Aromatic Steroids. Part I. Oxidation Products of 3-Methoxyoestra-1,3,5(10)-trien-17β-yl Acetate

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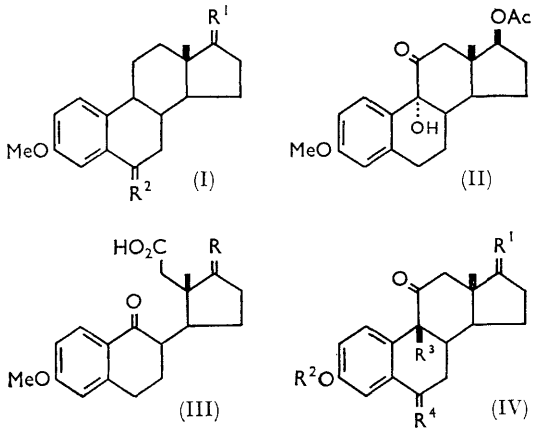
Re-examination of chromium trioxide oxidations of 3-methoxyoestra-1,3,5(10)-trien-17β-yl acetate (I; R^1 = OAc, · · · H, R^2 = H_2) has shown that the neutral products are a ketol (IV; R^1 = OAc, · · · H, R^2 = Me, R^3 = OH, R^4 = H_2), a 6-oxo-derivative (I; R^1 = OAc, · · · H, R^2 = O), a hydroxy-dione (IV; R^1 = O, R^2 = Me, R^3 = OH, R^4 = H_2), and a mixture of a hydroxy-dione (IV; R^1 = OAc, · · · H, R^2 = Me, R^3 = OH, R^4 = O) and a hydroxy-trione (IV; R^1 = R^4 = O, R^2 = Me, R^3 = OH). Evidence is presented that the 9-hydroxy-group of the ketol has a β-configuration rather than the α-configuration previously assigned. Acids from the oxidation include C-seco-acids (III; R = OAc, · · · H) and (III; R = O), and structures (VII) and (VIII) for lactones derived from the latter acid have been proposed.

In connection with o.r.d. and c.d. studies of some α-tetralones, we reported earlier that chromic acid oxidation of 3-methoxyoestra-1,3,5(10)-trien-17β-yl acetate (I; R^1 = OAc, · · · H, R^2 = H_2) afforded the 6-oxo-derivative (I; R^1 = OAc, · · · H, R^2 = O) in 43% yield.[1] In a recent patent, however, Suzuki [2] has

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

[2] Y. Suzuki, Jap. Pat., 3539/1966 (*Chem. Abs.*, 1966, **65**, 5505).

claimed that the oxidation products of 3-methoxyoestra-1,3,5(10)-trien-17β-yl acetate are 17β-acetoxy-9α-hydroxy-3-methoxyoestra-1,3,5(10)-trien-11-one (II) (35%) and the seco-derivative, 17β-acetoxy-3-methoxy-



9-oxo-9,11-seco-oestra-1,3,5(10)-trien-11-oic acid (III; R = OAc, · · · H) (45%). In view of the conflicting result and of current interest in the reported physiological activity of aromatic-ring-A 6-oxo-steroids,[3] the yields of any one product, the w/w percentage of product in the neutral fraction is given in parentheses. The major neutral product from each oxidation was indeed the 9-hydroxy-11-oxo-derivative (IV; R^1 = OAc, · · · H R^2 = Me, R^3 = OH, R^4 = H_2) of 3-methoxyoestra-1,3,5(10)-trien-17β-yl acetate, but evidence is presented below to show that the 9-hydroxy-group has a β-configuration rather than the α-configuration assigned by Suzuki. The minor neutral products from all oxidations were isolated in each case by chromatography on silica gel, and were identified as 17β-acetoxy-3-methoxyoestra-1,3,5(10)-trien-6-one (I; R^1 = OAc, · · · H, R^2 = O), 9β-hydroxy-3-methoxyoestra-1,3,5(10)-triene-11,17-dione (IV; R^1 = O, R^2 = Me, R^3 = OH, R^4 = H_2), and a mixture of what is believed to be 17β-acetoxy-9β-hydroxy-3-methoxyoestra-1,3,5(10)-triene-6,11-dione (IV; R^1 = OAc, · · · H, R^2 = Me, R^3 = OH, R^4 = O) and 9β-hydroxy-3-methoxyoestra-1,3,5(10)-triene-6,11,17-trione (IV; R^1 = R^4 = O, R^2 = Me, R^3 = OH) which could not be separated.

17β-Acetoxy-3-methoxyoestra-1,3,5(10)-trien-6-one (I; R^1 = OAc, · · · H, R^2 = O) was identified from its i.r. spectrum which showed the presence of an aryl keto-group ($\nu_{max.}$ 1675 cm.$^{-1}$), and by the chemical shift of its

Oxidation products of 3-methoxyoestra-1,3,5(10)-trien-17β-yl acetate

Compound (%)	CrO_3–HOAc	8N-CrO_3–H_2SO_4	4N-CrO_3–H_2SO_4
(I; R^1 = OAc, · · · H, R^2 = H_2)	5·0 (14·0)	6·0 (18·0)	3·5 (14·5)
(I; R^1 = OAc, · · · H, R^2 = O)	7·0 (17·6)	2·2 (6·5)	0·9 (3·7)
(IV; R^1 = OAc, · · · H, R^2 = Me, R^3 = OH; R^4 = H_2)	24·0 (61·0)	15·5 (46·0)	7·4 (31·0)
(IV; R^1 = O, R^2 = Me, R^3 = OH, R^4 = H_2)	1·0 (3·0)	8·2 (24·5)	9·8 (41·0)
(IV; R^1 = OAc, · · · H, R^2 = Me, R^3 = OH, R^4 = O) and (IV; R^1 = R^4 = O, R^2 = Me, R^3 = OH)	0·5 (1·3)	1·6 (4·8)	2·5 (10·0)

oxidations of 3-methoxyoestra-1,3,5(10)-trien-17β-yl acetate with 8N-chromium trioxide–sulphuric acid and with chromium trioxide–acetic acid have been re-investigated according to the respective methods of our earlier report [1] and of Suzuki.[2] The oxidation products from the use of 4N-chromium trioxide–50% aqueous sulphuric acid, a reagent used in a broader survey of the oxidation products of ring-A-aromatic steroids (Part II), are also reported. In the case of the latter reagent the effect of varying the mole ratio of chromium trioxide to substrate was also examined. For a series of oxidations on 50-mg. samples of the trienyl acetate (I; R^1 = OAc, · · · H, R^2 = H_2) in acetone at 0° and then at 20° for 18 hours, it was found by comparative t.l.c. that a chromium trioxide to substrate ratio of 8 : 1 gave the least return of starting material. An increase in the ratio caused an increase in the amount of intractable material formed in the reaction, as did also extension of the reaction time to 36 hours. Black intractable oils were also formed if the reaction mixture was not cooled during addition of the oxidant, or if the rate of addition of the latter was fast.

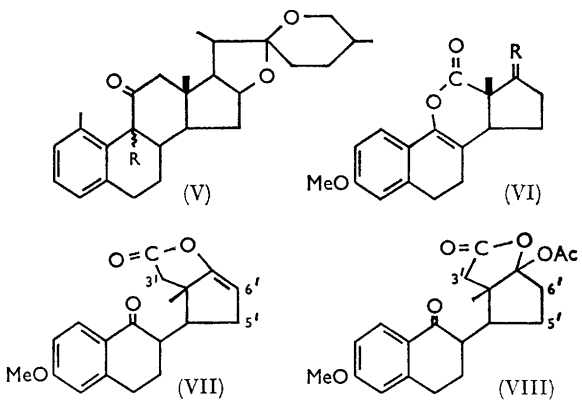
The composition of the neutral fraction from reaction with the three oxidants is shown in the Table. The percentage given is the w/w percentage of product from starting material, and, in order to compare relative 4-proton in the n.m.r. spectrum, which showed a downfield shift of 1·1 p.p.m. from that of the starting material (I; R^1 = OAc, · · · H, R^2 = H_2) as a result of its deshielding by the adjacent carbonyl group. Our product recorded earlier [1] was clearly a mixture, as shown by the fact that it melted 19° below the homogeneous material. 9β-Hydroxy-3-methoxyoestra-1,3,5(10)-triene-11,17-dione (IV; R^1 = O, R^2 = Me, R^3 = OH, R^4 = H_2) was obtained as a crystalline solid, and was shown to be identical with the major product from oxidation of 3-methoxyoestra-1,3,5(10)-trien-17-one (I; R^1 = O, R^2 = H_2). Also isolated from the neutral fraction of this latter oxidation were 3-methoxyoestra-1,3,5(10)-triene-6,17-dione (I; R^1 = R^2 = O), and a trace of impure 9β-hydroxy-3-methoxyoestra-1,3,5(10)-triene-6,11,17-trione (IV; R^1 = R^4 = O, R^2 = Me, R^3 = OH).

The oxidation products from 3-methoxyoestra-1,3,5(10)-trien-17β-yl acetate, which possess a 17-keto-group, apparently arise as a result of acid hydrolysis of the 17-acetoxy-group during the reaction, and oxidation of the resulting secondary alcohol. The acidity of the oxidising agents increases from left to

[3] K. Sakakibara, Jap. Pat., 9884/1964 (*Chem. Abs.*, 1964, **61**, 12,059); Y. Suzuki, Jap. Pat., 17,831/1964 (*Chem. Abs.*, 1965, **62**, 5318); 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).

right in the Table, and this is reflected in the increase in yields of 17-keto-products in the same direction, there appearing to be little hydrolysis of the acetoxy-group in acetic acid. It was also observed that the ratio of acidic to neutral fraction for each oxidation increases from left to right, suggesting that the rate of oxidation also increases with increasing acidity.

Evidence of a β-configuration for the 9-hydroxy-group of the methoxy-ketol (IV; R^1 = OAc, · · · H, R^2 = Me, R^3 = OH, R^4 = H_2), and thus a *cis* B/C ring fusion, arises from comparison of its i.r. and n.m.r. spectra with those of the 9α- and 9β-hydroxy-isomers of the closely related compound, 3-acetoxy-9-hydroxyestra-1,3,5(10)-triene-11,17-dione. The OH ($\nu_{max.}$ 3460 cm.$^{-1}$) and carbonyl ($\nu_{max.}$ 1708 cm.$^{-1}$) bands in the i.r. spectrum of the methoxy-ketol showed no change in height or position on dilution of a carbon tetrachloride solution, indicating intramolecular hydrogen-bonding between the 9-hydroxy- and C-11 carbonyl groups. For a compound with ring C in a chair conformation, Dreiding models show that a 9β-hydroxy-isomer, but not a 9α-hydroxy-isomer, is capable of intramolecular hydrogen-bonding. Hasegawa *et al.*[4] have shown that this type of hydrogen-bonding does occur in the 9β-isomer ($\nu_{max.}$ 3483, 1713 cm.$^{-1}$) of the acetoxy-dione (IV; R^1 = O, R^2 = Ac, R^3 = OH, R^4 = H_2) but not in the 9α-isomer ($\nu_{max.}$ 3609, 1730 cm.$^{-1}$). A similar effect has been observed for the meteogenone isomers (V; R = α- and β-OH).[5] A form in which ring C of the methoxy-ketol (IV; R^1 = OAc, · · · H, R^2 = Me, R^3 = OH, R^4 = H_2) was in a boat conformation would exhibit strong non-bonded interaction between the C-18 methyl and



9-hydroxy-groups, the latter being incapable of hydrogen-bonding since it would then be axial. A form capable of intramolecular hydrogen-bonding between 9α-hydroxy- and C-11 carbonyl groups, in which both rings B and C are in a boat conformation, can be constructed but it too would exhibit strong non-bonded interaction, in this case between the C-18 methyl group and the aromatic ring. The C-18 methyl group of such a form would be expected to show a marked shielding effect in the n.m.r. spectrum. No such shielding is shown, however, in the n.m.r. spectrum of the actual methoxy-ketol. Dreiding models also show that for a 9β-hydroxy-isomer the 1-proton lies within the cone of shielding of the C-11 carbonyl group, while for a 9α-hydroxy-isomer it lies just outside. A marked upfield shift of 0·32 p.p.m. for the 1-proton resonance (δ 6·76) in the n.m.r. spectrum of the methoxy-ketol from that observed in the trienyl acetate (I; R^1 = OAc, · · · H, R^2 = H_2) (δ 7·08) strongly supports the assignment of a 9β-configuration for the hydroxy-group. An upfield shift of 0·4 p.p.m. is shown for the 1-proton of the 9β-hydroxy-isomer of the dione (IV; R^1 = O, R^2 = Ac, R^3 = OH, R^4 = H_2), while a downfield shift of 0·13 p.p.m. is shown for the corresponding proton of the 9α-hydroxy-isomer, relative to 3-methoxyoestra-1,3,5(10)-trien-17-one (I; R^1 = O, R^2 = H).[4]

Chemical evidence for a 9β-hydroxy-configuration was obtained from a study of the zinc–acetic acid reduction of the hydroxy-dione (IV; R^1 = O, R^2 = Me, R^3 = OH, R^4 = H_2), which afforded after prolonged reaction (25 hours) a low yield (15%) of 3-methoxy-9β-oestra-1,3,5(10)-triene-11,17-dione (IV; R^1 = O, R^2 = Me, R^3 = H, R^4 = H_2) along with other unidentified minor products. Rosenfeld *et al.*[6] have found in general that if the hydroxy-group of an α-ketol cannot attain an axial conformation, no reduction to the saturated ketone occurs on treatment with zinc–acetic acid. Whereas a 9α-hydroxy-isomer of (IV; R^1 = O, R^2 = Me, R^3 = OH, R^4 = H_2) would already possess an axial hydroxy-group, the 9β-hydroxy-isomer would be required to adopt a boat conformation for ring C in order that its hydroxy-group would be axial. As pointed out above, the attainment of such a conformation would be unfavourable and in keeping with the difficulty of reductive dehydroxylation in the present case. Furthermore, evidence suggests that reduction of a 9α-hydroxy-group in the oestra-1,3,5(10)-triene series occurs much more readily,[4] although it would also lead to a 9βH-11-oxo-isomer, since studies on the stability of ring-A-aromatic 11-oxo-steroids have shown that 9αH-isomers are readily epimerised to the 9βH-isomers.[7]

Two acids were isolated from each oxidation, and were identified as 17β-acetoxy-3-methoxy-9-oxo-9,11-seco-oestra-1,3,5(10)-trien-11-oic acid (III; R = OAc, · · · H) and 3-methoxy-9,17-dioxo-9,11-seco-oestra-1,3,5(10)-trien-11-oic acid (III; R = O). The former acid (III; R = OAc, · · · H) was the major product from the chromium trioxide–acetic acid oxidation, while the dioxo-acid (III; R = O) was the major acid from the 4N- and 8N-chromium trioxide–sulphuric acid oxidations, but because of difficulty in their isolation no accurate assessment of their percentage yields could be made.

[4] H. Hasegawa and K. Tsuda, *Chem. and Pharm. Bull.* (*Japan*), 1964, **12**, 473.
[5] K. Igarashi, *Chem. and Pharm. Bull.* (*Japan*), 1961, **9**, 729.
[6] R. S. Rosenfeld, *J. Amer. Chem. Soc.*, 1967, **79**, 5540; D. K. Fukushima, S. Dobriner, and R. S. Rosenfeld, *J. Org. Chem.*, 1961, **26**, 5025.
[7] J. A. Edwards, P. Crabbe, and A. Bowers, *J. Amer. Chem. Soc.*, 1963, **85**, 3313; E. Caspi, E. Cullen, P. K. Grover, and N. Grover, *J. Chem. Soc.*, 1963, 2166; J. P. Connolly, R. O. Dorchai, and J. B. Thomson, *J. Chem. Soc.* (*C*), 1968, 461.

The latter acid was the more difficult to crystallise, but when oils remaining after crystallisation were treated with acetic anhydride–sodium acetate and chromatographed, two crystalline lactones, $C_{19}H_{20}O_4$ and $C_{21}H_{24}O_6$, were obtained. Since the acid (III; R = O) possesses 9- and 17-oxo-groups, there are two possible unsaturated lactones, (VI; R = O) and (VII), which could be derived from it. The lactone $C_{19}H_{20}O_4$ was assigned structure (VII) since its i.r. spectrum showed bands at 1684 (aryl CO), 800 (trisubstituted C=C), and 1820 cm.$^{-1}$ (lactone), and its n.m.r. spectrum (see Experimental) was consistent with this structure. The elemental analysis of the second lactone, $C_{21}H_{24}O_6$, showed that it could not be the second alternative (VI; R = O), and its i.r. spectrum, which exhibited carbonyl bands at 1798 (lactone), 1670 (aryl CO), and 1752 cm.$^{-1}$ (acetate), showed that it could not be the unsaturated lactone (VI; R = OAc, · · · H) derived from the seco-acid (III; R = OAc, · · · H). The aromatic proton resonance in the n.m.r. spectrum of this second lactone was identical with that of the lactone (VII), indicating that rings A and B were identical for the two compounds. From this evidence, and the absence of signals due to olefinic protons in the n.m.r. spectrum but the presence of an acetate signal, structure (VIII) is proposed for the second lactone. The acetoxy-lactone (VIII) was not an intermediate in the formation of the unsaturated lactone (VII) since further treatment of the former with acetic anhydride–sodium acetate gave none of the lactone (VII).

In addition to the above lactones, an oil was obtained which showed weak lactone peaks in the i.r. spectrum but which decomposed on attempted purification by preparative t.l.c. The oil was shown, however, to be identical with the product formed by treatment of 17β-acetoxy-3-methoxy-9-oxo-9,11-seco-oestra-1,3,5(10)-trien-11-oic acid with acetic anhydride–sodium acetate. The lactone (VI; R = OAc, · · · H) derived from this acid was unstable and decomposed when attempts were made to isolate it by chromatography.

EXPERIMENTAL

Unless otherwise stated, infrared and ultraviolet spectra were measured on Perkin-Elmer 237 and 137 spectrophotometers for chloroform and ethanolic solutions, respectively. N.m.r. spectra were determined in deuteriochloroform with tetramethylsilane as internal reference, using a Varian A60 spectrometer. O.r.d. measurements and optical rotations were carried out on a Jasco ORD/UV-5 spectrophotometer at 25° and, unless otherwise stated, are for chloroform solutions. Melting points were determined on a Kofler block. The general oxidation procedure and work-up is given in Part II.

3-Methoxyoestra-1,3,5(10)-trien-17β-yl Acetate (I; R^1 = OAc, · · · H, R^2 = H_2).— 3-Methoxyoestra-1,3,5(10)-trien-17-one (4·5 g.) in tetrahydrofuran (120 ml.) was added dropwise to a solution of lithium aluminium hydride (1·5 g.) in dry tetrahydrofuran at 0° (cf. ref. 8), and the mixture was heated under reflux for 1 hr. Work-up and chromatography of the product on silica gel gave 3-methoxyoestra-1,3,5(10)-trien-17β-ol (4·14 g., 94%) which crystallised from ethanol as needles, m.p. 121—122°, $[\alpha]_D$ +78° (*c* 0·43 in EtOH) [lit.,[8] m.p. 120·5—121·5°, $[\alpha]_D^{22}$ +77·4° (*c* 1·68 in $CHCl_3$)].

Acetylation with acetic anhydride–pyridine gave 3-methoxyoestra-1,3,5(10)-trien-17β-yl acetate (93%), needles (from methanol), m.p. 101—102° (lit.,[9] 103·5—104·5°), $[\alpha]_D$ +67° (*c* 0·67 in cyclohexane), $\lambda_{max.}$ 280 (ε 2540) and 287 mμ (ε 2770), δ(CCl_4) 0·80 (s, C-18 Me), 1·98 (s, OAc), 2·79 (m, C-6 benzylic H), 3·70 (s, aryl OMe), 4·65 (t, $J_{16,17}$ 6 c./sec., 17-H), 6·52 (d, J_{24} 2 c./sec., C-4 aromatic H), 6·58 (2d, J_{24} 2, J_{12} 8·5 c./sec., C-2 aromatic H), and 7·08 (d, J_{12} 8·5 c./sec., C-1 aromatic H).

Chromium Trioxide–Acetic Acid Oxidation of 3-Methoxyoestra-1,3,5(10)-trien-17β-yl Acetate (I; R^1 = OAc, · · · H, R^2 = H_2).—An ice-cold solution of the trienyl acetate (7·0 g.) in acetic acid (42 ml.) was treated dropwise with acetic acid (42 ml.) containing chromium trioxide (5·96 g.) which had been dissolved in water (3 ml.). The mixture was kept at 25° for 20 hr. and then worked up in the usual manner.

The pale yellow neutral oil (2·72 g.) was chromatographed on silica gel, to give starting material (328 mg.) from light petroleum–benzene (1 : 4) eluates. Benzene eluates yielded 17β-acetoxy-3-methoxyoestra-1,3,5(10)-trien-6-one (420 mg.) which crystallised from methanol as plates, m.p. 168—170° (lit.,[1] 149—151°) (Found: C, 73·7; H, 7·7; O, 18·7. Calc. for $C_{21}H_{26}O_4$: C, 73·7; H, 7·7; O, 18·7%), $\lambda_{max.}$ (cyclohexane) 251·5 (ε 9000), 257sh (ε 7840), and 320 mμ (ε 3170), $\nu_{max.}$ 1725 (17-OAc), 1675 (C-6 CO), 1608, 1570, and 1490 cm.$^{-1}$ (phenyl), δ 0·83 (s, C-18 Me), 2·08 (s, 17-OAc), 3·87 (s, aryl OMe), 4·76 (m, 17-H), 7·13 (2d, J_{12} 8·8, J_{24} 3 c./sec., C-2 aromatic H), 7·41 (d, J_{12} 8·8 c./sec., C-1 aromatic H), and 7·62 (d, J_{24} 3 c./sec., C-4 aromatic H), r.d. (*c* 0·418) $[\phi]_{589}$ −41°, $[\phi]_{500}$ +16°, $[\phi]_{450}$ +172°, $[\phi]_{400}$ +645°, $[\phi]_{355}$ +5900 (pk.), and $[\phi]_{340}$ +3430°.

Benzene–ether (49 : 1) eluates yielded 17β-acetoxy-9β-hydroxy-3-methoxyoestra-1,3,5(10)-trien-11-one (1·46 g.) as a gum which slowly crystallised, m.p. 45—50° (lit.,[2] 52—53°) (Found: C, 70·25; H, 7·5; O, 22·3. Calc. for $C_{21}H_{26}O_5$: C, 70·4; H, 7·3; O, 22·3%), $\lambda_{max.}$ 276 (ε 1789) and 283 mμ (ε 1660), $\nu_{max.}$ 3460 (intramol. bonded OH), 1730 (17-OAc), 1708 (C-11 CO), 1610, 1575, and 1501 cm.$^{-1}$ (phenyl), δ 0·83 (s, $W_{\frac{1}{2}}$ 2 c./sec., C-18 Me), 2·04 (s, 17-OAc), 2·33 (d, *J* 12·8 c./sec., 12α-H showing further fine splitting due to coupling with C-18 Me), 2·59 (d, *J* 12·8 c./sec., 12β-H), 2·81 (m, C-6 benzylic H), 3·80 (s, aryl OMe), 4·48 (s, OH), 4·70 (m, 17-H), and 6·76 (s, $W_{\frac{1}{2}}$ 1·6 c./sec., aromatic H), r.d. (*c* 0·415) $[\phi]_{589}$ +328°, $[\phi]_{550}$ +518°, $[\phi]_{500}$ +700°, $[\phi]_{350}$ +3360°, $[\phi]_{303}$ +15,700° (pk.), and $[\phi]_{282}$ 0°.

9β-Hydroxy-3-methoxyoestra-1,3,5(10)-triene-11,17-dione (IV; R^1 = O, R^2 = Me, R^3 = OH, R^4 = H_2).—Benzene–ether (97 : 3) eluates from the above column yielded the *product* (70 mg.) which crystallised from ether as needles, m.p. 132—133° (Found: C, 72·8; H, 7·3; O, 20·3. $C_{19}H_{22}O_4$ requires C, 72·6; H, 7·1; O, 20·4%), $\lambda_{max.}$ 277 (ε 1465) and 284 mμ (ε 1360), $\nu_{max.}$ 3465 (intramol. bonded OH), 1742 (C-17 CO), 1708 (C-11 CO), 1610, 1573, and 1500 cm.$^{-1}$ (phenyl), δ(CCl_4) 0·85 (s, $W_{\frac{1}{2}}$ 2·8 c./sec., C-18 Me), 2·22 (d, *J* 12·8 c./sec., 12α-H showing further fine splitting due to coupling with C-18 Me), 2·57 (d, *J* 12·8 c./sec., 12β-H), 2·76 (m, 6-H), 3·75 (s, aryl OMe), 4·05 (s, OH), and 6·64 (s, $W_{\frac{1}{2}}$ 3 c./sec., aromatic H), r.d. (*c* 0·100)

[8] A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 5366.

[9] Y. Urusibara and T. Nitta, *Bull. Chem. Soc. Japan*, 1941, **16**, 179.

$[\phi]_{589}$ +542°, $[\phi]_{500}$ +1210°, $[\phi]_{400}$ +2400°, $[\phi]_{350}$ +6300°, $[\phi]_{305}$ +30,000° (pk.), and $[\phi]_{290}$ +16,700°.

Later benzene–ether (97 : 3) eluates gave a mixture of 17β-acetoxy-9β-hydroxy-3-methoxyoestra-1,3,5(10)-triene-6,11-dione and 9β-hydroxy-3-methoxyoestra-1,3,5(10)-triene-6,11,17-trione which could not be separated, $\nu_{max.}$ 1740br (17-OAc and C-17 CO), 1712 (C-11 CO), and 1685 cm.$^{-1}$ (C-6 CO).

17β-*Acetoxy*-3-*methoxy*-9-*oxo*-9,11-*seco*-*oestra*-1,3,5(10)-*trien*-11-*oic Acid* (III; R = OAc, · · · H).—The crude acidic fraction (4·11 g., 59%) from the above oxidation was crystallised from aqueous methanol to give needles of 17β-acetoxy-3-methoxy-9-oxo-9,11-seco-oestra-1,3,5(10)-trien-11-oic acid, m.p. 139—140° (lit.,[2] 145°), $\lambda_{max.}$ 224 (ε 14,140) and 274 mμ (ε 18,600), $\nu_{max.}$ 3670 (OH), 3200br (H-bonded OH of CO_2H), 1726 (17-OAc), 1710 (CO_2H), and 1670 cm.$^{-1}$ (C-9 CO), δ 1·10 (s, C-18 Me), 1·99 (s, 17-OAc), 2·60 (m, C-6 protons), 2·96 (m, 12-H), 3·88 (s, aryl OMe), 5·09 (m, 17-H), 6·73 (d, J_{24} 2 c./sec., C-4 aromatic H), 6·85 (2d, J_{12} 8·6, J_{24} 2 c./sec., C-2 aromatic H), 8·00 (d, J_{12} 8·6 c./sec., C-1 aromatic H), and 8·89 (s, CO_2H), r.d. (*c* 0·766 in EtOH) $[\phi]_{589}$ −48°, $[\phi]_{500}$ −91°, $[\phi]_{400}$ −126° (tr.), $[\phi]_{366}$ 0°, $[\phi]_{354}$ +391° (pk.), $[\phi]_{349}$ +270° (tr.), $[\phi]_{342}$ +528° (pk.), $[\phi]_{335}$ 0°, and $[\phi]_{326}$ −250° (tr.).

Treatment of the acid (III; R = OAc, · · · H) with acetic anhydride–sodium acetate under reflux for 40 min. gave an oily product whose i.r. spectrum, $\nu_{max.}$ 1820w, 1780w, 1740s, and 1670m cm.$^{-1}$, indicated that only partial lactonisation had occurred, while t.l.c. showed the formation of two lactones which were unstable and which decomposed on chromatography.

4N-*Chromium Trioxide–Sulphuric Acid Oxidation of* 3-*Methoxyoestra*-1,3,5(10)-*trien*-17β-yl *Acetate* (I; R^1 = OAc, · · H, $R^2 = H_2$).—An ice-cold solution of the trienyl acetate (5·0 g.) in acetone (300 ml.) was treated dropwise with 4N-chromium trioxide–sulphuric acid [prepared from chromium trioxide (13·3 g.) and 50% aqueous sulphuric acid (100 ml.)], and the mixture was kept at 20° for 18 hr.

Chromatography of the neutral oil (1·23 g.) from oxidation, on silica gel, gave starting material (146 mg.), 17β-acetoxy-3-methoxyoestra-1,3,5(10)-trien-6-one (38 mg.), 17β-acetoxy-9β-hydroxy-3-methoxyoestra-1,3,5(10)-triene-11,17-dione (386 mg.), and a mixture of 17β-acetoxy-9β-hydroxy-3-methoxyoestra-1,3,5(10)-triene-6,11-dione and 9β-hydroxy-3-methoxyoestra-1,3,5(10)-triene-6,11,17-trione (100 mg.).

3-*Methoxy*-9,17-*dioxo*-9,11-*seco*-*oestra*-1,3,5(10)-*trien*-11-*oic Acid* (III; R = O).—The acidic oil (3·04 g.) from oxidation was chromatographed on silica gel. Initial chloroform eluates yielded oils, while later chloroform fractions gave the *product* (730 mg.) which crystallised from aqueous methanol as needles, m.p. 158—160° (Found: C, 68·8; H, 7·0; O, 24·2. $C_{19}H_{22}O_5$ requires C, 69·0; H, 6·7; O, 24·3%), $\lambda_{max.}$ 227 (ε 11,720) and 277 mμ (ε 15,500), $\nu_{max.}$ 1725 (C-17 CO), 1703 (CO_2H), 1670 (C-9 CO), 1600, 1573, and 1495 cm.$^{-1}$ (phenyl), δ 0·99 (s, C-18 Me), 2·93 (m, 12-H), 3·84 (s, aryl OMe), 6·65 (d, J_{24} 2 c./sec., C-4 aromatic H), 6·78 (2d, J_{12} 8·5, J_{24} 2 c./sec., C-2 aromatic H), and 7·92 (d, J_{12} 8·5 c./sec., C-1 aromatic H), r.d. (*c* 0·580 in EtOH) $[\phi]_{589}$ −42°, $[\phi]_{500}$ −57°, $[\phi]_{400}$ −33°, $[\phi]_{386}$ 0°, $[\phi]_{350}$ +271°, $[\phi]_{335}$ +427° (pk.), and $[\phi]_{316}$ +270°.

6-*Methoxy*-2-(3a-*methyl*-2-*oxo*-3,3a,4,5-*tetrahydro*[2H]-*cyclopenta*[b]*furan*-4-*yl*)-1,2,3,4-*tetrahydronaphthalen*-1-*one* (VII).—The oily fractions from chromatography above were treated with acetic anhydride–sodium acetate, and the product was chromatographed on silica gel. Initial benzene eluates yielded the *product* (167 mg.) which crystallised from methanol as plates, m.p. 126—127° (Found: C, 73·1; H, 6·4. $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·4%), $\lambda_{max.}$ 225 (ε 14,200), 276 (ε 16,800), and 288sh mμ (ε 14,300), $\nu_{max.}$ 1820 (lactone), 1684 (C-9 CO), 1602, 1573, and 1495 cm.$^{-1}$ (phenyl), $\nu_{max.}$ (CS_2) 800 cm.$^{-1}$ (trisubstd. C=C), δ 1·09 (s, 3a-ang. Me), 2·73 (s, $W_{\frac{1}{2}}$ 3 c./sec., 3′-H), 3·02 (m, C-4 benzylic H), 3·88 (s, aryl OMe), 4·94 (d, $J_{5'6'}$ 2·5 c./sec., olefinic 6′-H), 6·77 (d, J_{57} 2·5 c./sec., C-5 aromatic H), 6·88 (2d, J_{57} 2·5, J_{78} 8·8 c./sec., C-7 aromatic H), and 8·00 (d, J_{78} 8·8 c./sec., C-8 aromatic H), r.d. (*c* 0·03) $[\phi]_{589}$ +442°, $[\phi]_{450}$ +900°, $[\phi]_{400}$ +1310°, $[\phi]_{356}$ +2500° (pk.), $[\phi]_{347}$ +2140° (tr.), $[\phi]_{342}$ +2180° (pk.), $[\phi]_{331}$ +1682° (tr.), and $[\phi]_{300}$ +2680°.

Later benzene eluates from the previous column gave an oily mixture (208 mg.) which was identical (by t.l.c.) with those from attempts to lactonise 17β-acetoxy-3-methoxy-9-oxo-9,11-seco-oestra-1,3,5(10)-trien-11-oic acid.

6-*Methoxy*-2-(6a-*acetoxy*-3a-*methyl*-2-*oxo*-3,3a,4,5,6,6a-*hexahydro*[2H]*cyclopenta*[b]*furan*-4-*yl*)-1,2,3,4-*tetrahydro*-*naphthalen*-1-*one* (VIII).—Benzene–ether (99 : 1) eluates from the previous column gave the *product* (455 mg.), plates, m.p. 146—149° (from methanol) (Found: C, 68·1; H, 6·7. $C_{21}H_{24}O_6$ requires C, 67·7; H, 6·5%), $\lambda_{max.}$ 227 (ε 12,700), 280 (ε 16,000), and 290sh mμ (ε 14,250), $\nu_{max.}$ 1798 (lactone), 1752 (OAc), 1670 (C-9 CO), 1600, 1570, and 1493 cm.$^{-1}$ (phenyl), δ 1·31 (3a-ang. Me), 2·09 (s, OAc), 2·43 (s, 3′-H), 2·96 (m, C-4 benzylic H), 3·90 (s, aryl OMe), 6·79 (d, J_{57} 2·8 c./sec., C-5 aromatic H), 6·90 (2d, J_{57} 2·8, J_{78} 8·8 c./sec., C-7 aromatic H), and 8·05 (d, J_{78} 8·8 c./sec., C-8 aromatic H), r.d. (*c* 0·29) $[\phi]_{589}$ −270°, $[\phi]_{500}$ −436°, $[\phi]_{450}$ −539°, $[\phi]_{400}$ −730°, $[\phi]_{363}$ −1105° (pk.), $[\phi]_{351}$ −962° (tr.), $[\phi]_{342}$ −1052° (pk.), and $[\phi]_{337}$ −1015° (tr.).

Ether eluates yielded much intractable material.

8N-*Chromium Trioxide–Sulphuric Acid Oxidation of* 3-*Methoxyoestra*-1,3,5(10)-*trien*-17β-yl *Acetate* (I; R^1 = OAc, · · · H, $R^2 = H_2$).—An ice-cold solution of the trienyl acetate (2·0 g.) in acetone (120 ml.) was treated with 8N-chromium trioxide–sulphuric acid [10] (40 ml.), and the mixture was kept at 20° for 48 hr.

The reaction yielded a brown acidic oil (1·06 g.) and a pale yellow neutral oil (670 mg.). Treatment of the acidic oil in the same manner as for the acidic fraction from the 4N-chromium trioxide oxidation gave the seco-acid (III; R = O) (250 mg.), the lactone (VII) (120 mg.), the acetoxy-lactone (VIII) (86 mg.), and an oil (170 mg.) which had a similar composition to the product from attempted lactonisation of the seco-acid (III; R = OAc, · · · H).

Chromatography of the neutral oil on silica gel gave starting material (I; R^1 = OAc, · · · H, $R^2 = H_2$) (110 mg.), the 6-oxo-derivative (I; R^1 = OAc, · · · H, R^2 = O) (40 mg.), the ketol (IV; R^1 = OAc, · · · H, R^2 = Me, R^3 = OH, $R^4 = H_2$) (281 mg.), the hydroxy-dione (IV; R^1 = O, R^2 = Me, R^3 = OH, $R^4 = H_2$) (149 mg.), and a mixture (30 mg.) of the hydroxy-dione (IV; R^1 = OAc, · · · H, R^2 = Me, R^3 = OH, R^4 = O) and hydroxy-trione (IV; $R^1 = R^4$ = O, R^2 = Me, R^3 = OH) which could not be separated.

Oxidation of 3-*Methoxyoestra*-1,3,5(10)-*trien*-17-*one* (I; R^1 = O, $R^2 = H_2$).—A solution of 3-methoxyoestra-1,3,5(10)-trien-17-one (1·0 g.) in acetone (250 ml.) was

[10] A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 1953, 2548.

treated dropwise with 4N-chromium trioxide–sulphuric acid (20 ml.) at 0°, and the mixture then held at 20° for 18 hr. The reaction yielded a pale yellow neutral oil (475 mg.) and a brown acidic oil (500 mg.).

Chromatography of the neutral oil on silica gel and elution with benzene–ether (25 : 1) yielded unchanged material (30 mg., 3%). Elution with ether–benzene (3 : 50) yielded 3-*methoxyoestra*-1,3,5(10)-*triene*-6,17-*dione* (40 mg., 4%) which crystallised from ether as plates, m.p. 144—146° (Found: C, 76·5; H, 7·6. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·4%), $\lambda_{max.}$ 223 (ε 18,350), 255 (ε 15,900), and 324 mμ (ε 1645), $\nu_{max.}$ 1738 (C-17 CO), 1678 (C-6 CO), 1605, 1570, and 1493 $cm.^{-1}$ (phenyl), δ (CCl_4) 0·79 (s, C-18 Me), 3·87 (s, aryl OMe), 7·03 (2d, J_{12} 8·8, J_{24} 2·8 c./sec., C-2 aromatic H), 7·32 (d, J_{12} 8·8 c./sec., C-1 aromatic H), and 7·49 (d, J_{24} 2·8 c./sec., C-4 aromatic H), r.d. (*c* 0·390) $[\phi]_{589}$ +229°, $[\phi]_{500}$ +398°, $[\phi]_{400}$ +1580°, $[\phi]_{355}$ +6100° (pk.), and $[\phi]_{340}$ +4730°.

Later benzene–ether (50 : 3) eluates yielded 9β-hydroxy-3-methoxyoestra-1,3,5(10)-triene-11,17-dione (300 mg., 30%), m.p. and mixed m.p. 132—133° (identical i.r. and n.m.r. spectra). Elution of the column with ether gave crystalline material (7 mg.) which contained two compounds (t.l.c.) but which could not be purified further. The i.r. spectrum, $\nu_{max.}$ 3465 (OH), 1744 (C-17 CO), 1712 (C-11 CO), and 1688 $cm.^{-1}$ (C-6 CO), indicated that the product was mainly 9β-hydroxy-3-methoxyoestra-1,3,5(10)-triene-6,11,17-trione.

Lactonisation of the acidic fraction and work-up in the usual manner gave the lactone (VII) (155 mg.), m.p. and mixed m.p. 126—127°, and the acetoxy-lactone (VIII) (25 mg.), m.p. and mixed m.p. 146—149°.

Zinc–Acetic Acid Reduction of 9β-*Hydroxy*-3-*methoxyoestra*-1,3,5(10)-*triene*-11,17-*dione* (IV; R^1 = O, R^2 = Me, R^3 = OH, R^4 = H_2).—A solution of 9β-hydroxy-3-methoxyoestra-1,3,5(10)-triene-11,17-dione (250 mg.) in acetic acid (40 ml.) was heated under reflux with zinc dust (10 g.) until t.l.c. indicated that no starting material remained (25 hr.). Filtration of the cooled mixture and removal of solvent from the filtrate gave an oil which contained at least six compounds (t.l.c.). The oil was chromatographed on silica gel, to yield 3-methoxyoestra-1,3,5-triene-11,17-dione (40 mg.) as the major component.

[8/732 *Received, May 24th,* 1968]