THE PHOTOLYSIS OF 4,4-DIMETHYLANDROST-5-EN-17β-OL-3-ONE[1]

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Received March 16, 1966

ABSTRACT

The photolysis of 4,4-dimethylandrost-5-en-17β-ol-3-one (I) in aqueous tetrahydrofuran has been shown to give products of reduction, adducts with tetrahydrofuran, and 5-isopropyl-lactones VI and VII.

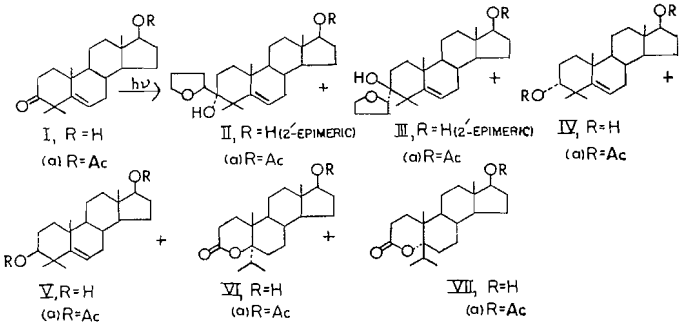
It is well known that the carbonyl chromophore of a β,γ-unsaturated ketone can overlap with the carbon–carbon double bond chromophore, giving rise to an exalted intensity of the $n \rightarrow \pi^*$ transition or to a shift towards longer wavelength of the chromophore. From this type of data, conformations of ring A of 4,4-dimethylcholest-5-en-3-one have been deduced (1, 2).

We were interested in determining whether this type of interaction would lead to products analogous to those formed in the solvolysis of cholesteryl derivatives in which the double bond of a β,γ-unsaturated tosylate interacts with the incipient carbonium ion. We therefore studied the photolysis of 4,4-dimethylandrost-5-en-17β-ol-3-one, which is readily available from testosterone (3).

RESULTS

Photolysis of a 0.033 *M* aqueous tetrahydrofuran solution of 4,4-dimethylandrost-5-en-17β-ol-3-one (I) in a helium atmosphere gave a mixture of products, which could be resolved by chromatographic means only with difficulty. When the crude reaction mixture was steam distilled, a reasonable separation of the residue was effected by a combination of chromatography on alumina and thin-layer chromatography (t.l.c.), with silica gel as the adsorbent. The purity of the components and the yields were established by gas–liquid chromatography (g.l.c.). The details of the separation procedure, as well as relevant analytical and spectral data, are described in the Experimental section.

Diols IV and V were obtained as a mixture which was not resolved. Oxidation with chromium trioxide in pyridine (4) gave in good yield 4,4-dimethylandrost-5-ene-3,17-dione (VIII), identical with the oxidation product of I. The diol mixture (IV and V) was then



[1]*This work was supported by the National Research Council of Canada. Abstracted from part of the Ph.D. thesis of R. T. T.*
[2]*Holder of a McGill University Fellowship, 1962–1963.*

acetylated. Gas–liquid chromatographic analysis of this mixture indicated the presence of two components (IV*a* and V*a*), with retention times identical with those of an authentic mixture of IV*a* and V*a*, obtained by sodium borohydride reduction of ketone I (3) followed by acetylation.

Diol III was characterized in the following manner. Acetylation with acetic anhydride in pyridine at room temperature gave a diol monoacetate III*a*. The mass spectrum of III*a* indicated it to be an adduct of ketone I*a* and tetrahydrofuran. The proton magnetic resonance (p.m.r.) spectrum[3] of III*a* showed the C_6-olefinic proton at 5.68 p.p.m. and a three-proton signal centered at 3.89 p.p.m., characteristic of the low-field protons in tetrahydrofuran. The most probable mode of attachment of the tetrahydrofuryl moiety was as depicted in III*a*. The synthesis of III*a* was therefore undertaken. Ketone I*a* was reacted with an ethereal solution of 2-furylmagnesium iodide (5). After acetylation, a low yield (high conversion) of product IX was obtained. Catalytic reduction of IX gave, after acetylation, the tetrahydrofuryl derivative III*a* in very low yield.

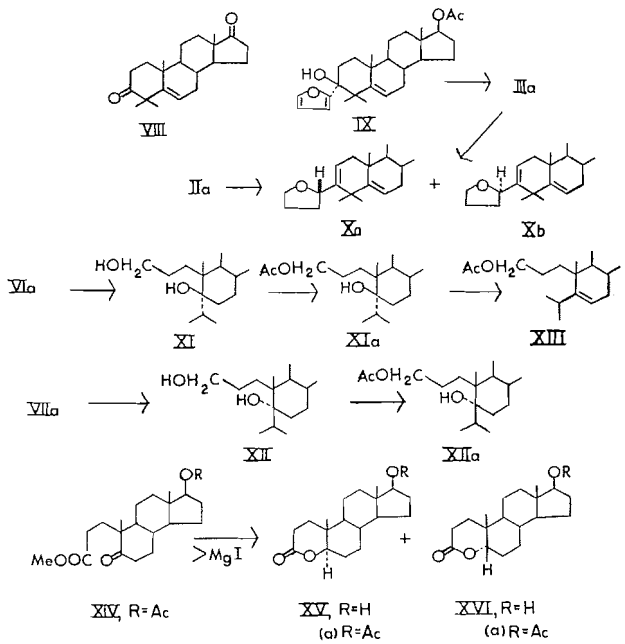
Diol II was apparently the C_3-epimer of diol III. It gave, upon acetylation, a diol monoacetate II*a*. Dehydration of this monoacetate with thionyl chloride in pyridine gave product X, identical with the product obtained by dehydration of diol monoacetate III*a*. Product X was a mixture of the 2′-epimers X*a* and X*b*. It could be resolved into its constituents[4] by t.l.c., with silver nitrate impregnated silica gel as the adsorbent and hexane–ether (6.5:3.5 v/v) as the developing solvent.

The configurational assignment at C-3 of II and III was based on the following arguments. The 3α-alcohol (axial) II had a higher chromatographic mobility on alumina (column). This criterion has often and successfully been applied for this type of assignment (6, 7). Similarly, II*a* had a larger R_f value than III*a* on t.l.c. with alumina as adsorbent (8, 9). Gas–liquid chromatography gave similar results when applied to II*a* and III*a* (10). Comparison of the mode of addition of 2-furylmagnesium iodide and ketone I*a* to that of similar Δ^5-3-ketones and Grignard reagents (11) confirmed the stereochemical assignment at C-3 of II and III.

Lactones VI and VII, which absorbed in the infrared at 1 740 cm^{-1}, were the third type of compound obtained. Both lactones gave monoacetates (VI*a* and VII*a*), which could be converted into triols (XI and XII) by lithium aluminium hydride treatment. Acetylation of XI and XII gave triol diacetates XI*a* and XII*a*, whose infrared spectra were superimposable and displayed hydroxyl bands at 3 620 cm^{-1}. The p.m.r. spectra of XI*a* and XII*a* showed a two-proton signal (triplet) at 4.09 p.p.m. (C—CH_2—OAc). Dehydration of XI*a* gave olefinic diacetate XIII (δ 5.62 p.p.m. (1H)). The mass spectrum of VII*a* showed a very small parent peak at *m/e* 376 and the base peak at *m/e* 333, corresponding to the loss of an isopropyl radical. The subsequent fragmentation pattern was essentially identical with the mass spectrum of the mixture of lactones XV*a* and XVI*a*.[5]

The stereochemical assignment at C-5 in lactones VI*a* and VII*a* was based on (*i*) differences in the molecular rotations (ΔM_D (VI*a* − VII*a*) = 308°) of these substances compared with those of the corresponding lactones (ΔM_D (XV − XVI) = 237°) described by Atwater and Ralls (12); (*ii*) the relative R_f values of triol diacetates XI*a* (0.87) and XII*a* (0.98) on t.l.c.[6] (8, 9); and (*iii*) the chemical shift of the 19-CH_3, which is more deshielded in the *trans*-lactone VI*a* (1.15 p.p.m.) than in the *cis*-lactone VII*a* (1.09 p.p.m.).

[3]*The p.m.r. spectra were taken in* $CDCl_3$ *(tetramethylsilane = 0 p.p.m.).*
[4]*A stereochemical assignment at C-2′ is discussed in the Ph.D. thesis of R. T. T.*
[5]*Lactones XV*a *and XVI*a *were obtained as a mixture from the attempted synthesis of lactones VI*a *and VII*a *outlined in the Experimental section.*
[6]*The procedure for the comparison is described in the Experimental section.*



The yields of the photoproducts in tetrahydrofuran–water (3:1 v/v) and in tetrahydrofuran were established by g.l.c. of the crude, steam distilled, and acetylated reaction mixtures, and are summarized in Table I.

TABLE I

Photoproduct	% yield: Tetrahydrofuran–water (3:1)	% yield: Tetrahydrofuran	Retention times* (min)
IV*a*	8	16	2.6
V*a*	8	4	2.2
II*a*	7	3	12.0
III*a*	6	0	15.2
VI*a*	7	0	9.3
VII*a*	6	0	4.7
A†	7	0	4.2

*Determined at 270° on a 6 ft × ¼ in. (inside diameter) glass column packed with 5% DC 710 on silanized Gas Chrom P; helium was used as the carrier gas at 30 p.s.i.
†Product A was not isolated.

DISCUSSION

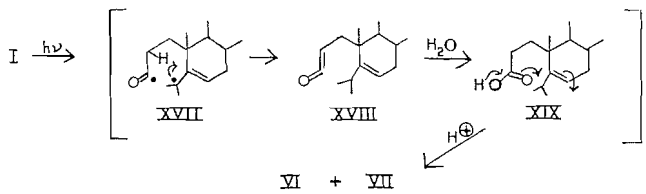
Diols IV and V are products of photoreduction, a well-documented (13, 14) occurrence in ketone photochemistry. Adducts II and III find complete analogy in the photochemical addition of tetrahydrofuran to acetone observed by Shima and Tsutsumi (15). Both reduction and adduct formation arise from $n \rightarrow \pi^*$ excitation of the ketone (I) carbonyl to a biradical triplet state (16). The intermediate biradical reacts with solvent molecules to give IV, V, II, and III in yields of 8, 8, 7, and 6%, respectively. When the photolysis of I was performed in tetrahydrofuran, the yields of IV, V, and II were 16, 4, and 3%, respectively, and no III could be detected.[7] This alteration in product distribution from

[7]*The irradiation was performed in a standard quartz water-cooled immersion apparatus.*

aqueous tetrahydrofuran to tetrahydrofuran most probably reflects the differences in solvation of the electronically excited species.

That the C_3—C_4 bond in ketone I underwent cleavage during the photolysis is evident from the presence of lactones VI (7%) and VII (6%).[7] The α-cleavage of ketones also arises from a biradical state, from which is generated an acyl and alkyl radical (17). It is to be expected that cleavage would occur between C-3 and C-4 to give the more stable biradical, e.g. lanostanone yields ca. 34% primary acid (18).

Lactones VI and VII are most likely formed by the known process outlined below. A similar transformation has recently been described (19). An olefinic acid (such as XIX) is known to give a δ-lactone under acidic conditions (20); recently, Mousseron-Canet *et al.* (21) explained their isolation of a δ-lactone from the photolysis of an olefinic acid similar to XIX on the basis of lactonization catalyzed by traces of acid.



Inspection of the g.l.c. spectrum showed that all major components but one were accounted for. This product A, present in approximately 7% yield, was not isolated. The balance of the isolated compounds indicated that no participation of the double bond has to be invoked to explain the products formed.

EXPERIMENTAL

Proton magnetic resonance spectra were recorded on a Varian A-60 (60 Mc.p.s.) spectrometer with deuteriochloroform as solvent and tetramethylsilane (0 p.p.m.) as internal standard. Infrared spectra were taken on Perkin–Elmer grating spectrophotometers, models 337 and 521, with carbon tetrachloride as solvent. Melting points were determined in open capillary tubes on a Gallenkamp apparatus, and are corrected. Optical rotations were measured on a Carl Zeiss photoelectric precision polarimeter. Ultraviolet absorption spectra were taken on a Beckman DK 1 recording spectrophotometer. Schwarzkopf Microanalytical Laboratories, Woodside 77, New York, and Dr. A. Bernhardt, Mülheim, Germany, performed the microanalyses. Mass spectra were recorded by S. Meyerson, American Oil Co., Whiting, Indiana, and by Morgan–Schaffer, Montreal, Quebec. Gas–liquid chromatographic determinations were made on a F and M model 700 gas chromatograph. All acetylations were performed with acetic anhydride in pyridine at room temperature. Silica gel 0.75 mm thick on 8 × 8 in. glass plates was used for plate chromatography, with water as the detector.

Irradiation of Ketone I (3) in Tetrahydrofuran–Water

Ketone I (6.67 g) dissolved in 500 ml of tetrahydrofuran–water (3:1 v/v) was irradiated[7] with a Hanovia 450 W lamp until no starting material remained by t.l.c. analysis (72 h). The addition of 4 g of sodium chloride to the reaction solution gave two layers, which were separated. The tetrahydrofuran layer was dried with magnesium sulfate and concentrated to give 13.03 g of viscous oil. This product was steam distilled and the residue extracted with 1% sodium hydroxide solution, which removed 0.975 g of acidic material. The remaining 7.17 g of oil was chromatographed on 300 g of alumina (activity II–III).

Elution with 120 ml of benzene–ether (9:1 v/v) gave 0.118 g of oil which was not characterized.

Further elution (320 ml) gave 0.321 g of an oil which was then acetylated. Plate chromatography with benzene–ether (4:1 v/v) as the developing solvent gave a major band with R_f 0.78. Ether elution of this band yielded 0.276 g of 17β-acetoxy-4,4-dimethyl-3β-(2-tetrahydrofuryl)androst-5-en-3α-ol (11*a*), m.p. 159.5–161°. Recrystallization from methanol raised the melting point to 160–162°; $[\alpha]_D^{25}$ −94° (*c*, 0.52 in $CHCl_3$); ν_{max} 3 592 (OH) and 1 052 cm^{-1} (C—O—C); δ 5.57 (1H, C=C$_6$—H), 3.80 (3H, poorly resolved CH_2—O—CH), and 1.21 and 1.16 p.p.m.; g.l.c. retention time 12.0 min.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.73; H, 9.99.

Continued elution (360 ml) with the same solvent gave 1.25 g of oil, which crystallized overnight from

methanol, m.p. 167–180°. Four recrystallizations from methanol provided 0.205 g of 4,4-dimethyl-3α-(2-tetrahydrofuryl)androst-5-ene-3β,17β-diol (III), m.p. 183–184°; $[\alpha]_D^{25}$ −73° (*c*, 1.37 in $CHCl_3$); ν_{max} 3 562 (tertiary OH) and 1 052 cm^{-1}; δ 5.62 (1H, broad) and 3.75 p.p.m. (4H, broad, O—C_{17}H and CH_2—O—CH).

Anal. Calcd. for $C_{25}H_{40}O_3$: C, 77.27; H, 10.38. Found: C, 77.52; H, 10.38.

Further elution (160 ml) gave 0.830 g of oil. Acetylation followed by plate chromatography in benzene–ether (4:1 v/v) gave two bands at R_f 0.85 and 0.73. The band with R_f 0.85 provided 0.085 g of epimeric 3-acetoxy-4,4-dimethylandrost-5-en-17β-ol acetate (IV*a* and V*a*), m.p. 157–160°; δ 4.58 (1H, triplet, AcO—C_{17}H) and 4.42 p.p.m. (1H, triplet, AcO—C_3H); g.l.c. retention times 2.6 and 2.2 min, respectively.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52. Found: C, 74.77; H, 9.62.

The band at R_f 0.73 gave 0.337 g of 17β-acetoxy-4,4-dimethyl-3α-(2-tetrahydrofuryl)androst-5-en-3β-ol (III*a*), m.p. 199–201°. An analytical sample was prepared by recrystallization from methanol, m.p. 201–202°; $[\alpha]_D^{25}$ −78° (*c*, 0.87 in $CHCl_3$); ν_{max} 3 562 (OH) and 1 052 cm^{-1}; δ 4.67 (1H, triplet, AcO—C_{17}H), 3.89 (3H, approximating a triplet, CH_2—O—CH), and 2.47 p.p.m. (OH, exchanged with D_2O); g.l.c. retention time 15.2 min.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.78; H, 10.08; mol. wt. 430 (mass spectrometry).

Continued elution (280 ml) provided an oil (0.563 g), from which III*a*, IV*a*, and V*a* were isolated by t.l.c. as described above.

Further elution (80 ml) gave 0.102 g of epimeric 3-hydroxy-4,4-dimethylandrost-5-en-17β-ol (IV and V), m.p. 201–204° (crystallization from ether). Three recrystallizations from acetone gave an analytical sample having m.p. 204–206°; ν_{KBr} 3 500 – 3 452 (broad) and 3 053 cm^{-1} (olefinic C—H); δ (pyridine) 3.87 (1H, triplet, O—C_{17}H), 3.48 (1H, triplet, O—C_3H), and 1.40 and 1.32 p.p.m. (3H each, two singlets, 4,4-dimethyl).

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.97; H, 10.82.

Elution (160 ml) with benzene–ether (8.5:1.5 v/v) gave 1.34 g of oil. Acetylation followed by hexane trituration of the recovered oil provided long fibers melting at 151–156°. Crystallization from hexane gave 0.184 g of 17β-acetoxy-5α-isopropyl-4-oxaandrostan-3-one (VI*a*), m.p. 162–163°; $[\alpha]_D^{25}$ +87° (*c*, 0.13 in $CHCl_3$); ν_{max} 1 740 (acetate carbonyl and δ-lactone), 1 425 (C—H of CH_2COO), and 1 391 and 1 382 cm^{-1} (isopropyl group); δ 2.62 (2H, AB system, CH_2—COO),[8] 1.20 and 1.12 (3H each, two doublets, J = 7 c.p.s., isopropyl Me_2), and 1.15 p.p.m. (19-Me); g.l.c. retention time 9.3 min (broad, with decomposition).

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.29; H, 9.77.

Elution with 250 ml of benzene–ether (1:1 v/v) gave 0.51 g of oil. Acetylation followed by plate chromatography in benzene–ether (3:1 v/v) gave a major band with R_f 0.51. Ether elution of this band provided 0.252 g of 17β-acetoxy-5β-isopropyl-4-oxaandrostan-3-one (VII*a*), m.p. 121–123.5° (crystallization from hexane); $[\alpha]_D^{25}$ +5° (*c*, 1.38 in $CHCl_3$); δ 2.48 (2H, AB system, CH_2—COO), 1.09 (19-Me), and 1.05 and 1.01 p.p.m. (3H each, two doublets, J = 7 c.p.s., isopropyl Me_2); g.l.c. retention time 4.7 min (with decomposition).

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.40; H, 9.57; mol. wt. 376 (mass spectrometry).

Oxidation of Epimeric 3-Hydroxy-4,4-dimethylandrost-5-en-17β-diol (IV and V) with Chromium Trioxide (4)

Chromium trioxide (61 mg) dissolved in 5 ml of pyridine was added to a solution of 140 mg of the mixture (IV and V) in 7 ml of pyridine. After having stood overnight, the reaction mixture was filtered through an asbestos pad and the inorganic residue was washed with two 10 ml portions of benzene. The usual work-up and plate chromatography of the recovered oil with benzene–ether (4:1 v/v) gave 99 mg of powder, m.p. 151–154°. One recrystallization from hexane–ether gave 83 mg of dione VIII, m.p. 161–162°; ν_{max} 1 734 and 1 705 cm^{-1} (ketones having five- and six-membered rings, respectively). No depression in the melting point was observed on admixture with the product obtained from the corresponding oxidation of I.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.41; H, 9.63.

17β-Acetoxy-4,4-dimethyl-3α-(2-furyl)androst-5-en-3β-ol (IX)

A mixture of I*a* (1.1 g) in 15 ml of ether and 2-furylmagnesium iodide (prepared by reacting 0.425 g of magnesium with 2.4 g of 2-iodofuran (5) in 6 ml of ether) was heated under reflux for 7 h. Ammonium chloride (20 ml of a 5% solution) was added to the cooled reaction mixture, followed by filtration through an asbestos pad. The ether layer was dried and concentrated to give 1.3 g of oil, which was then acetylated. Plate chromatography of the recovered oil with 15% ether in benzene gave two bands at R_f 0.61 and 0.54. The band at R_f 0.61 provided 0.401 g of I*a* (identified by mixed melting point and infrared spectrum). The band with R_f 0.54 gave an oil which provided a partially crystalline material when passed through 20 g of alumina (activity I) with benzene–ether (1:1) as eluent. Crystallization from methanol yielded 0.410 g of IX as platelets, m.p. 213–215°. Five recrystallizations from methanol raised the melting point to 215–216° (yellow color persisted); $[\alpha]_D^{25}$ −37° (*c*, 0.40 in $CHCl_3$); $\lambda_{max}^{Et_2O}$ 223 mμ (ϵ 4 700); ν_{max} 3 620 (OH) and 3 045 and 1 047 cm^{-1}; δ 7.23 (1H, complex splitting, C=$C_{5'}$H—O), 6.28 (2H, complex multiplet, C=$C_{3'}$H—$C_{4'}$H=C), and 2.58 p.p.m. (OH).

Anal. Calcd. for $C_{27}H_{38}O_4$: C, 76.02; H, 8.98. Found: C, 76.51; H, 8.47.

[8]*When the p.m.r. spectrum of lactone VIa was taken in 30% deuterium oxide in pyridine, the AB system (in* $CDCl_3$*) became a two-proton triplet centered at 2.79 p.p.m.*

Hydrogenation of IX

A mixture of Raney nickel (45 mg), acetate IX (150 mg), and ethanol (50 ml) was hydrogenated (3 100 p.s.i.) at 160 ± 4° for 17 h. Filtration and concentration gave 135 mg of oil. Acetylation followed by plate chromatography, with 30% ether in benzene, gave a series of closely moving bands with R_f values ranging from 0.98 to 0.17. Collection of the bands between R_f 0.98 and 0.55 and separation by plate chromatography with benzene–ether (4:1) gave a band at R_f 0.73 which provided 8 mg of oil. The oil crystallized from methanol, m.p. 196–198°, and was identical with III*a* obtained from photolysis (mixture melting point, comparison of t.l.c. behavior and infrared spectrum).

Dehydration of IIIa (or IIa) with Thionyl Chloride

Thionyl chloride (0.8 ml) was added dropwise to a stirred solution of 184 mg of III*a* in 6 ml of dry pyridine at 0°. After addition, stirring was continued at room temperature for 1 h. Ice chips were then added cautiously and 115 mg of oil was recovered by ether extraction. The oil crystallized from ethanol after 5 days, m.p. 148–151°. Plate chromatography of the product (X) with silver nitrate impregnated silica gel[9] as the adsorbent and 35% ether in hexane as the developing solvent gave two bands, detected by ultraviolet light at R_f 0.62 and 0.57, respectively. The band at R_f 0.62 provided 23 mg of 17β-acetoxy-4,4-dimethyl-3-(2-tetrahydrofuryl)androsta-2,5-diene (X*a*), m.p. 154–156°; $[\alpha]_D^{25}$ −59° (*c*, 0.96 in $CHCl_3$); ν_{max} 3 030 and 1 048 cm^{-1}; δ 5.84 (1H, unresolved, C=C$_2$—H), 5.60 (1H, broad, C=C$_6$—H), 4.32 (1H, triplet, O—C$_{2'}$H—C=O), and 3.87 p.p.m. (2H, poorly resolved, O—C$_{5'}$H$_2$—C); g.l.c. retention time 8.0 min.

Anal. Calcd. for $C_{27}H_{40}O_3$: C, 78.59; H, 9.77. Found: C, 78.78; H, 9.77.

The band with R_f 0.57 gave 20 mg of X*b*, m.p. 171–172.5°; $[\alpha]_D^{25}$ −74° (*c*, 0.94 in $CHCl_3$). The infrared and p.m.r. spectra were essentially the same as those for X*a*.

Anal. Calcd. for $C_{27}H_{40}O_3$: C, 78.59; H, 9.77. Found: C, 78.48; H, 9.74.

3,4-Seco-4,4-dimethylandrostane-3,5β,17β-triol (XI)

A solution of 318 mg of VI*a* in 10 ml of dry ether was added slowly to 126 mg of lithium aluminium hydride in 4 ml of ether. The mixture was heated under reflux for 1 h and worked up in the usual way to give 306 mg of XI, m.p. 184–187°. Three recrystallizations from ether–acetone raised the melting point to 196–198.5°; $[\alpha]_D^{25}$ +4° (*c*, 0.98 in pyridine).

Anal. Calcd. for $C_{21}H_{38}O_3$: C, 74.51; H, 11.32. Found: C, 74.35; H, 11.25.

Acetylation of XI (100 mg) gave 104 mg of 3,17β-diacetoxy-3,4-seco-4,4-dimethylandrostan-5β-ol (XI*a*) as an oil, which was shown to be homogeneous by t.l.c.; ν_{max} 3 620 (free OH) and 1 740 cm^{-1} (intense); δ 4.69 (1H, triplet, AcO—C$_{17}$H) and 4.09 p.p.m. (2H, triplet, C—CH$_2$—OAc).

3,17β-Diacetoxy-3,4-seco-4,4-dimethylandrost-5-ene (XIII)

The dehydration of 104 mg (oil) of XI*a* was carried out as described for III*a*. The resulting oil was purified by plate chromatography with 35% ether in hexane to give XIII, R_f 0.98; m.p. 116–116.5°; ν_{max} 1 742 cm^{-1} (intense); δ 5.62 (1H, poorly resolved, C=C$_6$—H), 4.67 (1H, triplet, AcO—C$_{17}$H), and 4.03 p.p.m. (2H, triplet, C—CH$_2$—OAc).

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97. Found: C, 74.19; H, 9.54.

3,4-Seco-4,4-dimethylandrostane-3,5α,17β-triol (XII)

Lactone VII*a* (112 mg) was treated as described for VI*a*. Triol XII (91 mg) was isolated, m.p. 143–144.5°; $[\alpha]_D^{24}$ +41° (*c*, 0.94 in pyridine).

Anal. Calcd. for $C_{21}H_{38}O_3$: C, 74.51; H, 11.32. Found: C, 74.18; H, 11.14.

Acetylation of 65 mg of XII provided 61 mg of 3,17β-diacetoxy-3,4-seco-4,4-dimethylandrostan-3α-ol (XII*a*), m.p. 141–143° after crystallization from methanol; $[\alpha]_D^{24}$ +1° (*c*, 0.6 in $CHCl_3$). The infrared spectrum was indistinguishable from that of XI*a*. The p.m.r. spectrum was also very similar to that of XI*a*.

Anal. Calcd. for $C_{25}H_{42}O_5$: C, 71.09; H, 9.95. Found: C, 70.97; H, 10.26.

Thin-Layer Chromatographic Comparison of XIa and XIIa

Both XI*a* and XII*a* were spotted on a microscope slide coated evenly (0.5 mm) with Woelm neutral alumina (for t.l.c.). With ethyl acetate – hexane (3:2 v/v) as the developing solvent, XII*a* had a R_f value of 0.98 whereas XI*a* was at R_f 0.87.

Attempted Synthesis of Lactones VIa and VIIa; Lactones XVa and XVIa

An ethereal solution of isopropylmagnesium iodide was added to 431 mg of 17β-acetoxy-5-oxo-3,5-seco-A-norandrostan-3-oic acid methyl ester (XIV)[10] in 35 ml of dry ether until t.l.c. analysis indicated that only a trace of XIV remained. Ammonium chloride (10 ml of a 3% solution) was then introduced and the ether solution dried and concentrated. Acetylation of the residual oil followed by plate chromatography with 30% ether in benzene gave two bands at R_f 0.77 and 0.54. Ether elution of the band at R_f 0.77 provided 120 mg

[9]*The plates ordinarily used for plate chromatography were sprayed with 5% silver nitrate solution until the adsorbent was saturated. The plates were then air dried overnight.*

[10]*Prepared from testosterone acetate in accordance with a procedure described by Atwater and Ralls (12), followed by treatment with diazomethane.*

of starting material (identified by infrared and p.m.r. spectra and mixed melting point), m.p. 90–91.5°. The other band (R_f 0.54) gave a mixture of 17β-acetoxy-4-oxa-5α-androstan-3-one (XV*a*) and the 5β-epimer (XVI*a*), m.p. 150–164°; ν_{max} 1 740 cm^{-1} (intense); δ 4.22 (0.6H, triplet, 5β-hydrogen of XVI*a*) and 3.70 p.p.m. (0.5H, broad, 5α-hydrogen of XV*a*).[11]

Anal. Calcd. for $C_{20}H_{30}O_4$: C, 71.85; H, 8.98. Found: C, 72.05; H, 9.01; mol. wt. 334 (mass spectrometry).

The Grignard reaction therefore resulted in only reduction and enolization.

ACKNOWLEDGMENTS

We thank Mr. K. Valentin for taking the p.m.r. spectra; Dr. G. Schilling and Mr. J. Kastner, Ayerst Laboratories, Montreal, for providing g.l.c. supports and performing the high-pressure catalytic reduction of IX; Mr. S. Meyerson, American Oil Co., for taking a mass spectrum; and G. D. Searle and Co., Syntex Corporation, and Ayerst Laboratories for generous gifts of starting material.

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[11]*House et al. (22) found that the 5-proton (axial) in a lactone such as XV absorbed at higher field (closer to tetramethylsilane) than its equatorial epimer (such as XVI).*