[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MAINE]

Steroids and Related Natural Products. VIII. Synthesis of Oxasteroids[1,2]

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Peroxydisulfuric acid oxidation of testosterone propionate, progesterone, and cholest-4-en-3-one has been shown to yield 3-oxo-17β-hydroxy-4-oxa-5α-androstane (I, after saponification), 3,20-dioxo-4-oxa-5α-pregnane (V) and 3-oxo-4-oxa-5α-cholestane (VII) respectively. Boron trifluoride etherate–lithium aluminum hydride reduction of δ-lactones I, V, and VII led to the corresponding tetrahydropyran derivatives (IIb, VIa, and VIII). Similar reduction of 3β-hydroxy-17-oxo-17a-oxa-D-homo-5α-androstane (XI) gave 3β-hydroxy-17a-oxa-D-homo-5α-androstane (XIIa). Diborane–boron trifluoride etherate was also found to reduce lactones to cyclic ethers, while reduction with diborane gave hemiacetals. Evidence in support of the structures and stereochemistry assigned to the lactones and their unusual reduction products has been summarized. A tentative mechanism is proposed for lactone → ether reduction employing diborane–boron trifluoride etherate.

Reduction of several 3β-acetoxy steroids to their respective 3β-ethoxy derivatives using a boron trifluoride–lithium aluminum hydride reagent[1] suggested that this novel reaction might simplify the preparation of certain oxygen heterocyclic compounds.[4] For example, one-step reduction of a lactone to its corresponding ether derivative would provide, in principle, a useful route to cyclic ethers.[5] The present study was undertaken to determine whether boron trifluoride etherate–lithium aluminum hydride reduction of a δ-lactone would yield a tetrahydropyran.

As part of another investigation concerned with the role of steroids in certain types of hormone-dependent cancer,[6] it was considered important to study first the ester→ether reduction reaction as a method for obtaining oxa steroids of biological interest. A number of oxa steroids have been prepared where the oxygen atom constitutes part of a lactone system;[7] however, only a few steroids have been described in which a normal-ether oxygen has been incorporated into the nucleus.[4a-c,8,9]

One of the first steroid δ-lactones selected for reduction was 3-oxo-17β-hydroxy-4-oxa-5α-androstane (I). This substance (I) was prepared from testosterone propionate by ozonolysis and reduction of the resulting keto acid with sodium borohydride, essentially as described by Atwater.[7b,10] Subsequently, it was found that lactone I could be readily prepared in one step by peroxydisulfuric acid (from potassium persulfate and sulfuric acid in glacial acetic acid) oxidation[11-13] of testosterone propionate. Boron trifluoride etherate – lithium aluminum hydride reduction of lactone I, followed by acetylation, gave 17β-acetoxy-4-oxa-5α-androstane (IIa, 45% yield after chromatography). Saponification led to alcohol IIb which was easily oxidized to 17-oxo-4-oxa-5α-androstane (IIc) with chromium trioxide. Microanalytical and infrared

(1) See G. R. Pettit and T. R. Kasturi, *J. Org. Chem.*, 26, 4553 (1961) for the previous paper in this series.

(2) This investigation was supported by PHS Research Grants CY-4074(C1) and CY-4074(C2) from the National Cancer Institute, Public Health Service.

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(4) Several of the studies resulting from this observation have been reported in preliminary communications: (a) G. R. Pettit and T. R. Kasturi, *J. Org. Chem.*, 25, 875 (1960); (b) G. R. Pettit and T. R. Kasturi, *J. Org. Chem.*, 26, 986 (1961); (c) G. R. Pettit, U. R. Ghatak, B. Green, T. R. Kasturi and D. Piatak, *J. Org. Chem.*, 26, 1685 (1961); (d) G. R. Pettit, T. R. Kasturi, B. Green, and J. Knight, *J. Org. Chem.*, 26, 2879 (1961).

(5) Procedures commonly used to effect reduction of esters or lactones employ: sodium in alcohol, hydrogenation over copper chromite catalyst, or one of several metal hydrides. The predictable product in each case is the corresponding alcohol. For leading references consult: (a) H. Adkins, *Org. Reactions*, 8, 1 (1954); (b) E. L. Wittbecker, H. K. Hall, Jr., and T. W. Campbell, *J. Am. Chem. Soc.*, 82, 1218 (1960); (c) N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience Publishers, Inc., New York, 1956, p. 391; (d) J. Rudinger and M. Ferles, *Hydrid Lithno-Hlinitý a příbuzná činidla v organické chemii*, Československé Akademie Věd, Praha, 1956, pp. 92 and 381; (e) E. Schenker, *Angew. Chem.*, 73, 81 (1961).

(6) See: *Biological Activities of Steroids in Relation to Cancer*, G. Pincus and E. P. Vollmer, eds., Academic Press, New York, 1960, for a survey of recent work in this area.

(7) A literature review pertinent to this subject has been prepared by T. L. Jacobs and R. B. Brownfield, *J. Am. Chem. Soc.*, 82, 4033 (1960). See also: (a) R. M. Dodson and C. G. Castle, U. S. Patent, 2,847,422 (Aug. 12, 1958); (b) N. W. Atwater and J. W. Ralls, *J. Am. Chem. Soc.*, 82, 2011 (1960); and (c) L. H. Knox, R. Villotti, F. A. Kincl, and H. J. Ringold, *J. Org. Chem.*, 26, 501 (1961).

(8) J. T. Edward and P. F. Morand, *Can. J. Chem.*, 38, 1325 (1960).

(9) T. L. Jacobs (ref. 7) has recently reported preparation of a substance which may be 6-oxacholestane.

(10) *Cf.*, also C. C. Bolt, *Rec. trav. chim.*, 70, 940 (1951).

(11) Peroxydisulfuric acid (persulfuric acid) oxidation of progesterone and cholest-4-en-3-one has been described by A. Salamon, *Z. physiol. Chem.*, 272, 61 (1941). In each case, the neutral product was assigned a 3-oxo-4-oxa-structure on the basis of elemental analyses and Rast molecular weight.

(12) Use of this reagent in the Baeyer-Villiger oxidation reaction has been reviewed by C. H. Hassall, *Org. Reactions*, 9, 73 (1957). For a recent summary of oxidations employing peroxymonosulfuric acid, its potassium salt, and Baeyer's persulfuric acid reagent (potassium persulfate, sulfuric acid, and potassium sulfate), see: R. J. Kennedy and A. M. Stock, *J. Org. Chem.*, 25, 1901 (1960). Addition of potassium persulfate to aqueous sulfuric acid solutions has recently been shown to give peroxymonosulfuric acid and hydrogen peroxide: Y. K. Gupta, *J. Indian Chem. Soc.*, 37, 755 (1960).

spectral data for substances IIa–c were consistent with the assigned structures.

At this point, it became desirable to evaluate the possibility of ether II having arisen from a glycol (*e.g.*, IIIa) intermediate by boron trifluoride-catalyzed dehydration. This mechanism was rejected when glycol IIIa, prepared by lithium aluminum hydride reduction of lactone I, was recovered in almost quantitative yield following treatment with boron trifluoride etherate in tetrahydrofuran.[14]

Since the reaction between boron trifluoride and lithium aluminum hydride in ether solution is known to yield diborane,[15] it seemed plausible that diborane in association with boron trifluoride might be responsible for the unusual lactone → ether reaction.[16,17] Reaction of lactone I in tetrahydrofuran containing boron trifluoride with diborane again gave tetrahydropyran IIb, although in lesser yield. A fair amount of glycol (III) was also isolated.

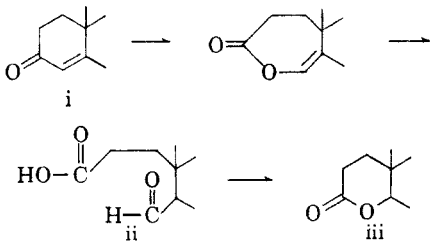
Discovery of the boron trifluoride etherate–diborane route to ether II led us to investigate next the reduction of lactone I with only diborane present.[18,19] Accordingly, a tetrahydrofuran solution of the lactone (I) was treated with diborane over three hours at room temperature. After adding ethanol, the solution was evaporated to dryness and then acetylated. The product of this reaction was distinctly different from either starting material or substances IIa and IIIb. Inspection of the elemental composition and infrared spectrum allowed assignment of a 3β-ethoxy-17β-acetoxy-4-oxa-5α-androstane (IV) structure.[20] Further support for this formulation was provided by related studies described in the sequel.

The ether synthesis was next used as part of a facile route to 20-oxo-4-oxa-5α-pregnane (VIa). Peroxydisulfuric acid oxidation[21] of progesterone provided a convenient source of 3,20-dioxo-4-oxa-5α-pregnane (V).[11] Reduction of lactone V with boron trifluoride etherate–lithium aluminum hydride and treatment of the product with an 8N chromic acid reagent[22] yielded 4-oxa steroid VIa. Trifluoroperoxyacetic acid oxidation of 20-ketone VIa to 17β-acetoxy-4-oxa-5α-androstane (IIa) confirmed the structures and A/B-*trans* stereochemistry assigned to lactone V and ketone VIa.[23]

Rapid conversion to 20-ethylenethioketal VIb was observed when boron trifluoride etherate was added to a solution of 20-ketone VIa in 1,2-ethanedithiol. Raney nickel desulfurization of thioketal VIb gave 4-oxa-5α-pregnane (VIc).

Convincing support for the structural and stereochemical assignments noted above was obtained in the following manner. Cholest-4-en-3-one was oxidized to 3-oxo-4-oxa-5α-cholestane (VII)[11] with peroxydisulfuric acid. The product (VII) was identical with an authentic sample of lactone VII[24] generously provided by Dr. J. T. Edward.[8] The tetrahydropyran derivative (VIII) arising from boron trifluoride etherate–lithium aluminum hydride reduction of lactone VII was identical with a specimen of 4-oxa-5α-cholestane (supplied by Dr. Edward[8]) prepared from 3,5β-dihydroxy-3,5-seco-A-nor-5α-cholestane (IX). A small quantity of glycol IX accompanied formation

(13) Comparatively few oxidations of α,β-unsaturated ketones with peracids have been reported (*cf.*, ref. 12). However, these examples indicate the importance of reaction conditions since α,β-epoxy ketone or α-hydroxy ketone formation may be favored over one of the two predictable Baeyer-Villiger products. Interestingly, persulfuric acid oxidation of the two α,β-unsaturated ketones described by Salamon (ref. 11) and substantiated by the present work may follow a more complex course. Possibly these oxidations proceed in part by the two-step Baeyer-Villiger sequence illustrated by *i* → *iii*: where the second oxidation step may begin with an aldehyde intermediate such as *ii*.



(14) The boron trifluoride–tetrahydrofuran addition compound has been described by D. E. McLaughlin, M. Tamres, and S. Searles, Jr., *J. Am. Chem. Soc.*, **82**, 5621 (1960).

(15) Leading references to early studies of this reaction may be found by consulting ref. 5c, p. 49. The results of a comprehensive investigation concerned with preparation of diborane have been described by H. C. Brown, K. J. Murray, L. J. Murray, J. A. Snover, and G. Zweifel, *J. Am. Chem. Soc.*, **82**, 4233 (1960).

(16) *Cf.*, ref. 4c, footnote 5.

(17) Reduction of 4-*t*-butylcyclohexanone to the *cis* alcohol using diborane in the presence of boron trifluoride etherate has recently been reported: W. M. Jones, *J. Am. Chem. Soc.*, **82**, 2528 (1960).

(18) The relative ease of reduction of several common organic functional groups by diborane has been investigated by H. C. Brown and W. Korktnyk, *J. Am. Chem. Soc.*, **82**, 3866 (1960). Although reduction of a lactone (γ-butyrolactone) by diborane has been reported, the product of this reaction was not noted: H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1136 (1957). *Cf.* also, ref. 4d and a review by: F. Schubert and K. Lang, *Angew. Chem.*, **72**, 994 (1960).

(19) It is noteworthy that bis-3-methyl-2-butylborane reduces γ-butyrolactone and γ-valerolactone to their respective hydroxyaldehyde derivatives: H. C. Brown and D. B. Bigley, *J. Am. Chem. Soc.*, **83**, 486 (1961).

(20) For a preliminary account of this new procedure for converting a lactone to its hemiacetal derivative, refer to ref. 4d.

(21) Cursory examination of a reaction between progesterone and perbenzoic acid has been reported by L. H. Sarett, *J. Am. Chem. Soc.*, **69**, 2899 (1947).

(22) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(23) Previous studies (ref. 1) have indicated that the ester reduction reaction usually follows a stereospecific course.

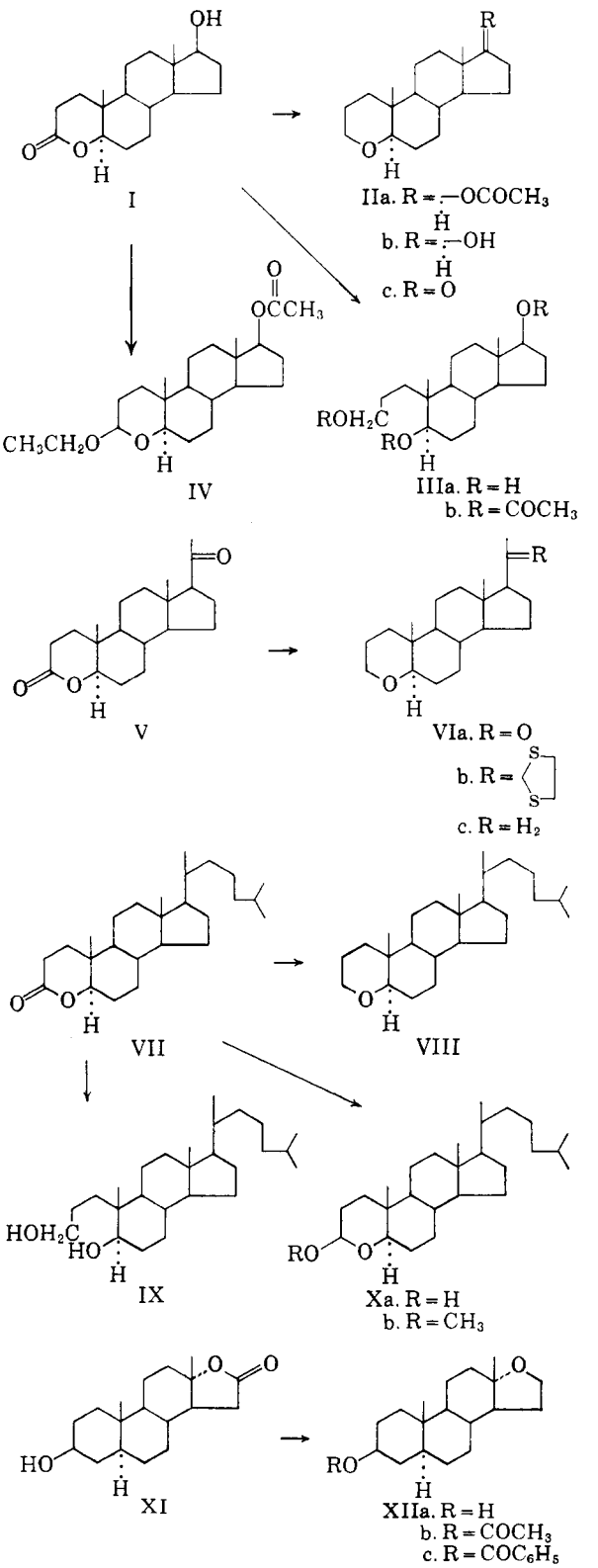
(24) The 5β-isomer (ref. 8) has been prepared by Baeyer-Villiger oxidation of 3-oxo-A-nor-5β-cholestane.

of 4-oxa steroid VIII. Attempted cyclodehydration of diol IX to ether VIII using boron trifluoride etherate was unsuccessful.

When reduction of lactone VII was repeated employing an aluminum chloride–sodium borohydride[25] reagent, only glycol IX was isolated. However, lactone VII was partially converted to 3-oxa steroid VIII by diborane–boron trifluoride etherate.

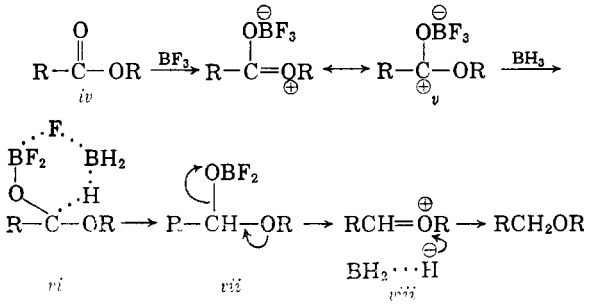
These experiments strengthened our premise that the actual reagent(s) affecting reduction might be derived from diborane–boron trifluoride etherate.[26] Consequently, the metal hydride component of the boron trifluoride etherate–lithium aluminum hydride reagent may only serve the purpose of converting boron trifluoride to diborane.

Reaction between diborane and δ-lactone VII in tetrahydrofuran solution yielded 3β-hydroxy-4-oxa-5α-cholestane (Xa).[19,27] Although evaporation of the crude hemiacetal with ethanol did not yield an ethoxy derivative (*cf.*, IV), treatment with hydrobromic acid in methanol produced 3β-methoxy-4-oxa-5α-cholestane (Xb). Chromic acid oxidation of hemiacetal Xa to the original lactone (VII) substantiated the proposed course of diborane reduction.

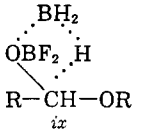


(25) A reaction mixture prepared from sodium borohydride and boron trifluoride etherate may also be used to effect lactone → ether reduction (*cf.*, ref. 4c). Aluminum chloride–lithium aluminum hydride mixtures normally reduce esters to alcohol derivatives. For example see: G. R. Pettit and W. J. Bowyer, *J. Org. Chem.*, **25**, 84 (1960).

(26) A thorough mechanistic appraisal of this reduction reaction cannot be made on the basis of experimental evidence now available; however, we would like to propose a working hypothesis. Assuming initial reaction (*e.g.*, iv → v) of the carbonyl group with boron trifluoride followed by diborane, then the first stage of reduction may involve an activated complex such as *vi*. Following transfer of hydride and fluoride (refer to R. Köster, *Angew. Chem.*, **73**, 66 (1961), and the interesting discussion of ketone reduction



by boron trifluoride etherate–trimethylamine borane in ref. 17) the reaction might then proceed *via* intermediate *vii* to the final reductive process summarized by *viii*. Transition state *ix* might also be considered for the second reduction stage. Obviously, this hypothesis represents only one of several possible mechanistic pathways.



(27) Assignment of a 3β-hydroxy configuration is based on the assumption that ring A of hemiacetal Xa exists in a chair conformation. A 3-hydroxy substituent would then be expected to assume the more stable 3β-equatorial configuration. Thus, 3α-substitution appeared unlikely when starting material was recovered from an equilibration reaction carried out with hemiacetal X in tetrahydrofuran containing hydrochloric acid. Dr. B. Green performed this experiment.

Boron trifluoride etherate–lithium aluminum hydride reduction of a δ-lactone derived from a tertiary alcohol presented no difficulty. Reduction of 3β-hydroxy-17-oxo-17a-oxa-D-homo-5α-androstane (XI)[28] to tetrahydropyran XIIa was readily accomplished.[4a]

The ketone → lactone → ether sequences described in the present study illustrate a useful synthetic route analogous to the well known ketone → lactam → amine procedures.

EXPERIMENTAL[29]

General procedures. Each of the reduction reactions was carried out employing anhydrous ethyl ether or redistilled anhydrous tetrahydrofuran as solvent. Before concentration, solvent extracts used in isolation procedures were dried over anhydrous sodium sulfate.

Colorless lithium aluminum hydride, purchased from Metal Hydrides, Inc., was used for lactone → ether reductions. Older samples (grey) of lithium aluminum hydride normally led to high yields of glycol. These reduction reactions were accomplished using a large molar excess of the boron trifluoride etherate–lithium aluminum hydride reagent. A preliminary study of reagent requirements indicated that 1 mole of ester is usually reduced in satisfactory yield to an ether by a reagent prepared from 2 moles of lithium aluminum hydride and 15 moles of boron trifluoride (in ether). The latter procedure was more convenient for reactions involving larger quantities of ester.

The general procedures employed for acetylation, saponification and chromatography have been previously described.[1]

3-Oxo-17β-hydroxy-4-oxa-5α-androstane (I). *A. From testosterone propionate.* Conversion of testosterone propionate (6.5 g.) to lactone I (1.3 g.), m.p. 178–180°, was accomplished employing the reaction sequence previously described in the case of testosterone benzoate.[7b]

B. Peroxydisulfuric acid oxidation of testosterone propionate. Potassium persulfate (9 g.) and concentrated sulfuric acid (10 g.) were mixed in a mortar and diluted with glacial acetic acid (150 ml). The resulting mixture was added to a solution of testosterone propionate (9 g.) in glacial acetic acid (150 ml.). Following a 7-day period of intermittent shaking at room temperature in the absence of light, the mixture was cooled and treated with aqueous 50% potassium hydroxide (40 ml.). Precipitated salts were removed by filtration and the filtrate evaporated to dryness (*in vacuo* at 60°). A solution of the residue in ether was washed successively with water, 5% sodium carbonate, and water. The solvent was removed and residual solid saponified (3 hr.) in a refluxing mixture of dioxane (100 ml.) and water (100 ml.)–potassium hydroxide (15 g.). After acidifying with dilute hydrochloric acid, the mixture was extracted with methylene chloride and the combined extract washed with water and concentrated to dryness. The residual solid (2 g.) melted at 174–176° after recrystallization from hexane–acetone. Recrystallization from the same solvent gave 1.78 g. of colorless prisms melting at 177–179°, $[\alpha]_D^{22}$ +91.7° (*c*, 1.38).

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 73.93; H, 9.65. Found: C, 73.99; H, 9.59.

The samples of lactone I prepared by procedures *A* and *B* were shown to be identical (by mixture melting point determination and infrared spectral comparison in both chloroform and potassium bromide) with a specimen of 3-oxo-17β-hydroxy-4-oxa-5α-androstane kindly provided by Dr. N. W. Atwater.[7b]

17β-Hydroxy-4-oxa-5α-androstane (IIb). A solution of lactone I (0.52 g.) in ethyl ether (60 ml.) containing 8 ml. of boron trifluoride etherate was added to a stirred suspension of lithium aluminum hydride (0.65 g.) in ethyl ether (80 ml.). Addition of the lactone solution was carried out with cooling (ice bath) over a 15-min. period. Stirring was continued at 0–5° for 45 min. and at reflux for 2 hr. After cooling and cautious addition of cold dilute hydrochloric acid, the ethereal layer was separated and washed with aqueous sodium bicarbonate and water. The residue obtained by removing solvent was acetylated and chromatographed on activated alumina. Elution with petroleum ether 40–60°)–benzene (1:1) gave 0.26 g.[30] of solid melting at 96–99°. Two recrystallizations from hexane yielded a pure specimen of *17β-acetoxy-4-oxa-5α-androstane* (IIa) as stout rods; m.p. 104–105°, $[\alpha]_D^{22}$ +42.8° (*c*, 1.19), $\nu_{max}^{CHCl_3}$ 1720, 1256, 1104, 1086, and 1044 cm.$^{-1}$

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06; O, 14.98. Found: C, 74.91; H, 9.94; O, 15.18.

Saponification of acetate IIa and recrystallization of the product from methanol-water yielded a pure sample of *17β-hydroxy-4-oxa-5α-androstane* melting at 204–206°; colorless needles, $[\alpha]_D^{22}$+43.8°, (*c*, 1.18), ν_{max}^{KBr} 3260, 1104, 1088, and 1060 cm.$^{-1}$

Anal. Calcd. for $C_{18}H_{30}O_2$: C, 77.71; H, 10.79; active H, 0.36. Found: C, 77.21; H, 10.70; active H, 0.40.

17-Oxo-4-oxa-5α-androstane (IIc). A solution of alcohol IIb (0.1 g.) in acetone (15 ml.) was treated with an 8*N* chromic acid reagent[22] until oxidation appeared complete. The mixture was diluted with water, extracted with ether and the combined extract washed with water. Removal of solvent and recrystallization from hexane gave an analytical sample (0.06 g.) as colorless needles; m.p. 117–119°, $[\alpha]_D^{22}$ +114.5° (*c*, 0.97), ν_{max}^{KBr} 1736, 1104, 1084, 1060, 1040, and 1020 cm.$^{-1}$

Anal. Calcd. for $C_{18}H_{28}O_3$: C, 78.21; H, 10.21; O, 11.58. Found: C, 78.08; H, 10.24; O, 11.63.

3,5β,17β-Trihydroxy-3,5-seco-A-nor-5α-androstane (IIIa). A solution of 3-oxo-17β-hydroxy-4-oxa-5α-androstane (I, 1.17 g.) in tetrahydrofuran (35 ml.) was added during a 10-min. period to a cool (ice bath) solution of lithium aluminum hydride (0.76 g.) in tetrahydrofuran (25 ml.). Stirring was continued while the mixture was heated at reflux for 3 hr. After cooling, addition (caution) of dilute hydrochloric acid and extraction with ether, the combined extract was dried and concentrated *in vacuo*. The residual solid (1.2 g.), m.p. 207–210°, recrystallized from methanol-water as colorless flakes; m.p. 210–212°, $[\alpha]_D^{22}$ −12.8° (*c*, 1.37), ν_{max}^{KBr} 3260 (broad) cm.$^{-1}$

Anal. Calcd. for $C_{18}H_{32}O_3$: C, 72.92; H, 10.88; O, 16.19. Found: C, 72.79; H, 10.97; O, 16.34.

Acetylating the triol (IIIa) afforded *3,5β,17β-triacetoxy-3,5-seco-A-nor-5α-androstane* (IIIb). An analytical specimen recrystallized from methanol as needles melting at 126–127°, $[\alpha]_D^{22}$ 0.0°, ν_{max}^{KBr} 1730 and 1240 cm.$^{-1}$

Anal. Calcd. for $C_{24}H_{38}O_6$: C, 68.22; H, 9.07; O, 22.72. Found: C, 67.87; H, 9.00; O, 23.04.

Treatment of 3,5β,17β-trihydroxy-A-nor-5α-androstane (IIIa), *with boron trifluoride etherate.* A solution of triol IIIa (0.52 g.) in tetrahydrofuran (50 ml.) containing boron trifluoride etherate (5 g.) was heated at reflux for 2 hr. The gelatinous precipitate which separated during the first 2 min. at

(28) M. F. Murray, B. A. Johnson, R. L. Pederson, and A. C. Ott, *J. Am. Chem. Soc.*, 78, 981 (1956).

(29) Melting point determinations were performed using open Kimble glass capillaries (silicone oil bath) and are uncorrected. Infrared spectra were recorded by Dr. R. A. Hill of this department. Optical rotation (chloroform solution) measurements were provided by Drs. Weiler and Strauss, Oxford, England. Microanalytical data were obtained in the laboratory of Dr. A. Bernhardt, Mülheim, Germany.

(30) A similar yield of this product was obtained when the reduction reaction was performed in tetrahydrofuran solution.

reflux was collected after 2 hr. of continued heating and washed with water. The resulting solid (m.p. 195–200°) melted at 210–212° after two recrystallizations from methanol-water. A mixture melting point determination of this product with starting material (IIIa) was undepressed.

Diluting the tetrahydrofuran filtrate with water, extraction with ether, and removal of solvent led to a trace of oily product which was not further investigated

Diborane-boron trifluoride etherate reduction of 3-oxo-17β-hydroxy-4-oxa-5α-androstane (I). Dry nitrogen containing diborane, generated during a 20-min. period by adding sodium borohydride (0.26 g.) in bis-2-ethoxyethyl ether (6 ml.) to a solution of boron trifluoride etherate (1.5 g.) in bis-2-ethoxyethyl ether (2 ml.), was washed with dry tetrahydrofuran and passed into a solution of lactone I (0.22 g.) in tetrahydrofuran (8 ml.)–boron trifluoride etherate (1.5 g.). Before diluting with ethanol and water, the diborane generator and reaction mixture was swept with nitrogen for an additional 2 hr. The aqueous mixture was extracted with ether and the combined extract evaporated to dryness. The residue was acetylated and chromatographed on activated alumina. Elution with petroleum ether-(b.p. 40–60°) benzene (1:1) yielded 0.08 g. of semisolid product. Recrystallization from hexane gave 17β-acetoxy-4-oxa-5α-androstane (IIa), m.p. 103–104°. Further elution with 1:2 petroleum ether (40–60°)-benzene provided *3,5β,17β-triacetoxy-3,5-seco-A-nor-5α-androstane* (IIIb, 0.1 g.).

The identity of each product was established by mixture melting point comparison with authentic samples (see above).

3β-Ethoxy-17β-acetoxy-4-oxa-5α-androstane (IV). Diborane was prepared as described in the preceding experiment, from sodium borohydride (0.51 g.) and boron trifluoride etherate (2.9 g.) in bis-2-ethoxyethyl ether (18 ml.), and swept with dry nitrogen through tetrahydrofuran into a solution of 3-oxo-17β-hydroxy-4-oxa-5α-androstane (I, 0.44 g.) in tetrahydrofuran (15 ml.). A slow stream of nitrogen was passed through the system over a 3-hr. period. Ethanol (5 ml.) was then added to the original lactone solution and the solvent removed *in vacuo* (steam bath). The residue was acetylated and chromatographed on activated alumina. Petroleum ether (40–60°) benzene (1:1) eluted 0.31 g. of solid melting at 128–130°. Two recrystallizations from methanol gave colorless needles; m.p. 131–132°, $[\alpha]_D^{22}$ +100° (*c*, 1.33), ν_{max}^{KBr} 1734, 1249, 1124, 1098, 1064, and 1036 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 72.52; H, 9.89; O, 17.59. Found: C, 72.05; H, 9.65; O, 17.99.

3,20-Dioxo-4-oxa-5α-pregnane (V). Progesterone (12 g.) was oxidized in glacial acetic acid (1200 ml.) with peroxydisulfuric acid, prepared from potassium persulfate (36 g.) and concentrated sulfuric acid (40 g.), as previously described (*cf.*, oxidation of testosterone propionate and ref. 11). The neutral product (8.4 g.) was recrystallized several times from ether and acetone–isopropyl ether; yield 2.5 g., m.p. 158–160° (lit.,[11] m.p. 154°), ν_{max}^{KBr} 1732 and 1703 cm.$^{-1}$

The *semicarbazone* derivative exhibited a decomposition point of 272–274° (lit.,[11] d.p. 260–264°).

Essentially the same yield of lactone V was obtained when oxidation of progesterone was allowed to proceed for only 3 days.

20-Oxo-4-oxa-5α-pregnane (VIa). Lithium aluminum hydride (0.38 g.)–boron trifluoride etherate (18 ml.) reduction of 3,20-dioxo-4-oxa-5α-pregnane (V, 0.79 g.) in tetrahydrofuran (60 ml.) was carried out as previously illustrated with 3-oxo-17β-hydroxy-4-oxa-5α-androstane (I). The crude product was dissolved in acetone (20 ml.) and treated with *ca.* 0.5 ml. of an 8*N* chromic acid reagent.[32] After dilution with water and extraction with ether, the ethereal extract was washed successively with water, 5% sodium carbonate solution, and water. Removal of solvent left 0.74 g. of residue which was chromatographed on activated alumina. The solid (0.54 g.) eluted with petroleum ether 40–60°–benzene (1:4) recrystallized from hexane as colorless plates (VIa, 0.35 g.) melting at 144–145°; $[\alpha]_D^{22}$ +126° (*c*, 0.65), ν_{max}^{KBr} 1702, 1104, 1086, and 1044 cm.$^{-1}$

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59; O, 10.51. Found: C, 78.82; H, 10.52; O, 10.65.

The *semicarbazone* derivative recrystallized from ethanol-water as colorless crystals, d.p. 264–266°.

Anal. Calcd. for $C_{21}H_{35}O_2N_3$: C, 69.77; H, 9.76; N, 11.66. Found: C, 69.43; H, 9.62; N, 11.38.

Baeyer-Villiger oxidation of 20-oxo-4-oxa-5α-pregnane (VIa). A stirred mixture composed of 20-ketone VIa (0.5 g.), methylene chloride (13 ml.), and disodium hydrogen phosphate (1 g.) was treated over a 15-min. period with a solution prepared from trifluoroacetic anhydride[31] (1.5 ml.), 90% hydrogen peroxide (0.3 ml.), and methylene chloride (10 ml.). Stirring was continued at room temperature for 90 min. The mixture was diluted with ether, filtered and washed with 10% sodium carbonate solution, and water. Removal of solvent yielded a residue (0.5 g.) which was chromatographed on acid-washed alumina. Petroleum ether (40–60°)–benzene (1:1) eluted a crude sample (0.45 g.), m.p. 94–98°, of *17β-acetoxy-4-oxa-5α-androstane* (IIa). Recrystallization from hexane provided a specimen melting at 104–105°. The structure of this product was confirmed by mixture melting point and infrared spectral comparison (chloroform) with the substance (IIa) prepared from testosterone propionate.

4-Oxa-5α-pregnane 20-ethylenethioketal (VIb). To a solution of 20-oxo-4-oxa-5α-pregnane (VIa, 0.18 g.) in 1,2-ethanedithiol (0.45 ml.) was added 0.45 ml. of boron trifluoride etherate. Crystalline material began to separate from the solution within several minutes. Following a 15-min. period at room temperature, the mixture was diluted with methanol. The precipitated solid (0.18 g.), m.p. 200–202°, was collected, washed with methanol, and recrystallized from the same solvent. A pure specimen was obtained as colorless needles melting at 202–203°.

Anal. Calcd. for $C_{22}H_{36}OS_2$: C, 69.44; H, 9.54; S, 16.82. Found: C, 69.10; H, 9.51; S, 16.39.

4-Oxa-5α-pregnane (VIc). A mixture of thioketal VIb (0.15 g.) and W-4 Raney nickel[32] (*ca.* 5 g.) in ethanol (40 ml.) was heated at reflux for 24 hr. The nickel-containing products were collected and washed with 10 ml. of ethanol. Removal of solvent from the combined filtrate gave a residue which was chromatographed on activated alumina. Elution with 3:1 petroleum ether 40–60°–benzene yielded a colorless crystalline solid (0.09 g.) melting at 105–107°. Recrystallization from methanol gave an analytical specimen; m.p. 107–108°, $[\alpha]_D^{22}$ +56.0° (*c*, 0.92), ν_{max}^{KBr} 1129, 1104, 1092, and 1042 cm.$^{-1}$

Anal. Calcd. for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.35; H, 11.57.

3-Oxo-4-oxa-5α-cholestane (VII). Peroxydisulfuric acid (prepared from 45 g. of potassium persulfate and 50 g. of concd. sulfuric acid) oxidation[11] of cholest-4-en-3-one (15 g.) in glacial acetic acid (1500 ml.) was carried out as illustrated with testosterone propionate. The oily neutral product (9.5 g.) crystallized from ethanol as colorless plates (5.2 g.), m.p. 116–118°. Recrystallization from the same solvent raised the m.p. to 118–119° (lit.,[8,11] m.p. 116° and 116–117°), $[\alpha]_D^{22}$ +81.4° (*c*, 1.33).

The lactone (VII) was identical (mixture melting point determination and infrared spectral comparison in potassium bromide) with an authentic sample, m.p. 116–117°, donated by Dr. J. T. Edward.[8]

4-Oxa-5α-cholestane (VIII). Reduction of 3-oxo-4-oxa-5α-cholestane (VII, 1.17 g.) with the boron trifluoride etherate (12 ml.)–lithium aluminum hydride (0.57 g.) reagent was easily accomplished in tetrahydrofuran (60 ml.) solution. The reaction was performed and initial product iso-

(31) *Cf.*, M. F. Hawthorne, W. D. Emmons, and K. S. McCallum, *J. Am. Chem. Soc.*, 80, 6393 (1958).

(32) A. A. Pavlic and H. Adkins, *J. Am. Chem. Soc.*, 68, 1471 (1946).

lated as described in the case of 3-oxo-17β-hydroxy-4-oxa-5α-androstane (I). Trituration of the crude product with 25 ml. of petroleum ether 40–60° eliminated 1.2 g. of an insoluble viscous oil.[33] Chromatographing the petroleum ether solution on activated alumina and elution with the same solvent yielded 4-oxa-5α-cholestane (0.69 g.), m.p. 92–93°. Two recrystallizations from pentane-methanol gave a pure sample melting at 93–94° (lit.,[8] m.p. 89–90°), $[\alpha]_D^{22}$ +45.7° (*c*, 1.33). The product (VIII) was found to be identical with an authentic sample[8] of 4-oxa-5α-cholestane, melting at 90–91°, by mixture melting point and infrared spectral comparison (potassium bromide).

Continued elution with ether-methanol led to isolation of 3,5β-dihydroxy-3,5-seco-A-nor-5α-cholestane (IX, 0.3 g.) m.p. 135–137°. Recrystallization from methanol raised the melting point to 136–137°. This material did not depress the melting point of an authentic specimen of IX prepared as described by Edward[8] and as described in the following experiment.

Aluminum chloride–sodium borohydride reduction of 3-oxo-4-oxa-5α-cholestane (VII). A solution of aluminum chloride (1.3 g.) and 3-oxo-4-oxa-5α-cholestane (0.39 g.) in bis-2-ethoxyethyl ether (15 ml.) was added over a 30-min. period to a stirred solution of sodium borohydride (0.19 g.) in bis-2-ethoxyethyl ether (15 ml.). Following an additional 1-hr. period at room temperature, the mixture was heated at 70° for 2 hr., cooled, and diluted with 2*N* hydrochloric acid. The aqueous mixture was extracted with ether and the combined extract washed with water. The residue obtained by concentrating the solvent *in vacuo* was chromatographed on activated alumina. Elution with 1:1 petroleum ether 40–60°–benzene yielded 0.02 g. of an oily substance which was not investigated further. Ether-methanol elution led to isolation of 3,5β-dihydroxy-3,5-seco-A-nor-5α-cholestane (IX, 0.34 g.), m.p. 136–138°. The identity of this substance was verified as noted in the preceding experiment.

Treatment of 3,5β-dihydroxy-3,5-seco-A-nor-5α-cholestane (IX) *with boron trifluoride etherate.* A solution of diol IX (0.4 g.) in ether (25 ml.) containing boron trifluoride etherate (3.8 g.) was heated at reflux for 3 hr. After washing with water, the solvent was removed *in vacuo* and the residue chromatographed on activated alumina. Petroleum ether–benzene (1:1) eluted an oil (0.06 g.) which resisted crystallization. Elution with ether-methanol (95:5) yielded 0.32 g. of starting material melting at 136–138°.

Diborane-boron trifluoride etherate reduction of 3-oxo-4-oxa-5α-cholestane (VII). Diborane prepared from sodium borohydride (0.20 g.) and boron trifluoride etherate (1.2 g.) in bis-2-ethoxyethyl ether (5 ml.) was allowed to react (3 hr.) with a solution of lactone VII (0.39 g.) in tetrahydrofuran (15 ml.) containing boron trifluoride etherate (2 ml.). The reaction was carried out as described for analogous reduction of lactone I and the crude oily product chromatographed on acid-washed alumina. Petroleum ether (b.p. 40–60°)–benzene (1:1) elution gave a semisolid (VIII, 0.07 g.) followed by 0.3 g. of unchanged lactone (VII), m.p. 116–118°. After recrystallization from pentane-methanol, the sample of *4-oxa-5α-cholestane* (VIII) melted at 92–93°.

The composition of these products was confirmed by mixture melting point determination with authentic samples.

3β-Hydroxy-4-oxa-5α-cholestane (Xa). A solution of 3-oxo-4-oxa-5α-cholestane (0.39 g.) in tetrahydrofuran (15 ml.) was treated over a 3-hr. period with diborane prepared from sodium borohydride (0.20 g.) and boron trifluoride etherate (1.1 g.) in bis-2-ethoxyethyl ether (5 ml.). The reaction was performed as described for preparation of androstane derivative IV. After addition of ethanol (2 ml.) and ethyl ether to the tetrahydrofuran solution, it was washed with water and the ethereal extract concentrated to dryness. The residue was chromatographed on acid-washed alumina. Elution with ether yielded 0.28 g. of material melting at 170–175°. Repeated recrystallization from methylene chloride–acetone gave *3β-hydroxy-4-oxa-5α-cholestane* as colorless needles: m.p. 197–199°, $[\alpha]_D^{22}$ +106° (*c*, 0.88), ν_{max}^{KBr} 3350, 1090, 1040, and 1000 cm.$^{-1}$

Anal. Calcd. for $C_{26}H_{46}O_2$: C, 79.94; H, 11.87; O, 8.19. Found: C, 79.61; H, 11.52; O, 8.58.

In another experiment, ethanol (5 ml.) was added to the crude reaction mixture obtained by reduction of lactone VII (0.78 g., with diborane from 0.4 g. of sodium borohydride and 2.3 g. of boron trifluoride etherate) and the solution evaporated *in vacuo* (steam bath). Recrystallizing the residue from methylene chloride–acetone gave 0.45 g. of crude *hemiacetal Xa* melting at 175–180°. Another recrystallization from the same solvent mixture raised the m.p. to 193–195°.

3β-Methoxy-4-oxa-5α-cholestane (Xb). A solution of 3β-hydroxy-4-oxa-5α-cholestane (Xa, 0.2 g.) in ethyl ether (5 ml.)–methanol (10 ml.) containing a drop of 48% hydrobromic acid was allowed to stand at room temperature for *ca.* 12 hr. After partial evaporation followed by dilution with ether, the solvent was washed with water and concentrated to an oil (0.15 g.). The residue was dissolved in petroleum ether (40–60°) and chromatographed on activated alumina. The petroleum ether eluate gave a solid (0.11 g.) melting at 104–106°. Two recrystallizations from acetone yielded colorless flakes; m.p. 106–107°, $[\alpha]_D^{22}$ +104° (*c*, 0.67), ν_{max}^{KBr} 1132, 1063, and 1042 cm.$^{-1}$

Anal. Calcd. for $C_{27}H_{48}O_2$: C, 80.14; H, 11.96; O, 7.91. Found: C, 80.45; H, 11.85; O, 7.47.

Chromic acid oxidation of 3β-hydroxy-4-oxa-5α-cholestane (Xa). A solution of hemiacetal Xa (0.2 g.) in acetone (40 ml.) was treated with an 8*N* chromic acid reagent[22] until oxidation was complete. The mixture was diluted with water and the precipitated material (0.15 g.), m.p. 106–110°, collected. Three recrystallizations from ethanol yielded a sample of *3-oxo-4-oxa-5α-cholestane* (VII) melting at 116–118°. Infrared spectral comparison and mixture melting point determination with an authentic sample (VII) established the structure of this product.

Treatment of 3β-hydroxy-4-oxa-5α-cholestane (Xa) *with hydrochloric acid.* A solution of hemiacetal Xa (0.10 g.) in tetrahydrofuran (10 ml.) containing 1 drop of concd. hydrochloric acid was allowed to remain at room temperature for 20 hr. After concentrating the solvent to *ca.* 5 ml. (*in vacuo* at 0°) and diluting with water, the colorless solid which separated was collected by extraction with ethyl ether. Removal of solvent yielded a 0.097-g. residue melting at 150–160°. The crude product was dissolved in petroleum ether–benzene (1:1) and chromatographed on acid-washed alumina. Following two recrystallizations from chloroform-acetone, the fraction (0.075 g.) eluted with ethyl ether weighed 0.030 g., and melted at 190–192°. The product (Xa) was found (by mixture melting point determination and infrared spectral comparison) to be identical with starting material (Xa).

3β-Hydroxy-17a-oxa-D-*homo-5α-androstane* (XIIa). A solution of 3β-hydroxy-17-oxo-17a-oxa-D-homo-5α-androstane[28] (XI, 0.46 g.) in ethyl ether (150 ml.) was reduced with lithium aluminum hydride (0.59 g.)–boron trifluoride etherate (7 ml.) according to the procedure employed with lactone I. The crude alcohol was acetylated and chromatographed on activated alumina. The fraction eluted with 1:1 petroleum ether 40–60°)–benzene weighed 0.18 g. and melted at 143–145°. A pure specimen of 3β-acetoxy-17a-oxa-D-homo-5α-androstane (XIIb) recrystallized from hexane as colorless rods: m.p. 145–146°, $[\alpha]_D^{25}$ −18.0° (*c*, 1.23), ν_{max}^{KBr} 1715, 1120, 1092, and 1030.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25; O, 14.35. Found: C, 75.64; H, 10.30; O, 14.29.

(33) Secondary reaction(s) involving tetrahydrofuran was considered responsible for this material. See: W. J. Bailey and F. Marktscheffel, *J. Org. Chem.*, **25**, 1797 (1960); and for a pertinent review: H. Meerwein, D. Delfs, and H. Morschel, *Angew. Chem.*, **72**, 927 (1960).

An analytical sample of *3β-hydroxy-17a-oxa*-D-*homo-5α-androstane* (XIIa), prepared by saponifying the corresponding acetate derivative, recrystallized from methanol-water as colorless needles melting at 181–183°; $[\alpha]^{20}_{D}$ 0.0°, ν^{KBr}_{max} 3401, 1120, 1090, 1060, 1046, and 1026 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{32}O_2$(292): C, 78.03; H, 11.03; O, 10.94; active H, 0.34. Found: C, 77.54; H, 10.82; O, 11.56; active H, 0.28; mol. wt. (Rast), 297.

Treating alcohol XIIb, in pyridine solution, with benzoyl chloride (1 hr., steam bath) led to 3β-benzoyloxy-17a-oxa-D-homo-5α-androstane (XIIc); colorless needles from methanol, m.p. 162–164°, ν^{KBr}_{max} 1712, 1120, and 1098 cm.$^{-1}$

Anal. Calcd. for $C_{26}H_{36}O_3$: C, 78.71; H, 9.15; O, 12.10. Found: C, 78.36; H, 9.07; O, 12.17.

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[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN AND OF STANFORD UNIVERSITY]

Ring-A α-Acetoxy Ketones in the Cholestane Series

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The unambiguous synthesis of six isomeric keto acetates, 2α-, 2β-, 4α-, and 4β-acetoxycholestane-3-one and 3α- and 3β-acetoxycholestane-2-one, was undertaken in order to clarify a number of erroneous structural assignments in the literature as well as to prove the structures of the compounds produced by the action of potassium acetate and by tetramethylammonium acetate on 2α-bromocholestane-3-one.

α-Acetoxy ketones of known configuration and conformation were desired for NMR spectroscopy studies.[1] In exploring the availability of such substances in the cholestane series, we discovered that the situation as reported in the literature was confused; we therefore attempted to clarify matters. A compound, m.p. 148–149°, which is an inseparable mixture of 2α-acetoxycholestane-3-one (XI) and 4α-acetoxycholestane-3-one (XVI), has been shown[2] to be produced by the displacement of bromine from 2α-bromocholestane-3-one by potassium or sodium acetate in refluxing acetic acid. In an effort to prepare pure 2α-acetoxycholestane-3-one (XI) we tried the reaction of 2α-bromocholestane-3-one with tetramethylammonium acetate in refluxing acetone.[3] The product was shown to be identical with a substance prepared *via* the acyloin condensation of 2,3-secocholestane-2,3-dioic acid dimethyl ester and assigned the structure 3β-acetoxycholestane-2-one.[4] From the same acyloin reaction which produced 3β-hydroxycholestane-2-one, Sheehan and Erman isolated a compound which was assigned the structure 2-hydroxycholestane-3-one. The properties of the acetate of this ketol,[4] however, corresponded to those reported[2] for the complex of 2α- and 4α-acetoxycholestane-3-one. This complex, moreover, had been reduced and hydrolyzed by Ruzicka, Plattner, and Furrer,[5] who did not realize that they were dealing with a mixture. Unlikely structural assignments were made to a number of the resulting bewildering array of products.

In order to try to clarify the confusion and to ascertain the exact composition of the complex of 2α- and 4α-acetoxycholestane-3-one, the unequivocal synthesis of six keto acetates was undertaken: 2α-, 2β-, 4α-, and 4β-acetoxycholestane-3-one and 3α- and 3β-acetoxycholestane-2-one.

Synthesis of the keto acetates. An unambiguous method was employed. Diaxial hydroxy acetates were obtained by acetolysis of the appropriate epoxides. Oxidation by Jones' reagent[6] gave the axial α-acetoxy ketones which could be converted to their equatorial epimers by acid-catalyzed epimerization.

2α-Bromocholestane-3-one[7] was reduced to a mixture of bromohydrins,[8,9] one of which was converted to 2β,3β-oxidocholestane[9] (I) by the action of potassium hydroxide in isopropyl alcohol. This epoxide was cleaved with acetic acid to 2β-hydroxy-3α-acetoxycholestane (II), m.p. (dimorphic) 111–112.5° and 138.7–139.2°, $[\alpha]_D$ +42.2°, according to the procedure which Furst and Plattner[10] used to convert 2α,3α-oxidocholestane to 2β-acetoxy-3α-hydroxycholestane. Acetylation pro-

(1) See K. L. Williamson and W. S. Johnson, *J. Am. Chem. Soc., in press.*

(2) L. F. Fieser and M. A. Romero, *J. Am. Chem. Soc.*, **75**, 4716 (1953).

(3) See *inter alia* A. Streitwieser, Jr., and J. R. Wolfe, Jr., *J. Am. Chem. Soc.*, **79**, 903 (1957); H. L. Goering, T. D. Nevitt, and E. F. Silversmith, *J. Am. Chem. Soc.*, **77**, 4042 (1955); and J. Steigman and L. P. Hammett, *J. Am. Chem. Soc.*, **59**, 2536 (1937).

(4) J. C. Sheehan and W. F. Erman, *J. Am. Chem. Soc.*, **79**, 6050 (1957).

(5) L. Ruzicka, Pl. A. Plattner, and M. Furrer, *Helv. Chim. Acta*, **27**, 727 (1944).

(6) (a) R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 457 (1953); (b) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953); (c) T. G. Halsall, R. Hodges, and E. R. H. Jones, *J. Chem. Soc.*, 3019 (1953); (d) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(7) A. Butenandt and A. Wolff, *Ber.*, **68**, 2091 (1935).

(8) L. F. Fieser and W. Y. Huang, *J. Am. Chem. Soc.*, **75**, 4837 (1953).

(9) E. J. Corey, *J. Am. Chem. Soc.*, **75**, 4832 (1954).

(10) A. Furst and Pl. A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949).