Reduction of δ-Lactones and Hindered Esters with Diborane[1]

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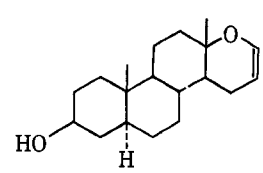
Reduction of certain esters and acetals to ethers (**5** to **6**, **9** to **10**, and **9** to **11**) with diborane–tetrahydrofuran has been studied in detail. The experimental results were also interpreted in terms of possible mechanistic pathways for ester → ether, ester → hemiacetal, and acetal → ether reduction reactions using boron hydride reagents.

The reduction of a variety of esters to ethers has been investigated employing lithium aluminum hydride or sodium borohydride and a large excess of boron trifluoride.[3] The reducing agent in such reactions was presumed to be diborane with excess Lewis acid serving to form a necessary oxonium ion.[3a,4] While this interpretation may still be generally valid, we would like to report a few examples of such reactions where employment of a large excess of boron trifluoride etherate is not necessary. Also, the scope and possible mechanism of the reduction of esters with borane reagents was examined.

Results

Although reduction of lactone **1** (Chart I) with sodium borohydride–boron trifluoride etherate was found in the present study to give 44% ether **2a** and 42% glycol **3**, the analogous reaction of lactone **4** has been shown to give only the corresponding glycol in nearly quantitative yield.[5] This example serves to further illustrate the effect of alkyl substituents in the vicinity of the ester group upon the course of reaction.[6] Reduction of lactone **1** with diborane–tetrahydrofuran–boron trifluoride etherate gave a lower yield of ether **2a** (21%) and a higher yield of glycol **3** (52%)[7] and suggested that the borohydride anion might be participating in the reduction reaction. Utility of the Lewis acid, boron trifluoride, was emphasized by the 70% yield of glycol **3** arising from reduction of lactone **1** with diborane–tetrahydrofuran;[8] only a trace of ether **2a** could be detected. While esters such as ethyl caproate upon reduction with diborane–tetrahydrofuran were reported to provide good yields of the corresponding alcohols,[9] sterically hindered ester **5** upon reduction with excess (3 mol equiv) diborane–tetrahydrofuran provided 70–90% yields of ether **6a**.[10] We believe that this is the first unequivocal example of the reduction of an ester to an ether by diborane–tetrahydrofuran *alone*[11] and emphasizes again that substituents near the ester group favor ether formation.

Versatility of borane reduction involving conformationally stable δ-lactones is amply illustrated by the following reactions. Reduction of δ-lactones **7** and **9** with sodium borohydride–boron trifluoride gave tetrahydropyrans **8a** (75%) and **10a** (44%). Under identical conditions hemiacetal **8b** and methyl acetal **10b** reacted with sodium borohydride–boron trifluoride to yield the same tetrahydropyrans, **8a** (44%) and **10a** (47%), respectively. The acetal reduction reactions demonstrate that sodium borohydride–boron trifluoride can reduce such functional groups to ethers. Methyl acetal **10b** was used instead of hemiacetal **10c** because of more favorable solubility behavior. Treatment of lactone **1** and ester **5** with sodium borodeuteride–boron trifluoride gave ethers **2b** (41%) and **6b** (70%), respectively, thus illustrating a method for labeling the α position of certain β-substituted ethers. Reaction of δ-lactones **7** and **9** with approximately 1 mol equiv of diborane–tetrahydrofuran for a short period yielded the corresponding hemiacetals, **8b** (82%) and **10c** (95%).[12] Prolonged treatment of δ-lactone **9** with 1 mol equiv of diborane–tetrahydrofuran gave (52%) dihydropyran **11** or with approximately 3 mol equiv of diborane–tetrahydrofuran, tetrahydropyran **10a** (55%).[13] The new route to dihydropyrans represented by transformation **9** → **11** may result from elimination of the dialkoxyborine precursor of hemiacetal **10c**. The product olefin **11** might



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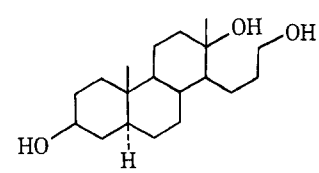

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(1) (a) Steroids and Related Natural Products. 64. For part 63, refer to G. R. Pettit and T. R. Kasturi, *J. Med. Chem.*, **13**, 1244 (1970). (b) For a preliminary report pertaining to part of this study, see G. R. Pettit and J. R. Dias, *Chem. Commun.*, 901 (1970). (c) This investigation was supported by Public Health Service Research Grants CA-10115-02 and CA-11451-01 from the National Cancer Institute and is based in part on the Ph.D. dissertation of J. R. Dias, Arizona State University, 1970.

(2) NIH Predoctoral Fellow, 1968–1970.

(3) (a) G. R. Pettit and T. R. Kasturi, *J. Org. Chem.*, **26**, 4557 (1961); (b) G. R. Pettit and W. J. Evers, *Can. J. Chem.*, **44**, 1097 (1966).

(4) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, pp 48, 49.

(5) G. R. Pettit, B. Green, T. R. Kasturi, and U. R. Ghatak, *Tetrahedron*, **18**, 953 (1962).

(6) See G. R. Pettit and D. M. Piatak, *J. Org. Chem.*, **27**, 2127 (1962), for other examples.

(7) In prior experiments we also observed that the diborane–tetrahydrofuran–boron trifluoride reagent leads to lower yields of ether than with lithium aluminum hydride–boron trifluoride.[3a]

(8) Previously it was shown that optimum yields of ether were obtained when boron trifluoride etherate was present in a large excess;[6] *cf.* K. M. Biswas and A. H. Jackson, *J. Chem. Soc. C*, 1667 (1970).

(9) H. C. Brown and W. Korytnyk, *J. Amer. Chem. Soc.*, **82**, 3866 (1960).

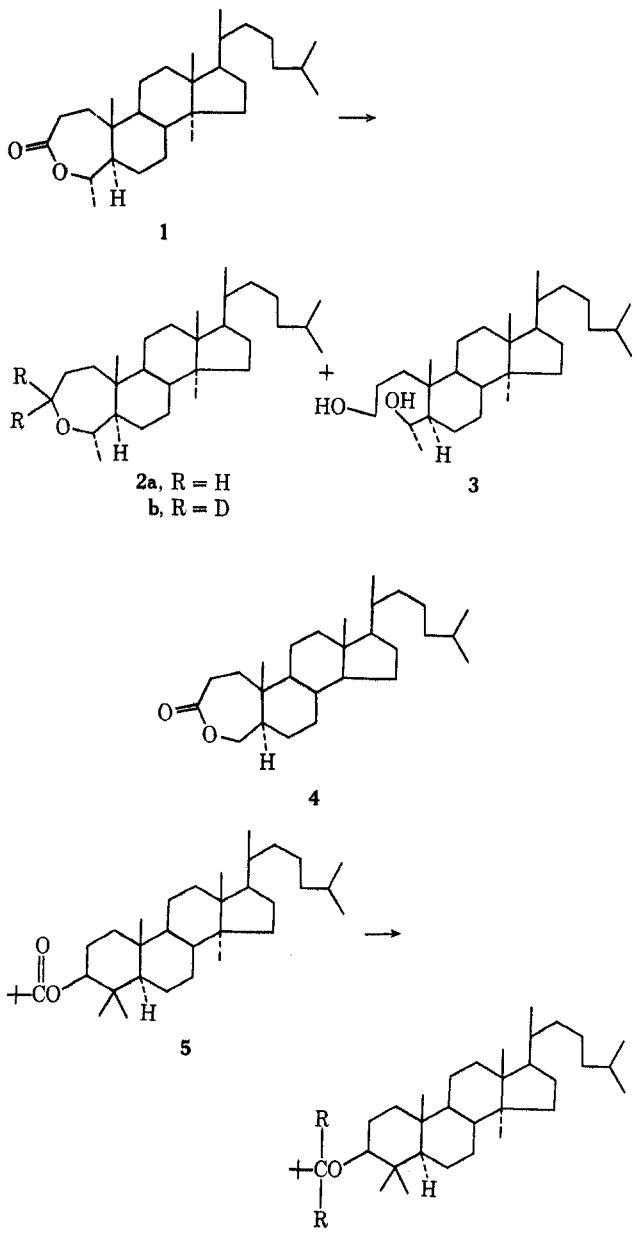
(10) Neopentyl ether **6a** would be difficult to prepare in good yield by the usual Williamson ether synthesis.

(11) Propyl ethers have been detected in the reaction of diborane–tetrahydrofuran with propionyl derivatives of alginic acid: J. H. Manning and J. W. Green, *J. Chem. Soc. C*, 2357 (1967). The reduction of amides to amines with diborane–tetrahydrofuran is formally analogous to these reactions. See W. V. Curran and R. B. Angier, *J. Org. Chem.*, **31**, 3867 (1966), for pertinent examples.

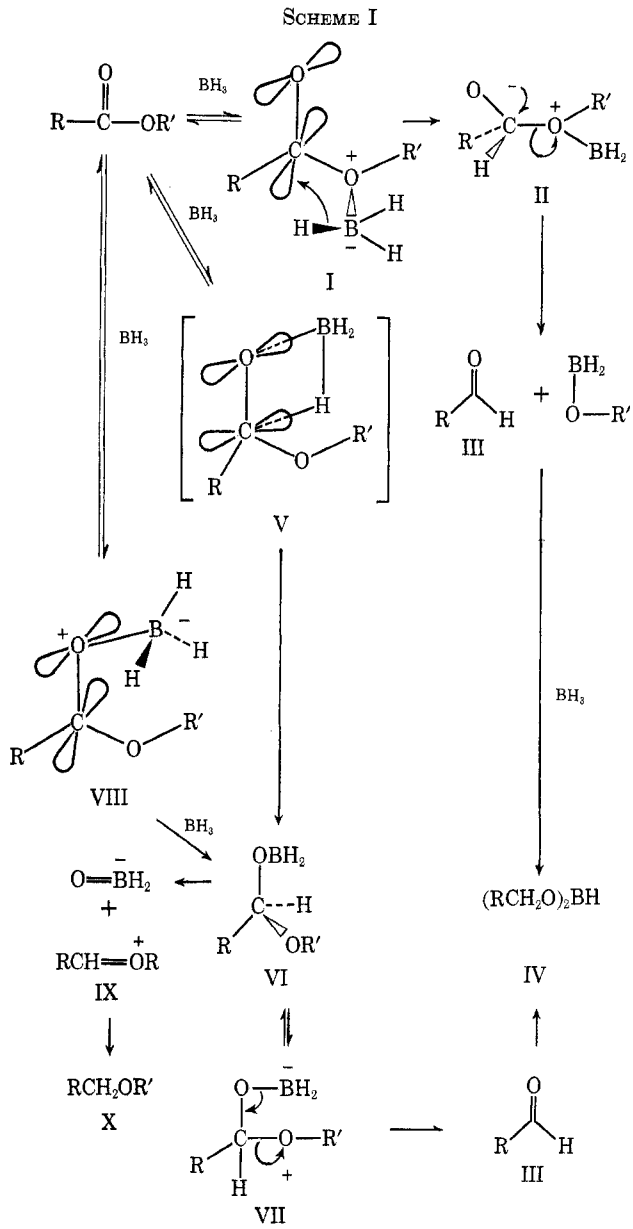
(12) G. R. Pettit, J. C. Knight, and W. J. Evers, *Can. J. Chem.*, **44**, 807 (1966).

(13) Reaction of coumarin with diborane–tetrahydrofuran has been reported to give a tetrahydropyran: B. S. Kirkiacharian and D. Raulais, *C. R. Acad. Sci.*, **269c**, 464 (1969); W. C. Still and D. J. Goldsmith, *J. Org. Chem.*, **35**, 2282 (1970).

CHART I



SCHEME I



then undergo hydroboration to **10a** with excess diborane–tetrahydrofuran.[14,15]

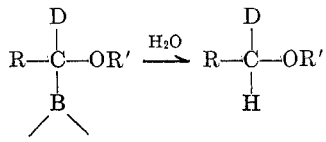
Discussion

Scheme I, an elaboration of one previously given,[15] presents some possible reaction pathways in the reduction of esters with borane. This scheme is quite general in that ethers (X) and products corresponding to intermediates IV (*cf.* alcohol **3**), VI (*cf.* hemiacetals **8b**, **10c**), and IX (*cf.* dihydropyran **11**) have all been isolated by just varying conditions or substrates. Reduction of acetals **8b** and **10b** to tetrahydropyrans **8a** and **10a**, respectively, supports the possibility that VI is an immediate precursor of IX or X. Isolation of deuterated eth-

(14) Alternatively, an oxygen-stabilized carbonium ion intermediate (*cf.* IX) may be reduced.

(15) In early work it was shown that diborane reduction of ketones and aldehydes (*e.g.*, acetaldehyde) involved only two of the three hydrogens of borane: H. C. Brown, H. I. Schlesinger, and A. B. Burg., *J. Amer. Chem. Soc.*, **61**, 673 (1939). The electronegativity requirements of two oxygens attached to borane must contribute to inertness of the third hydrogen, since all three hydrogens are consumed in the reaction of diborane with olefins (*e.g.*, propene).

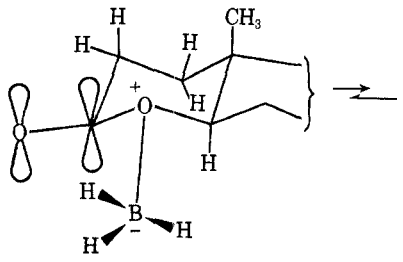
ers **2b** and **6b** is consistent with the proposed mechanistic modes presented in Scheme I and excludes the possibility expressed in eq 1. Isolation of cyclic hemiacetals



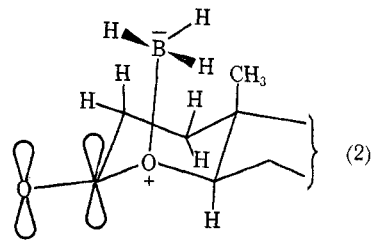
(1)

8b and **10c** demonstrates that for these systems the conversion of VI to IX is the rate-determining step. Possible F strain due to substituents in the vicinity of the ester function would inhibit formation of intermediates I or VII and thus favor ether formation (VI to X) by thwarting alcohol production.

The conversion of fused δ-lactones to alcohols can be made less favorable by inhibiting transformation I to II and/or VI to VII. Facile intramolecular hydride transfer in I can only occur when the O–B–H bonds lie in the same plane as the p orbital of the carbonyl carbon. Thus the axial-like conformer ii of eq 2 is the one which



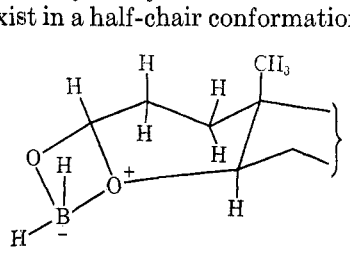
i



(2)

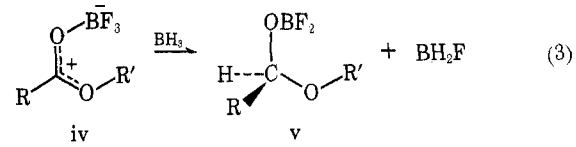
ii

is favorably disposed for intramolecular hydride transfer but is less populated than the equatorial-like conformer i due to 1,3-diaxial interaction of the O–BH_3 group with the 19-methyl and the C-2 hydrogen. The conversion of VI to VII would be retarded in δ-lactones in comparison to acyclic esters because of involvement of the strained bicyclic system iii in which the lactone ring would exist in a half-chair conformation.



iii

In the above discussion, no distinction between the two possible paths (I → II → III or VI → VII → III) by which alcohols are formed was intended. However, to explain how the Lewis acid enhances ether formation one is forced to favor the I → II → III path, *i.e.*, alcohols are formed *via* coordination of borane with alkoxy oxygen; this is a conclusion reached previously.[15] If one assumes that VI → VII → III is mainly inoperative, then boron trifluoride coordination with the carbonyl oxygen would increase production of v (*cf.* VI),[3a,16] whereas coordination with the alkoxy oxygen would be uneventful. Here iv would have a more intense charge and be more prominent than VIII. To explain why a



(3)

iv v

mixture of sodium borohydride–boron trifluoride gives a higher yield of ether than a mixture of diborane–tetrahydrofuran–boron trifluoride, one is again led to favor the I → II → III path since a higher immediate concentration of BH_3 in the latter system would result in a higher population if I and not greatly influence the fate of intermediate VI. In this respect, the more nucleophilic borohydride anion would increase the rate of reaction proceeding through VIII → VI → X.[17]

Conclusion

The preceding experimental observations can be rationalized if we presume that the reaction paths proceeding through V and VII are mainly inoperative and alcohols are formed by initial coordination of borane to the alkoxy oxygen; factors disturbing this coordination slow alcohol production and permit alternative reaction paths to become more important. This mechanism eliminates the necessity of postulating a fluoroborohydride intermediate[16] with selective reducing properties. The latter proposal was excluded by the first example of ether formation from a hindered ester using only diborane–tetrahydrofuran. Also, there is no reason to believe that in the reactions utilizing sodium borohydride–boron trifluoride etherate, in a mixture of tetrahydrofuran–diglyme, that all the borohydride anion is instantaneously converted to diborane.[18] Instead, in the reactions where sodium borohydride and diglyme were added last, the conversion of sodium borohydride to diborane is probably slow enough to allow some participation by the borohydride anion.

Experimental Section

The diborane–tetrahydrofuran solution (approximately 1.0 *M* in borane), sodium borohydride (98%), and sodium borodeuteride were obtained from the Metal Hydrides Division of Ventron, Beverly, Mass. Boron trifluoride etherate (7.9 mmol/ml), practical grade obtained from J. T. Baker Chemical Co., was redistilled, bp 123–125° (729 Torr). Tetrahydrofuran was distilled from lithium aluminum hydride and stored over molecular sieves (4A). Diglyme was also stored over molecular sieves (4A). The reactions with sodium borohydride and diborane–tetrahydrofuran were performed with exclusion of moisture, and solvents were concentrated under reduced pressure on a rotating evaporator.

Alumina (Merck acid washed and basic) and silica gel (E. Merck, A. G. Darmstadt, Germany, 0.2–0.5 mm) were used for column chromatography. Silica gel HF_{254} (E. Merck) was used

(16) Refer to R. Koster, *Angew. Chem.*, **73**, 66 (1961).

(17) In this connection, it should be noted that, under usual reaction conditions, carboxylic acid esters are not reduced by sodium borohydride.

(18) Commercial sodium borohydride used with a poor solvent, such as ether, results in a slow reaction with boron trifluoride giving a low yield of diborane: H. C. Brown and P. A. Tierney, *J. Amer. Chem. Soc.*, **80**, 1552 (1958). In the present study diglyme, a generally inferior solvent for steroids, was mixed with tetrahydrofuran, a poor solvent for sodium borohydride.

for preparative thin layer while silica gel HF_{254} spread on microscope slides was used for thin layer chromatograms (tlc). The chromatograms were usually developed with benzene–ethyl acetate (5:1) and observed after using iodine vapor or by charring with 2% ceric sulfate in 2 *N* sulfuric acid. The preparative thin layer plates were viewed under ultraviolet light.

Elemental microanalyses were performed by the laboratory of Dr. A. Bernhardt, 5251 Elbach uber Engelskirchen, West Germany. All samples submitted for analysis exhibited a single spot on a tlc. Melting points were determined on a Kofler melting point apparatus. All spectra were recorded by the author or Miss K. Reimer as follows: infrared, recorded on Beckman IR-12 in potassium bromide or chloroform solution; pmr, recorded on a Varian A-60 (60 MHz) in deuteriochloroform (TMS internal standard). The mass spectra were determined using an Atlas CH-4B (low resolution) or Atlas SM-1B (high resolution) by Dr. P. Brown, E. Bebee, and R. Scott.

3-Oxo-4-oxa-4aα,14α-dimethyl-*A*-homo-5α-cholestane (1).—Reaction of 3-oxo-5α-lanostane with *m*-chloroperbenzoic acid in the presence of sulfuric acid yielded 29% of lactone 1:[19] mp 185.5–186.2° (needles from ethyl acetate); ν_{max} (0.1 *M* in chloroform) 1730 cm^{-1}; pmr δ 4.50 (m, 1 p, 4β-H), 2.58 (m, 2 p, C-2), 1.25 (d, J = 6.5 Hz, 4α-CH_3), 0.98 (s, 19-CH_3), 0.92 (peak), 0.80 (peak); RD in chloroform (*c* 1.75 g/100 ml) $[\alpha]_{650}$ +12°, $[\alpha]_{589}$ +15°, $[\alpha]_{500}$ +24°, $[\alpha]_{400}$ +42°, $[\alpha]_{300}$ +92°, $[\alpha]_{264}$ +114° (peak), $[\alpha]_{250}$ +71°, and $[\alpha]_{240}$ 0.0°; mass spectrum M^+ 430 (100%).

Anal. Calcd for $C_{29}H_{50}O_2$: C, 80.87; H, 11.70. Found: C, 80.68; H, 11.83.

4-Oxa-4aα,14α-dimethyl-*A*-homo-5α-cholestane (2a). Method A.—Sodium borohydride (90 mg, 2.3 mmol) was added to δ-lactone 1 (215 mg, 0.5 mmol) in tetrahydrofuran (3 ml, 24 mmol)–boron trifluoride etherate (2 ml). After evolution of gas subsided, diglyme (2 ml) was added to the heterogeneous mixture, which was allowed to stand for 0.5 hr and then heating at reflux for 1.5 hr. The cooled mixture was treated with saturated sodium carbonate and water (5 ml). The ethereal phase was separated and the aqueous portion was extracted with ether (five 10-ml portions). The combined ether extract was concentrated and chromatographed (preparative thin layer) on silica gel using benzene as mobile phase. Elution of the higher R_f band with ether yielded 91 mg (44%) of ether 2a as white plates: mp 69–70°; ν_{max} (KBr) 2940, 1450, 1360, and 1145 cm^{-1}; pmr δ 3.59 (m, 3 p, C-3 and C-4a), 1.22 (s), 1.10 (s), and 0.80 (s); mass spectrum 261 (100%), $M^+ - 15$ (30%), and M^+ 416 (33%).

Anal. Calcd for $C_{29}H_{52}O$ (416.7): C, 83.58; H, 12.58. Found: C, 83.68; H, 12.63.

Elution of the lower R_f band with ether containing 10% methanol yielded 93 mg (42%) of glycol **3** as colorless needles: mp 154.5–156.0°; ν_{max} (KBr) 3370, 2940, 1450, 1370, and 1060 cm^{-1}; pmr δ 4.05 (m, 1 p, C-4a), 3.61 (m, 2 p, C-3), 2.70 (s, 2 p, removed by D_2O), 1.18 (s), 1.10 (s), 0.93 (s, 6 p), 0.83 (s), and 0.76 (s); mass spectrum 263 (100%), $M^+ - 18$ (15%), $M^+ - 15$ (4%), $M^+ - 2$ (432, 0.1%).

Anal. Calcd for $C_{29}H_{54}O_2$ (434.7): C, 80.12; H, 12.52. Found: C, 80.00; H, 12.16.

Method B.—In method B reaction conditions identical with those summarized in method A were used except that diborane–tetrahydrofuran (2.4 ml) was substituted for sodium borohydride–tetrahydrofuran. The yield of ether 2a was 44 mg (21%) and of glycol **3** was 113 mg (52%).

3,4-Dihydroxy-4(*S*),14α-dimethyl-3,4-seco-5α-cholestane (3). Method A.—Diborane–tetrahydrofuran (3 ml or 6 ml) was added to a solution of lactone 1 (0.43 g) in tetrahydrofuran (6 ml). After the reaction mixture was allowed to stand for 16 hr or 0.5 hr, respectively, ice–water (16 ml) was added. The white solid was collected (0.33 g) and recrystallized from ethyl acetate to afford 0.27 g of glistening needles, mp 155.8–156.8°; the spectrum of alcohol **3** was identical with that already described in the preceding experiment.

Method B.—Lithium aluminum hydride (55 mg) was added to a solution of lactone 1 (43 mg) in tetrahydrofuran (5 ml). After standing at room temperature for approximately 1 week, the gray gelatinous mass was treated with ice–water (5 ml). The solid was collected, washed with diluted hydrochloric acid, and recrystallized from ethyl acetate. Glistening needles (25 mg), mp 156–157°, were obtained having identical tlc and spectra with that product obtained by method A.

Lanostanyl Neopentyl Ether (6a).—A 2.40-g specimen of 3β-pivaloxy-5α-lanostane (**5**) was made in quantitative yield from the reaction of 3β-hydroxy-5α-lanostane with pivaloyl chloride in tetrahydrofuran–pyridine: mp 186–188° (colorless needles from ethyl acetate); ν_{max} 1720 (sharp) and 1160 cm^{-1}; pmr δ 4.47 (hump, 1 p, C-3 axial hydrogen), and 1.23 (s, 9 p, pivalate methyls).

Anal. Calcd for $C_{35}H_{62}O_2$: C, 81.65; H, 12.14. Found: C, 81.70; H, 11.90.

A closed vessel containing a solution composed of ester **5** (0.69 g, 1.33 mmol), tetrahydrofuran (3.6 ml), and diborane–tetrahydrofuran (5.0 ml) was allowed to stand at room temperature for 3 days. Methanol (40 ml) was added and solvent was evaporated. Preparative thin layer chromatography using ligroin (bp 60–90°) as mobile phase and elution of the lower zone with ether gave 53 mg (9%) of 3β-hydroxy-5α-lanostane. Elution of the upper zone with ether yielded 0.53 g (79%) of ether **6a**: mp 183.0–184.0 (needles); ν_{max} (0.1 *M* in chloroform) 2960, 1470 (med), 1370, and 11.08 cm^{-1} (str); pmr δ 3.25 (d, 1 p, J = 8 Hz), 2.84 (d, 1 p, J = 8 Hz), 2.62 (hump, 1 p, 3α-H), 0.83 (large peak), and 0.78 (peak); mass spectrum 373 (100%) and M^+ 500 (2.5%).

Anal. Calcd for $C_{35}H_{64}O$ (500): C, 83.93; H, 12.88. Found: C, 84.22; H, 13.00.

4-Oxa-14α-methyl-5β-cholestane (8a). Method A. From Lactone 7.—A mixture of δ-lactone 7[20] (0.20 g, 0.5 mmol), tetrahydrofuran (2 ml), boron trifluoride etherate (2 ml, 16 mmol), and sodium borohydride (90 mg, 2.3 mmol) was allowed to stand until evolution of gas subsided. Diglyme (2 ml) was added and the mixture was allowed to stand at room temperature for 30 min. The mixture was heated at reflux for 2 hr, cooled, and treated with water (3 ml) followed by saturated sodium carbonate. Ether (12 ml) was added and the ethereal layer was washed with water (20 ml) and saturated sodium chloride (20 ml). Solvent was removed, and the residue was separated by preparative thin layer chromatography (benzene mobile phase and elution of uppermost zone with ether) to give 0.15 g (75%) of an oil which crystallized as needles upon storage under reduced pressure: mp 53–59°; ν_{max} (neat) 2960, 1460, 1370, 1090, and 1020 cm^{-1}; pmr δ 4.04 (crude doublet, J = 12 Hz, 1 p, 3α-H), 3.50 (doublet, J = 12 Hz, 1 p, 3β-H), 3.10 (peak, 1 p, 5β-H), 0.93 (s, C-19), 0.88 (s), 0.83 (s) and 0.80 (s); mass spectrum M^+ 388.3717 (100%; Beynon calculated mass 388.3705).

Anal. Calcd for $C_{27}H_{48}O$: C, 83.43; H, 12.45. Found: C, 83.22; H, 12.02.

Method B. From Acetal 8b.—A solution of lactone 7 (0.40 g, 1.0 mmol), tetrahydrofuran (2 ml), and diborane–tetrahydrofuran solution (1.4 ml) was allowed to stand at room temperature for 30 min. The reaction mixture was treated with methanol (10 ml) and concentrated to dryness. A solution of the residue in ethyl acetate–chloroform was filtered (Filter aid) and the solvent was removed to yield 0.40 g of hemiacetal **8b** as a colorless solid: mp 124–134°; ν_{max} (KBr) 3450, 2960, 1460, 1370, 1010, and 930 cm^{-1}; pmr δ 5.36 (peak, 0.5 p, equatorial 3α-H), 4.57 (hump, 0.5 p, axial 3β-H), 3.30 (peak, 1 p, 5β-H), 0.83 (m, 18 p, methyl); mass spectrum 371 (100%), $M^+ - 15$ (86%), and M^+ 404 (9%).

Anal. Calcd for $C_{27}H_{48}O_2$ (404.7): C, 80.14; H, 11.96. Found: C, 79.99; H, 11.88.

A solution of hemiacetal **8b** (0.12 g) in methanol (15 ml) containing 1 drop of concentrated hydrobromic acid was allowed to stand at room temperature for 2 days. The reaction mixture was concentrated, and the residue was purified by preparative thin layer chromatography using benzene–petroleum ether (bp 30–60°) (5:1) as mobile phase. Elution (ether) of the upper zone yielded 58 mg of the epimeric methyl acetals as an oil: ν_{max} (neat) 2960, 1460, 1370, 1120, 1060, and 1010 cm^{-1}; pmr δ 4.74 (peak, 0.7 p, equatorial 3α-H), 4.30 (hump, 0.3 p, axial 3β-H), 3.58 (peak, 1 p, 5β-H), 3.47 (s, 0.9 p, 3α-methoxy), 3.35 (s, 2.1 p, 3β-methoxy), and 0.83 (m, 18 p).

A mixture of hemiacetal **8b** (0.23 g), tetrahydrofuran (2.5 ml), boron trifluoride etherate (2 ml), and sodium borohydride (90 mg) was allowed to stand at room temperature for 20 min. Diglyme (2 ml) was added and 30 min later the mixture was heated at reflux for 1.5 hr and cooled. After adding water, saturated sodium carbonate, and ether (30 ml in three aliquots)

(19) J. S. E. Holker, W. R. Jones, and P. J. Ramm, *J. Chem. Soc. C*, 357 (1969).

(20) G. R. Pettit and J. R. Dias, *Can. J. Chem.*, **47**, 1091 (1969).

the ethereal extract was washed with water and saturated sodium chloride solution. The ether was removed and the yellow oil was separated by preparative thin layer chromatography using benzene as mobile phase. Elution of the upper zone with ether yielded 0.10 g (44%) of oil which solidified during several days storage in a vacuum desiccator. The needles, mp 53–60°, obtained were identical[21] with a specimen of ether **8a**.

3β-Hydroxy-17a-oxa-*D*-homo-5α-androstane (10a).[3a] Method A. From Lactone 9.—Sodium borohydride (0.28 g, 7 mmol) was added to a mixture of lactone **9** (0.47 g, 1.5 mmol), tetrahydrofuran (5 ml), and boron trifluoride etherate (6 ml, 48 mmol). After generation of gas terminated and 0.5 hr elapsed, diglyme (5 ml) was slowly (to prevent frothing) added. After standing at room temperature for 28 hr methanol (10 ml) was added and solvent was concentrated to 5 ml. Water (50 ml) was added to the suspension, and the brown solid was collected. Preparative thin layer chromatography (with 45:45:10 benzene–ethyl acetate–methanol) and elution of the upper zone with ether gave 0.20 g (44%) of ether **10a** as a granular white solid: mp 182.5–185.0°; ν_{max} (KBr) 3450 (sharp), 2960, 1440, 1380, and 1080 cm^{-1}; pmr δ 3.67 (m, 3 p, 3α proton and C-17), 2.22 (s, 1 p, removed by D_2O), 1.15 (s, 3 p, C-19), and 0.76 (s, 3 p, C-18); mass spectrum M$^+$ 292 (8%).

Method B. From Acetal 10b.—A solution of hemiacetal **10c**[22] (0.56 g) contaminated with glycol **12** in absolute methanol (25 ml) containing 1 drop of concentrated hydrobromic acid was allowed to stand for 48 hr. The reaction mixture was concentrated, and the residue was purified by preparative thin layer chromatography with benzene–ethyl acetate–methanol (45:45:10). Upon elution (ether) of the upper zone 0.38 g of the epimeric methyl acetals **10b** was obtained as colorless needles: mp 115–125° (clearing at 190–200°); ν_{max} (KBr) 3500 (med), 2960, 1450, 1380, 1130, and 1070 cm^{-1}; pmr δ 4.68 (peak, 0.7 p, equatorial 17α-H), 3.59 (hump, 1.3 p, axial 3α-H and 17β-H), 3.45 (s, 2 p, 17α-methoxy), 3.38 (s, 1 p, 17β-methoxy), 1.15 (s, 3 p, C-19), and 0.78 (s, 3 p, C-18); mass spectrum 215 (100%), 234 (57%), M$^+$ − 32 (56%, loss of methanol), M$^+$ − 15 (3%), M$^+$ 322 (0.1%).

Anal. Calcd for $C_{20}H_{34}O_3$ (322.5): C, 74.49; H, 1063. Found: C, 74.37; H, 10.69.

Elution (ether) of the lower zone gave 0.10 g of glycol **12** as prisms: mp 224–226° (from ethyl acetate–methanol); ν_{max} (KBr) 3350 (broad and strong), 2960, 1440, 1370, 1340, 1150, 1080, 1040, and 940 cm^{-1}; pmr (DMSO-d_6) δ 3.59 (m, 6 p, partially removed by D_2O), 0.97 (s, 3 p, C-19), and 0.71 (3, 3 p, C-18); mass spectrum 221 (100%), M$^+$ − 33 (58%), M$^+$ − 18 (28%), M$^+$ − 15 (39%), M$^+$ 310 (33%).

Anal. Calcd for $C_{19}H_{34}O_3$ (310.5): C, 73.50; H, 11.04. Found: C, 73.62; H, 10.58.

Sodium borohydride (0.28 g, 7 mmol) was added to a solution of 3-methyl acetal **10b** (0.50 g, 1.5 mmol) in tetrahydrofuran (5 ml)–boron trifluoride etherate (6 ml, 48 mmol). After 0.5 hr diglyme (5 ml) was added and the solution was allowed to stand at room temperature for 32 hr. Methanol (10 ml) and then water (20 ml) were added and the white solid was collected. Preparative thin layer chromatography (45:45:10 benzene–ethyl acetate–methanol) and ether elution of the uppermost zone gave 0.21 g (47%) of ether **10a**, mp 182.0–183.5° (platelets from ethyl acetate).[21]

3β,17-Dihydroxy-17a-oxa-*D*-homo-5α-androstane (10c).[22]—Diborane–tetrahydrofuran (4.3 ml, approximately 1 mol equiv) was allowed to react with lactone **9** (1.23 g) in tetrahydrofuran (5 ml) for 0.5 hr at room temperature. To the clear gel was added methanol. Evaporation of solvent gave 1.23 g of a mixture corresponding to hemiacetal **10c** containing some glycol **12** (estimated to be 18% as evidenced by a less mobile spot on tlc). This colorless, crystalline material gave mp 159–194°; ν_{max} (KBr) 3400 (str and broad), 2930, 1440, 1370, 1120, 1070, 1030, and 950 cm^{-1}; pmr ($CDCl_3$–DMSO-d_6) δ 5.00 (peak, 1.5 p, equatorial 17α-H), 3.59 (hump, 1.5 p, axial 3α-H and 17β-H), 1.15 (s, 3 p, C-19), and 0.77 (s, 3 p, C-18).

3,3-Dideuterio-4-oxa-4aα,14α-dimethyl-*A*-homo-5α-cholestane (2b).—The experiment described above for obtaining ether **2a** was repeated using sodium borodeuteride instead of sodium borohydride. Separation by preparative thin layer chromatography using benzene–ethyl acetate (20:1) as mobile phase and ether for final elution led to 86 mg (41%) of ether **2b** as colorless plates: mp 69.8–70.8°; ν_{max} (KBr) 2940, 2090 (vw C–D stretch), 1450 (med), 1360 (med), and 1160 (med); pmr 212 (m, 1 p, C-4a), 73 (s), 66 (s), 56 (s), and 49 Hz (s); mass spectrum 235 (100%), M$^+$ − 15 (29%), M$^+$ 418 (33%). Elution of the lower band yielded 73 mg of glycol as needles: mp 156.9–157.8°; ν_{max} (KBr) 3380 (broad), 2940, 2080 (vw C–D stret), 1450 (med), 1360 (med), 1070 (w), and 1050 cm^{-1} (w); pmr δ 4.05 (m, 1 p, C-4a), 2.48 (s, 2 p, OH), 1.18 (s), 1.08 (s), 0.93 (s), and 0.83 (broad s); M$^+$ − 2434.

1,1-Dideuterioneopentyl Lanostanyl Ether (6b).—Sodium borodeuteride (0.18 g, 4.6 mmol) was added to a chilled suspension of ester **5** (0.50 g, 1.0 mmol) in tetrahydrofuran (2 ml)–boron trifluoride etherate (4 ml, 36 mmol). Diglyme (4 ml) and more tetrahydrofuran (2 ml) were added. After heating at reflux for 2 days, the reaction mixture was treated with saturated sodium bicarbonate (20 ml) and extracted with ether (two 30-ml portions). The ethereal extract was concentrated and the solid residue was chromatographed using silica gel (50 g of 0.2–0.5 mm). Elution with ligroin (200 ml, bp 60–90°) gave 0.34 g (70%) of ether **6b** as colorless needles: mp 178–182°; ν_{max} (0.1 *M* in chloroform) 2960, 2160 (vw C–D stretch), 2060 (vw C–D stretch), 1470 (med), 1370, and 1126 cm^{-1} (str); pmr δ 2.62 (hump, 1 p, 3α-H), 0.92 (large peak), and 0.78 (peak); mass spectrum 373 (100%), M$^+$ 502 (3%).

Further elution with benzene yielded 0.15 g (29%) of recovered starting ester **5**.

3β-Hydroxy-17a-oxa-*D*-homo-5α-androst-16-ene (11). Diborane–tetrahydrofuran (2.5 ml) was added to a solution of lactone **9** (735 mg, 2.4 mmol) in tetrahydrofuran (4.2 ml). When the vitreous gel became fluid (2 to 4 days), methanol (20 ml) was added and the solvent was concentrated. The residue was purified by preparative thin layer chromatography using ligroin (bp 60–110°)–ethyl acetate (5:7) as mobile phase. Ether elution of the second uppermost zone yielded 60 mg (8%) of saturated ether **10a**. Elution of the uppermost zone gave 0.36 g (52%) of vinyl ether **11** as a glassy substance, mp 98–102° (pure by tlc and pmr). Recrystallization from aqueous acetone yielded colorless needles: mp 144–147°; ν_{max} (KBr) 3400, 2940, 1635 (med vinyl ether C = C stretch), 1440, 1370, 1210, 1080, 1050, and 870 cm^{-1}; pmr δ 6.24 (d, 1 p, J = 6 Hz, C-17), 4.65 (crude t, 1 p, C-16), 3.60 (hump, 1 p, 3α-H), 1.13 (s, 3 p, C-19), and 0.78 (s, 3 p, C-18); mass spectrum 215 (100%), M$^+$ 290 (72%).

Anal. Calcd for $C_{19}H_{30}O_2$ (290.5): C, 78.57; H, 10.41. Found: C, 78.67; H, 10.36.

3β-Hydroxy-17a-oxa-*D*-homo-5α-androstane (10a) from Reaction of Diborane–Tetrahydrofuran with 3β-Hydroxy-17-oxo-17a-oxa-5α-androstane (9).—A tetrahydrofuran solution (2.1 ml) of lactone **9** (0.52 g, 1.7 mmol) was treated with diborane–tetrahydrofuran (1.8 ml) at room temperature for 0.5 hr. The clear gel was broken and more diborane–tetrahydrofuran (3.6 ml) was added. When the reaction mixture became fluid (2 to 4 days) methanol was added (20 ml) and the solvent was concentrated. Preparative thin layer chromatography of the colorless oily residue using ligroin (bp 60–100°)–ethyl acetate (5:7) as mobile phase yielded 0.28 g (55%) of ether **10c**[20] from the uppermost band (ether elution), mp 183.5–185.0° (prisms from ligroin–ethyl acetate).

Registry No.—**1**, 31656-58-3; **2a**, 31705-57-4; **2b**, 31705-58-5; **3**, 31659-48-0; **5**, 31659-49-1; **6a**, 28414-91-7; **6b**, 31659-51-5; **8a**, 21857-93-2; **8b**, 31659-53-7; **8b** (α-methyl acetal), 31659-54-8; **8b** (β-methyl acetal), 31656-59-4; **10a**, 6947-41-7; **10b**, 31659-56-0; **10c**, 31659-57-1; **11**, 28414-87-1; **12**, 31705-59-6; diborane, 19287-45-7.

(21) The mutual identity of both specimens was confirmed by mixture melting point determination, comparison of infrared and pmr spectra, and tlc behavior.

(22) G. R. Pettit, T. R. Kasturi, B. Green, and J. C. Knight, *J. Org. Chem.*, **26**, 4773 (1961).