[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. LVII.[1] Cycloethylene Ketals of Androstane-3,6,17-trione. Synthesis of Androstan-3-one-6β,17β-diol

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Androstane-3,6,17-trione (I), readily prepared from dehydroepiandrosterone, can be converted to the 3-monoketal II, the 3,6-diketal III or the 3,16,17-triketal IV depending upon the reaction conditions employed. Sodium borohydride reduction of the diketal III and subsequent acid hydrolysis furnished androstane-3,6-dione-17β-ol (VI). A similar reaction sequence carried out with the monoketal II led to androstan-3-one-6β,17β-diol (Xa), which on Wolff–Kishner reduction followed by chromic acid oxidation afforded androstane-6,17-dione (XII).

In connection with an extended program of biological testing of various steroids we required the hitherto unknown androstan-3-one-6β,17β-diol (Xa), the 6β-hydroxy analog of the anabolic agent androstan-3-one-17β-ol ("Dihydrotestosterone" or "Neodrol") used in the treatment of breast cancer.[2] This diol-one cannot be prepared by catalytic hydrogenation of 6β-hydroxytestosterone (VII), the corresponding Δ^4-derivative recently synthesized in these laboratories,[3] since hydrogenation of 6β-hydroxy-Δ^4-3-ketones has been shown to lead to compounds of the 5β ("normal") configuration.[4] Chemical reduction of 6β-hydroxytestosterone (VII) with lithium in liquid ammonia is also inapplicable as the reaction results in the reductive removal of the 6β-hydroxy grouping.[3a] This paper records the synthesis of androstan-3-one-6β,17β-diol (Xa) by a route which employs dehydroepiandrosterone (Δ^5-androsten-3β-ol-17-one) as starting material.

The oxidation of dehydroepiandrosterone with chromic acid to Δ^4-androstene-3,6,17-trione[5] and zinc reduction of the latter to androstane-3,6,17-trione (I)[6] have been recorded previously. The next step involves formation of the 3-cycloethylene ketal II. The usual method for ketal formation (heating with ethylene glycol and benzene containing *p*-toluenesulfonic acid) was expected to lead to poly-ketalization, and for this reason the more specific *p*-toluenesulfonic acid-catalyzed interchange reaction with 2-methyl-2-ethyl-1,3-dioxolane[7] was investigated. Under the usual conditions (boiling for several hours),[7] the 3,6,17-triketal IV was the major product, while the 3,6-diketal III was mainly formed when the time was reduced to 30 minutes. Only by allowing the reaction to proceed for *ca.* 5 minutes and then immediately cooling the solution could a satisfactory yield (66%) of the 3-monoketal II be obtained.

The structure of the triketal IV was based on the elemental analysis and the absence of carbonyl absorption in the infrared. The diketal showed a band at 1736 cm.$^{-1}$ but not at 1700 cm.$^{-1}$, indicating the presence of a ketone in a five-membered but not in a six-membered ring. Only structure III meets this requirement, and confirmation for this assignment was obtained through sodium borohydride reduction and subsequent acid hydrolysis. The resulting androstane-3,6-dione-17β-ol (VI) proved to be identical with that obtained by base rearrangement of 6β-hydroxytestosterone (VII),[3] and by acid treatment of 6-bromotestosterone acetate (VIII).[8] The monoketal showed infrared bands at 1736 and 1700 cm.$^{-1}$, and could therefore be either the 3-monoketal II or the 6-monoketal. Its eventual transformation to androstane-6,17-dione (XII) (*vide infra*) confirms structure II, which is the one expected from the relative reactivities of the carbonyl functions in androstane-3,6,17-trione (I) as based on inspection of models.

Reduction of the monoketal II with sodium borohydride and cleavage of the resulting dihydroxyketal IX with *p*-toluenesulfonic acid in acetone furnished the required androstan-3-one-6β,17β-diol (Xa), further characterized as the diacetate Xb, in 56% yield. The hydroxyl group at C-6 is assigned the β-configuration on the following grounds: (a) A similar reduction of a 3,6-diketone (of the 22a-spirostane series) with sodium borohydride,[9] as well as reductions of a 6-ketone,[10] Δ^2-6-ketone,[11] 3β-hydroxy-6-ketone,[12] 3α-hydroxy-6-ketone,[12] 3α-chloro-6-ketone,[12] 3α-bromo-6-ketone[12] and 3,6-diketone[11] (of the cholestane series) with lithium aluminum hydride all led predominantly to the 6β-hydroxy isomers.[13] (b) The M_D contribution of the hydroxy grouping at C-6 was found to be −65.[14] This negative value is in line with that

(1) Paper LVI, F. Sondheimer, O. Mancera and G. Rosenkranz, THIS JOURNAL, **76**, 5020 (1954).

(2) *Cf.* G. C. Escher, J. M. Heber, H. Q. Woodward, J. H. Farrow and F. E. Adair, New York, N. Y., Symposium on Steroids in Experimental and Clinical Practice, The Blakiston Co., 1951; G. C. Escher, J. H. Farrow, D. W. Sved, G. Robbins, H. Q. Woodward and N. E. Treves, paper presented at the American Federation for Clinical Research, Southern Section, New Orleans, La. (Jan., 1953) (in press).

(3) (a) C. Amendolla, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.*, 1226 (1954); (b) J. Romo, G. Rosenkranz, C. Djerassi and F. Sondheimer, *J. Org. Chem.*, in press.

(4) J. S. Moffatt, *J. Chem. Soc.*, 812 (1947).

(5) A. Butenandt and B. Riegel, *Ber.*, **69**, 1163 (1936).

(6) M. I. Ushakov and A. I. Lyutenberg, *J. Gen. Chem.* (*U.S.S.R.*), **9**, 69 (1939).

(7) H. J. Dauben, B. Löken and H. J. Ringold, THIS JOURNAL, **76**, 1359 (1954).

(8) F. Sondheimer, S. Kaufmann, J. Romo, H. Martinez and G. Rosenkranz, *ibid.*, **75**, 4712 (1953).

(9) J. Romo, G. Rosenkranz and F. Sondheimer, *ibid.*, **76**, 5169 (1954). See also C. W. Shoppee and R. J. Stephenson, *Chem. and Ind.*, 311 (1954).

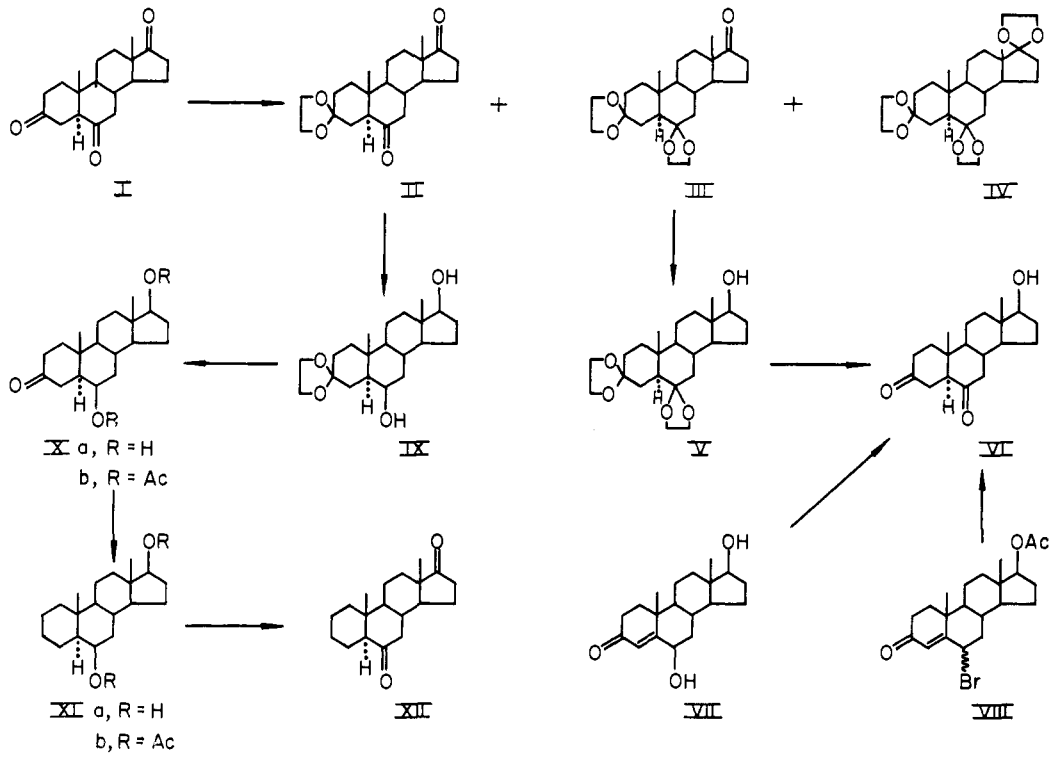
(10) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 3361 (1952).

(11) *Idem.*, *ibid.*, 3374 (1952).

(12) *Idem*, *ibid.*, 1790 (1952).

(13) For the similarity of the steric course of reductions with lithium aluminum hydride and sodium borohydride, *cf.* W. G. Dauben, R. A. Micheli and J. F. Eastham, THIS JOURNAL, **74**, 3852 (1952). The fact that the lithium aluminum hydride reduction of a 3,5-cyclo-6-ketone gave mainly the 6α-ol (reference 10) is doubtlessly due to the special steric factors operative in the *i*-steroid.

(14) Androstan-3-one-17β-ol, the C-6 desoxy derivative, showed $[\alpha]_D$ +32°, M_D +93 (determined in these laboratories).



(−36) reported[15] for a 6β-hydroxy function, but is opposed to the positive contribution (+61) reported[15] for a 6α-hydroxy function.

Reduction of Xa by the Wolff–Kishner–Minlon method[16] furnished androstane-6β,17β-diol (XIa), which on chromic acid oxidation was converted to androstane-6,17-dione (XII). The latter exhibited properties in good agreement with those of the known substance,[17] and was shown to differ from androstane-3,17-dione which would have resulted had the original monoketal been the C-6 rather than the C-3 compound.

Experimental[18]

3-Ethylenedioxyandrostane-6,17-dione (II).—A mixture of 25.0 g. of androstane-3,6,17-trione (I)[5,6] and 1.0 g. of *p*-toluenesulfonic acid in 300 cc. of 2-methyl-2-ethyl-1,3-dioxolane (previously freed of ethylene glycol by distillation over lithium aluminum hydride) was refluxed (at 570 mm.) for 5 minutes, and then immediately cooled in ice. The monoketal II (12.3 g., m.p. 216–220°) which had precipitated was collected, and the filtrate was diluted with benzene, washed with sodium bicarbonate and water, dried and evaporated. Chromatographic purification on 650 g. of neutral alumina furnished another 2.25 g. of the monoketal II with m.p. 213–216° from the fractions eluted with benzene–ether (4:1), whereas the earlier fractions eluted with hexane–benzene (1:4) and benzene afforded 2.1 g. of the diketal III with m.p. 193–196° (*vide infra*). The total oily fractions were recovered from the chromatogram, diluted with 20 cc. of acetone, and allowed to stand overnight with 0.5 g. of *p*-toluenesulfonic acid at room temperature. This procedure caused the precipitation of another 4.4 g. of the monoketal II with m.p. 214–216° (total yield 18.95 g., 66%).[19] Crystallization from acetone led to the analytical specimen with m.p. 219–221°, $[\alpha]_D$ +55°, $\nu_{max}^{CHCl_3}$ 1736 and 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.51; H, 8.89.

3,6-Diethylenedioxyandrostan-17-one (III).—The ketal formation was performed by distilling slowly 8.00 g. of the trione I with 0.32 g. of *p*-toluenesulfonic acid in 100 cc. of 2-methyl-2-ethyl-1,3-dioxolane (distilled over lithium aluminum hydride) for 30 minutes. Isolation with benzene followed by chromatography on 400 g. of neutral alumina furnished 1.45 g. (13%) of the triketal IV (m.p. 141–143°; *vide infra*) from the fractions eluted with hexane–benzene (3:2 and 2:3), 3.12 g. (30%) of the diketal III (m.p. 192–196°) with hexane–benzene (1:4) and benzene, and 0.62 g. (7%) of the monoketal II (m.p. 212–216°) with benzene–ether (4:1). Crystallization of the diketal III from acetone afforded the analytical sample with m.p. 197–199°, $[\alpha]_D$ +58°, $\nu_{max}^{CHCl_3}$ 1736 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.74; H, 9.04.

3,6,17-Triethylenedioxyandrostane (IV).—A solution of 500 mg. of the trione I in 8 cc. of 2-methyl-2-ethyl-1,3-dioxolane (redistilled through a small Vigreux column, and probably containing traces of ethylene glycol) was distilled slowly with 20 mg. of *p*-toluenesulfonic acid for 5 hours (*ca.* 3 cc. of distillate collected). Isolation with benzene and crystallization from ether–pentane yielded 310 mg. (43%) of the triketal IV with m.p. 142–145°. Further crystallization from acetone–hexane led to a sample with m.p. 149–151°, $[\alpha]_D$ −14°, no infrared absorption in the carbonyl region.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.10; H, 8.88.

Androstane-3,6-dione-17β-ol (VI).—A solution of 500 mg. of the diketal III in 20 cc. of ethanol containing 2 cc. of

(15) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, p. 216, no. 29.

(16) Huang Minlon, THIS JOURNAL, **71**, 3301 (1949).

(17) A. Butenandt and L. A. Suranyi, *Ber.*, **75**, 591 (1942).

(18) Melting points are uncorrected. Unless noted otherwise rotations were determined (at 20°) in chloroform solution. We would like to thank Mrs. P. Lopez for these measurements as well as for the infrared spectra which were determined on a Perkin–Elmer model 12C single beam spectrophotometer with sodium chloride prism. Thanks are due to Mrs. A. Gonzalez for the microanalyses.

(19) The *p*-toluenesulfonic acid–acetone treatment was first performed in order to recover androstane-3,6,17-trione. The reproducible obtention of the 3-monoketal by direct precipitation was unexpected, and the explanation is at present obscure.

water was allowed to stand overnight at room temperature with 500 mg. of sodium borohydride. The excess reagent was then decomposed by the dropwise addition of acetic acid until effervescence ceased. Evaporation to small volume and addition of water yielded the crude hydroxy-diketal V ($\nu_{max}^{CHCl_3}$ free hydroxyl band only), which without purification was cleaved by being allowed to stand with 50 mg. of *p*-toluenesulfonic acid in 12 cc. of acetone overnight at room temperature. Addition of water furnished 220 mg. of the diketo-alcohol VI with m.p. 225–228°. The analytical sample was crystallized from chloroform–hexane and showed m.p. 234–236°, $[\alpha]D$ −8° (the value of +9° reported previously[8] should read −9°), $\nu_{max}^{CHCl_3}$ 1700 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.71; H, 9.44.

Identity with specimens of VI obtained by base treatment[8] of 6β-hydroxytestosterone (VII) and by acid treatment[8] of 6-bromotestosterone acetate (VIII) was established through mixture m.p. determination and infrared comparison.

Androstan-3-one-6β,17β-diol (Xa).—The monoketal II (15.0 g.) dissolved in 650 cc. of ethanol containing 50 cc. of water was reduced overnight at room temperature with 15.0 g. of sodium borohydride. Decomposition of excess reagent with acetic acid, followed by evaporation to small volume and addition of water afforded 14.7 g. of the crude dihydroxy ketal IX (ν_{max}^{mull} free hydroxyl band only). This material was dissolved in 200 cc. of acetone and allowed to stand overnight with 1.4 g. of *p*-toluenesulfonic acid. Addition of water followed by several crystallizations of the resulting precipitate from methanol afforded 7.4 g. (56%) of androstan-3-one-6β,17β-diol (Xa) with m.p. 242–244°, $[\alpha]D$ +9°, MD +28, ν_{max}^{mull} 1700 cm.$^{-1}$ and free hydroxyl band.[20]

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.82; H, 9.80.

(20) The fact that this 6β,17β-diol-3-one required several crystallizations until it was obtained pure, and was then obtained in only 56% yield, strongly suggests that some of the 6α,17β-diol-3-one also was formed. However, no attempt at isolation of the latter product was made.

The 6,17-diacetate Xb was prepared in the usual way (pyridine–acetic anhydride, steam-bath, 1 hour) and after crystallization from ether exhibited m.p. 129–130°, $\nu_{max}^{CHCl_3}$ 1718 and 1700 cm.$^{-1}$, no free hydroxyl band.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 71.15; H, 8.66.

Androstane-6β,17β-diol (XIa).—A solution of 1.25 g. of androstan-3-one-6β,17β-diol (Xa) was refluxed with 20 cc. of ethylene glycol and 3 cc. of 85% hydrazine hydrate for 1 hour, cooled and treated with 2.75 g. of potassium hydroxide and 2 cc. of water. The open flask was heated until the inside temperature reached 190°, a reflux condenser was attached and the solution was refluxed a further 4 hours. Cooling and addition of water yielded 1.15 g. (96%) of the diol XIa with m.p. 201–206°. The analytical sample was crystallized from chloroform–ether and showed m.p. 207–209°, $[\alpha]D$ +7°, ν_{max}^{mull} free hydroxyl band only.

Anal. Calcd. for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 78.32; H, 11.29.

The 6,17-diacetate XIb was crystallized from acetone–methanol and exhibited m.p. 93–94°, ν_{max}^{mull} 1718 cm.$^{-1}$, no free hydroxyl band.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.61; H, 9.83.

Androstane-6,17-dione (XII).—Androstane-6β,17β-diol (0.20 g.) dissolved in 10 cc. of acetic acid was oxidized with 0.10 g. of chromic acid for two hours at room temperature. Addition of water, extraction with ether and crystallization of the product from acetone–methanol afforded 0.11 g. of androstane-6,17-dione (XII) with m.p. 132–133°, $[\alpha]D$ +94°, $\nu_{max}^{CHCl_3}$ 1736 and 1700 cm.$^{-1}$ (reported m.p. 134–135°[17]). The compound was different from androstane-3,17-dione (m.p. 131–132°) as evidenced by a strong depression in m.p. on mixture, and differences in the infrared spectrum.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 78.93; H, 9.76.

SYNTEX S. A.
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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE CHEMICAL DIVISION OF MERCK & CO., INC.]

Approaches to the Total Synthesis of Adrenal Steroids. X. A New Method for the Attachment of Ring D. Part D

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A synthesis of racemic 11-ketoprogesterone from 2β,4b-dimethyl-1β-carbomethoxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4α-ol (Ib) is described. Reduction of Ib with lithium aluminum hydride followed by selective tosylation of the primary hydroxyl and oxidation of the secondary hydroxyl group provides the keto tosylate IIIa. Oxidation of the methallyl side chain to the acetonyl derivative Va and closure of the five-membered ring yields predominantly the 17-isopregnene VIIa. Equilibration of the latter gives the normal isomer VIIIa which may be hydrolyzed to *dl*-11-ketoprogesterone (IX). The same method is applied to the synthesis of derivatives in the *dl*-11α- and 11β-hydroxyprogesterone series.

The substituted dodecahydrophenanthrenes of structure I[1] require only the establishment of a carbon–carbon bond between the potential C_{16}- and C_{17}-positions for completion of the steroid nucleus. It has been found that this ring closure can be accomplished at any of three oxidation levels of the two-carbon side chain. The present communication describes ring closures with the C_1 side chain at the lowest of the three oxidation levels.[2]

Reduction of 2β,4b-dimethyl-1β-carboxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,-10,10aβ-dodecahydrophenanthrene-4α-ol (Ia) or the corresponding methyl ester Ib with lithium aluminum hydride produced the dihydroxy derivative IIa in good yield. This compound, on treatment with a slight excess of *p*-toluenesulfonyl chloride in pyridine, was esterified selectively at the primary hydroxyl group affording the crystalline monotosylate IIIc in excellent yield. Attempts to prepare a ditosylate using excess reagent led only to non-crystalline material. Oxidation of IIIc with the chromium trioxide–pyridine complex[3] afforded the corresponding 4-keto tosylate (IIIa).

The keto tosylate IIIa reacted readily with one equivalent of osmium tetroxide to form an osmate

(1) G. E. Arth, G. I. Poos, R. M. Lukes, F. M. Robinson, W. F. Johns, M. Feurer and L. H. Sarett, THIS JOURNAL, **76**, 1715 (1954).

(2) The two other methods will be published as Parts XII and XIII of this series.

(3) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).