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STEROIDS AND RELATED NATURAL PRODUCTS—X

REDUCTION OF LACTONES[1,2]

G. R. PETTIT, B. GREEN, T. R. KASTURI and U. R. GHATAK
Department of Chemistry, University of Maine, Orono, Maine

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Abstract—Boron trifluoride etherate–lithium aluminum hydride reduction of 12β-hydroxy-14ξ-rosane 16-carboxylic acid lactone (IIa), dihydroabietic γ-lactone (IIIa) and 3β-hydroxy-7-oxo-7a-oxa-B-homo-5α-cholestane (Xa) was found to yield the corresponding oxolane (IIb and IIIb) and oxepane (Xb, after acetylation) derivatives. Similar reduction of several lactones prepared from primary alcohols resulted in essentially complete conversion to their respective glycols. For example, only 3,4-dihydroxy-3,4-seco-5α-androstane (IX) was isolated following reduction of 3-oxo-3a-oxa-A-homo-5α-androstane (VII). The present study suggests that boron trifluoride–lithium aluminum hydride reduction of esters will increasingly favor ether formation as branching adjacent to the ester alkyl-oxygen moiety increases.

ONE of the first recorded ether syntheses, conversion of ethanol to ethyl ether, was accomplished by Cordus in 1540.[3] Intermolecular condensation of alcohols has continued to provide a useful avenue to symmetrical ethers. However, syntheses of unsymmetrical ethers usually require more elaborate techniques.[4] Preparation of unsymmetrical ethers by direct reduction of the corresponding esters or lactones would seem to present a useful synthetic method. However, Mettler's[5] electrolytic reduction of several benzoates to their respective benzyl ether and alcohol derivatives appears to represent the first and only success in this area prior to 1958.[6]

A study of ester → ether reduction was undertaken following discovery that a boron trifluoride etherate–lithium aluminum hydride reagent would convert smilagenin acetate to a series of 3β-ethoxy steroids.[6,7] Subsequently, this reaction was used to prepare ethers from a variety of δ-lactones,[6,8,9] derived from secondary and tertiary

[1] Previous contribution: G. R. Pettit and B. Green, *J. Org. Chem.* **26**, 4673 (1961).

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[3] F. Beilstein, *Handbuch der Organischen Chemie* Vol. I; p. 293, Voss Verlag, Hamburg (1893).

[4] Compare the work of Rose and Wittstock, *Pogg. Ann.* **48**, 463 (1840) [*Chem. Zentr.* **11**, 2 (1840)]; A. W. Williamson, *J. Chem. Soc.* **4**, 229 (1851); A. W. Williamson, *Liebigs Ann.* **81**, 77 (1852); S Marasse, *Ibid* **152**, 59 (1869); L. M. Norton and C. O. Prescott, *Amer. Chem. J.* **6**, 241 (1884); and the recent studies of R. H. Baker and W. B. Martin, *J. Org. Chem.* **25**, 1496 (1960); S. Searles, D. G. Hummel, S. Nukina and P. E. Throckmorton, *J. Amer. Chem. Soc.* **82**, 2928 (1960); J. Kalvoda, G. Anner, D. Arigoni, K. Heusler, H. Immer, O. Jeger, M. Lj. Mihailović, K. Schaffner and A. Wettstein, *Helv. Chim. Acta* **44**, 186 (1961); R. Lombard and G. Ambroise, *Bull. Soc. chim. Fr.* 230 (1961); P. Piganiol, J. Cheymol, J. Seyden-Penne and P. Chabrier, *Ibid.* 255 (1961); and J. S. Mills and V. Petrow, *Chem. & Ind.* 946 (1961).

[5] C. Mettler, *Ber. Dtsch. Chem. Ges.* **37**, 3692 (1904).

[6] Cf. G. R. Pettit and T. R. Kasturi, *J. Org. Chem.* **26**, 4553 (1961). Recently, J. N. Ray, A. Mukherji and N. D. Gupta, *J. Ind. Chem. Soc.* **38**, 705 (1961), reported reduction of acetyl methyl salicylate to *o*-ethoxy methyl benzoate using aluminum amalgam.

[7] G. R. Pettit and T. R. Kasturi, *J. Org. Chem.* **25**, 875 (1960).

[8] G. R. Pettit, U. R. Ghatak, Brian Green, T. R. Kasturi and D. M. Piatak, *J. Org. Chem.* **26**, 1685 (1961).

[9] G. R. Pettit and T. R. Kasturi, *J. Org. Chem.* **26**, 4557 (1961).

alcohols, and ethers from two 3β-acetoxy steroids.[6] A study concerned with evaluating the biological importance of oxasteroids[9] has led us to investigate the course of this unusual reduction reaction with several five-, six-, and seven-membered lactones.

The diterpenoid mold metabolite rosenonolactone (I)[10] was converted to lactone IIa as previously reported.[11] Boron trifluoride-lithium aluminium hydride reduction of the γ-lactone (IIa) gave tetrahydrofuran IIb in 59% yield. Similarly, reduction of dihydroabietic γ-lactone (IIIa)[8] yielded ether IIIb (44%) accompanied by glycol IV (40% yield). The structures assigned ethers IIb and IIIb were consistent with their chromatographic behavior on activated alumina, infrared spectra, and elemental compositions.[12] Selection of the γ-lactones was primarily based on the degree of difficulty anticipated in preparing the corresponding tetrahydrofurans by conventional methods.

Formation of ethers containing two primary carbon to oxygen bonds usually offers no special preparative problems. Therefore, reduction of esters prepared from a primary alcohol were not included in earlier phases[6,9] of this investigation. However, interest in the possibility of steric and or electronic effects influencing the course of reduction led to a study of several lactones derived from primary alcohols.

Attention was first turned to preparation[13] and boron trifluoride–lithium aluminum hydride reduction of α-campholide (V). Interestingly, the corresponding glycol was obtained in high yield and several related attempts to prepare an ether derivative gave similar results. Experiments described in the sequel indicate that a reduction pathway leading to almost complete hydrogenolysis may be the general case with esters of this type.[14]

Two seven-membered lactones containing a primary alkyl-oxygen group were next selected for study. Initially 3β-acetoxy-17-oxo-5α-androstane (VIa) was converted to 3β-hydroxy-5α-androstane (VIb) as described by Ruzicka *et al.*[15] It was eventually found that reduction of 17-ketone VIa was more conveniently effected by Raney nickel desulfurization of ethylenethioketal VIc or by employing a modified Wolff-Kishner reduction.[16] Chromium trioxide-pyridine oxidation of alcohol VIb led to acceptable yields of 3-oxo-5α-androstane (VId) and trifluoroperoxyacetic acid oxidation[17] of this ketone provided an improved route to 3-oxo-3a-oxo-A-homo-5α-androstane (VII).[18] Peroxyacetic acid oxidation was less satisfactory for the latter transformation. Analogous Baeyer-Villiger[19] oxidation of 3-oxo-5α-cholestane gave

[10] Footnote 6 in ref. 8.

[11] A. Harris, A. Robertson and W. B. Whalley, *J. Chem. Soc.* 1799 (1958). The "rosane" nomenclature used here and in the present work has been discussed by B. Green in a Ph.D. dissertation submitted (1959) to the University of Liverpool.

[12] Consult ref. 8 for a preliminary communication of these results.

[13] R. R. Sauers, *J. Amer. Chem. Soc.* **81,** 925 (1959).

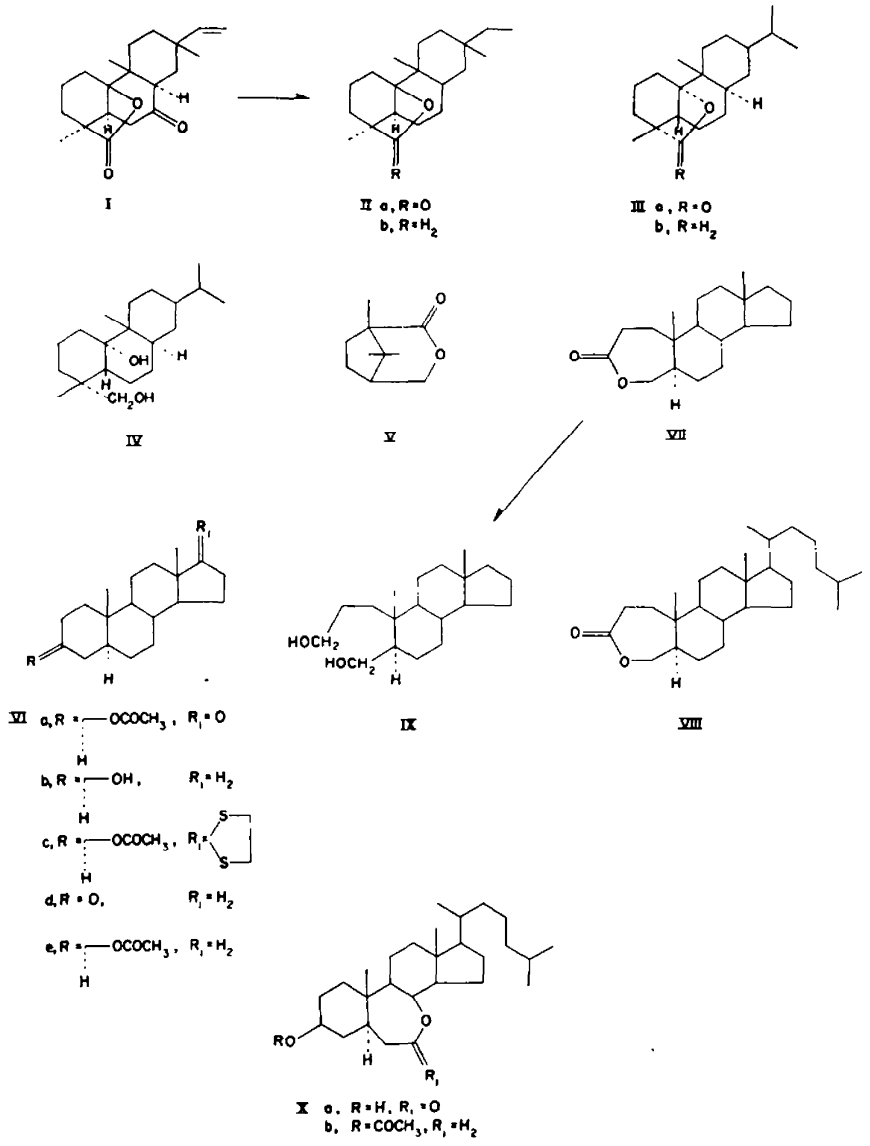
[14] Additional support for this observation will be presented in a subsequent paper by G. R. Pettit and D. M. Piatak.

[15] L. Ruzicka, V. Prelog and P. Meister, *Helv. Chim. Acta* **28,** 1651 (1945).

[16] Wolff-Kishner reduction of 3β-hydroxy-17-oxo-5α-androstane and an improved reduction procedure for 3β-hydroxy-17-oxo-androst-5-ene have recently been described by C. W. Shoppee and G. Kreuger, *J. Chem. Soc.* 3641 (1961).

[17] M. F. Hawthorne, W. D. Emmons and K. S. McCallum, *J. Amer. Chem. Soc.* **80,** 6393 (1958).

[18] This substance was originally prepared using peroxybenzoic acid: V. Prelog, L. Ruzicka, P. Meister and P. Wieland, *Helv. Chim. Acta* **28,** 618 (1945).



3-oxo-3a-oxa-A-homo-5α-cholestane (VIII).[20] As with α-campholide, only the corresponding glycols (cf. IX) were isolated following boron trifluoride–lithium aluminum hydride reduction of lactones VII and VIII. Any influence on the course of these reduction reactions by lactone-ring size was discounted when 3β-hydroxy-7-oxo-7a-oxa-B-homo-5α-cholestane (Xa), prepared[21] from cholesterol, was treated with the boron trifluoride–lithium aluminum hydride reagent. Following acetylation and chromatographic purification, 3β-acetoxy-7a-oxa-B-homo-5α-cholestane (Xb)[12] was

[19] Recent studies of this reaction have been described by P. R. Sauers and G. P. Ahearn, *J. Amer. Chem. Soc.* **83**, 2759 (1961); and J. Meinwald and E. Frauenglass, *Ibid.* **82**, 5235 (1960).

[20] V. Burckhardt and T. Reichstein, *Helv. Chim. Acta* **25**, 1434 (1942).

[21] H. Heusser, A. Segre and Pl. A. Plattner, *Helv. Chim. Acta* **31**, 1183 (1948).

isolated in 50% yield. These experiments suggest that increasing branching adjacent to the alkyl-oxygen segment of the ester will increasingly favor ether formation.

EXPERIMENTAL

The general procedures employed are described in an earlier contribution.[6] Activated alumina refers to Merck aluminum oxide, "suitable for chromatography". M. ps. were observed using open Kimble glass capillaries and are uncorrected. IR and optical rotation (chloroform solution) data were provided, respectively, by Dr. R. A. Hill of this laboratory and Drs. Weiler and Strauss, Oxford, England. The IR spectrum of each previously known intermediate was found to be consistent with its assigned structure. Microanalyses were carried out in the laboratory of Dr. A. Bernhardt, Mülheim, Germany.

12β,16-Epoxy-14ξ-rosane (IIb)

A tetrahydrofuran (25 ml) solution containing boron trifluoride etherate (10 ml) and γ-lactone IIa (0·80 g)[10] was added, during 30 min, to a cold (ice-bath) slurry of lithium aluminum hydride (0·2 g), in tetrahydrofuran (25 ml, under nitrogen). Stirring was continued for 1 hr at ice-bath temp and 1 additional hr at reflux. After cooling and cautious addition of ethyl acetate and 2N HCl (50 ml), the aqueous layer was saturated with ammonium chloride and extracted with ether. Evaporation (*in vacuo*) of solvent from the combined ethereal extract gave an oil (0·75 g) which was dissolved in pet ether and chromatographed on activated alumina. The fraction (0·45 g) of colorless oil eluted with pet ether was distilled *in vacuo* (0·03 mm) at 110° (bath temp). The IR spectrum (neat) of pure tetrahydrofuran IIb, $[\alpha]_D^{22}$ +81·9° (*c*, 1·02), exhibited absorption at 1048 and 1038 cm^{-1} (Found: C, 82·67; H, 11·70; O, 6·00; active H, 0·0. $C_{20}H_{34}O$ requires: C, 82·69; H, 11·80; O, 5·51%).

12α,15-Epoxy-12-nor-13β-methyl-11β,14α-abietane (IIIb)

Reduction of dihydroabietic γ-lactone (IIIa, 1·78 g)[8] was carried out essentially as described in the preceding experiment. In this case, ethyl ether was substituted for tetrahydrofuran. The oily product (1·7 g) was triturated with pet ether and the resulting solution chromatographed on activated alumina. Elution with 9:1 pet ether–benzene gave 0·74 g of tetrahydrofuran IIIb. Eventual elution with ether–methanol (1:1) led to glycol IV (0·71 g), m.p. 125–130°. Following recrystallization from pet ether, IV melted at 135–136·5° (lit,[22] m.p. 137·5–138·5 and 149–150°). The oily ether fraction (IIIb) was dissolved in pet ether and rechromatographed on activated alumina. A portion of the product (IIIb, 0·70 g, 40%), ν_{max}^{pure} 1040 and 1018 cm^{-1}, eluted with pet ether, was purified for microanalysis by evaporative distillation (bath temp 120–122°) during 18 hr at 0·2–0·3 mm. The pure colorless oil exhibited $[\alpha]_D^{22}$ −35·3° (*c*, 0·78). (Found: C, 82·72; H, 11·58; O, 5·69. $C_{20}H_{34}O$ requires: C, 82·69; H, 11·80; O, 5·51%).

Lithium aluminum hydride–boron trifluoride reduction of α-campholide (V)

A sample of δ-lactone V (1·6 g, m.p. 206–208°)[13] was reduced as indicated for preparation of 12α, 15-epoxy-12-nor-13β-methyl-11β,14α-abietane (IIIb). Removal of solvents was effected using a distilling column in order to avoid loss of any volatile product during isolation and subsequent chromatographic purification. The crude product (1·48 g, crystallized on cooling) was triturated with pet ether and chromatographed on activated alumina (60 g). Elution with 2 l. of the same solvent gave only a trace of colorless oil. Continued elution with ethyl ether led to the diol derivative (1·31 g) of lactone V which recrystallized from methylene chloride–pet ether as colorless needles, m.p. 135–137° (lit,[13] m.p. 135·5–137·5°).

3β-Acetoxy-5α-androstane 17-ethylenethioketal (VIc)

In a typical experiment boron trifluoride etherate (0·8 ml) was added to a solution of 3β-acetoxy-17-oxo-5α-androstane (VIa, 0·75 g)[23] in 1,2-ethanedithiol (0·8 ml). After 5 min the mixture was triturated with methanol (10 ml), filtered and the collected solid (0·8 g, m.p. 178–180°) washed with methanol. A pure sample recrystallized as colorless needles from hexane; m.p. 178–180°, $[\alpha]_D^{22}$ −23·2° (*c*, 1·11). (Found: C, 67·54; H, 8·80; O, 7·98; S, 15·44. $C_{23}H_{36}O_2S_2$ requires: C, 67·57; H, 8·88; O, 7·89; S, 15·44%).

[22] L. A. Subluskey and T. F. Sanderson, *J. Amer. Chem. Soc.* **76**, 3512 (1954).
[23] H. Levy and R. P. Jacobsen, *J. Biol. Chem.* **171**, 71 (1947).

3β-Acetoxy-5α-androstane (VIe)

Raney nickel (ca. 3 g, W-4)[24] was added to a solution of thioketal VIc (0·5 g) in ethanol (50 ml). After heating the mixture at reflux for 18 hr and then filtering, the nickel-containing residue was washed with hot ethanol and the combined filtrate concentrated *in vacuo*. The residue was dissolved in pet ether–benzene (3 : 1) and chromatographed on activated alumina. Elution with the same solvent yielded a solid (0·38 g) m.p. 88–90°, $\nu_{max}^{CHCl_3}$ 1730 and 1260 cm^{-1} (Found: C, 79·16; H, 10·68. $C_{21}H_{34}O_2$ requires: C, 79·20; H, 10·76%).

3β-Hydroxy-5α-androstane (VIb)

(a) *Saponification of 3β-acetoxy-5α-androstane* (VIe). Conversion of acetate VIe (4 g) to alcohol VIb was accomplished during 1 hr in refluxing 1N methanolic potassium hydroxide (200 ml). Recrystallization of the crude product from acetone gave 3·2 g m.p. 153–155° (lit,[15] m.p.151–152°).

(b) *Wolff-Kishner reduction of 3β-acetoxy-17-oxo-5α-androstane* (VIa). A solution composed of redistilled diethylene glycol (100 ml), 3β-acetoxy-17-oxo-5α-androstane (VIa, 5·6 g)[23] and 10 ml of anhydrous hydrazine (redistilled from potassium hydroxide) was heated at reflux 1 hr. After addition of an alkoxide solution prepared from sodium (1·5 g) and diethylene glycol (100 ml), the reaction mixture temp was maintained at 180° (by distillation of lower-boiling components) for 18 hr. The mixture was cooled and poured into water and the precipitated product collected, washed with water and recrystallized from acetone; yield, 3·5 g, m.p. 153–155°.

3-*oxo*-5α-*Androstane* (VId)

A solution of 3β-hydroxy-5α-androstane (VIb, 3·0 g) in pyridine (30 ml) was gradually added to a pyridine (30 ml)–chromium trioxide (3 g) complex.[25] After shaking, the mixture was allowed to remain 18 hr at room temp. The dark-red mixture was diluted with water (300 ml) and extracted with benzene–ether (1 : 1). After filtering, the combined solvent extract was washed with water and concentrated *in vacuo* to dryness. A solution of the residue in pet ether–benzene (1 : 1) was chromatographed on activated alumina. Elution with the same solvent gave 2·6 g of crystalline product (VId), m.p. 90–95°. Recrystallization from hexane yielded colorless needles (2·2 g) m.p. 94–96° (lit,[18] m.p. 98–99°).

3-*oxo*-3a-*oxa*-A-*homo*-5α-*Androstane* (VII)

(a) *Oxidation by trifluoroperoxyacetic acid.* In a typical experiment, a solution of trifluoroperoxyacetic acid, prepared from trifluoroacetic anhydride (3 ml) and 90% hydrogen peroxide (0·6 ml) in methylene chloride (25 ml), was added (15-min period) to a stirred solution of 3-oxo-5α-androstane (VId, 1·3 g) in methylene chloride (40 ml) containing suspended disodium hydrogen phosphate (2 g). Stirring was continued at room temp for 90 min. After dilution with ethyl ether followed by filtration, the ethereal solution was washed with aqueous sodium carbonate (10%) and water. Evaporating the solvent led to a residue, m.p. 176–179°; wt. 0·45 g after 3 recrystallizations from acetone–hexane. Another recrystallization from the same solvent provided a pure sample of *lactone* VII, m.p. 179–180° (lit,[18] m.p. 180–181°).

(b) *Oxidation with peroxyacetic acid.* Commercial 38% peroxyacetic acid (15 g) was added to a solution of ketone VId (2·1 g) in glacial acetic acid (40 ml). Before diluting with water, the reaction mixture was maintained at room temp 24 hr. The solid product was collected, dissolved in methanol (75 ml) and diluted with 10% methanolic potassium hydroxide (150 ml)–water (10 ml). After 1 hr at reflux, the mixture was filtered, diluted with water and finally extracted with ether. The aqueous solution was acidified with 3N HCl (15 ml) and heated (steam-bath) 1 hr. Precipitated material was collected and recrystallized from acetone–hexane to yield 0·35 g lactone VII, m.p. 175–178°.

3,4-*Dihydroxy*-3,4-*seco*-5α-*androstane* (IX)

Lithium aluminum hydride-boron trifluoride reduction of lactone VII (0·44 g) in ethyl ether solution was performed as illustrated for preparation of tetrahydrofuran IIIb. Triturating the crude product (0·45 g) with pet ether (25 ml) left a crystalline residue (0·36 g), m.p. 156–160°: m.p. 158–160°

[24] A. A. Pavlic and H. Adkins, *J. Amer. Chem. Soc.* **68**, 1471 (1946).
[25] For example, see B. Ellis and V. Petrow, *J. Chem. Soc.* 4417 (1956).

and wt. 0·28 g following recrystallization from acetone–pet ether. An analytical specimen recrystallized from benzene–pet ether as colorless needles; m.p. 158–160°, $[\alpha]_D^{22}$ −21·0° (*c*, 0·95), ν_{max}^{KBr} 3250 cm^{-1} (Found: C, 77·20; H, 11·37; O, 11·11. $C_{19}H_{34}O_2$ requires: C, 77·55; H, 11·56; O, 10·88%).

The pet ether solution obtained following trituration of the crude product was chromatographed on activated alumina (15 g). Elution with pet ether (300 ml) gave only a trace of colorless oil.

Repeating the entire experiment led to almost identical results.

3-*oxo*-3a-*oxa*-A-*homo*-5α-*cholestane* (VIII)

Baeyer-Villiger oxidation of 3-oxo-5α-cholestane (1·0 g) was performed using the trifluoroperoxyacetic acid prodecure described for preparation of lactone VII. The crude solid product recrystallized from ether–methanol as colorless plates; yield, 0·65 g.m.p. 185–186°. Recrystallization from the same solvent raised the m.p. to 188–189° (lit,[20] m.p. 186–187°).

Lithium aluminum hydride–boron trifluoride reduction of 3-*oxo*-3a-*oxa*-A-*homo*-5α-*cholestane* (VIII)

Reduction of lactone VIII (0·85 g) was carried out exactly as described for γ-lactone II. The crystalline product was dissolved in pet ether and chromatographed on activated alumina (20 g). Elution with pet ether, and subsequently with pet ether containing increasing quantities of benzene, gave only a few milligrams of oil. Finally, elution with chloroform–methanol gave 3,4-dihydroxy-3,4-seco-5α-cholestane[26] as major product.

3β-*Acetoxy*-7a-*oxa*-B-*homo*-5α-*cholestane* (Xb)

The general boron trifluoride–lithium aluminum hydride procedure (cf. IIb) was used to reduce 3β-hydroxy-7-oxo-7a-oxa-B-homo-5α-cholestane (0·73 g).[21] In this example, reduction was accomplished in ethyl ether solution and the crude product acetylated (1 : 1 acetic anhydride–pyridine, 1 hr at steam-bath temp). A solution of the acetates in pet ether was chromatographed on activated alumina. The crystalline fraction eluted with 3 : 1 and 2 : 1 pet ether–benzene weighed 0·42 g. A portion (0·38 g, the purer fractions as evidenced by m.p. behaviour) of this material was recrystallized from methanol; yield, 0·19 g, m.p. 102–104°. Two additional recrystallizations from methanol gave a pure specimen of 3β-acetoxy-7a-oxa-B-homo-5α-cholestane as colorless blades; m.p. 103–104°, $[\alpha]_D^{22}$ +42·2° (*c*, 1·2), ν_{max}^{KBr} 1727, 1250, 1138, 1120, 1110 and 1030 cm^{-1} (Found: C, 77·81 and 77·77; H, 11·04 and 11·12; O, 11·26. $C_{29}H_{50}O_3$ requires: C, 77·97; H, 11·28; O, 10·75%).

The IR spectrum of a fraction (0·13g) eluted with benzene indicated that it was predominantly ether Xb.

[26] C. Scholtissek, H. Endo and H. Lettré, *Liebigs Ann.* **598**, 139 (1956).