analysis. The mother liquor was concentrated under vacuum to incipient crystallization, and a second crop of crystalline cholesterol was removed. Concentration under vacuum was repeated until the mother liquor volume was 5 ml (for 2-g samples) or 10 ml (for 5-g samples). The concentrated mother liquor was preparatively chromatographed on 0.25 mm chromatoplates of silica gel HF_{254} using benzene–ethyl acetate (17:8) in triple ascending irrigations. The sterol hydroperoxide zone was located and eluted from the chromatoplate with 5–10 ml of acetone, the acetone was removed under vacuum, and the sterol residue was redissolved in 100 μl of acetone for analysis.

Replicate experiments were handled by a more direct method. The mother liquor obtained by crystallization of cholesterol and concentration was evaporated under vacuum and the sterol residue was subjected to analysis without intermediate preparative thin layer chromatography. Essentially identical results were obtained by the two different sample preparation methods.

Sample Analysis.—Mother liquor sterols in 100 μl of acetone were subjected to thin layer chromatography with up to 100–200 μg of total sterols applied to the chromatoplate per analysis. Reference sterols were run on the same chromatoplate. Each sample was analyzed as such and also after reduction on the chromatoplate with 20 μl of a 10% sodium borohydride solution in methanol.[17] In that no 7-ketone IV was detected in these samples by ultraviolet light absorption of the chromatoplate reduction with borohydride gave product alcohols solely from the sterol hydroperoxides present. Each chromatoplate was visualized with *N,N*-dimethyl-*p*-phenylenediamine and 50% sulfuric acid for identification with confidence of each detected sterol component. In each case IIIa was the first sterol product to be detected in irradiated samples, with IIa forming more slowly and at much reduced levels. No Ia could be detected as such or as the reduced product Ib.

Samples of mother liquor (2–10 μl) were analyzed by gas chromatography on SP-2401 and OV-210 columns at the same time.[1] Uniform and characteristic elution curves were obtained for all samples, in which IIIa and V predominated. Typical elution curves are given in Figure 1 in which 3% OV-210 columns were used. Key relative retention times noted are 1.00, reference cholesterol; 2.17, VI; 2.45, IIIb; 5.04, IV. Cholesta-4,6-dien-3-one would appear at 3.46 and IIIb at 2.27.

Stability Experiments.—Pure samples of Ia, IIa, and IIIa were exposed to the same irradiation conditions. In the case of ^{60}Co γ radiation, exposure times of 30 min were also used. Analysis of these samples by both thin layer and gas chromatography established that thermal decomposition only had occurred, with no evidence of conversion of Ia to IIa, of IIa to IIIa, or of conversion of IIIa to other hydroperoxides.

1,2-^{3}H-Cholesterol 7β-Hydroperoxide (IIIa).—An aliquot (*ca.* 10 μCi) of 1,2-^{3}H-cholesterol was chromatographed on 0.25 mm thick silica gel HF_{254} chromatoplates irrigated three times with benzene–ethyl acetate (17:8), and the eluted radioactive cholesterol was rechromatographed a second time. Dilution with 500 mg of crystalline highly purified carrier cholesterol gave a sample assaying 29,700 dpm/mg. A portion of this material (200 mg) in a small glass vial open to the air was irradiated with ^{60}CO γ radiation for 8 hr, after which time the irradiated sample was dissolved in 200 ml of methanol, chilled overnight, and the resultant crystalline 1,2-^{3}H-cholesterol filtered. The solvent was evaporated under vacuum, and the sterol residue was dissolved in a minimum volume of acetone and chromatographed on 0.25 mm thick silica gel HF_{254} chromatoplates using benzene–ethyl acetate (17:8) with triple irrigation in the usual fashion. The IIIa zone was located and excised from the chromatoplate. The 1,2-^{3}H-IIIa was eluted with acetone. Rechromatography of the material twice more using the same system sufficed to give pure 1,2-^{3}H-IIIa free from IIa and other detectable sterols. Only one component (1,2-^{3}H-IIIa) was detected on thin layer chromatograms or on gas chromatography on 2% SP-2401. Sodium borohydride reduction gave only one radioactive component identified as IIIb, with no other detectable sterols present. The radioactive IIIa was dissolved in 1 ml of acetone, and 50-μl aliquots were assayed for radioactivity to determine yields of 5.8 and 7.4% for two separate preparations.

Registry No.—Cholesterol, 57-88-5.

(15) Solvents were redistilled prior to use. All sterols used were of high purity as judged by melting point, infrared absorption spectral, and thin layer and gas chromatographic criteria. Thin layer chromatography was conducted on 0.25 mm thick 20 × 20 cm chromatoplates of silica gel HF_{254} (E. Merck GmbH., Darmstadt) using benzene–ethyl acetate (17:8) and triple ascending irrigation by techniques previously described in detail.[9d] Typical mobility data with IIIa serving as unit mobility follow: IIIa, 1.00; IIa, 0.91; Ia, 0.91; IIb, 0.53; IIIb, 0.60; Ib, 0.76. Sterol hydroperoxides were detected by *N,N*-dimethyl-*p*-phenylenediamine used as a spray.[10] Sterols were also detected by their characteristic colors developed with 50% aqueous sulfuric acid used as a spray.[9d]

Gas chromatography was conducted by procedures previously described in detail,[16] but using 2–3% SP-2401 and 2–3% OV-210 liquid phases on 100–120 mesh Supelcoport (Supelco Inc., Bellefonte, Pa.) for the confident resolution of IIb and IIIb.[1] Retention data for the several sterols involved in this study were essentially the same as those previously reported.[1]

(16) J. E. van Lier and L. L. Smith, *Anal. Biochem.*, **24**, 419 (1968).

(17) L. L. Smith and J. C. Price, *J. Chromatogr.*, **26**, 509 (1967).

The Stereoselectivities of Lithium Aluminum Trialkoxyhydrides

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The modification of lithium aluminum hydride ($LiAlH_4$) by the addition of various alcohols (or ketones), and subsequent use of the resulting lithium aluminum alkoxyhydrides (1) in the reduction of the model system dihydroisophorone (2), has led to two basic conclusions.[1] First, lithium aluminum alkoxyhydrides are generally more highly stereoselective than $LiAlH_4$ itself, presumably because of the greater bulk of the alkoxyhydride reagents. It was recognized[1,2] that certain alkoxyhydrides, such as lithium aluminum tri-*tert*-butoxyhydride, were less stereoselective than their apparent bulk suggested. This was explained by Ashby and coworkers,[3] who showed that, while the

(1) H. Haubenstock and E. L. Eliel, *J. Amer. Chem. Soc.*, **84**, 2363 (1962).

(2) H. C. Brown and H. R. Deck, *ibid.*, **87**, 5620 (1965); for a review on alkoxyaluminum hydrides, see J. Malek and M. Cerny, *Synthesis*, (5), 217 (1972).

(3) E. C. Ashby, J. P. Sevenair, and F. R. Dobbs, *J. Org. Chem.*, **36**, 197 (1971).

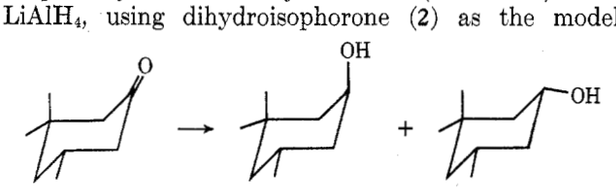
reagents **1** may be associated in tetrahydrofuran, lithium aluminum tri-*tert*-butoxyhydride was monomeric over a wide concentration range. Furthermore, association was shown to be an important factor in determining stereoselectivity.

The second conclusion was that the reductions of certain ketones with $LiAlH_4$ do not appear to involve the intervention of lithium aluminum alkoxyhydrides (**1**) as active reducing species owing to a proposed rapid disproportionation of such species to $LiAlH_4$, the only effective reducing agent, and to $LiAl(OR)_4$,[1] for example, eq 1.

$$\underset{\mathbf{1}}{4LiAlH(OR)_3} \longrightarrow 3LiAl(OR)_4 + LiAlH_4 \qquad (1)$$

The main evidence for the above proposal involves the following: (1) an insensitivity of stereoselectivity to method of reduction, *i.e.*, direct addition using excess hydride or inverse addition of an equivalent quantity of hydride;[1,4,5] (2) instability of **1** when R is isopropyl or *sec*-butyl;[6] (3) AlH_4^- is more reactive than $LiAlH(OR)_3$;[6,7] (4) the intermediate species **1** presumably formed by reaction of $LiAlH_4$ with 3 mol of addend isopropyl alcohol or cyclohexanone showed the same stereoselectivity in the reduction of dihydroisophorone (**2**) as $LiAlH_4$ itself.[1,8,9]

This paper reports studies of the stereoselectivities of alkoxyhydrides (**1**) formed from the reaction of 3 mol of primary or secondary alcohols (or ketone) with $LiAlH_4$, using dihydroisophorone (**2**) as the model



2 *trans*-**3** *cis*-**3**

ketone substrate. It extends the scope of the earlier work,[1] describes a new, highly stereoselective reagent, and discusses the effect of the steric requirements of the reagent as a factor in stereoselective reductions. The results are shown in Table I, which also includes some earlier data[1] for comparison.

Results

Entry 1, Table I, shows the reduction of **2** with $LiAlH_4$ itself, entries 2–5 show the effects on stereoselectivity of a series of primary alkoxy groups of increasing steric size, while entries 6–10 do the same for secondary alkoxy groups.

Considering the primary alkoxyhydrides, it is seen from Table I that the reagents formed from methyl alcohol and ethyl alcohol (entries 2 and 3) show greater stereoselectivity than $LiAlH_4$ itself. The more highly hindered isobutyl alcohol (entry 4) and neopentyl alcohol (entry 5), however, form *less* stereoselective reagents. The reason is probably that given by Ashby,[3] that the methoxyhydride (and probably also ethoxyhydride) reagents are highly associated. This would imply that the isobutoxyhydride and neopentoxyhydride are less associated and possibly monomeric. This is consistent with the greater bulk of these latter two reagents, which may reduce association effects. The highly hindered lithium aluminum tri-*tert*-butoxyhydride was found to be monomeric in THF.[3]

TABLE I

REDUCTION OF **2** WITH $LiAlH_4$ AND MODIFIED REAGENTS[a]

Entry	Addend[b]	Reagent concn[c]	*trans*-(axial) **3**, %
1		0.76	52–55,[d,e] 53[f]
2	CH_3OH		75[d]
3	CH_3CH_2OH		83[d]
4	$(CH_3)_2CHCH_2OH$	0.31	57[f,g]
5	$(CH_3)_3CCH_2OH$	0.19, 0.48	60,[f,h] 60[f,i,j]
6	$CH_3CHOHCH_3$	0.40	54,[d] 55[f,k]
7	$CH_3CH_2CHOHCH_3$	0.19	63[f,l]
8	$(CH_3)_2CHCHOHCH_3$	0.19	59[f,m]
9	$(CH_3)_3CCHOHCH_3$	0.31, 0.19, 0.06	75,[f] 77,[f,n] 80[f,o]
10	$(CH_3)_3CCOC(CH_3)_3$	0.48	98[f,p]
11	Cyclohexanone		58[d,q]
12	Cyclopentanol	0.31	57[f,r]

[a] In diethyl ether. [b] 3 mol addend per mole ketone. [c] Molarity after addition of addend to $LiAlH_4$. [d] Reference 1. [e] Includes direct and inverse method of addition. [f] This work. [g] *Ca.* 1% **2** in product. [h] 34% **2** in product. [i] Separate experiment. [j] 10% **2** in product. [k] Trace of **2** in product. [l] 48% **2** in product. [m] 16% **2** in product. [n] 9% **2** in product. [o] 31% **2** in product. [p] 6% **2** in product. [q] 48% **2** in product. [r] 13% **2** in product.

The data for the secondary alkoxyhydrides are quite interesting. Reagents formed from isopropyl alcohol, *sec*-butyl alcohol, 3-methyl-2-butanol, cyclohexanone, and cyclopentanol (entries 6–8, 11, 12) showed the same or slightly higher stereoselectivities as $LiAlH_4$. This could either mean that the disproportionation mechanism[1] of hydride reduction is correct or it could be that *these* alkoxyhydrides are simply not stereoselective in the reduction of **2**. However, the reagents formed from 3,3-dimethyl-2-butanol (entry 9) and di-*tert*-butyl ketone (entry 10) are highly selective, with the latter giving the less stable axial alcohol[10] almost exclusively. Clearly, with these two more hindered secondary addends, disproportionation cannot be a major factor. It may be that steric hindrance (B strain) lowers the stability of the disproportionation product, *i.e.*, the tetraalkoxyaluminum species.[11] While experiments establishing the degree of association of these reagents would be useful,[3] it does not appear likely that the increase in stereoselectivity in going from entry 8 to entry 9 and then to entry 10 can be due to a significant increase in association, and the increase is attributed to steric approach control[8] due to the bulky alkoxy groups. It should be noted that lithium aluminum tri-*tert*-butoxyhydride is quite highly selective in the reduction of **2** in both ether (73% *trans*-**3**) and tetrahydrofuran (88% *trans*-**3**).[1]

While considerable amounts of unreacted **2** were found in some of the reduction products (Table I), equilibration of the products is known not to occur in these hydride reductions.[9,12,13] Duplicate experiments showed that the results are highly reproducible.

(4) D. J. Cram and F. D. Greene, *J. Amer. Chem. Soc.*, **75**, 6005 (1953).
(5) Y. Senda, S. Mitsui, R. Ono, and S. Hosokawa, *Bull. Chem. Soc. Jap.*, **44**, 2737 (1971).
(6) H. C. Brown and C. J. Shoaf, *J. Amer. Chem. Soc.*, **86**, 1079 (1964).
(7) G. Hesse and R. Schrödel, *Justus Liebigs Ann. Chem.*, **607**, 24 (1957).
(8) E. L. Eliel and Y. Senda, *Tetrahedron*, **26**, 2411 (1970).
(9) For further support of the disproportionation, see D. C. Ayres and R. Sawdaye, *Chem. Commun.*, 527 (1966).
(10) E. L. Eliel and H. Haubenstock, *J. Org. Chem.*, **26**, 3504 (1961).
(11) See also O. Cervinka, *Collect. Czech. Chem. Commun.*, **30**, 2403 (1965).
(12) A. H. Beckett, N. J. Harper, A. D. J. Balon, and T. H. E. Watts, *Tetrahedron*, **6**, 319 (1959).
(13) O. R. Vail and D. M. S. Wheeler, *J. Org. Chem.*, **27**, 3803 (1962).

In summary, the steric bulk of primary alkoxy groups in alkoxyhydrides (1) does not appear to have a major effect on their stereoselectivities. However, bulky secondary (and tertiary) alkoxy groups provide reagents with considerable steric requirements. The reagent formed from di-*tert*-butyl ketone is a remarkably highly selective one and should prove useful in synthetic applications. The great preference for formation of the less stable isomer, *trans*-**3**, compares with that observed in the kinetically controlled reduction of **2** with triisobutylaluminum.[14]

Experimental Section

Isopropyl alcohol, *sec*-butyl alcohol, isobutyl alcohol, and cyclopentanol were chromatoquality reagents purchased from Matheson Coleman and Bell. The other addends were commercially obtained and their purities were checked by glc. Gas–liquid partition chromatography was carried out with a Hewlett-Packard 5750 gas chromatograph. For the analyses of the reduction product, a 10-ft 10% Carbowax 20M acid washed and silanized column was used at 145°.

Reaction of $LiAlH_4$ with 3,3-Dimethyl-2-butanol. Reduction of Dihydroisophorone (2).—The procedure for this reaction is typical of that used in all the reductions. Standardized lithium aluminum hydride in ether (40 ml, 0.28 *M*, 0.011 mol of $LiAlH_4$) was added by pipet to a 250-ml reactor equipped with a magnetic stirrer, equilibrated addition funnel, and condenser. A solution of the alcohol (3.373 g, 0.033 mol) in 15 ml of diethyl ether was added dropwise, with stirring. After stirring for 20 min, a solution of **2**[10] (1.54 g, 0.011 mol) in 10 ml of ether was added dropwise. After 30 min, the cooled reaction mixture was hydrolyzed with water, followed by 10% sulfuric acid. The aqueous portion was extracted with ether and the combined ether solution was washed with saturated sodium bicarbonate and salt solution and dried over anhydrous $MgSO_4$. The solution was concentrated by distillation through a 18-in. helix packed fractionating column (oil bath temperature to 63°). The concentrated solution was directly analyzed by glc showing 77% of the *trans* (axial)-**3** and 23% of *cis*-**3**. Unreacted **2** represented 9% of the three components.

Registry No.—**1** (R = H), 16853-85-3; **1** (R = Me), 12076-93-6; **1** (R = Et), 17250-30-5; **1** (R = *i*-Bu), 38884-26-3; **1** [R = $(CH_3)_3CCH_2$], 38884-27-4; **1** (R = *i*-Pr), 38960-86-0; **1** (R = *sec*-Bu), 38884-28-5; **1** [R = $(CH_3)_2CHCHCH_3$], 38884-29-6; **1** [R = $(CH_3)_3$-$CCHCH_3$], 38884-30-9; **1** (R = *t*-BuCHBu-*t*), 38884-31-0; **1** (R = cyclohexyl), 38884-32-1; **1** (R = cyclopentyl), 38884-33-2; **2**, 873-94-9; *cis*-**3**, 933-48-2; *trans*-**3**, 767-54-4; 3,3-dimethyl-2-butanol, 464-07-3.

(14) H. Haubenstock and E. B. Davidson, *J. Org. Chem.*, **28**, 2772 (1963).

Base-Induced Cyclizations of Diethyl 4-Oxa-6-heptyne-1,1-dicarboxylate[1]

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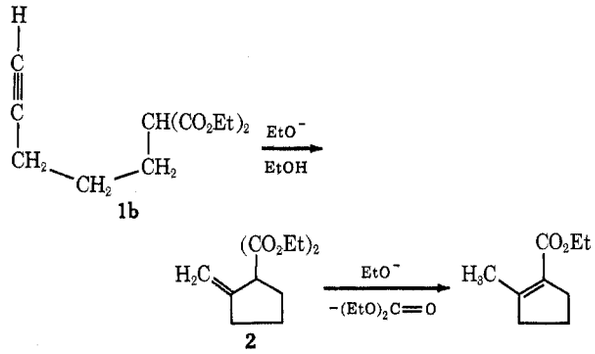
As a continuation of efforts[2] directed toward determining the scope and limitations of reactions with base of compounds that can be represented generally by **1**, we prepared diethyl 4-oxa-6-heptyne-1,1-di-

$$HC{\equiv}CCH_2Y(CH_2)_nZH$$
1

carboxylate [**1a**, Y = O, Z = $C(CO_2Et)_2$, n = 2] and studied its reaction with sodium ethoxide in ethanol and potassium *tert*-butoxide in dimethyl sulfoxide.

Eglinton and Whiting[3] reported that it was possible to isolate 1,1-dicarboethoxy-2-methylenecyclopentane (**2**) from the reaction of diethyl malonate, sodium ethoxide, and 4-pentynyl *p*-toluenesulfonate in refluxing ethanol, and they showed that the product arose by cyclization of the intermediate diethyl 5-hexyne-1,1-dicarboxylate [**1b**, Y = CH_2, Z = $C(CO_2Et)_2$, n = 1].[4] They observed that, when more than 1 equiv of sodium ethoxide was used, decarboethoxylation of the cyclic diester and migration of the double bond took place.



Significantly, Eglinton and Whiting[3] found that diethyl 6-heptyne-1,1-dicarboxylate [**1**, Y = CH_2, Z = $C(CO_2Et)_2$, n = 2] would not cyclize under conditions which converted **1b** to **2**.

1a was prepared conveniently by alkylation of diethyl malonate with 6-bromo-4-oxa-1-hexyne.[5] Treatment of **1a** with a slight excess of sodium ethoxide in boiling ethanol for 8 hr gave a 78% conversion to a 1:1.4 mixture of 4-carboethoxy-5,6-dihydro-3-methyl-1,4-oxin (**3**) and 4-carboethoxy-2,3,6,7-tetrahydrooxepin (**4**), which could be separated by fractional distillation. In a separate experiment a 74% yield of diethyl carbonate was also obtained. Structures were assigned to **3** and **4** on the basis of their spectroscopic properties and analytical data.

By analogy with the behavior of propargyloxyethanols (**1**, Y = Z = O, n = 2) when treated with base in hydroxylic solvents,[2a] the first step in formation of **3** and **4** can be pictured as intramolecular nucleophilic addition of substituted malonate anion to the internal and terminal acetylenic carbons to give the diesters **3a** and **4a**.[6] In the presence of excess base, this is followed by decarboethoxylation of the diesters with formation of diethyl carbonate and migration of the double bonds. It seems likely that decarboethoxylation

(1) Supported in part by Grant CA-10740 from the U. S. Public Health Service.

(2) (a) A. T. Bottini and J. G. Maroski, *J. Org. Chem.*, **38**, 1455 (1973); (b) A. T. Bottini and E. F. Böttner, *ibid.*, **31**, 586 (1966), and references cited therein.

(3) G. Eglinton and M. C. Whiting, *J. Chem. Soc.*, 3052 (1953).

(4) Similar cyclizations of *cis*-hex-5-yn-3-ene-1,1-dicarboxylates to 1,1-dicarboethoxy-2-methylene-3-cyclopentenes have been reported. See M. V. Mavrov and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1559 (1967), and references cited therein.

(5) D. Black, S. Landor, A. Patel, and P. Whiter, *J. Chem. Soc. C*, 2260 (1967).

(6) The faster rate of cyclization of **1a** relative to diethyl 6-heptyne-1,1-dicarboxylate[3] on treatment with sodium ethoxide in ethanol is most likely due to the electron-withdrawing effect of oxygen, which makes the acetylenic carbons more susceptible to nucleophilic attack.