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

$\Delta^{5,7}$-STEROIDS. XII.[1,2] STEROIDAL CYCLIC KETALS. I. CYCLIC KETALS OF $\Delta^{4,7}$-3-KETOSTEROIDS

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Fernholz and Stavely (1) have noted that when a Δ^4-3-ketosteroid is treated with ethylene glycol (benzene, *p*-toluenesulfonic acid), the resulting ketal was formed with coincident rearrangement of the double bond to the C-5,6 position; thus, Δ^4-cholestene-3-one (Ia) was transformed into Δ^5-cholestene-3-one-ethylene ketal (IIa). These investigators presented the following evidence in support of the assigned structure IIa. Compound IIa on treatment with perbenzoic acid afforded the α-oxide which was converted by chromic acid oxidation into cholestane-5α-ol-3,6-dione. This compound was previously described by Ruzicka and Bosshard (2) who prepared it from cholesterol-α-oxide. Also it was demonstrated by Fernholz and Stavely (1) that palladium catalyst hydrogenation of IIa gave cholestane-3-one-ethylene ketal identical with the product obtained by them directly from cholestane-3-one,[4] and that acid hydrolysis of a Δ^5-3-keto-ethylene ketal regenerated the original Δ^4-3-ketone grouping.

It may be concluded from the work of Hauptmann (3) that this rearrangement of the double bond does not occur in the analogous preparation of Δ^4-cholestene-3-one-ethylene thioketal (VII) from Ia with ethanedithiol (zinc chloride, sodium sulfate). The high positive rotation of VII, and its conversion to Δ^4-cholestene by Raney nickel hydrogenolysis established the structure of the thioketal (VII). As an incidental experiment we have also prepared Δ^4-cholestene-3-one-ethylene thioketal (VII), whose properties were in good agreement with those reported for this compound by Hauptmann.

Unfortunately, the problem as to whether formation of an ethylene hemithioketal from a Δ^4-3-ketosteroid is accompanied with or without coincident rearrangement of the double bond remains unsolved. In this connection, recent work by Romo, Rosenkranz, and Djerassi (4) may be cited. These investigators have assumed that the reaction of β-mercaptoethanol with a Δ^4-3-ketosteroid proceeded with least alteration of structure. Hence, the double bond was placed at its original site, the C-4,5 position.

In this and subsequent papers of this series, we wish to report on our results obtained in extending the work of Fernholz and Stavely to other steroidal ketones.

[1] Paper XI, Antonucci, Bernstein, Giancola, and Sax, *J. Am. Chem. Soc.*, **73**, 5860 (1951).

[2] Presented in part before the Organic Group at the Fourth Annual Meeting of the New York Section, American Chemical Society, New York, N. Y., February 8, 1952.

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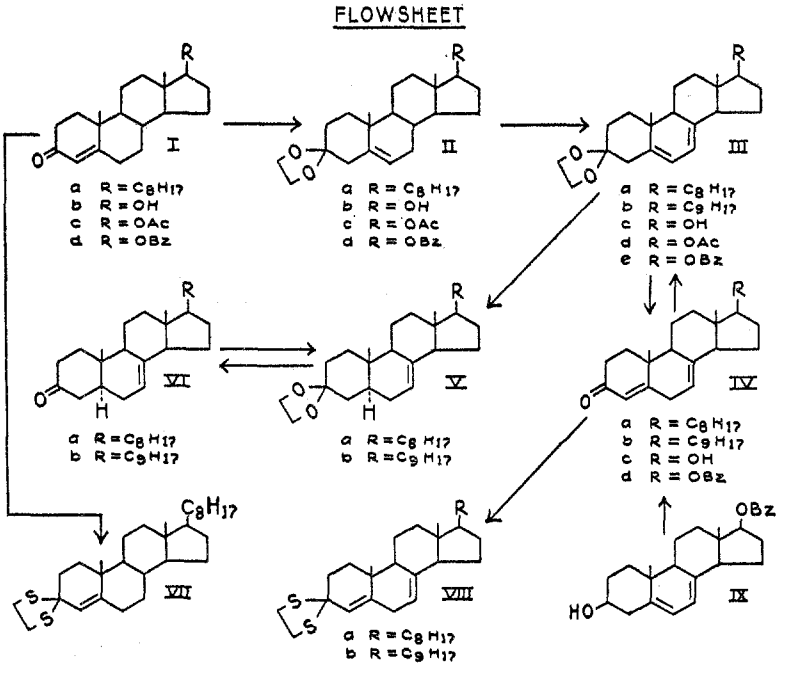
[4] Moreover, we would like to point out that the negative rotatory power of the Δ^5-ketal (II) may be considered as corroborative evidence for the assigned structure.

Our first objective in the utilization of this cyclic-ketal reaction was its application to $\Delta^{4,7}$-3-ketosteroids. It was reasoned that the formation of the ethylene ketal accompanied by rearrangement of the double bond would afford a $\Delta^{5,7}$-steroid. In this way, moreover, further evidence for the migration of the double bond would be obtained. This has been found to be the case. Ergosterone ($\Delta^{4,7,22}$-ergostatriene-3-one) (IVb) on treatment with ethylene glycol gave $\Delta^{5,7,22}$-ergostatriene-3-one-ethylene ketal (IIIb). In a similar manner $\Delta^{5,7}$-cholestadiene-3-one-ethylene ketal (IIIa) was prepared from 7-dehydrocholestenone ($\Delta^{4,7}$-cholestadiene-3-one) (IVa). The structures IIIa and b assigned to these compounds were substantiated by ultraviolet absorption analysis, and chemical transformations. Both compounds showed the unique selective absorption maxima characteristic of a $\Delta^{5,7}$-steroid, namely at about 272, 282 and 293–294 mμ



(5). Moreover, $\Delta^{5,7,22}$-ergostatriene-3-one-ethylene ketal (IIIb) was converted into $\Delta^{7,22}$-ergostadiene-3-one-ethylene ketal (Vb) (λ_{max} none) by hydrogenation with Raney nickel catalyst (W-2) in ether-alcohol solution. The same product was obtained by sodium and alcohol reduction. Compound Vb was converted into the known $\Delta^{7,22}$-ergostadiene-3-one (VIb) (6). Treatment of VIb with ethylene glycol gave back the ketal (Vb), identical in all respects with the product obtained from the $\Delta^{5,7}$-ketal (IIIb). Similarly, $\Delta^{5,7}$-cholestadiene-3-ethylene ketal (IIIa) was converted into Δ^{7}-cholestene-3-one-ethylene ketal (Va), which on hydrolysis gave the known Δ^{7}-cholestene-3-one (VIa) (7). The latter on treatment with ethylene glycol gave back Va.

It was also established that compounds of structures III and IV are mutually interconvertible, since acid (dilute sulfuric acid, or aqueous acetic acid) hydroly-

sis of $\Delta^{5,7,22}$-ergostatriene-3-one-ethylene ketal (IIIb) gave ergosterone (IVb), and *not* isoergosterone. Hydrolysis of $\Delta^{5,7}$-cholestadiene-3-one-ethylene ketal gave a syrup which was difficult to crystallize, but which was characterized with 2,4-dinitrophenylhydrazine. The hydrazone so obtained was identical with an authentic sample of $\Delta^{4,7}$-cholestadiene-3-one-2,4-dinitrophenylhydrazone.

Concurrent to the above investigations with ethylene glycol, we initiated a study of the reaction between $\Delta^{4,7}$-3-ketosteroids and ethanedithiol. When $\Delta^{4,7,22}$-ergostatriene-3-one (IVb) was treated with ethanedithiol at room temperature (benzene, zinc chloride, sodium sulfate) there was obtained a product which on the basis of its optical rotation ($[\alpha]_D$ +74.9°), ultraviolet absorption spectrum (only end absorption);[5] and its positive Tortelli-Jaffé color test was assigned the tentative structure VIIIb. Similarly, $\Delta^{4,7}$-cholestadiene-3-one (IVa) was converted into $\Delta^{4,7}$-cholestadiene-3-one-ethylene thioketal (VIIa) (tentative).

However, when the reaction of $\Delta^{4,7}$-3-ketosteroids with ethanedithiol was carried out under forcing conditions (benzene reflux, *p*-toluenesulfonic acid, constant water-removal), inconsistent results were obtained. This reaction is now being further investigated. The results to-date indicate, moreover, that no $\Delta^{5,7}$-steroids are formed. This interesting result also pertains to the reaction with β-mercaptoethanol.

With the establishment of the structure (IIa) of the ethylene ketal of Δ^4-cholestene-3-one as indicated, our next objective was to submit this compound to the conditions of the NBS[6] method employed in this laboratory (5) for the formation of $\Delta^{5,7}$-steroids. The product so obtained would be identical with the ethylene ketal (IIIa) prepared from $\Delta^{4,7}$-cholestadiene-3-one (IVa). This proved to be the case. Thus, it was established that the ethylene ketal grouping is stable under free radical NBS conditions. Moreover, the formation of IIIa from IIa may be considered as further evidence for the structure IIa. The crude $\Delta^{5,7}$-cholestadiene-3-one-ethylene ketal (IIIa) so obtained was about 93% pure, and this represented a "crude" yield of 53%. Pure material was obtained in about 44% yield. This "pure" yield of material was obtained without an exhaustive recrystallization of the mother liquor fractions. An ultraviolet absorption spectrum analysis of the crude material revealed an inflection at 241–242 mμ (ϵ 2240). In our opinion, this represents the presence of a trace of 7-dehydrocholestenone (IVa), and not the usual NBS by-product, which in this case would be $\Delta^{4,6}$-cholestadiene-3-one-ethylene ketal. In fact, it is our opinion that the ethylene ketal grouping at C-3 appears to hinder the usual allylic shift associated with the formation of $\Delta^{5,7}$-from Δ^5-steroids by the NBS method. The presence of the $\Delta^{4,7}$-3-ketone (IVa) may be attributed to trace hydrolysis of the $\Delta^{5,7}$-ketal (IIIa). In a future publication we plan to discuss in detail the NBS bromination of Δ^5-3-ketals. Suffice it to say here, that this grouping at C-3 affords the highest yields ever recorded for the preparation of $\Delta^{5,7}$-steroids.

[5] In our hands, Δ^4-cholestene-3-one ethylene thioketal (VII) showed no selective absorption in the ultraviolet between 220–300 mμ; only end absorption was present, Cf. Fukushima, Liebermann, and Praetz, *J. Am. Chem. Soc.*, **72**, 5205 (1950).

[6] NBS = N-Bromosuccinimide.

Finally, we have extended these reactions to steroidal hormones, and results obtained in the "testosterone" series will be presented here.

In a previous publication (5), the preparation of $\Delta^{5,7}$-androstadiene-3β,17β-diol-17-benzoate (IX) was reported. This compound on Oppenauer oxidation gave $\Delta^{4,7}$-androstadiene-17β-ol-3-one-benzoate (IVd), which exhibited a single ultraviolet absorption maximum at 232 mμ and inflection points at 271 and 279 mμ. The location of the maximum at 232 mμ may be ascribed to the resultant effect of the two chromophoric groups in the molecule, which when acting independently show maxima at 229, 273, and 280 mμ for the benzoate group,[7] and 237–238.5 mμ for the Δ^4-3-keto moiety.[8] The magnitude of the molecular extinction coefficient of the 232 mμ maximum (ϵ 30,800) indicated that there is more or less additivity of the two chromophoric groupings. Compound IVd on treatment with ethylene glycol (benzene, *p*-toluenesulfonic acid) resulted in the formation of $\Delta^{5,7}$-androstadiene-17β-ol-3-one-17-benzoate-3-ethylene ketal (IIIe) which possessed the characteristic ultraviolet absorption spectrum of a $\Delta^{5,7}$-steroid benzoate, λ_{max} 229 (17-benzoate), 271, 281, 293 mμ ($\Delta^{5,7}$). The structure of compound IIIe was further established by an independent synthesis from testosterone benzoate (Id). The latter, on treatment with ethylene glycol, gave Δ^5-androstene-17β-ol-3-one-17-benzoate-3-ethylene ketal (IId), which on bromination with NBS, followed by dehydrobromination with *s*-collidine in xylene, was converted into $\Delta^{5,7}$-androstadiene-17β-ol-3-one-17-benzoate-3-ethylene ketal (IIIe) identical in all respects with the material obtained from $\Delta^{4,7}$-androstadiene-17β-ol-3-one-benzoate (IVd) described above. Alkaline hydrolysis of the benzoate (IIIe) gave $\Delta^{5,7}$-androstadiene-17β-ol-3-one-ethylene ketal (IIIc), which, on subsequent hydrolysis with dilute sulfuric acid, was converted into $\Delta^{4,7}$-androstadiene-17β-ol-3-one (7-dehydrotestosterone) (IVc). An attempt to convert compound IVd directly into compound IVc by hydrolysis of the benzoate group with potassium hydroxide was not successful. This reaction did not seem promising and was not investigated further.

$\Delta^{5,7}$-Androstadiene-17β-ol-3-one-ethylene ketal (IIIc) was also prepared from testosterone acetate (Ic) by the same route used in the case of the above benzoate, *i.e.*, Ic $\rightarrow$ Δ^5-androstene-17β-ol-3-one-17-acetate-3-ethylene ketal (IIc) $\rightarrow$ $\Delta^{5,7}$-androstadiene-17β-ol-3-one-17-acetate-3-ethylene ketal (IIId) $\rightarrow$ IIIc. Compound IIc in this sequence of reactions was also prepared from testosterone (Ib) by formation of Δ^5-androstene-17β-ol-3-one-ethylene ketal (IIb), followed by acetylation of the 17β-hydroxyl group with acetic anhydride in pyridine.

EXPERIMENTAL

Absorption spectra. All spectra were determined with a Beckman quartz spectrophotometer (Model DU, National Technical Laboratories, So. Pasadena, California), and were determined in absolute alcohol.

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[7] Bernstein and Sax, *J. Org. Chem.*, **16**, 679 (1951): Cholesteryl benzoate: $\epsilon_{229.5}$ 15,300, ϵ_{273} 970, ϵ_{280} 760.

[8] Antonucci, Bernstein, Giancola, and Sax, *J. Org. Chem.*, **16**, 1453 (1951): Δ^4-androstene-3,17-dione: $\epsilon_{238.5-240}$ 15,800.

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. The rotation generally was determined for two wavelengths, 5893 Å (D), and 5461 Å (Hg).

Petroleum ether. The petroleum ether fraction used had b.p. 64–66° (unless otherwise stated) and was purified with concentrated sulfuric acid and potassium permanganate.

Δ^5-*Cholestene-3-one-ethylene ketal* (IIa). A stirred mixture of 31.8 g. of Δ^4-cholestene-3-one (Ia), 770 ml. of benzene, and 40 ml. of ethylene glycol was slowly distilled for 15 minutes for removal of traces of water, *p*-toluenesulfonic acid monohydrate (0.3 g.) was added, and the mixture was stirred and refluxed for 4.5 hours (continuous water-removal adapter). Saturated sodium bicarbonate solution was added to the cooled mixture, and the benzene layer was separated. The extract was washed twice with water, dried, and evaporated *in vacuo*. The residue was recrystallized from ether-methanol, wt. 13.4 g., m.p. 132–132.6°. One further recrystallization gave 11.85 g., m.p. 133.5–134.5°.

One gram of this material was recrystallized twice more from ether-methanol, wt. 0.8 g., m.p. 134–135°;[9] λ_{max} none; $[\alpha]_D^{30}$ −31.4°, $[\alpha]_{Hg}^{30}$ −38.9° (18.5 mg., α_D −0.29°, α_{Hg} −0.36°) α_{Hg}/α_D 1.24, $[M]_D$ −134°.

Anal. Calc'd for $C_{29}H_{48}O_2$ (428.67): C, 81.25; H, 11.29.
Found: C, 81.34; H, 11.33.

$\Delta^{5,7}$-*Cholestadiene-3-one-ethylene ketal* (IIIa). *A.* A mixture of 2 g. of $\Delta^{4,7}$-cholestadiene-3-one (IVa), 3.5 ml. of ethylene glycol, 100 ml. of benzene, and 40 mg. of *p*-toluenesulfonic acid monohydrate was reacted in the manner described above (4 hours reflux). The crude material so obtained was dissolved in a mixture of ether and acetone, and the solution was filtered. Concentration gave 1.17 g. of practically pure IIIa, m.p. 135.5–137°, λ_{max} 271, 282, and 294 mμ, ε10,600; 11,500; and 7,000, respectively. From the mother liquor by concentration and simultaneous addition of acetone there was obtained 150 mg., m.p. 122–127°. Recrystallization of the main fraction from acetone gave 0.70 g., m.p. 136–137.4°, λ_{max} 271.5, 282, and 293.5 mμ, ε10,800; 11,600; and 6,750, respectively; $[\alpha]_D^{31}$ −14.3°, $[\alpha]_{Hg}^{31}$ −24.8° (21 mg., α_D −0.15°, α_{Hg} −0.26°) α_{Hg}/α_D 1.73; $[M]_D$ −61°.

Anal. Calc'd for $C_{29}H_{46}O_2$ (426.66): C, 81.63; H, 10.87.
Found: C, 81.49; H, 11.07.

B. A mixture of 1.0 g. Δ^5-cholestene-3-one-ethylene ketal (IIa), 0.50 g. of NBS, and 20 ml. of petroleum ether (b.p. 64–66°, freed of unsaturates) was refluxed while irradiated for 3 minutes by the heat and light of a photospot lamp (RSP-2, General Electric Co.). To the still refluxing mixture was added 0.2 ml. of *s*-collidine. The mixture was filtered (succinimide, wt. 0.28 g., m.p. 119–124°), and the filtrate was evaporated *in vacuo*. The residue was dissolved in 15 ml. of xylene and 0.2 ml. of *s*-collidine, and was refluxed for 12 minutes. The mixture was cooled, and the collidine hydrobromide was separated by filtration. The filtrate was evaporated *in vacuo* and the residue was crystallized from acetone, wt. 0.58 g., m.p. 133–135° (also, m.p. 125–127°, resolidification, and remelt at 200–215°); λ_{max} 241–242 (inflection), 263–264 (plateau), 271–271.5, 282, and 293–294 mμ, ε2,200; 7,200; 10,400; 11,050; and 6,400 respectively; (crude material 91% pure based on ϵ_{282} 12,100; crude yield 53%). Two recrystallizations from acetone gave 0.44 g. of pure IIIa, m.p. 137.5–139.5°. One further recrystallization did not alter the m.p., λ_{max} 262–262.5 (inflection), 271, 282, and 293.5–294 mμ, ε7,950; 11,400; 12,100; and 7,000 respectively, λ_{min} 227–228, 276–277, and 290 mμ, ε1,250; 9,650; and 6,300, respectively; $[\alpha]_D^{29}$ −16.6°, $[\alpha]_{Hg}^{29}$ −27.0° (28.9 mg., α_D −0.24°, α_{Hg} −0.39°) α_{Hg}/α_D 1.63, $[M]_D$ −71°. Pure yield; 44%.

$\Delta^{5,7,22}$-*Ergostatriene-3-one-ethylene ketal* (IIIb). A mixture of 15 g. of ergosterone (IVb), 18 ml. of ethylene glycol, 700 ml. of benzene, and 400 mg. of *p*-toluenesulfonic acid monohydrate was reacted in the manner described above. The benzene extract was evaporated *in vacuo* to near dryness; addition of ethanol gave pale yellow crystals, wt. 10.2 g., m.p 154–156°. Recrystallization of an aliquot from ethanol gave pure IIIb, pale yellow crystals,

[9] Fernholz (1), m.p. 133°, $[\alpha]_D$ −28°.

m.p. 155–157.5°, λ_{max} 271, 282, and 294 mμ, ε11,300; 12,050; and 6,900, respectively, $[\alpha]_D^{25}$ −26.3°, $[\alpha]_{Hg}^{25}$ −33.6° (13.7 mg., α_D −0.18°, α_{Hg} −0.23°) α_{Hg}/α_D 1.28; $[M]_D$ −115°.

In another run the optical rotation was $[\alpha]_D^{30}$ −31.3°, $[\alpha]_{Hg}^{30}$ −41.3° (17.9 mg. α_D −0.28°, α_{Hg} −0.37°) α_{Hg}/α_D 1.32, $[M]_D$ −137°.

Anal. Calc'd for $C_{30}H_{46}O_2$ (438.67): C, 82.13; H, 10.57.

Found: C, 82.26; H, 10.81.

Hydrolysis of $\Delta^{5,7,22}$*-ergostatriene-3-one-ethylene ketal. A.* A mixture of 100 mg. of the ketal (IIIb) in 3.3 ml. of methanol and 6 ml. of ethanol was treated with 0.17 ml. of concentrated sulfuric acid in 2 ml. of water. The mixture was refluxed in a nitrogen atmosphere for ½ hour (after complete solution), cooled, and treated with a few drops of water. This gave crystals which were collected after ice-cooling of the mixture. Recrystallization of the crude product from acetone-water and acetone gave pure ergosterone (IVb), m.p. 131–131.5°, λ_{max} 238 mμ, ε14,200.

B. A solution of 3.85 g. of IIIb in 80 ml. of 90% acetic acid was heated on the steam-bath for 20 minutes. During this time a deep yellow color developed. Water was added to the hot solution until a general turbidity persisted. The cooled mixture afforded 3.03 g. of IVb, m.p. 130–131.5°. Recrystallization from acetone gave 2.58 g., m.p. 132.5–134°, λ_{max} 238 mμ, ε14,800. From the mother liquors by concentration, and addition of water there was obtained 0.24 g., m.p. 131–132°, and 0.13 g., m.p. 129.5–131.5°.

Dinitrophenylhydrazone of 7-dehydrocholestenone. The $\Delta^{5,7}$-ketal (IIIa) (70 mg.) was dissolved in 10 ml. of glacial acetic acid. The hot solution was treated with several ml. of water, and the solution was heated on the steam-bath for ½ hour. During this time several additional ml. of water was added, and the cooled mixture was extracted with benzene. The extract was washed with water, sodium bicarbonate solution, and finally with water. It was dried with magnesium sulfate, treated with Norit, and filtered. Evaporation *in vacuo* yielded an oil.

The oil was dissolved in 5 ml. of glacial acetic acid, treated with 70 mg. of 2,4-dinitrophenylhydrazine, and the mixture was heated on the steam-bath for 10 minutes. The cooled mixture was filtered and the crystals so obtained were washed with ethanol. Recrystallization from chloroform-alcohol gave 20 mg. of pure hydrazone, m.p. 213–215° d., $\lambda^{1\%CA}_{max}$[10] 255–256 and 385–389 mμ; ε18,700; 30,200, respectively. An authentic sample possessed m.p. 210–210.5° d., $\lambda^{1\%CA}_{max}$ 255–256 and 385–389 mμ; ε19,100; 31,000, respectively.[11]

Δ^7*-Cholestene-3-one-ethylene ketal* (Va). *A.* A mixture of 2 g. of the $\Delta^{5,7}$-ketal (IIIa) dissolved in 160 ml. of absolute ether-absolute alcohol (3:1), and about 1 g. of Raney nickel catalyst (W-2) was shaken in a hydrogen atmosphere for 1.5 hours. The catalyst was removed by filtration through Celite, and the filtrate was concentrated with simultaneous addition of alcohol. This gave 1.7 g. of crude Va, m.p. 111–113.5°, λ_{max} none. Two recrystallizations from alcohol gave 1.2 g. of pure Va, m.p. 115–116°, $[\alpha]_D^{27}$ +19.2°, $[\alpha]_{Hg}^{27}$ +23.5° (23 mg., α_D +0.22°, α_{Hg} +0.27°) α_{Hg}/α_D 1.23; $[M]_D$ +82°.

Anal. Calc'd for $C_{29}H_{48}O_2$ (428.67): C, 81.25; H, 11.29.

Found: C, 81.06; H, 11.44.

B. A mixture of 320 mg. of Δ^7-cholestene-3-one (VIa), 60 ml. of benzene, 3 ml. of ethylene glycol, and 80 mg. of *p*-toluenesulfonic acid monohydrate was reacted in the manner described above. The crude product so obtained was recrystallized from acetone-methanol, wt. 250 mg., m.p. 117–118°, and two times from alcohol, m.p. 116–117°; $[\alpha]_D^{27}$ +19.6°, $[\alpha]_{Hg}^{27}$ +22.6° (26.6 mg., α_D +0.26°, α_{Hg} +0.30°) α_{Hg}/α_D 1.15; $[M]_D$ +84°.

Δ^7*-Cholestene-3-one* (VIa). A refluxing solution of 1 g. of Δ^7-cholestene-3-one-ethylene ketal (Va) in 60 ml. of alcohol was treated over a period of 10 minutes with 10 ml. of 10% (v/v) sulfuric acid. The mixture was refluxed for 1¼ hours after the addition of the acid,

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[10] Solvent was 1% chloroform-absolute alcohol; the substance was dissolved in 1 ml. of chloroform and rapidly diluted to 100 ml. with absolute alcohol.

[11] The complete characterization of the 2,4-dinitrophenylhydrazone of $\Delta^{4,7}$-cholestadiene-3-one will be presented in a future publication.

cooled, and the crystals which separated were collected and washed with alcohol, wt. 600 mg., m.p. 144–146°. Recrystallization from methanol gave 450 mg. of pure VIa, m.p. 146.147°,[12] $[\alpha]_D^{20}$ +25.8°, $[\alpha]_{Hg}^{20}$ +31.5° (24.8 mg., α_D +0.32°, α_{Hg} +0.39°), α_{Hg}/α_D 1.22, $[M]_D$ +99°

$\Delta^{7,22}$-*Ergostadiene-3-one-ethylene ketal* (Vb). *A.* Compound IIIb (5 g.) was hydrogenated in the manner described for Va. This gave 4.15 g. of product, m.p. 162–164°, λ_{max} none. A 0.5-g. portion of this material was recrystallized from acetone-methanol, m.p. 163–165° λ_{max} none, $[\alpha]_D^{29}$ −4.5°, −7.0° (40.0 mg., 45.6 mg., α_D −0.09°, −0.16°, respectively); $[M]_D$ −20°, −31°.

Anal. Calc'd for $C_{30}H_{48}O_2$ (440.68): C, 81.76; H, 10.98.

Found: C, 81.77; H, 11.18.

B. A refluxing solution of 2 g. of IIIb in 200 ml. of absolute alcohol was treated over a period of 3 hours with 90 g. of sodium; intermittently portions of absolute alcohol were added for a total of 1050 ml. The cooled mixture was poured into crushed ice and water, and was thoroughly extracted with ether. The extract was washed three times with water, dried, treated with Norit, and filtered through Celite. The residue obtained on evaporation of the ether was recrystallized from absolute alcohol, wt. 1.33 g., m.p. 161–163°. Recrystallization from absolute alcohol gave 1.17 g. of Vb, m.p. 162–163°, λ_{max} none, $[\alpha]_D^{31}$ −12.2° (45.8 mg., α_D −0.28°).

C. A mixture of 340 mg. of $\Delta^{7,22}$-ergostadiene-3-one (VIb), 40 ml. of benzene, 2 ml. of ethylene glycol, and 80 mg. of *p*-toluenesulfonic acid monohydrate was reacted in the manner described above. The crude product so obtained was recrystallized from alcohol and acetone-alcohol, wt. 260 mg., m.p. 162–163°; $[\alpha]_D^{20}$ −4.8° (42 mg., α_D −0.10°).

Infrared absorption analysis showed the samples of Vb obtained in (*A*), (*B*), and (*C*) were identical in all respects.

$\Delta^{7,22}$-*Ergostadiene-3-one* (VIb). A refluxing solution of 1 g. of $\Delta^{7,22}$-ergostadiene-3-one-ethylene ketal in 60 ml. of alcohol was treated with 10 ml. of dilute sulfuric acid (10% v/v) and the mixture was refluxed for 1 hour and was cooled. The crystals which separated were washed with alcohol, wt. 0.77 g., m.p. 183–185°. Recrystallization from acetone-methanol gave 0.5 g. of pure VIb, m.p. 185–187°,[13] λ_{max} none, $[\alpha]_D^{29}$ 0.

Δ^4-*Cholestene-3-one-ethylene thioketal* (VII). A solution of 1 g. of Δ^4-cholestene-3-one (I) in 10 ml. of benzene was treated with 2 g. of anhydrous sodium sulfate, 1 g. of freshly fused zinc chloride, and 0.8 ml. of ethanedithiol. The mixture was allowed to stand at room temperature for 64 hours, and the product was worked up in ether-benzene. The extract was washed with sodium carbonate solution and water. The dried extract was evaporated, and the residue was crystallized from acetone, wt. 0.95 g., m.p. 110–111°, λ_{max} none. Two recrystallizations from acetone gave 0.75 g., m.p. 112–114°[14] (the m.p. was found to be dependent on the manner performed), $[\alpha]_D^{27}$ +104°, $[\alpha]_{Hg}^{27}$ +128° (10.35 mg., α_D +0.54°, α_{Hg} +0.66°) α_{Hg}/α_D 1.22, $[M]_D$ +478°.

Anal. Calc'd for $C_{29}H_{48}S_2$ (460.79): C, 75.59; H, 10.50; S, 13.92.

Found: C, 75.39; H, 10.70; S, 14.27.

$\Delta^{4,7}$-*Cholestadiene-3-one-ethylene thioketal* (VIIIa). Compound IVa (1 g.) was treated with ethanedithiol in the manner described above for VII. Recrystallization of the crude product from acetone afforded 0.64 g. of VIIIa, m.p. 95–103°, λ_{max} no selective absorption in U.V. (end absorption only; 220–300 mμ); $[\alpha]_D^{20}$ +108°, $[\alpha]_{Hg}^{29}$ +134° (13.15 mg., α_D +0.71°, α_{Hg} +0.88°) α_{Hg}/α_D 1.24, $[M]_D$ +495°.

Anal. Calc'd for $C_{29}H_{46}S_2$ (458.78): C, 75.92; H, 10.11; S, 13.98.

Found: C, 76.03; H, 10.30; S, 14.16, 14.43.

$\Delta^{4,7,22}$-*Ergostatriene-3-one-ethylene thioketal* (VIIIb). Compound IVb (1 g.) was treated with ethanedithiol in the manner described above for VII. Recrystallization of the crude product from acetone afforded 0.19 g. of VIIIb, m.p. 114.5–115.2°, λ_{max} no selective ab-

[12] von Buser (7); m.p. 146–147°, $[\alpha]_D^{20}$ +24.7° ± 2°.

[13] Barton and Cox (6), m.p. 184.5°, $[\alpha]_D$ +2°.

[14] Hauptmann (3): m.p. 106–107°, $[\alpha]_D^{27}$ +119°.

sorption in U.V. (end absorption only; 220–300 mμ); $[\alpha]_D^{28}$ +74.9°, $[\alpha]_{Hg}^{28}$ +90.5° (14.15 mg., α_D +0.53°, α_{Hg} +0.64°) α_{Hg}/α_D 1.21, $[M]_D$ +352°. *Positive Tortelli-Jaffé test.*

Anal. Calc'd for $C_{30}H_{46}S_2$ (470.79): C, 76.53; H, 9.85; S, 13.62.

Found: C, 76.74; H, 10.10; S, 13.55.

$\Delta^{4,7}$-Androstadiene-17β-ol-3-one-benzoate (IVd). *$\Delta^{5,7}$-Androstadiene-3β,17β-diol-17-benzoate* (IX) (2 g.) in 140 ml. of toluene and 30 ml. of cyclohexanone was oxidized in the usual manner with 2.05 g. of aluminum isopropoxide (4.85 ml. of toluene stock solution). The crude product was crystallized from aqueous acetone-methanol, followed by recrystallization from dilute acetone, and acetone-petroleum ether (b.p. 66–68°); wt. 0.64 g., m.p. 142.5–143.5°; λ_{max} 232–233 mμ, ε30,800; $[\alpha]_D^{29}$ +74°, $[\alpha]_{Hg}^{29}$ +87.4° (11.0 mg., α_D +0.44°, α_{Hg} +0.52°) α_{Hg}/α_D 1.18; $[M]_D$ +289°.

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

Found: C, 79.65; H, 8.01.

Δ^5-Androstene-17β-ol-3-one-17-benzoate-3-ethylene ketal (IId). A mixture of 15 g. of testosterone benzoate (IVc), 120 ml. of ethylene glycol, 400 ml. of benzene, and 450 mg. of *p*-toluenesulfonic acid monohydrate was reacted in the manner described above (reflux 4 hours). Crystallization of the crude product from acetone-alcohol-benzene gave 7.0 g., m.p. 206–214°. Successive recrystallizations from acetone-carbon tetrachloride-ethyl acetate, and from ethyl acetate gave 5.0 g., m.p. 218–221.5°. An aliquot was recrystallized twice more from ethyl acetate; m.p. 220–222.5°; λ_{max} 229, 271–272, 280–281 mμ, ε14,500; 690; 670 respectively; $[\alpha]_D^{29}$ +15°, $[\alpha]_{Hg}^{29}$ +18° (13.3 mg., α_D +0.10°, α_{Hg} +0.12°) α_{Hg}/α_D 1.20; $[M]_D$ +66°.

Anal. Calc'd for $C_{28}H_{36}O_4$ (436.57): C, 77.03; H, 8.31.

Found: C, 76.80; H, 8.27.

$\Delta^{5,7}$-Androstadiene-17β-ol-3-one-17-benzoate-3-ethylene ketal (IIIe). *A.* Testosterone benzoate-3-ethylene ketal (IId) (2.17 g.) in carbon tetrachloride was brominated and dehydrobrominated in the usual manner. This gave 1.22 g. of crude material; m.p. 185–202°; λ_{max} 229, 271, 281, 293 mμ; ε15,200; 11,600; 11,900; 6,550, respectively (50% yield based on ϵ_{281} 13,300). Three recrystallizations from acetone gave 790 mg.; m.p. 213–214°; λ_{max} 229, 271, 281, 293 mμ; ε15,100; 12,800; 13,300; 7,100, respectively; $[\alpha]_D^{29}$ +14.8° (29.8 mg., α_D +0.22°); $[M]_D$ +64°.

B. A mixture of 0.5 g. of $\Delta^{4,7}$-androstadiene-17β-ol-3-one-benzoate (IVd), 4 ml. of freshly distilled ethylene glycol, 17 ml. of benzene, and 15 mg. of *p*-toluenesulfonic acid monohydrate was reacted in the manner described (reflux 3.5 hours). Crystallization of the crude product from acetone gave 0.26 g.; m.p. 200–209°. Two recrystallizations from acetone-methanol gave 0.22 g.; m.p. 212.5–215°; λ_{max} 229, 271, 281, 293 mμ; ε14,600; 12,200; 6,800, respectively; $[\alpha]_D^{27}$ +17.5° (12.55 mg., α_D +0.11°); $[M]_D$ +76°.

Anal. Calc'd for $C_{25}H_{34}O_4$ (434.55): C, 77.39; H, 7.89.

Found: C, 77.08; H, 8.00.

$\Delta^{5,7}$-Androstadiene-17β-ol-3-one-ethylene ketal (IIIc). *A.* A solution of 125 mg. of $\Delta^{5,7}$-androstadiene-17β-ol-3-one-17-benzoate-3-ethylene ketal (IIIe) in 5 ml. of alcohol was treated with 16 ml. of 5% methanolic potassium hydroxide. The mixture was refluxed for 1 hour (nitrogen atmosphere), diluted with water, cooled, and filtered; wt. 90 mg.; m.p. 231–240°. Three recrystallizations from dilute acetone gave 67.5 mg. pure IIIc; m.p. 238–240°; λ_{max} 271, 281, 293 mμ; ε9,850; 10,500; 6,000, respectively; $[\alpha]_D^{23}$ −45.2°, $[\alpha]_{Hg}^{23}$ −62.6° (11.5 mg., α_D −0.26°, α_{Hg} −0.36°) α_{Hg}/α_D 1.39; $[M]_D$ −149°. Yield, 84%.

Anal. Calc'd for $C_{21}H_{30}O_3$ (330.45): C, 76.32; H, 9.15.

Found: C, 75.90; H, 9.29.

B. $\Delta^{5,7}$-Androstadiene-17β-ol-3-one-17-acetate-3-ethylene ketal (IIId) (0.5 g.) was treated with 0.2 g. of potassium hydroxide in 0.5 ml. of water and 15 ml. of ethanol. The mixture was refluxed for ½ hour and worked up in the same manner as above. Recrystallization from dilute acetone gave 0.37 g.; m.p. 238–243°; λ_{max} 271, 281–281.5, 293 mμ; ε10,100; 10,600; 6,100, respectively.

$\Delta^{4,7}$-Androstadiene-17β-ol-3-one (IVc). Dilute sulfuric acid (4.4 ml., 8.5%, v/v) was added

to a solution of 200 mg. of $\Delta^{5,7}$-androstadiene-17β-ol-3-one-ethylene ketal (IIIc) in 25 ml. of alcohol. The solution was refluxed for ¾ hour (nitrogen atmosphere), diluted with a large volume of water, and the crystals were collected; wt. 150 mg.; m.p. 150° unsharp. Recrystallization from acetone-petroleum ether gave 96 mg.; m.p. 161–163°; λ_{max} 238.5, ϵ15,100; $[\alpha]_D^{28}$ +22.1°, $[\alpha]_{Hg}^{28}$ +28.7° (9.05 mg., α_D +0.10°, α_{Hg} +0.13°) α_{Hg}/α_D 1.30; $[M]_D$ +63°.

Anal. Calc'd for $C_{19}H_{26}O_2$ (286.40): C, 79.68; H, 9.15.

Found:[15] C, 79.16; H, 9.28.

Δ^5-*Androstene-17β-ol-3-one-ethylene ketal* (IIb). A mixture of 2.0 g. of testosterone (IV), 9.0 ml. of freshly distilled ethylene glycol, 150 ml. of benzene, and 30 mg. of *p*-toluenesulfonic acid monohydrate was reacted in the manner described above (reflux 3.5 hours). The crude product, on recrystallization from dilute acetone, and acetone gave 1.0 g. of pure IIb; m.p. 185–188°.[16]

Δ^5-*Androstene-17β-ol-3-one-17-acetate-3-ethylene ketal* (IIc). *A.* A mixture of 50 g. of testosterone acetate (IVb), 360 ml. of freshly distilled ethylene glycol, 1100 ml. of benzene, and 1.3 g. of *p*-toluenesulfonic acid monohydrate was reacted in the manner described (reflux 5.5 hours). The crude product was recrystallized from acetone and acetone-methanol to give 21.6 g.; m.p. 203–205°; λ_{max} none.

B. A solution of 0.75 g. of testosterone ethylene ketal (Ib) in 5 ml. of pyridine was acetylated at room temperature with 0.75 ml. of acetic anhydride. Two crystallizations of the crude product from acetone gave 0.56 g.; m.p. 203–205°; λ_{max} none; $[\alpha]_D^{29}$ −52.1°, $[\alpha]_{Hg}^{29}$ −64.5° (24.3 mg., α_D −0.63°, α_{Hg} −0.78°) α_{Hg}/α_D 1.24; $[M]_D$ −195°.

Anal. Calc'd for $C_{23}H_{34}O_4$ (374.50): C, 73.76; H, 9.15.

Found: C, 73.80; H, 9.30.

$\Delta^{5,7}$-*Androstadiene-17β-ol-3-one-17-acetate-3-ethylene ketal* (IIId). Testosterone acetate ethylene ketal (IIc) (1.87 g.) in 10 ml. of petroleum ether and 25 ml. of carbon tetrachloride was brominated in the usual manner with 1.07 g. of NBS. The dehydrobromination was carried out with 1 ml. of *s*-collidine in 45 ml. of xylene. Purification of the crude product from dilute acetone, and petroleum ether gave 0.6 g. of pure IIId; m.p. 179–181°; λ_{max} 271, 281, 293 mμ; ϵ11,000; 11,700; 6,750, respectively; $[\alpha]_D^{29}$ −72.1°, $[\alpha]_{Hg}^{29}$ −94.8° (29.1 mg., α_D −1.05°, α_{Hg} −1.38°) α_{Hg}/α_D 1.31; $[M]_D$ −268°. Yield, 32%.

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

Found: C, 73.93; H, 8.83.

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SUMMARY

1. Additional evidence for the structure of Δ^5-cholestene-3-one-ethylene ketal has been presented.

2. Reaction of a $\Delta^{4,7}$-3-ketosteroid with ethylene glycol proceeded with rearrangement of the C-4,5 double bond to afford a $\Delta^{5,7}$-steroid. Hydrolysis of the $\Delta^{5,7}$-ketal gave back the original $\Delta^{4,7}$-3-ketosteroid and *not* the $\Delta^{4,6}$-3-ketosteroid. This was demonstrated with ergosterone and 7-dehydrocholestenone.

3. $\Delta^{5,7}$-Cholestadiene-3-one-ethylene ketal has been prepared also from the corresponding Δ^5-ketal by bromination of the latter with NBS followed by dehydrobromination with *s*-collidine in xylene.

[15] The analysis indicated solvation or hydration of the product (dried at approximately 140°/0.2 mm. for 5 hours).

[16] Fernholz (1); m.p. 183°.

4. Hydrogenation of $\Delta^{5,7,22}$-ergostatriene-3-one-ethylene ketal afforded $\Delta^{7,22}$-ergostadiene-3-one-ethylene ketal which on hydrolysis was converted into the known $\Delta^{7,22}$-ergostadiene-3-one. Treatment of the latter with ethylene glycol gave back the $\Delta^{7,22}$-ketal. The same series of transformations were carried out with $\Delta^{5,7}$-cholestadiene-3-one-ethylene ketal.

5. The preparation of $\Delta^{4,7}$-androstadiene-17β-ol-3-one (7-dehydrotestosterone) is described.

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