STEROIDS AND RELATED NATURAL PRODUCTS

XXVIII. STEREOCHEMISTRY OF 3-HYDROXY-4-OXA-5α-CHOLESTANE AND RELATED HEMIACETALS[1,2]

GEORGE R. PETTIT,[3] JOHN C. KNIGHT,[4] AND WILLIAM J. EVERS

Department of Chemistry, University of Maine, Orono, Maine, and Department of Chemistry, Arizona State University, Tempe, Arizona

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ABSTRACT

Several new 3-hydroxy-4-oxa type steroidal hemiacetals (V and VII) have been prepared by diborane reduction of the corresponding δ-lactones. A detailed proton magnetic resonance study of the hemiacetal (IX*a*) derived from 3-oxo-4-oxa-5α-cholestane (VIII) indicated that diborane reduction led in each case to an epimeric mixture. Treating hemiacetal IX*a* with methanol – hydrochloric acid gave a mixture of acetals IX*b* and IX*c*. Pure specimens of the epimeric acetals were obtained by preparative thin-layer chromatography, and configurational assignments based on proton magnetic resonance studies were provided for each isomer. Allowing lactone VIII (in tetrahydrofuran solution) to react with 1 equivalent of diborane during 4 min resulted in approximately 80% conversion into hemiacetal IX*a*, and provided an illustration of the potential utility of the reduction reaction.

After the discovery (2) that certain steroidal lactones could conveniently be reduced to cyclic hemiacetals with diborane, the reduction reaction was applied (2, 3) to four A-ring steroidal lactones.[5] The first hemiacetal prepared in our laboratory by the diborane route was 3ξ-hydroxy-4-oxa-5α-cholestane (IX*a*), and the isomer (m.p. 197–199°) that was characterized was assumed (2*b*) to represent the 3β-equatorial epimer. Concurrently, Edward and his colleagues (4*c*) performed the same experiment by a lithium aluminium hydride procedure and isolated one isomer (m.p. 188–190°) that was assigned, on the basis of molecular rotation studies, the 3α-axial configuration. Although fractional recrystallization of the hemiacetal failed to reveal the presence of the 3β-isomer, a solution of the hemiacetal in tetrahydrofuran–water was found (4*c*) to represent 45% equatorial isomer and 55% axial epimer. Later, when we began a general study of the lactone → hemiacetal reduction reaction with diborane, the stereochemistry of A-ring steroidal hemiacetals became of increasing importance. Accordingly, a detailed examination of hemiacetal IX*a* was undertaken by proton magnetic resonance (p.m.r.) spectroscopy, and the study was expanded to include related hemiacetals representing the androstane (V) and pregnane (VII*a*) ring systems.

Synthesis of the required hemiacetals was conveniently achieved as follows. First, dehydroepiandrosterone (I) was converted into 3-oxo-androst-4-ene (II) essentially as previously reported (6) and the ketone was oxidized to lactone III*a* with peroxydisulfuric acid (2*b*, 3*a*). For chemical and subsequent biological comparative purposes, lactone III*a* was reduced by boron trifluoride – sodium borohydride to tetrahydropyran III*b* and by lithium aluminium hydride to diol IV. Then lactone III*a* in tetrahydrofuran was readily reduced to hemiacetal V by externally generated (sodium borohydride – boron trifluoride)

[1] *For part XXVII of this series, see ref. 1.*

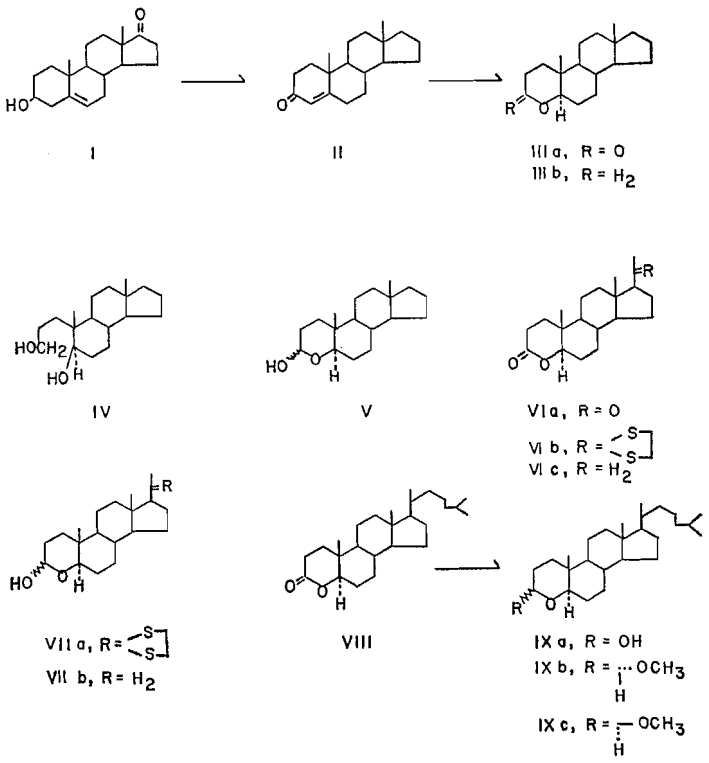
[2] *Based on part of the Ph.D. dissertation submitted by W. J. Evers to the Graduate School, University of Maine, Orono, Maine, December 1964.*

[3] *Correspondence should be addressed to this author at the Department of Chemistry, Arizona State University, Tempe, Arizona.*

[4] *Smith, Kline, and French Postdoctorate Fellow, 1962.*

[5] *Meanwhile, a variety of other steroidal hemiacetals have been prepared from the corresponding lactone by specialized lithium aluminium hydride or sodium borohydride techniques (4). In the same period, several novel approaches to steroidal hemiacetals and (or) acetal derivatives were also reported (5).*

diborane. Next, progesterone was converted (2*b*) into lactone VI*a*. Treating the 20-ketone (VI*a*) with boron trifluoride – ethanedithiol yielded thioketal VI*b*. Raney nickel desulfurization (7) of ethylenethioketal VI*b* gave the required lactone (VI*c*). Diborane (externally generated) reduction of lactones VI*b* and VI*c* provided the corresponding hemiacetal derivatives (VII*a* and VII*b*). At this point, the reduction reaction appeared to be of a general nature, and the necessary experimental conditions were more carefully defined, lactone VIII being used as a model substrate. Eventually, a 4 min reaction period at room temperature and with equivalent quantities of standard diborane in tetrahydrofuran[6] was found to convert lactone VIII in good yield (approximately 80%) into hemiacetal IX*a*. The remaining product, as evidenced by thin-layer chromatography, was the corresponding diol resulting from further reduction. In general, a 30 min reaction period was found to be satisfactory.



A chromatographically pure specimen of hemiacetal IX*a*, m.p. 185–190°, in deuteriochloroform was found by p.m.r. spectral comparison (Fig. 1) with specimens of 3β-hydroxy-5α-cholestane (8) and 3α-hydroxy-5α-cholestane (9) to represent a mixture of 3β- and 3α-epimers in approximately equal amounts. In the 5α-steroid series an axial C-3 proton generally exhibits a broad response upfield from the more well defined signal usually exhibited by an equatorial C-3 proton (10). The p.m.r. spectra of the 3-hydroxy-5α-cholestanes (Fig. 1) were in agreement with these observations. The 3β-hydroxy epimer of hemiacetal IX*a* displayed a broad 3α-proton signal at 4.58 δ and a broad 5α-proton signal centered at 3.07 δ. Corresponding signals at 5.08 (3β-proton) and 3.6–3.8 (5α-proton) δ of the composite spectrum were attributed to the 3α-hydroxy isomer (IX*a*).

[6]*Recently 1M borane in tetrahydrofuran has become commercially available (metal hydride division of Ventron Corporation) and is now being routinely employed (e.g. for preparation of hemiacetals) in our laboratory.*

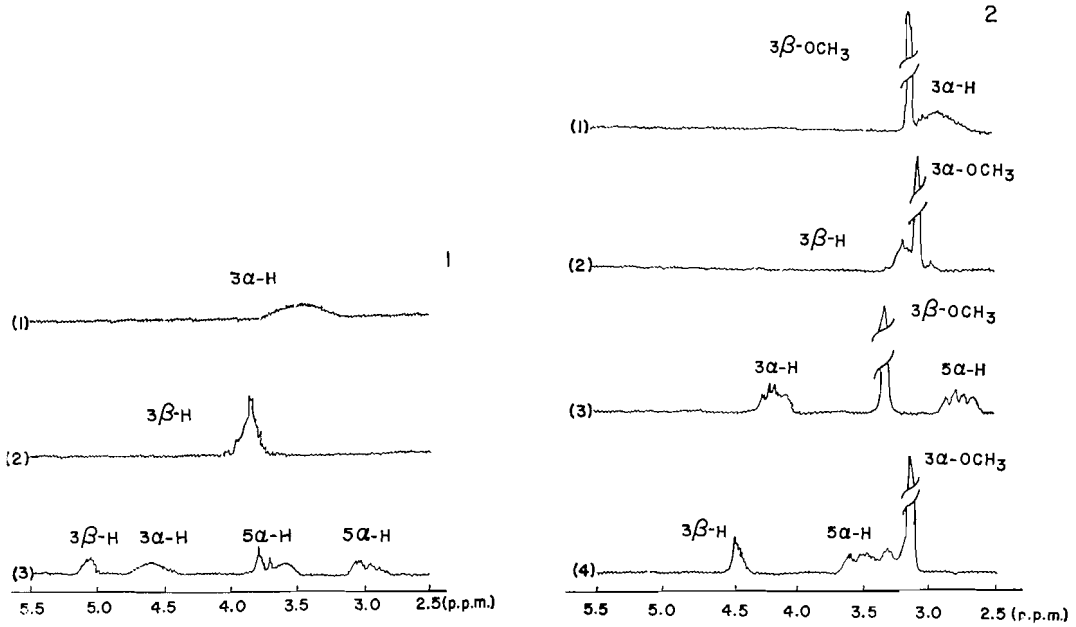


FIG. 1. The p.m.r. spectra of 3β-hydroxy-5α-cholestane (1), 3α-hydroxy-5α-cholestane (2), and the epimeric 3α- and 3β-hydroxy-4-oxa-5α-cholestanes (3) in deuteriochloroform. Resonance frequencies are recorded downfield from tetramethylsilane at 0.0 δ.

FIG. 2. The p.m.r. spectra of 3β-methoxy-5α-cholestane (1), 3α-methoxy-5α-cholestane (2), 3β-methoxy-4-oxa-5α-cholestane (3), and 3α-methoxy-4-oxa-5α-cholestane (4) in benzene recorded as noted in Fig. 1.

Analogous p.m.r. evidence was compiled and used to assign configurations to the epimeric methylacetals (IX*b* and IX*c*) derived from hemiacetal IX*a*.[7] Preparative thin-layer chromatography was used to separate the epimeric mixture of methylacetals obtained by treating hemiacetal IX*a* with methanol containing a drop of hydrochloric acid. By this method, pure specimens of the axial (IX*b*, m.p. 101–102°) and equatorial (IX*c*, m.p. 79–80°) epimers were obtained. A comparison (Fig. 2) of the p.m.r. spectra of both epimers in benzene solution with the p.m.r. spectra of 3α-methoxy- (13) and 3β-methoxy-5α-cholestane confirmed the structures previously assigned by Edward and collaborators.[7,8] Interestingly, the 5α-proton of the axial hydroxyl (IX*a*) and methoxy (IX*b*) isomers gave a p.m.r. signal displaced downfield by 0.6–0.7 δ from that of the C-3 equatorial isomers.[9]

A survey of hemiacetals V and VII indicated that each represented (in deuteriochloroform solution) a nearly equal mixture of epimers. Thus, the anomeric effect in 3-hydroxy-4-oxa steroids, in solution, is as important as conformational factors, and in the case of 3-methoxy-4-oxa-5α-steroids becomes of major importance. These conclusions reached on the basis of p.m.r. data support and confirm the earlier conclusions of Edward and his colleagues (4*c*, 11) regarding the stereochemistry of 3-hydroxy-4-oxa-5α-cholestane (IX*a*).

[7]*The isomeric acetals corresponding to structures IXb and IXc were prepared (2b, 4c, 11) in conjunction with earlier studies of hemiacetal IXa. The isomer, m.p. 98–99.5°, obtained from hemiacetal IXa and methanol – hydrogen chloride was shown (4c), on the basis of careful mutarotation determinations, to represent a 3α-methoxy configuration. Similarly, the β-anomer (m.p. 74–76°) obtained (11) by acid-catalyzed isomerization of the 3α-methoxy epimer was assigned structure IXc. Before these reports Fieser and his colleagues isolated a sample of the acetal melting at 89–92° (12).*

[8]*Edward and Puskas (11) also noted that acid-catalyzed isomerization of the 3-methoxy anomers favored formation of the 3α-methoxy isomer in the approximate ratio 7:3. A p.m.r. spectrum of the crude methylation product in benzene solution, prepared as described in the Experimental section, clearly verified the 3α-methoxy epimer as the major product.*

[9]*An example of 1,3-diaxial deshielding in the reverse direction, that is, of a C-3 proton by a bromine substituent at C-5, has been recorded (14).*

EXPERIMENTAL

The diethyl ether, diglyme (diethylene glycol dimethyl ether), and tetrahydrofuran were redistilled from sodium or lithium aluminium hydride and stored over sodium wire. Final purification of diglyme by distillation from lithium aluminium hydride in one case (observed by Dr. A. K. Das Gupta) resulted in an explosion. The same observation has recently been reported by Watson (15). In view of these experiences, distillation of diglyme from lithium aluminium hydride is not now recommended. All other solvents and boron trifluoride etherate were also redistilled. The sodium borohydride was used as supplied by Metal Hydrides, Inc. Each reduction reaction was conducted in a nitrogen atmosphere. Solvent extracts of aqueous solutions were dried over magnesium sulfate. Activated alumina refers to Merck "suitable for chromatography". Thin-layer chromatography plates were prepared with silica gel G (E. Merck, AG, Darmstadt) and developed with concentrated sulfuric acid.

A Kofler melting point apparatus was employed for melting point determinations (corrected). Optical rotation (chloroform solution) and elemental composition values were determined, respectively, in the laboratories of Dr. P. Demoen, Janssen Pharmaceutica, Beerse, Belgium, and Dr. A. Bernhardt, Mülheim, Germany. The infrared (potassium bromide) and p.m.r. spectra were recorded by Dr. R. A. Hill (University of Maine).

3-Oxo-4-oxa-5α-androstane (IIIa)

After chromatography on activated alumina in 1:1 petroleum ether – benzene, 3-oxo-androst-4-ene (II) (10 g (6)) was obtained as colorless needles, m.p. 106–108°. Oxidation to lactone III*a* was accomplished as previously described for 19-nortestosterone acetate (3*a*) with a reagent prepared from sulfuric acid (28 g), potassium persulfate (26 g), and glacial acetic acid (500 ml). The crude lactone (III*a*) was crystallized from petroleum ether – acetone as tacky yellow prisms (4.4 g). A solution of the product in 1:1 petroleum ether – benzene was percolated through a column of neutral alumina (Merck, Darmstadt) and, after removal of solvent, the filtrate residue was crystallized from petroleum ether – acetone as colorless needles (1.9 g), m.p. 115–116°. Repeated recrystallization from the same solvent mixture did not alter the melting point, and an analytical specimen exhibited $[\alpha]_D^{22}$ +77.3° (*c*, 1.25) and ν_{max} 1 735 cm^{-1}.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.61; H, 10.27.

3,5β-Dihydroxy-3,5-seco-A-nor-5α-androstane (IV)

A solution of lactone III*a* (0.5 g) in tetrahydrofuran (20 ml) was reduced with lithium aluminium hydride (0.5 g in 30 ml of tetrahydrofuran) by the technique employed with 3-oxo-17β-hydroxy-4-oxa-5α-androstane (see ref. 3*a*). The diol (IV) was recrystallized from chloroform–methanol as needles weighing 0.45 g and melting at 189–190°. Several recrystallizations from the same solvent mixture provided an analytical sample (unchanged melting point); $[\alpha]_D^{22}$ 0.0° (*c*, 1.31);[10] ν_{max} 3 300, 1 085, 1 065, 1 040, and 1 025 cm^{-1}.

Anal. Calcd. for $C_{18}H_{32}O_2$: C, 77.09; H, 11.50; active H, 0.72. Found: C, 76.99; H, 11.26; active H, 0.62.

3ξ-Hydroxy-4-oxa-5α-androstane (V)

A solution of lactone III*a* (0.60 g) in tetrahydrofuran (20 ml) was treated with diborane generated from sodium borohydride (0.7 g) and boron trifluoride etherate (2.0 g) in diglyme (35 ml) as noted in earlier experiments (2, 3*a*). A solution of the solid product in 3:1 benzene–chloroform was chromatographed on neutral alumina. Elution with 60 ml of the same solvent mixture led to the recovery of lactone III*a* (0.05 g). Continued elution provided the epimeric hemiacetals (V). Three recrystallizations from chloroform – petroleum ether gave needles (0.40 g) melting at 188–192° (sintering from 178°). A thin-layer chromatogram of the hemiacetal mixture on Kieselguhr G (with chloroform or 19:1 chloroform–methanol as mobile phase) indicated that the analytical specimen represented only hemiacetal V: the epimeric mixture displayed $[\alpha]_D^{22}$ +56.4° (*c*, 1.17); ν_{max} 3 300, 1 115, 1 082, 1 042, and 1 030 cm^{-1}; p.m.r. (deuteriochloroform solution) response at 0.7, 0.95, 1–2 (broad), 3.1, 3.2, 4.75 (broad), and 5.2 δ.

Anal. Calcd. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86; active H, 0.36. Found: C, 77.92, 77.81; H, 11.01, 10.89; active H, 0.40.

Further elution of the column with 1:1 chloroform–methanol gave 0.10 g, m.p. 189–190°, of diol IV.[11]

4-Oxa-5α-androstane (IIIb)

Reduction of lactone III*a* (1.0 g) to tetrahydropyran III*b* was accomplished with the sodium borohydride (0.3 g) – boron trifluoride etherate (15 g) reagent in diglyme (30 ml) as previously described (1). A solution of the crude product in petroleum ether was passed through a column of activated alumina. After removal of the solvent *in vacuo* the residue was recrystallized from methanol–water; yield 0.45 g. Four recrystallizations from the same solvent yielded a pure specimen as colorless needles; m.p. 56–57°; $[\alpha]_D^{20}$ +34.7° (*c*, 1.86); ν_{max} 1 085, 1 105 cm^{-1}.

Anal. Calcd. for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 82.35, 82.34; H, 11.77, 11.46.

[10] *Methanol as solvent.*

[11] *By mixture melting point determination and infrared spectral comparison, the substance was found to be identical with an authentic sample.*

3-Oxo-4-oxa-5α-pregnane 20-Ethylenethioketal (VIb)

A solution of 3,20-dioxo-4-oxa-5α-pregnane (1.0 g, VI*a* (2*b*)) in boron trifluoride etherate (11 g) – ethanedithiol (3.0 g) was prepared at room temperature. Within a few minutes, the thioketal crystallized from solution as colorless needles. After a total of 1.5 h the mixture was cooled and diluted with methanol; the thioketal (VI*b*) was collected, washed with methanol, and recrystallized from acetone to yield 0.81 g melting at 237–239°; $[\alpha]_D^{23}$ +68.8° (*c*, 1.25); ν_{max} 1 740 cm^{-1}.

Anal. Calcd. for $C_{22}H_{34}O_2S_2$: C, 66.96; H, 8.69; S, 16.26. Found: C, 66.70; H, 8.58; S, 16.54.

3ξ-Hydroxy-4-oxa-5α-pregnane 20-Ethylenethioketal (VIIa)

Conversion of lactone VI*b* (0.45 g) in tetrahydrofuran (20 ml) into the epimeric mixture of hemiacetals corresponding to structure VII*a* was accomplished with diborane generated from sodium borohydride (0.5 g) and boron trifluoride etherate (2.9 g) in diglyme (18 ml) as described for hemiacetal V. The epimeric hemiacetals were recrystallized from chloroform – petroleum ether as colorless needles (0.32 g) melting at 187–188°; $[\alpha]_D^{21}$ 0.0°; ν_{max} 3 350 cm^{-1}.

Anal. Calcd. for $C_{22}H_{36}O_2S_2$: C, 66.60; H, 9.15; S, 16.17. Found: C, 66.28, 66.07; H, 8.89, 9.07; S, 16.36, 16.55.

3-Oxo-4-oxa-5α-pregnane (VIc)

Raney nickel (30 ml, W-4 (7)) was added to a solution of thioketal VI*b* (2.0 g) in ethanol (150 ml), and the mixture was heated at reflux for 4 h. After the solution was filtered, the nickel residue was washed with warm ethanol and the combined filtrate was concentrated to a colorless solid. Recrystallization from ethanol – petroleum ether gave 0.49 g of needles melting at 186–187°. Placing the nickel residues in a Soxlet apparatus and extracting with ethanol gave 0.16 g, and final dissolution of the nickel by-products in hydrochloric acid gave another 0.22 g of crude product. An analytical sample that was recrystallized from methanol – petroleum ether melted at 188–190°; $[\alpha]_D^{23}$ +107.4° (*c*, 0.619); ν_{max} 1 740 cm^{-1}.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.38; H, 10.33.

3ξ-Hydroxy-4-oxa-5α-pregnane (VIIb)

Lactone VI*c* (0.3 g) in tetrahydrofuran (20 ml) was reduced to a mixture of epimeric hemiacetals (VII*b*, 0.2 g) by (see V) diborane prepared from sodium borohydride (0.4 g) and boron trifluoride etherate (2.2 g). Recrystallization from chloroform – petroleum ether yielded colorless crystals melting at 161–163°; $[\alpha]_D^{23}$ 69.3° (*c*, 1.0); ν_{max} 3 350 cm^{-1}.

Anal. Calcd. for $C_{20}H_{34}O_2$ (306): C, 78.38; H, 11.18; O, 10.44; active H, 0.33. Found: C, 78.33, 77.93; H, 11.19, 11.11; O, 10.79; active H, 0.25; mol. wt. (Rast) 271.

3ξ-Hydroxy-4-oxa-5α-cholestane (IXa)

In a typical experiment, 0.38 *M* borane in tetrahydrofuran (30 ml (16)) was added at room temperature to 3-oxo-4-oxa-5α-cholestane (5.1 g, VIII). Before dilution with water (10 ml) and extraction with diethyl ether (60 ml), the solution was allowed to stand for 0.5 h. The combined ethereal extracts were washed with water and dried (potassium carbonate). Removal of solvent *in vacuo* gave a solid residue (5.0 g). A solution of the crude product in tetrahydrofuran–benzene (1:3) was chromatographed on silica gel (250 g). Elution with the same solvent mixture led to 4.2 g of hemiacetal IX*a*, m.p. 183–190°. Recrystallization from either methylene chloride – acetone or tetrahydrofuran–ligroin (b.p. 90–120°) gave a specimen (IX*a*) melting at 185–190°. In both cases, thin-layer chromatograms (7:3 benzene – diethyl ether being used as the mobile phase) and mixture thin-layer chromatograms with an authentic sample (2*b*) indicated the presence of only hemiacetal IX*a* (see Fig. 1). Melting points of 188–190° (4*c*) and 197–199° (2*b*), representing different proportions of the epimeric hemiacetals, have been reported.

When the preceding experiment was repeated with 0.5 g of lactone VIII (and with appropriately adjusted amounts of the other reagents) for a total reaction time of 4 min, essentially the same result was obtained. A thin-layer chromatogram of the crude product suggested the presence of approximately 80% hemiacetal IX*a* accompanied by 3,5β-dihydroxy-3,5-seco-A-nor-5α-cholestane (2*b*). However, conducting the same reaction with one-half the previous quantity of diborane and a 30 min reaction period yielded a mixture (as evidenced by a thin-layer chromatogram) composed of approximately equal amounts of lactone VIII, hemiacetal IX*a*, and the diol resulting from complete reduction.

3α-Methoxy- and 3β-Methoxy-4-oxa-5α-cholestane (IXb and IXc)

A solution composed of the epimeric hemiacetals (0.40 g, IX*a*) prepared above, tetrahydrofuran (7 ml), methanol (15 ml), and 1 drop of concentrated hydrochloric acid was prepared by warming the mixture for approximately 3 min. Next, the solution was cooled and concentrated (*in vacuo*) to a crystalline residue. Six 0.06 g portions of the crude product were applied to each of six preparative silica gel G (1 mm layer) thin-layer chromatography plates. Each plate was developed 3 times with 9:1 hexane – diethyl ether, and the bands were identified by holding the plate in iodine vapor for a few seconds. Two very close bands were observed at approximately the middle of the plate, and each was carefully collected. Elution of the less-polar component with diethyl ether gave 0.19 g of acetal IX*b*, which was rechromatographed on four preparative thin-layer plates. By this means, a 0.16 g sample of 3α-methoxy-4-oxa-5α-cholestane (IX*b*) melting at 98–101.5° was obtained. Recrystallization from acetone raised the melting point to 101–102.5° (melting points of 98–99.5° and 106–107° have been reported (2*b*, 4*c*)).

The more polar acetal was eluted from the silica gel in the same manner, and rechromatographed (twice) on two preparative silica gel thin-layer plates to yield 0.06 g of 3β-methoxy-4-oxa-5α-cholestane (IX*c*) melting at 77–80°. Two recrystallizations from acetone and one from methanol–acetone raised the melting point to 79–80° (ref. 11 reports m.p. 78°).

The configuration assigned to each hemiacetal was supported by a p.m.r. study (see Fig. 2).

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REFERENCES

1. G. R. PETTIT, H. KLINGER, N. O. JORGENSEN, and J. OCCOLOWITZ. Phytochemistry. In press.
2. (*a*) G. R. PETTIT, T. R. KASTURI, B. GREEN, and J. C. KNIGHT. J. Org. Chem. **26**, 4773 (1961). (*b*) G. R. PETTIT and T. R. KASTURI. J. Org. Chem. **26**, 4553 (1961).
3. (*a*) G. R. PETTIT, A. K. DAS GUPTA, and U. R. GHATAK. Steroids, **1**, 137 (1963). (*b*) R. PAPPO. U. S. Patent No. 3,101,350 (August 20, 1963); Chem. Abstr. **60**, 596 (1964).
4. (*a*) W. S. JOHNSON, J. C. COLLINS, JR., R. PAPPO, M. B. RUBIN, P. J. KROPP, W. F. JOHNS, J. E. PIKE, and W. BARTMANN. J. Am. Chem. Soc. **85**, 1409 (1963). (*b*) K. HEUSLER and A. WETTSTEIN. Helv. Chim. Acta, **45**, 347 (1962). (*c*) J. T. EDWARD, P. F. MORAND, and I. PUSKAS. Can. J. Chem. **39**, 2069 (1961). (*d*) N. W. ATWATER. J. Am. Chem. Soc. **83**, 3071 (1961).
5. G. NOMINE, R. BUCOURT, and A. PIERDET. Fr. Patent No. 1,366,725 (July 17, 1964); Chem. Abstr. **61**, 14751 (1964). D. BERTIN and J. PERRONNET. Bull. Soc. Chim. France, 564 (1964). W. F. JOHNS. U.S. Patent No. 3,137,690 (June 16, 1964); Chem. Abstr. **61**, 4428 (1964). J. E. PIKE, M. A. REBENSTORF, G. SLOMP, and F. A. MACKELLAR. J. Org. Chem. **28**, 2499 (1963). K. HEUSLER, J. KALVODA, P. WIELAND, G. ANNER, and A. WETTSTEIN. Helv. Chim. Acta, **45**, 2575 (1962).
7. C. W. SHOPPEE and G. KRUEGER. J. Chem. Soc. 3641 (1961).
8. G. R. PETTIT and E. VAN TAMELEN. Org. Reactions, **12**, 356 (1962).
9. G. R. PETTIT and D. M. PIATAK. J. Org. Chem. **27**, 2127 (1962). M. NEEMAN and W. S. JOHNSON. Org. Syn. **41**, 9 (1961).
9. A. WINDAUS and C. UIBRIG. Ber. **47**, 2384 (1914). A. FURST and P. A. PLATTNER. Helv. Chim. Acta, **32**, 275 (1949).
10. D. A. SWANN and J. H. TURNBULL. Tetrahedron, **20**, 1265 (1964). R. E. COUNSELL. Tetrahedron, **15**, 202 (1961). L. F. FIESER and T. GOTO. J. Am. Chem. Soc. **82**, 1693 (1960). J. N. SHOOLERY and M. T. ROGERS. J. Am. Chem. Soc. **80**, 5121 (1958).
11. J. T. EDWARD and I. PUSKAS. Can. J. Chem. **40**, 711 (1962).
12. L. F. FIESER, T. GOTO, and B. K. BHATTACHARYYA. J. Am. Chem. Soc. **82**, 1700 (1960).
13. M. NEEMAN, M. J. CASERIO, J. D. ROBERTS, and W. S. JOHNSON. Tetrahedron, **6**, 36 (1959).
14. A. VAN DER GEN. Ph.D. Dissertation, University of Amsterdam, Amsterdam, Netherlands. 1964.
15. H. R. WATSON. Chem. Ind. London, 665 (1964).
16. G. ZWEIFEL and H. C. BROWN. Org. Reactions, **13**, 1 (1963).