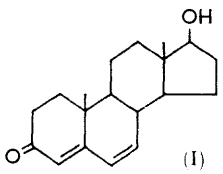
32. *Steroids Containing Ring* A *Aromatic. Part II.*[1] *Hydrogenolysis of Ring* A *Phenols.*

By E. Caspi, E. Cullen, and P. K. Grover.

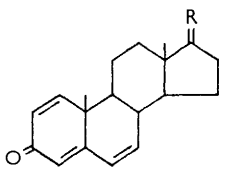
Hydrogenolysis of steroids containing a phenolic ring A has been investigated. 3-Tosyloxy- and 1-methyl-3-tosyloxy-œstra-1,3,5(10)-trien-17-one were reduced with hydrogen and Raney nickel, the acyloxy-group being replaced by hydrogen. The analogous reduction of 1-methyl-3-tosyloxyœstra-1,3,5(10)-triene-11,17-dione and 4-methyl-1-tosyloxyœstra-1,3,5(10)-trien-17-one failed but the replacement was effected by reduction of the respective diethyl phosphate esters with sodium and liquid ammonia. Observations pertaining to the Clemmensen reduction of 3-hydroxy-1-methylœstra-1,3,5(10)-triene-11,17-dione are also reported.

In Part I [1] of this series the synthesis of 4-methyl-steroids without oxygen in an aromatic ring A by the dienol–benzene rearrangement was reported. The preparation of such steroids by hydrogenolysis of steroids containing a phenolic ring A is reported in the present paper.

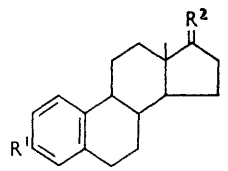
The reaction was modelled on œstrone toluene-*p*-sulphonate (IIIa) which was shaken with Raney nickel [2] in an atmosphere of hydrogen,[3] to yield after reoxidation œstra-1,3,5(10)-trien-17-one (IIIb). The product was assigned the structure (IIIb) on the basis of its analysis ($C_{18}H_{22}O$), and its infrared spectrum which had no bands for a hydroxyl group. The monoketone (IIIb), on reduction with lithium aluminium hydride, gave œstra-1,3,5(10)-trien-17β-ol (IIIc). However, if an old sample of Raney nickel was used, the major product obtained was œstradiol, together with a small amount of



(I)



(IIa: R = β-OH)
(IIb: R = O)



(IIIa: R^1 = OTs, R^2 = O)
(IIIb: R^1 = H, R^2 = O)
(IIIc: R^1 = H, R^2 = β-OH)

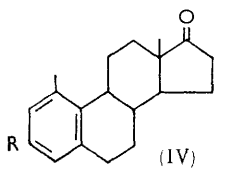
œstrone toluene-*p*-sulphonate. For further experiments freshly prepared Raney nickel was used and its activity was tested each time with œstrone toluene-*p*-sulphonate.

We then turned to the preparation of 1-methyl-substituted compounds by analogous reduction of 1-methylœstrone 3-toluene-*p*-sulphonate. Dehydrogenation of testosterone with 2,3-dichloro-5,6-dicyanobenzoquinone in the presence of catalytic amounts of hydrogen chloride [4] gave 17β-hydroxyandrosta-4,6-dien-3-one (I) in excellent yield. The diene (I) was then dehydrogenated under neutral conditions,[5] yielding 17β-hydroxyandrosta-1,4,6-trien-3-one (IIa) and a small amount of the corresponding 17-ketone (IIb). The compound (IIa) was subsequently oxidized to the 17-ketone (IIb). When steroidal secondary alcohols were dehydrogenated under neutral conditions with the quinone named above, partial oxidation of the hydroxyl group was unusually observed. The phenol (IVa) was prepared from the trienedione (IIb) by the method of Djerassi *et al.*[6] and then was converted into the toluene-*p*-sulphonate (IVb). When this ester was

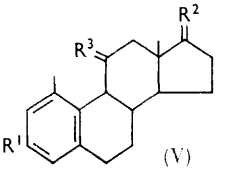
[1] Part I, Caspi, Grover, Grover, Lynde, and Nussbaumer, *J.*, 1962, 1710.
[2] Mozingo, Wolf, Harris, and Follens, *J. Amer. Chem. Soc.*, 1943, **65**, 1015.
[3] Sarin and Seshadri, *Tetrahedron*, 1960, **8**, 64.
[4] Ringold and Turner, *Chem. and Ind.*, 1962, 211.
[5] Burn, Kirk, and Petrow, *Proc. Chem. Soc.*, 1960, 14.
[6] Djerassi, Rosenkranz, Romo, Pataki, and Kaufmann, *J. Amer. Chem. Soc.*, 1950, **72**, 4540.

shaken with Raney nickel and hydrogen, a mixture of steroids was obtained from which, after reoxidation, 1-methylœstra-1,3,5(10)-trien-17-one (IVc) was isolated (its infrared spectrum had no hydroxyl band).

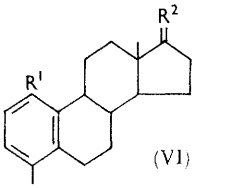
It became then, of interest, to prepare 1-methyl-11-oxygenated derivatives from 1-methyl-3-tosyloxyœstra-1,3,5(10)-triene-11,17-dione (Vc). The 3-acetate (Va) was prepared by the method of Bailey *et al.*[7] and was saponified to the phenol (Vb) and then converted into the toluene-*p*-sulphonate (Vc). When hydrogenolysis of this was attempted as described above, the product was only 3,17β-dihydroxyœstra-1,3,5(10)-trien-11-one (Ve), whose structure was assigned because of the analysis and an infrared band at 1680 cm.$^{-1}$; with acetic anhydride and pyridine it gave the 3,17β-diacetate (Vf), which had the correct analysis and in its nuclear magnetic resonance spectrum showed, among others, bands at τ 4·89, 5·03, 5·15 for the 17α-proton, at τ 7·75 for the phenolic acetate, and at τ 8·05 for the 17β-acetate. The structure of the diol (Ve) was confirmed by oxidation to the hydroxy diketone (Vb). It was then hoped that a better electron-withdrawing substituent at C-3, *i.e.*, a naphthalene-2-sulphonyl group, might induce homolysis of the C–O bond. When hydrogenolysis of 1-methyl-3-naphthalene-2′-sulphonyloxyœstra-1,3,5(10)-triene-11,17-dione (Vd) was attempted, again 3,17β-dihydroxy-1-methylœstra-1,3,5(10)-trien-11-one (Ve) was obtained as the sole product. The infrared spectrum of



(IV)



(V)



(VI)

(IV)	R	(V)	R^1	R^2	R^3	(V)	R^1	R^2	R^3	(VI)	R^1	R^2
a	OH	a	OAc	O	O	f	OAc	β-OAc	O	a	OH	O
b	OTs	b	OH	O	O	g	OH	H_2	O	b	OTs	O
c	H	c	OTs	O	O	h *	OH	H_2	H_2	c	OH	β-OH
		d	ONs	O	O	i	O·PO_3Et_2	O	O	d	O·PO_3Et_2	O
		e	OH	β-OH	O	j *	H	O	O	e	H	O

* 9ξ. Ts = *p*-$C_6H_4Me{\cdot}SO_2{\cdot}$. Ns = 2-$C_{10}H_7{\cdot}SO_3{\cdot}$.

this compound (Ve) is of interest. In potassium bromide the 11-ketone band was shifted to 1680 cm.$^{-1}$, and in chloroform solution the band moved back to its expected position at 1714 cm.$^{-1}$, which did not change on dilution. It appears that the ketone was hydrogen-bonded in the crystalline lattice.[8] The diacetate (Vf) in potassium bromide showed two bands at 1725 and 1710 cm.$^{-1}$, as expected. Thus it became evident that an 11-keto-group interfered with the hydrogenolysis of the phenol sulphonate esters.

Removal of the hydroxyl group from 3-hydroxy-1-methylœstra-1,3,5(10)-triene-11,17-dione (Vb) was achieved by reduction of diethyl 1-methyl-11,17-dioxoœstra-1,3,5(10)-trien-3-yl phosphate (Vi) with sodium and liquid ammonia.[9,10] The mixture of steroids obtained yielded, after oxidation, 1-methylœstra-1,3,5(10)-triene-11,17-dione (Vj), whose structure was consistent with the analysis and infrared spectrum. However, under the conditions of the experiment, epimerization at C-9 could have occurred and this is being investigated.

We then attempted hydrogenolysis of 4-methyl-1-tosyloxyœstra-1,3,5(10)-trien-17-one (VIb). The phenol (VIa) was prepared by the method of Dreiding and Voltman [11] and

[7] Bailey, Elks, Oughton, and Stephenson, *J.*, 1961, 4535.
[8] Jones and Gallagher, *J. Amer. Chem. Soc.*, 1959, **81**, 5242, in particular footnote 26.
[9] Kenner and Williams, *J.*, 1955, 522; Wenkert and Jackson, *J. Amer. Chem. Soc.*, 1958, **80**, 217.
[10] Fishman and Tomasz, *J. Org. Chem.*, 1962, **27**, 365.
[11] Wilds and Djerassi, *J. Amer. Chem. Soc.*, 1946, **68**, 2125; Dreiding and Voltman, *ibid.*, 1954, **76**, 537.

was then converted into the tosyl derivative (VIb). The sole product isolated was 4-methyl-œstra-1,3,5(10)-triene-1,17β-diol (VIc). However, 4-methylœstra-1,3,5(10)-trien-17-one was prepared by reduction, with sodium in liquid ammonia, of diethyl 4-methyl-17-oxo-œstra-1,3,5(10)-trien-3-yl phosphate (VId) and subsequent oxidation. Attempts to prepare the phosphate (VId) by the method successful for the preparation of the 3-phosphate ester (Vi) failed. The required ester was obtained by prolonged boiling (96 hr.) of the phenol (VIa) with a large excess of diethyl phosphite in the presence of triethylamine. The crude ester (VId) was reduced with sodium and liquid ammonia. The mixture obtained yielded 4-methylœstra-1,3,5(10)-trien-17-one (VIe) after oxidation.

Inspection of models indicated possible shielding of the 11-ketone by the 1-methyl group in compound (Vb). The fact that during the attempted hydrogenolysis of the ester (Vc) the 11-ketone group remained unchanged supported this assumption. To test the hypothesis, the alcohol (Vb) was submitted to a Clemmensen reduction under conditions which led to the removal of both carbonyl groups from 4-methylœstra-1,3,5(10)-triene-11,17-dione.[1] The main products were 3-hydroxy- (Vg) and 3,17β-dihydroxy-1-methylœstra-1,3,5(10)trien-11-one (Ve). 1-Methylœstra-1,3,5(10)-trien-3-ol (Vh) (no infrared carbonyl band) was also present in the reaction mixture, but the amount was insufficient for characterisation. When the phenol (Vb) was reduced by a modified[12] Wolff–Kishner method, a phenolic product (Vh) devoid of carbonyl absorption was obtained. The product resisted crystallization even after careful chromatography and conversion into a tosyl derivative. We assume that the syrup was a mixture of 9α- and 9β-isomers formed under the strongly alkaline conditions employed.[13]

Experimental

Infrared spectra were taken for potassium bromide discs and chloroform solution as indicated. Ultraviolet spectra (for methanol solutions) were taken with Cary spectrophotometers model 11 MS or 14. M. p.s were determined on a hot stage and are corrected. Nuclear magnetic resonance spectra were determined for solutions in deuterochloroform with tetramethylsilane as internal standard, on a Varian high-resolution spectrometer model V4300B. Analyses were made by W. J. Kirsten, Uppsala, Sweden, and Illini Microanalytical Lab., Urbana, Ill., U.S.A.

Œstra-1,3,5(10)-*trien*-17-*one* (IIIb).—To a solution of œstrone toluene-*p*-sulphonate (IIIa) (0·6 g.) in ethyl alcohol (50 ml.) was added an excess of Raney nickel, and hydrogen was bubbled through the stirred solution at room temperature. The reaction was stopped when a test portion showed no bands at 1175 and 1185 cm.$^{-1}$ (3 hr.). The mixture was filtered over "Celite," and the catalyst washed with alcohol. The filtrate was concentrated, diluted with water, and extracted with ether. The ether extract was washed with 2N-sodium hydroxide and water, dried (Na_2SO_4), and concentrated. The oil obtained was dissolved in pyridine (2 ml.) and added to a suspension of chromic acid (0·40 g.) in pyridine (2 ml.). The resulting mixture was set aside at room temperature for 3 hr. Ethyl acetate (30 ml.) was added, and the solid that separated was filtered over "Celite." The filtrate was washed with 2N-hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried (Na_2SO_4), and concentrated under reduced pressure. The syrupy *ketone* obtained crystallized from methanol as colourless needles, m. p. 135—136°, $[\alpha]_D^{24}$ +400° (in dioxan), $\lambda_{max.}$ (in MeOH) 213 (ε 7100), 267 (ε 470), and 272 mμ (ε 480), $\nu_{max.}$ (in KBr) 3000, 1725, 750, and 740 cm.$^{-1}$ (Found: C, 84·4; H, 8·7. $C_{18}H_{22}O$ requires C, 84·9; H, 8·7%).

Œstra-1,3,5(10)-*trien*-17β-*ol* (IIIc).—To a solution of œstra-1,3,5(10)-trien-17-one (IIIb) (40 mg.) in ether (5 ml.) and tetrahydrofuran (0·5 ml.), lithium aluminium hydride (40 mg.) was added, and the mixture was heated under reflux for 3 hr. The excess of lithium aluminium hydride was decomposed by acetone and water. The white precipitate was filtered over "Celite." The filtrate was concentrated under reduced pressure to a small volume, diluted with water, and extracted with ethyl acetate. The extract was washed with water, dried

[12] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487; 1949, **71**, 3301.
[13] Cole, Johnson, Robins, and Walker, *J.*, 1962, 244.

(Na_2SO_4), and concentrated. The solid obtained recrystallized from methylene chloride–hexane, yielding the *alcohol* as prisms, m. p. 109—110°, $[\alpha]_D^{24}$ +80° (in dioxan), $\lambda_{max.}$ (in MeOH) 213 (ε 8400), 267 (ε 500), and 272 mμ (ε 500), $\nu_{max.}$ (in KBr) 3280, 3000, 1575, 1050, 752, and 735 cm.$^{-1}$ (Found: C, 83·8; H, 9·1. $C_{18}H_{24}O$ requires C, 84·3; H, 9·4%).

17β-*Hydroxyandrosta*-4,6-*dien*-3-*one* (I).—To a solution of testosterone (5 g.) in anhydrous dioxan (200 ml.) was added 2,3-dichloro-5,6-dicyanobenzoquinone (5 g.). Hydrogen chloride was blown on the surface for 30 sec., then the solution was set aside for 15 min. After the separated solid had been filtered off, nitrogen was bubbled through the filtrate for 15 min. The filtrate was diluted with methylene chloride (100 ml.) and poured over a dry column of neutral alumina (250 g.). Elution with methylene chloride–acetone (1 : 1) gave an oil which crystallized from acetone as needles, m. p. 210—211° (lit.,[14] 211°), $\lambda_{max.}$ (in MeOH) 285 mμ (ε 28,000), $\nu_{max.}$ (in KBr) 3380, 1640, 1615, and 1587 cm.$^{-1}$.

17β-*Hydroxyandrosta*-1,4,6-*trien*-3-*one* (IIa).—To 17β-hydroxyandrosta-4,6-dien-3-one (I) (3 g.) in anhydrous dioxan (120 ml.) was added 2,3-dichloro-5,6-dicyanobenzoquinone (3 g.), and then the solution was heated under reflux for 24 hr. The separated solid was filtered off and washed with methylene chloride. The filtrate was worked up as described above. Elution of the column with methylene chloride–acetone (1 : 1) gave, in the first eluate the diketone (IIb), and then the alcohol (IIa). The oily alcohol crystallized from ethyl acetate as needles, m. p. 156—158° (lit.,[15] 156—157·5°), $\lambda_{max.}$ (in MeOH) 225 (ε 12,000), 258 (ε 10,000), and 301 mμ (ε 13,500), $\nu_{max.}$ (in KBr) 3315, 1640, 1610, and 1590 cm.$^{-1}$ (Found: C, 79·9; H, 8·45. Calc. for $C_{19}H_{24}O_2$: C, 80·2; H, 8·5%).

Androsta-1,4,6-*triene*-3,17-*dione* (IIb).—(i) The diketone obtained in the previous experiment crystallized from ethyl acetate as needles, m. p. 164—165°, $\nu_{max.}$ (in KBr) 1740, 1651, 1625, and 1600 cm.$^{-1}$.

(ii) A solution of 17β-hydroxyandrosta-1,4,6-trien-3-one (IIa) (1 g.) in pyridine (5 ml.) was added to a suspension of chromic acid (1 g.) in pyridine (3 ml.). The mixture was kept at room temperature for 3 hr., then worked up as described above. The solid obtained crystallized from ethyl acetate, yielding needles, m. p. and mixed m. p. 164—165° (lit.,[16] 164—165°), having the correct infrared spectrum.

3-*Tosyloxy*-1-*methylœstra*-1,3,5(10)-*trien*-17-*one* (IVb). To a solution of 3-hydroxy-1-methylœstra-1,3,5(10)-trien-17-one [6] (IVa) (200 mg.; m. p. 250—252°) in anhydrous pyridine (4 ml.) at 0° was added a precooled solution of toluene-*p*-sulphonyl chloride (500 mg.) in pyridine (4 ml.). After the mixture had been stored at 0° for 16 hr., it was poured on ice and hydrochloric acid. The solid was collected and crystallized from methanol, yielding the *ester* as needles, m. p. 167—170°, $\nu_{max.}$ (in KBr) 1722, 1590, 1190, and 1178 cm.$^{-1}$ (Found: C, 70·8; H, 6·9. $C_{26}H_{30}O_4S$ requires C, 71·2; H, 6·9%).

1-*Methylœstra*-1,3,5(10)-*trien*-17-*one* (IVc).—Hydrogen was bubbled through a stirred solution of 1-methyl-3-tosyloxyœstra-1,3,5(10)-trien-17-one (IVb) (280 mg.) in ethyl alcohol (20 ml.) to which an excess of Raney nickel was added. The reaction was followed by taking infrared spectra of test portions, and was ended when the bands at 1190 and 1178 cm.$^{-1}$ disappeared (3 hr.). The mixture was worked up as previously described.[1] The oil obtained (170 mg.) was added in pyridine (2 ml.) to a suspension of chromic acid (170 mg.) in pyridine (2 ml.), and the mixture was kept at room temperature for 3 hr., then worked up in the conventional manner. The brown oil obtained was chromatographed on neutral alumina. Elution with benzene–chloroform (4 : 1) gave a solid *ketone* which crystallized from methanol as needles, m. p. 143—145°, $[\alpha]_D^{25}$ +270° (in dioxan), $\lambda_{max.}$ (in MeOH) 215 (shoulder) (ε 10,700) and 267 mμ (ε 245), $\nu_{max.}$ (in KBr) 1720, 1575, 785, and 770 cm.$^{-1}$ (Found: C, 83·6, 83·3, 83·2; H, 8·7, 9·1, 9·1. $C_{19}H_{24}O,\frac{1}{4}H_2O$ requires C, 83·6; H, 9·0%).

3-*Hydroxy*-1-*methylœstra*-1,3,5(10)-*triene*-11,17-*dione* (Vb).—(i) To a solution of 3-acetoxy-1-methylœstra-1,3,5(10)-triene-11,17-dione [7] (Va) [2 g., m. p. 206—208° (lit., 203—208°)] in anhydrous methanol (75 ml.) was added 2N-methanolic sodium methoxide (4 ml.). After 5 min. at room temperature water (0·5 ml.) was added, and after another 3 min. water (5 ml.) and acetic acid (8 ml.) were added. The solution was concentrated under reduced pressure, diluted with water, and extracted with ethyl acetate. The ethyl acetate extract was washed with aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and concentrated. The

[14] Sondheimer, Velasco, Batres, and Rosenkranz, *Chem. and Ind.*, 1954, 1482.
[15] Kaufmann, Pataki, Rosenkranz, Romo, and Djerassi, *J. Amer. Chem. Soc.*, 1950, **72**, 4531.
[16] Djerassi, Rosenkranz, Romo, Kaufmann, and Pataki, *J. Amer. Chem. Soc.*, 1950, **72**, 4534.

yellow oily *phenol* obtained crystallized from ethyl acetate as tablets, m. p. 230—232°, $\lambda_{max.}$ (in MeOH) 225 (shoulder) (ε 9000) and 282 mμ (ε 1700), $\nu_{max.}$ (in KBr) 3320, 1720, 1680, 1590, and 1575 cm.$^{-1}$ (Found: C, 76·6; H, 7·4. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·4%).

(ii) 3,17β-Dihydroxy-1-methylœstra-1,3,5(10)-trien-11-one (Ve) (40 mg.) in pyridine (1 ml.) was added to a suspension of chromic acid (45 mg.) in pyridine (1 ml.). The mixture was kept at room temperature for 2 hr. and was worked up as described above. The recovered steroids crystallized from ethyl acetate, giving a small amount of starting material in the first crop, followed by the phenol (Vb). This recrystallized from ethyl acetate, yielding needles, m. p. and mixed m. p. 230—232°, having the correct infrared spectrum.

1-*Methyl*-3-*tosyloxyœstra*-1,3,5(10)-*triene*-11,17-*dione* (Vc).—To a solution of 3-hydroxy-1-methylœstra-1,3,5(10)-triene-11,17-dione (Vb) (300 mg.) in pyridine (3 ml.) at 0°, a precooled solution of toluene-*p*-sulphonyl chloride (600 mg.) in pyridine (5 ml.) was added. The mixture was left at 0° for 16 hr., then worked up as above. The solid *ester* crystallized from methanol as needles, m. p. 174—176°, $\nu_{max.}$ (in KBr) 1722, 1695, 1575, 1185, 1162, and 775 cm.$^{-1}$ (Found: C, 69·0; H, 6·2. $C_{26}H_{28}O_5S$ requires C, 69·0; H, 6·2%).

1-*Methyl*-3-*naphthalene*-2′-*sulphonyloxyœstra*-1,3,5(10)-*triene*-11,17-*dione* (Vd).—To a solution of 3-hydroxy-1-methylœstra-1,3,5(10)-triene-11,17-dione (Vb) (500 mg.) in pyridine (4 ml.), cooled to 0°, a precooled solution of naphthalene-2-sulphonyl chloride (1 g.) in pyridine (4 ml.) was added. The mixture was stored in a refrigerator for 16 hr., then poured on ice and hydrochloric acid, and the separated solid was filtered off and crystallized from methanol, yielding the *ester* as needles, m. p. 191—192°, $\nu_{max.}$ (in KBr) 1720, 1710, 1590, and 1185 cm.$^{-1}$ (Found: C, 71·0; H, 5·8. $C_{29}H_{28}O_5S$ requires C, 71·3; H, 5·8%).

3,17β-*Dihydroxy*-1-*methylœstra*-1,3,5(10)-*trien*-11-*one* (Ve).—Hydrogen was passed through a solution of 1-methyl-3-tosyloxyœstra-1,3,5(10)-triene-11,17-dione (Vc) (400 mg.) in ethyl alcohol (50 ml.) containing suspended Raney nickel until a portion did not absorb at 1185 or 1162 cm.$^{-1}$. The mixture was worked up as described above. The *dihydroxy-ketone* obtained crystallized from ethyl acetate as needles, m. p. 255—257°, $[\alpha]_D^{22}$ +320° (in dioxan), $\lambda_{max.}$ (in MeOH) 225 (shoulder) (ε 13,000) and 282 mμ (ε 1900), $\nu_{max.}$ (in KBr) 3420, 3220, 1680, 1608, and 1583 (Found: C, 76·5; H, 8·6. $C_{19}H_{24}O_3$ requires C, 76·0; H, 8·0%).

(ii) When the above experiment was repeated with the 3-naphthalene-2-sulphonate (Vd) the same product was obtained, having m. p. and mixed m. p. 255—257° (from ethyl acetate) and the same infrared spectrum.

(iii) Elution of the column from the Clemmensen reduction of 3-hydroxy-1-methylœstra-1,3,5(10)-triene-11,17-dione (Vb) with benzene–ethyl acetate (1 : 1) also yielded the product (Ve) (identical infrared spectrum; m. p. and mixed m. p.).

3,17β-*Diacetoxy*-1-*methylœstra*-1,3,5(10)-*trien*-11-*one* (Vf).—To 3,17β-dihydroxy-1-methylœstra-1,3,5(10)-trien-11-one (Ve) (50 mg.) in pyridine (1 ml.) was added acetic anhydride (0·5 ml.). After 16 hr. the mixture was worked up in the usual manner, to yield the *diacetate*, prisms (from methanol), m. p. 180—182°, $\nu_{max.}$ (in KBr) 1725, 1710, 1575, 1245, 1220, and 1200 cm.$^{-1}$, τ 3·27, 4·89, 5·03, 5·15, 6·34, 6·48, 7·22, 7·39, 7·51, 7·75, 7·96, 8·05, and 9·18 (Found: C, 71·9; H, 7·2. $C_{23}H_{28}O_5$ requires C, 71·8; H, 7·3%).

3-*Hydroxy*-1-*methylœstra*-1,3,5(10)-*triene*-11-*one* (Vg).—Hydrogen chloride was bubbled for 5 hr. through a mixture of 3-hydroxy-1-methylœstra-1,3,5(10)-triene-11,17-dione (Vb) (1 g.), dioxan (180 ml.), concentrated hydrochloric acid (200 ml.), and zinc amalgam (140 g.) at 100°. After cooling, the solution was filtered, diluted with water (3 l.), and extracted with methylene chloride–ether (1 : 3). The extract was washed with aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and concentrated. The oil obtained was chromatographed on silica gel. Elution with benzene–ethyl acetate (19 : 1) gave an oily *hydroxy-ketone* which crystallized from methylene chloride and hexane as needles, m. p. 191—193°, $[\alpha]_D^{24}$ +310° (in dioxan), $\lambda_{max.}$ (in MeOH) 210 (shoulder) (ε 7500) and 282 mμ (ε 1600), $\nu_{max.}$ (in KBr) 3330, 1700, 1613, and 1585 cm.$^{-1}$ (Found: C, 79·8; H, 8·6. $C_{19}H_{24}O_2$ requires C, 80·2; H, 8·5%)

4-*Methyl*-1-*tosyloxyœstra*-1,3,5(10)-*trien*-17-*one* (VIb).—To 1-hydroxy-4-methylœstra-1,3,5(10)-trien-17-one [11] (VIa) (180 mg.; m. p. 247—249°) in pyridine (2 ml.) at 0° was added a precooled solution of toluene-*p*-sulphonyl chloride (400 mg.) in pyridine (2 ml.). After 16 hr. at 0° the mixture was worked up as described above, to yield the *ester* as prisms (from methanol), m. p. 132—133°, $\nu_{max.}$ (in KBr) 1722, 1562, 1197, and 1175 cm.$^{-1}$ (Found: C, 70·9; H, 6·6. $C_{26}H_{30}O_4S$ requires C, 71·2; H, 6·9%).

4-*Methylœstra*-1,3,5(10)-*triene*-1,17β-*diol* (VIc).—Hydrogen was bubbled through a solution

of the preceding ester (VIb) (200 mg.) in ethyl alcohol (40 ml.) containing an excess of Raney nickel until a portion did not absorb at 1197 or 1175 cm.$^{-1}$. Working up as usual and crystallization from methanol gave needles, m. p. 231—233° alone or mixed with 4-methylœstra-1,3,5(10)-triene-1,17β-diol [11] (VIc); the infrared spectra were identical.

Diethyl 1-*Methyl*-11,17-*dioxoœstra*-1,3,5(10)-*trien*-3-*yl Phosphate* (Vi).—To a solution of 3-hydroxy-methylœstra-1,3,5(10)-triene-11,17-dione (Vb) (350 mg.) in anhydrous tetrahydrofuran (5 ml.) and carbon tetrachloride (10 ml.), freshly distilled triethylamine (0·3 ml.) and diethyl phosphite (0·25 ml.) were added. The solution was left at room temperature for 72 hr. The precipitated triethylamine hydrochloride was collected. The filtrate was diluted with chloroform and washed with 5% sulphuric acid, 5% aqueous sodium hydroxide, and water, then dried (Na_2SO_4). Concentration under reduced pressure gave the *phosphate*, as a yellow oil which crystallized from light petroleum (b. p. 30—60°) as prisms, m. p. 132—133°, $\nu_{max.}$ (in KBr) 1720, 1710, 1580, 1275, 1045, and 1025 cm.$^{-1}$ (Found: C, 63·6; H, 7·3. $C_{23}H_{31}O_6P$ requires C, 64·0; H, 7·2%).

1-*Methyl*-9ξ-*œstra*-1,3,5(10)-*triene*-11,17-*dione* (Vj).—To the phosphate (Vi) (200 mg.), dissolved in anhydrous tetrahydrofuran (15 ml.) and liquid ammonia (32 ml.), sodium (160 mg.) was slowly added until a blue colour persisted. After 5 min., ethyl alcohol was added, and the volatile components were removed. The residue was diluted with water and extracted repeatedly with ethyl acetate. The combined extracts were washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. The residue (115 mg.) in pyridine (2 ml.) was added to a suspension of chromic acid (120 mg.) in pyridine (2 ml.) and kept at room temperature for 2 hr., then worked up as described above. The yellow oily *diketone* (Vj) crystallized from ethyl acetate as colourless prisms, m. p. 190—192°, $[\alpha]_D^{24}$ +450° (in $CHCl_3$), $\lambda_{max.}$ (in MeOH) 263 (ε 400) and 215 mμ (shoulder) (ε 1100), $\nu_{max.}$ (in KBr) 3090, 1720, 1710, 1575, and 785 cm.$^{-1}$ (Found: C, 80·2; H, 8·0. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·8%).

Huang-Minlon Reduction of 3-*Hydroxy*-1-*methylœstra*-1,3,5(10)-*triene*-11,17-*dione* (Vb).—The diketone (Vb) (400 mg.) and 85% aqueous hydrazine hydrate (1·4 ml.) were added to potassium hydroxide (1·8 g.) in diethylene glycol (13·5 ml.), and the mixture was heated at 140° for 1 hr. The temperature was increased slowly until the temperature in the flask reached 200° and was kept thereat for 4 hr. The solution was poured on ice and hydrochloric acid, and then extracted with methylene chloride–ether (1 : 3). The extract was washed with aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and concentrated under reduced pressure. The oil obtained (300 mg.) was chromatographed on silica gel. Elution with hexane–benzene (2 : 3) gave a colourless syrupy phenol (Vh) which resisted crystallization; it had $\nu_{max.}$ (in KBr) 3430, 1590, and 1575 cm.$^{-1}$. This was converted as usual into a toluene-*p*-sulphonate but that also resisted crystallization even after chromatography; it had $\nu_{max.}$ (in KBr) 1580, 1185, and 1175 cm.$^{-1}$.

4-*Methylœstra*-1,3,5(10)-*trien*-17-*one* (VIe).—A mixture of the phenol (VIa) (503 mg.), dry tetrahydrofuran (8 ml.), dry carbon tetrachloride (15 ml.), triethylamine (2·0 ml.), and diethyl phosphite (3 ml.) was refluxed for 72 hr. with the exclusion of moisture. More of the triethylamine (2 ml.) and diethyl phosphite (3 ml.) were added, and refluxing was continued for 24 hr. Portions were removed at intervals, and the reaction was stopped when the hydroxyl band in the infrared spectrum disappeared. The ester (VId) was recovered as described above (0·9 g.).

A portion of the crude ester (450 mg.) was dissolved in dry tetrahydrofuran (15 ml.) and liquid ammonia (60 ml.). Metallic sodium (500 mg.) was added in portions until a blue colour persisted. After 5 min. ethanol was added, and the steroids were recovered as described above. The yellow glass (140 mg.) was added in pyridine (3 ml.) to chromium trioxide (140 mg.) in pyridine (3 ml.). After the mixture had been kept at room temperature for 3 hr., the product (VIe) was recovered with ethyl acetate. The residue, crystallized from methanol, had m. p. 184—186°, undepressed on admixture with an authentic sample.[1] The infrared spectra of the samples were identical.

Storing a mixture of the phenol (VIa) (310 mg.), dry tetrahydrofuran (5 ml.), carbon tetrachloride (10 ml.), triethylamine (0·27 ml.), and diethyl phosphite (0·23 ml.) for 72 hr. at room temperature led to the recovery of the starting material.

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