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°[11]). 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.
APARTADO 2679
MEXICO, D. F.

[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

BY W. F. JOHNS, R. M. LUKES AND L. H. SARETT

RECEIVED MAY 14, 1954

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]

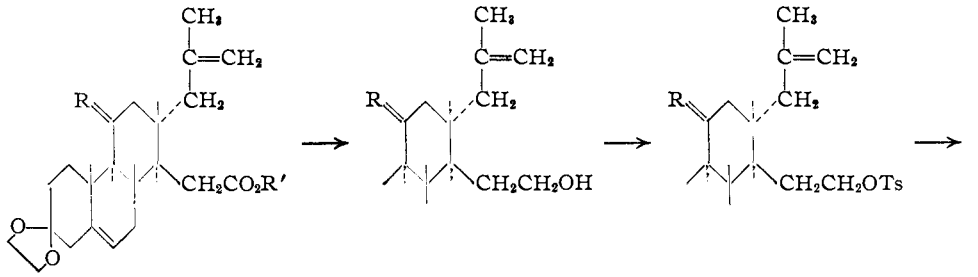
Reduction of 2β,4b-dimethyl-1β-carboxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,-10,10aβ-dodecahydrophenanthrene-4α-ol (Ia) or the corresponding methyl ester Ib with lithium aluminum hydride produced the dihydroxy derivative IIa in good yield. This compound, on treatment with a slight 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.

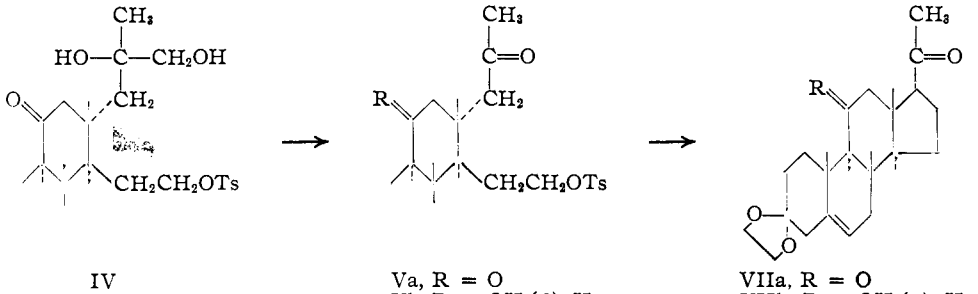
(3) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).



Ia, R = OH (α), H; R′ = H
Ib, R = OH (α), H; R′ = CH_3
Ic, R = O; R′ = CH_3

IIa, R = OH (α), H
IIb, R = OH (β), H

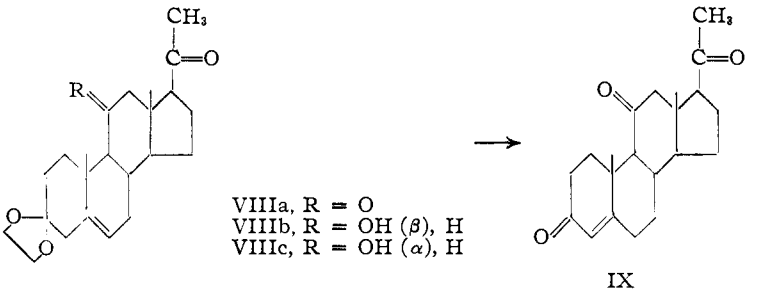
IIIa, R = O
IIIb, R = OH (β), H
IIIc, R = OH (α), H



IV

Va, R = O
Vb, R = OH (β), H
Vc, R = OH (α), H

VIIa, R = O
VIIb, R = OH (β), H
VIIc, R = OH (α), H



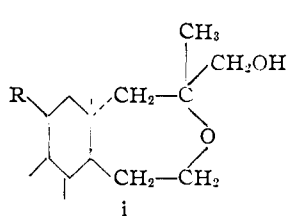
VIIIa, R = O
VIIIb, R = OH (β), H
VIIIc, R = OH (α), H

IX

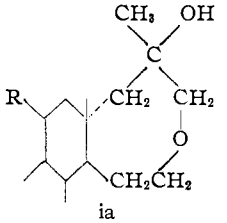
ester which was hydrolyzed to a non-crystalline mixture of isomeric glycols IV. The entire glycol mixture was treated with periodic acid to produce the acetonyl tosylate Va[4] in 60% yield with about 25% of a by-product.[5]

(4) Conversion of the methallyl to the acetonyl side chain by this method has been previously described: L. H. Sarett, W. F. Johns, R. E. Beyler, R. M. Lukes, G. I. Poos and G. E. Arth, THIS JOURNAL, **75**, 2112 (1953).

(5) Related by-products were also encountered with the 4α- and 4β-hydroxy tosylates following hydroxylation-cleavage. Data on the structure of these compounds were consistent only with a cyclic oxide structure such as i which was doubtless formed during alkaline



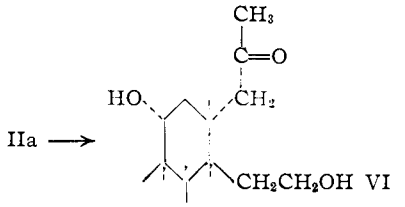
i



ia

hydrolysis of the tosylate osmate esters. Elemental analyses and infrared spectra were in agreement with this formulation. Acid hydrolysis of the 7-ethylene ketal of the 4-keto by-product led to the corresponding α,β-unsaturated ketone which was stable to acid. This acid stability eliminated the possibility of a cyclic lactol structure derived from the acetonyl-2-hydroxyethyl compounds (*e.g.*, VI). Acetylation of the 4β-hydroxy by-product led to a monoacetate. The alternate cyclic oxide structure ia (R = 4β-OH) involving the primary hydroxyl function would have no readily acetylatable hydroxyl group.

An attempt to alter the sequence of reactions by oxidizing the methallyl group prior to selective tosylation proved unsatisfactory. Hydroxylation and cleavage of the diol IIa produced the acetonyl



diol VI in good yield. From the reaction of VI with *p*-toluenesulfonyl chloride in pyridine, none of the desired acetonyl monotosylate Vc could be isolated.

A short time after the addition of one molecular equivalent of sodium methoxide to a solution of the tosylate Va in methanol, the cyclized product crystallized from the reaction mixture. Chromatography showed that this material consisted predominantly of *dl*-Δ^5-3-ethylenedioxy-17α-pregnene-11,-20-dione (VIIa) with the normal 17β-isomer VIIIa

present in smaller amount. A satisfactory procedure for equilibration of the side chain at C-17 entailed the use of refluxing potassium carbonate in aqueous methanol. The equilibration of other 20-ketopregnanes with alkali has been described previously[6] and the resulting mixtures have been found to consist predominantly of the normal (17β) pregnane. Similarly the equilibration of VIIa afforded principally the 17β-pregnene VIIIa.

The 3-ethylenedioxy derivative of *dl*-11-ketoprogesterone (VIIIa) provided the first opportunity for comparison with a known steroid. The infrared spectra of VIIIa and the 3-ethylenedioxy derivative of 11-ketoprogesterone[7] in chloroform were identical. Hydrolysis of VIIIa with perchloric acid in tetrahydrofuran gave *dl*-11-ketoprogesterone (IX) with the same infrared spectrum (in solution) as authentic 11-ketoprogesterone.

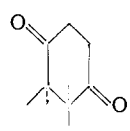
For the synthesis of the 3-dioxolane of *dl*-11β-hydroxyprogesterone (VIIIb) the keto ester Ic[1] was reduced with lithium aluminum hydride affording the 4β-hydroxy derivative IIb[8] as the main product. Tosylation of this compound gave the ester IIIb, which was hydroxylated with osmium tetroxide and cleaved to yield the acetonyl tosylate Vb and a by-product.[5] Cyclization of Vb and epimerization proceeded smoothly to give the equilibrium mixture of 17-normal and 17-isopregnenes VIIb and VIIIb. Purification of the desired *dl*-Δ^5-3-ethylenedioxypregnene-11β-ol-20-one (VIIIb) was accomplished by chromatography and fractional crystallization. Correlation of VIIIb with the 11-keto compound VIIIa was accomplished by oxidation with chromium trioxide–pyridine.

Racemic Δ^5-3-ethylenedioxypregnene-11α-ol-20-one (VIIIc) was produced by the same sequence of reactions starting with the methallyl diol IIa. Reaction with osmium tetroxide and periodate cleavage of the methallyl tosylate IIIa gave the acetonyl tosylate Vc again with a substantial amount of by-product.[5] Cyclization of the acetonyl tosylate Vc was effected by methanolic sodium methoxide, producing directly an equilibrium mixture of 17-normal (VIIIc) and 17-isopregnenes (VIIc). Confirmation of the structure of each was made by oxidation to the known 11-keto analogs (VIIa and VIIIa) with chromium trioxide–pyridine.

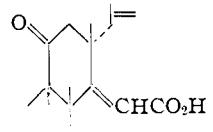
(6) See, for example, A. Butenandt and G. Fleischer, *Ber.*, **70B**, 96 (1937); R. B. Moffett and W. M. Hoehn, THIS JOURNAL, **66**, 2098 (1944).

(7) J. M. Constantin, A. C. Haven and L. H. Sarett, *ibid.*, **75**, 1716 (1953).

(8) It is interesting to note that the C$_4$-keto function is reduced to a β-hydroxyl group in this case. The C$_4$-ketone of perhydrophenanthrenes with a carbonyl group (ii, ref. 3) or exocyclic carbon–carbon double bond at C$_1$ (iii, ref. 1) is reduced to a C$_4$-α-hydroxyl group with lithium aluminum hydride or sodium borohydride. The increased steric hindrance at C$_4$ (*cf.* D. H. R. Barton, *J. Chem. Soc.*, 1034 (1953)) with C$_1$ saturated cannot be due entirely to the β-configuration of the C$_1$ side chain for a reduction of the C$_1$-α-epimer again produced predominantly the C$_4$-β-hydroxyl group. The increased steric hindrance at C$_4$ may then be associated with a conformational change of the C ring.



ii



iii

Experimental[9]

A. The 11-Keto Series. 2β,4b-Dimethyl-1β-(2-hydroxyethyl)-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,-10,10aβ-dodecahydrophenanthrene-4α-ol (IIa).—To 2.56 g. of 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) in 200 ml. of tetrahydrofuran was added a solution of 800 mg. of lithium aluminum hydride in 8 ml. of the same solvent. After stirring overnight at room temperature the reaction was quenched by cautious addition of water. Filtration through Supercel followed by a chloroform wash of the filter cake and distillation of the combined solvents *in vacuo* afforded a crystalline residue. Recrystallization from acetone gave 2.05 g. (85%) of the dihydroxy compound IIa, m.p. 206–208°. The analytical sample melted at 200–201°, 214–215°; $\lambda_{max.}$ 3.03, 6.04 μ.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 73.56; H, 9.55.

Reduction of the corresponding hydroxy acid Ia was accomplished by adding a slurry of 2.54 g. of the acid in 500 ml. of hot tetrahydrofuran to a vigorously stirred solution of 2.5 g. of lithium aluminum hydride in 300 ml. of boiling tetrahydrofuran. After 45 minutes heating, the reaction was cooled and then quenched by cautious addition of water. Following the procedure above 1.81 g. (74%), m.p. 206–210°, of the diol was obtained. Chromatography of the remaining material gave an additional 0.46 g. (18%).

2β,4b-Dimethyl-1β-(2-tosyloxyethyl)-2-methallyl-7-ethylenedioxy - 1,2,3,4,4aα,4b,5,6,7,8,10,10aβ - dodecahydrophenanthrene-4α-ol (IIIc).—The diol IIa (2.47 g.) was dissolved in 13 ml. of pyridine and the solution was concentrated to 10 ml., cooled to 0° and 1.48 g. of *p*-toluenesulfonyl chloride was added. The mixture was stirred until homogeneous and then allowed to stand at 0° overnight during which time crystals of pyridine hydrochloride separated. Aqueous sodium bicarbonate was added cautiously and the solution was stirred at 0° for ten minutes. Extraction with ether followed by an aqueous sodium bicarbonate wash and removal of all solvent *in vacuo* gave an amorphous residue. Crystallization from ether gave in two crops 3.39 g. (98%) of the monotosylate, m.p. 130–135° (dec.).[10] Recrystallization from benzene–petroleum ether gave the analytical sample, m.p. 162–163° (no decomposition until after the sample had melted); $\lambda_{max.}$ 2.95, 6.08 μ.

Anal. Calcd. for $C_{31}H_{44}O_6S$: C, 68.35; H, 8.14; S, 5.88. Found: C, 68.10; H, 8.17; S, 5.93.

Formation of a ditosylate was attempted by treating 60 mg. of the dihydroxy compound IIa in 0.6 ml. of dry pyridine with 100 mg. of *p*-toluenesulfonyl chloride. After 60 hours the reaction was worked up as described above yielding 75 mg. of residue. Chromatography on alumina gave only relatively non-polar oils. The material failed to crystallize but was thought to possess no free C-4 hydroxyl group by virtue of the total weight of the residue and the ease of elution from alumina.

2β,4b-Dimethyl-1β-(2-tosyloxyethyl)-2-methallyl-7-ethylenedioxy - 1,2,3,4,4aα,4b,5,6,7,8,10,10aβ - dodecahydrophenanthrene-4-one (IIIa).—A solution of 3.37 g. of the hydroxytosylate IIIc in 30 ml. of pyridine was added at 0° to a slurry of the chromium trioxide–pyridine complex formed from 3.7 g. of chromium trioxide and 40 ml. of pyridine. After stirring at room temperature overnight the reaction was diluted with water and extracted with ether. The extract was washed with water, dried, and concentrated to dryness *in vacuo*. Crystallization of the residue from ether afforded 2.85 g. (85%) of the keto tosylate IIIa, m.p. 115–120°.[10] Recrystallization from ether gave a constant melting sample, m.p. 161–162°; $\lambda_{max.}$ 5.87, 6.09 μ. The melt-

(9) All melting points were taken on a Kofler micro hot-stage. Infrared spectra are of the crystalline solids in Nujol unless otherwise noted.

(10) The methallyl tosylates III were all nicely crystalline compounds although the once-crystallized materials often had low melting points. That this was due to not more than a few per cent. of impurity was shown by chromatographic analysis. The lower melting points may be attributed to the peculiar thermal decomposition of the tosylates in which a trace of impurity at one point initiates melting which in turn rapidly causes melting of the entire sample. These tosylates were relatively unstable at room temperature unless highly purified. They could be purified by alumina chromatography if the contact time was kept short.

ing point of this compound was not depressed on admixture with starting material.

Anal. Calcd. for $C_{31}H_{42}O_6S$: C, 68.62; H, 7.80; S, 5.91. Found: C, 68.63; H, 7.93; S, 6.14.

2β,4b-Dimethyl-1β-(2-tosyloxyethyl)-2-acetonyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4-one (Va).—To 445 mg. of the keto tosylate IIIa in 5 ml. of benzene was added 208 mg. of osmium tetroxide. After stirring for two hours at room temperature the mixture was dissolved in 7 ml. of ethanol and shaken for 20 minutes with a solution of 0.7 g. of sodium sulfite in 4 ml. of water. The mixture was then filtered through Supercel yielding a colorless filtrate which was evaporated to a small volume *in vacuo* and diluted with water. A chloroform extract was washed with water, dried and concentrated to dryness *in vacuo*. The resulting amorphous residue (450 mg.) was dissolved in 4 ml. of methanol and 1 ml. of pyridine. To this solution was added 250 mg. of paraperiodic acid in 1 ml. of water. After standing at room temperature for 30 minutes the reaction was diluted with water and extracted with chloroform. The extract was washed, dried and concentrated *in vacuo*. The non-crystalline residue (450 mg.) was adsorbed on 8 g. of acid-washed alumina. With petroleum ether–ether there was eluted 265 mg. (59%) of low melting acetonyl tosylate Va. Several recrystallizations from ether gave a pure sample, m.p. 104–107°, $\lambda_{max.}$ 5.82 μ.

Anal. Calcd. for $C_{30}H_{40}O_7S$: C, 66.15; H, 7.40; S, 5.89. Found: C, 66.15; H, 7.19; S, 5.99.

Further elution with ether–chloroform yielded 120 mg. of partially crystalline material which was recrystallized from ether to give a by-product,[6] m.p. 174–178°; $\lambda_{max.}$ 2.95, 5.82 μ.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.31; H, 8.51.

Hydrolysis with a trace of hydrochloric acid in boiling acetone afforded the corresponding 7-keto-$\Delta^{8,8a}$ by-product which after recrystallization from ethanol, ethyl acetate and benzene melted at 206°; $\lambda_{max.}$ 3.0, 5.85, 6.03, 6.19 μ.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.26; H, 8.72.

This compound was recovered unchanged after standing overnight in 2 *N* hydrogen chloride in absolute ethanol and after boiling in 5% hydrochloric acid in 50% aqueous acetone.

***dl*-Δ⁵-3-Ethylenedioxy-17α-pregnene-11,20-dione (VIIa).**—Reaction with osmium tetroxide and cleavage (as described above) of 2.68 g. of methallyl tosylate IIIa gave 2.3 g. of non-crystalline mixture containing Va.[11] The entire product in 45 ml. of anhydrous methanol was treated with 2.3 ml. of 2 *N* methanolic sodium methoxide. Within five minutes the solution began to deposit crystals rapidly. The reaction mixture was kept at 0° overnight and then was diluted with water and extracted with chloroform. The washed and dried extract gave a partially crystalline residue which was chromatographed on 80 g. of acid-washed alumina. Eluted first with petroleum ether–ether was 590 mg. of the 17α-isomer VIIa melting at 200–210°. Crystallization from acetone afforded a pure sample, m.p. 214–216°; $\lambda_{max.}$ 5.85, 5.92 μ.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.26; H, 8.58.

Further elution with petroleum ether–ether gave 400 mg. of a difficultly separable mixture containing the 17β-isomer. (A typical chromatographic separation of this mixture is given below.) Finally, elution with chloroform afforded 600 mg. of crystalline by-product,[6] melting at 171–175° after recrystallization from ether (see above).

***dl*-Δ⁵-3-Ethylenedioxypregnene-11,20-dione (VIIIa).**—One hundred sixty-five milligrams of the 17α-pregnene VIIa in 20 ml. of methanol was treated with a solution of 0.4 g. of potassium carbonate in 3 ml. of water. The solution was heated under reflux for three hours and the methanol was distilled. The resulting aqueous suspension was extracted with chloroform, and the washed and dried extract was concentrated to dryness *in vacuo*. The crystalline residue (165 mg.) was chromatographed on acid-washed alumina. There was obtained first 38 mg. of starting material; second, 13 mg. of a crystalline mixture of the two isomers, m.p. 166–176°; and last, 114 mg. of the 17-normal pregnene VIIIa, m.p. 173–179°. Careful recrystallization from ethanol and ethyl acetate gave the pure compound, m.p. 181.5–183.0°; $\lambda_{max}^{CHCl_3}$ 5.84, 5.92 μ; spectrum identical with that of authentic 11-ketoprogesterone 3-dioxolane.[7]

Anal. Found: C, 74.34; H, 8.36.

It was also possible to accomplish the epimerization by treating 165 mg. of the 17α-pregnene in 5 ml. of benzene and 2 ml. of anhydrous methanol with 6 millimoles of 2 *N* sodium methoxide. After two hours at room temperature the reaction was diluted with water and extracted with chloroform. The extract yielded approximately the same mixture as described above.

***dl*-11-Ketoprogesterone (IX).**—A solution of 100 mg. of the 17β-pregnene VIIIa in 2 ml. of tetrahydrofuran was treated with 1 ml. of 3 *N* aqueous perchloric acid and allowed to stand at room temperature for four hours. After the addition of excess aqueous sodium bicarbonate, the solution was extracted with ether. From the washed and dried extract 84 mg. of crystalline product was obtained. Recrystallization from methanol and from ether gave pure *dl*-11-ketoprogesterone, m.p. 175–176°, $\lambda_{max}^{CHCl_3}$ 5.84, 5.98, 6.15 μ; spectrum identical with that of authentic 11-ketoprogesterone.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.76; H, 8.59. Found: C, 76.72; H, 8.65.

B. The 11β-Hydroxy Series. 2β,4b-Dimethyl-1β-(2-hydroxyethyl)-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,-4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol (IIb).—Thirteen grams of the 4-keto ester Ic[12] in 200 ml. of tetrahydrofuran was added slowly to a rapidly stirred solution of 6 g. of lithium aluminum hydride in 300 ml. of tetrahydrofuran. The stirring was continued for 20 minutes, and then the reaction mixture was quenched by the cautious addition of 25 ml. of water. The mixture was filtered through Supercel, and the filtrate was evaporated *in vacuo*, leaving a crystalline residue. Recrystallization from ethyl acetate afforded 10.3 g. (85%) of IIb, m.p. 181–183°; $\lambda_{max.}$ 2.95, 6.08 μ.

Anal. Found: C, 73.91; H, 9.61.

2β,4b-Dimethyl-1β-(2-tosyloxyethyl)-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol (IIIb).—A solution of 10.3 g. of the diol IIb in 30 ml. of pyridine was cooled to 0° and treated with 6.5 g. (1.3 equivalents) of *p*-toluenesulfonyl chloride. The mixture was shaken for a half-hour, and then stored at 0° overnight, during which time pyridine hydrochloride precipitated. The mixture was cautiously diluted with 75 ml. of saturated aqueous sodium bicarbonate solution with stirring and cooling and then extracted twice with chloroform. Evaporation of the combined extracts left a gum which crystallized from ether; yield 13.0 g. (90%) of IIIb, m.p. 140–141°; $\lambda_{max.}$ 2.87, 2.92, 6.10 μ.

Anal. Found: C, 68.10; H, 7.95; S, 6.27.

***dl*-Δ⁵-3-Ethylenedioxypregnene-11β-ol-20-one (VIIIb).**—A solution of 13.0 g. of the tosylate IIIb, in 120 ml. of benzene was treated with 6.5 g. of osmium tetroxide. After 35 minutes the mixture was diluted with 800 ml. of ethanol and then with 540 ml. of water containing 36 g. of sodium sulfite. The resulting mixture was shaken for a half-hour and filtered. The ethanol and benzene were evaporated from the filtrate *in vacuo*, and the residual aqueous mixture was extracted twice with chloroform. Evaporation of the combined extracts left 15 g. of amorphous residue which was dissolved in 115 ml. of methanol and 25 ml. of pyridine and treated with a solution of 8.5 g. of paraperiodic acid in 25 ml. of water. After a half-hour the methanol was evaporated *in vacuo*, and the remaining aqueous solution was extracted twice with chloroform. Evaporation of the chloroform left 13 g. of amorphous residue which was dissolved in

(11) In order to avoid losses of material through purification of the acetonyl tosylates V, it was found practical to treat the entire reaction product with sodium methoxide. The yields realized were substantially higher and the amount of by-product (ref. 5) was approximately the same.

(12) Prepared by the chromic anhydride-pyridine oxidation of 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, ref. 1). Pure Ic had m.p. 140–141° from ether; $\lambda_{max}^{CCl_4}$ 5.73, 5.82, 6.05 μ. *Anal.* Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.10; H, 8.49.

100 ml. of dry methanol and to the solution was added 14 ml. of 2 *N* sodium methoxide in methanol. After standing overnight the mixture was poured into water, the methanol was evaporated *in vacuo*, and the aqueous suspension was extracted twice with chloroform. The combined extracts were evaporated *in vacuo*, leaving an amorphous residue which was boiled for 3 hours in 50% aqueous methanolic 1 *N* potassium carbonate solution. The methanol was evaporated *in vacuo*, and the aqueous solution was extracted with chloroform. The amorphous residue which remained after evaporation of the chloroform was chromatographed over 400 g. of acid-washed alumina which had been activated with acetone. With 9:1 benzene–ether there was eluted 4.5 g. of crystalline material from which 2.0 g. (22%) of pure *dl*-Δ^5-3-ethylenedioxypregnene-11β-ol-20-one (VIIIb) was separated by fractional crystallization from benzene; m.p. 160°, 188–189°, 199–200°; $\lambda_{max.}$ 2.88, 5.90 μ.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.72; H, 8.90.

Further elution with ethyl acetate provided 2.8 g. of by-product[5] melting at 210–215° after recrystallization from methanol, ethyl acetate and benzene, $\lambda_{max.}$ 2.86 μ.

Anal. Calcd. for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 70.86; H, 9.60.

Acetylation of 97 mg. of this by-product (m.p. 210–215°) with acetic anhydride–pyridine provided 105 mg. of crude monoacetate, m.p. 170–180°. The pure compound was obtained by recrystallization from methanol and ethyl acetate; m.p. 190–191°; $\lambda_{max}^{CHCl_3}$ 2.90, 5.78 μ.

Anal. Calcd. for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.63; H, 8.99.

Oxidation of VIIIb.—One hundred milligrams of VIIIb was oxidized with 100 mg. of chromium trioxide in 2 ml. of pyridine by the usual procedure. There was obtained a good yield of *dl*-Δ^5-3-ethylenedioxypregnene-11,20-dione melting at 177–181°; not depressed on admixture with VIIIa.

C. The 11α-Hydroxy Series. 2β,4b-Dimethyl-1β-(2-tosyloxyethyl)-2-acetonyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4α-ol (Vc).—A solution of 5.73 g. of the hydroxy tosylate IIIc in 50 ml. of benzene and 10 ml. of tetrahydrofuran with 2.94 g. of osmium tetroxide was stirred overnight at room temperature. To the reaction mixture 180 ml. of ethanol and a solution of 18 g. of sodium sulfite in 120 ml. of water were added. After shaking the reaction mixture for 20 minutes, it was filtered through Supercel and the filtrate evaporated to a small volume under reduced pressure. Dilution with water and extraction with chloroform, followed by washing, drying and evaporating the solvent *in vacuo* gave 6 g. of an amorphous residue.

This material was dissolved in 65 ml. of methanol and 16 ml. of pyridine and was treated with a solution of 4 g. of paraperiodic acid in 11 ml. of water. After standing at room temperature for one hour the reaction mixture was diluted with water and extracted with chloroform. From the washed and dried extract was obtained 5.2 g. of a non-crystalline mixture. Chromatography yielded first 3.08 g. of amorphous material (composed largely of the acetonyl tosylate Vc) from which there was obtained 900 mg. of crystalline material, m.p. 113–117°. Recrystallization from ether gave the pure compound, m.p. 122–123°; λ_{max} 2.95, 5.90 μ.

Anal. Calcd. for $C_{30}H_{42}O_7S$: C, 65.90; H, 7.74; S, 5.86. Found: C, 65.63; H, 7.71; S, 6.05.

More polar eluants afforded 1.8 g. of a by-product.[5] Several recrystallizations from ethanol gave a sample with m.p. 244–247°, $\lambda_{max.}$ 2.95 μ.

Anal. Calcd. for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 70.84; H, 9.06.

***dl*-Δ^5-3-Ethylenedioxypregnene-11α-ol-20-one. 17-Iso (VIIc) and 17-Normal (VIIIc) Isomers.**—To a solution of 150 mg. of pure acetonyl tosylate Vc in 1.5 ml. of methanol was added 1.05 equivalents of 2 *N* methanolic sodium methoxide. The solution was stirred at room temperature overnight during which time no appreciable precipitate formed. Dilution of the reaction mixture with water and extraction with chloroform gave 103 mg. of an amorphous mixture. When chromatographed on acid-washed alumina there was eluted first 32 mg. of the 17-iso isomer VIIc, analytical m.p. 200–202°, $\lambda_{max.}$ 2.95–3.0, 5.91 μ.

Anal. Found: C, 73.93; H, 9.22.

Further elution gave 40 mg. of the 17-normal pregnene VIIIc, which after recrystallization from benzene–petroleum ether and ethyl acetate melted at 146–148°, 168–170°, $\lambda_{max.}$ 3.15, 5.85 μ.

Oxidation of VIIc.—A solution of 9 mg. of *dl*-Δ^5-3-ethylenedioxy-17α-pregnene-11α-ol-20-one (VIIc) in 0.5 ml. of pyridine was added to a slurry of the chromium trioxide–pyridine complex prepared from 50 mg. of chromium trioxide in 1 ml. of pyridine and allowed to stand at room temperature overnight. The reaction mixture was diluted with water and extracted with ether. The 9 mg. of residue gave 6 mg. of pure *dl*-Δ^5-3-ethylenedioxy-17α-pregnene-11,20-dione (VIIa), m.p. and mixed m.p. 212–214°.

Oxidation of VIIIc.—A solution of 6 mg. of dl-Δ^5-3-ethylenedioxypregnene-11α-ol-20-one (VIIIc) in 0.5 ml. of pyridine was treated as above. The 6 mg. of residue yielded 3 mg. of the pure 17-normal pregnene VIIIa, m.p. and mixed m.p. 181–183°.

2β,4b-Dimethyl-1β-(2-hydroxyethyl)-2-acetonyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4α-ol (VI).—To 1.55 g. of the diol IIa in 15 ml. of benzene and 5 ml. of tetrahydrofuran was added 1.1 equivalents of osmium tetroxide. After 40 minutes a gel which had formed was broken by addition of 20 ml. of benzene. At the end of an hour the reaction mixture was dissolved in 65 ml. of ethanol and treated with a solution of 7 g. of sodium sulfite dissolved in 40 ml. of water. The solution was shaken for 20 minutes, allowed to settle and the clear upper layer decanted and filtered through Supercel. The lower layer was washed thoroughly with ethanol and filtered. The combined filtrates were concentrated to a small volume *in vacuo*, diluted with water, and extracted with chloroform. The washed and dried extract was concentrated under reduced pressure affording 1.37 g. of a crystalline residue.

The mixture was dissolved in 10 ml. of methanol and 3 ml. of pyridine and was treated with a solution of 1.1 g. of paraperiodic acid in 7 ml. of water at room temperature for 20 minutes. After dilution with water an extraction with chloroform gave 1.10 g. of a crystalline residue. Recrystallization from ethyl acetate yielded 0.96 g. of the acetonyl diol VI, m.p. 176–179°. Recrystallization from ether gave the analytical sample, m.p. 182.5–183.0°, $\lambda_{max.}$ 2.90, 5.83 μ.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.25. Found: C, 70.65; H, 9.23.

An attempt to prepare the acetonyl tosylate Vc gave two crystalline compounds of unknown structure: A, m.p. 145–153°, $\lambda_{max.}$ 3.16, 5.84, 6.03 μ; B, m.p. 132–137°, $\lambda_{max.}$ 3.03, 5.97 μ.

Anal. Found: C, 73.38; H, 8.88.

D. 2β,4b-Dimethyl-1α-(2-hydroxyethyl)-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol.—To 130 mg. of lithium aluminum hydride in 1.3 ml. of tetrahydrofuran was added 356 mg. of 2β,4b-dimethyl-1α-carbomethoxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4-one[1] in 5.5 ml. of tetrahydrofuran. At the end of one-half hour the solution was cautiously treated with a few drops of water. Filtration through Supercel and concentration of the filtrate *in vacuo* gave 324 mg. of crystalline residue. Chromatography afforded 200 mg. of the 2β,4b-dimethyl-1α-(2-hydroxyethyl)-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol which melted at 169–170° after recrystallization from ether; $\lambda_{max.}$ 2.90, 6.09 μ.

Anal. Found: C, 74.09; H, 9.67.

Later eluates gave crystalline mixtures followed by 40 mg. of the 2β,4b-dimethyl-1α-(2-hydroxyethyl)-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydroxyphenanthrene-4α-ol, m.p. 176–179°. Recrystallization from ether gave a sample melting at 181–182°, λ_{max} 3.0, 6.06 μ, identical with a sample prepared by the lithium aluminum hydride reduction of 2β,4b-dimethyl-1α-carbomethoxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,-4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4α-ol.[1]

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