[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION,
AMERICAN CYANAMID COMPANY]

STEROIDAL CYCLIC KETALS. VII.[1] TRANSFORMATION PRODUCTS OF ADRENOSTERONE. $\Delta^{4,\,9(11)}$ANDROSTADIENE-3,17-DIONE

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In previous papers of this series (1), synthetic routes were developed for the transformation of Δ^4-androstene-3,11,17-trione (adrenosterone) into Δ^4-androstene-11β-ol-3,17-dione (I), Δ^4-androstene-11α-ol-3,17-dione (II), and a number of related $C_{19}O_3$-steroids.

Subsequently, our efforts have been directed to a study of certain chemical conversions involving I and II; *i.e.*, the preparation of $\Delta^{4,\,9(11)}$androstadiene-3,17-dione (III)[2] from I, the preparation of the known (2) $\Delta^{4,\,11}$-androstadiene-3,17-dione (IV) from II, and the preparation of I from II by means of a Walden inversion. The last two conversions were of special interest to us, and warranted an experimental study, although theoretical considerations (*vide infra*) predicted difficulty in accomplishing them.

Reaction of a C_{11}β-hydroxysteroid with a number of reagents leads to facile dehydration with the formation of a $\Delta^{9(11)}$steroid. The reagents successfully employed for this transformation are conc'd hydrochloric acid-glacial acetic acid (3), phosphorus oxychloride-pyridine (4), thionyl chloride-pyridine (5), and boron trifluoride etherate-glacial acetic acid (6). Thus, Δ^4-androstene-11β-ol 3,17-dione (I) on being refluxed for ½ hour in 20% conc'd hydrochloric acid-glacial acetic acid was converted (although in poor yield) into the expected $\Delta^{4,\,9(11)}$androstadiene-3,17-dione (III). In striking contrast, the 11α-epimer (II) under similar conditions was primarily acetylated to afford Δ^4-androstene-11α-ol-3,17-dione acetate (V), and unchanged starting material. Likewise, Δ^5-androstene-11α-ol-3,17-dione bisethylene ketal (VI)[3] gave II in low yield. The acidic conditions of the reaction removed, as anticipated, the protective ketal groups. In this experiment the 11α-acetate was undoubtedly present but was not isolated. The stability of an 11α-hydroxyl group under these conditions has been previously noted by Long and Gallagher (7) with methyl 3α,11α-dihydroxycholanate, and by the Upjohn group (8) with Δ^4-pregnene-11α-ol-3,20-dione. The latter group also observed the formation of the 11α-acetate.

These results may be understood by an examination of the following considerations. Conformational analysis (9) shows that a C_{11}β-hydroxyl group forms a polar bond, whereas the C_{11}α-epimer forms an equatorial bond (energetically more stable). Ionic elimination reactions proceed most readily when the two

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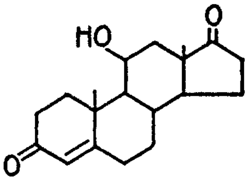
[1] Paper VI, Bernstein, Littell, and Williams, *J. Org. Chem.*, **18**, 1418 (1953).

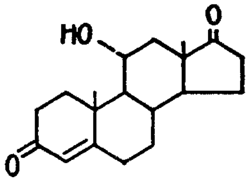
[2] Reichstein, U.S. Patent 2,409,798 (October 22, 1946), has described the dehydration of I by refluxing the latter with 20% conc'd hydrochloric acid-glacial acetic acid to afford III, and possibly $\Delta^{4,\,8}$-androstadiene-3,17-dione. No experimental details were given, and neither compound was characterized.

[3] In almost all of the experiments described, the ketal derivatives have been intentionally used. Thus, the reactions served more adequately for "model substance work".

substituents on adjacent carbons form polar bonds. In addition, Barton states that another requirement for *trans* elimination is that the four centers participating in the elimination reaction shall lie in one plane for maximal ease of reaction. From Figures I (C_9–C_{11} axis), and III (C_{11}–C_{12} axis), it can be readily seen that a $C_{11}\beta$-hydroxyl group fulfills the requirements for facile ionic elimination. The subsequent formation of a $\Delta^{9(11)}$-steroid rather than a Δ^{11}-steroid is energetically sound. A $\Delta^{9(11)}$-steroid will be more stable than the corresponding Δ^{11}-steroid as the former has three α-hydrogens in hyperconjugation with it as compared with the latter where only one α-hydrogen is present (10). The $C_{11}\alpha$-hydroxyl group fulfills neither of the two above stated requirements for facile ionic elimination. This is shown by Figures II (C_9–C_{11} axis), and IV (C_{11}–C_{12} axis). Moreover, S_N2 displacement of an 11α-hydroxyl group may not proceed evidently due to steric hindrance. An E1 elimination reaction, in our opinion, would predominate over any S_N1 displacement. Consequently, the hydrochloric acid merely provides



I



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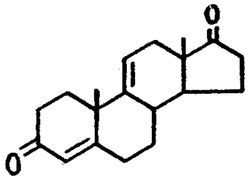
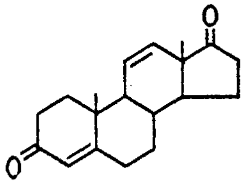


III



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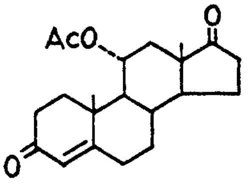
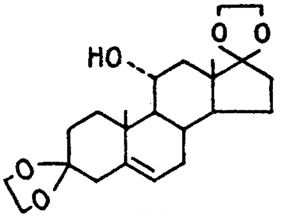
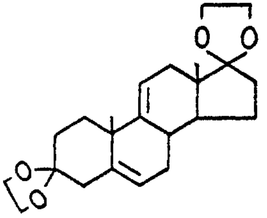


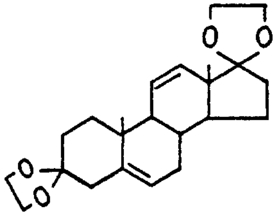
V



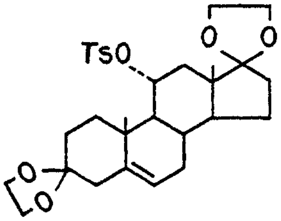
VI



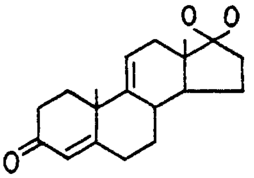
VII



VIII



IX



X

a proton for catalyzing the esterification. However, treatment of the 11α-hydroxy-bisketal (III) with phosphorus oxychloride-pyridine at room-temperature led to an elimination of the elements of water. Only $\Delta^{5,9(11)}$-androstadiene-3,17-dione bisethylene ketal (VII) was isolated (94 % "crude" yield); and, apparently, no $\Delta^{5,11}$-compound (VIII) was formed. The absence of an hydroxyl function was confirmed by infrared analysis. Aqueous acetic acid hydrolyzed the ketal groups, and $\Delta^{4,9(11)}$-androstadiene-3,17-dione (III) was obtained. The product was identical with that formed from the 11β-hydroxy-3,17-dione (I) with conc'd hydrochloric acid-glacial acetic acid. The diene (III) was further characterized by the preparation of a bis-2,4-dinitrophenylhydrazone.

This resultant elimination of a $C_{11}\alpha$-hydroxyl group to afford a $\Delta^{9(11)}$-steroid may be conveniently explained by an E1 mechanism. An E2 mechanism may be ruled out as it requires a prior S_N2 displacement. The latter, as pointed out, is unlikely on steric grounds.

We next examined the chemical properties of Δ^{5}-androstene-11α-ol-3,17-dione tosylate bisethylene ketal (IX). This compound was prepared in the usual manner by tosylation of the 11α-hydroxy-bis ketal (VI) in pyridine. However, it proved difficult to prepare in an analytically pure state. Whereas the correct

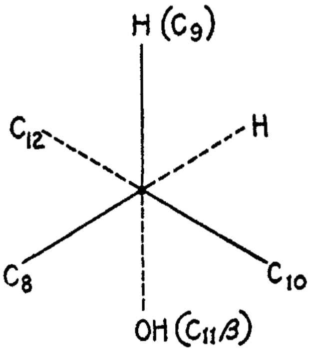


Fig I

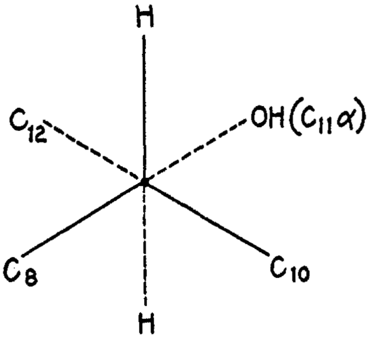


Fig II

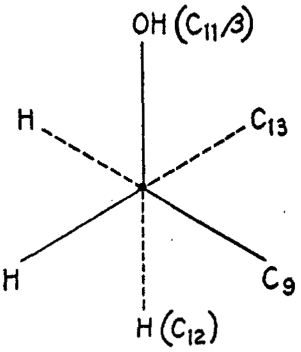


Fig III

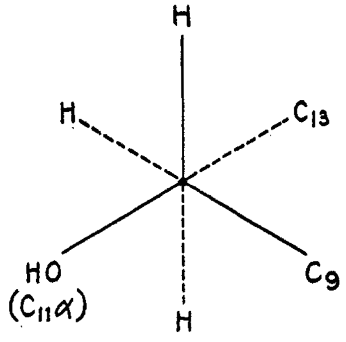


Fig IV

carbon and hydrogen values were obtained, the sulfur value was low. Infrared analysis revealed the presence of a possible trace of hydroxyl group, indicative of starting material. Although subsequent transformations were necessarily performed on material of this purity, the conclusions drawn are undoubtedly valid.

The tosylate (IX) when refluxed in absolute alcohol was converted into not quite pure $\Delta^{5,9(11)}$-bisketal (VII), which on aqueous acetic acid hydrolysis yielded pure $\Delta^{4,9(11)}$-androstadiene-3,17-dione (III). Moreover, the tosylate (IX) on being refluxed for 4 hours with 5% alcoholic potassium hydroxide gave, as the major product, $\Delta^{5,9(11)}$-androstadiene-3,17-dione bisethylene ketal (VII), and a small quantity of the 11α-hydroxy-bisketal (VI). The same results were obtained with potassium acetate in aqueous acetone (reflux 6 hours). Finally, the tosylate (IX) was refluxed with *s*-collidine for 23 hours. The following products were obtained: $\Delta^{5,9(11)}$-bisketal (VII) (major product), $\Delta^{4,9(11)}$-androstadiene-3,17-dione 17-ethylene ketal (X), and the 11α-hydroxy-bisketal (VI). The presence of the monoketal (X) may be ascribed to partial hydrolysis during the workup procedure.

These results[4] with the 11α-tosyloxy-bisketal (IX), where neither Walden inversion nor formation of a Δ^{11}-steroid[5] occurred, may be explained as above on the basis of conformational analysis and steric considerations. The formation of the diene (X) requires an E1 mechanism.

Summarily, it appears unpromising to employ any of the conventional methods for Walden inversion of a $C_{11}\alpha$-hydroxycompound to the corresponding $C_{11}\beta$-epimer, or for formation of a Δ^{11}-steroid from a $C_{11}\alpha$-hydroxycompound. These results confirm *a priori* theoretical considerations.

The structure of $\Delta^{4,9(11)}$-androstadiene-3,17-dione (II) was based on analogous reactions with other 11-oxygenated steroids (4–7). Compound II was submitted to oxidation with chromic acid-glacial acetic acid according to Reich and Lardon (11) ($\Delta^{9(11)} \rightarrow \Delta^{9(11)}$-12-ketone). This resulted principally in the loss of starting material. However a trace of an unknown material was isolated, but in insufficient quantity for definitive examination.

EXPERIMENTAL

Melting points. All m.p.'s are uncorrected, and were determined with uncalibrated Anschütz thermometers.

Optical rotations. The sample was dissolved in chloroform to make a 2-ml. solution, and the rotation was determined in a 1-dm. semi-micro tube for the wavelength 5893 A(D) .

Absorption spectra. The ultraviolet spectra were determined in absolute alcohol with a

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[4] In this connection, certain observations with 11-bromosteroids are pertinent. Gallagher and Long, *J. Biol. Chem.*, **162**, 495 (1946), found that methyl 3α-acetoxy-11β-bromo-12-ketocholanate on being refluxed for 3 hours with pyridine gave in excellent yield the $\Delta^{9(11)}$-12-ketocompound. [This confirmed the finding of Seebeck and Reichstein, *Helv. Chim. Acta*, **26**, 536 (1943).] On the other hand, the 11α-bromo-epimer was recovered unchanged under these conditions. Alther and Reichstein, *Helv. Chim. Acta*, **26**, 492 (1943), have cited an example where the 11α-bromo-12-ketone moiety is stable to reflux in pyridine, but not in *s*-collidine. The latter treatment gave a $\Delta^{9(11)}$-12-ketosteroid.

[5] The formation of $\Delta^{4,11}$-androstadiene-3,17-dione (IV) from Δ^{4}-androstene-12α-ol-3,17-dione tosylate by reflux in *s*-collidine (2) is readily understood on application of conformational analysis (polar-$C_{11}\beta$-hydrogen, polar-C_{12} α-tosyloxy).

Beckman quartz spectrophotometer (Model DU). The infrared spectra (Nujol mulls) were determined with a Perkin-Elmer spectrophotometer (Model 21).

Petroleum ether. The fraction used was either b.p. 64–66°, or 66–68°, and was purified with concentrated sulfuric acid, and potassium permanganate.

Reaction of Δ^4*-androstene-11β-ol-3,17-dione* (I) *with 20% conc'd hydrochloric acid-glacial acetic acid.* A mixture of the 11β-hydroxy-dione (I) (0.25 g.) in conc'd hydrochloric acid (2 ml.) and glacial acetic acid (8 ml.) was refluxed for ½ hour, cooled, and poured into ice-water. The resulting crystals were collected; 135 mg., pale yellow, m.p. 180.5–184° with previous softening. One recrystallization from acetone-petroleum ether, and three recrystallizations from aqueous acetone gave 55 mg. of a product, m.p. 190.5–192.5°, with previous softening at 189°, negative Beilstein test for halogen. Infrared analysis revealed the presence of an hydroxyl group at 3333 cm^{-1}. This impure product in benzene was adsorbed on an aluminum oxide[6] column, which was washed successively with petroleum ether, benzene, 5% ether-benzene, and 10% ether-benzene. The latter eluted the product. Four recrystallizations to constant m.p. from aqueous acetone gave 6 mg. of pure $\Delta^{4,9(11)}$-androstadiene-3,17-dione (III); m.p. 202.5–204.5°; $[\alpha]_D^{24}$ +224° (4.65 mg., α_D +0.52°), $[M]_D$ +636. Its infrared spectrum was identical with that of the reaction product from the 11α-hydroxy-bisketal (VI) in pyridine with phosphorus oxychloride followed by hydrolysis (*vide infra*).

Reaction of Δ^4*-androstene-11α-ol-3,17-dione* (II) *with 20% conc'd hydrochloric acid-glacial acetic acid.* The 11α-hydroxy-dione (II) (0.25 g., m.p. 228.5–230.5° with previous softening) in glacial acetic acid (8 ml.), and conc'd hydrochloric acid (2 ml.) was refluxed for ½ hour, cooled, and poured into ice-water. Salt was added, and the mixture was neutralized with solid sodium bicarbonate. The product was extracted with ethyl acetate, and the extract was washed with saline, dried, and evaporated *in vacuo*. The residue was dissolved in acetone, treated with Norit, and concentrated with the simultaneous addition of petroleum ether. The crystals so obtained were collected; 68 mg., m.p. about 205–218°. Recrystallization from acetone-petroleum ether gave 51 mg. of starting material; m.p. 222.5–228° with previous softening.

The initial mother liquor on evaporation afforded 135 mg., m.p. 116–118°, cloudy melt. One recrystallization from ether, and two from ether-petroleum ether gave 21 mg. of Δ^4-androstene-11α-ol-3,17-dione acetate (V); m.p. 122.5–123.5°; λ_{max} 238–239.5 mμ (ε15,500);[7] I. R.: λ_{max} no hydroxyl, 1735 cm^{-1} (acetate, and C_{17}-carbonyl), 1681 cm^{-1} (C_3-carbonyl), 1245 and 1228 cm^{-1} (acetate 'C—O' stretch); $[\alpha]_D^{23}$ +121° (7.3 mg., α_D +0.44°), $[M]_D$ +416.

Anal. Calc'd for $C_{21}H_{28}O_4$ (344.44): C, 73.22; H, 8.19.

Found: C, 72.88; H, 8.01.

Reaction of Δ^5*-androstene-11α-ol-3,17-dione bisethylene ketal* (VI) *with 20% conc'd hydrochloric acid-glacial acetic acid.* The 11α-hydroxy-bisketal (VI) (0.5 g.) in glacial acetic acid (8 ml.), and conc'd hydrochloric acid (2 ml.) was refluxed for ½ hour, and worked up as above in ethyl acetate. The extract on evaporation gave an oil which was crystallized from benzene-petroleum ether; 93 mg., m.p. 190–212° with previous softening; I.R.: λ_{max} 3390 cm^{-1} (hydroxyl), 1735 cm^{-1} (C_{17}-carbonyl), 1650 cm^{-1} (C_3-carbonyl), 1605 cm^{-1} (Δ^4). The infrared spectrum was identical with that of an authentic sample of Δ^4-androstene-11α-ol-3,17-dione (II). Three recrystallizations from acetone-petroleum ether gave 63 mg. of pure II; m.p. 227–228.5°.

$\Delta^{5,9(11)}$*-Androstadiene-3,17-dione bisethylene ketal* (VII) *from* Δ^5*-androstene-11α-ol-3,17-dione bisethylene ketal* (VI) *with phosphorus oxychloride-pyridine.*

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[6] Merck, washed with petroleum ether, and dried at 110° for 4 hours.

[7] The λ_{max} 238–239.5 mμ of the 11α-ol-acetate (V) corroborates the observation that acetylation of an 11α-hydroxy-Δ^4-3-ketosteroid (λ_{max} 241 mμ) produces an hypsochromic effect of about 2 mμ; see, Antonucci, Bernstein, Heller, Lenhard, Littell, and Williams, *J. Org. Chem.*, **18**, 70 (1953), and Bernstein, Lenhard, and Williams, ref. 1b. It is interesting to note that acetylation of an 11β-hydroxy-Δ^4-3-ketosteroid likewise produces such an hypsochromic effect; see, Oliveto, Gerold, Weber, Jorgensen, and Hershberg, Abstracts of Papers, Organic Chemists Discussion Group, Meeting-In-Miniature, North Jersey Section, American Chemical Society, Newark, N. J., January 26, 1953.

A. The 11α-hydroxy-bisketal (VI) (100 mg.) in pyridine (1 ml.) was treated with phosphorus oxychloride (0.11 ml.), and the mixture was allowed to stand at room-temperature overnight. Water was added (ice cooling), and the resulting oil crystallized; 89 mg. (94% "crude" yield); negative Beilstein test for halogen; m.p. 145–149° with previous softening. Four recrystallizations from aqueous acetone afforded 43 mg. of the $\Delta^{5,\,9\,(11)}$-bisketal (VII); m.p. 152.5–154° (90–160° thermometer) $\lambda_{\max}$ none (end absorption); I.R.: $\lambda_{\max}$ no hydroxyl, no carbonyl, 1095 cm^{-1} (ketal)[8], $[\alpha]_D^{23}$ −46° (17.5 mg., α_D −0.40°), $[M]_D$ −172.

Anal. Calc'd for $C_{23}H_{32}O_4$ (372.49): C, 74.16; H, 8.66.

Found: C, 74.66; H, 8.15.

B. In another run with VI (0.2 g.), phosphorus oxychloride (0.22 ml.), and pyridine (2 ml.), there was obtained 26 mg. of VII after four recrystallizations from ether-petroleum ether (constant m.p. on last three recrystallizations); m.p. 154.5–156° (150–210° thermometer). Its infrared spectrum was identical with those obtained for samples of VII prepared from the 11α-tosyloxy-bisketal (IX) under a variety of conditions.

Hydrolysis of $\Delta^{5,\,9\,(11)}$*-androstadiene-3,17-dione bisethylene ketal (VII).* A solution of VII (318 mg., prepared from the 11α-hydroxy-bisketal (VI) with phosphorus oxychloride-pyridine) in glacial acetic acid (2 ml.) was treated with water (2 ml.), and the mixture was warmed on the steam-bath for 20 minutes. It was cooled, and water was added. This afforded 224 mg. (92% "crude" yield) of pale yellow crystals; m.p. 197–200°, with previous softening. One recrystallization from ether (petroleum ether wash); and four from aqueous acetone gave 100 mg. of pure $\Delta^{4,\,9\,(11)}$-androstadiene-3,17-dione (III)[9]: m.p. 202.5–204.5°; $\lambda_{\max}$ 238 mμ (ε 16,800); I.R.: $\lambda_{\max}$ no hydroxyl, 1740 cm^{-1} (C_{17}-carbonyl), 1667 cm^{-1} (C_3-carbonyl), 1620 cm^{-1} (double bond), no ketal band at 1080–1100 cm^{-1}, $[\alpha]_D^{23}$ +214° (20.55 mg., α_D +2.20°), $[M]_D$ +607.

The analysis indicated solvation. However, it was subsequently found that recrystallization from acetone-petroleum ether gave an analytically pure product (*vide infra*).

Anal. Calc'd for $C_{19}H_{24}O_2$ (284.38): C, 80.24; H, 8.51.

Found: C, 78.53; H, 8.66.

Bis-2,4-dinitrophenylhydrazone, m.p. 293.5° d. (from chloroform-ethanol), $\lambda_{\max}^{CHCl_3}$ 258–260 mμ (ε 30,100), and 377–381 mμ (ε 53,500).

Anal. Calc'd for $C_{31}H_{32}N_8O_8$ (644.63): C, 57.74; H, 5.01; N, 17.39.

Found: C, 57.41; H, 5.85; N, 17.27.

Δ^5*-Androstene-11α-ol-3,17-dione 11-tosylate 3,17-bisethylene ketal* (IX). The 11α-hydroxy-bis-ketal (VI) (3 g.) in pyridine (25 ml.) (methanol-ice bath) was treated with *p*-toluenesulfonyl chloride (1.74 g.). The mixture was kept cold for about 2 hours, and then at room-temperature overnight. The mixture was poured into ice-water, and the resulting crystals were collected; 3.66 g. (87% "crude" yield); m.p. 121–127° d. with previous softening; I. R.: $\lambda_{\max}$ possible trace of hydroxyl), 1610 cm^{-1} (tosyl), no carbonyl, 1176 cm^{-1} (tosyl), 1086 cm^{-1} (ketal), 921 cm^{-1} (tosyl?).

Anal. Calc'd for $C_{30}H_{40}O_7S$ (544.69): C, 66.16; H, 7.40; S, 5.88.

Found: C, 64.72; H, 7.98; S, 4.77.

A portion (0.25 g.) was recrystallized four times from ether-petroleum ether, m.p. 125–129° d., I.R.: $\lambda_{\max}$ possible trace hydroxyl, 1603 cm^{-1} (tosyl), no carbonyl, 1174 cm^{-1} (tosyl), 1092 cm^{-1} (ketal), 920 cm^{-1} (tosyl?).

Anal. Found: C, 65.80; H, 7.66; S, 4.32; 3.88; 4.03.

Chemical properties of Δ^5*-androstene-11α-ol-3,17-dione 11-tosylate 3,17-bisethylene ketal* (IX). *A. Absolute alcohol reflux followed by aqueous acetic acid hydrolysis.* A solution of the 11α-tosyloxy-bisketal (IX) (0.5 g., m.p. 121–127° d.) in absolute alcohol (50 ml.) was refluxed for 16.5 hours. The solution was exaporated *in vacuo*, and the residue was extracted with ether. The extract was washed with dilute sodium bicarbonate solution, water, and dried. Evaporation *in vacuo* gave a white powder which was dissolved in 50% (v./v.) aqueous acetic acid (10 ml.) and heated on the steam-bath for 20 minutes. Addition of water to

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[8] *One* of the principal 'C—O' stretch bands of an ethylene ketal.

[9] Meystre and Wettstein (2) have recorded the following physical constants for $\Delta^{4,\,11}$-androstadiene-3,17-dione; m.p. 175–177°; $\lambda_{\max}^{alc}$ 238 mμ (log ε 4.22); $[\alpha]_D^{23}$ +200 ± 4° ($CHCl_3$).

the hot solution gave crystals which were collected after the mixture was cooled; 196 mg., m.p. about 195–202° with previous browning, dark red-brown melt. Recrystallization from acetone-petroleum ether-ether, and acetone-petroleum ether gave 140 mg., m.p. 199–202° with previous softening, red-brown melt. The product in benzene (5 ml.) was adsorbed on an aluminum oxide column (20 g., 7⁄16″ × 9½″). The product was fractionally eluted successively with petroleum ether (1 × 100 ml.), benzene (1 × 100 ml.), 5% ether-benzene (1 × 100 ml.) and 10% ether-benzene (11 × 100 ml.). Fractions 5–14 inclusive were combined and the product was recrystallized two times from acetone-petroleum ether; 74 mg. of pure $\Delta^{4,9(11)}$-dione (III); m.p. 202–204°, λ_{max} 238–239 mμ (ε16,600); I.R.: λ_{max} no hydroxyl, 1740 cm^{-1} (C_{17}-carbonyl), 1667 cm^{-1} (C_3-carbonyl), 1620 cm^{-1} (double bond), no ketal at 1080–1100 cm^{-1}, $[\alpha]_D^{24}$ +215° (10.9 mg., α_D +1.17°), $[M]_D$ +611.

Anal. Calc'd for $C_{19}H_{24}O_2$ (284.38): C, 80.24; H, 8.51.

Found: C, 80.00; H, 8.89.

B. 5% Alcoholic potassium hydroxide. The 11α-tosyloxy-bisketal (IX) (0.4 g., m.p. 121–129° d., with previous softening) in 5% alcoholic potassium hydroxide (15 ml.) was refluxed for 4 hours. It was cooled, water was added, and the crystals were collected; m.p. 145° unsharp. Two recrystallizations from ether-petroleum ether, and one from ether gave 44 mg. of Δ^5-androstene-11α-ol-3,17-dione bisethylene ketal (VI); m.p. 219–221.5° with previous softening. Its infrared spectrum was identical with that of an authentic sample.

The mother liquors (first excluded) were combined, evaporated, and in benzene (10 ml.) were adsorbed on an aluminum oxide column (10 g., 5⁄16″ × 7½″). The product was fractionally eluted successively with petroleum ether (2 × 100 ml.), 10% benzene-petroleum ether (8 × 100 ml.), 25% benzene-petroleum ether (1 × 100 ml.), and ether (1 × 600 ml.). The second petroleum ether elution was combined with the 10% benzene-petroleum ether elutions, and on evaporation gave about 170 mg., m.p. below 145°. Two recrystallizations from ether-petroleum ether (to constant m.p.) gave 58 mg. of the $\Delta^{5,9(11)}$-bisketal (VII); m.p. 154–155° (90–160° thermometer), 156–157° (150–210° thermometer). Its infrared spectrum was identical with that obtained with the samples of $\Delta^{5,9(11)}$-bisketal (VII) prepared from the 11α-hydroxy-bisketal (VI) (phosphorus oxychloride-pyridine), and from the 11α-tosyloxy-bisketal (IX) (potassium acetate-aqueous acetone; *s*-collidine).

C. Potassium acetate in aqueous acetone. The 11α-tosyloxy-bisketal (IX) (0.4 g., m.p. 121–129° d.) in a solution of anhydrous potassium acetate (0.4 g.) in water (10 ml.) and acetone (15 ml.) was refluxed for 6 hours. Water was added to the warm solution, which was then cooled. The crystals so obtained were collected; 275 mg., m.p. 140–155° (infrared analysis showed the absence of an acetate group). Three recrystallizations from ether-petroleum ether, and one from ether (petroleum ether wash) gave 35 mg. of the 11α-hydroxybisketal (VI); m.p. 217.5–221.5° with previous softening. Its infrared spectrum was identical with that of an authentic sample.

The mother liquors (first excluded) were combined, and were evaporated *in vacuo.* The residue was dissolved in 6 ml. of benzene, was adsorbed on an aluminum oxide column (10 g., 5⁄16″ × 7½″); and was chromatographed as follows:

CHROMATOGRAPH

FRACTION NO.	VOLUME	SOLVENT	COMMENT
1	200 ml.	Petroleum ether	—
2	100 ml.	10% Benzene-petroleum ether	—
3	1300 ml.	25% Benzene-petroleum ether	Crystals
4	300 ml.	50% Benzene-petroleum ether	Trace of crystals
5	100 ml.	Benzene	—
6	100 ml.	10% Ether-benzene	—
7	100 ml.	25% Ether-benzene	—
8	100 ml.	50% Ether-benzene	Trace of crystals
9	1100 ml.	Ether	Crystals

Fraction 3 was dissolved in ether, treated with Norit, and filtered through Celite. Concentration with simultaneous addition of petroleum ether gave 100 mg. of the $\Delta^{5,9(11)}$-bisketal (VII); m.p. 156–157° (150–210° thermometer). One further recrystallization did not alter the m.p. Its infrared spectrum was identical with that obtained with the samples of $\Delta^{5,9(11)}$-bisketal (VII) prepared from the 11α-hydroxy-bisketal (VI) (phosphorus oxychloride-pyridine), and from the 11α-tosyloxy-bisketal (IX) (5% alcoholic potassium hydroxide; *s*-collidine). $[\alpha]^{23}_{D}$ −40° (18.2 mg., α_D −0.36°), $[M]_D$ −149.

Anal. Found: C, 73.85; H, 8.92.

Fraction 9 was recrystallized from ether-petroleum ether; 26 mg., m.p. 205–207.5° [impure Δ^5-androstene-11α-ol-3,17-dione bisethylene ketal (VI) as shown by infrared analysis].

D. s-Collidine. A mixture of the 11α-tosyloxy-bisketal (IX) (1.5 g., m.p. 121–127° d., *Anal.* Found: S, 4.77.) and *s*-collidine (10 ml.) was refluxed for 23 hours, cooled, and treated with sodium bicarbonate. The mixture was steam-distilled for the removal of excess *s*-collidine. The product was extracted with ethyl acetate, washed, dried, and evaporated *in vacuo*. The residue was crystallized with difficulty from aqueous acetone; a white flocculent solid, and a pale yellow soft solid were obtained. The latter was removed mechanically; Fraction *1A*, about 0.45 g. The former was collected by filtration, and was washed with water; 0.41 g., m.p. 110–140° with previous softening. One recrystallization from aqueous acetone gave 0.14 g., m.p. about 125–145°, with previous softening, cloudy melt (Fraction *1B*).

Fraction *1A*, and the mother liquors from Fraction *1B* were combined, and extracted with ethyl acetate. Evaporation *in vacuo* gave an oil (Fraction *1C*).

Fraction *1B* (130 mg.) in 50% aqueous acetic acid (5 ml.) was heated on the steam-bath for 15 minutes. Water was added to the hot solution, which was then cooled; this gave a semi-solid. This material was poured into a saturated sodium bicarbonate solution, and the product was extracted with ethyl acetate. Evaporation gave an oil which solidified on the addition of a small amount of ether. The residue was dissolved in ether, treated with Norit, and filtered through Celite. Concentration gave 51 mg. (yellow; petroleum ether wash), m.p. 195–200°, with previous softening. Recrystallization from aqueous acetone, and two times from acetone-petroleum ether gave 39 mg. of $\Delta^{4,9(11)}$-androstadiene-3,17-dione (III) (not pure); m.p. 197–200°, with previous softening, I.R.: λ_{max} 3475 cm^{-1} (hydroxyl), 1743 cm^{-1} (C_{17}-carbonyl), 1667 cm^{-1} (C_3-carbonyl), 1620 cm^{-1} (double bond), no ketal at 1080–1100 cm^{-1}.

Fraction *1C* in benzene (about 10 ml.) was adsorbed on an aluminum oxide column (27 g., 7/16″ × 13″), and was chromatographed in the following manner.

CHROMATOGRAPH

FRACTION NO.	VOLUME	SOLVENT	COMMENT
1	200 ml.	Petroleum ether	—
2	100 ml.	10% Benzene-petroleum ether	—
3	100 ml.	25% Benzene-petroleum ether	Crystals
4	500 ml.	50% Benzene-petroleum ether	Crystals
5	100 ml.	Benzene	—
6	100 ml.	Benzene	Crystals
7	700 ml.	5% Ether-benzene	Crystals
8	200 ml.	10% Ether-benzene	Trace of oil
9	200 ml.	25% Ether-benzene	Trace of oil
10	200 ml.	50% Ether-benzene	Oil
11	900 ml.	Ether	Crystals
12	200 ml.	1% Methanol-ether	—

Fractions 3 and 4 were combined, and were recrystallized three times from aqueous acetone; 0.15 g. of $\Delta^{5,9(11)}$-androstadiene-3,17-dione bisethylene ketal (VII); m.p. 152.5–

156° (90–160° thermometer), 155–157.5° (150–210° thermometer) $[\alpha]_D^{24}$ −49° (19.25 mg., α_D −0.47°). Admixture m.p. determination showed the product to be identical with VII, prepared by the routes described above. However, infrared analysis revealed a trace impurity which proved difficult to remove completely by chromatography (aluminum oxide) followed by recrystallization from ether-petroleum ether.

Fractions 6 and 7 were combined, dissolved in ether, and concentrated. This gave crystals which were collected with the aid of petroleum ether; 86 mg., m.p. 202–205°, with previous softening. Three recrystallizations from ether (petroleum ether wash) gave 31 mg. of pure $\Delta^{4,9(11)}$-androstadiene-3,17-dione 17-ethylene ketal (X); m.p. 207.5–209°; λ_{max} 239 mμ (ϵ 16,500); I.R.: λ_{max} no hydroxyl, 1675 cm^{-1} (C_3-carbonyl), 1620 cm^{-1} (double bond), 1109 cm^{-1} (ketal); $[\alpha]_D^{24}$ +50° (14.7 mg., α_D +0.37°).

Anal. Calc'd for $C_{21}H_{28}O_3$ (328.44): C, 76.79; H, 8.59.

Found: C, 76.55; H, 8.54.

Hydrolysis with 50% aqueous acetic acid in the usual manner gave after recrystallization from aqueous acetone pure $\Delta^{4,9(11)}$-androstadiene-3,17-dione, m.p. 202–204° with previous softening. Admixture m.p. determination and infrared analysis showed identity with an authentic sample.

Fraction 11 was dissolved in acetone, treated with Norit, and filtered through Celite. Concentration with the addition of water gave crystals; 46 mg., m.p. 207.5–220° with previous softening. Two recrystallizations from acetone-petroleum ether gave 33 mg. of pure Δ^5-androstene-11α-ol-3,17-dione bisethylene ketal (VI), m.p. 218–221°. Its infrared spectrum was identical with that of an authentic sample.

Treatment of $\Delta^{4,9(11)}$*-androstadiene-3,17-dione* (III) *with chromic acid.* To a solution of III (141 mg.) in glacial acetic acid (1 ml.) was added a 2% chromic acid–glacial acetic acid solution (equivalent to 49 mg. of chromic anhydride). The mixture was allowed to stand at 29° for 17 hours; and then was evaporated *in vacuo*. The residue was extracted with ether; and the extract was washed successively with 1 *N* sulfuric acid, dilute sodium carbonate solution, and water. The dried ether solution was evaporated. The residue (108 mg.) in benzene (5 ml.) was adsorbed on an aluminum oxide column (5 g., 5/16″ × 3¾″). The column was eluted successively with petroleum ether, 10%-, 25%-, and 50%- benzene-petroleum ether, benzene, 5%-, 10%-, 25%, and 50% ether-benzene, ether, and 1% methanol-ether.

The 50% benzene-petroleum ether, and benzene eluates were combined, and the crystals were recrystallized from ether-petroleum ether, and acetone-petroleum ether; 70 mg., m.p. 202–203.5°. Infrared analysis showed the material to be identical with starting material.

The 10% ether-benzene, and 25% ether-benzene eluates contained a trace of crystals which were combined, and recrystallized from ether-petroleum ether; 2.5 mg., m.p. about 255° d. and previous browning. The identity of this material has not been established.

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SUMMARY

1. Δ^4-Androstene-11β-ol-3,17-dione (I) was refluxed in 20% conc'd hydrochloric acid-glacial acetic acid to form $\Delta^{4,9(11)}$-androstadiene-3,17-dione (III). The 11α-epimer (II) under similar conditions was primarily acetylated to afford Δ^4-androstene-11α-ol-3,17-dione acetate (V), and unchanged starting material.

2. Treatment of Δ^5-androstene-11α-ol-3,17-dione bisethylene ketal (III) with phosphorus oxychloride-pyridine at room-temperature led to an E1 elimination, and $\Delta^{5,9(11)}$-androstadiene-3,17-dione bisethylene ketal (VII) was obtained. No $\Delta^{5,11}$-bisketal (VIII) was apparently formed. Aqueous acetic acid hydrolysis gave

$\Delta^{4,9(11)}$-androstadiene-3,17-dione (III), identical with the product prepared from Δ^{4}-androstene-11β-ol-3,17-dione (I).

3. The chemical properties of Δ^{5}-androstene-11α-ol-3,17-dione tosylate bisethylene ketal (IX) were investigated under a variety of conditions (solvolysis, acetolysis, and elimination), all of which resulted primarily in the formation of the $\Delta^{5,9(11)}$-bisethylene ketal (VII). Neither Walden inversion nor formation of a $\Delta^{5,11}$-diene was observed.

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