Steroids and Related Natural Products. XI. Reduction of Esters to Ethers[1-3]

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Received January 3, 1962

Direct reduction of dihydroabietic γ-lactone (Ia), the isomeric butyl esters (IIIb–d) of cholanic acid, and *t*-butyl-5α-pregnane 20S-carboxylic acid (Va) to the corresponding ethers (Ib, IVa, IVc, IVd, and VI) has been accomplished. Reduction was carried out using a reagent prepared from sodium borohydride and boron trifluoride, in diglyme–tetrahydrofuran. Boron trifluoride with either lithium aluminum hydride or lithium borohydride proved less satisfactory. Increasing conversion of the butyl esters (IIIb–d) to ethers (7–76% yield) was observed as the alcohol group varied from normal to tertiary. Similar reduction of 3β-formyloxy-5α-cholestane and 3β-formyloxy-5α-lanostane (VIIa) gave the corresponding 3β-methoxy steroids. The sensitivity of this unique ester → ether reduction reaction to structural variations in the ester group has been discussed.

Early in our study of lithium aluminum hydride–boron trifluoride etherate reduction of lactones to ethers, it became evident that the yield of cyclic ether was a function of certain structural features adjacent to the lactone group.[1,4] The yield of ether appeared to increase markedly as the alcohol portion of the lactone varied from primary to tertiary. Since these observations were based on somewhat unrelated examples it was necessary, for mechanistic reasons,[5] to provide more substantial evidence.

An investigation directed at determining optimum conditions for ester→ether reduction was first undertaken. Dihydroabietic γ-lactone (Ia),[1,4] a substance of favorable steric complexity, was selected for model experiments. Eventually it was noted that a reagent corresponding to thirty moles of boron trifluoride etherate and two of lithium aluminum hydride per mole of ester would convert γ-lactone Ia to tetrahydrofuran Ib in good yield (80%). Increasing the quantity of boron trifluoride etherate to fifty moles gave essentially the same result (77% yield). Using less than 15–20 moles of boron trifluoride led to incomplete reduction.

Comparable yields (75–81%) of ether Ib were obtained using either ethyl ether or tetrahydrofuran as solvent. However, use of tetrahydrofuran with the lithium aluminum hydride–boron trifluoride reagent led to a substance[6] of limited solubility in petroleum ether, which generally proved troublesome during chromatographic isolation of product Ib.

Substitution of lithium aluminum hydride by either lithium or sodium borohydride was next explored. Selection of these hydrides was based on the premise that a diborane–boron trifluoride reagent[5] was actually responsible for ester→ether reduction. Both borohydrides are known[7] to generate diborane in the presence of boron trifluoride etherate. While lithium borohydride proved somewhat less satisfactory (64% yield of Ib) than lithium aluminum hydride, sodium borohydride in diglyme–tetrahydrofuran gave an identical yield (80%) of ether Ib. Since only reasonably pure and colorless lithium aluminum hydride gave[5] reliable results in this type of reaction, the more stable sodium borohydride was chosen for subsequent work.

Application of the reduction reaction to a suitable series of isomeric esters was necessary to confirm and illustrate a changing reaction pathway with increasing branching in the ester alcohol moiety. The three isomeric butyl esters of 5β-cholanic acid (IIIa) appeared to meet all essential requirements.

Cholic acid was oxidized to 3,7,12-trioxo-5β-cholanic acid[8] and the latter reduced to 5β-cholanic acid (IIIa)[9] as previously reported. The acid chloride of 5β-cholanic acid was treated with *n*-butyl alcohol and the resulting ester IIIb reduced employing the sodium borohydride–boron trifluoride procedure. The corresponding ether IVa was isolated in 7% yield[10] and shown to be identical with an authentic sample prepared from the potassium derivative of alcohol IVb and butyl bromide. Analogous preparation and subsequent

(1) Part X, G. R. Pettit, B. Green, T. R. Kasturi, and U. R. Ghatak, *Tetrahedron*, in press.

(2) Based on part of a thesis submitted (1962) by D. M. Piatak to the Graduate School, University of Maine, in partial fulfillment of requirements for the Ph.D. degree.

(3) This investigation was supported by PHS Research Grants CY-4074 (C2) and CY-4074(C3) from the National Cancer Institute, Public Health Service.

(4) *Cf.* G. R. Pettit, U. R. Ghatak, B. Green, T. R. Kasturi, and D. M. Piatak, *J. Org. Chem.*, **26**, 1685 (1961).

(5) Refer to G. R. Pettit and T. R. Kasturi, *J. Org. Chem.*, **26**, 4557 (1961).

(6) See J. Kollonitsch, *J. Am. Chem. Soc.*, **83**, 1515 (1961), and ref. 5, footnote 33.

(7) Two interesting reviews pertinent to this subject have been prepared by H. C. Brown, "Organometallic Chemistry," H. Zeiss, ed., Reinhold Publishing Corp., New York, 1960, p. 150; and *Tetrahedron*, **12**, 117 (1961).

(8) L. F. Fieser and M. S. Newman, *J. Am. Chem. Soc.*, **57**, 961 (1935).

(9) Huang-Minlon, *J. Am. Chem. Soc.*, **71**, 3301 (1949).

(10) Interestingly, lithium aluminum hydride–boron trifluoride reduction of two lactones derived from primary alcohols (ref. 1) did not yield any significant amount of ether.

reduction of the secondary (IIIc) and tertiary butyl (IIId) esters gave ethers IVc and IVd in 41 and 76% yields, respectively. Similar reduction of the phenyl (IIIe) and *p*-methyl phenyl esters (IIIf) gave only alcohol IVb.[11] These experiments supported our tentative conclusions and verified utility of the ester→ether reduction reaction as a route to ethers derived from tertiary alcohols.[12]

Ester Va was next prepared in order to evaluate the effect of increased steric crowding adjacent to the carbonyl group of a *t*-butyl ester. Conversion of 3β-acetoxy-Δ⁵-pregnene 20-S-carboxylic acid to 3-oxo-5α-pregnane 20S-carboxylic acid (Vb),[13] using the route described by Fernholz, followed by Wolff-Kishner reduction of ketone Vb yielded 5α-pregnane 20S-carboxylic acid (Vc). Preparation and subsequent boron trifluoride–sodium borohydride reduction of *t*-butyl ester Va was accomplished as with ester IVd. In this case, the structural change did not appear to influence production of ether VI (76% yield).

An attempt to assess steric and/or hyperconjugation effects employing two similar esters derived from secondary alcohols led to the following series of experiments. The formate esters (*e.g.*, VIIa) of 3β-hydroxy-5α-cholestane and 3β-hydroxy-5α-lanostane (VIIb)[14] were prepared using formic acid. Both esters were subjected to lithium aluminum hydride–boron trifluoride reduction. Although rather poor conversion (8 and 21%, respectively) to 3β-methoxy-5α-cholestane and 3β-methoxy-5α-lanostane (VIIc) resulted,[15] the relative proportion of each product was consistent with an earlier study[16] involving the corresponding acetate derivatives. Sodium borohydride–boron trifluoride reduction of formate VIIa gave a slightly higher yield (28%) of methoxy ether (VIIc). Comparison with authentic samples of 3β-methoxy-5α-cholestane and 3β-methoxy-5α-lanostane, prepared by unequivocal procedures, confirmed the structural assignments. For example, a Williamson-type[17] reaction between the potassium derivative of alcohol VIIb and methyl iodide provided methyl ether VIIc (34% yield).

The preceding study clearly indicates that increased alkyl branching adjacent to the ester alcohol group favors ester→ether reduction.

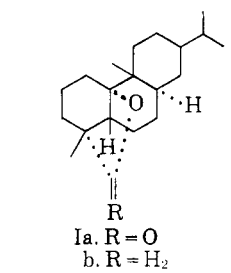
Experimental

The reduction reactions were carried out using redistilled (from sodium) tetrahydrofuran and diglyme or anhydrous ethyl ether. Boron trifluoride etherate was also redistilled. Lithium aluminum hydride,[18] lithium borohydride, and sodium borohydride were used as supplied by Metal Hydrides, Inc.

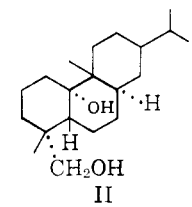
Acetylation and chromatographic procedures were performed essentially as described in a prior investigation.[16]

Melting points were observed employing a Fisher-Johns apparatus and are uncorrected. Optical rotation determinations (chloroform solution) were performed in the laboratory of Drs. Weiler and Strauss, Oxford, England. Dr. R. A. Hill of this department recorded the infrared spectra. Elemental analytical data was provided by Dr. A. Bernhardt, Mülheim, Germany.

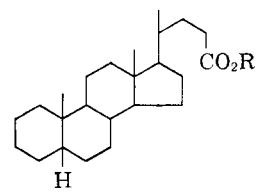
12α,15-Epoxy-12-nor-13β-methyl-11β,14α-abietane (Ib). A. Reduction with Lithium Aluminum Hydride.—A solution composed of boron trifluoride etherate (42.5 g., 0.3 mole),[19] dihydroabietic γ-lactone (Ia, 3.0 g., 0.01 mole),[4]



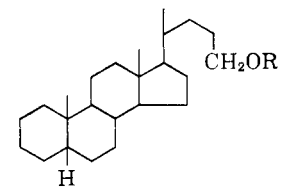
Ia. R = O
b. R = H_2



II



IIIa. R = H
b. R = $CH_2(CH_2)_2CH_3$
c. R = $CH(CH_3)CH_2CH_3$
d. R = $C(CH_3)_3$
e. R =
f. R =



IVa. R = $CH_2(CH_2)_2CH_3$
b. R = H
c. R = $CH(CH_3)CH_2CH_3$
d. R = $C(CH_3)_3$

and ethyl ether (100 ml.) was added dropwise (during 15–20 min.) to a cooled (ice bath) and stirred mixture (under nitrogen) of lithium aluminum hydride (0.75 g., 0.02 mole) in ethyl ether (100 ml.). Stirring and cooling were continued for 1 hr. before heating at reflux 1 hr. After cooling and addition (caution) of 2 *N* hydrochloric acid (50 ml.) and water, the product was extracted with ether. The combined etheral extract was concentrated to an oily residue which was triturated with petroleum ether (2 × 100

(11) Possibly, phenyl esters IIIe and IIIf underwent cleavage, catalyzed by boron trifluoride, prior to reduction.

(12) A variety of methods have been used to prepare ethers from tertiary alcohols, but none appear to present the simplicity inherent in one-step reduction of the corresponding ester. The following references are pertinent to this subject: J. Kondakow, *Zurn. Russk. Fis. Khim. Obshchestva*, **19**, 300 (1887) [*Chem. Zentr.*, **58**, 1250 (1887)]; W. Mamontoff, *Zurn. Russk. Fis. Khim. Obshchestva*, **29**, 230 (1897) [*Chem. Zentr.*, **68**, II, 408 (1897)]; T. W. Evan and K. R. Edlund, *Ind. Eng. Chem.*, **28**, 1186 (1936); R. E. Juday, *J. Org. Chem.*, **22**, 532 (1957); S. O. Lawesson and N. C. Yang, *J. Am. Chem. Soc.*, **81**, 4230 (1959); D. J. Cram and K. C. Dewhirst, *J. Am. Chem. Soc.*, **81**, 5963 (1959); S. O. Lawesson, T. Busch, and C. Berglund, *Acta Chim. Scand.*, **15**, 260 (1961); and J. J. Van Daalen, A. Kraak, and J. F. Arens, *Rec. trav. chim.*, **80**, 810 (1961).

(13) E. Fernholz, *Ann.*, **507**, 128 (1933). Absolute configuration at C-20 (Vb) has been assigned using the elegant system proposed by R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

(14) A specimen of alcohol VIIb was prepared from isocholesterol (crude lanosterol): see C. S. Barnes and A. Palmer, *Australian J. Chem.*, **10**, 334 (1957).

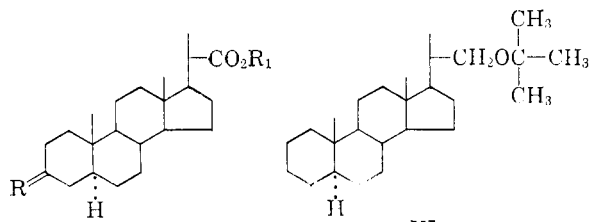
(15) A preliminary report of this new route to methyl ether derivatives was presented in ref. 4.

(16) G. R. Pettit and, T. R. Kasturi, *J. Org. Chem.*, **26**, 4553 (1961). Lithium aluminum hydride–boron trifluoride reduction of 3β-acetoxy-5α-cholestane and 3β-acetoxy-5α-lanostane gave the respective ethoxy ethers (*e.g.*, VIId) in 15 and 38% yields.

(17) A. W. Williamson, *J. Chem. Soc.*, **4**, 229 (1851).

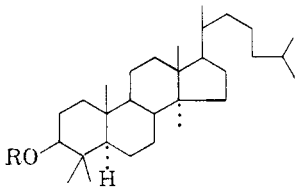
(18) Consult, introduction to the Experimental of ref. 5. In this study the hydride container was stored in a desiccator.

(19) This component was added last.



Va. R = H_2, R_1 = $C(CH_3)_3$
b. R = O, R_1 = H
c. R = H_2, R_1 = H

VI



VIIa. R = CHO
b. R = H
c. R = CH_3
d. R = CH_2CH_3

ml.). The resulting solution was chromatographed on activated alumina (70 g.) and eluted with petroleum ether. Essentially pure (as evidenced by its infrared spectrum) oxide Ib (2.3 g., 80%) was isolated using this procedure. Combined product (11.4 g.) from several experiments was distilled through an 8-cm. Vigreux column. The fraction (8.9 g.) boiling at 129–132° (0.2 mm.)[1,4] was collected.

When tetrahydrofuran was used as solvent, the yield (81%) of ether Ib was essentially unchanged.

The presence of ether Ib was not detected when this reaction was repeated employing equivalent quantities (0.02 mole) of boron trifluoride and lithium aluminum hydride (in ethyl ether or tetrahydrofuran). Changing the quantity of boron trifluoride, for example, to 0.06, 0.15 and 0.5 mole, however, led to ether Ib in 36, 42, and 77% yields, respectively.

B. Reduction with Lithium Borohydride.—When the reduction reaction described in part A was repeated using lithium borohydride and tetrahydrofuran as solvent, the yield (1.85 g.) of product (Ib) was 64%.

C. Reduction with Sodium Borohydride.—The above procedure was repeated using sodium borohydride (0.75 g., 0.02 mole) in place of lithium borohydride and diglyme (50 ml.) as initial solvent for the hydride. Otherwise, reduction and isolation of product (80%) was accomplished as described in part A.

When the reaction was repeated by adding a solution of sodium borohydride (0.02 mole) in diglyme (50 ml.) to the lactone mixture (ice bath), the yield of ether Ib (1.6 g.) was only 54%.

***n*-Butyl 5β-cholanate (IIIb).**—A solution of cholanic acid (IIIa, 2.2 g.)[9] in oxalyl chloride (10 ml.) was heated at reflux for 30 min. Excess oxalyl chloride was removed *in vacuo* and *n*-butyl alcohol (10 ml.)–pyridine (10 ml.) added to the residue. After an overnight period at room temperature, the mixture was successively diluted with ether, washed with 2 *N* hydrochloric acid, and washed with water. Removal of solvents (*in vacuo*) gave an oily residue which was dissolved in petroleum ether and filtered through activated alumina (5 g.). Crystallization of the crude product (2.7 g.) from ethyl acetate gave 2.0 g. (79%) melting at 52–53°. Recrystallization from the same solvent afforded a pure specimen as colorless needles; m.p. 52–53°, $[\alpha]^{23}D$ +37.7° (*c* 1.36), $\gamma_{max.}^{CHCl_3}$ 1725 cm.$^{-1}$. Windaus and Bohne[20] reported a melting point of 87°.

24-*n*-Butoxy-5β-cholane (IVa). A. From *n*-Butyl 5β-cholanate.—Reduction of the ester (IIIb, 1.2 g.) in tetrahydrofuran (45 ml.) containing boron trifluoride etherate (12.5 g.) was accomplished employing sodium borohydride (0.23 g.) in diglyme (20 ml.) as described above (*cf.*, Ib). The crude product, dissolved in petroleum ether, was chromatographed on activated alumina. Elution with the same solvent gave 0.08 g. (7%) of colorless oil. Crystallization from ethyl acetate–methanol yielded colorless needles melting at 40–40.5°. The product (IVa) was identical (mixture melting point determination and infrared spectral comparison) with an authentic sample (described below).

B. From 24-Hydroxy-5β-cholane (IVb).—A mixture of potassium (0.17 g.) and 24-hydroxy-5β-cholane (1.5 g.)[21] in toluene (20 ml.) was stirred and heated at reflux for 6 hr. The solvent was removed *in vacuo* and replaced with a solution of butyl bromide (5 ml.) in dimethylformamide (10 ml.). After heating at 70–100° for 2 hr., the mixture was cooled, diluted with ether, and washed with water. The residue obtained by evaporating (*in vacuo*) solvent was chromatographed in petroleum ether on activated alumina and eluted with the same solvent. The oily product (0.65 g., 37%) crystallized from ethyl acetate–methanol and melted at 38–40°. Repeated recrystallization from the same solvent mixture led to a pure sample; colorless needles, m.p. 41.5–42.5°, $[\alpha]^{21}D$ +23.9° (*c* 1.20), $\nu_{max}^{CHCl_3}$ 1122 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{50}O$: C, 83.51; H, 12.52. Found: C, 83.50; H, 12.22.

***s*-Butyl 5β-Cholanate (IIIc).**—Esterification of cholanic acid (2.6 g.) with *s*-butyl alcohol (10 ml.) and chromatographic purification of the product was accomplished as described for preparation of ester IIIb. Crystallization from ethyl acetate–methanol yielded 2.1 g. (70%) of *s*-butyl ester IIIc, m.p. 44–46°. Following recrystallization from the same solvent, the analytical sample melted at 46–47°: $[\alpha]^{23}D$ +20.3° (*c* 1.28), $\gamma_{max}^{CHCl_3}$ 1720 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.82; H, 11.33.

24-*s*-Butoxy-5β-cholane (IVc).—A 1.2-g. sample of *s*-butyl ester IIIc was reduced with the sodium borohydride–boron trifluoride etherate reagent as reported for the *n*-butyl derivative (IVa). Chromatographing the crude material in petroleum ether and eluting with the same solvent gave 0.47 g. (41%) of oily product (IVc) which crystallized from ethyl acetate–methanol in colorless plates, m.p. 41.5–42.5°. Recrystallization from the same solvent mixture gave an analytical sample; m.p. 42–43°, $[\alpha]^{23}D$ +22° (*c* 1.29), $\nu_{max}^{CHCl_3}$ 1083 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{50}O$: C, 83.51; H, 12.52. Found: C, 83.38; H, 12.96.

***t*-Butyl 5β-Cholanate (IIId).**—The acid chloride from cholanic acid (5 g.) and oxalyl chloride (20 ml.) was treated with a solution composed of *t*-butyl alcohol (20 ml.) and pyridine (20 ml.). Following a 3-hr. period of heating (steam bath), the crude product was isolated and crystallized from ethanol; yield, 3.4 g. (69%), m.p. 80–84°. Recrystallization from chloroform–methanol gave colorless needles (2.7 g., 47%) melting at 86–88°; $[\alpha]^{22}D$ +23.9° (*c* 1.25), $\nu_{max}^{CHCl_3}$ 1716 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.54; H, 11.35.

24-*t*-Butoxy-5β-cholane (IVd).—Reduction of the *t*-butyl ester (IIId, 2.0 g.) was carried out in tetrahydrofuran (70 ml.)–diglyme (25 ml.) using sodium borohydride (0.37 g.) and boron trifluoride etherate (21 g.) as described previously (*i.e.*, IIIb). A solution of the crude product in petroleum ether was chromatographed on activated alumina. The crystalline substance (1.47 g., 76%) eluted with petroleum ether melted at 87–89°. Two recrystallizations from ethyl acetate–methanol followed by two more from acetone yielded a pure sample of colorless plates; m.p. 95–95.5°, $[\alpha]^{23}D$ +20.7° (*c* 1.32), $\nu_{max}^{CHCl_3}$ 1074 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{50}O$: C, 83.51; H, 12.52. Found: C, 83.55; H, 12.19.

Phenyl 5β-cholanate (IIIe).—A pyridine (10 ml.) solution

(20) A. Windaus and A. Bohne, *Ann.*, **433**, 278 (1923).

(21) F. Wessely and W. Swoboda, *Monatsh. Chem.*, **82**, 437 (1951).

of phenol (2.0 g.) was added to the acid chloride prepared from cholanic acid (3.0 g.) and oxalyl chloride (10 ml.). Following an overnight reaction period at room temperature, the product was isolated (*cf.*, IIIb) and crystallized from acetone–water to yield 2.1 g. (58%) melting at 71–73°. Repeated recrystallization from the same solvent mixture provided an analytical specimen as colorless crystals; m.p. 77.5–78.5°, $[\alpha]^{23}D$ +17.1° (*c* 1.22), $\nu_{max}^{CHCl_3}$ 1746 cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{44}O_2$: C, 82.51; H, 10.16. Found: C, 82.33; H, 9.90.

Reduction of Phenyl 5β-Cholanate (IIIe).—The phenyl ester IIIe (1.2 g.) was reduced as previously described (*e.g.*, IIIb) and the crude product chromatographed on activated alumina. Elution with petroleum ether *did not* yield the corresponding ether. Continued elution with 9:1 petroleum ether–benzene gave, instead, 0.5 g. of 24-hydroxy-5β-cholane. Mixture melting point determination and infrared spectral comparison with an authentic sample[21] confirmed this observation.

***p*-Methylphenyl 5β-Cholanate (IIIf).**—The *p*-tolyl ester was prepared from *p*-methylphenol (2.0 g.) and the acid chloride from 3.5 g. of cholanic acid as noted for the phenyl ester (IIIe). In this case, the crude product was chromatographed on activated alumina. Elution with 5:1 petroleum ether–benzene yielded an oil (3.0 g., 70%) which crystallized from acetone (Norit A) as colorless needles, m.p. 92–97°. Repeated recrystallization from acetone raised the melting point to 100.5–101.5°, $[\alpha]^{22}D$ +18.7° (*c* 1.20), ν_{max}^{KBr} 1762 cm.$^{-1}$.

Anal. Calcd. for $C_{31}H_{46}O_2$: C, 82.61; H, 10.29. Found: C, 82.54; H, 10.11.

Sodium borohydride–boron trifluoride etherate reduction of this substance (0.98 g.), as illustrated with phenyl ester IIIe, again gave 24-hydroxy-5β-cholane as exclusive product.

5α-Pregnane 20S-Carboxylic Acid (Vc).—A mixture of 3-oxo-5α-pregnane 20S-carboxylic acid (Vb, 1.9 g.),[13] 85% hydrazine hydrate (5 ml.), and diethylene glycol (15 ml.) was heated at reflux for 45 min. After cooling, potassium hydroxide (1.5 g.) was added. The condenser was removed and the solution temperature increased to 190–200°. The condenser was then replaced and heating at reflux continued for 2 hr. Cooling, followed by dilution with water and 2 *N* hydrochloric acid, precipitated the reduced acid (1.65 g., 89%), m.p. 190–200°.[13] The crude product did not require further purification when employed in the following experiment.

***t*-Butyl 5α-Pregnane-20S-carboxylate (Va).**—The 20-carboxylic acid Vc (1.65 g.) was converted to *t*-butyl ester Va employing the general procedure used with 5β-cholanic acid (see, IIId). The crude oily product (0.55 g., 28%) crystallized from ethyl acetate–methanol as colorless blades, m.p. 114–117°. Repeated recrystallization from this solvent led to a pure sample melting at 121–122°, $[\alpha]^{22}D$ 0.0° (*c* 1.24), ν_{max}^{KBr} 1725 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{44}O_2$: C, 80.35; H, 11.41. Found: C, 80.45; H, 11.43.

20S-*t*-Butoxymethylene-5α-pregnane (VI).—A solution of the ester (Va, 0.23 g.) in tetrahydrofuran (10 ml.) containing boron trifluoride ethereate (2.5 g.) was allowed to react with sodium borohydride (0.045 g.) in diglyme (5 ml.) as described above (*cf.*, Ib). The crude product, in petroleum ether, was chromatographed on activated alumina. Elution with petroleum ether gave 0.17 g. (76%) of ***t*-butoxy ether VI,** m.p. 114–118°. One recrystallization from ethyl acetate–methanol afforded 0.15 g. (68%) melting at 121–122°. Further recrystallization from this solvent mixture yielded pure colorless needles; m.p. 122.5–123°, $[\alpha]^{22}D$ +19° (*c* 1.26), ν_{max}^{KBr} 1197, 1078, 1035, and 1008 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{46}O$: C, 83.35; H, 12.38. Found: C, 83.66; H, 12.09.

3β-Methoxy-5α-cholestane.—Reduction of 3β-formyloxy-5α-cholestane (2.0 g.)[22] in tetrahydrofuran (140 ml.) using the lithium aluminum hydride (0.38 g.)–boron trifluoride etherate (22 g.) reagent was accomplished as described using lactone Ia. Following chromatographic purification, the oily product (0.16 g., 8%), eluted with petroleum ether, crystallized from chloroform–methanol, and melted at 82–84°. Comparison (mixture melting point and infrared spectra) with an authentic sample (m.p. 84–85.5°) of 3β-methoxy-5α-cholestane[23] established identity of the product.

3β-Formyloxy-5α-lanostane (VIIa).—A solution of 3β-hydroxy-5α-lanostane (VIIb, 2.5 g.)[14] in dioxane (50 ml.)–formic acid (100 ml., 85–90%) was heated at reflux 1.5 hr. and then stored overnight at room temperature. After dilution with water and extraction with chloroform, the combined extract was washed successively with water, 5% aqueous sodium bicarbonate, and water. Removal of solvent, *in vacuo*, and recrystallization of the residue from chloroform–methanol afforded 2.1 g. (77%) of formate VIIa, m.p. 136–138°. Several recrystallizations from the same solvent mixture gave pure colorless needles melting at 140.5–141.5°; $[\alpha]^{22}D$ +36.8° (*c* 1.23), $\nu_{max}^{CHCl_3}$ 1710 cm.$^{-1}$.

Anal. Calcd. for $C_{31}H_{54}O_2$: C, 81.16; H, 11.87. Found: C, 80.84; H, 11.68.

3β-Methoxy-5α-lanostane (VIIc). A. By Reduction of 3β-Formyloxy-5α-lanostane.—The sodium borohydride (0.22 g.)–boron trifluoride etherate (12.7 g.) procedure (refer to Ib) was first employed to reduce formate VIIc (1.34 g.). A solution of the crude product in petroleum ether was chromatographed on activated alumina. Elution with petroleum ether gave 0.36 g. (28%) of oil (VIIc) which crystallized from chloroform-methanol as colorless needles, m.p. 137–138°. The product was identical (mixture melting point determination and infrared spectral comparison) with a specimen (m.p. 137–138.5°) of 3β-methoxy-5α-lanostane prepared in procedure B.

An analogous experiment employing 1.37 g. of formate VIIa (in tetrahydrofuran solution) and the lithium aluminum hydride (0.23 g.)–boron trifluoride etherate (12.7 g.) technique (*cf.*, Ib) provided, after chromatographic purification, 0.28 g. (21%) of oily product (VIIc). In this case, crystallization from chloroform–methanol led to a lower-melting (128–132°) sample of colorless needles. However, an infrared spectral study of this substance and the oily fractions reported above indicated that each was essentially pure 3β-methoxy-5α-lanostane.

B. By Methylation of 3β-Hydroxy-5α-lanostane (VIIb).—To a stirred suspension of potassium (0.16 g.) in 15 ml. of refluxing toluene was added 3β-hydroxy-5α-lanostane (1.8 g.)[14] in toluene (15 ml.). When alkoxide formation appeared complete, the mixture was cooled and methyl iodide (12 ml.) added. A second quantity (5 ml.) of methyl iodide was added after 24 hr. at reflux. Heating was continued for another 24-hr. period before adding *ca.* 3 ml. of *t*-butyl alcohol. The mixture was poured into water, extracted with ether, and the combined ethereal extract evaporated to dryness *in vacuo*. A petroleum ether solution of the residue was chromatographed on activated alumina and eluted with the same solvent. The crystalline product, 0.64 g., (34%) melted at 128–131°. Recrystallization from chloroform–methanol raised the melting point to 137–138.5°. A pure specimen crystallized from the same solvent as colorless needles; m.p. 138–139°, $[\alpha]^{20}D$ +49.9° (*c* 1.29), $\nu_{max}^{CHCl_3}$ 1096 cm.$^{-1}$.

Anal. Calcd. for $C_{31}H_{56}O$: C, 83.71; H, 12.69. Found: C, 83.44; H, 12.63.

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