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

STEROIDAL CYCLIC KETALS. V.[1] TRANSFORMATION PRODUCTS OF ADRENOSTERONE. THE SYNTHESIS OF RELATED $C_{19}O_3$-STEROIDS

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Adrenosterone (Δ^4-androstene-3,11,17-trione) (IV) is one of the numerous steroids isolated from the adrenal cortex (1). This compound, which may or may not be an oxidative artifact elaborated during the isolation of the various components of the gland, possesses "androgenic" activity to an appreciable extent (¼–⅕th that of androsterone, comb growth assay) (1, 2). It, therefore, was of interest to us to undertake an investigation in which the adrenosterone molecule would be modified at the C_{11} and C_{17} positions in such a manner as to maintain the Δ^4-3-keto-moiety, and to assay the transformation products for "androgenic" and related biological activities. A number of such conversions have been successfully executed, and a description of them form the basis of this publication.

In a recent note from this laboratory (3) the conversion of adrenosterone (IV) into Δ^4-androstene-11α-ol-3,17-dione (epimeric with III) was described. This was accomplished by reduction of the diketal (I) prepared from IV in 72% yield) with lithium-ethanol-liquid ammonia to afford in 58% yield[2] Δ^5-androstene-11α-ol-3,17-dione-di-ethylene ketal (epimeric with II). Δ^4-Androstene-11α-ol-3,17-dione was obtained in 60% yield by hydrolysis of the diketal with aqueous acetic acid.

It now has been found, as expected, that reduction of the diketal (I) with lithium aluminum hydride afforded the 11β-hydroxy-di-ketal (II) (83% yield). Compound II was recovered unchanged when submitted to mild acetylation conditions (acetic anhydride-pyridine at room-temperature). Hydrolysis with aqueous acetic acid removed the ketal protective groupings, and the known (4) Δ^4-androstene-11β-ol-3,17-dione (III) was formed (82% yield). This compound, although incompletely characterized, had previously been obtained in degradative studies on Reichstein's Substances E and M.

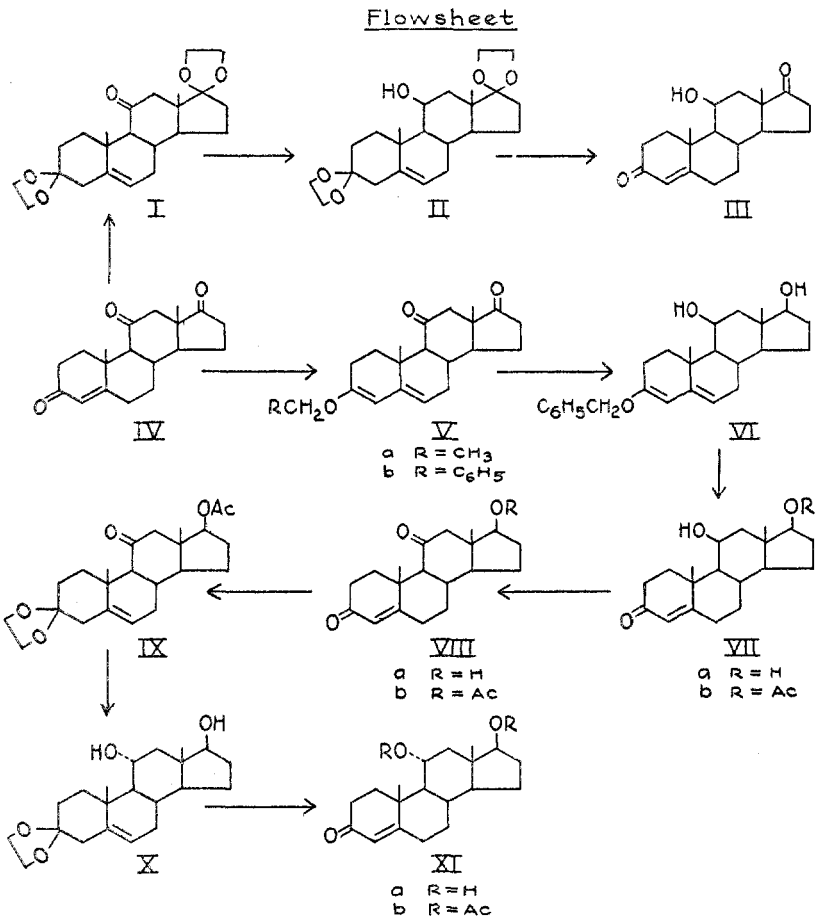
Treatment of adrenosterone (IV) with benzyl alcohol (benzene, *p*-toluenesulfonic acid) gave in 36% yield the enol-ether (Vb). It was found more advantageous to utilize this derivative rather than the corresponding ethyl ether (Va) for further transformations. The latter was obtained in poor yield, and its elemental analysis was only fair. However, the absorption spectrum, λ_{max} 241 mμ, ϵ 19,400; supported the assigned structure (Va). Reduction of the benzyl

[1] Paper IV, Bernstein, Littell, and Williams, *J. Am. Chem. Soc.*, **75**, 1481 (1953). Presented in part before the Organic Discussion Group at the Fifth Annual Meeting-In-Miniature of the North Jersey Section, American Chemical Society, Newark, N. J., January 26, 1953.

[2] Further development of this reduction method has led to an increased yield of 90%; for procedure, see preparation of X.

ether (Vb) with lithium aluminum hydride in ether gave in 64% yield the diol (VI). Δ^4-Androstene-11β,17β-diol-3-one (11β-hydroxytestosterone) (VIIa) was obtained on hydrolysis of the ketal groups (83% yield). Acetylation under mild conditions gave the 17-mono-acetate (VIIb).

Acetylation of VIIa without purification of the acetate (VIIb) followed by chromic acid oxidation at room-temperature gave Δ^4-androstene-17β-ol-3,11-



dione-acetate (VIIIb) (55% yield from VIIa). The free steroid (11-ketotestosterone) (VIIIa) was obtained in 90% yield by hydrolysis of VIIIb with potassium carbonate.

Δ^4-Androstene-17β-ol-3,11-dione-acetate (VIIIb) was converted in the usual manner into the ketal (IX) (58% yield). The coincident rearrangement of the double bond to the C_{5-6} position has been previously discussed (5). Reduction of the ketal (IX) with lithium-ethanol-liquid ammonia gave in 89% yield (as hydrate) Δ^5-androstene-11α,17β-diol-3-one-ethylene ketal (X). The free steroid, Δ^4-androstene-11α,17β-diol-3-one (XIa), was obtained on aqueous acetic acid

hydrolysis (53% yield).[3] The properties of XIa were in good agreement with those reported by Murray and Peterson (6). These investigators prepared this compound by the microbiological oxidation of testosterone. The identity was further established by infrared analysis, and by spectral analysis in concen trated sulfuric acid. In both cases, the spectra were identical.[4] The diol (XIa) on acetylation gave the expected di-acetate (XIb).

The structures of the products obtained in the above transformations may be supported collectively by the following arguments.

The *generally* stereospecific reduction of the C_{11}-carbonyl group with lithium aluminum hydride and related metal hydrides to afford the C_{11}-β-hydroxy-compound has been amply demonstrated (7). A C_{11}-β-substituent (polar conformation) is considered less stable than a corresponding C_{11}-α-substituent (equatorial conformation) (8). Thus, one would anticipate that reduction of a C_{11}-carbonyl group would yield primarily the equatorial C_{11}-α-hydroxy-compound (frontal attack). However, with metal hydrides of the type mentioned steric effects prevail over energetic effects, and rear attack (C_{11}-β-formation) is favored (9). This may be ascribed to the over-all size of the, *e.g.*, aluminum hydride ion, the species participating in the nucleophilic reduction (10). However, this laboratory has recently reported (11) an example in which this type of reduction elaborated simultaneously the 11α-hydroxy-compound in very low yield. It appears that frontal attack may be possible to a *very minor extent.* Equilibration studies on hydrocortisone, and 11-epi-hydrocortisone with lithium aluminum hydride support this conclusion. Both compounds were stable, and not converted into the other epimeric form to any noticeable degree.

Reduction of a C_{11}-carbonyl group under different conditions, such as lithium-ethanol-liquid ammonia (3), or sodium-propanol (12) is stereospecific in the opposite direction, *i.e.*, the reduction favors the formation of the C_{11}-α-hydroxy-compound (90% or higher yields). (No information is available on the simultaneous formation in low percentage yields of the 11β-epimers.) Accordingly, a frontal-attack has resulted. The manner in which this "opposite" directional attack proceeds may possibly be understood by an examination of the proposed mechanism of such hydrogenations (electron transference or addition from the lithium surface followed by protonization from the ethanol) (13). Here, the small sizes of the hydrogenation elements (lithium, protons, and electrons) make steric effects inoperable, and the favored frontal-attack may take place. Such an argument does not pertain to catalytic hydrogenation conditions (platinum-acetic acid), wherein the C_{11}-β-hydroxy-compound is formed (14). Due to steric effects, the surface of the catalyst may make contact with the carbonyl group only from the rear.

[3] An exploratory study of the preparation of XIa directly from the benzyl ether (Va) by reduction with sodium and propanol followed by hydrolysis led to an unexpected finding, which warrants further investigation. It appeared that hydrogenolysis of the benzyl ether took place during the sodium-propanol treatment. The hydrogenation product upon oxidation gave androstane-3,11,17-trione as shown by infrared analysis.

[4] We are indebted to The Upjohn Company for a sample of XIa.

The configuration of a C_{11}-hydroxyl group may be indicated by its capacity for acetylation under mild conditions (acetic anhydride-pyridine, room-temperature) (9a, 15). A C_{11}-α-hydroxyl group is readily acetylated whereas the 11β-epimer is not. This reaction has been utilized for this purpose throughout this investigation.

Reduction of a C_{17}-carbonyl group with lithium aluminum hydride is considered to be generally a stereospecific reaction to afford the C_{17}-β-hydroxy-compound (9a, 16).

The optical rotations conform to the generalization recently established for correlating the rotations of 11-oxygenated steroids (11, 17); *i.e.*, for a group of corresponding 11-oxygenated steroids the order of decreasing positive rotation

TABLE I

OPTICAL ROTATIONS OF 11-OXYGENATED STEROIDS

11-KETOCOMPOUND $[\alpha]_D$	11β-HYDROXYCOMPOUND $[\alpha]_D$	11α-HYDROXYCOMPOUND $[\alpha]_D$
Δ^4-Androstene-3,11,17-trione (Adrenosterone) +277° (AA)[a]	Δ^4-Androstene-11β-ol-3,17-dione +203° (AA)	Δ^4-Androstene-11α-ol-3,17-dione +146° (AA)
Δ^4-Androstene-17β-ol-3,11-dione +255° (C)[a]	Δ^4-Androstene-11β,17β-diol-3-one +136° (C)	Δ^4-Androstene-11α,17β-diol-3-one +87° (C)
Δ^5-Androstene-3,11,17-trione-3,17-di-ethylene ketal −41° (C)	Δ^5-Androstene-11β-ol-3,17-dione-di-ethylene ketal −60° (C)	Δ^5-Androstene-11α-ol-3,17-dione-di-ethylene ketal −71° (C)

[a] AA = Absolute alcohol; C = Chloroform.

will be: 11 keto > 11β-hydroxy > 11α-hydroxy (Table I). The ketals listed conform to this generalization, which observation is in contrast to our previous experience with these derivatives (11).

The course of the transformations were conveniently followed and corroborated by spectral analyses. A generalization has been proposed (11) that 11-keto-Δ^4-3-ketosteroids exhibit a maximum at about 238 mμ (range 237–238 mμ) whereas the 11-hydroxy-compounds (α- or β-configuration) exhibit one at about 242 mμ (range 240–242.5 mμ). An examination of Table II reveals that the maxima of the herein pertinent Δ^4-3-ketosteroids are in accord with this generalization. It is to be noted that the λ_{max} 238–239 mμ of Δ^4-androstene-11α,17β-diol-3-one-di-acetate (XI) is in agreement with the suggestion that acetylation of an 11α-hydroxy-Δ^4-3-ketosteroid produces such an hypsochromic effect of about 2 mμ (11).

The absorption spectra of a number of these compounds have been determined in 97% sulfuric acid (solution allowed to stand 2 hours at 25° prior to deter-

mination; conc'n about 7×10^{-6} m./100 ml.).[5] The quantitative aspects of the spectra are recorded in Table III. The six steroids listed have unique spectra. Moreover, the C_{11}-epimeric pairs of compounds may be easily differentiated

TABLE II

ULTRAVIOLET ABSORPTION MAXIMA; 11-OXYGENATED-Δ^4-3-KETOSTEROIDS. SOLVENT: ABSOLUTE ALCOHOL

COMPOUND	λ_{max} mμ
A. 11-Ketocompounds	
Δ^4-Androstene-3,11,17-trione	237[a]
Δ^4-Androstene-17β-ol-3,11-dione	237.5
Δ^4-Androstene-17β-ol-3,11-dione-acetate	237–238
B. 11-Hydroxycompounds.	
Δ^4-Androstene-11β-ol-3,17-dione	240–241
Δ^4-Androstene-11α-ol-3,17-dione	241[b]
Δ^4-Androstene-11β,17β-diol-3-one	242
Δ^4-Androstene-11β,17β-diol-3-one-17-acetate	241
Δ^4-Androstene-11α,17β-diol-3-one	241–242
Δ^4-Androstene-11α,17β-diol-3-one-di-acetate	238–239

[a]Ref. 11. [b]Ref. 3.

TABLE III

ABSORPTION SPECTRA IN 97% SULFURIC ACID AT 25° (2 Hours' standing)

COMPOUND	MAX.[a] mμ $(E^{1\%}_{1\,cm.})$	MIN.[a] mμ $(E^{1\%}_{1\,cm.})$
Δ^4-Androstene-3,11,17-trione	283 (524)	230 (62)
Δ^4-Androstene-11β-ol-3,17-dione	283 (467), 380 (443), 402 (257) (I), 460 (129)	241 (157), 322 (62), 433 (95)
Δ^4-Androstene-11α-ol-3,17-dione	284 (466), 381 (340), 400 (214) (I), 465 (110)	235 (148), 322 (71), 433 (76)
Δ^4-Androstene-11β,17β-diol-3-one	295 (582), 385 (177)	236 (141), 340 (50)
Δ^4-Androstene-11α,17β-diol-3-one	300 (659), 390 (55), 470 (27) (I)	238 (164), 367 (14)
Δ^4-Androstene-17β-ol-3,11-dione	285 (563), 350 (41)	230 (105), 330 (36)

[a]The maxima and minima are designated by a single wavelength, representative of the band which may or may not extend over a wide range. I = inflection or plateau.

by this type of spectral analysis (Fig. I, II, and III). A similar observation has been recorded for hydrocortisone and 11-epi-hydrocortisone (11). In regard to Δ^4-androstene-11β-ol-3,17-dione (III) and its 11α-epimer, the "two-hour" spectra (Fig. II), do not show as marked a difference as that obtained after

[5] In this connection, see, Zaffaroni, *J. Am. Chem. Soc.*, **72,** 3828 (1950); Reich, Nelson, and Zaffaroni, *J. Biol. Chem.*, **187,** 411 (1950); Schneider, *J. Biol. Chem.*, **194,** 337 (1952).

Fig. I

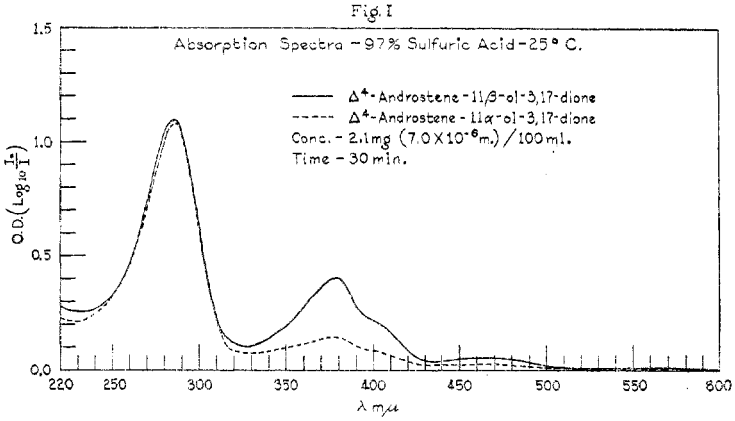


Fig. II

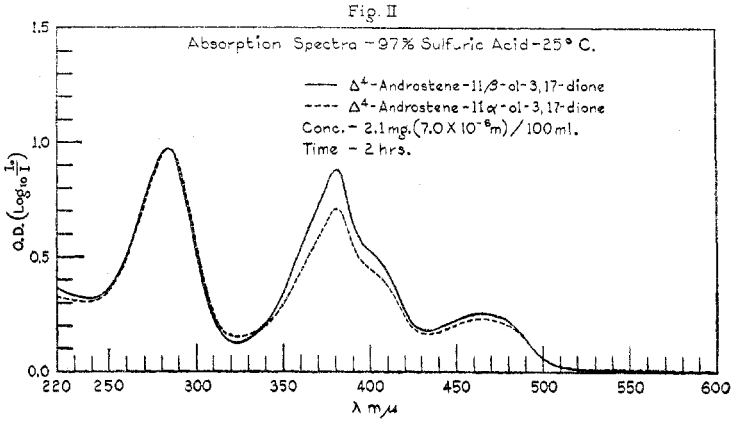
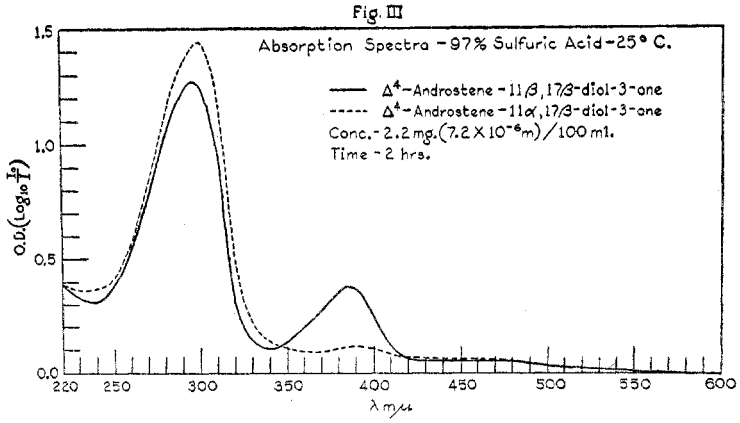


Fig. III



only ½ hour standing (Fig. I). Detailed "time-studies" of such epimeric compounds have been carried out, and the results will be presented in a future publication.

Finally, the infrared spectra of Δ^5-androstene-11β-ol-3,17-dione-diethylene ketal and its 11α-epimer were similar but were easily differentiated. This was likewise true for the epimeric Δ^4-androstene-11-ol-3,17-dione's, and the epimeric Δ^4-androstene-11,17β-diol-3-one's.

The results obtained on the biological assay of these adrenosterone transformation products will be presented later by others.

EXPERIMENTAL

Absorption spectra. The ultraviolet spectra were determined in absolute alcohol with a Beckman quartz spectrophotometer (Model DU). The sulfuric acid spectra were determined with a Cary recording spectrophotometer (Model 11S). The infrared spectra (Nujol mulls) were determined with a Perkin-Elmer recording infrared spectrophotometer (Model 21).

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

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

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

Yields. The stated yields are for preparations of sufficient purity for further transformations.

Δ^5-Androstene-11β-ol-3,17-dione-3,17-di-ethylene ketal (II). Δ^5-Androstene-3,11,17-trione-3,17-di-ethylene ketal (I) (0.92 g.) [IR: λ_{max} 1695 cm^{-1} (11-keto), 1098 cm^{-1} (ketal)][6] (3) in ether (200 ml.) was treated with 10 ml. of a saturated ethereal solution of lithium aluminum hydride in the manner previously described (11) (reflux 2 hours). The crude product was recrystallized from ether, and afforded 0.68 g., m.p. 199–200°, and 0.09 g., m.p. 200.5–202° (83% yield). An 100 mg.-portion of the principal fraction was recrystallized further from ether; 50 mg., m.p. 200–202°; IR: λ_{max} 3532 cm^{-1} (hydroxyl), 1095 cm^{-1} (ketal); $[\alpha]_D^{30}$ −60° (25 mg., α_D −0.75°); $[M]_D$ −234°.

Anal. Calc'd for $C_{25}H_{44}O_5$ (390.50): C, 70.74; H, 8.78.
Found: C, 70.47; H, 9.01.

A portion (19 mg.) of II on treatment with acetic anhydride and pyridine gave starting material; 11 mg., m.p. 200–202°. Admixture melting point determination, no depression, and infrared analysis showed complete identity with II.

Δ^4-Androstene-11β-ol-3,17-dione (III). The diketal (II) (0.63 g.) in glacial acetic acid (10 ml.) was treated with water (3⅓ ml.), and was heated on the steam-bath for 20 minutes The mixture was cooled, and poured cautiously into saturated sodium bicarbonate solution. The resulting crystals were collected, and washed with a copious amount of water; 0.40 g. (82% yield); m.p. 198–200°; λ_{max} 240–241 mμ, ϵ 14,200. An 100-mg. portion was recrystallized from acetone-petroleum ether; 84 mg., m.p. 199–200°; λ_{max} 240–241 mμ, ϵ 14,600; IR: λ_{max} 3365 cm^{-1} (hydroxyl), 1732 cm^{-1} (17-keto), 1640 cm^{-1} (3-keto), 1620 cm^{-1} (shoulder, Δ^4); $[\alpha]_D^{28}$ +203° (14.3 mg., absolute alcohol, α_D +1.45°); $[M]_D$ +612°. Literature (4): m.p. 190–192° (corr.).

Anal. Calc'd for $C_{19}H_{26}O_3$ (302.40): C, 75.46; H, 8.67.
Found: C,75.30; H,8.82.

3-Ethoxy-$\Delta^{3,5}$-androstadiene-11,17-dione (Va). Adrenosterone (IV) (0.6 g., 0.002 m) [IR: λ_{max} no hydroxyl, 1730 cm^{-1} (17-keto), 1695 cm^{-1} (11-keto), 1660 cm^{-1} (3-keto), 1600

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

cm^{-1} (Δ^4)] in benzene (5 ml.), and absolute alcohol (0.35 ml., 0.006 m.) was treated with ethyl orthoformate (0.37 ml., 0.0023 m.), and about 2 drops of 8% hydrogen chloride in absolute alcohol. The mixture was refluxed for 2 hours, and evaporated *in vacuo*. The residue was dissolved in benzene, and the solution was washed with dilute potassium carbonate, and water, dried and evaporated *in vacuo*. The oil so obtained crystallized on treatment with alcohol containing a trace of pyridine; 0.29 g., m.p. about 130–139° with previous softening. Two recrystallizations from methanol containing a trace of pyridine gave 73 mg. of Va, m.p. 154–154.5°, λ_{max} 241 mμ, ϵ 19,000. One further recrystallization gave 25 mg., m.p. 153–155°, λ_{max} 241 mμ, ϵ 19,400; IR: λ_{max} 1730 cm^{-1} (17-keto), 1700 (11-keto), 1644 and 1620 cm^{-1} ($\Delta^{3,5}$); $[\alpha]_D^{31}$ ±0° (12.8 mg., chloroform containing a trace of pyridine, α_D +0.01°); $[M]_D$ ±0°.

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

Found: C, 76.23, 75.95; H, 8.51, 8.90.

3-Benzyloxy-$\Delta^{3,5}$-androstadiene-11,17-dione (Vb). *A.* A mixture of adrenosterone (IV) (0.2 g., 0.00067 m.), benzyl alcohol 0.1 ml. ≅ 0.105 g., 0.00098 m.), benzene (10 ml.), and *p*-toluenesulfonic acid monohydrate (5 mg.) was refluxed for 5 hours (constant water-removal adapter). Evaporation *in vacuo*, trituration of the residue with cold alcohol containing a trace of pyridine, and filtration gave 125 mg., m.p. 143–159°. Five recrystallizations from alcohol containing a trace of pyridine gave 43 mg. of pure Vb, m.p. 170–174° with previous softening; λ_{max} 240–241.5 mμ, ϵ 21,100; IR: λ_{max} 1739 cm^{-1} (17-keto), 1695 cm^{-1} (11-keto), 1643 and 1616 cm^{-1} ($\Delta^{3,5}$), 729 cm^{-1} (phenyl); $[\alpha]_D^{32}$ ±0° (13.8 mg., chloroform containing a trace of pyridine, α_D ±0.00°); $[M]_D$ ±0°.

Anal. Calc'd for $C_{26}H_{30}O_3$ (390.50): C, 79.96; H, 7.74.

Found: C, 80.11; H, 7.98.

B. In another run with IV (0.88 g.), benzene (45 ml.), benzyl alcohol (0.44 ml.), and *p*-toluenesulfonic acid monohydrate (20 mg.) by essentially the above procedure (reflux 16½ hours), there was obtained 0.41 g. (36% yield) of Vb, m.p. 167–173°, with previous softening.

3-Benzyloxy-$\Delta^{3,5}$-androstadiene-11β,17β-diol (VI). Compound Vb (0.8 g.) in ether (450 ml.) was treated with an ethereal solution of lithium aluminum hydride (20 ml., 0.73 m.), and was refluxed for 1½ hours. The excess hydride was decomposed cautiously with water, and the mixture was filtered. The ether solution was washed with saline, dried and concentrated with simultaneous addition of petroleum ether. This afforded 0.52 g. of VI (64% yield), m.p. 160–161.5° with previous softening. An 100-mg. portion was recrystallized twice from ether-petroleum ether, m.p. 160.5–163° with previous softening, λ_{max} 240.5–241 mμ, ϵ 22,300; IR: 3470 cm^{-1} (hydroxyl), no carbonyl, 1644 and 1620 cm^{-1} ($\Delta^{3,5}$), 730 cm^{-1} (phenyl); $[\alpha]_D^{24}$ −89° (20.4 mg., chloroform containing a trace of pyridine, α_D −0.91°); $[M]_D$ −351°.

Anal. Calc'd for $C_{26}H_{34}O_3$ (394.53): C, 79.15; H, 8.69.

Found: C, 78.89; H, 8.81.

Δ^4-Androstene-11β,17β-diol-3-one (VIIa). *A.* Compound VI (156 mg.) in glacial acetic acid (4 ml.) was treated with water (4 ml.), and the mixture was heated on the steam-bath for 20 minutes. It was cooled, and poured cautiously into saturated sodium bicarbonate solution. Salt was added, and the product was extracted with ethyl acetate. Evaporation *in vacuo* gave a solid residue which was recrystallized from acetone-petroleum ether; 82 mg., (68% yield); m.p. 235–236.5°; λ_{max} 242 mμ, ϵ 14,900; IR: λ_{max} 3420 cm^{-1} (hydroxyl), 1652 cm^{-1} (3-keto), 1613 cm^{-1} (Δ^4); $[\alpha]_D^{30}$ +136° (5.45 mg., α_D +0.37°); $[M]_D$ +413°.

Anal. Calc'd for $C_{19}H_{28}O_3$ (304.41): C, 74.96; H, 9.27.

Found: C, 74.67; H, 9.33.

B. In another run with VI (1.57 g.) and 50% acetic acid (35 ml.) there was obtained 0.82 g., m.p. 236–238.5° ($\epsilon_{242-248}$ 14,800), 0.13 g., m.p. 233.5–236.5°, and 0.054 g., m.p. 235–237.5° with previous softening. Yield, 83%.

Δ^4-Androstene-11β,17β-diol-3-one-17-acetate (VIIb). Compound VII (54 mg.) in pyridine (1 ml.) was acetylated with acetic anhydride (1 ml.) at room temperature (64 hours). The

crude oily product obtained from an ethyl acetate extract was dissolved in ether, and the solution was treated with petroleum ether until a turbidity persisted. It was allowed to stand at room-temperature for several days during which time almost all of the solvent had spontaneously evaporated, and crystals were obtained. Petroleum ether was added, and removed by decantation. The residue was crystallized from ether-petroleum ether; 19 mg., m.p. 143–148° with previous softening. Two recrystallizations from acetone-petroleum ether gave pure VIIb; 16 mg., m.p. 149.5–151.5°; λ_{max} 241 mμ, ε 16,100; IR: λ_{max} 3480 cm^{-1} (hydroxyl), 1710 cm^{-1} (acetate 'carbonyl' stretch), 1675 cm^{-1} (3-keto), 1615 cm^{-1} (Δ^4), 1253 cm^{-1} (acetate 'C—O' stretch); $[\alpha]_D^{24}$ +121° (11.1 mg., α_D +0.67°); $[M]_D$ +419°.

Anal. Calc'd for $C_{21}H_{30}O_4$ (346.45): C, 72.80; H, 8.73.

Found: C, 72.73; H, 8.80.

Δ⁴-Androstene-17β-ol-3,11-dione-acetate (VIIIb). The diol (VII) (0.3 g.) in pyridine (3 ml.) was acetylated with acetic anhydride (3 ml.) at room-temperature (24 hours). The mixture was poured into ice-water, and the product was extracted with ethyl acetate. Evaporation afforded an oil which crystallized on being worked; about 0.3 g.

The crude acetate was dissolved in glacial acetic acid (5 ml.), cooled, and treated with chromic anhydride (0.18 g.) dissolved in water (3 drops) and glacial acetic acid (5 ml.). The mixture was allowed to stand at room temperature (24°) for 1¾ hours. Addition of water, and a few drops of methanol afforded crystals which were collected and washed with water; 185 mg. (55% yield); m.p. 162–165.5°. Three recrystallizations from acetone-petroleum ether gave 98 mg. of pure VIIIb; m.p. 166.5–167.5°; λ_{max} 237–238 mμ, ε 14,200; IR: λ_{max} 1724 cm^{-1} (acetate 'carbonyl' stretch), 1695 cm^{-1} (11-keto), 1670 cm^{-1} (3-keto), 1613 cm^{-1} (Δ^4), 1230 and 1215 cm^{-1} (acetate 'C—O' stretch); $[\alpha]_D^{24}$ +173° (15 mg., α_D +1.30°); $[M]_D$ +595°.

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

Found: C, 73.45; H, 8.32.

Δ⁴-Androstene-17β-ol-3,11-dione (VIIIa)[7]. The acetate (VIIIb) (85 mg.) in alcohol (7 ml.) was treated with potassium carbonate (40 mg.) in water (0.3 ml.), and was refluxed for 2 hours. Water was added, and the product was extracted with ethyl acetate. Evaporation *in vacuo* gave crystals which were recrystallized from acetone-petroleum ether; 67 mg. (90% yield); m.p. 186.5–187.5°. One further recrystallization did not alter the m.p. appreciably; 58 mg., m.p. 187–187.5°; λ_{max} 237.5 mμ, ε 14,000; IR: λ_{max} 3255 cm^{-1} (hydroxyl), 1700 cm^{-1} (11-keto), 1663 cm^{-1} (3-keto), 1608 cm^{-1} (Δ^4); $[\alpha]_D^{24}$ +225° (12.45 mg., α_D +1.40°); $[M]_D$ +680°.

Anal. Calc'd for $C_{19}H_{26}O_3$ (302.40): C, 75.46; H, 8.67.

Found: C, 75.21; H, 8.87.

Δ⁵-Androstene-17β-ol-3,11-dione-acetate-3-ethylene ketal (IX). A mixture of VIIIb (0.7 g.), benzene (50 ml.), ethylene glycol (5 ml.), and *p*-toluenesulfonic acid monohydrate (20 mg.) was reacted in the previously described manner (5) (reflux 5 hours). The crude crystalline product was recrystallized from ether; 0.46 g. (58% yield). An 100-mg. portion on recrystallization from ether (petroleum ether wash) afforded 71 mg. of IX; m.p. 181.5–183°; IR: λ_{max} 1733 cm^{-1} (acetate 'carbonyl' stretch), 1700 cm^{-1} (11-keto), 1237 cm^{-1} (acetate 'C—O'stretch), 1088 cm^{-1} (ketal); $[\alpha]_D^{23}$ −32° (9.25 mg., α_D −0.15°); $[M]_D$ −124°.

Anal. Calc'd for $C_{23}H_{32}O_5$ (388.49): C, 71.10; H, 8.30.

Found: C, 71.04; H, 8.55.

Δ⁵-Androstene-11α,17β-diol-3-one-ethylene ketal (X). A mixture of IX (425 mg.), dioxane

[7] After completion of this work, and preparation of the manuscript for publication there appeared a paper by Herzog, Jevnik, Perlman, Nobile, and Hershberg, *J. Am. Chem. Soc.* **75**, 266 (1953), in which there was described the preparation of Δ⁴-androstene-17β-ol-3,11-dione (VIIIa) by a biochemical reduction of adrenosterone as well as by a chemical transformation of etiocholane-17β-ol-3,11-dione; m.p. 181–182.4°; $[\alpha]_D^{25}$ +177.8° (acetone); ϵ_{238} 14,400 (alcohol). Redetermination of the rotation of our sample of VIIIa in acetone gave $[\alpha]_D^{23}$ +181°, which is in excellent agreement with the Schering value.

(2 ml.), absolute alcohol (2 ml.), and liquid ammonia (75 ml.) was reacted with lithium metal (400 mg.) in the previously described manner (3). After the excess ammonia had spontaneously evaporated, water was added, and the product was collected and washed with water; 355 mg. (89% yield as hydrate); m.p. 212.5–220°. An 100-mg. portion was recrystallized from acetone-petroleum ether; 53 mg., m.p. 216.5–221°; IR: λ_{max} 3300, 3215, and 3140 cm^{-1} (hydroxyl), 1655 cm^{-1} (Δ^5), 1090 cm^{-1} (ketal); $[\alpha]_D^{23}$ −37° (9.1 mg., α_D −0.17°); $[M]_D$ −135° (as hydrate).

Anal. Calc'd for $C_{21}H_{32}O_4 \cdot H_2O$ (366.48): C, 68.82; H, 9.35.
Found: C, 68.97; H, 9.30.

Δ^4-Androstene-11α,17β-diol-3-one (XIa). Compound X (297 mg.) was hydrolyzed with 8 ml. of 75% (v/v) acetic acid in the manner described above for III, except that the product was extracted with ethyl acetate. The crude oil was crystallized from ethyl acetate; 132 mg. (53% yield based on hydrated starting material); m.p. 177–179°. Two further recrystallizations from ethyl acetate gave 49 mg., m.p. 179.5–180.5°, with previous softening at 178.5°, λ_{max} 241–242 mμ, ε 14,300; IR: λ_{max} 3390 and 3288 cm^{-1} (hydroxyl), 1652 cm^{-1} (3-keto), 1600 cm^{-1} (Δ^4); $[\alpha]_D^{23}$ +87° (11.3 mg., α_D +0.49°); $[M]_D$ +264°. Literature (6): m.p. 181–181.5° with previous softening at 178°; $[\alpha]_D^{23}$ +93° (chloroform).

Δ^4-Androstene-11α,17β-diol-3-one-diacetate (XIb). The diol (XIa) (80 mg.) was acetylated with acetic anhydride (1 ml.) and pyridine (1 ml.). The crude product, 89 mg. (87% yield), m.p. 193–199.5° with previous softening, was recrystallized to constant m.p. from acetone-petroleum ether; 51 mg., m.p. 200–202°; λ_{max} 238–239 mμ, ε 15,700; IR: λ_{max} no hydroxyl, 1724 cm^{-1} (acetate 'carbonyl' stretch), 1660 cm^{-1} (3-keto), 1607 cm^{-1} (Δ^4), 1247 cm^{-1} (acetate 'C—O' stretch); $[\alpha]_D^{24}$ +61° (12.8 mg., α_D +0.39°); $[M]_D$ +237°.

Anal. Calc'd for $C_{25}H_{32}O_5$ (388.49): C, 71.10; H, 8.30.
Found: C, 70.79; H, 8.49.

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SUMMARY

Synthetic methods are described for the conversion of adrenosterone (IV) into Δ^4-androstene-11β-ol-3,17-dione (III), Δ^4-androstene-11β,17β-diol-3-one (VIIa), Δ^4-androstene-11α,17β-diol-3-one (XIa), and Δ^4-androstene-17β-ol-3,11-dione (VIIIa).

Certain generalizations regarding optical rotatory power, and ultraviolet absorption spectra of these 11-oxygenated steroids are discussed.

Their absorption spectra (220–600 mμ) in 97% sulfuric acid at 25° have been determined.

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