Aromatic Steroids. Part IV.[1] Chromium Trioxide Oxidation of Some Oestra-1,3,5(10),9(11)-tetraenes

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Chromium trioxide oxidation of 3-methoxyoestra-1,3,5(10),9(11)-tetraenes gives the same major products as those obtained from 3-methoxyoestra-1,3,5(10)-trienes, *viz.* 9β-hydroxy-11-oxo- and 9-oxo-9,11-seco-11-oic acid derivatives. Oxidation of 17-oxo-oestra-1,3,5(10),9(11)-tetraen-3-yl acetate, however, gives a 9α-hydroxy-11-oxo derivative. A path leading to the oxidation products is discussed.

In Parts II [2] and III [1] we reported results from the chromium trioxide oxidation of a series of oestra-1,3,5(10)-trienes and 19-norcholesta-1,3,5(10)-trienes bearing substituents in the aromatic ring. In the case of 3-methoxy ring-A aromatic steroids devoid of blocking groups in the C-1 position, 9β-hydroxy-11-oxo- and 9-oxo-9,11-seco-11-oic acid derivatives were the major products but in all other cases, 6-oxo-derivatives were the principal compounds formed. The different behaviour of 3-methoxy-compounds towards oxidation was attributed to the activating effect of the electron-donating methoxy-group on the *para*-benzylic position, and its ability to stabilize an electron deficiency. It was suggested that the 9β-hydroxy-11-oxo-derivatives were formed *via* a 9(11)-dehydro-derivative. Support for such a route has been gained from the chromium trioxide oxidation of the C-3 substituted oestra-1,3,5(10),9(11)-tetraenes (I; $R^1 = O$, $R^2 = Me$), (I; $R^1 = OAc$, $\cdots H$, $R^2 = Me$), (I; $R^1 = O$, $R^2 = Ac$), and (I; $R^1 = H_2$, $R^2 = Me$). The first three of these compounds were each prepared from oestrone and hydrocortisone by the application of standard methods. 3-Methoxyoestra-1,3,5(10),9(11)-tetraene was prepared (55%) by reduction of the 17β-tosylate of 3-methoxyoestra-1,3,5(10),9(11)-tetraen-17β-ol (I; $R^1 = OH$, $\cdots H$, $R^2 = Me$) with lithium aluminium hydride in refluxing dioxan, the reductive elimination failing at lower reaction temperatures, *e.g.* in refluxing ether [3] or tetrahydrofuran.

Initial attempts to prepare 3-methoxyoestra-1,3,5(10),9(11)-tetraene (I; $R^1 = H_2$, $R^2 = Me$) were by dehydrogenation and deoxygenation of oestrone methyl ether. It was considered desirable to remove the 17-oxo-group before dehydrogenation since treatment of the ethylene acetal of oestrone methyl ether with 2,3-dichloro-5,6-dicyanobenzoquinone at 20° for 5 min. had been reported [4] to give 77% of the ring D-opened dihydrophenanthrene (II; $R = CO_2{\cdot}CH_2{\cdot}CH_2{\cdot}OH$). Reaction of 3-methoxyoestra-1,3,5(10)-triene [2] with 2,3-dichloro-5,6-dicyanobenzoquinone at 20° for 24 hr. was slower than expected and t.l.c. of the product indicated the presence of considerable starting material in addition to two more polar constituents. The ratio of products to starting material was not changed to any great extent after a further 24 hours under reflux. Chromatography

[1] Part III, R. C. Cambie, Valerie F. Carlisle, and T. D. R. Manning, *J. Chem. Soc.* (*C*), 1969, 1240.
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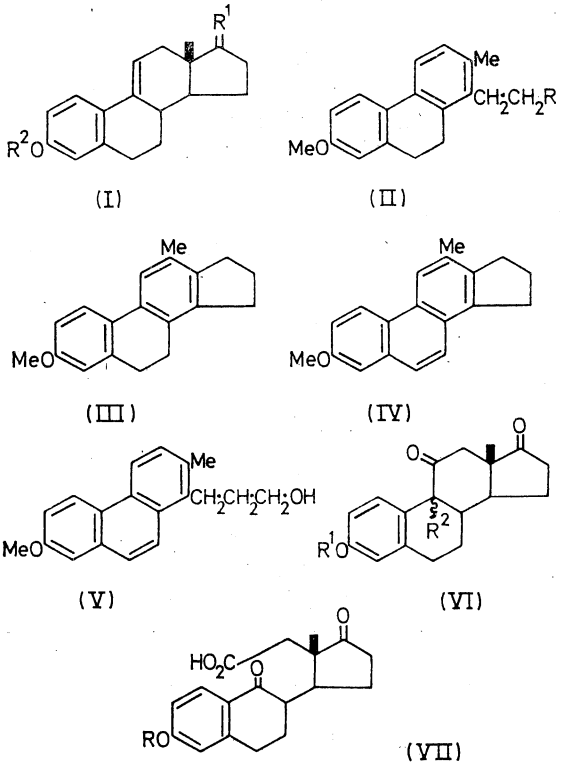
of the mixture on alumina gave starting material (12%) and only a small amount of the desired 3-methoxyoestra-1,3,5(10),9(11)-tetraene. The other products were identified as the dihydrophenanthrene (III) (7%) and the



phenanthrene (IV) (14%) the formation of each of which requires a migration of the C-18 methyl group to C-12. The structures of the dehydrogenation products followed from comparison of their spectra with those of similar compounds,[4-6] and, in the case of the dihydrophenanthrene, from its mass spectrum which confirmed the molecular formula $C_{19}H_{20}O$. Chemical shifts in the n.m.r. spectra (Table 1) were in close agreement with those recorded for the compounds (II; R = CH_2·OH) and (V).[5] Further treatment of the dihydrophenanthrene (III) with dichlorodicyanobenzoquinone gave the phenanthrene (IV). The reaction of 3-methoxyoestra-1,3,5(10)-triene with chloranil in refluxing dioxan for 6 hr. also gave starting material (17%), the dihydrophenanthrene (III) (28%), the phenanthrene (IV) (4%), and a small amount of 3-methoxyoestra-1,3,5(10),9(11)-tetraene. Functionalisation at C-17 appears to play an important part in determining the product of dehydrogenation since the present result differs from that of Cross and his co-workers [5] who obtained a ring D-cleaved steroidal dihydrophenanthrene as the major product from treatment of 3-methoxyoestra-1,3,5(10)-trien-17-one with chloranil.

All four compounds, (I; R^1 = O, R^2 = Me), (I; R^1 = OAc, ··· H, R^2 = Me), (I; R^1 = H_2, R^2 = Me), and (I; R^1 = O, R^2 = Ac) were oxidised in acetone at −18° with 4N-chromium trioxide [7] in 40% aqueous sulphuric acid with a mole ratio of chromium trioxide to substrate of 8 : 1. The first three compounds each gave, as the major products (Table 2), the same 9β-hydroxy-11-oxo- and 9-oxo-9,11-seco-11-oic acid derivatives as those obtained earlier from oxidation of the corresponding 3-methoxyoestra-1,3,5(10)-trienes.[1,7] A low yield of a compound tentatively identified as the 6-oxo-derivative of the ketol (VI; R^1 = Me, R^2 = β-OH) was also obtained from oxidation of the ketone (I; R^1 = O, R^2 = Me), but minor products in both acid and neutral fractions from this and the other oxidations were not isolated. Oxidation of 17-oxo-oestra-1,3,5(10),9(11)-tetraen-3-yl acetate (I; R^1 = O, R^2 = Ac) was slower than in the other cases and gave a complex mixture which included starting material and deacetylated products. After reacetylation, 11,17-dioxo-oestra-1,3,5(10)-triene-3,9α-diol 3-acetate (VI; R^1 = Ac, R^2 = α-OH) [8] and 3-acetoxy-9,17-dioxo-9,11-seco-oestra-1,3,5(10)-trien-11-oic acid (VII; R = Ac) were isolated from the neutral and acidic fractions respectively. The α-configuration of the 9-hydroxy-group of the ketol (VI; R^1 = Ac, R^2 = α-OH) was established from

TABLE 1

Chemical shifts (δ in p.p.m.) of dihydrophenanthrene and phenanthrene derivatives * (J in Hz)

Compound	Aryl Me	3-OMe	Benzylic H's	1-H	2-H	4-H	11-H	12-H
(III)	2·20	3·67	2·53—3·04	7·48	6·67	6·57	7·16	
				$J_{1,2}$ 9	$J_{1,2}$ 9	br,s		
					$J_{2,4}$ 2·5			
(II; R = CH_2·OH) [5]	2·31	3·74	2·53—2·90	7·54	6·74	6·68	7·38	6·98
				$J_{1,2}$ 7·4	$J_{1,2}$ 7	$J_{2,4}$ 2·0	$J_{11,12}$ 7·8	
					$J_{2,4}$ 2·0			
(IV) †	2·46	3·93	2·87—3·48	8·54	7·23	7·23	8·19	
				$J_{1,2}$ 10	$J_{1,2}$ 10	br,s		
					$J_{2,4}$ 2·2			
(V) [5]	2·50	3·90	3·00—3·40	8·50	7·22	7·17	8·33	7·36
				$J_{1,2}$ 7·3	$J_{1,2}$ 7	$J_{2,4}$ 1·9	$J_{11,12}$ 8·2	
					$J_{2,4}$ 1·9			

* Steroid numbering is used for comparison purposes. † δ 7·63 (2H, s, 6, 7-ArH).

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[7] R. C. Cambie and T. D. R. Manning, *J. Chem. Soc.* (*C*), 1968, 2603.

[8] H. Hasegawa and K. Tsuda, *Chem. and Pharm. Bull.* (*Japan*), 1964, **12**, 473.

dilution studies of the i.r. spectrum which indicated the absence of intramolecular hydrogen bonding.[8,9] This was supported by the n.m.r. spectrum in which the chemical shift of the C-1 proton was 0·34 p.p.m. downfield from that in the spectrum of 3-methoxyoestra-1,3,5(10)-trien-17-one.[7]

In Part III [1] it was suggested that 9-hydroxy-11-oxo-derivatives were formed by initial hydroxylation at the C-9 position followed by dehydration to a 9(11)-unsaturated derivative which was then oxidised further, possibly *via* a 9α,11α-epoxide.[10] Evidence exists that the initial product from chromic acid oxidation of a tertiary benzylic carbon atom is the corresponding tertiary alcohol [11] and a recent report has shown that treatment of a 9-hydroxy-3-methoxyoestra-1,3,5(10)-triene with chromic acid does, in fact, give a 9(11)-dehydro-derivative.[12] The formation of the same major products from oxidation of 3-methoxyoestra-1,3,5(10),9(11)-tetraenes as from 3-methoxyoestra-1,3,5(10)-trienes lends support to the suggestion that the former are intermediates in the oxidation of the latter. The formation of a 9-hydroxy-11-oxo-derivative as the major product from oxidation of 17-oxo-oestra-1,3,5(10),9(11)-tetraen-3-yl acetate is in contrast with the formation of a 6-oxo-derivative as the major product from oestra-1,3,5(10)-trien-3-yl acetates,[2] and confirms the directing effect of a 3-methoxy-group in the oxidation of oestratrienes. Should further oxidation of an oestratetraene occur through a 9α,11α-epoxide and a 9,11-diol then formation of 9β-hydroxy-derivatives from 3-methoxy-compounds reflects abnormal opening of the epoxide ring,[13] and it would appear that the electron-donating properties of the 3-methoxy group are sufficient to facilitate breaking of the C–O bond at C-9 in preference to that at C-11. The formation of a 9α-hydroxy-11-oxo-derivative from 17-oxo-oestra-1,3,5(10),9(11)-tetraen-3-yl acetate however, *via* a 9,11-diol would reflect normal axial attack at the C-11 position of an intermediate epoxide.[13] The 9-oxo-9,11-seco-11-oic acid derivatives could arise as cleavage products of a 9(11)-dehydro-derivative or a 9,11-diol, or through oxidation of a 9-hydroxy-11-oxo derivative itself. Evidence for the last possibility was obtained by oxidation of 9β-hydroxy-3-methoxyoestra-1,3,5(10)-triene-11,17-dione (VI; R^1 = Me, R^2 = β-OH) under the conditions used above which afforded a 34% conversion into the corresponding 9-oxo-9,11-seco-11-oic acid (VII; R = Me).

TABLE 2

Oxidation products of 3-substituted oestra-1,3,5(10),9(11)-tetraenes (I)

R^1	R^2	9-Hydroxy-11-oxo-derivs.	9-Oxo-9,11-seco-11-oic acid	9-Hydroxy-6,11-dioxo-deriv.	Starting material
O	Me	23(49)	31(57)	0·6 (1·4)	
OAc, · · · H	Me	37(67)	35(78)		
H_2	Me	35(70)	28(70)		
O	Ac	28(64)	18(34)		2·7 (5·7)

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

EXPERIMENTAL

For general experimental conditions and for the general oxidation procedure see Parts I [7] and II,[2] respectively.

3-Hydroxyoestra-1,3,5(10),9(11)-tetraen-17-one (I; R^1 = O, R^2 = H).—Hydrocortisone acetate was dehydrated,[14] dehydrogenated with 2,3-dichloro-5,6-dicyanobenzoquinone, and aromatised [15] to 20-oxo-oestra-1,3,5(10),9(11)-tetraene-3,17α,21-triol 21-acetate [15] which was then hydrolysed with 10% aqueous hydrochloric acid and oxidised with sodium bismuthate to yield 3-hydroxyoestra-1,3,5(10),9(11)-tetraen-17-one.[16] The phenol was also prepared from hydrocortisone by first removing the side chain and then carrying out the dehydration, dehydrogenation, and aromatisation steps, or from oestrone (62% yield) by the action of 2,3-dichloro-5,6-dicyanobenzoquinone in dry methanol at 20°; methyl ether (I; R^1 = O, R^2 = Me), m.p. 145—147°, $[\alpha]_D$ +276° (*c* 0·5) (lit.,[17] 146—147°, lit.,[18] $[\alpha]_D$ +299°); acetate (I; R^1 = O, R^2 = Ac), m.p. 124—126°, $[\alpha]_D$ +244° (*c* 1·13) (lit.,[15] m.p. 125—126°, lit.,[19] $[\alpha]_D$ +234°).

3-Oxo-androsta-1,4-diene-11β,17β-diol 17-Acetate.—11β,17β-Dihydroxyandrost-4-en-3-one 17β-acetate [20] was dehydrogenated with 2,3-dichloro-5,6-dicyanobenzoquinone in dry dioxan (reflux, 5½ hr.). Chromatography of the product from benzene on deactivated alumina gave *3-oxo-androsta-1,4-diene-11β,17β-diol 17-acetate* (69%) as plates (from light petroleum–benzene), m.p. 190—192°, $[\alpha]_D$ +95° (*c* 1·1) (Found: C, 73·4; H, 8·1. $C_{21}H_{28}O_4$ requires C, 73·2; H, 8·2%), $\lambda_{max.}$ 245 mμ (ε 13,800); $\nu_{max.}$ 3500—3400 (intermol. H-bonded OH), 1725 (17-OAc), 1670 (conj. CO), 1625 (conj. C=C), and 1270—1210 cm.$^{-1}$ (OAc); δ 1·10 (s, 18-ang. Me), 1·48 (s, 19-ang. Me), 2·03 (s, 17-OAc), 2·63—2·87 (m, 11-OH), 4·30—4·69 (m, 17-α-H), 6·02br (s, 4-H), 6·23 (2d, $J_{1,2}$ 10 c./sec., $J_{2,4}$ 2 c./sec., 2-H), and 7·34 (d, $J_{1,2}$ 10 c./sec., 1-H).

Oestra-1,3,5(10),9(11)-tetraene-3,17β-diol 17-Acetate (I; R^1 = OAc, · · · H, R^2 = H).—3-Oxo-androsta-1,4-diene-11β,17β-diol 17-acetate was dehydrated with toluene-*p*-sulphonyl chloride and sulphur dioxide [14] to give 3-oxo-androsta-1,4,9(11)-trien-17β-yl acetate (73%), m.p. 141—143°, $[\alpha]_D$ −20° (*c* 0·16) (lit.,[21] m.p. 135°, $[\alpha]_D$ −26°), which was aromatised with zinc in aqueous pyridine. Chromato-

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[6] G. G. Hazen and D. W. Rosenburg, *J. Org. Chem.*, 1964, **29**, 1930.

graphy of the product on alumina and crystallisation from methanol–ether gave *oestra*-1,3,5(10),9(11)-*tetraene*-3,17β-*diol* 17-*acetate* (47%) as needles, m.p. 209—211°, $[\alpha]_D$ +82° (*c* 0·64) (Found: C, 76·6; H, 7·8; O, 15·6. $C_{20}H_{24}O_3$ requires C, 76·9; H, 7·7; O, 15·4%), $\lambda_{max.}$ 263 (ε 19,600) and 300 mμ (ε 3210); $\nu_{max.}$ 1725 (17-OAc), and 1630 cm.$^{-1}$ (conj. C=C); δ 0·82 (s, 18-ang. Me), 2·08 (17-OAc), 2·67—2·87 (m, 6-benzylic H), 4·62—4·90 (m, 17-α-H), 5·95—6·13 (m, 11-H), 6·54br (s, 4-ArH), 6·61 (2d, $J_{1,2}$ 9 c./sec., $J_{2,4}$ 2·5 c./sec., 2-ArH), and 7·43 (d, $J_{1,2}$ 9 c./sec., 1-ArH).

3-*Methoxyoestra*-1,3,5(10),9(11)-*tetraen*-17β-*yl Acetate* (I; R^1 = OAc, ··· H, R^2 = Me).—Oestra-1,3,5(10),9(11)-tetraen-3,17β-diol 17-acetate was methylated with potassium and methyl iodide in dry benzene (reflux, 3 hr.) to yield 3-*methoxyoestra*-1,3,5(10),9(11)-*tetraen*-17β-*yl acetate* (95%) which crystallised from light petroleum–ether as needles, m.p. 116—118°, $[\alpha]_D$ +46° (*c* 0·3) (Found: C, 77·4; H, 8·1; O, 15·05. $C_{21}H_{26}O_3$ requires C, 77·3; H, 8·0; O, 14·7%), $\lambda_{max.}$ 264 (ε 19,600), and 299sh mμ (ε 3670); $\nu_{max.}$ 1735 (17-OAc), and 1625 cm.$^{-1}$ (conj. C=C); δ (CCl_4) 0·79 (s, 18-ang. Me), 1·99 (s, 17-OAc), 2·64—2·93 (m, 6-benzylic H), 3·69 (s, 3-OMe), 4·51—4·83 (m, 17-α-H), 5·85—6·07 (m, 11-H), 6·44br (s, 4-ArH), 7·03 (2d, $J_{1,2}$ 9 c./sec., $J_{2,4}$ 2·5 c./sec., 2-ArH), and 7·36 (d, $J_{1,2}$ 9 c./sec., 1-ArH).

The methoxy acetate was also prepared in similar yield from 3-methoxyoestra-1,3,5(10),9(11)-tetraen-17-one by quantitative reduction (reflux, 1 hr.) with lithium aluminium hydride in tetrahydrofuran and then acetylation.

3-*Methoxyoestra*-1,3,5(10),9(11)-*tetraen*-17β-*yl Toluene*-p-*sulphonate* (I; R^1 = *p*-$MeC_6H_4SO_2$, ··· H, R^2 = Me).—3-Methoxyoestra-1,3,5(10),9(11)-tetraen-17β-ol [22] was converted into the *tosylate* (89%) with toluene-*p*-sulphonyl chloride and pyridine (20°, 24 hr.). The product crystallised from ether as leaflets, m.p. 135—136° (Found: C, 71·1; H, 6·7; O, 14·6. $C_{26}H_{30}O_4S$ requires C, 71·2; H, 6·9; O, 14·7%) (correct u.v., i.r., and n.m.r. spectra).

3-*Methoxyoestra*-1,3,5,(10),9(11)-*tetraene* (I; R^1 = H_2, R^2 = Me).—The tosylate (6·41 g.) in dry dioxan (640 ml.) was heated under reflux with lithium aluminium hydride (4·43 g.) for 24 hr. Isolation of the product in the normal manner followed by chromatography on alumina gave, from light petroleum–benzene (9 : 1) eluates, 3-*methoxyoestra*-1,3,5(10),9(11)-*tetraene* (2·24 g., 55%) as prisms (from ether), m.p. 85—87·5°, $[\alpha]_D$ +99° (*c* 0·56) (Found: C, 85·2; H, 9·0; O, 5·8. $C_{19}H_{24}O$ requires C, 85·0; H, 9·0; O, 6·0%), $\lambda_{max.}$ 268 (ε 18,000), and 281sh mμ (ε 6080); $\nu_{max.}$ (CS_2) 1625 cm.$^{-1}$ (conj. C=C); δ 0·78 (s, 18-ang. Me), 2·78—3·10 (m, 6-benzylic H), 3·87 (s, 3-OMe), 6·21—6·44br (t, 11-H), 6·83br (s, 4-ArH), 6·93 (d, $J_{1,2}$ 9·6 c./sec., $J_{2,4}$ 2·5 c./sec., 2-ArH), and 7·80 (d, $J_{1,2}$ 9·6 c./sec., 1-ArH).

Dehydrogenation of 3-*Methoxyoestra*-1,3,5(10)-*triene*.—A solution of 3-methoxyoestra-1,3,5(10)-triene [2] (1·69 g.) in dry benzene (80 ml.) was treated (20°, 24 hr., and then reflux, 24 hr.) with 2,3-dichloro-5,6-dicyanobenzoquinone (1·42 g.) in dry benzene (80 ml.) and the product was chromatographed on deactivated alumina. Elution with light petroleum–benzene (9 : 1) gave starting material (0·20 g., 12%), and mixtures of starting material and 3-methoxyoestra-1,3,5(10),9(11)-tetraene (0·19 g., 12%).

Later light petroleum–benzene eluates gave 3-*methoxy*-12-*methyl*-18-*noroestra*-1,3,5(10),8,11,13-*hexaene* (50 mg., 3%) which crystallised from ethanol–ether as plates, m.p. 94—96°, $[\alpha]_D$ 0° (*c* 0·94) [Found: C, 86·1; H, 7·9; O, 6·5%; *M* (mass spectrum) 264·1510. $C_{19}H_{20}O$ requires C, 86·3; H, 7·6; O, 6·1%; *M*, 264·1514], $\lambda_{max.}$ 283 mμ (ε 20,900); $\nu_{max.}$ 3030, 3010 (aromatic CH), 1605, 1570 (Ph), and 1240, 1045 cm.$^{-1}$ (COC str.), n.m.r. (CCl_4) see Table 1.

Further light petroleum–benzene eluates gave 3-methoxy-12-methyl-18-noroestra-1,3,5(10),6,8,11,13-heptaene (0·16 g., 10%) which crystallised from light petroleum–ether as needles, m.p. 146—148°, $\lambda_{max.}$ 212 (log ε 4·50), 228 (4·42), 236·5 (4·39), 262 (5·05), 282 (4·32), 293 (4·18), 306 (4·03), 320 (3·89), 341·5 (3·86), and 355 mμ (3·91); $\nu_{max.}$ 3050—3030 (aromatic CH), 1615, 1600 (Ph), 1250, 1200, and 1035 cm.$^{-1}$ (COC str.), n.m.r. see Table 1.

Mixtures of the compounds (III) and (IV) (0·14 g.) accounted for 8% of the product.

Dehydrogenation of 3-methoxyoestra-1,3,5(10)-triene (2·7 g.) with chloranil (6·44 g.) in dry dioxan (168 ml.) under reflux for 6 hr. followed by chromatography as above gave starting material (0·47 g., 17%), and a mixture of starting material and 3-methoxyoestra-1,3,5(10),9(11)-tetraene (0·50 g., 19%). Preparative t.l.c. of later fractions gave the dihydrophenanthrene (III; 0·50 g., 19%), and a 2 : 1 mixture of this compound and the phenanthrene (IV) (0·34 g., 13%).

Treatment of the dihydrophenanthrene (III) (0·56 g.) with 2,3-dichloro-5,6-dicyanobenzoquinone (1·68 g.) in dioxan (14 ml.) at 20° for 20 hr. followed by work-up of the product as above gave a 1 : 2 mixture of starting material and the phenanthrene (IV) (56%).

Oxidation of 3-*Methoxyoestra*-1,3,5(10),9(11)-*tetraen*-17-*one* (I; R^1 = O, R^2 = Me).—A solution of 3-methoxyoestra-1,3,5(10),9(11)-tetraen-17-one (2·5 g.) in acetone (625 ml.) was treated dropwise at −18° with 4N-chromium trioxide–40% sulphuric acid (53 ml.) and the temperature was allowed to rise to 20° over 11 hr. Work-up gave a yellow neutral gum (1·32 g.) and a brown acidic gum (1·56 g.).

The neutral fraction was chromatographed on silica gel and the benzene–ether eluate (19 : 1) was further purified by preparative t.l.c. to give 9β-hydroxy-3-methoxyoestra-1,3,5(10)-triene-11,17-dione [7] (0·65 g., 23%), m.p. and mixed m.p. 132—133°, $[\alpha]_D$ +205° (*c* 0·76) (identical u.v., i.r., and n.m.r. spectra).

Also isolated was a small amount of 9β-hydroxy-3-methoxyoestra-1,3,5(10)-trien-6,11,17-trione (18 mg., 0·6%), $\nu_{max.}$ 3490—3440 (intramol. bonded OH), 1745 (17-CO), 1712 (11-CO), and 1690 cm.$^{-1}$ (6-CO); δ 0·96 (s, 18-ang. Me), 4·00 (s, 3-OMe), and 6·94—8·04 (m, 1,2,4-ArH).

Chromatography of the acid fraction on silica gel gave 9,17-dioxo-3-methoxy-9,11-seco-oestra-1,3,5(10)-trien-11-oic acid [7] (0·89 g., 31%), m.p. and mixed m.p. 158—160°, $[\alpha]_D$ −89° (*c* 0·18) (identical u.v., i.r., and n.m.r. spectra).

Oxidation of 3-*Methoxyoestra*-1,3,5(10),9(11)-*tetraen*-17β-*yl Acetate* (I; R^1 = OAc, ··· H, R^2 = Me).—Oxidation of the keto-acetate (2·0 g.) in acetone (500 ml.) with 4N-chromium trioxide–40% sulphuric acid (42·5 ml.) gave a neutral oil (1·2 g.) and an acidic solid (1·02 g.).

Chromatography of the neutral oil on silica gel and elution with benzene–ether (49 : 1) gave 3-methoxy-11-oxo-oestra-1,3,5(10)-triene-9β,17β-diol 17-acetate [7] (0·80 g., 37%) as an oil, $[\alpha]_D$ +78° (*c* 0·64) (identical u.v., i.r., and n.m.r. spectra).

Chromatography of the acidic fraction on silica gel and elution with benzene–ether (9 : 1) gave 17β-acetoxy-3-methoxy-9-oxo-9,11-seco-oestra-1,3,5(10)-trien-11-oic acid [7] (0·80 g., 35%), m.p. and mixed m.p. 141—143°, $[\alpha]_D$ −20° (*c* 0·50) (identical u.v., i.r., and n.m.r. spectra).

[22] E. Farkas and J. M. Owen, *J. Medicin. Chem.*, 1966, **9**, 510.

Oxidation of 3-*Methoxyoestra*-1,3,5(10),9(11)-*tetraene* (I; $R^1 = H_2$, R^2 = Me).—Oxidation of the tetraene (2·0 g.) in acetone (500 ml.) with 4N-chromium trioxide–40% sulphuric acid (52 ml.) gave a neutral oil (1·13 g.) and an acidic gum (0·89 g.).

Preparative t.l.c. of the neutral fraction gave 9β-hydroxy-3-methoxyoestra-1,3,5(10)-trien-11-one [2] (0·79 g., 35%), m.p. and mixed m.p. 114—116°, $[\alpha]_D$ +174° (*c* 0·57) (identical u.v., i.r., and n.m.r. spectra).

Chromatography of the acidic gum on silica gel and elution with benzene–ether (19 : 1) gave 3-methoxy-9-oxo-9,11-seco-oestra-1,3,5(10)-trien-11-oic acid [2] (0·62 g., 28%), m.p. and mixed m.p. 70—71°, $[\alpha]_D$ −28° (*c* 0·10) (identical u.v., i.r., and n.m.r. spectra).

Oxidation of 17-*Oxo-oestra*-1,3,5(10),9(11)-*tetraen*-3-*yl Acetate* (I; $R^1 = O$, R^2 = Ac).—Oxidation of the keto-acetate (2·0 g.) in acetone (500 ml.) with 4N-chromium trioxide–40% sulphuric acid (42·5 ml.) gave a neutral oil (0·95 g.), and an acidic oil (1·2 g., 60%).

Chromatography of the neutral fraction on silica gel and elution with benzene–ether (19 : 1) gave starting material (54 mg., 3%) and a mixture of 11,17-dioxo-oestra-1,3,5(10)-triene-3,9α-diol and its 3-acetate (0·60 g.). The mixture was acetylated with acetic anhydride–pyridine to yield 11,17-dioxo-oestra-1,3,5(10)-triene-3,9α-diol 3-acetate (0·61 g., 28%) which crystallised from methylene dichloride–light petroleum as prisms, m.p. 250—252°, $[\alpha]_D$ +347° (*c* 1·32) (lit.,[8] m.p. 235—243°, $[\alpha]_D$ +349°); $\nu_{max.}$ 3520—3460 (inter-mol. bonded OH), 1745 (17-CO), 1725 (3-OAc and 11-CO), 1613, 1586 (Ph), 1230—1200 (COC str.), 1190, 1148, and 1010 cm.$^{-1}$; δ 0·84 (s, 18-ang. Me), 2·32 (s, 3-OAc), 4·61—4·88 (m, 9-OH), 7·07br (s, 4-ArH), 7·13 (2d, $J_{1,2}$ 10 c./sec., $J_{2,4}$ 2 c./sec., 2-ArH), and 7·58 (d, $J_{1,2}$ 10 c./sec., 1-ArH).

Chromatography and preparative t.l.c. of the acid fraction gave 3-*acetoxy*-9,17-*dioxo*-9,11-*seco-oestra*-1,3,5(10)-*trien*-11-*oic acid* (0·41 g., 18%) which formed plates (from ether), m.p. 45—70°, $[\alpha]_D$ +17° (*c* 0·31) (Found: C, 66·3; H, 6·55; O, 26·0. $C_{20}H_{22}O_6,\frac{1}{2}Et_2O$ requires C, 66·6; H, 6·9; O, 26·2%), $\lambda_{max.}$ 210 (ε 15,200) and 250 mμ (10,100); $\nu_{max.}$ 3540—2560 (H-bonded OH of CO_2H), 1740br (17-CO and 3-OAc), 1710 (CO_2H), 1685 (9-CO), 1605, 1585 (Ph), 1230—1200 and 1185 cm.$^{-1}$ (COC str.); δ 1·05 (s, 18 ang. Me), 2·37 (s, 3-OAc), 7·28—7·45 (m, 1,2-ArH, 11-CO_2H), 7·20br (s, 4-ArH), 7·22 (2d, $J_{1,2}$ 10 c./sec., $J_{2,4}$ 2·5 c./sec., 2-ArH), and 8·17 (d, $J_{1,2}$ 10 c./sec., 1-ArH).

Oxidation of 9β-*Hydroxy*-3-*methoxyoestra*-1,3,5(10)-*triene*-11,17-*dione* (VI; R^1 = Me, R^2 = β-OH).—Oxidation of the ketol (0·5 g.) in acetone (125 ml.) with 4N-chromium trioxide–40% sulphuric acid (10·5 ml.) gave starting material (0·20 g., 40%) from the neutral fraction. Chromatography of the acidic gum (0·22 g.) on silica gel gave 9,17-dioxo-3-methoxy-9,11-seco-oestra-1,3,5(10)-trien-11-oic acid [7] (0·18 g., 34%), m.p. and mixed m.p. 70—71° (identical i.r. and n.m.r. spectra).

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