Aromatic Steroids. Part II.[1] Chromium Trioxide Oxidation of Some Oestra-1,3,5(10)-trienes

By **R. C. Cambie,* Valerie F. Carlisle, C. J. Le Quesne,** and **T. D. R. Manning,** Department of Chemistry, University of Auckland, Auckland, New Zealand

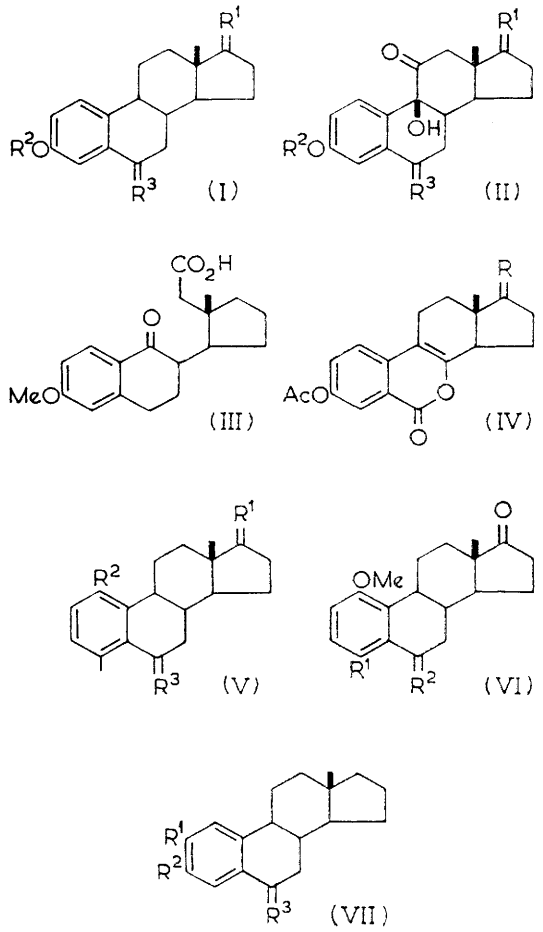
The effect of varying the position and nature of aryl substituents on the oxidation of oestra-1,3,5(10)-trienes with chromium trioxide has been examined. The deshielding effect of a C-6 keto-group is discussed.

DURING a re-examination [1] of the chromium trioxide oxidation of 3-methoxyoestra-1,3,5(10)-trien-17β-yl acetate (I; $R^1 = OAc, \cdots H$, $R^2 = Me$, $R^3 = H_2$) the major product was found to be the 9β-hydroxy-11-oxo-derivative (II; $R^1 = OAc, \cdots H$, $R^2 = Me$, $R^3 = H_2$).[2] Minor neutral products were the 6-oxo-derivative (I; $R^1 = OAc, \cdots H$, $R^2 = Me$, $R^3 = O$), the hydroxy-dione (II; $R^1 = O$, $R^2 = Me$, $R^3 = H_2$), and a mixture of the hydroxy-dione (II; $R^1 = OAc, \cdots H$, $R^2 = Me$, $R^3 = O$) and hydroxy-trione (II; $R^1 = R^3 = O$, $R^2 = Me$). Ring-c oxygenated products were also formed during the oxidation of 3-methoxyoestra-1,3,5(10)-trien-17-one (I; $R^1 = O$, $R^2 = Me$, $R^3 = H_2$) [1] and 3-ethoxy-oestra-1,3,5(10)-trien-17β-yl acetate (I; $R^1 = OAc, \cdots H$, $R^2 = Et$, $R^3 = H_2$).[2] 6-Oxo-derivatives are the only neutral products reported however, from the chromium trioxide oxidation of other ring-A-aromatic steroids.[3-7] We have examined the effect of varying the position and nature of aryl substituents on the oxidation of ring-A-aromatic steroids, especially in view of current interest in the physiological properties of their 6-oxo-derivatives.[8] Reported here are the products from the chromium trioxide oxidation of some ring-A-substituted oestra-1,3,5(10)-trienes; products from oxidation of substituted 19-norcholesta-1,3,5(10)-trienes will be reported in Part III.

From the oxidation of 3-methoxyoestra-1,3,5(10)-trien-17β-yl acetate (I; $R^1 = OAc, \cdots H$, $R^2 = Me$, $R^3 = H_2$) 17-oxo-derivatives were obtained, presumably arising by acid hydrolysis of the 17-acetoxy-group

[1] Part I, R. C. Cambie and T. D. R. Manning, *J. Chem. Soc.*, **1968**, 2603.
[2] Y. Suzuki, Japan. P. 17,831/1964 (*Chem. Abs.*, 1965, **62**, 5318)
[3] B. Longwell and O. Wintersteiner, *J. Biol. Chem.*, 1940, **133**, 219.
[4] E. Schwenk, U.S.P. 2,294,938/1942 (*Chem. Abs.*, 1943, **37**, 1016).
[5] E. Caspi, D. M. Piatak, and P. K. Grover, *J. Chem. Soc.* (*C*), 1966, 1034.
[6] H. Dannenberg and H. J. Gross, *Annalen*, 1966, **692**, 180.
[7] R. Knuppen and H. Breuer, *Annalen*, 1961, **639**, 194.
[8] K. Sakakibara, Japan. P. 9884/1964 (*Chem. Abs.*, 1964, **61**, 12,059); A. Bowers and O. Halpern, U.S.P. 3,159,621/1964 (*Chem. Abs.*, 1965, **62**, 7845); U.S.P. 3,201,428/1965 (*Chem. Abs.*, 1965, **63**, 11,664).

followed by oxidation of the resulting secondary alcohol. The oxidation of 3-methoxyoestra-1,3,5(10)-triene (I; $R^1 = R^3 = H_2$, $R^2 = Me$) was expected to lead to fewer products, and was therefore examined in detail.



Three neutral oxidation products, 9β-hydroxy-3-methoxyoestra-1,3,5(10)-trien-11-one (II; $R^1 = R^3 = H_2$, $R^2 = Me$), 9β-hydroxy-3-methoxyoestra-1,3,5(10)-triene-6,11-dione (II; $R^1 = H_2$, $R^2 = Me$, $R^3 = O$), and 3-methoxyoestra-1,3,5(10)-trien-6-one (I; $R^1 = H_2$, $R^2 = Me$, $R^3 = O$), were obtained, and 3-methoxy-9-oxo-9,11-seco-oestra-1,3,5(10)-trien-11-oic acid (III) was isolated from the acidic fraction. Thus ring-c-oxygenated derivatives were formed when a strong electron-donating group such as methoxy- was substituted at C-3; the hydroxy-ketone was the major product in each case (see Table 1). Evidence for the β-configuration of the 9-hydroxy-group of 17β-acetoxy-9-hydroxy-3-methoxyoestra-1,3,5(10)-trien-11-one (II; $R^1 = OAc$, $\cdots H$, $R^2 = Me$, $R^3 = H_2$) was presented in Part I.[1] Assignment of a similar configuration for 9-hydroxy-products in the present work follows from comparison of n.m.r. and i.r. spectra with those of the trienyl acetate.

[9] R. C. Cambie, L. N. Mander, A. K. Bose, and M. S. Manhas, *Tetrahedron*, 1964, **20**, 409.

In previous work[3,9] the 6-oxo-derivative (I; $R^1 = OAc$, $\cdots H$, $R^2 = Ac$, $R^3 = O$) was the only neutral product isolated from the chromium trioxide–acetic acid oxidation of oestra-1,3,5(10)-triene-3,17β-diyl diacetate (I; $R^1 = OAc$, $\cdots H$, $R^2 = Ac$, $R^3 = H_2$), while in Part I [1] it was shown the the greatest yield of hydroxy-ketone from 3-methoxyoestra-1,3,5(10)-trien-17β-yl acetate (I; $R^1 = OAc$, $\cdots H$, $R^2 = Me$, $R^3 = H_2$) was formed when the oxidant was 4N-chromium

TABLE 1

Oxidation products of 3-substituted oestra-1,3,5(10)-trienes (I)

R^1	R^2	R^3	Starting material returned	6-Oxo-deriv.	9-Hydroxy-11-oxo-derivs.	9-Hydroxy-6,11-dioxo-derivs.	Ref.
H_2	Me	H_2	1·0 (3·5)	1·0 (3·5)	16·0 (55·0)	11·0 (38·0)	*
$OAc, \cdots H$	Me	H_2	3·5 (14·5)	0·9 (3·7)	17·2 (72·0)	2·5 (10·0)	1
O	Me	H_2	3·0 (7·9)	4·0 (10·5)	30·0 (79·0)	0·7 (2·0)	1
H_2	Ac	H_2	6·0 (14·5)	18·0 (44·0)			*
$OAc, \cdots H$	Ac	H_2	3·2 (6·5)	29·0 (60·8)			9

* Present work.

Figures shown are the percentage (w/w) of product from starting material, with the percentage (w/w) of product in the neutral fraction in parentheses.

trioxide–50% aqueous sulphuric acid. We therefore examined the 4N-chromium trioxide oxidation of oestra-1,3,5(10)-trien-3-yl acetate (I; $R^1 = R^3 = H_2$, $R^2 = Ac$), since if a hydroxy-ketone was produced at all during the oxidation, the greatest yield should be obtained under these conditions. During the actual oxidation, hydrolysis of the acetate group occurred but after re-acetylation of the neutral fraction, 3-acetoxyoestra-1,3,5(10)-trien-6-one was the only neutral product isolated; no hydroxy-ketone formation was observed. Deacetylation has been observed during mild treatment of other α-tetralones with acid or base or even during chromatography on alumina.[10] The acid fraction from oxidation, when treated with acetic anhydride–sodium acetate, afforded 3-acetoxy-7-oxa-oestra-1,3,5(10),8-tetraen-6-one (IV; $R = H_2$), analogous to the unsaturated lactone (IV; $R = OAc$, $\cdots H$) from the oxidation of oestra-1,3,5(10)-triene-3,17β-diyl diacetate.[3] According to Longwell and Wintersteiner [3] chromic acid oxidation of ring-A-aromatic steroids proceeds beyond the monoketone stage to the 6,7-diketone, which is oxidised further to the keto-acid that ultimately forms the unsaturated lactone. A large amount of intractable tar obtained from both the neutral and the acidic fraction from oxidation of the acetate (I; $R^1 = R^3 = H_2$, $R^2 = Ac$) was probably due to formation of

[10] E. Wenkert, P. Beak, R. W. J. Carney, J. W. Chamberlin, D. B. R. Johnston, C. D. Roth, and A. Tahara, *Canad. J. Chem.*, 1963, **41**, 1924.

quinonoid products by oxidation of the phenolic group [11] formed during hydrolysis.

There appears to be no convenient way of introducing a methoxy-group at C-4 of a ring-A-aromatic steroid but derivatives with the more weakly electron-donating methyl group in this position are readily prepared by dienone–phenol rearrangements of 1,4-dien-3-ones. Caspi *et al.*[5] have reported the oxidation of the 4-methyloestra-1,3,5(10)-trienes (V; R^1 = OAc, ··· H, R^2 = H, $R^3 = H_2$), (V; R^1 = O, R^2 = H, $R^3 = H_2$), and (V; $R^1 = R^3 = H_2$, R^2 = H) with chromium trioxide in acetic acid. In each case the corresponding 6-oxo-derivative was the only product isolated from the neutral fraction. Likewise, although a number of minor products were formed (as shown by t.l.c.), the 6-oxo-derivative was the only isolable neutral product from oxidations of 4-methyloestra-1,3,5(10)-triene-1,17β-diyl diacetate (V; R^1 = OAc, ··· H, R^2 = OAc, $R^3 = H_2$),[12] 1-acetoxy-4-methyloestra-1,3,5(10)-trien-17β-yl benzoate (V; R^1 = OBz, ··· H, R^2 = OAc, $R^3 = H_2$), or 4-methylpregna-1,3,5(10)-triene-1,20β-diyl diacetate [V; R^1 = CH(OAc)Me, ... H, R^2 = OAc, $R^3 = H_2$],[13] where an acetate group is present at C-1.

Since a methoxy-group at C-1 might be expected to activate the C-9 position in a similar way to a C-3 methoxy-group, the oxidation of 1-methoxy-4-methyloestra-1,3,5(10)-trien-17β-yl benzoate (V; R^1 = OBz, ··· H, R^2 = OMe, $R^3 = H_2$) was examined. Although the neutral fraction from the reaction was shown by t.l.c. to be composed of at least fourteen compounds, no products were isolated in sufficient quantity or of sufficient purity to be positively identified. Similarly, oxidation of 1-methoxy-4-methyloestra-1,3,5(10)-trien-17-one (V; R^1 = O, R^2 = OMe, $R^3 = H_2$) gave a large number of products, but in this case low yields of compounds identified as the 6-oxo-derivative (V; $R^1 = R^3$ = O, R^2 = OMe), the keto-aldehyde (VI; R^1 = CHO, $R^2 = H_2$), and the diketo-acid (VI; $R^1 = CO_2H$, R^2 = O) were obtained after repeated preparative t.l.c. No evidence was obtained for the formation of a 9-hydroxy-11-oxo-derivative in either of these oxidations, in agreement with the fact that Dreiding models of the 1-methoxy-4-methyloestra-1,3,5(10)-trienes show that the methoxy-group completely blocks the C-11 position. Increased susceptibility of the C-4 methyl group to oxidation would be expected, however.

Oxidation of an oestra-1,3,5(10)-triene with a 2-methyl substituent was also examined. Oestra-1,3,5(10)-trien-3-ol (I; $R^1 = R^3 = H_2$, R^2 = H) was converted into the 2-methyl-derivative (VII; R^1 = Me, R^2 = OH, $R^3 = H_2$) by a Mannich reaction with formaldehyde and diethylamine followed by hydrogenolysis.[14] The C-3 phenolic group was then removed by Kenner desoxygenation of its diethyl phosphate ester with lithium in liquid ammonia.[15] Oxidation of the resulting 2-methyl derivative with chromium trioxide in acetic acid afforded mainly starting material; 2-methyloestra-1,3,5(10)-trien-6-one (VII; R^1 = Me, R^2 = H, R^3 = O) was the only other product isolated from the neutral fraction.

Caspi and his co-workers [16] have found that the effect of a C-11 keto-group on the n.m.r. spectrum of a ring-A-aromatic steroid is to shield a methyl group at C-1 and to deshield a methyl group at C-4. In each case examined in the present survey, the C-4 methyl resonance underwent a large paramagnetic shift (average 0·39 p.p.m.) on introduction of a C-6 keto-group. A Dreiding model of a ring-A-aromatic 6-oxo-steroid with ring C in a chair conformation reveals an almost rigid structure with the plane of the trigonal carbon atom nearly coincident with the plane of the aromatic ring and hence with the C-4 methyl group. The large downfield shift of the C-4 methyl resonance is thus explicable in terms of mutual reinforcement of the diamagnetic anisotropic shielding effects of the aromatic ring and the C-6 keto-group. The effect is not restricted to the C-4 methyl group; comparison of corresponding oestra-1,3,5(10)-trienes with and without C-6 keto-groups (Table 2) shows that all substituents on the aromatic ring, including protons, are deshielded by a C-6 keto-group.

TABLE 2

Deshielding effect of a 6-oxo-group $\Delta\delta \equiv [(R^3 = O) - (R^3 = H_2)]$

	C(1)–H	C(2)–H	C-3 substituent	C(4)–H
(I; R^1 = OAc, ··· H, R^2 = Me)	0·33	0·55	0·17	1·16
(I; $R^1 = H_2$, R^2 = Ac)	0·33	0·52	0·13	1·10
(I; R^1 = O, R^2 = Me)	0·08	0·28	0·07	0·81
(I; $R^1 = H_2$, R^2 = Me)	0·08	0·31	0·04	0·85
(I; $R^1 = H_2$, R^2 = H)	0·17	0·48	—	1·18
		C-2 substituent	C(3)-H	
(VII; R^1 = Me, R^2 = H)	0·25	0·16	0·36	1·20
	C-1 substituent	C(2)–H		C(4)–Me
(V; R^1 = O, R^2 = OMe)	0·10	0·15	0·37	0·38
(V; R^1 = OAc, ··· H, R^2 = OAc)	0·14	0·22	0·42	0·45
(V; R^1 = OBz, ··· H, R^2 = OMe)	0·09	0·26	0·48	0·44
(V; R^1 = OBz, ··· H, R^2 = OH)	—	0·21	0·51	0·44
(V; R^1 = OBz, ··· H, R^2 = OAc)	0·06	0·02	0·25	0·24
[V; R^1 = CH(OAc)Me, R^2 = OAc]	0·10	0·07	0·25	0·30

EXPERIMENTAL

For general experimental conditions see Part I.[1]

General Oxidation Procedure.—Unless otherwise stated,

[11] L. F. Fieser, *Org. Synth.*, Coll. Vol. I, 1944, p. 383.
[12] H. Dutler, H. Bosshard, and O. Jeger, *Helv. Chim. Acta*, 1957, **40**, 494.
[13] F. Sondheimer and G. Rosenkranz, U.S.P. 3,055,915/1962 (*Chem. Abs.*, 1963, **58**, 8010).
[14] T. L. Patton, *J. Org. Chem.*, 1960, **25**, 2148.
[15] G. W. Kenner and N. R. Williams, *J. Chem. Soc.*, 1955, 522; *cf.* A. H. Goldkamp, W. M. Hoehn, R. A. Mikulec, E. F. Nutting, and D. L. Cook, *J. Medicin. Chem.*, 1965, **8**, 409.
[16] E. Caspi, T. A. Wittstruck, and P. K. Grover, *Chem. and Ind.*, 1962, 1716.

the steroid was dissolved in acetone (freshly distilled from potassium permanganate) and the solution was treated dropwise at 0° with 4N-chromium trioxide in 50% aqueous sulphuric acid.* The mixture was kept at 20° for 18 hr., methanol was added to destroy the excess of oxidising agent, and the mixture was extracted with ether. The ether layer was washed with water and any remaining formic or sulphuric acid was removed with dilute sodium hydrogen carbonate solution. The point where the acidic reaction products began to react with the sodium hydrogen carbonate was recognised by colouration of the extract (*cf.* ref. 3). The ether phase was then extracted exhaustively with saturated sodium hydrogen carbonate solution, washed with water, dried, and concentrated to yield the neutral products. The red sodium hydrogen carbonate extracts were acidified and extracted with ether to yield the acidic reaction products.

Oxidation of 3-*Methoxyoestra*-1,3,5(10)-*triene*.—A solution of the methoxy-triene (I; $R^1 = R^3 = H_2$, $R^2 = Me$) [17,18] (1·0 g.), in acetone (60 ml.) was oxidised with 4N-chromium trioxide–sulphuric acid (20 ml.) to yield neutral (0·37 g.) and acidic (0·25 g.) products as yellow oils.

The acidic oil was adsorbed on silica gel. Initial chloroform eluates gave a yellow oil which gave the monohydrate of 3-*methoxy*-9-*oxo*-9,11-*seco*-*oestra*-1,3,5(10)-11-*oic acid*, as needles (20%), m.p. 70—71° (from aqueous ethanol) (Found: C, 68·4; H, 7·9; O, 23·7. $C_{19}H_{24}O_4,H_2O$ requires C, 68·2; H, 7·8; O, 23·9%. Found for sample dried to constant wt.: C, 72·0; H, 7·8. $C_{19}H_{24}O_4$ requires C, 72·1; H, 7·65%), $\lambda_{max.}$ 203 (ε 27,020), 224 (17,230), and 274 (22,610) mμ, $\nu_{max.}$ 3670 (OH), 3200br (H-bonded OH of CO_2H), 1710 (CO_2H), and 1672 [C(9)O] cm.$^{-1}$, δ 1·08 (s, C-18 angular Me), 2·45 (m, C-6 protons), 2·98 (m, C-12 protons), 3·86 (s, aryl OMe), 6·40 (s, CO_2H), 6·81 (d, $J_{2,4}$ 2·2 c./sec., C-4 aromatic H), 6·94 (dd, $J_{1,2}$ 8·3 c./sec., $J_{2,4}$ 2·2 c./sec., C-2 aromatic H), and 8·09 (d, $J_{1,2}$ 8·3 c./sec., C-1 aromatic H), r.d. (*c* 0·664 in EtOH) $[\phi]_{589}$ −80°, $[\phi]_{420}$ −133br,tr, $[\phi]_{355}$ +535pk, $[\phi]_{352}$ +499tr, $[\phi]_{343}$ +770pk, $[\phi]_{335}$ 0, and $[\phi]_{325}$ −483tr.

The neutral product was washed sparingly with cold ether. The insoluble solid gave 9β-*hydroxy*-3-*methoxy*-*oestra*-1,3,5(10)-*triene*-6,11-*dione* (0·12 g., 11%) as needles, m.p. 227° (subl. 224°) (from methanol) (Found: C, 72·5; H, 7·0; O, 20·6. $C_{19}H_{22}O_4$ requires C, 72·6; H, 7·0; O, 20·4%), $\lambda_{max.}$ 225 (ε 19,700) and 320 (2360) mμ, $\nu_{max.}$ 3463 (intramol. bonded OH), 1715 [C(11)O], 1695 [C(6)O], 1609, 1575, 1500 (Ph), and 1110 (C-9 OH) cm.$^{-1}$, δ 0·78 (d, $J_{12\alpha,18}$ 0·5 c./sec., C-18 angular Me), 2·25 (d, $J_{12\alpha,12\beta}$ 12·5, $J_{12\alpha,18}$ 0·5 c./sec., C-12α H), 2·61 (dd, $J_{7\alpha,7\beta}$ 16·8, $J_{7\alpha,8}$ 5 c./sec., C-7β H), 2·63 (d, $J_{12\alpha,12\beta}$ 12·5 c./sec., C-12β H), 3·34 (2d, $J_{7\alpha,7\beta}$ 16·8, $J_{7\alpha,8}$ 5 c./sec., C-7α H), 3·88 (s, aryl OMe), 4·59 (s, OH), 6·84 (d, $J_{1,2}$ 8 c./sec., C-1 aromatic H), 7·13 (dd, $J_{1,2}$ 8·9, $J_{2,4}$ 3 c./sec., C-2 aromatic H), and 7·60 (d, $J_{2,4}$ 3 c./sec., C-4 aromatic H), r.d. (*c* 0·032 in EtOH) $[\phi]_{589}$ +442°, $[\phi]_{400}$ +2350, $[\phi]_{360}$ +4320, $[\phi]_{328}$ +30,600pk, $[\phi]_{313}$ 0, $[\phi]_{300}$ −33,590tr, and $[\phi]_{282}$ −9560.

The ether washings were concentrated and the yellow oil was adsorbed on silica gel. Elution with light petroleum–benzene (1 : 1) yielded starting material (10 mg., 1%); elution with light petroleum–benzene (1 : 2) then gave 3-methoxyoestra-1,3,5(10)-trien-6-one (10 mg., 1%) which gave needles, m.p. and mixed m.p. 89—90° (from methanol) (physical constants for this compound are recorded later).

Elution of the column with ether–benzene (1 : 5) yielded 9β-*hydroxy*-3-*methoxyoestra*-1,3,5(10)-*trien*-11-*one* (0·16 g., 16%), which gave plates, m.p. 115—116° (from ether) (Found: C, 76·1; H, 8·1; O, 15·6. $C_{19}H_{24}O_3$ requires C, 76·0; H, 8·1; O, 16·0%), $\lambda_{max.}$ 225 (ε 6800), 277 (1460), and 284 (1325) mμ, $\nu_{max.}$ (CCl_4) 3463 (intramol. bonded OH), 1711 [C(11)O], 1610, 1575, 1501 (Ph), and 1110 (OH) cm.$^{-1}$, δ(CCl_4) 0·76 (s, $W_{\frac{1}{2}}$ 2 c./sec., C-18 angular Me), 2·20 (d, J 12·8 c./sec., C-12α H, showing further fine splitting due to coupling with C-18 Me), 2·51 (d, J 12·8 c./sec., C-12β H), 2·79 (m, C-6 protons), 3·80 (s, aryl OMe), 4·24 (s, OH), and 6·75 (s, aromatic protons), r.d. (*c* 0·294 in EtOH) $[\phi]_{589}$ +536°, $[\phi]_{400}$ +1470, $[\phi]_{330}$ +8000, $[\phi]_{309}$ +15,000pk, $[\phi]_{291}$ 0, $[\phi]_{270}$ −8180°, and $[\phi]_{230}$ −10,110br,tr.

Oestra-1,3,5(10)-*trien*-3-*yl Acetate* (I; $R^1 = R^3 = H_2$, R^2 = Ac).—Acetylation of oestra-1,3,5(10)-trien-3-ol (2·5 g.) with acetic anhydride–pyridine (20°; 24 hr.) gave *oestra*-1,3,5(10)-*trien*-3-*yl acetate* (2·7 g., 97%) which gave needles, m.p. 85—86° (from methanol), $[\alpha]_D$ +94° (*c* 0·72 in cyclohexane) (Found: C, 80·0; H, 8·85; O, 11·0. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·8; O, 10·7%), $\lambda_{max.}$ (cyclohexane) 214 (ε 9420), 270 (825), and 276 (775) mμ, $\nu_{max.}$ 1760 (C-3 OAc), 1615, 1580, 1500 (Ph), 1240 (OAc), and 832 (2 adjacent aromatic protons) cm.$^{-1}$, δ 0·75 (s, C-18 angular Me), 2·17 (s, C-3 OAc), 2·84 (m, C-6 and C-9 benzylic protons), 6·71 (d, C-4 aromatic H), 6·76 (dd, $J_{1,2}$ 8, $J_{2,4}$ 3 c./sec., C-2 aromatic H), and 7·19 (d, $J_{1,2}$ 8 c./sec., C-1 aromatic H), r.d. (*c* 0·35) $[\phi]_{589}$ +180°, $[\phi]_{400}$ +481, $[\phi]_{341}$ +752pk, $[\phi]_{299}$ +222tr, and $[\phi]_{290}$ +655.

Oxidation of Oestra-1,3,5(10)-*trien*-3-*yl Acetate*.—A solution of oestra-1,3,5(10)-trien-3-yl acetate (2·9 g.) in acetone (180 ml.) was oxidised with 4N-chromium trioxide–sulphuric acid (60 ml.). During the oxidation partial hydrolysis of the C-3 acetoxy-group occurred and the sodium hydrogen carbonate-insoluble portion of the product was therefore acetylated with acetic anhydride–pyridine. This gave a brown oil (1·59 g.) which was chromatographed on silica gel. Initial benzene eluates yielded starting material (0·22 g., 6%); later benzene eluates gave 3-*acetoxyoestra*-1,3,5(10)-*trien*-6-*one* (0·70 g., 18%) which gave needles, m.p. 152—154° (from aqueous methanol) (Found: C, 77·2; H, 7·9. $C_{20}H_{24}O_3$ requires C, 76·9; H, 7·7%), $\lambda_{max.}$ 209 (ε 27,450), 248 (11,090), and 297 (2390) mμ, $\nu_{max.}$ 1763 (C-3 OAc), 1670 [C(6)O], 1608, 1575, 1480 (Ph), and 1180 (aryl CO) cm.$^{-1}$, δ 0·78 (s, C-18 angular Me), 2·30 (s, aryl OAc), 7·28 (dd, $J_{2,4}$ 2·6, $J_{1,2}$ 8·6 c./sec., C-2 aromatic H), 7·52 (d, $J_{1,2}$ 8·6 c./sec., C-1 aromatic H), and 7·81 (d, $J_{2,4}$ 2·6 c./sec., C-4 aromatic H), r.d. (*c* 0·420 in EtOH) $[\phi]_{589}$ 0°, $[\phi]_{400}$ +433, $[\phi]_{352}$ +2638pk, $[\phi]_{330}$ +1186, and $[\phi]_{313}$ 0.

Further elution of the column yielded only dark brown intractable oils (0·67 g.).

Chromatography of the acidic fraction on silica gel did not effect purification. This oil (1·93 g.) was treated with acetic anhydride–sodium acetate under reflux and the product was chromatographed on silica gel. Elution with benzene gave 3-*acetoxy*-7-*oxa*-*oestra*-1,3,5(10),8-*tetraen*-6-*one* (0·84 g., 22%) which gave needles, m.p. 155—156° (from methanol) (Found: C, 73·4; H, 6·7. $C_{19}H_{20}O_4$ requires C, 73·1; H,

* This oxidising agent was used since a 50% aqueous sulphuric acid medium was found to yield the highest yield of hydroxyketone.[1] A 4N-solution of chromium trioxide is the strongest possible in this medium.

[17] A. Butenandt and U. Westphal, *Z. physiol. Chem.*, 1934, **223**, 147 (*Chem. Abs.*, 1934, **28**, 3114).

[18] K. J. Sax, R. H. Blank, R. H. Evans, L. I. Feldman, and C. E. Holmlund, *J. Org. Chem.*, 1964, **29**, 2351.

6·5%), $\lambda_{max.}$ 201 (ε 17,300), 221 (14,900), 227sh (13,020), 272sh (9510), and 280 (9760) mμ, $\nu_{max.}$ 1750br (C-3 OAc), 1640 (α-pyrone), 1610, 1580, 1490 (Ph), and 1190 (CO) cm.$^{-1}$, δ 0·88 (s, C-18 angular Me), 2·28 (s, C-3 OAc), 6·93 (m, C-2 and C-4 aromatic protons), and 7·42 (d, $J_{1,2}$ 8·9 c./sec., C-1 aromatic H), r.d. (*c* 0·44 in EtOH) $[\phi]_{589}$ 0°, $[\phi]_{400}$ −398, $[\phi]_{330}$ −2730, $[\phi]_{304}$ −5930tr, and $[\phi]_{296}$ −5315.

Later eluates yielded a brown intractable gum (0·9 g.).

3-*Hydroxyoestra*-1,3,5(10)-*trien*-6-*one* (I; $R^1 = H_2$, R^2 = H, R^3 = O).—3-Acetoxyoestra-1,3,5(10)-trien-6-one (0·24 g.) was saponified with 5% methanolic potassium hydroxide solution in the usual manner and the product gave 3-*hydroxyoestra*-1,3,5(10)-*trien*-6-*one* (0·21 g.) as needles, m.p. 185—186° (from chloroform–light petroleum) (Found: C, 79·7; H, 8·3. $C_{18}H_{22}O_2$ requires C, 80·0; H, 8·2%), $\lambda_{max.}$ 203 (ε 15,920), 222 (19,700), 255 (8460), and 327 (2900) mμ, $\nu_{max.}$ 3580 (OH), 3295br (H-bonded OH), 1670 [C(6)O], 1610, 1580, 1500 (Ph), 1258 (aryl CO), 1230br (OH), 872 (isolated aromatic H), and 833 (2 adjacent aromatic protons) cm.$^{-1}$, δ 0·74 (s, C-18 angular Me), 7·13 (dd, $J_{1,2}$ 8·6, $J_{2,4}$ 2·4 c./sec., C-2 aromatic H), 7·30 (s, C-3 OH), 7·36 (dd, $J_{1,2}$ 8·6, $J_{1,4}$ 1·0 c./sec., C-1 aromatic H), and 7·76 (dd, $J_{2,4}$ 2·4, $J_{1,4}$ 1·0 c./sec., C-4 aromatic H), r.d. (*c* 0·625 in EtOH) $[\phi]_{589}$ +67°, $[\phi]_{400}$ +1380, $[\phi]_{367}$ +3088pk, and $[\phi]_{351}$ +1832.

3-*Methoxyoestra*-1,3,5(10)-*trien*-6-*one*, prepared with dimethyl sulphate and anhydrous potassium carbonate in acetone under reflux, gave plates, m.p. 89—90° (from aqueous methanol) (Found: C, 79·8; H, 8·7. $C_{19}H_{24}O_2$ requires C, 80·2; H, 8·5%), $\lambda_{max.}$ 224 (ε 15,700), 257 (5500), and 326 (1950) mμ, $\nu_{max.}$ 1678 [C(6)O], 1608, 1570, 1495 (Ph), and 1240 (CO) cm.$^{-1}$, δ (CCl_4) 0·75 (s, C-18 angular Me), 3·83 (s, aryl OMe), 6·97 (dd, $J_{1,2}$ 8·8, $J_{2,4}$ 3 c./sec., C-2 aromatic H), 7·27 (d, $J_{1,2}$ 8·8 c./sec., C-1 aromatic H), and 7·42 (d, $J_{2,4}$ 3 c./sec., C-4 aromatic H), r.d. (*c* 0·49 in EtOH) $[\phi]_{589}$ +107°, $[\phi]_{500}$ +250, $[\phi]_{400}$ +890, $[\phi]_{355}$ +4400pk, and $[\phi]_{340}$ +2800.

1,17β-*Diacetoxy*-4-*methyloestra*-1,3,5(10)-*trien*-6-*one* (V; R^1 = OAc, · · · H, R^2 = OAc, R^3 = O).—A solution of 4-methyloestra-1,3,5(10)-triene-1,17β-diyl diacetate [12] (1·62 g.) in glacial acetic acid (5 ml.) was treated with chromium trioxide (1·44 g.) which had been dissolved in the minimum amount of water and then diluted to 15 ml. with glacial acetic acid. The mixture was kept at 20° for 3 days, and then worked up in the usual manner. The neutral fraction was chromatographed on alumina. Elution with benzene and benzene–ether (1 : 1) gave 1,17β-*diacetoxy*-4-*methyloestra*-1,3,5(10)-*trien*-6-*one* (0·48 g.) as needles, m.p. 155—157° (Found: C, 71·8; H, 7·7; O, 20·6. $C_{23}H_{28}O_5$ requires C, 71·85; H, 7·3; O, 20·7%), $\lambda_{max.}$ 250 (ε 11,240) and 303 (3560) mμ, $\nu_{max.}$ (CCl_4) 1765 (C-1 OAc), 1745 (C-17 OAc), 1690 [C(6)O], 1250 (C-17 OAc), and 1205 (C-1 OAc) cm.$^{-1}$, δ 0·88 (s, C-18 angular Me), 2·08 (s, C-17 OAc), 2·32 (s, C-1 OAc), 2·55 (s, C-9 benzylic H), 2·63 (s, C-4 Me), 4·78 (m, C-17 H), 7·08 (d, $J_{2,3}$ 8 c./sec., C-3 aromatic H), and 7·16 (d, $J_{2,3}$ 8 c./sec., C-2 aromatic H), r.d. (*c* 0·459 in MeOH) $[\phi]_{589}$ +173°, $[\phi]_{386}$ +478sh, $[\phi]_{370}$ +569pk, $[\phi_{339}$ 0°, and $[\phi]_{335}$ −38tr.

1-*Acetoxy*-4-*methyloestra*-1,3,5(10)-*trien*-17β-*yl Benzoate* (V; R^1 = OBz, · · · H, R^2 = OAc, $R^3 = H_2$).—A solution of acetic anhydride (19 ml.) and perchloric acid (0·15 ml., 72%) in dry ethyl acetate (75 ml.) was added to a solution of 17β-benzoyloxyandrosta-1,4-dien-3-one (2·33 g.) in ethyl acetate (75 ml.) and the mixture was kept at 20° for 45 min. Work-up in the usual manner gave 1-*acetoxy*-4-*methyloestra*-1,3,5(10)-*trien*-17β-*yl benzoate* (2·10 g., 83%) as tablets, m.p. 187—189° (from acetone) (Found: C, 77·8; H, 7·5. $C_{28}H_{32}O_4$ requires C, 77·75; H, 7·5%), $\lambda_{max.}$ 230 (ε 13,300) and 270 (1090) mμ, $\nu_{max.}$ 1765 (C-1 OAc), 1720 (C-17 OBz), 1605, and 1590 (Ph) cm.$^{-1}$, δ (CCl_4) 1·0 (s, C-18 angular Me), 2·21 and 2·25 (2s, C-4 Me and C-1 OAc), 2·68br (m, C-6 and C-9 benzylic protons), 5·0 (m. C-17, H), 6·78 (d, $J_{2,3}$ 8 c./sec., C-3 aromatic H), 7·03 (d, $J_{2,3}$ 8 c./sec., C-2 aromatic H), and 7·38—7·62 and 8·01—8·18 (2m, C-17 OBz).

1-*Hydroxy*-4-*methyloestra*-1,3,5(10)-*trien*-17β-*yl Benzoate* (V; R^1 = OBz, · · · H, R^2 = OH, $R^3 = H_2$).—Hydrolysis of 1-acetoxy-4-methyloestra-1,3,5(10)-trien-17β-yl benzoate (1·0 g.) with 5% methanolic potassium hydroxide gave 1-*hydroxy*-4-*methyloestra*-1,3,5(10)-*trien*-17β-*yl benzoate* (0·88 g., 97%), which gave needles, m.p. 214—216° (from light petroleum–ether) (Found: C, 80·2; H, 7·6; O, 12·3. $C_{26}H_{30}O_3$ requires C, 80·0; H, 7·7; O, 12·3%), $\lambda_{max.}$ 216 (ε 9,600), 231 (11,400) and 286 (1400) mμ, δ 0·98 (s, C-18 angular Me), 2·12 (s, C-4 Me), 4·76—5·08 (t, C-17 H), 5·44 (s, C-1 OH), 6·48 (d, $J_{2,3}$ 8 c./sec., C-3 aromatic H), 6·78 (d, $J_{2,3}$ 8 c./sec., C-2 aromatic H), and 7·31—7·47 and 7·91—8·09 (2m, C-17 OBz).

1-*Methoxy*-4-*methyloestra*-1,3,5(10)-*trien*-17β-*yl Benzoate* (V; R^1 = OBz, · · · H, R^2 = OMe, $R^3 = H_2$).—Methylation of 1-hydroxy-4-methyloestra-1,3,5(10)-trien-17β-yl benzoate (0·50 g.) with potassium and methyl iodide in dry benzene, gave 1-*methoxy*-4-*methyloestra*-1,3,5(10)-*trien*-17β-*yl benzoate* (0·50 g., 96%) as needles, m.p. 123—125° (from aqueous acetone) (Found: C, 80·0; H, 8·1; O, 11·7. $C_{27}H_{32}O_3$ requires C, 80·2; H, 8·0; O, 11·9%), $\lambda_{max.}$ 218 (ε 16,000), 230 (23,000), and 284 (2700) mμ, δ 0·97 (s, C-18 angular Me), 2·10 (s, C-4 Me), 3·68 (s, C-1 OMe), 4·85br (t, C-17 H), 6·43 (d, $J_{2,3}$ 8 c./sec., C-3 aromatic H), 6·77 (d, $J_{2,3}$ 8 c./sec., C-2 aromatic H), and 7·28—7·47 and 7·88—8·04 (2 m, C-17 OBz).

17β-*Benzoyloxy*-1-*hydroxy*-4-*methyloestra*-1,3,5(10)-*trien*-6-*one* (V; R^1 = OBz, · · · H, R^2 = OH, R^3 = O).—Chromium trioxide (1·57 g.), dissolved in the minimum quantity of water and then diluted with acetic acid (16 ml.), was added dropwise to an ice-cold solution of 1-acetoxy-4-methyloestra-1,3,5(10)-trien-17β-yl benzoate (2·05 g.) in acetic acid (30 ml.). The mixture was kept at 20° for 24 hr. and then worked up.

The solid neutral residue (1·54 g.) was chromatographed on alumina to give starting material (0·13 g., 6·4%) from benzene eluates. Benzene–ether (3 : 1) eluates yielded 17β-*benzoyloxy*-1-*hydroxy*-4-*methyloestra*-1,3,5(10)-*trien*-6-*one* (0·58 g., 30%) which gave tablets, m.p. 245—247° (from ethanol–chloroform) (Found: C, 77·5; H, 7·0; O, 15·8. $C_{26}H_{28}O_4$ requires C, 77·2; H, 7·0; O, 15·8%), $\lambda_{max.}$ 218 (ε 16,000), 232 (24,000), 262 (6400), and 332 (2300) mμ, $\nu_{max.}$ 3400—3300 (OH), 1715 (C-17 OBz), 1690 [C(6)O], 1605, 1580 (Ph), 1280, and 1120 (OBz) cm.$^{-1}$, δ 1·01 (s, C-18 angular Me), 2·56 (s, C-4 Me), 5·0 (m, C-17 H), 6·87 (C-1 OH), 6·99 (s, C-2 and C-3 aromatic protons), and 7·43—7·65 and 8·00—8·20 (2m, C-17 OBz).

1-*Acetoxy*-17β-*benzoyloxy*-4-*methyloestra*-1,3,5(10)-*trien*-6-*one* (V; R^1 = OBz, · · · H, R^2 = OAc, R^3 = O).—Acetylation of 17β-benzoyloxy-1-hydroxy-4-methyloestra-1,3,5(10)-trien-6-one (0·21 g.) with acetic anhydride–pyridine (20°; 24 hr.) gave 1-*acetoxy*-17β-*benzoyloxy*-4-*methyloestra*-1,3,5(10)-*trien*-6-*one* (0·22 g., 94%) as plates, m.p. 178—180° (from light petroleum–ether) (Found: C, 75·8; H, 6·8; O, 17·8. $C_{28}H_{30}O_5$ requires C, 75·3; H,

6·8; O, 17·9%), $\lambda_{max.}$ 221 (ε 10,800), 229 (8900), 250 (4300), and 304 (1100) mμ, δ 0·97 (s, C-18 angular Me), 2·27 (s, C-1 OAc), 2·59 (s, C-4 Me), 4·28—5·12 (t, C-17 H), 7·03 and 7·05 (2d, $J_{2,3}$ 8 c./sec., C-2 and C-3 aromatic protons), and 7·25—7·55 and 7·86—8·13 (2m, C-17 OBz).

17β-*Benzoyloxy*-1-*methoxy*-4-*methyloestra*-1,3,5(10)-*trien*-6-*one* (V; R^1 = OBz, · · · H, R^2 = OMe, R^3 = O).—Methylation of 17β-benzoyloxy-1-hydroxy-4-methyloestra-1,3,5(10)-trien-6-one (0·1 g.) with potassium and methyl iodide in dry benzene (reflux; 6 hr.), gave after work-up and chromatography on alumina, 17β-benzoyloxy-1-methoxy-4-methyloestra-1,3,5(10)-trien-6-one (0·1 g.) as a yellow gum, $\lambda_{max.}$ 220sh (ε 19,000), 231 (25,000), 258 (6300) and 327 (2600) mμ, $\nu_{max.}$ (CCl_4) 1720 (C-17 OBz), 1690 [C(6)O], and 1605 and 1585 (Ph) cm.$^{-1}$, δ 0·98 (s, C-18 angular Me), 2·54 (s, C-4 Me), 3·77 (s, C-1 OMe), 4·93br (t, C-17 H), 6·91 (d, $J_{2,3}$ 8 c./sec., C-3 aromatic H), 7·03 (d, $J_{2,3}$ 8 c./sec., C-2 aromatic H), and 7·33—7·52 and 7·92—8·12 (2m, C-17 OBz).

Oxidation of 1-*Methoxy*-4-*methyloestra*-1,3,5(10)-*trien*-17-*one* (V; R^1 = O, R^2 = OMe, R^3 = H_2).—Chromium trioxide (15·65 g.) dissolved in water (42 ml.) and then diluted with acetic acid (378 ml.), was added dropwise to a solution of 1-methoxy-4-methyloestra-1,3,5(10)-trien-17-one [19] (14·05 g.) in acetic acid (420 ml.) and acetone (980 ml.) cooled to −30°. The temperature of the mixture was allowed to rise to 0° during 10 hr., and the product was worked up in the usual manner.

The yellow neutral oil (12·07 g.) was subjected to repeated preparative t.l.c., which yielded starting material (5·59 g., 40%) and only two identifiable products, as yellow gums, 1-methoxy-4-methyloestra-1,3,5(10)-triene-6,17-dione (30 mg., 0·2%), $\nu_{max.}$ (CCl_4) 1745 [C(17)O], 1690 [C(6)O], and 1580 (Ph) cm.$^{-1}$, δ 0·94 (s, C-18 angular Me), 2·47 (s, C-4 Me), 3·78 (s, C-1 OMe), 6·82 (d, $J_{2,3}$ 8·2 c./sec., C-3 aromatic H), and 6·93 (d, $J_{2,3}$ 8·2 c./sec., C-2 aromatic H), and 4-formyl-1-methoxyoestra-1,3,5(10)-trien-17-one (0·48 g., 3·3%), $\lambda_{max.}$ 212 (ε 13,000), 233 (12,000) and 276 (8800) mμ, $\nu_{max.}$ (CCl_4) 2720, [C(4)HO] 1745 [C(17)O], 1700 (C-4 ArCHO), and 1580 (Ph) cm.$^{-1}$, δ(CCl_4) 0·83 (s, C-18 angular Me), 3·87 (s, C-1 OMe), 6·76 (d, $J_{2,3}$ 8 c./sec., C-2 aromatic H), 7·50 (d, $J_{2,3}$ 8 c./sec., C-3 aromatic H), and 9·62 (s, C-4 aldehydic H).

Preparative t.l.c. of the acidic fraction (0·92 g.) yielded 1-methoxy-6,17-dioxo-oestra-1,3,5(10)-triene-4-carboxylic acid (70 mg., 0·5%) as a yellow gum, $\lambda_{max.}$ 217 (ε 20,000) and 262 (6600) mμ, $\nu_{max.}$ 2700—2500 (C-4 CO_2H), 1745 [C(17)O], 1690br [C-4 aryl CO_2H and C(6)O], 1585, and 1570 (Ph) cm.$^{-1}$, δ 0·88 (s, C-18 angular Me), 3·81 (s, C-1 OMe), 6·67 (d, $J_{2,3}$ 8 c./sec., C-2 aromatic H), and 7·88 (d, $J_{2,3}$ 8 c./sec., C-3 aromatic H).

2-*Diethylaminomethyloestra*-1,3,5(10)-*trien*-3-*ol* (VII; R^1 = CH_2NEt_2, R^2 = OH, R^3 = H_2).—Formaldehyde (37%, 4·7 ml.) was added in two equal portions during 2 hr. to a solution of oestra-1,3,5(10)-trien-3-ol (1·99 g.) in benzene (24 ml.), ethanol (40 ml.), and diethylamine (7·8 ml.). The mixture was heated under reflux for 16 hr.; chromatography of the product on alumina then gave 2-*diethylaminomethyloestra*-1,3,5(10)-*trien*-3-*ol* (1·20 g., 44%) which gave needles, m.p. 97—99° (from aqueous acetone) (Found: C, 81·0; H, 10·35; N, 4·1. $C_{23}H_{35}NO$ requires C, 80·9; H, 10·3; N, 4·1%), $\lambda_{max.}$ 229 (ε 5100) and 288 (3040) mμ, $\nu_{max.}$ 3420—3320 (C-3 OH), 1610, and 1580 (Ph) cm.$^{-1}$, δ 0·73 (s, C-18 angular Me), 1·07 (t, J 7 c./sec., Me of ethyl groups), 2·52 (q, J 7 c./sec., CH_2 of ethyl groups), 3·71 (s, C-2 CH_2N), 6·54 (s, C-4 aromatic H), and 6·89 (s, C-1 aromatic H), r.d. (*c* 0·292 in EtOH) $[\phi]_{589}$ +596°, $[\phi]_{500}$ +842, $[\phi]_{400}$ +1345, and $[\phi]_{292}$ +3050pk.

2-*Methyloestra*-1,3,5(10)-*trien*-3-*ol* (VII; R^1 = Me, R^2 = OH, R^3 = H_2).—A suspension of Raney nickel catalyst (W7; 20 g.) in a solution of 2-diethylaminomethyloestra-1,3,5(10)-trien-3-ol (2·05 g.) in ethanol (320 ml.) was was heated under reflux for 22 hr. with continuous stirring. Work-up and chromatography on silica gel gave 2-*methyloestra*-1,3,5(10)-*trien*-3-*ol* (7·20 g., 74%) as needles, m.p. 105—108° (from light petroleum) (Found: C, 84·65; H, 9·8; O, 5·8. $C_{19}H_{26}O$ requires C, 84·4; H, 9·7; O, 5·9%), $\lambda_{max.}$ 204 (ε 14,300) and 278 (3090) mμ, δ 0·73 (s, C-18 angular Me), 2·18 (s, C-2 aromatic Me), 2·76br (m, C-6 and C-9 benzylic protons), 5·09 (s, C-3 OH), 6·48 (s, C-4 aromatic H), and 7·05 (s, C-1 aromatic H).

Diethyl 2-*Methyloestra*-1,3,5(10)-*trien*-3-*yl Phosphate* [VII; R^1 = Me, R^2 = $OP(O)OEt_2$, R^3 = H_2].—Triethylamine (0·6 ml.) was added slowly with vigorous shaking to an ice-cooled solution of 2-methyloestra-1,3,5(10)-trien-3-ol (1·17 g.) in carbon tetrachloride (10 ml.) and diethyl phosphite (0·6 ml.) and the reaction mixture kept overnight at 20°. Work-up, followed by chromatography of the product on silica gel gave *diethyl* 2-*methyloestra*-1,3,5(10)-*trien*-3-*yl phosphate* (1·47 g., 92%), which gave plates, m.p. 73—76° (from light petroleum) (Found: C, 68·1; H, 9·1. $C_{23}H_{35}O_4P$ requires C, 68·0; H, 8·7%), $\lambda_{max.}$ 217 (ε 7980), 273 (1270), and 281 (1330) mμ, δ 0·74 (s, C-18 angular Me), 1·37 (t, J 7 c./sec., CH_3 of ethyl protons), 2·28 (s, C-2 aromatic Me), 2·84br (m, C-6 and C-9 benzylic protons), 4·18 and 4·32 (2q, J 7 c./sec., CH_2 of ethyl protons), and 7·06 and 7·17 (2s, C-1 and C-4 aromatic protons).

2-*Methyloestra*-1,3,5(10)-*triene* (VII; R^1 = Me, R^2 = H, R^3 = H_2).—Diethyl 2-methyloestra-1,3,5(10)-trien-3-yl phosphate (1·46 g.) was stirred with liquid ammonia (10 ml.) while lithium (50 mg.) was added in portions during 2 hr. Diethyl ether (5 ml.) was added, and the mixture was stirred for another 1 hr. before the ammonia was allowed to evaporate off. Extraction with ether followed by chromatography on alumina gave 2-*methyloestra*-1,3,5(10)-*triene* (0·48 g., 50%), as needles, m.p. 84—86° (from ethyl acetate) (Found: C, 89·5; H, 10·3. $C_{19}H_{26}$ requires C, 89·7; H, 10·3%), $\lambda_{max.}$ (cyclohexane) 213 (ε 6540) and 272 (1010) mμ, δ (CCl_4) 0·74 (s, C-18 angular Me), 2·25 (s, C-2 aromatic Me), 2·77br (m, C-6 benzylic protons), 6·82 (s, C-3 and C-4 aromatic protons), and 7·01 (s, C-1 aromatic H), r.d. (*c* 0·861) $[\phi]_{589}$ +339°, $[\phi]_{500}$ +538, $[\phi]_{400}$ +791, and $[\phi]_{280}$ +3075pk.

2-*Methyloestra*-1,3,5(10)-*trien*-6-*one* (VII; R^1 = Me, R^2 = H, R^3 = O).—Chromium trioxide (0·48 g.) dissolved in the minimum quantity of water and then diluted with acetic acid (3 ml.) was added dropwise to an ice-cold solution of 2-methyloestra-1,3,5(10)-triene (0·37 g.) in acetic acid (2 ml.) and diethyl ether (5 ml.). The mixture was kept at 20° for 18 hr. and then worked up.

The yellow neutral gum (0·36 g.), which contained at least eight products (t.l.c.), was chromatographed on silica gel to give starting material (0·18 g., 50%) from initial benzene eluates. Later benzene eluates yielded 2-*methyloestra*-1,3,5(10)-*trien*-6-*one* (64 mg., 17%), which gave needles, m.p. 116—119° (from light petroleum) (Found: C, 84·8; H, 8·95. $C_{19}H_{24}O$ requires C, 85·0; H, 9·0%), $\lambda_{max.}$ 206 (ε 21,400), 255 (16,100), and 292 (3830) mμ, $\nu_{max.}$ 1675

[19] C. Djerassi and C. R. Scholz, *J. Org. Chem.*, 1948, **13**, 697.

[C(6)O] and 1605 (Ph) cm.$^{-1}$, δ 0·74 (s, C-18 angular Me), 2·41 (C-2 aromatic Me), 7·18br (d, $J_{3,4}$ 8 c./sec., C-3 aromatic H), 7·26br (s, C-1 aromatic H), and 8·02 (d, $J_{3,4}$ 8 c./sec., C-4 aromatic H).

4-Methyl-19-norpregna-1,3,5(10)-triene-1,20β-diyl Diacetate [V; R^1 = CH(OAc)Me, · · · H, R^2 = OAc, R^3 = H_2].—To a solution of 20β-acetoxypregna-1,4-dien-3-one [13] (1·85 g.) in acetic anhydride (50 ml.) was added a 5% solution of fused anhydrous zinc chloride [20] in glacial acetic acid (10 ml.), and the mixture was kept at 20° for 24 hr. under nitrogen. The excess of acetic anhydride was hydrolysed with cold 10% potassium hydroxide solution, and the precipitated solid gave *4-methyl-19-norpregna-1,3,5(10)-triene-1,20β-diyl diacetate* (1·73 g.) as needles, m.p. 198—200° (from ethanol), $[\alpha]_D$ +150° (*c* 1·0) (lit.,[13] m.p. 198—200°) (Found: C, 75·05; H, 8·65; O, 16·1. $C_{25}H_{34}O_4$ requires C, 75·3; H, 8·6; O, 16·0%), $\nu_{max.}$ 1765 (C-1 OAc), 1730 (C-20β OAc), 1250 (C-20β OAc), and 1220 (C-1 OAc) cm.$^{-1}$, $\nu_{max.}$ (CS_2) 806 cm.$^{-1}$ (2 adjacent aromatic protons), δ 0·70 (s, C-18 angular Me), 1·18 (d, *J* 6 c./sec., C-21 Me coupled with C-20 H), 2·03 (s, C-20 OAc), 2·18 (s, C-1 OAc), 2·26 (s, C-4 Me), 2·61 (m, C-6 and C-9 benzylic protons), 4·89 (m, C-20 H), 6·72 (d, $J_{2,3}$ 7·5 c./sec., C-3 aromatic H), and 7·01 (d, $J_{2,3}$ 7·5 c./sec., C-2 aromatic H).

1,20β-Diacetoxy-4-methyl-19-norpregna-1,3,5(10)-trien-6-one [V; R^1 = CH(OAc)Me, · · · H, R^2 = OAc, R^3 = O].—A solution of the pregnatriene diacetate (4·23 g.) in glacial acetic acid (20 ml.) was oxidised with chromium trioxide (3·53 g.) dissolved in the minimum amount of water and then diluted with glacial acetic acid (86 ml.). The mixture was kept at 20° for 24 hr. and then worked up. The neutral fraction was chromatographed from benzene on alumina. Initial fractions eluted with benzene gave starting material (0·65 g.); succeeding fractions yielded *1,20β-diacetoxy-4-methyl-19-norpregna-1,3,5(10)-trien-6-one* (2·32 g.), contaminated with a trace of 20β-acetoxy-1-hydroxy-4-methyl-19-norpregna-1,3,5(10)-trien-6-one. Re-acetylation with acetic anhydride–pyridine gave the pure diacetate which gave needles, m.p. 238—239° (from chloroform–acetone) (Found: C, 73·0; H, 7·9; O, 19·1. $C_{25}H_{32}O_5$ requires C, 73·0; H, 7·8; O, 19·4%), $\lambda_{max.}$ 223 (ε 5130), 251 (7240), and 304 (1950) mμ, $\nu_{max.}$ 1765 (C-1 OAc), 1735 (C-20β OAc), 1690 [C(6)O], 1590 (Ph), 1260—1180 (C-20β and C-1 OAc), and 812 (2 adjacent aromatic protons) cm.$^{-1}$, δ 0·70 (s, C-18 angular Me), 1·18 (d, $J_{20,21}$ 7 c./sec., C-21 Me), 2·05 (s, C-20 OAc), 2·28 (s, C-1 OAc), 2·56 (s, C-4 Me), 4·85 (m, C-20 H), 6·97 (d, $J_{2,3}$ 8 c./sec., C-3 aromatic H), and 7·08 (d, $J_{2,3}$ 8 c./sec., C-2 aromatic H), r.d. (*c* 0·504) $[\phi]_{589}$ +172°, $[\phi]_{390}$ +1585sh, $[\phi]_{373}$ +1789pk, $[\phi]_{341}$ +1277tr, and $[\phi]_{320}$ +2270.

[8/1760 *Received, December 2nd,* 1968]

[20] P. Morand and J. Lyall, *Chem. Rev.*, 1968, **68**, 85.