m.p. 85° dec., $[\alpha]^{22}_{D}$ +85° (c 0.807 in acetone), λ_{max}^{EtOH} 238 mμ (log ε 4.2); ν_{max}^{KBr} 1612 and 1665 (Δ^4-3-ketone), 1705 (double band of 11- and 20-ketones), 3400 cm.$^{-1}$ (21-hydroxy).

Anal. Calcd. for $C_{21}H_{27}O_4Br$: C, 59.57; H, 6.43; Br, 18.88. Found: C, 59.35; H, 6.95; Br, 18.40.

Reacetylation.—A solution of 99 mg. of XVII in 5 cc. of pyridine was treated with 2 cc. of acetic anhydride and kept for 20 hours at room temperature in the dark in an argon atmosphere. The usual working-up gave 60 mg. of a foamy material, the infrared spectrum of which was identical with that of authentic acetate XVIIa. The product was dissolved in benzene–ethyl acetate (85:15) and filtered through 1 g. of silica gel. Thus there was obtained crystalline XVIIa, m.p. 108–112° dec., not depressed upon admixture of authentic XVIIa.

$\Delta^{4,16}$-21-Acetoxy-3,11,20-trioxopregnadiene (XVIII).—A solution of 315 mg. of 17α-bromo-11-dehydrocorticosterone acetate (XVIIa) in 10 cc. of pyridine was refluxed for 40 minutes in a nitrogen atmosphere. The product was extracted with ether and worked up in the usual way. The resulting crude amorphous product (275 mg.) showed the infrared spectrum of XVIII. Chromatography on aluminum oxide gave 165 mg. of a clear oil which was rechromatographed on silica gel. Benzene–ethyl acetate (89:11, 85:15 and 80:20) eluted 48 mg. of crystalline $\Delta^{4,16}$-21-acetoxy-3,11,20-trioxopregnadiene (XVIII), m.p. 175–182°, λ_{max}^{EtOH} 237 mμ (log ε 4.3); the melting point was not depressed upon admixture of an authentic sample[26] and the infrared spectra of both products were identical.

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[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, THE WEIZMANN INSTITUTE OF SCIENCE]

Syntheses in the Cardiac Aglycone Field. III.[1] The Conversion of a 14α- to a 14β-Hydroxy Group in the Androstane Series. The Ultraviolet Spectra of Δ^{15}-Androsten-17-ones

BY FRANZ SONDHEIMER, SUMNER BURSTEIN AND RAPHAEL MECHOULAM

RECEIVED NOVEMBER 10, 1959

A method for converting the readily available androstane-3β,14α-diol-17-one 3-monoacetate (I) to the corresponding 14β-hydroxy compound Va is described, which involves successive dehydration of I to the Δ^{14}-17-one II, peracid oxidation to the 14β,15β-oxide III, rearrangement to the 14β-hydroxy-Δ^{15}-17-one IV and hydrogenation. The chemical evidence for the structures assigned to the 14β-hydroxy compounds IV and Va is supplemented by the optical rotatory dispersion data. Δ^{15}-Androsten-3β-ol-17-one (XV) and the corresponding 14-iso compound XVI have also been prepared. The anomalous ultraviolet spectra of the various Δ^{15}-androsten-17-ones are discussed.

Nearly all of the naturally occurring cardiac-active steroidal lactones possess a 14β-hydroxy substituent[2] and the introduction of this grouping into the steroid nucleus is therefore a prerequisite for the successful synthesis of this important group of compounds. Until now only one method for bringing about 14β-hydroxylation has been described, which uses steroidal $\Delta^{14,16}$-dienes as intermediates.[3]

As opposed to the 14β-hydroxy group, the 14α-hydroxy group can be introduced directly in one step into simple steroids by microbiological means[4] and also, in the androstane series, by chemical means.[5] Our objective was to effect the conversion of the resulting 14α-hydroxy steroids to the corresponding 14β-hydroxy compounds. In this paper we describe the realization of this type of transformation in the androstane series by a four-step route which proceeds in high yield at each step.[6]

The starting material for our work was androstane-3β,14α-diol-17-one 3-monoacetate (I), readily prepared from dehydroisoandrosterone acetate dibromide by chromic acid oxidation, zinc debromination and catalytic hydrogenation.[5,7] The compound I was dehydrated by means of potassium bisulfate in acetic anhydride. The resulting Δ^{14}-androsten-3β-ol-17-one acetate (II),[5,8] m.p. 156°, was obtained in 70% yield when the reaction was carried out in the refluxing anhydride, but only little dehydration occurred under the recommended conditions (95–100° for 15 minutes).[5]

Treatment of the unsaturated acetoxy-ketone II with perbenzoic acid gave 70% of one pure oxide, m.p. 160°, and no other isomer could be isolated. Unlike Δ^{14}-steroids containing a β-orientated side-chain at C-17, which are hydrogenated from the α-side[9], Δ^{14}-androsten-17-ones have been found to

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(1) For Part II, see F. Sondheimer and S. Burstein, *Proc. Chem. Soc.*, 228 (1959).

(2) For a review, see L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, Chapter 20.

(3) P. A. Plattner, L. Ruzicka, H. Heusser, *et al.*, *Helv. Chim. Acta*, **29**, 942 (1946); **30**, 385, 395, 1342 (1947).

(4) S. H. Eppstein, P. D. Meister, D. H. Peterson, H. C. Murray, H. M. Leigh Osborn, A. Weintraub, L. M. Reineke and R. C. Meeks, Abstracts of Papers, 123rd Meeting of the American Chemical Society, Los Angeles, Calif., March, 1953, p. 5C; THIS JOURNAL, **80**, 3382 (1958); J. Fried, R. W. Thoma, D. Perlman, J. E. Herz and A. Borman, *Recent Progr. Hormone Research*, **11**, 157 (1955); E. J. Agnello, B. L. Bloom and G. D. Laubach, THIS JOURNAL, **77**, 4684 (1955); A. Schubert, D. Onken, R. Siebert and K. Heller, *Ber.*, **91**, 2549 (1958).

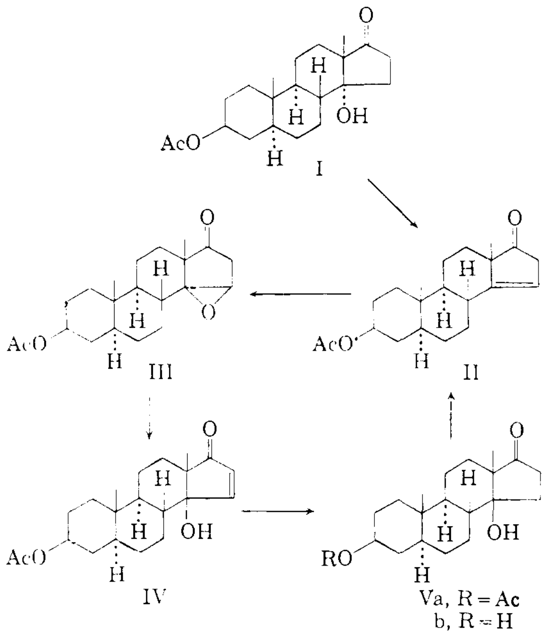
(5) A. F. St. André, H. B. MacPhillamy, J. A. Nelson, A. C. Shabica and C. R. Scholz, THIS JOURNAL, **74**, 5506 (1952). The orientation of the 14-hydroxyl group was not specified definitely by these authors, but was later shown to be alpha by Eppstein *et al.*[4]

(6) For a preliminary communication, see footnote 1.

(7) Although compound I itself has not been obtained microbiologically, Eppstein, *et al.*,[4] have converted testosterone by incubation with *M. griseo-cyanus* to 14α-hydroxytestosterone, which was oxidized to Δ^4-androsten-14α-ol-3,17-dione. The latter could undoubtedly be transformed to I, *e.g.*, through successive chemical reduction of the double bond, preferential reduction of the 3-ketone with sodium borohydride and acetylation.

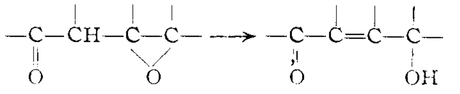
(8) This substance has also been prepared, though only in very low yield, by the dehydrobromination of 16α-bromo-isoandrosterone acetate (R. Pappo, B. M. Bloom and W. S. Johnson, THIS JOURNAL, **78**, 6347 (1956)).

(9) *Inter al.*, F. Schenck, K. Buchholz and O. Wiese, *Ber.*, **69**, 2696 (1936); M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **21**, 828 (1938); F. Hunziker and T. Reichstein, *ibid.*, **28**, 1472 (1945); A. Lardon and T. Reichstein, *Pharm. Acta Helv.*, **27**, 287 (1952).



add hydrogen from the β-side to give 14-isoandrostane derivatives.[5] Attack of peracids on the Δ^{14}-17-one II was therefore expected also to occur from the β-side, to give the 14β,15β-oxide III, and this assignment was subsequently proved to be correct (*vide infra*).

β,γ-Oxido-ketones of type A are known to undergo a facile rearrangement on treatment with alkali to the corresponding γ-hydroxy-α,β-unsaturated ketones B. Thus, steroidal 9α,11α-oxido-7-ketones are rearranged to the 11α-hydroxy-Δ^8-7-ketones,[10] 5β,10β-oxido-3-keto-19-norsteroids yield the 10β-hydroxy-Δ^4-3-ketones[11] and the production of acetophenone from 4,5-oxido-1-acetylcyclohexene by means of sodamide[12] doubtlessly takes place by an analogous mechanism. As expected, treatment of the β,γ-oxido-ketone III with alkali resulted in the same type of rearrangement. The best conditions were found to be sodium carbonate in refluxing aqueous *t*-butyl alcohol[13] which yielded 75% of Δ^{15}-androstene-3β,14β-diol-17-one 3-monoacetate (IV), m.p. 155°, the acetate grouping at C-3 being unaffected. That the rearrangement product is a 14β-hydroxy-Δ^{15}-17-ketone follows from the optical rotatory dispersion curve (which is discussed below) and the appearance of bands at 2.90 (hydroxyl) and 5.85 μ (α,β-unsaturated cyclopentenone) in the infrared. The ultraviolet spectrum (λ_{max} 213 mμ, ε, 13,000), however, was found to be considerably different from that of Δ^{15}-androsten-17-ones unsubstituted at C-14 and the ultraviolet spectra of these systems are discussed further below.



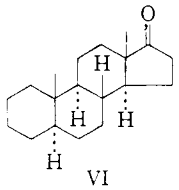
$$-\underset{\underset{O}{\|}}{C}-CH-\underbrace{\overset{|}{C}-\overset{|}{C}}_{O}- \longrightarrow -\underset{\underset{O}{\|}}{C}-\overset{|}{C}=\overset{|}{C}-\underset{\underset{OH}{|}}{\overset{|}{C}}-$$

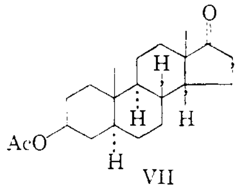
A B

The hydrogenation of the Δ^{15}-double bond of IV in ethyl acetate over a palladium–charcoal catalyst proceeded smoothly and produced over 80% of androstane-3β,14β-diol-17-one 3-monoacetate (Va), m.p. 182°. As expected, the latter substance no longer showed high-intensity absorption in the ultraviolet. In the carbonyl region of the infrared, it showed one band at 5.78 μ (superimposed acetate and cyclopentanone). Saponification led to the free diol Vb, m.p. 187°.

The hydrogenation product Va on treatment with potassium bisulfate in boiling acetic anhydride was found to undergo smooth dehydration to the Δ^{14}-androsten-3β-ol-17-one acetate (II) from which it was derived, and it must therefore be a hydroxy-androstan-3β-ol-17-one acetate. The extra hydroxyl group has to be at the tertiary 14-position, as no reaction occurred on attempted acetylation with acetic anhydride and pyridine. The substance was clearly different from the 14α-hydroxy-compound I and hence it must have the postulated 14β-hydroxy structure Va. It follows that the precursors III and IV also have the 14β-oxygenated structures assigned to them.

The structure assigned to the 14β-hydroxy-17-ketone Va is also borne out by the optical rotatory dispersion (R.D.). data.[16] In Fig. 1 the R.D. curve of this substance is compared with that of the corresponding 14α-hydroxy-17-ketone I and it is apparent that the peak of the C–D *cis*-fused ketone Va appears at shorter wave-length and is less intense than that of the C–D *trans*-fused ketone I. This behavior parallels that of the compounds lacking the 14-hydroxyl group, as is evident from the R.D. curves of androstan-17-one (VI)[17] and of 14-isoandrostan-3β-ol-17-one acetate (VII),[17] also shown in Fig. 1 for comparison.


VI



VII

The difference in the R.D. curves between C–D *cis* and *trans*-fused 17-ones is much more pronounced with the 15-dehydro compounds (Fig. 2). Thus, whereas the curve of Δ^{15}-androsten-3β-ol-17-one (XV) exhibits a single negative Cotton effect, the corresponding 14β-isomer XVI[18] shows a

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(10) *Inter al.*, C. Djerassi, E. Batres, M. Velasco and G. Rosenkranz, THIS JOURNAL, **74**, 1712 (1952).

(11) J. P. Ruelas, J. Iriarte, F. Kincl and C. Djerassi, *J. Org. Chem.*, **23**, 1744 (1958).

(12) E. A. Braude, E. R. H. Jones, F. Sondheimer and J. B. Toogood, *J. Chem. Soc.*, 607 (1949).

(13) *t*-Butyl alcohol rather than a primary alcohol was used as solvent, since it is known that methanol adds to the double bond of Δ^{15}-androsten-17-ones under the influence of base.[14,15]

(14) W. S. Johnson and W. F. Johns, THIS JOURNAL, **79**, 2005 (1957).

(15) J. Fajkos, *Chem. Listy*, **51**, 1894 (1957); *Collection Czechoslov. Chem. Commun.*, **23**, 2154 (1958).

(16) The R.D. curves were determined through the courtesy of Prof. C. Djerassi, Stanford University, Stanford, Calif. For details of this technique, see C. Djerassi "Optical Rotary Dispersion, Applications to Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1960.

(17) C. Djerassi, R. Riniker and B. Riniker, THIS JOURNAL, **78**, 6362 (1956).

(18) The preparation of XV and XVI are described in the sequel.

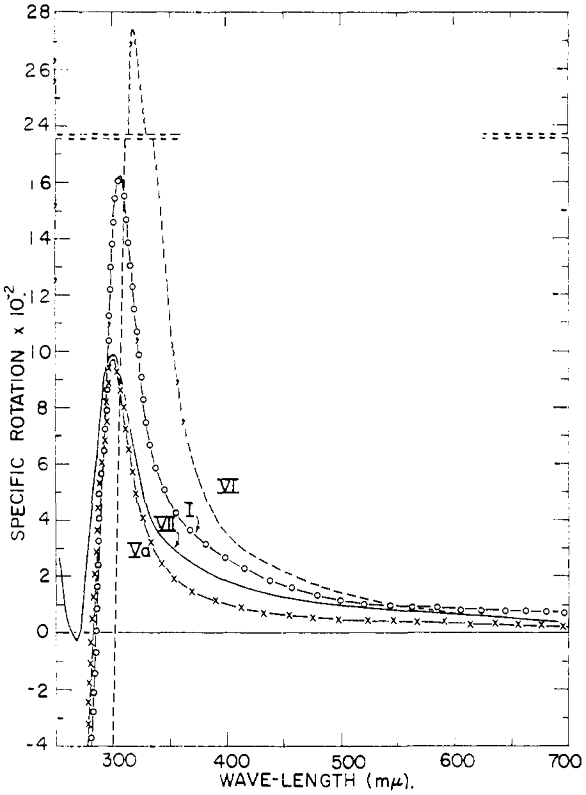


Fig. 1.—Rotatory dispersion curves of androstane-3β,14α-diol-17-one 3-monoacetate (I, in methanol), androstane-3β,14β-diol-17-one 3-monoacetate (Va, in methanol), androstan-17-one (VI, in dioxane) and 14-isoandrostan-3β-ol-17-one acetate (VII, in methanol).

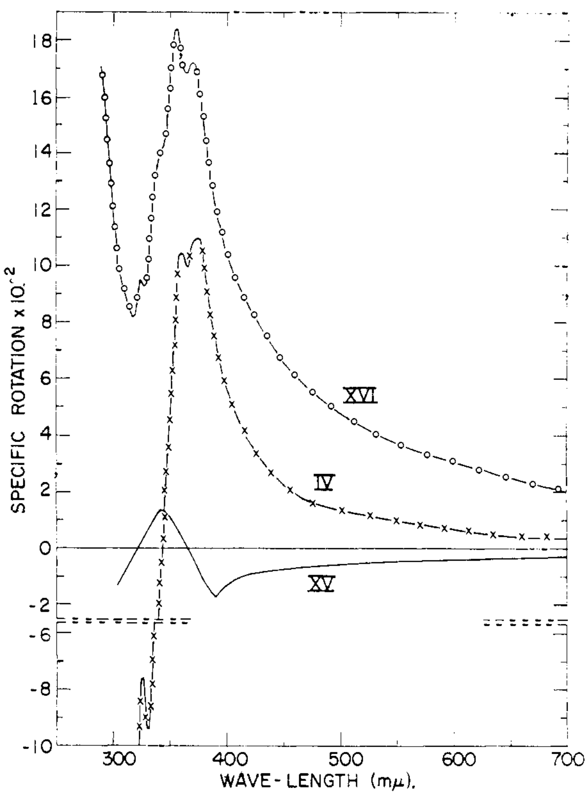
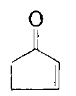
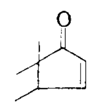


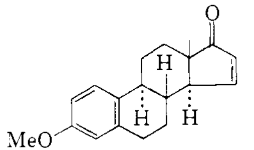
Fig. 2.—Rotatory dispersion curves (in dioxane) of Δ^{15}-androstene-3β,14β-diol-17-one 3-monoacetate (IV), Δ^{15}-androsten-3β-ol-17-one (XV) and Δ^{15}-14-isoandrosten-3β-ol-17-one (XVI).

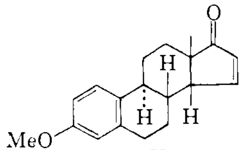
positive multiple Cotton effect curve. The curve of the above described Δ^{15}-androstene-3β,14β-diol-17-one 3-monoacetate (IV) is similar in shape to that of XVI down to *ca.* 320 mμ, also showing a positive multiple Cotton effect, and this behavior strongly favors the assigned structure.

The Ultraviolet Spectra of Δ^{15}-Androsten-17-ones.—As reported above, the 14β-hydroxy-Δ^{15}-17-one IV exhibits an ultraviolet maximum at 213 mμ. The position of this maximum appears to be normal when compared with that of the monocyclic models 2-cyclopenten-1-one (VIII) ($\lambda_{\max}$ 218 mμ)[19] and 4,5,5-trimethyl-2-cyclopenten-1-one (IX) ($\lambda_{\max}$ 221 mμ),[20] bearing in mind that in other γ-hydroxy-α,β-unsaturated ketones (*e.g.*, steroidal 6β-hydroxy-Δ^4-3-ones,[21] 3β-hydroxy-Δ^4-6-ones[21] and 19-nor-10β-hydroxy-Δ^4-3-ones[11]), the γ-hydroxyl group causes a hypsochromic shift of 3–6 mμ. The ultraviolet spectra of the two steroidal Δ^{15}-17-ones X and XI in the estrone methyl ether series are apparently also normal, the high-intensity maxima of the 14α-compound X having been reported to lie at 223 mμ and that of the 14β-compound XI at 221 mμ.[14]


VIII


IX


X


XI

In view of the above, it was surprising that Δ^{15}-androsten-3β-ol-17-one (XV), which was prepared recently by Fajkos,[22] was reported to exhibit $\lambda_{\max}$ 233 mμ, *i.e.*, 12 mμ higher than the monocyclic model IX. Confirmation was provided by an independent synthesis of XV carried out by ourselves. The method employed, summarized in the scheme XII[8,22,23] → XIII → XIV → XV, follows the route used by Johnson and Johns[14] for the preparation of 15-dehydroestrone methyl ether (X). The structure of the Δ^{15}-androsten-3β-ol-17-one (XV) thus obtained in *ca.* 25% over-all yield was confirmed by the infrared band at 5.86 μ (α,β-unsaturated cyclopentenone) and through catalytic hydrogenation to androstan-3β-ol-17-one. The unsaturated

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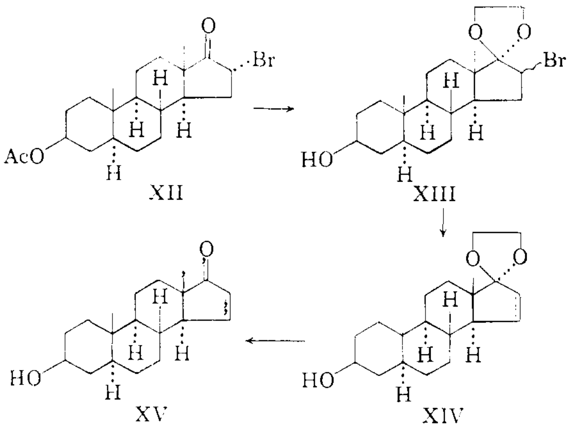
[19] H. J. Dauben, E. A. Youngman and H. Ringold, quoted by W. M. Schubert and W. A. Sweeney, THIS JOURNAL, **77**, 2297 (1955).

[20] R. L. Frank, R. Armstrong, J. Kwiatek and H. A. Price, *ibid.*, **70**, 1379 (1948).

[21] L. Dorfman, *Chem. Revs.*, **53**, 72 (1953), Table 12.

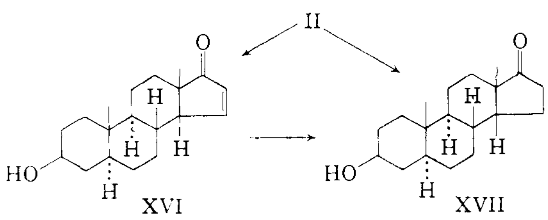
[22] J. Fajkos, *Chem. Listy*, **51**, 1885 (1957); *Collection Czechoslov. Chem. Commun.*, **23**, 1559 (1958).

[23] J. Fajkos, *Chem. Listy*, **48**, 1800 (1954); *Collection Czechoslov. Chem. Commun.*, **20**, 312 (1955).



ketone XV showed physical properties in reasonably good agreement with those reported by Fajkos,[22] including an ultraviolet maximum at 231 mμ.

A possible reason for the unusually high wave length maximum of the Δ^{15}-17-one XV could be the fact that this substance contains a strained *trans*-fused cyclopentenone ring. In that case, the less strained *cis*-fused compound, Δ^{15}-14-isoandrosten-3β-ol-17-one (XVI), should have a more normal spectrum. This 14β-compound, m.p. 137°, was prepared by us in *ca.* 30% yield by the double bond isomerization of the Δ^{14}-17-one II with boiling aqueous sulfuric acid–dioxane, or preferably with potassium hydroxide in refluxing aqueous *t*-butanol.[13] The presence of the Δ^{15}-17-one system in the product was indicated by the appearance of a band at 5.88 μ in the infrared, while the 14β-configuration was confirmed through the non-identity with the 14α-compound XV and through catalytic hydrogenation to 14-isoandrostan-3β-ol-17-one (XVII), identical with that obtained[5] by the hydrogenation of the Δ^{14}-17-one II and subsequent saponification. The 14β-configuration had been expected in view of the finding of Johnson and Johns[14] that 15-dehydroestrone methyl ether (X) with *p*-toluenesulfonic acid in boiling benzene is isomerized *via* the Δ^{14}-isomer to the Δ^{15}-14β-compound XI.



Rather unexpectedly, the 14β-Δ^{15}-17-one XVI thus obtained showed an ultraviolet maximum at 229 mμ. Both the isomers XV and XVI therefore show abnormally high wave length maxima and the anomaly is essentially independent of the C–D ring junction.

We now come to the problem why the two Δ^{15}-17-ones X and XI in the estrone methyl ether series show apparently normal spectra.[14] The most likely explanation appeared to be that the estrone methyl ether chromophore shows strong end absorption in the 220 mμ region besides the medium-intensity maxima at *ca.* 280 mμ, and that the superposition of this absorption onto the absorption of the Δ^{15}-17-one chromophore at *ca.* 230 mμ is responsible for the lowering of the maxima of X and XI. That this is indeed the case is apparent from Figs. 3 and 4. Figure 3 shows the ultraviolet absorption spectrum between 220 and 240 mμ of estrone methyl ether (EME) and of the ring A-saturated Δ^{15}-17-one XV, as well as the summation curve. It can be seen that the latter is very similar to that of an authentic sample of 15-dehydroestrone methyl ether (X) (kindly provided by Prof. W. S. Johnson),[14] the calculated maximum being at 225 mμ (ε 15,200) *versus* the observed value of 224 mμ (ε 14,900). In Fig. 4 the same procedure in the 14β-series has been carried out; it is apparent that the summation curve of estrone methyl ether and the ring A-saturated 14β-Δ^{15}-17-one XVI is similar to that of authentic 15-dehydro-14-isoestrone methyl ether (XI),[14] the calculated maximum being at 223 mμ (ε 16,800) *versus* the observed value of 222 mμ (ε 17,100).[24]

It appears therefore that in general steroidal Δ^{15}-17-ones both in the 14α- and 14β-series absorb at *ca.* 230 mμ, *i.e.*, *ca.* 10 mμ higher than the monocyclic models X and XI. It may be noted that other α,β-unsaturated cyclopentenones which form part of fused systems show similar unexpectedly high wave length maxima, *e.g.*, photo-γ-tropolone methyl ether (cyclopentenone fused to a cyclobutene,[25] a cyclopentenone seco-acid derived from delphinine,[26] etc. Another unusual feature is the fact that introduction of a 14β-hydroxyl group into XVI to give IV causes a decrease in the ultraviolet maximum of 16 mμ and also an intensity increase of *ca.* 50%. Although the exact reasons for these anomalies are not known at present, it is evident that the ultraviolet absorption properties of complex cyclopentenones can vary considerably and that caution must be exercised when the spectra of such compounds are used for obtaining structural information.

Acknowledgments.—This work was supported by a research grant (No. H-2476) of the U. S. National Institutes of Health. We are also indebted to Prof. W. S. Johnson, University of Wisconsin, Madison, for samples of 15-dehydroestrone methyl ether and 15-dehydro-14-isoestrone methyl ether and to Prof. C. Djerassi, Stanford University, Stanford, Calif., for the rotatory dispersion determinations. Dehydroisoandrosterone acetate was kindly provided by Syntex S.A., Mexico City.

Experimental[27]

Androstane-3β,14α-diol-17-one 3-monoacetate (I),[5] R.D. (Fig. 1) in methanol (*c* 0.06): $[\alpha]_{700}$ +73°, $[\alpha]_{589}$ +85°, $[\alpha]_{308}$ +1625°, $[\alpha]_{280}$ −619°.

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[24] To be completely accurate, the summation curve of 14-isoestrone methyl ether and of XVI should have been calculated and compared with XI. However this estrone methyl ether isomer was not available to us and there is no reason to believe its spectrum in the region under discussion to be appreciably different from that of estrone methyl ether.

[25] O. L. Chapman and D. J. Pasto, THIS JOURNAL, **80**, 6685 (1958).

[26] K. Wiesner, F. Bickelhaupt and Z. Valenta, *Tetrahedron*, **4**, 418 (1958); K. Wiesner, F. Bickelhaupt and D. R. Babin, *Experientia*, **15**, 93 (1959).

[27] Melting points are uncorrected. All chromatograms were carried out with Merck "acid-washed" alumina. Rotations were

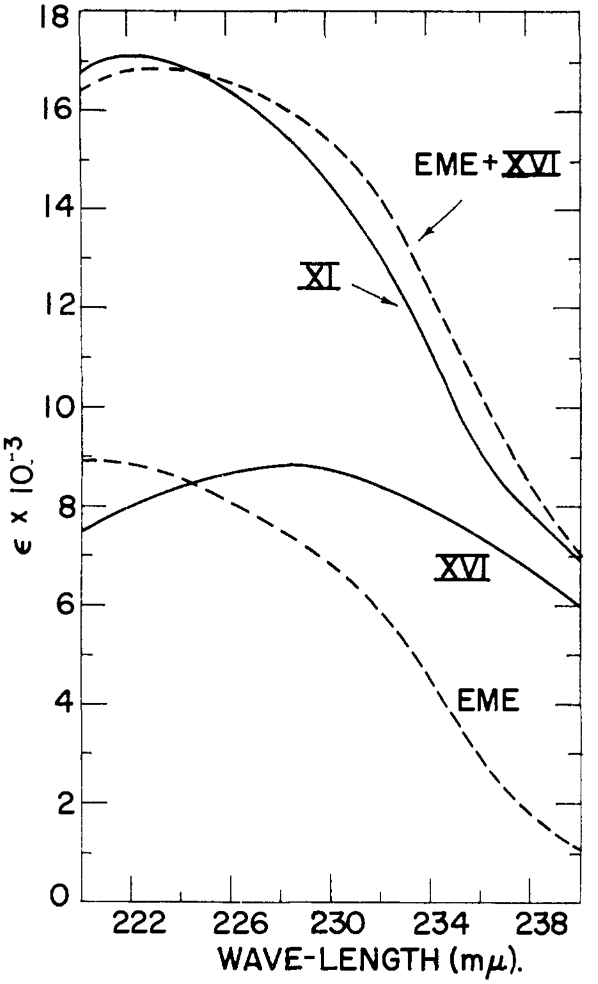

Fig. 3.—Ultraviolet absorption curves between 220 and 240 mμ (in 95% ethanol) of estrone methyl ether (EME), Δ^{15}-androsten-3β-ol-17-one (XV), the summation curve (EME + XV) and 15-dehydroestrone methyl ether (X).

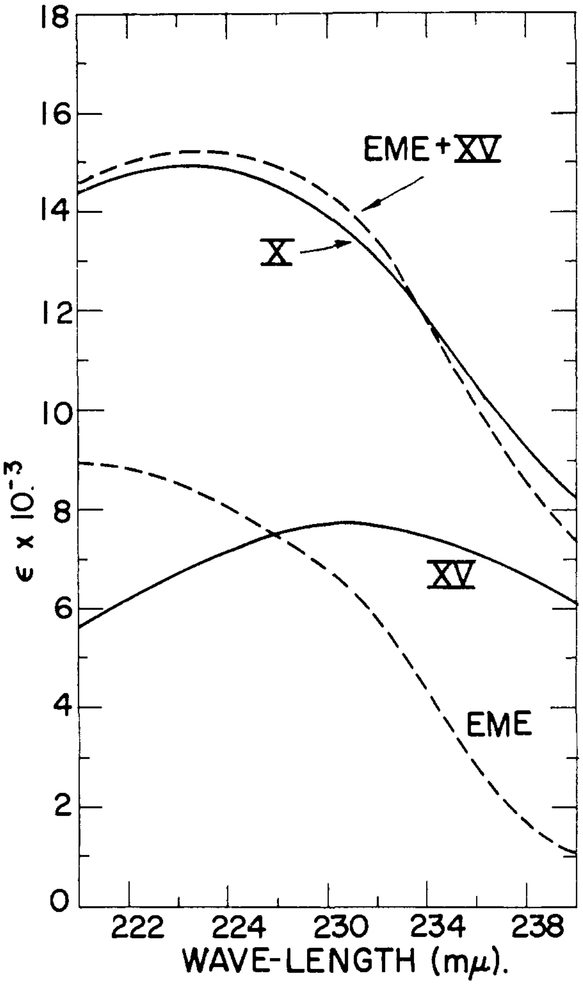

Fig. 4.—Ultraviolet absorption curves between 220 and 240 mμ (in 95% ethanol) of estrone methyl ether (EME), Δ^{15}-14-isoandrosten-3β-ol-17-one (XVI), the summation curve (EME + XVI) and 15-dehydro-14-isoestrone methyl ether (XI).

Δ^{14}-Androsten-3β-ol-17-one Acetate (II).—Potassium hydrogen sulfate (400 mg., freshly fused) was added to a solution of 770 mg. of androstane-3β,14α-diol-17-one 3-monoacetate (I) (m.p. 192–196°)[5] in 5 cc. of acetic anhydride and the mixture was boiled under reflux for 1 hr. with exclusion of moisture. The solution was cooled, diluted with ether and washed well with sodium bicarbonate solution. The organic layer was then washed with water, dried and evaporated. Crystallization of the residue from aqueous methanol gave the Δ^{14}-compound II (520 mg., 71%), m.p. 154–156°, $[\alpha]_D$ +112°; infrared band at 5.78 μ (superimposed acetate and cyclopentanone); no high-intensity absorption in the ultraviolet (reported: m.p. 150–152°,[8] 158–159°,[5] $[\alpha]_D$ +116°[5]).

Only little dehydration occurred when the reaction was carried out at 95–100° for 15 minutes.[5]

14β,15β-Oxido-androstan-3β-ol-17-one Acetate (III).—The Δ^{14}-17-one II (400 mg.) was dissolved in 15 cc. of dry chloroform and treated with 2 equivalents of perbenzoic acid in benzene. After being allowed to stand in the dark at room temperature for 48 hr., the solvent was evaporated. The residue was chromatographed on 10 g. of alumina and the fractions eluted with benzene were crystallized from aqueous methanol. The resulting oxide III weighed 290 mg. (69%) and showed m.p. 159–160°, $[\alpha]_D$ +105°; infrared band at 5.78 μ (superimposed acetate and cyclopentanone); no high-intensity absorption in the ultraviolet.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 73.07; H, 8.97.

Δ^{15}-Androstene-3β,14β-diol-17-one 3-Monoacetate (IV).—A 20% aqueous sodium carbonate solution (15 cc.) was added to a solution of 183 mg. of the oxide III in 4 cc. of *t*-butyl alcohol and the mixture was boiled under reflux in nitrogen for 1 hr. Water and ether were added to the cooled mixture and the organic layer was washed with water, dried and evaporated. Crystallization of the residue from acetone–hexane gave 135 mg. (74%) of the unsaturated ketone IV, m.p. 153–155°; infrared bands (KBr disk) at 2.90 (hydroxyl), 5.78 (acetate) and 5.85 μ (α,β-unsaturated cyclopentenone); λ_{max} 213 mμ (ε, 13,000); R.D. (Fig. 2) in dioxane (*c* 0.07): $[\alpha]_{700}$ +37°, $[\alpha]_{589}$ +69°, $[\alpha]_{375}$ +1100°, $[\alpha]_{365}$ +1000°, $[\alpha]_{358}$ +1041°, $[\alpha]_{330}$ −948°, $[\alpha]_{325}$ −756°, $[\alpha]_{300}$ −1545°.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.38; H, 8.77.

Androstane-3β,14β-diol-17-one 3-Monoacetate (Va).—A solution of 106 mg. of the unsaturated ketone IV in 10 cc. of ethyl acetate was shaken in hydrogen over 100 mg. of a 5% pre-reduced palladium–charcoal catalyst at room temperature and atmospheric pressure. After 10 minutes, 1.02 molar equivalents of hydrogen had been absorbed and

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determined at room temperature in chloroform. Ultraviolet spectra were measured in 95% ethanol solution on a Unicam model S.P. 500 spectrophotometer. Infrared spectra were determined in chloroform solution (unless stated otherwise) on a Baird double-beam recording spectrophotometer with sodium chloride optics. Analyses were carried out in our microanalytical laboratory under the direction of Mr. Erich Meier.

uptake stopped. The catalyst was removed and the solvent was evaporated. Crystallization of the residue from acetone–hexane gave 87 mg. (82%) of androstane-3β,14α-diol-17-one 3-monoacetate (Va), m.p. 181–182°; infrared bands at 2.88 (hydroxyl) and 5.78 μ (superimposed acetate and cyclopentanone); no high-intensity absorption in the ultraviolet; R.D. (Fig. 1) in methanol (*c* 0.06): $[\alpha]_{700}$ +21°, $[\alpha]_{589}$ +35°, $[\alpha]_{300}$ +980°, $[\alpha]_{280}$ −421°. The m.p. was depressed by *ca.* 20° on admixture with the corresponding 14α-hydroxy compound I (m.p. 192–196°).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.80; H, 9.50.

Androstane-3β,14β-diol-17-one (Vb).—The monoacetate Va was saponified by being boiled under reflux for 1 hr. with aqueous methanolic potassium hydroxide. Isolation with ether and crystallization from acetone-hexane gave the diol Vb, m.p. 186–187°, [α]D +41°; infrared bands at 2.88 (hydroxyl) and 5.76 μ (cyclopentanone).

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.30; H, 9.81.

Re-acetylation with acetic anhydride–pyridine (overnight at room temperature) regenerated the 3-monoacetate Va, m.p. 179–181°, undepressed on admixture with the previously described material.

Dehydration of Androstane-3β,14β-diol-17-one 3-Monoacetate (Va) to Δ^{14}-Androsten-3β-ol-17-one Acetate (II).—The dehydration of the 14β-hydroxy compound Va with potassium hydrogen sulfate in boiling acetic anhydride was carried out exactly as described above for the corresponding 14α-hydroxy compound I. Chromatography of the product on alumina, followed by crystallization of the fractions eluted with benzene from aqueous methanol, yielded the Δ^{14}-compound II, m.p. 153–155°. No depression in m.p. was observed on admixture with the previously described sample and the infrared spectra were identical in every respect.

16α-Bromoandrostan-3β-ol-17-one Acetate (XII).—This substance[8,22,23] was prepared in over 80% yield by the bromination of the enol acetate of epiandrosterone acetate, as described by Pappo, *et al.*[8] It showed m.p. 172–173°, [α]D +36°; reported[23] m.p. 173–174°, [α]D +38.5°. When the solvent was removed at room temperature (instead of at 10°),[8] a mixture of the 16α- together with the 16β-bromo compound was formed. The latter showed m.p. 148–149°, [α]D +89°; reported[23] m.p. 146–147°, [α]D +92°.

16-Bromo-17-ethylenedioxyandrostan-3β-ol (XIII).—A solution of 2.4 g. of the 16α-bromo-ketone XII, 0.42 g. of *p*-toluenesulfonic acid monohydrate and 21 cc. of ethylene glycol in 110 cc. of toluene was distilled very slowly (high reflux ratio) through a Vigreux column for *ca.* 50 hr. The solution was cooled, washed with a saturated sodium bicarbonate solution and well with water. It was then dried and evaporated. Crystallization from acetone-petroleum ether and then from methanol gave 1.47 g. (61%) of the bromo-ketal XIII, m.p. 188–191°, the acetate group at C-3 having been lost presumably by ester interchange. Further crystallization from methanol gave the analytical sample, m.p. 194–196°, [α]D −37°, hydroxyl band but no carbonyl bands in the 5.7–6.0 μ region of the infrared.

Anal. Calcd. for $C_{21}H_{33}O_3Br$: C, 61.02; H, 7.99. Found: C, 60.88; H, 8.02.

Δ^{15}-Androsten-3β-ol-17-one (XV).—A solution of 0.80 g. of potassium in 40 cc. of dry *t*-butyl alcohol was distilled to dryness under reduced pressure. Xylene (40 cc.) was added, removed by distillation under reduced pressure and this procedure was repeated twice more. A solution of 1.12 g. of the bromo-ketal XIII in 40 cc. of xylene was then added and the mixture was heated under reflux in nitrogen for 18 hr. The mixture was cooled, and water and ether were added. The organic layer was then washed with water, dried and evaporated. The residual oily crude 17-ethylenedioxy-Δ^{15}-androsten-3β-ol (XIV) (0.82 g.) could not be induced to crystallize and was employed in the next step. It gave a negative Beilstein test for halogen.

This material was dissolved in 60 cc. of acetone, 40 mg. of *p*-toluenesulfonic acid monohydrate and 10 cc. of water were added and the solution was allowed to stand at room temperature for 2 hr. Ether was then added and the solution was washed with sodium bicarbonate solution, dried and evaporated. The residual oil, which showed λ_{max} 232 mμ (ε 4,900), was dissolved in a little benzene and chromatographed on 30 g. of alumina.

Elution with benzene-ether (10:1) gave a solid material which after crystallization from acetone–petroleum ether weighed 85 mg. and showed m.p. 170–172°. It was identified as androstan-3β-ol-17-one by direct comparison (mixture m.p., infrared spectrum) with an authentic sample (m.p. 173–174°).

Further elution with benzene-ether (10:1) yielded a mixture, which on crystallization from acetone–petroleum ether melted over a wide range (m.p. 75-120°). It showed infrared bands at 5.75 μ (saturated 17-one) as well as at 5.86 μ (Δ^{15}-17-one).

Finally benzene-ether (10:1) eluted material which on crystallization from acetone-petroleum ether gave the required Δ^{15}-androsten-3β-ol-17-one (XV) (0.28 g., 36% from XIII), m.p. 150–155°, λ_{max} 231 mμ (ε 6900). Further crystallization gave a pure specimen, m.p. 162–163°, [α]D −66°, infrared band at 5.86 μ (α,β-unsaturated cyclopentenone); λ_{max} 231 mμ (ε 7,600) (Fig. 3); R.D. (Fig. 2) in dioxane (*c* 0.16): $[\alpha]_{700}$ −29°, $[\alpha]_{589}$ −44°, $[\alpha]_{390}$ −175°, $[\alpha]_{342}$ +136°, $[\alpha]_{316}$ −112° (reported[22] m.p. 163–164°, [α]D −65°, λ_{max} 233 mμ (ε 6,900).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.94; H, 9.72.

Hydrogenation of Δ^{15}-Androsten-3β-ol-17-one (XV) to Androstan-3β-ol-17-one.—A solution of the unsaturated ketone XV (6.01 mg.) in 3 cc. of ethanol was hydrogenated in a micro-hydrogenating apparatus over a pre-reduced platinum catalyst. After 5 minutes, 1.03 molar equivalents of hydrogen had been absorbed and uptake stopped. The catalyst was removed, the solvent was evaporated and the residue was crystallized from methanol. The resulting androstan-3β-ol-17-one, m.p. 174–175°, was found to be identical with an authentic sample (m.p. 173–174°), as evidenced by the non-depression of the m.p. on admixture and the identity of the infrared spectra.

Δ^{15}-14-Isoandrosten-3β-ol-17-one (XVI).—A 2 *N* potassium hydroxide solution (25 cc.) was added to a solution of 200 mg. of Δ^{14}-androsten-3β-ol-17-one acetate (II) in 25 cc. of *t*-butyl alcohol and the mixture was boiled under reflux in nitrogen for 1 hr. The mixture was diluted with water and extracted with ether. The resulting material [λ_{max} 228 mμ (ε 2,800)] was then chromatographed on 15 g. of alumina and the fractions eluted with benzene–ether (1:1) were crystallized from acetone–petroleum ether. The resulting Δ^{15}-17-ketone XVI weighed 55 mg. (32%) and showed m.p. 132–135°. Further crystallization led to the analytical specimen, m.p. 135–137°; infrared band at 5.88 μ (α,β-unsaturated cyclopentenone); λ_{max} 229 mμ (ε 8,700) (Fig. 4); R.D. (Fig. 2) in dioxane (*c* 0.11): $[\alpha]_{700}$ +199°, $[\alpha]_{589}$ +308°, $[\alpha]_{372}$ +1720°, $[\alpha]_{366}$ +1680°, $[\alpha]_{356}$ +1840°, $[\alpha]_{342}$ +1410° (infl.), $[\alpha]_{328}$ +930°, $[\alpha]_{324}$ +946°, $[\alpha]_{318}$ +825°, $[\alpha]_{290}$ +1710°. A considerable m.p. depression was observed on admixture with the corresponding 14α-compound XV (m.p. 162-163).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.88; H, 9.64.

The double bond isomerization of the Δ^{14}-17-ketone II could also be effected with acids. When a solution containing 10 mg. of II in 2 cc. of dioxane and 2 cc. of 2*N* aqueous sulfuric acid was boiled under reflux in nitrogen for 1 hr., the product after isolation with ether showed λ_{max} 229 mμ (ε 2,300).

Hydrogenation of Δ^{15}-14-Isoandrosten-3β-ol-17-one (XVI) to 14-Isoandrostan-3β-ol-17-one (XVII).—A solution of the unsaturated ketone XVI (10.3 mg.) in 3 cc. of ethanol was shaken in hydrogen over a pre-reduced platinum catalyst. After 15 minutes, 1.06 molar equivalents of hydrogen had been absorbed and uptake stopped. Crystallization of the product from aqueous methanol yielded 14-isoandrostan-3β-ol-17-one, m.p. 158–161°, no high-intensity absorption in the ultraviolet. There was no depression in m.p. on admixture with an authentic sample of XVII (m.p. 160–162°),[5] prepared by hydrogenation of Δ^{14}-androsten-3β-ol-17-one acetate (II) and subsequent saponification; the infrared spectra were also identical. A m.p. depression of over 20° was observed on admixture with a sample of androstan-3β-ol-17-one (m.p. 172–174°).

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