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The Structure and Function of Oestrogens. III* 3,17β-Dihydroxy-6-oxaoestra-1,3,5(10),8(9)-tetraen-7-one and Related Steroidal Coumarins

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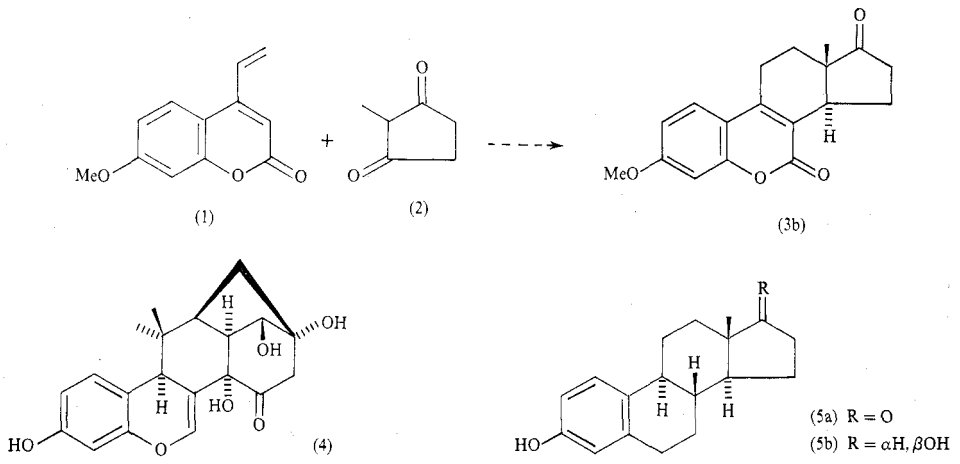
Abstract

A Pechmann condensation of resorcinol, or resorcinol monomethyl ether with ethyl *t*-7a-methyl-1,5-dioxo-*r*-3a,4,5,6,7,7a-hexahydroindan-*c*-4-carboxylate (10b) gave 3-hydroxy-6-oxaoestra-1,3,5(10),8(9)-tetraene-7,17-dione (3a), or the corresponding 3-methoxy compound (3b), respectively. Reduction of 3-hydroxy-6-oxaoestra-1,3,5(10),8(9)-tetraene-7,17-dione (3a) with sodium borohydride gave 3,17β-dihydroxy-6-oxaoestra-1,3,5(10),8(9)-tetraen-7-one (11).

Compounds (3a) and (11) were tested for oestrogenic activity.

Introduction

We required compounds (3a) and (3b) and related coumarin-like analogues of oestrone (5a) to test them for oestrogenic activity, and also as synthetic intermediates.



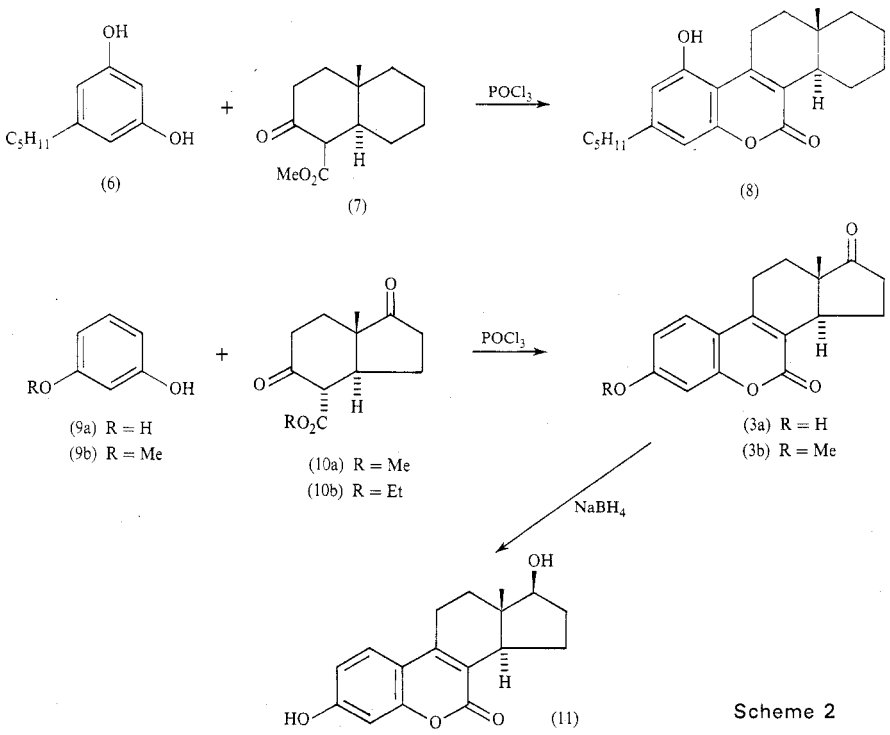
Scheme 1

Two routes were considered. One was to effect conjugate Michael addition of 2-methylcyclopentane-1,3-dione (2) onto 7-methoxy-4-vinylcoumarin (1) (Scheme 1), then to cyclize, and to hydrogenate the 14,15-double bond selectively in a manner analogous to the well known Torgov synthesis[1,2] of oestrone (5a). The second

* Part II, *Aust. J. Chem.*, 1979, **32**, 1107.

[1] Ananchenko, S. N., and Torgov, I. V., *Tetrahedron Lett.*, 1963, 1553.
[2] Koshoev, K. K., Ananchenko, S. N., and Torgov, I. V., *Khim. Prir. Soedin.*, 1965, **1**[3], 172.

approach (Scheme 2) was to carry out a Pechmann condensation of the *trans*-hydrindane diketo esters (10a) or (10b) with resorcinol (9a) or its methyl ether (9b) to give compounds (3a) or (3b) directly. Razdan *et al.*[3] had used a similar reaction between olivetol (6) and the *trans*-decalin derivative (7) to make compound (8) which they required as an analogue of tetrahydrocannabinol. We chose to use the second route (Scheme 2), at least in the first instance, because it should lead unambiguously to *trans* stereochemistry of the C/D ring junction. Two additional reasons for choosing Scheme 2 are (i) that by using enantiomerically pure (10) of known[4] absolute stereochemistry one would obtain either enantiomer of (3a) or (3b); (ii) phenolic compounds such as (3a) should be obtainable directly, thus avoiding a demethylation step.



Scheme 2

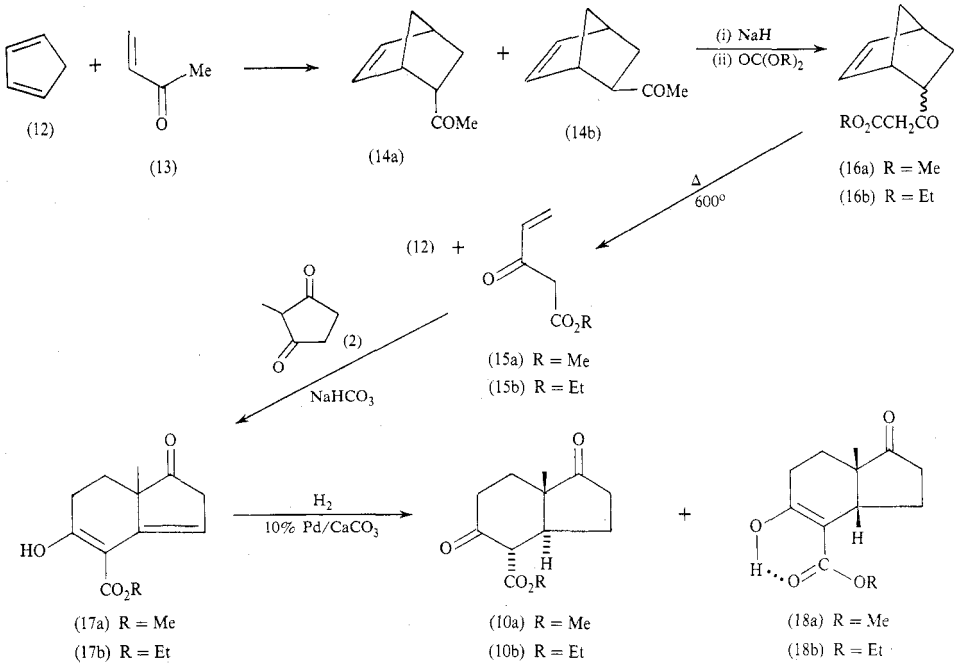
While our work was in progress a report by a Canadian group described the synthesis of (3b) and some related compounds by the 4-vinylcoumarin route (Scheme 1).[5] Their objective was the synthesis of steroidal analogues of the very potent plant oestrogen miroestrol (4).

We now report the direct synthesis of both (3a) and (3b) by means of the Pechmann reaction, and the reduction of (3a) to give the oestradiol analogue (11).

[3] Razdan, R. K., Pars, H. G., Granchelli, F. E., and Harris, L. S., *J. Med. Chem.*, 1968, **11**, 377.
[4] Michelli, R. A., Hajos, Z. G., Cohen, N., Parrish, D. R., Portland, L. A., Sciamanna, W., Scott, M. A., and Wehrli, P. A., *J. Org. Chem.*, 1975, **40**, 675.
[5] Findlay, J. A., Mebe, P., Stern, M. D., and Givner, M. L., *Can. J. Chem.*, 1980, **58**, 1427.

Synthesis

The key intermediates in the synthesis of the bicyclic diketo esters (10a) and (10b) are the vinyl keto esters (15a) and (15b). A method[6,7] previously used by us[8] for the synthesis of (15b) is tedious and gives a relatively low overall yield in five steps from β-propiolactone. In the present work we used a better method briefly outlined in 1972 by Stork and Guthikonda[9] who, however, have not published the experimental details. Two other methods have been described recently.[10,11] The Stork procedure (Scheme 3) entails the Diels–Alder addition of cyclopentadiene (12) and methyl vinyl



Scheme 3

ketone (13) to give a mixture of *endo* and *exo* isomers (14a) and (14b) of 1-(bicyclo-[2,2,1]hept-5-en-2-yl)ethanone, treatment of which with sodium hydride followed by dimethyl or diethyl carbonate gave an *endo,exo* mixture of the β-keto esters (16a) or (16b), respectively. Pyrolysis of (16a) or (16b) at 600° in vacuum gave 80% of the vinyl keto esters (15a) and (15b). This corresponds to a yield of 50% from methyl vinyl ketone. The yields of (16a) and (16b) in the carboalkoxylation step were comparable (82–84%), but a longer reaction time was required for complete

[6] Nazarov, I. N., and Zav'ylov, S. I., *Zh. Obshch. Khim.*, 1953, **23**, 1703 (*Chem. Abstr.*, 1954, **48**, 13667h).
[7] Wenkert, E., Afonso, A., Bredenberg, J. B., Kaneko, C., and Tahara, A., *J. Am. Chem. Soc.*, 1964, **86**, 2038.
[8] Collins, D. J., and Tomkins, C. W., *Aust. J. Chem.*, 1977, **30**, 443.
[9] Stork, G., and Guthikonda, R. N., *Tetrahedron Lett.*, 1972, 2755.
[10] Van den Goorbergh, J. A. M., and van der Gen, A., *Tetrahedron Lett.*, 1980, 3621.
[11] Wenkert, E., Ceccherelli, P., and Fugiel, R. A., *J. Org. Chem.*, 1978, **43**, 3982.

reaction of (14a,b) with dimethyl carbonate than with diethyl carbonate. This reaction proceeded cleanly in 1,2-dimethoxyethane or in tetrahydrofuran, but failed completely when diethyl ether was used as the solvent.

Ethyl 3-oxopent-4-enoate (15b) has been condensed with 2-methylcyclopentane-1,3-dione (2) to give (17b) by heating under reflux in toluene containing pyridine.[12] We found that a cleaner product is obtained according to the method of Nomine *et al.*[13] Thus, a mixture of (15b) and 2-methylcyclopentane-1,3-dione (2) was stirred vigorously for 2·5 h in boiling aqueous 0·1 M sodium bicarbonate to give 60% of the pure recrystallized enolic diketo ester (17b). By a similar procedure the corresponding methyl ester (17a) was obtained in 53% yield. Hydrogenation of the ethyl ester (17b) over palladium/calcium carbonate gave 77% of the corresponding *trans*-perhydroindanone (10b) together with 23% of the enolic *cis* isomer (18b) (cf.[8]). Similarly, the methyl ester (17a) gave the *trans*-perhydroindanone (10a) and the *cis* isomer (18a) in the ratio 85 : 15. In a German patent Eder and Lorenz[14] have claimed that the esters (17a) and (17b) can be hydrogenated over palladium/charcoal in benzene containing triethylamine to give exclusively the *trans*-perhydroindanones (10a) and (10b). No experimental details were given. When a procedure of this type was applied in the hydrogenation of (17a) there was no appreciable change in the *cis*/*trans*-ratio of products. However, in the case of the ethyl ester (17b) the product contained 95% of the required *trans*-fused ester (10b), but the reaction was slow, requiring 24 h for completion. It was then found that hydrogenation of the ethyl ester (17b) in ethyl acetate containing a small amount of triethylamine was complete within 2 h, and chromatography of the product on silica gel gave 85% of the *trans*-fused ester (10b), and about 5% of the enolic *cis*-perhydroindanone (18b).

Initial attempts to effect a Pechmann reaction between resorcinol monomethyl ether (9b) and the diketo ester (10b) by using polyphosphoric acid as catalyst led to the formation of complex mixtures of products. It was then found that the reaction could be effected in refluxing toluene containing phosphorus oxytrichloride to give the tetracyclic coumarin (3b) in 40% yield. The use of refluxing benzene or 1,2-dimethoxyethane at 100° led to inferior yields. Resorcinol (9a) also reacted smoothly with the diketo ester (10b) in toluene containing phosphorus oxytrichloride to give the steroidal coumarin (3a) in 68% yield.

Compounds (3a) and (3b) showed ultraviolet spectra typical of the coumarin chromophore. The proton n.m.r. spectrum of the 3-methoxy compound (3b) measured in (D)chloroform showed a singlet for the angular methyl group at δ 0·91 and a doublet of doublets at 2·45 (J 20·7 and 7·8 Hz) for the ring junction proton, H 14. The three aromatic protons showed a resonance pattern typical of a 1,2,4-trisubstituted aromatic system, with H 1 appearing as a doublet at δ 7·48 (J H 1, H 2, 9·4 Hz). The ^{13}C n.m.r. spectrum was also consistent with structure (3b) and the mass spectrum showed the parent ion at m/z 298.

The ^{1}H and ^{13}C n.m.r. spectra of the 3-hydroxy compound (3a) measured in (D_6)dimethyl sulfoxide were similar to the corresponding spectra of the 3-methoxy compound (3b) but there was an exchangeable proton resonance at δ 10·38. The mass spectrum showed the parent ion at m/z 284.

[12] Grinenko, G. S., Popova, E. V., and Maksimov, V. I., *Zh. Org. Khim.*, 1969, **5**, 1329.
[13] Nomine, G., Amiard, G., and Torelli, V., *Bull. Soc. Chim. Fr.*, 1968, 3664.
[14] Eder, U., and Lorenz, H. P., Ger. Offen., 2,131,230, 21 December 1972 (*Chem. Abstr.*, 1973, **78**, 71769d).

Reduction of 3-hydroxy-6-oxaoestra-1,3,5(10),8(9)-tetraene-7,17-dione (3a) with sodium borohydride in aqueous dimethylformamide gave 3,17β-dihydroxy-6-oxaoestra-1,3,5(10),8(9)-tetraen-7-one (11).

The ^{1}H n.m.r. spectrum of (11) measured in (D_6)dimethyl sulfoxide showed the angular methyl group at δ 0·63 and two exchangeable protons at 4·64 and 10·31; the 17α-proton was part of a ten-proton envelope which included the 11, 12, 15 and 16 methylene groups, and H 14α.

The assignment of β orientation of the 17-hydroxyl group of (11) is based on analogy with numerous similar reductions of 17-keto steroids, and is strongly supported by the ^{13}C n.m.r. spectrum which showed a chemical shift of $-2·1$ ppm for the angular methyl group, C 18, relative to C 18 of the corresponding 17-ketone (3a). This compares with the value of $-2·7$ ppm observed for the shift of C 18 in the transformation of oestrone 3-methyl ether into 17β-oestradiol 3-methyl ether, whereas the corresponding figure for the 17α-oestradiol derivative is $+3·2$ ppm.[15]

The complete, but tentative assignments of the ^{13}C n.m.r. spectra given in the experimental section are based on analogy with the spectra of 7-methoxycoumarin,[16] oestrone,[15] and chemical shift considerations.

It is conceivable, but unlikely, that the *trans*-ring junction of the bicyclic diketo ester (10b) was not preserved in the 6-oxasteroids (3a) and (3b). In the first place, the *trans*-fused bicyclic diketo ester (10b) was found to be unchanged after 4 h at reflux in benzene containing phosphorus oxytrichloride. That stereochemical integrity is retained during the Pechmann reaction with resorcinol, or its monomethyl ether, is indicated by the fact that the ^{1}H n.m.r. spectra of the crude reaction products showed no methyl singlets other than those for pure (3a) or (3b). Also, the ^{13}C n.m.r. chemical shift pattern of the carbon atoms in rings C and D is consistent with a *trans* C/D ring junction.[15] The ^{1}H n.m.r. spectrum of (3b) is consistent with the partial data reported for this compound prepared by the 4-vinylcoumarin route (Scheme 1).[5]

Oestrogenic Activity

Randomly bred mice of the QS strain were used to compare the oestrogenic activity of oestradiol (5b), 3-hydroxy-6-oxaoestra-1,3,5(10),8(9)-tetraene-7,17-dione (3a) and 3,17β-dihydroxy-6-oxaoestra-1,3,5(10),8(9)-tetraene-7-one (11). All compounds were administered subcutaneously in peanut oil on the morning of day 1 and day 2, and vaginal smears were taken on the afternoon of day 3 and the morning and afternoon of day 4.[17] With 10 animals per group a total positive score of 30 is possible. The results are presented in Table 1 which shows that the 100-μg dose of both test compounds elicited an essentially complete response even though at the 10-μg level there was virtually no sign of activity. This unusually steep dose response together with the nature of the smears suggested that these compounds might show prolonged activity. Accordingly the animals which received the highest doses (1000 μg) of the test compounds or of oestradiol (0·1 μg) were smeared once weekly for the following six weeks. The effects of oestradiol had disappeared completely within a week, but the oestrogenic response to the oestrone analogue (3a) persisted

[15] Blunt, J. W., and Stothers, J. B., *Org. Magn. Reson.*, 1977, **9**, 439.
[16] Lapper, R. D., *Tetrahedron Lett.*, 1974, 4293.
[17] Emmens, C. W., *J. Endocrinol.*, 1957, **16**, 148.

for up to three weeks, and the oestradiol analogue (11) was still about 50% effective after six weeks.

Table 1. Oestrogenic activity measured by vaginal smear assay in mice

Ten animals per group. *D*, Daily dose (μg) injected subcutaneously in peanut oil; *N*, number of positive smears (out of 30); *R*, positive response

Oestradiol (5b)			Oestrone analogue (3a)			Oestradiol analogue (11)		
D	*N*	*R* (%)	*D*	*N*	*R* (%)	*D*	*N*	*R* (%)
0·01	11	38	10	1	3	10	0	0
0·1	26	87	100	28	93	100	30	100
			1000	29	97	1000	30	100

The persistent oestrogenic effect of these steroidal coumarins might have something to do with reversible opening of the B-ring lactone, and perhaps *trans*-esterification of a functional group at the receptor active site. Even though their net activity is low, compounds such as (11) might be useful in studies of the mode of action of oestrogens at the molecular level.

Experimental

Melting points and boiling points are uncorrected. Microanalyses were carried out by the Australian Microanalytical Service, Melbourne. Ultraviolet spectra were measured with a Cary 17 spectrophotometer. Infrared spectra were measured with a Jasco IRA-1 grating infrared spectrophotometer and refer to thin films for liquids and Nujol mulls for solids. The abbreviations used to describe the absorptions are s, strong; m, medium; w, weak. Proton nuclear magnetic resonance (^{1}H n.m.r.) spectra were measured at 60 MHz with a Varian Associates A50/60 spectrometer. Spectra recorded at 90 MHz were obtained with a Bruker WH90, or a Perkin–Elmer R32 spectrometer. ^{1}H n.m.r. data are reported as follows: chemical shifts (δ) in ppm from tetramethylsilane as an internal standard (δ 0·00). Multiplicity: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; etc., m, multiplet; b, broad; exch., hydroxyl proton exchanges on shaking with D_2O. ^{13}C nuclear magnetic resonance spectra were measured at 22·63 MHz with a Bruker WH90 spectrometer and chemical shifts are relative to internal tetramethylsilane. Partial assignments in some cases were made by the multiplicities of the off-resonance spectra and the chemical shifts. Mass spectra were measured with a V.G. Micromass 7070 F spectrometer at 70 eV. The principal ion peaks (m/z) are reported together with their intensities ($m/z > 10\%$) relative to the base peak. Other ions of lower intensities are reported when they appear to be of interest.

Long-column chromatography was carried out on silica gel (100–200 mesh). Flash chromatography was carried out on Merck silica gel (40–63 μm). Preparative gas–liquid chromatography (g.l.c.) was carried out on a Varian Aerograph Autoprep A 700 chromatograph. Thin-layer chromatography (t.l.c.) was carried out on glass plates, 20 cm by 7 cm for analytical separations, coated with Merck PF 254 silica gel, activated at 100° for 1 h. Pyrolyses were carried out in a silica tube (40 by 2·6 cm i.d.) packed with 1 cm lengths of silica tubing. The central section (30 cm) was heated with an external electric furnace (Type 70-T, Hevi-Duty Heating Equipment Co., Watertown, Wisconsin, U.S.A.), and a chromel–alumel thermocouple placed just touching the external of the silica tube in the central part of the oven. Pyrolyses were performed at 600° and at pressure of approximately 2 mmHg. Light petroleum refers to the fraction of boiling point 60–68°.

(a) 2-Methylcyclopentane-1,3-dione (2)

This compound was prepared by a minor modification of the method of Schick *et al.*[18] Finely powdered succinic anhydride (100 g) was added portionwise, under nitrogen, to a stirred solution of aluminium trichloride (400 g) in anhydrous nitromethane (400 ml), kept at room temperature. The mixture was heated gently until vigorous gas evolution had begun. When the gas evolution had

[18] Schick, H., Lehmann, G., and Hilgetag, G., *Chem. Ber.*, 1969, **102**, 3238.

ceased, propanoyl chloride (278 g) was added quickly to the dark brown mixture with continual stirring. The mixture was heated to 80° for 3 h, cooled to room temperature, then poured onto ice (800 g) and left overnight at −10°C. The brown crystalline product was collected and recrystallized from water with charcoal to give the pure enolic dione as colourless crystals (70·3 g, 63%), m.p. 213–214° (sealed capillary) (lit.[18] 214–216°). ^{1}H n.m.r. δ (60 MHz, $(CD_3)_2SO$) 1·52, s, Me; 2·40, s, $2\times CH_2$; 10·5, very broad, OH (exch.). ^{13}C n.m.r. δ ($(CD_3)_2SO$) 5·8, q, Me; 30·2, t, C4, C5; 111·8, s, C2; 194·4, s, C1, C3.

(*b*) endo/exo-*1*-(*Bicyclo*[*2,2,1*]*hept-5-en-2-yl*)*ethanone* (*14a*) *and* (*14b*)

This compound was synthesized by the method of Dinwiddie *et al.*[19] A cooled solution of freshly distilled methyl vinyl ketone (139 g) in ether (150 ml) was mixed with freshly distilled cyclopentadiene (132 g) in ether (150 ml) and the mixture was allowed to warm to room temperature. The heat of reaction caused vigorous reflux of the solvent. The mixture was allowed to stand overnight, then the solvent was removed in vacuum. Distillation gave a mixture of (14a) and (14b) as a colourless liquid (195·4 g, 80%), b.p. 80°/15 mm (lit.[19] 72–73°/12 mm).

A sample of the above isomeric mixture was subjected to preparative g.l.c. on a 4 ft by 3/8 in. column of 20% Carbowax 20 M on Chromosorb A (45–60 mesh), helium being used as carrier gas (120 ml/min). The oven, collector and detector temperatures were 125°, 190° and 240° respectively.

(i) endo-*1*-(*Bicyclo*[*2,2,1*]*hept-5-en-2-yl*)*ethanone* (*14a*).—R_t 15·3 min. ν_{max} (film) 1707s (C=O), 1572w (C=C), 1447m, 1427m, 1357s, 1337s, 1292w, 1272m, 1256w, 1225m, 1187s, 1172s, 1157m, 1132m, 1107m, 1097w, 1967w, 997m, 962w, 937m, 917w, 907w, 897w, 852w, 837m, 822m, 792w, 742m, 722s, 677w cm^{-1}. ^{1}H n.m.r. δ (60 MHz, $CDCl_3$) 1·32–1·87, m, H3*endo*, H3*exo*, H7*anti*, H7*syn*; 2·12, s, Me; 2·80–3·39, m, H1, H4, H2*exo*; 5·88, dd, *J* 6·0 Hz, 3·0 Hz, H5; 6·18, dd, *J* 6·0 Hz, 3·3 Hz, H6. ^{13}C n.m.r. δ ($CHCl_3$) 27·4, t, C3; 29·1, q, Me; 42·7, 45·8 and 52·3, d, C1, C2, C4; 50·0, t, C7; 131·3 and 137·8, d, C5, C6; 208·8, s, CO. Mass spectrum: *m/z* 136 (M, 16%), 93 (21), 91 (12), 77 (14), 71 (27), 66 (100), 58 (14), 43 (28).

(ii) exo-*1*-(*Bicyclo*[*2,2,1*]*hept-5-en-2-yl*)*ethanone* (*14b*).—R_t 10·4 min. ν_{max} (film) 1710s (C=O), 1570w (C=C), 1460m, 1445m, 1355s, 1330s, 1286m, 1275m, 1260m, 1225m, 1170s, 1155m, 1135w, 1095w, 1025m, 995w, 975w, 950w, 935w, 905w, 885w, 870w, 850m, 815m, 780m, 765w, 705s, 680w cm^{-1}. ^{1}H n.m.r. δ (60 MHz, $CDCl_3$) 1·18–1·48, m, H3*endo*, H7*anti*, H7*syn*; 1·72–2·08, m, H3*exo*; 2·21, s, Me; 2·25–2·55, m, H2*endo*; 2·80–3·10, m, H1, H4; 6·18, apparent t (splitting 1·8 Hz), H5, H6. ^{13}C n.m.r. δ ($CDCl_3$) 29·1, t, C3; 29·8, q, Me; 41·7, 45·4 and 51·7, d, C1, C2, C4; 45·9, t, C7; 135·8 and 138·2, d, C5, C6; 210·5, s, CO. Mass spectrum: *m/z* 136 (M, 16%), 93 (14), 91 (13), 77 (14), 71 (27), 66 (100), 43 (37).

(*c*) *Methyl* endo/exo-*3*-(*Bicyclo*[*2,2,1*]*hept-5-en-2-yl*)-*3-oxopropanoate* (*16a*)

To sodium hydride (12·6 g, 80% suspension in paraffin, washed with light petroleum) was added dry tetrahydrofuran (400 ml) and dry dimethyl carbonate (54 g), after which the stirred mixture was brought to reflux. A solution of an *endo*/*exo* mixture of 1-(bicyclo[2,2,1]hept-5-en-2-yl)ethanone (27·2 g) in tetrahydrofuran (100 ml) was added dropwise to the refluxing solution during 45 min. The mixture was refluxed in an atmosphere of nitrogen for 16 h and then cooled to room temperature; glacial acetic acid (16 ml) was added and the solvent was removed. After addition of water the mixture was extracted with chloroform to give a brown oil. Distillation gave the β-keto ester (16a) as a colourless liquid (32·5 g, 84%), b.p. 83–84°/0·5 mm (lit.[9] 87–88°/0·8 mm). ν_{max} (film) 1745s (ester C=O), 1705s (C=O), 1625m (C=C), 1435m, 1405m, 1330s, 1310s, 1255s, 1165m, 1085m, 1015m, 940w, 905w, 850w, 830w, 775w, 700w cm^{-1}. ^{1}H n.m.r. δ (60 MHz, $CDCl_3$) 1·18–1·51, m, 3H; 1·73–2·13, m, 1H; 2·36–2·69, m, 1H; 2·79–3·38, m, 2H; 3·48, s, 2H, $COCH_2$*endo*; 3·57, s, 2H, $COCH_2$*exo*; 3·73, s, OMe; 5·78–6·32, m, H5, H6. Mass spectrum: *m/z* 194 (M, 3%), 129 (27), 97 (10), 66 (100), 55 (22), 39 (12), 22 (32).

(*d*) *Ethyl* endo/exo-*3*-(*Bicyclo*[*2,2,1*]*hept-5-en-2-yl*)-*3-oxopropanoate* (*16b*)

To sodium hydride (25·2 g, 80% suspension, washed) was added dry tetrahydrofuran (800 ml) and dry diethyl carbonate (141·6 g), after which the stirred mixture was brought to reflux. A solution

[19] Dinwiddie, J. G., and McManus, S. P., *J. Org. Chem.*, 1965, **30**, 766.

of the ketones (14a) and (14b) (54·4 g) in tetrahydrofuran (200 ml) was added dropwise to the refluxing solution during 3·75 h; the mixture was then refluxed for a further 30 min. Workup as above and distillation gave *ethyl* endo/exo-*3-(bicyclo[2,2,1]hept-5-en-2-yl)-3-oxopropanoate* (16b) as a colourless liquid (68·1 g, 82%), b.p. 101°/0·4 mm (Found: C, 69·2; H, 7·5. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%). ν_{max} (film) 1745s (ester C=O), 1710s (C=O), 1640m (C=C), 1620m, 1575w, 1465m, 1445m, 1410m, 1390m, 1365s, 1330s, 1305s, 1260s, 1160s, 1115m, 1095s, 1035s, 950w, 925m, 910m, 860m, 840w, 820w, 780w, 719s, 680w cm^{-1}. ^1H n.m.r. δ (60 MHz, $CDCl_3$) 1·27, t, J 7·0 Hz, ester Me; 1·33–2·14, m, 4H; 2·38–3·41, m, 3H; 3·47, s, $COCH_2$*endo*; 3·56, s, $COCH_2$*exo*; 4·22, q, J 7·0 Hz, OCH_2; 5·80–6·35, m, H5, H6. Mass spectrum m/z 208 (M, 3%), 143 (36), 121 (11), 97 (16), 66 (100), 55 (28).

(*e*) *Methyl 3-Oxopent-4-enoate* (*15a*)

To the top of a vertical silica pyrolysis tube, kept at 600°C, was added the freshly distilled methyl norbornenyl keto ester (16a) over a period of 75 min. The pressure in the apparatus was maintained at approximately 2 mm by a vacuum pump and a nitrogen bleed. The crude unsaturated ester was collected in a vapour trap kept at −30°C, and the cyclopentadiene was collected in a liquid nitrogen trap. The crude product was immediately distilled to give methyl 3-oxopent-4-enoate as a colourless liquid (9·68 g, 80%), b.p. 62°/16 mm (lit.[9] 78–81°/18 mm). ν_{max} (film) 3100m (OH), 1740s (ester, C=O), 1660s, 1649s, 1610s, 1590s, 1445s, 1395s, 1345m, 1320s, 1230s, 1140s, 1075m, 1035s, 1020s, 980s, 940s, 880m, 840w, 810s, 725m cm^{-1}. ^1H n.m.r. δ (60 MHz, $CDCl_3$): (i) enol form, 3·78, s, OMe; 5·13, s, COC**H**=COH, 5·56, apparent t (splitting 6·5 Hz), CH_2=C**H**; 6·10–6·49, m, CH=C$\mathbf{H_2}$; (ii) keto form, 3·67, s, CH_2CO_2; 3·75, s, OMe; 5·97, dd, J 8·8 Hz, 3·8 Hz, C**H**=CH_2; 6·10–6·49, m, CH=C$\mathbf{H_2}$.

(*f*) *Ethyl 3-Oxopent-4-enoate* (*15b*)

Pyrolysis of the ethyl norbornenyl keto ester (16b) in the manner described above for the corresponding methyl ester, and distillation of the product gave ethyl 3-oxopent-4-enoate in 78% yield, b.p. 79–81°/21 mm (lit.[6] 76–77°/16 mm). ν_{max} (film) 3095m (OH), 1740s (ester, C=O), 1655s, 1640s, 1605m, 1590s, 1420m, 1385m, 1350m, 1320m, 1395m, 1230s, 1145s, 1090w, 1035s, 980m, 940m, 810m, 725m cm^{-1}. ^1H n.m.r. δ (60 MHz, $CDCl_3$): (i) enol form, 1·30, t, J 7·5 Hz, Me; 4·25, q, J 7·5 Hz, OCH_2; 5·13, s, COC**H**=COH; 5·56, apparent t (splitting 6·5 Hz), CH_2=C**H**; 6·08–6·5, m, CH=C$\mathbf{H_2}$; (ii) keto form, 1·27, t, J 7·5 Hz, Me; 3·65, q, OCH_2CH_3; 5·95, dd, J 9·0 Hz, 3·8 Hz, CH=CH_2; 6·08–6·50, m, CH=C$\mathbf{H_2}$.

(*g*) *Methyl 5-Hydroxy-7a-methyl-1-oxo-2,6,7,7a-tetrahydro-1H-indene-4-carboxylate* (*17a*)

According to the procedure of Nomine *et al.*[13] a mixture of methyl 3-oxopent-4-enoate (6·53 g), 2-methylcyclopentane-1,3-dione (5·8 g) and 0·1 M $NaHCO_3$ solution (18 ml) was vigorously stirred at 100° for 2·5 h. The mixture was kept at 70° for 17 h with continual stirring. Water was added to the cooled solution and the aqueous phase was extracted with chloroform. Evaporation of the washed and dried (Na_2SO_4) extract gave a thick brown oil. Distillation gave a light yellow oil (110–125°/0·2 mm) which crystallized upon addition of methanol. Recrystallization from methanol gave the pure enolized *β-keto ester* (6·01 g, 53%) as colourless prisms, m.p. 95–96° (Found: C, 64·7; H, 6·2. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·4%). ν_{max} (Nujol) 3480w (OH), 1745s (C=O), 1645s, 1625m, 1590s, 1470s, 1420m, 1400w, 1355m, 1340w, 1290s, 1280s, 1255s, 1220m, 1200m, 1160m, 1090w, 1075s, 1060m, 1010w, 1000w, 970w, 940w, 920w, 880w, 860s, 830s, 805w, 770w, 730w, 665 cm^{-1}. ^1H n.m.r. δ (90 MHz, $CDCl_3$) 1·13, s, Me; 1·47–3·07, m, 2 × CH_2; 2·88, dd, J 23·2 Hz, 2·6 Hz, =CH–C**H**HCO; 3·29, dd, J 23·2 Hz, J 2·0 Hz, =CH–CHHCO; 3·88, s, OMe; 6·06, t, J 2·5 Hz, olefinic H3; 10·18, s, enolic OH (exch.). Mass spectrum m/z 222 (M, 42%), 194 (11), 190 (18), 163 (13), 162 (100), 147 (20), 91 (21), 79 (12), This compound was previously prepared in these laboratories by Tomkins.[20]

(*h*) *Ethyl 5-Hydroxy-7a-methyl-1-oxo-2,6,7,7a-tetrahydro-1H-indene-4-carboxylate* (*17b*)

This compound was synthesized as described above for the methyl ester rather than by the less convenient pyridine/toluene procedure.[8,12] Thus, a mixture of ethyl 3-oxopent-4-enoate (12·37 g),

[20] Tomkins, C. W., M.Sc. Thesis, Monash University, 1974.

2-methylcyclopentane-1,3-dione (9·9 g) and 0·1 M $NaHCO_3$ (31 ml) gave, after distillation, the ethyl ester as a yellow oil (b.p. 110–140°/0·5 mm) which crystallized upon addition of methanol. Recrystallization from methanol gave the ester (12·10 g, 60%) as colourless prisms, m.p. 94–95° (lit.[13] 95°). The spectral data were as reported previously.[8]

*(i) Hydrogenation of Methyl 5-Hydroxy-7a-methyl-1-oxo-2,6,7,7a-tetrahydro-1*H*-indene-4-carboxylate (17a)*

A solution of the unsaturated keto ester (1·5 g) in anhydrous ethanol (150 ml) was hydrogenated over 10% palladium/calcium carbonate (0·15 g) at room temperature and atmospheric pressure. Evaporation of the filtered solution gave a colourless oil. Flash chromatography on silica gel and elution with ethyl acetate/light petroleum (1 : 5) afforded *methyl 5-hydroxy-7a-methyl-1-oxo-cis-3a,6,7,7a-tetrahydroindan-4-carboxylate* (18a) (0·20 g, 13%), which crystallized from diisopropyl ether as colourless prisms, m.p. 61–62° (Found: $M^{+\cdot}$, 224·105 ± 0·002. $C_{12}H_{16}O_4$ requires $M^{+\cdot}$, 224·1047). ν_{max} (Nujol) 1730s (C=O), 1650s, 1610s, 1445m, 1425m, 1400m, 1360m, 1345m, 1310w, 1275s, 1245m, 1220s, 1205s, 1190s, 1165m, 1110w, 1090m, 1065s, 1050m, 1025m, 960w, 915w, 885w, 870w, 860w, 830m cm^{-1}. ^1H n.m.r. δ (90 MHz, $CDCl_3$) 1·07, s, Me; 1·22–3·10, m, 4 × CH_2 and ring junction H; 3·80, s, OMe; 10·70, s, OH (exch.). Mass spectrum: *m/z* 224 (M, 61%), 195 (11), 193 (15), 192 (48), 168 (22), 167 (17), 164 (17), 163 (26), 150 (24), 141 (11), 137 (35), 136 (100), 135 (24), 122 (19), 95 (15), 80 (11), 79 (20), 77 (11), 68 (26), 55 (15). Further elution with the same solvent gave methyl *t*-7a-methyl-1,5-dioxo-*r*-3a,4,5,6,7,7a-hexahydroindan-*c*-4-carboxylate (10a) (1·3 g, 87%), which crystallized from diisopropyl ether as colourless crystals, m.p. 92–94° (lit.[21] 91–92°). ν_{max} (Nujol) 1730s (five-membered ring C=O, ester C=O), 1710s (six-membered ring C=O), 1440m, 1420m, 1405w, 1350m, 1330w, 1310m, 1305m, 1290w, 1265w, 1255w, 1240w, 1230w, 1195s, 1180m, 1160m, 1150w, 1115m, 1065m, 1035m, 1005w, 995m, 985m, 970w, 940m, 910w, 880w, 860w, 830w, 820m, 745m cm^{-1}. ^1H n.m.r. δ (90 MHz, $CDCl_3$) 1·17, s, Me; 1·58–2·78, m, 4 × CH_2 and ring junction H; 3·52, d, *J* 14·0 Hz, H4; 3·78, s, OMe. Mass spectrum: *m/z* 224 (M, 22%), 193 (27), 192 (27), 164 (24), 150 (13), 149 (11), 148 (13), 147 (19), 137 (14), 136 (30), 126 (13), 125 (100), 123 (16), 122 (21), 121 (14), 113 (16), 110 (19), 109 (30), 108 (16), 100 (65), 81 (24), 79 (22), 69 (38), 68 (35), 55 (37).

*(j) Hydrogenation of Ethyl 5-Hydroxy-7a-methyl-1-oxo-2,6,7,7a-tetrahydro-1*H*-indene-4-carboxylate (17b)*

A solution of the unsaturated keto ester (2·0 g) in ethyl acetate (200 ml) containing triethylamine (2·0 g) was hydrogenated over 10% palladium/charcoal (0·2 g) at room temperature and atmospheric pressure. Chromatography of the colourless oil on silica gel (60 g) and elution with light petroleum/ethyl acetate (24 : 1) gave ethyl 5-hydroxy-7a-methyl-1-oxo-*cis*-3a,6,7,7a-tetrahydroindan-4-carboxylate (18b) (0·09 g, 4·5%) which crystallized from diisopropyl ether as colourless crystals, m.p. 55–56° (lit.[8] 59–60°). The spectral data were as reported previously.[8] Further elution with light petroleum/ethyl acetate (21 : 4) gave ethyl *t*-7a-methyl-1,5-dioxo-*r*-3a,4,5,6,7,7a-hexahydroindan-*c*-4-carboxylate (10b) (1·7 g, 85%) which crystallized from diisopropyl ether as colourless prisms, m.p. 53–54° (lit.[13] 56°). The spectral data were reported previously.[8]

(k) 3-Methoxy-6-oxaoestra-1,3,5(10),8(9)-tetraene-7,17-dione (3b)

To a solution of *m*-methoxyphenol (0·05 g) and ethyl *t*-7a-methyl-1,5-dioxo-*r*-3a,4,5,6,7,7a-hexahydroindan-*c*-4-carboxylate (0·10 g) in dry toluene (4 ml) was added phosphorus oxytrichloride (0·5 g). The solution was refluxed in an atmosphere of nitrogen for 5 h. The volatile materials were removed under vacuum and the residue was recrystallized from benzene to afford 3-methoxy-6-oxaoestra-1,3,5(10),8(9)-tetraene-7,17-dione as fine colourless needles (0·06 g, 40%), m.p. 223–225° (dec.) (lit.[5] 223–225°) (Found: C, 72·0; H, 6·0. Calc. for $C_{18}H_{18}O_4$: C, 72·5; H, 6·1%). λ_{max} (EtOH) 220 (ε 16190), 325 nm (15559). ν_{max} (Nujol) 1735s (five-membered ring C=O), 1715s, 1615s, 1605s, 1505m, 1445s, 1420w, 1385m, 1345w, 1285m, 1265m, 1255s, 1220m, 1205w, 1175m, 1160w, 1145w, 1135w, 1105m, 1085w, 1065m, 1050w, 1035w, 1025w, 990w, 975w, 960w, 950w, 890m, 840w, 825w, 815m, 795w, 780m, 695 cm^{-1}. ^1H n.m.r. (90 MHz, $CDCl_3$) 0·91, s, 13-Me; 1·49–3·12, m, 4 × CH_2; 2·45, dd, *J* 20·7 Hz, 7·8 Hz, H14α; 3·87, s, OMe; 6·80–6·91, m, H2, H4; 7·48,

[21] Sakai, K., and Amemiya, S., *Chem. Pharm. Bull.*, 1970, **18**, 641.

apparent d, J 9·4 Hz, H1. ^{13}C n.m.r. ($CDCl_3$) 13·7, q, C18; 22·8, t, C15; 24·6, t, C11; 27·8, t, C12; 36·5, t, C16; 43·8, d, C14; 47·8, s, C13; 55·7, q, OMe; 100·6, d, C4; 112·4, d, C2; 113·1, s, C10; 119·8, s, C8; 124·8, d, C1; 148·7, s, C9; 154·2, s, C5; 160·7, s, C7; 162·1, s, C3; 218·4, s, C17. Mass spectrum: m/z 298 (M, 100), 270 (16), 256 (15), 255 (52), 243 (24), 242 (36), 241 (36), 229 (36), 227 (11), 69 (12).

(*l*) *3-Hydroxy-6-oxaoestra-1,3,5(10),8(9)-tetraene-7,17-dione* (*3a*)

To a solution of resorcinol (0·5 g) and the *trans*-fused diketo ester (10b) (1·0 g) in dry toluene (40 ml) was added phosphorus oxytrichloride (2·0 g). The solution was refluxed for 3 h in an atmosphere of nitrogen. Removal of the volatiles in vacuum and crystallization from a mixture of methanol and *N*-methylpyrrolidone gave *3-hydroxy-6-oxaoestra-1,3,5(10),8(9)-tetraene-7,17-dione* as colourless plates (1·0 g, 68%), m.p. 300–303° (dec.) (Found: C, 71·9; H, 5·9. $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·7%). λ_{max} (EtOH) 217 nm (ε 16585), 328 (ε 16864). ν_{max} (Nujol) 3240m (OH), 1730s (five-membered ring C=O), 1680s, 1610s, 1595s, 1560m, 1510w, 1420w, 1335w, 1310w, 1285w, 1260m, 1250m, 1220m, 1170m, 1130w, 1105m, 1070m, 1055m, 1030w, 990w, 965w, 950w, 855m, 820m, 800w, 780m, 700w cm^{-1}. ^{1}H n.m.r. δ (90 MHz, $(CD_3)_2SO$) 0·79, s, Me; 1·97–3·86, m, 4 × CH_2, H14α; 6·62–6·84, m, H1, H4; 7·55, d, J 8·5 Hz, H1; 10·38, s, OH (exch.). ^{13}C n.m.r. δ ($(CD_3)_2SO$) 13·1, q, C18; 22·4, t, C15; 24·0, t, C11; 26·8, t, C12; 35·9, t, C16; 42·5, d, C14; 47·1, s, C13; 101·8, d, C4; 111·6, s, C10; 112·7, d, C2; 118·2, s, C8; 125·7, d, C1; 149·1, s, C9; 153·5, s, C5; 159·8, s, C7; 160·3, s, C3; 217·6, s, C17. Mass spectrum: m/z 284 (M, 100), 256 (18), 242 (16), 241 (48), 240 (14), 229 (31), 228 (40), 227 (51), 215 (37), 213 (16).

(*m*) *3,17β-Dihydroxy-6-oxaoestra-1,3,5(10),8(9)-tetraen-7-one* (*11*)

To a mixture of 3-hydroxy-6-oxaoestra-1,3,5(10),8(9)-tetraene-7,17-dione (0·1 g) in dimethylformamide (3 ml) containing water (0·5 ml) was added sodium borohydride (0·012 g). The mixture was stirred at room temperature for 16 h then the solution was neutralized and the solvents were removed. Trituration of the residue with water gave a white solid which crystallized from a mixture of dimethylformamide and water to give *3,17β-dihydroxy-6-oxaoestra-1,3,5(10),8(9)-tetraen-7-one* as colourless needles (0·07 g, 70%), m.p. 325–330° (dec.) (Found: C, 71·2; H, 6·3; $M^{+\cdot}$, 286·122 ± 0·003. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%; $M^{+\cdot}$, 286·1204). λ_{max} (EtOH) 221 nm (ε 13663), 327 (ε 15001). ν_{max} (Nujol) 3335m (OH), 1675s (C=O), 1620s, 1600m, 1560s, 1510w, 1425w, 1355w, 1330w, 1305w, 1275m, 1245w, 1200w, 1160m, 1150m, 1130m, 1090w, 1075w, 1065w, 1045w, 1020, 1000w, 955w, 920w, 855w, 820w, 790m, 730w cm^{-1}. ^{1}H n.m.r. δ (90 MHz, $(CD_3)_2SO$) 0·63, s, Me; 1·17–3·84, m, 4 × CH_2, H17α, H14α; 4·64, bs, OH (exch.); 6·64–6·82, m, H2, H4; 7·51, d, J 8·5 Hz, H1; 10·31, bs, OH (exch.). ^{13}C n.m.r. δ ($(CD_3)_2SO$) 11·0, q, Me; 24·1, t, C15; 24·4, t, C11; 30·2, t, C16; 31·7, t, C12; 42·6, d, C14; 42·8, s, C13; 77·8, d, C17; 101·8, d, C4; 111·8, s, C10; 112·6, d, C2; 119·9, s, C8; 125·5, d, C1; 148·4, s, C9; 153·4, s, C5; 159·9, s, C3, C7. Mass spectrum: m/z 286 (M, 100), 253 (19), 243 (27), 242 (13), 229 (38), 228 (18), 227 (87), 215 (23), 213 (13), 201 (17), 177 (18), 176 (93), 163 (30), 125 (13), 124 (29), 115 (11), 111 (16), 110 (30).

(*n*) *Treatment of Ethyl* t-*7a-Methyl-1,5-dioxo*-r-*3a,4,5,6,7,7a-hexahydroindan*-c-*4-carboxylate* (*10b*) *with Phosphorus Oxytrichloride*

The ester (100 mg) was heated under reflux for 4 h in benzene (4 ml) containing phosphorus oxytrichloride (100 mg). The solution remained colourless and t.l.c. analysis (ether/hexane 1 : 1) showed only a single spot for the starting material.

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