

## Totally Synthetic Steroid Heterocycles. Part 1. Synthesis of Intermediate Precursors of 16-Oxa- and 16-Thia-D-homoestrogens

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The total synthesis of 16-oxa- and 16-thia-D-homoestrogen derivatives is described. A straightforward synthesis of 16-thia- and 16-oxa-3-methoxy-D-homoestra-1,3,5(10),8,14-pentaen-17a-one (8a and b) and their 6-didehydro derivatives (24a and b) is achieved by condensation of 2-methyl-5-thia- and -5-oxacyclohexane-1,3-dione (1a and b) with 6-methoxy-1,2,3,4-tetrahydronaphthylidene-ethylisothiuronium acetate (5). The ethyl homologues (9a and b) are also prepared using the corresponding diones (2a and b). An alternative route to the estrapentaene (8a) starting with Michael addition of 6-*m*-methoxyphenylhex-1-en-3-one (25) to the dione (1a) also produces 3-methoxy-9,10-seco-16-thia-D-homoestra-1,3,5(10),8(14)-tetraene-9,17a-dione (29).

DURING the last decade, much attention has been devoted to the synthesis of heterocyclic steroids<sup>1</sup> in view of their biological interest. In particular, azasteroids which contain one or more nitrogens at almost every position of the steroid nucleus have been prepared. Several types of oxa- and thia-steroids have been also synthesized but so far these have been largely limited to compounds with the heteroatoms in rings A and B.<sup>2,3</sup> This prompted us to synthesize novel ring D oxa- and

thia-steroids. In this paper, we report the synthesis of precursors of 16-oxa- and 16-thia-D-homoestrogens. The methods normally used for the total synthesis of carbocyclic estrogens appeared to be suitable for our purpose by substituting 2-substituted 5-oxa- and 5-thia-cyclohexane-1,3-diones<sup>4</sup> which had already been prepared as new heterocyclic synthons.

Our first synthesis was based on the Torgov-Ananchenko coupling reaction<sup>5</sup> of the hetero-diones (1) and

<sup>1</sup> For comprehensive reviews, see (a) P. Morand and J. Lyall, *Chem. Rev.*, 1968, **68**, 85; (b) H. O. Huisman, *Bull. Soc. chim. France*, 1968, 13; (c) A. A. Akhrem and Y. A. Titor, 'Total Steroid Synthesis,' Plenum Press, New York, 1970; (d) H. O. Huisman, *Angew. Chem. Internat. Edn.*, 1971, **10**, 450; (e) H. O. Huisman, 'Total Synthesis of Heterocyclic Steroidal Systems,' *Steroids*, vol. 8, MTP International Review of Science, ed. W. F. Johns, Butterworths, London, 1973; (f) R. T. Blickenstaff, A. C. Ghosh, and G. C. Wolf, 'Total Synthesis of Steroids,' Academic Press, New York 1974.

<sup>2</sup> For thia-steroids see (a) N. A. McGinnis and R. Robinson, *J. Chem. Soc.*, 1941, 404; (b) L. J. Griggs, Ph.D. Thesis, University of Michigan, 1965; (c) A. Fravolin, G. Grandolini, and A. Martani, *Gazzetta*, 1973, **103**, 1073.

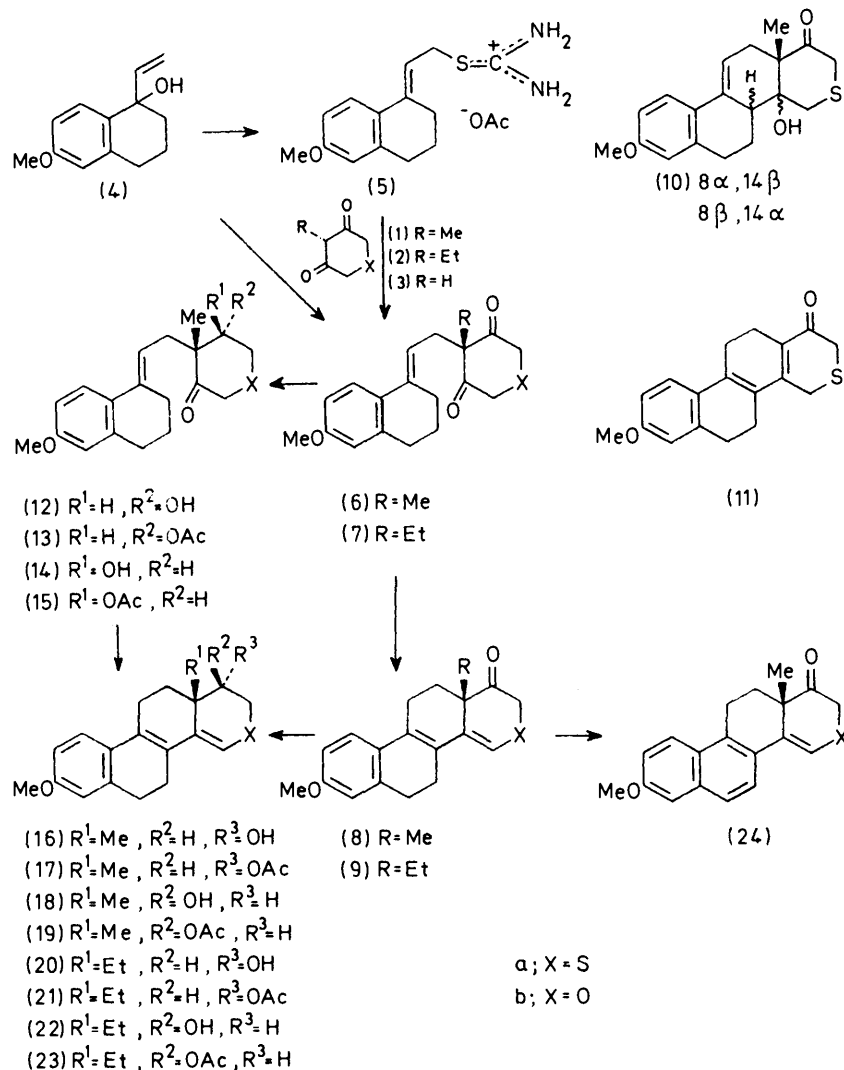
<sup>3</sup> For oxasteroids see (a) J. S. Baran, *J. Medicin Chem.*, 1967, **10**, 1039; (b) T. R. Kasturi and T. Arunachalam, *Indian J. Chem.*, 1970, **8**, 203; (c) Ch. R. Engel and M. N. Roy Chowdhury, *Tetrahedron Letters*, 1968, 2107; (d) Ch. R. Engel, R. C. Rastogi, and M. N. Roy Chowdhury, *Steroids*, 1972, **19**, 1; (e) Ch. R. Engel, S. Salvi, and M. N. Roy Chowdhury, *ibid.*, 1975, **25**, 781; (f) P. Rosen and G. Oliva, *J. Org. Chem.*, 1973, **38**, 3040.

<sup>4</sup> T. Terasawa and T. Okada, *J. Org. Chem.*, 1977, **42**, 1163.

<sup>5</sup> (a) S. N. Ananchenko, V. Ye. Limanov, V. N. Leonov, V. N. Rzhizhnikov, and I. V. Torgov, *Tetrahedron*, 1962, **18**, 1355; (b) S. N. Ananchenko and I. V. Torgov, *Tetrahedron Letters*, 1963, 1553; for a review see also (c) J. Weill-Raynal, *Bull. Soc. chim. France*, 1969, 4561.

(2) with the vinyl alcohol (4), readily available from 6-methoxy-1-tetralone (Scheme 1). Refluxing the dione (1a) and the vinyl alcohol (4) in a mixture of *t*-butyl alcohol and xylene (1 : 2) gave only a low yield of the seco-dione (6a). When acetic acid was used in place of *t*-butyl alcohol, coupling led to a mixture of the estrapentaene (8a) and the intermediate ketol (10). After the crude mixture was heated with toluene-*p*-sulphonic acid in benzene, the pentaene (8a) was obtained as a sole product but the overall yield was moderate.

b) in yields of 80%. Cyclodehydration of the former compounds was best carried out by brief treatment with toluene-*p*-sulphonic acid in boiling benzene. Thus, the pentaenes (8) and (9) were accessible in two steps from the diones (1) and (2), respectively, in overall yield of 60–80%. In this connection, condensation of the dione (3a) with the isothiuronium salt (5) followed by acid-catalysed cyclization was also realized and the product, conjugated ketone (11), was obtained in 54% overall yield.



SCHEME 1

The condensation could be considerably improved by utilizing the modified procedure of Kuo *et al.*<sup>6</sup> Condensation of the diones (1a and b) with the isothiuronium acetate (5), conveniently derived from the vinyl alcohol (4), occurred smoothly at room temperature in 50% ethanol, affording the crystalline seco-diones (6a and b) in 85 and 91% yield, respectively. Similarly, the seco-diones (7a and b) were obtained from the diones (2a and

<sup>6</sup> C. H. Kuo, D. Taub, and N. L. Wendler, *J. Org. Chem.*, 1968, **33**, 3126.

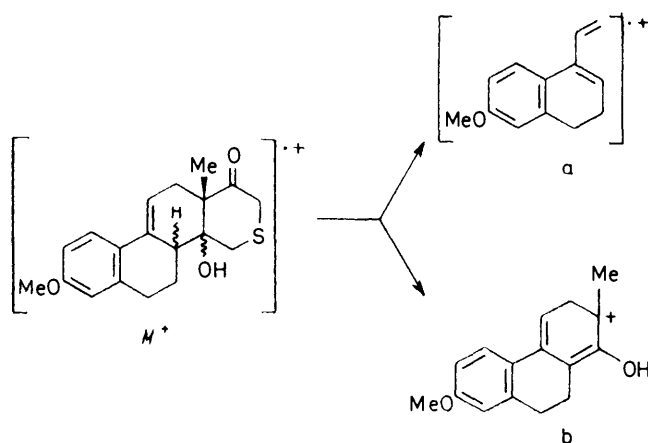
The preservation of the styrene double bond in the seco-diones (6) and (7) was confirmed by characteristic u.v. absorptions (267–268 nm) coupled with n.m.r. signals for one olefinic proton ( $\delta$  5.62–5.66). The i.r. spectra show two carbonyl bands, characteristic of 2,2-disubstituted cyclohexane-1,3-diones.<sup>7</sup> The frequency difference between the thia- (1 722–1 728 and 1 693–1 694 cm<sup>-1</sup>) and oxa-series (1 740–1 744 and 1 711–

<sup>7</sup> S. N. Ananchenko, I. V. Berzin, and I. V. Torgov, *Bull. Acad. Sci. U.S.S.R.*, 1960, 1525.

1 714  $\text{cm}^{-1}$ ) as well as the corresponding carbocyclic compound (1 725 and 1 694  $\text{cm}^{-1}$ ) may be rationalized in terms of inductive effect of the heteroatom. Analogous i.r. behaviour was observed in the single carbonyl absorption of the pentaenones (8) and (9) (a, 1 705 and 1 703  $\text{cm}^{-1}$ ; b, 1 721 and 1 715  $\text{cm}^{-1}$ ). These structures were supported by u.v. and n.m.r. data. The u.v. spectra of the oxa-series exhibit absorption maxima at 313.5 nm similar to those of the carbocyclic series (310 nm), indicating the presence of an extended styrene chromophore. The maxima are shifted bathochromically by 20 nm in the spectra of the thia-series (333 nm), probably due to resonance stabilization by a conjugated sulphur atom. The maxima are shifted bathochromically by 20 nm in the spectra of the thia-series (333 nm), probably due to resonance stabilization by a conjugated sulphur atom. The n.m.r. resonances for 15-H in the oxa-series (8b) and (9b) ( $\delta$  6.83 and 6.88) appear at lower field than those of the thia-series (8a) and (9a) ( $\delta$  6.37 and 6.38) and of the carbocyclic series ( $\delta$  6.00), because of the electronegativity of the vicinal heteroatoms. The signals for the 13-methyl group in the pentaenones (8a and b) occur at  $\delta$  1.37 and 1.28, respectively, compared with  $\delta$  1.21 in the carbocyclic series. These differences, caused by variation in the deshielding effect of the 17 $\alpha$ -carbonyl function, reflect different spatial environments around the carbonyl groups depending on the conformations of the heterorings.\*

On leaving the seco-dione (6a) in benzene containing toluene-*p*-sulphonic acid at 20° overnight, the ketol (10) was again formed together with the pentaenone (8a). The ketol was shown to be a mixture of two isomers separated by preparative t.l.c. Of the two probable structures, the minor isomer, acid-labile and undergoing ready dehydration, was assigned 8 $\beta$ ,14 $\alpha$ -stereochemistry and the major one, 8 $\alpha$ ,14 $\beta$ -stereochemistry. Spectral evidence confirmed this assignment. The u.v. absorptions (265 and 264.5 nm) of the isomers, characteristic of styrene with a trisubstituted double bond, were consistent with the 9(11)-didehydro structure<sup>8</sup> which was also supported by the n.m.r. signals for 11-H ( $\delta$  6.15 and 6.25). The resonance for the 13-methyl group in the major isomer ( $\delta$  1.31) is at lower field than that for the minor compound ( $\delta$  1.20), suggesting a *cis*-relationship between the methyl and hydroxy-groups in the former. The i.r. spectrum of a dilute solution of the minor compound in carbon tetrachloride shows a bonded hydroxy absorption (3 497  $\text{cm}^{-1}$ ) associated with intramolecular hydrogen bonding between the ring sulphur atom and the hydroxy-group. The corresponding band (3 562  $\text{cm}^{-1}$ ) is accompanied by a free hydroxy-band (3 610  $\text{cm}^{-1}$ ) in the case of the major isomer. Therefore, a rigid *c/d* *trans* structure is favoured for the minor isomer. The mass spectrum of the ketol (10) demonstrates, in addition to *m/e* 330 ( $M^+$ ) and 312 ( $M^+ - 18$ ), other prominent peaks corresponding to *m/e* 186 (ion a), 187, and 241 (ion b). The ratio  $M^+ - 18 : M^+$  is five times greater in the spectrum of the minor than in that of

the major isomer. Alternatively, the relative intensity of the ion b peak formed by bond cleavage at the *c/d* ring fusion, is lower in the spectrum of the minor isomer relative to the major one. This finding accords with the results of Wulfson *et al.*<sup>9</sup> (Scheme 2).



SCHEME 2

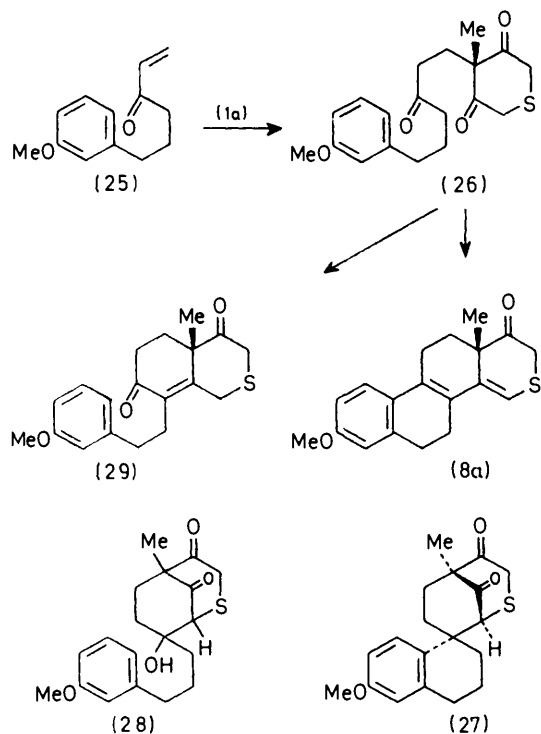
The pentaenone (8a) was reduced with lithium aluminium hydride in tetrahydrofuran to the 17 $\alpha$ -epimeric alcohols (16a) and (18a) in a 4.4 : 1 ratio, indicating a distinct preference for the 17 $\alpha$ -ol, whereas the pentaenone (8b) was converted into the 17 $\beta$ -ol exclusively. Similar reduction of the higher homologues (9a and b) proceeded to form the corresponding 17 $\beta$ -ols overwhelmingly. These epimeric alcohols and their acetates (16)–(19) were also produced *via* the seco-ketols and their acetates (12)–(15) from the seco-diones (6) by partial reduction followed by acid cyclization. Selective treatment of the seco-diones (6a and b) with lithium tri-*t*-butoxyaluminium hydride resulted in exclusive reduction of one carbonyl group, the seco-ketols (12a) and (14a) (1 : 1.4) and (12b) and (14b) (5.3 : 1) being formed. Ring closure of these seco-ketols and their acetates (12)–(15) was effected by refluxing in methanol containing concentrated hydrochloric acid or benzene containing toluene-*p*-sulphonic acid. Thus, the pentaenols (16a) and (18a) [also their acetates (17a) and (19a)] were obtained from the seco-dione (6a) in nearly equal amounts (1 : 1.2), while the pentaenacetates (17b) and (19b) [also the pentaenols (16b) and (18b)] were formed from the seco-dione (6b) in a 5.5 : 1 ratio. Consequently, preparation of the minor epimeric alcohol by direct reduction of the pentaenone (8) favoured the route (6)  $\rightarrow$  (12) + (14)  $\rightarrow$  (16) + (18). In practice, the pentaenol (16b) and its acetate (17b) were accessible only by this route. The configurations of the 17 $\alpha$ -hydroxy-groups of the pentaenols (16) and (18), and accordingly the corresponding seco-ketols (12) and (14), were determined unequivocally by n.m.r. data. The 17 $\alpha$ -proton resonates as a triplet at  $\delta$  4.98 (*J* 3 Hz) in the acetate (17a) and 4.90 (*J* 2 Hz) in the acetate (17b), whereas the

\* This problem will be discussed in a later Part.

<sup>8</sup> G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall, and H. Smith, *J. Chem. Soc.*, 1963, 5072.

<sup>9</sup> N. S. Wulfson, V. I. Zaretskii, V. L. Sadovkaya, A. V. Zakharychev, S. N. Annachenko, and I. V. Torgov, *Tetrahedron*, 1967, **23**, 3667.

same proton gives a quartet at  $\delta$  5.06 ( $J$  5 and 10.5 Hz) in the acetate (19a) and 5.00 ( $J$  5 and 10 Hz) in the acetate (19b). These  $J$  values agree with  $17\alpha\beta\text{-H}_{eq}$  and  $17\alpha\alpha\text{-H}_{ax}$  configurations for the epimeric acetates (17) and (19), respectively, if the heteroring D assumes a chair conformation. Regardless of the flexibility of ring D, clear proof for the stereochemistry at C-17a was obtained from n.m.r. studies using a europium shift reagent; this indicated that the 13-methyl and 17a-hydroxy-groups are *cis* to each other in the pentaenol (18). On this basis, the same conclusion regarding the configuration of the 17a-hydroxy-group can be more conveniently drawn from i.r. data. For a dilute carbon tetrachloride solution, the hydroxy-group appears to be completely intramolecularly bonded in the  $\alpha$ -ol (16) (a, 3 553; b, 3 585  $\text{cm}^{-1}$ ) and fully free in the  $\beta$ -ol (18)



SCHEME 3

(a, 3 632; b, 3 633  $\text{cm}^{-1}$ ). This was also the case for the higher homologues (20) (a, 3 554  $\text{cm}^{-1}$ ) and (22) (a, 3 631; b, 3 632  $\text{cm}^{-1}$ ), thus allowing the stereochemical assignment.

Dehydrogenation of the pentaene (8a) was effected by treatment with chloranil in boiling xylene to give the expected naphthalene (24a) but in low yield. Conversion of the oxa-series (8b) into the corresponding compound (24b) was carried out by refluxing with selenium dioxide in acetic acid. Similar results were obtained with palladium-charcoal in boiling *p*-cymene. The *B*-aromatic structure was supported by u.v. and n.m.r. evidence.

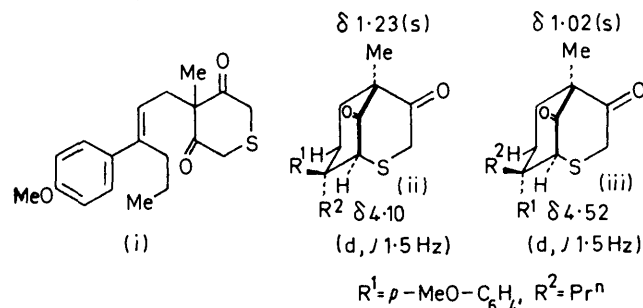
Another sequence investigated for the synthesis of the pentaene (8a) was the Smith-Hughes method<sup>8</sup>

(Scheme 3). Michael condensation of the dione (1a) with the known vinyl ketone<sup>8</sup> (25) in boiling xylene containing pyridine gave the trione (26) which was cyclodehydrated directly to the pentaene (8a). Of the various conditions attempted for the cyclization, the best yields were obtained with phosphoric acid-phosphoric anhydride (2 : 1) in benzene. However, the reaction was invariably accompanied by small amounts of a side product. The bridged dione structure (27) was assigned to this compound on the basis of its spectral data.\* Since the bridged dione (27) is no longer convertible to the pentaene (8a) under these conditions, the former compound presumably arises from intramolecular aldolization of the trione (26) *via* a bridged precursor (28) which is in equilibrium with the trione (26) in the Michael adduct. Alternatively, the adduct was treated by boiling in toluene containing triethylamine and benzoic acid with continuous removal of the water formed. Closure of ring C was very sluggish leading to the unsaturated dione (29). The overall yield was at best 30%, even with extremely prolonged boiling (100–190 h). All other attempts to improve the yield were unsuccessful. The structure of the unsaturated dione (29) was apparent from its i.r. (1 714 and 1 672  $\text{cm}^{-1}$ ) and u.v. spectra (219 and 250 nm). The compounds thus obtained [(8), (24), and (29)] were envisaged as key intermediates for the title heteroestrogens.

## EXPERIMENTAL

M.p.s were determined on a calibrated Kofler hot-stage apparatus. I.r. spectra were recorded on a JASCO-DS-403G spectrophotometer and u.v. spectra on a Hitachi EPS-3T spectrophotometer. N.m.r. spectra were taken on a Varian A-60 instrument using tetramethylsilane as internal standard. Mass spectra were determined using a Hitachi RMU-6 mass spectrometer (70 eV). Preparative t.l.c. was carried out on 100 × 20 × 0.075 cm or 20 × 20 × 0.2 cm glass plates coated with silica gel GF<sub>254</sub> (type 60; Merck). Alumina used for column chromatography was of activity grade I (Woelm) and made up to activity grade II or III as indicated by the addition of 3 or 6% water prior to use. Silica gel columns used silica gel 60 (grain size 0.063–0.2

\* Conclusive evidence came from the n.m.r. spectra by comparison with those for the related diastereoisomers (ii) and (iii), which were obtained by acid-catalysed cyclization of compound (i) with toluene-*p*-sulphonic acid in boiling xylene (unpublished work). The n.m.r. spectrum of the bridged dione (27),  $\delta$  1.23 and 3.96, reveals close similarity in chemical shifts of the signals for the methyl and bridgehead protons to those of compound (ii) rather than (iii).



mm; Merck). Usual work-up means washing extracts with water and then brine, drying ( $\text{Na}_2\text{SO}_4$ ), filtration, and evaporation *in vacuo*.

**3-Methoxy-8,14-*seco*-16-thia-D-homoestra-1,3,5(10),-9(11)-tetraene-14,17a-dione (6a).**—(a) A stirred mixture of 6-methoxy-1-vinyltetralol (4) (4.08 g, 20 mmol), obtained by the Grignard reaction of 6-methoxy-1-tetralone and 2-methyl-5-thiacyclohexane-1,3-dione (1a) (2.88 g, 20 mmol), in dry xylene (25 ml) and dry *t*-butyl alcohol (12 ml) was refluxed under nitrogen for 2.5 h. The cooled mixture was poured into water and extracted with ether. The ether extract was washed with aqueous 5% potassium hydrogencarbonate solution and then worked up as usual. Crystallization of the residue from ether gave the *seco*-dione (6a) (1.43 g, 21.7%), m.p. 90—91°, identical with an authentic sample.

(b) To a stirred mixture of 6-methoxy-1,2,3,4-tetrahydronaphthylidene-ethylisothiuronium acetate (5) (32.2 g, 0.1 mol) and 2-methyl-5-thiacyclohexane-1,3-dione (1a) (14.4 g, 0.1 mol), was added aqueous 50% alcohol (500 ml). A clear solution was formed from which the product precipitated. Stirring was continued for 3 h at room temperature. The precipitate, on standing in the refrigerator overnight, was filtered, washed with cold aqueous alcohol, and then air-dried to give the *seco*-dione (6a) (28.0 g, 84.8%), m.p. 91.5—92.5°. Recrystallization from dichloromethane-ether gave an analytical sample, m.p. 93—94°,  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 1 728, 1 694 (CO), 1 605, 1 567, and 1 493  $\text{cm}^{-1}$  (styrene);  $\lambda_{\text{max}}$  (EtOH) 267 and 300sh nm ( $\epsilon$  18 100 and 5 600);  $\delta(\text{CDCl}_3)$  1.38 (3 H, s, 13-Me), 3.36, 3.50 (4 H, dd, *J* 14.5 Hz,  $\text{S}\cdot\text{CH}_2\cdot\text{CO}$ ), 3.76 (3 H, s, OMe), 5.62br (1 H, t, *J* 7.5 Hz, 11-H), and 6.6—7.5 (3 H, m, ArH) (Found: C, 68.9; H, 6.65; S, 9.85.  $\text{C}_{19}\text{H}_{22}\text{O}_3\text{S}$  requires C, 69.05; H, 6.7; S, 9.7%).

**3-Methoxy-8,14-*seco*-16-oxa-D-homoestra-1,3,5(10),9(11)-tetraene-14,17a-dione (6b).**—The reaction was carried out according to (b) above, using 2-methyl-5-oxacyclohexane-1,3-dione (1b) (3.0 g, 23.4 mmol), the salt (5) (8.3 g, 25.7 mmol), and aqueous 50% alcohol (160 ml). Stirring was continued for 4 h with occasional warming at 40—50°. The yield of the *seco*-dione (6b) was 6.90 g (93.7%), m.p. 142—144°. Recrystallization from dichloromethane-ether afforded an analytical sample, m.p. 143—144°,  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 1 744, 1 714 (CO), 1 605, 1 569, and 1 497  $\text{cm}^{-1}$  (styrene);  $\nu_{\text{max}}$  (EtOH) 268 and 300sh nm ( $\epsilon$  16 000 and 5 100);  $\delta(\text{CDCl}_3)$  1.36 (3 H, s, 13-Me), 3.78 (3 H, s, OMe), 4.18, 4.34 (4 H, dd, *J* 18 Hz,  $\text{O}\cdot\text{CH}_2\cdot\text{CO}$ ), 5.64br (1 H, t, *J* 7.5 Hz, 11-H), and 6.6—7.5 (3 H, m, ArH) (Found: C, 72.4; H, 7.1.  $\text{C}_{19}\text{H}_{22}\text{O}_4$  requires C, 72.6; H, 7.05%).

**3-Methoxy-18-methyl-8,14-*seco*-16-thia-D-homoestra-1,3,5(10),9(11)-tetraene-14,17a-dione (7a).**—The reaction was carried out in the manner above, using 2-ethyl-5-thiacyclohexane-1,3-dione (2a) (0.89 g, 5.63 mmol), the salt (5) (1.82 g, 5.64 mmol), and aqueous 50% alcohol (160 ml). The yield of the *seco*-dione (7a) was 1.56 g (80.1%), m.p. 69—71°. An analytical sample was obtained by recrystallization from ether-pentane, m.p. 72—72.5°,  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 1 722, 1 693 (CO), 1 606, 1 568, and 1 493  $\text{cm}^{-1}$  (styrene);  $\lambda_{\text{max}}$  (EtOH) 267 and 300sh nm ( $\epsilon$  17 000 and 4 900);  $\delta(\text{CDCl}_3)$  0.83 (3 H, t, *J* 7.5 Hz, 13-Me), 3.36 (4 H, s,  $\text{S}\cdot\text{CH}_2\cdot\text{CO}$ ), 3.78 (3 H, s, OMe), 5.66br (1 H, t, *J* 7.5 Hz, 11-H), and 6.6—7.5 (3 H, m, ArH) (Found: C, 69.55; H, 7.0; S, 9.45.  $\text{C}_{20}\text{H}_{24}\text{O}_3\text{S}$  requires C, 69.75; H, 7.0; S, 9.3%).

**3-Methoxy-18-methyl-8,14-*seco*-16-oxa-D-homoestra-1,3,5(10),9(11)-tetraene-14,17a-dione (7b).**—The reaction was

performed as above, using 2-ethyl-5-oxacyclohexane-1,3-dione (2b) (2.26 g, 15.9 mmol), the salt (5) (5.13 g, 15.9 mmol), and aqueous 50% alcohol (130 ml). Stirring was continued for 18 h at room temperature. The yield of the *seco*-dione (7b) was 4.17 g (79.9%), m.p. 59—60°. The analytical sample was prepared by recrystallization from methanol, m.p. 60.5—61°,  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 1 740, 1 711 (CO), 1 605, 1 567, and 1 493  $\text{cm}^{-1}$  (styrene);  $\lambda_{\text{max}}$  (EtOH) 267.5 and 300sh nm ( $\epsilon$  15 800 and 4 600);  $\delta(\text{CDCl}_3)$  0.83 (3 H, t, *J* 7.5 Hz, 13-Me), 3.77 (3 H, s, OMe), 4.19 (4 H, s,  $\text{O}\cdot\text{CH}_2\cdot\text{CO}$ ), 5.62br (1 H, t, *J* 8 Hz, 11-H), and 6.6—7.5 (3 H, m, ArH) (Found: C, 72.9; H, 7.4.  $\text{C}_{20}\text{H}_{24}\text{O}_4$  requires C, 73.15; H, 7.35%).

**3-Methoxy-16-thia-D-homoestra-1,3,5(10),8,14-pentaene-17a-one (8a).**—(a) A stirred mixture of the vinyl alcohol (4) (4.08 g, 20 mmol) and the dione (1a) (2.88 g, 20 mmol) in xylene (25 ml) and acetic acid (12 ml) was refluxed under nitrogen for 4 h. After toluene-*p*-sulphonic acid (100 mg) was added, the mixture was refluxed for another 1 h, concentrated to a small volume, and then extracted with ether. The extract was washed with aqueous 5% potassium hydrogencarbonate and then worked up as usual. The residue was chromatographed over alumina (Activity I; 30 g). Elution with light petroleum-benzene (7 : 3) gave, on trituration with ether-pentane, the pentaenone (8a) (2.47 g, 39.6%), m.p. 93—96°, identical with an authentic sample.

(b) A solution of the *seco*-dione (6a) (6.6 g, 20 mmol) in dry benzene (100 ml) containing toluene-*p*-sulphonic acid (0.3 g) was heated under reflux for 10 min. The cooled solution was poured into water and the benzene layer was separated. The aqueous layer was extracted with ether. The organic layers were combined, washed with aqueous 5% sodium hydrogencarbonate, and then worked up as usual. The gummy residue was chromatographed on alumina (Activity II; 30 g). The fractions eluted with benzene were collected and evaporated. The residue was crystallized from dichloromethane-ether, giving the pentaenone (8a) (5.78 g, 92.7%), m.p. 94—96°. Recrystallization from the same solvent afforded an analytical specimen, m.p. 95—96°,  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 1 705 (CO), 1 608, 1 563, and 1 496  $\text{cm}^{-1}$  (extended styrene);  $\lambda_{\text{max}}$  (EtOH) 320sh, 333, and 345sh nm ( $\epsilon$  27 500, 33 000, and 25 500);  $\delta(\text{CDCl}_3)$  1.37 (3 H, s, 13-Me), 3.37, 3.51 (2 H, dd, *J* 14 Hz,  $\text{S}\cdot\text{CH}_2\cdot\text{CO}$ ), 3.80 (3 H, s, OMe), 6.37br (1 H, s, 15-H), and 6.6—7.4 (3 H, m, ArH) (Found: C, 73.3; H, 6.5; S, 10.6.  $\text{C}_{19}\text{H}_{20}\text{O}_2\text{S}$  requires C, 73.05; H, 6.45; S, 10.25%).

**3-Methoxy-16-oxa-D-homoestra-1,3,5(10),8,14-pentaene-17a-one (8b).**—A solution of the *seco*-dione (6b) (5.07 g, 16.1 mmol) in dry benzene (160 ml) containing toluene-*p*-sulphonic acid (0.5 g) was refluxed for 45 min. The cooled solution was worked up as described above. The crude product was chromatographed on alumina (Activity I; 30 g). The eluates with benzene were collected and the solvent was evaporated. The pasty residue was crystallized from ether to give the pentaenone (8b) (4.09 g, 85.6%), m.p. 112—113°. Recrystallization from dichloromethane-ether provided an analytical specimen, m.p. 113—115°,  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 1 721 (CO), 1 618, 1 604, 1 563, and 1 495  $\text{cm}^{-1}$  (extended styrene);  $\lambda_{\text{max}}$  (EtOH) 301sh, 313.5, and 327sh nm ( $\epsilon$  23 500, 28 200, and 20 100);  $\delta(\text{CDCl}_3)$  1.28 (3 H, s, 13-Me), 3.80 (3 H, s, OMe), 4.20, 4.61 (2 H, dd, *J* 18 Hz,  $\text{O}\cdot\text{CH}_2\cdot\text{CO}$ ), 6.83 (1 H, s, 15-H), and 6.6—7.3 (3 H, m, ArH) (Found: C, 76.75; H, 6.7.  $\text{C}_{19}\text{H}_{20}\text{O}_3$  requires C, 77.0; H, 6.8%).

**3-Methoxy-18-methyl-16-thia-D-homoestra-1,3,5(10),8,14-pentaen-17a-one (9a).**—A solution of the seco-dione (7a) (1.52 g, 4.4 mmol) in dry benzene (20 ml) containing toluene-*p*-sulphonic acid (0.15 g) was heated under reflux for 15 min. The mixture was worked up as described above. The crude product was purified through alumina (Activity I; 15 g) by elution with benzene to furnish, on trituration with ether-pentane, the *pentaenone* (9a) (1.1 g, 76.6%), m.p. 104–106°. An analytical specimen was obtained by recrystallization from ether, m.p. 105.5–106.5°,  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 703 (CO), 1 608, 1 561, and 1 493 cm<sup>-1</sup> (extended styrene);  $\lambda_{\max}$  (EtOH) 320sh, 332, and 345sh nm ( $\epsilon$  25 000, 29 900, and 23 500);  $\delta$ (CDCl<sub>3</sub>) 0.80 (3 H, t, *J* 7.5 Hz, 13-Me), 3.40 (2 H, s, S-CH<sub>2</sub>-CO), 3.79 (3 H, s, OMe), 6.38br (1 H, s, 15-H), and 6.6–7.3 (3 H, m, ArH) (Found: C, 73.35; H, 6.7; S, 10.0. C<sub>20</sub>H<sub>22</sub>O<sub>2</sub>S requires C, 73.6; H, 6.8; S, 9.8%).

**3-Methoxy-18-methyl-16-oxa-D-homoestra-1,3,5(10),8,14-pentaen-17a-one (9b).**—A solution of the seco-dione (7b) (4 g, 12.2 mol) in dry benzene (130 ml) containing toluene-*p*-sulphonic acid (0.4 g) was heated under reflux for 0.5 h. The cooled solution was passed through alumina (Woelm; Activity II; 30 g) followed by elution with benzene. The eluates were collected and evaporated. The residue was crystallized from ether-pentane, leaving the *pentaenone* (9b) (3.14 g, 82.9%), m.p. 62–63°. This material was recrystallized from the same solvent to give an analytical sample, m.p. 63–64.5°,  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 715 (CO), 1 617, 1 604, 1 563, and 1 494 cm<sup>-1</sup> (extended styrene);  $\lambda_{\max}$  (EtOH) 301sh, 313.5, and 327sh nm ( $\epsilon$  23 400, 28 200, and 19 500);  $\delta$ (CDCl<sub>3</sub>) 0.84 (3 H, t, *J* 7.5 Hz, 13-Me), 3.79 (3 H, s, OMe), 4.19, 4.46 (2 H, dd, *J* 18 Hz, O-CH<sub>2</sub>-CO), 6.88 (1 H, s, 15-H), and 6.6–7.3 (3 H, m, ArH) (Found: C, 77.05; H, 7.1. C<sub>20</sub>H<sub>22</sub>O<sub>3</sub> requires C, 77.4; H, 7.15%).

**14-Hydroxy-3-methoxy-16-thia-D-homoestra-1,3,5(10),9-(11)-tetraen-17a-one (10).**—(a) A mixture of the vinyl alcohol (4) (4.08 g, 20 mmol) and the dione (1a) (2.88 g, 20 mmol) in xylene (25 ml) and acetic acid (12 ml) was boiled under nitrogen for 10 h. The mixture was cooled, concentrated, and extracted with ether. After the usual work-up, the residue (5.8 g) obtained was chromatographed on alumina (Activity I; 30 g). Elution with light petroleum-benzene (7:3) gave, on trituration with ether, the *pentaenone* (8a) (0.87 g, 13.9%), m.p. 93–95°, identical with an authentic sample. Further elution with benzene alone yielded a crude mixture of two components, from which the major component (0.83 g) was separated, on trituration with ether, as a crystalline solid, m.p. 157–161°. The crystallization residue was collected and purified by preparative t.l.c. [benzene-ethyl acetate (9:1)] which gave, on crystallization from ether, another crop of the major (0.27 g), m.p. 158–162° (total 1.1 g, 16.7%), and the minor component (0.046 g, 0.7%), m.p. 205–208°. Recrystallization from dichloromethane-ether provided analytical samples. The major and minor compounds were assigned the 8 $\alpha$ ,14 $\beta$ - and 8 $\beta$ ,14 $\alpha$ -structures, respectively (see text). The 8 $\alpha$ ,14 $\beta$ -isomer had m.p. 163–165°,  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 706 (CO), 1 609, 1 572, and 1 502 cm<sup>-1</sup> (styrene);  $\nu_{\max}$  (dilute CCl<sub>4</sub>) 3 610sh (free OH) and 3 562 cm<sup>-1</sup> (bonded OH);  $\lambda_{\max}$  (EtOH) 264.5 nm ( $\epsilon$  18 900);  $\delta$ (CDCl<sub>3</sub>) 1.31 (3 H, s, 13-Me), 3.75 (3 H, s, OMe), 6.25 (1 H, m, 11-H), and 6.5–7.6 (3 H, m, ArH); *m/e* 186 (63%, ion a), 187 (53), 240 (89), 241 (85, ion b), 312 (16, *M*<sup>+</sup> - 18), and 330 (100, *M*<sup>+</sup>) (Found: C, 68.85; H, 6.65; S, 9.7. C<sub>19</sub>H<sub>22</sub>O<sub>3</sub>S requires C, 69.05; H, 6.7; S, 9.7%). The 8 $\beta$ ,14 $\alpha$ -isomer had m.p. 207–209°;  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 703 (CO), 1 606, 1 569, and

1 501 cm<sup>-1</sup> (styrene);  $\nu_{\max}$  (dilute CCl<sub>4</sub>) 3 497 cm<sup>-1</sup> (bonded OH);  $\lambda_{\max}$  (EtOH) 265 nm ( $\epsilon$  19 600);  $\delta$ (CDCl<sub>3</sub>) 1.20 (3 H, s, 13-Me), 3.78 (3 H, s, OMe), 6.15 (1 H, m, 11-H), and 6.6–7.6 (3 H, m, ArH); *m/e* 186 (48%, ion a), 187 (100), 240 (5), 241 (20, ion b), 312 (38, *M*<sup>+</sup> - 18), and 330 (47, *M*<sup>+</sup>) (Found: C, 68.8; H, 6.7; S, 9.65%).

(b) A solution of the seco-dione (6a) (330 mg, 1 mmol) in benzene (5 ml) containing toluene-*p*-sulphonic acid (15 mg) was stirred at 20° for 17 h. The benzene solution was washed with aqueous 5% sodium hydrogencarbonate and water, dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvent evaporated. The residue was purified by preparative t.l.c. [benzene-ethyl acetate (9:1)] which afforded the *pentaenone* (8a) (127 mg, 40.6%) and the epimeric ketols (10), 8 $\beta$ ,14 $\alpha$ - (less polar) (11 mg, 3.2%) and 8 $\alpha$ ,14 $\beta$ -isomer (more polar) (127 mg, 38.5%).

**3-Methoxy-16-thia-D-homo-18-norestra-1,3,5(10),8,13-pentaen-17a-one (11).**—A mixture of 5-thiacyclohexane-1,3-dione (3a) (2.02 g, 15.5 mmol) and the salt (5) (5 g, 15.5 mmol) in aqueous 50% alcohol (80 ml) was stirred at room temperature overnight. The mixture was extracted with dichloromethane and worked up as usual. The residue (4.5 g) was dissolved in benzene (70 ml) containing toluene-*p*-sulphonic acid (0.25 g). The solution was refluxed for 30 min and then poured into cold aqueous 5% sodium hydrogencarbonate and the benzene layer separated. The aqueous layer was extracted again with dichloromethane. The organic layers were combined and worked up as usual. The residue was purified through alumina (30 g) by eluting with benzene. From the combined eluates, there was obtained, on crystallization from dichloromethane-ether, the *pentaenone* (11) (2.5 g, 54.0%), m.p. 140–142°. Recrystallization from the same solvent gave an analytical specimen, m.p. 140–141°,  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 641 (conjugated CO), 1 605, 1 523, and 1 497 cm<sup>-1</sup> (extended styrene);  $\lambda_{\max}$  (EtOH) 400 nm ( $\epsilon$  18 700);  $\delta$ (CDCl<sub>3</sub>) 3.81 (3 H, s, OMe), 6.6–7.4 (3 H, m, ArH), and no olefinic proton signal; *m/e* 298 (*M*<sup>+</sup>) (Found: C, 72.25; H, 6.05; S, 10.7. C<sub>18</sub>H<sub>18</sub>O<sub>2</sub>S requires C, 72.45; H, 6.1; S, 10.75%).

**14 $\alpha$ - and 14 $\beta$ -Hydroxy-3-methoxy-8,14-seco-16-thia-D-homoestra-1,3,5(10),9(11)-tetraen-17a-one (12a) and (14a) and their Acetates (13a) and (15a).**—To a stirred ice-cold suspension of lithium tri-*t*-butoxyaluminum hydride (6.6 g, 26 mmol) in dry tetrahydrofuran (90 ml) was added dropwise over 20 min under nitrogen a solution of the seco-dione (6a) (3.3 g, 10 mmol) in dry tetrahydrofuran (90 ml). The mixture was stirred at room temperature for 5 h. Water (1.9 ml) was then added dropwise at 0°. The inorganic salts were removed by filtration and washed with ether. The combined filtrate was concentrated and extracted with ether. The usual work-up left a crystalline residue (3.5 g) which was found to be a mixture of the 14-epimers. A portion (500 mg) of the residue was purified by preparative t.l.c. [benzene-ethyl acetate (9:1) with triple development] which separated the 14 $\alpha$ -*ol* (12a) (less polar) (164.3 mg) and the 14 $\beta$ -*ol* (14a) (more polar) (232.8 mg); the product ratio is 1:1.4. Two crystallizations from ether-pentane gave analytical samples. The 14 $\alpha$ -*ol* (12a) had m.p. 87–89°,  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 701 (CO), 1 605, 1 567, and 1 492 cm<sup>-1</sup> (styrene);  $\nu_{\max}$  (dilute CCl<sub>4</sub>) 3 621 (free OH) and 3 511 cm<sup>-1</sup> (bonded OH);  $\nu_{\max}$  (EtOH) 266 nm ( $\epsilon$  18 800) (Found: C, 68.35; H, 7.25; S, 9.8. C<sub>19</sub>H<sub>24</sub>O<sub>3</sub>S requires C, 68.65; H, 7.3; S, 9.65%). The *acetate* (13a) was prepared by treatment with acetic anhydride-pyridine, m.p. 106.5–109° (ether-pentane). Recrystallization from ether

gave an analytical specimen, m.p. 109–110°,  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 737 (OAc), 1 711 (CO), 1 605, 1 567, and 1 492 cm<sup>-1</sup> (styrene);  $\lambda_{\max}$  (EtOH) 266 nm ( $\epsilon$  19 200);  $\delta$ (CDCl<sub>3</sub>) 1.23 (3 H, s, 13-Me), 2.09 (3 H, s, OAc), 3.76 (3 H, s, OMe), 5.16 (1 H, t, *J* 6 Hz, 14-H), 5.58 (1 H, t, *J* 7.5 Hz, 11-H), and 6.6–7.5 (3 H, m, ArH) (Found: C, 67.0; H, 7.0; S, 8.25%. C<sub>21</sub>H<sub>26</sub>O<sub>4</sub>S requires C, 67.35; H, 7.0; S, 8.55%). The 14 $\beta$ -ol (14a) had m.p. 90–92°,  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 704 (CO), 1 606, 1 567, and 1 493 cm<sup>-1</sup> (styrene);  $\nu_{\max}$  (dilute CCl<sub>4</sub>) 3 621 (free OH) and 3 515 cm<sup>-1</sup> (bonded OH);  $\lambda_{\max}$  (EtOH) 266 nm ( $\epsilon$  19 300) (Found: C, 68.35; H, 7.25; S, 9.5%). The acetate (15a), prepared as above, was obtained as a viscous oil,  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 739 (OAc), 1 710 (CO), 1 606, 1 568, and 1 493 cm<sup>-1</sup> (styrene);  $\lambda_{\max}$  (EtOH) 266 nm ( $\epsilon$  16 500);  $\delta$ (CDCl<sub>3</sub>) 1.20 (3 H, s, 13-Me), 2.06 (3 H, s, OAc), 3.76 (3 H, s, OMe), 5.25 (1 H, q, *J* 3.5 and 7 Hz, 14-H), 5.73 (1 H, t, *J* 7 Hz, 11-H), and 6.6–7.5 (3 H, m, ArH) (Found: C, 66.95; H, 6.95; S, 8.3%).

14 $\alpha$ - and 14 $\beta$ -Hydroxy-3-methoxy-8,14-seco-16-oxa-D-homoestra-1,3,5(10),9(11)-tetraen-17a-one (12b) and (14b) and their Acetates (13b) and (15b).—The reaction was carried out in a manner similar to the preparation of the seco-ketols (12a) and (14a), by using the seco-dione (6b) (0.94 g, 3 mmol), lithium tri-*t*-butoxyaluminium hydride (1.53 g, 6 mmol), and dry tetrahydrofuran (total 60 ml). A portion (400 mg) of the crude product (viscous syrup) was purified by preparative t.l.c. [benzene-ethyl acetate (4 : 1) with triple development] which separated the 14 $\alpha$ -ol (12b) (less polar) (198.8 mg) and 14 $\beta$ -ol (14b) (more polar) (37.5 mg); the product ratio is 5.3 : 1. The 14 $\alpha$ -ol (12b) was a viscous syrup,  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 721 (CO), 1 606, 1 568, and 1 497 cm<sup>-1</sup> (styrene);  $\nu_{\max}$  (dilute CCl<sub>4</sub>) 3 627 (free OH), 3 573, and 3 499 cm<sup>-1</sup> (bonded OH). The acetate (13b) was prepared as a crystalline solid, m.p. 91–94° (pentane). Recrystallization from dichloromethane-ether gave an analytical sample, m.p. 95–96°,  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 728 (CO, OAc), 1 606, 1 569, and 1 498 cm<sup>-1</sup> (styrene);  $\lambda_{\max}$  (EtOH) 266 nm ( $\epsilon$  19 100);  $\delta$ (CDCl<sub>3</sub>) 1.33 (3 H, s, 13-Me), 2.07 (3 H, s, OAc), 3.78 (3 H, s, OMe), 5.16 (1 H, t, *J* 3.5 Hz, 14-H), 5.73br (1 H, t, *J* 8 Hz, 11-H), and 6.6–7.5 (3 H, m, ArH) (Found: C, 70.1; H, 7.35%. C<sub>21</sub>H<sub>26</sub>O<sub>5</sub> requires C, 70.35; H, 7.3%).

The 14 $\beta$ -ol (14b) was a viscous syrup,  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 718 (CO), 1 606, 1 566, and 1 496 cm<sup>-1</sup> (styrene);  $\nu_{\max}$  (dilute CCl<sub>4</sub>) 3 627 (free OH) and 3 573 cm<sup>-1</sup> (bonded OH). The acetate (15b) was prepared as above as a crystalline solid, m.p. 86–88° (pentane). Recrystallization from ether-pentane gave an authentic specimen, m.p. 92–94°,  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 728 (CO, OAc), 1 606, 1 569, and 1 498 cm<sup>-1</sup> (styrene);  $\lambda_{\max}$  (EtOH) 267 nm ( $\epsilon$  18 400);  $\delta$ (CDCl<sub>3</sub>) 1.20 (3 H, s, 13-Me), 2.06 (3 H, s, OAc), 3.77 (3 H, s, OMe), 5.22 (1 H, t, *J* 4 Hz, 14-H), 5.74br (1 H, t, *J* 8 Hz, 11-H), and 6.6–7.5 (3 H, m, ArH) (Found: C, 70.4; H, 7.3%).

3-Methoxy-16-thia-D-homoestra-1,3,5(10),8,14-pentaen-17 $\alpha$ - (16a) and -17 $\beta$ -ol (18a) and their Acetates (17a) and (19a).—From (8a). To an ice-cold stirred slurry of lithium aluminium hydride (114 mg, 3 mmol) in dry tetrahydrofuran (1 ml) was added dropwise over a 15 min period a solution of the pentaenone (8a) (312 mg, 1 mmol) in dry tetrahydrofuran (5 ml). Stirring was continued for 1.5 h at room temperature. The mixture was decomposed with ethyl acetate, poured into cold water, and extracted with ether. The usual work-up left an oil (305 mg) which was purified by preparative t.l.c. [benzene-ethyl acetate (9 : 1) with double development], yielding the 17 $\alpha$ -ol (16a) (less polar)

(237.5 mg, 75.5%) and 17 $\beta$ -ol (18a) (more polar) (53.8 mg, 17.1%); the product ratio was 4.4 : 1. Two crystallizations from dichloromethane-ether or acetone-ether gave authentic samples. The 17 $\alpha$ -ol (16a) had m.p. 140–142°,  $\nu_{\max}$  (dilute CCl<sub>4</sub>) 3 553 cm<sup>-1</sup> (bonded OH);  $\lambda_{\max}$  (EtOH) 318sh, 329.5, and 345 nm ( $\epsilon$  30 800, 40 400, and 30 800);  $\delta$ (CDCl<sub>3</sub>) 0.99 (3 H, s, 13-Me), 3.78 (3 H, s, OMe), 6.13br (1 H, s, 15-H), and 6.6–7.3 (3 H, m, ArH) (Found: C, 72.4; H, 7.05; S, 10.2%. C<sub>19</sub>H<sub>22</sub>O<sub>2</sub>S requires C, 72.55; H, 7.05; S, 10.2%). The acetate (17a) was a crystalline solid m.p. 136–137° (ether-light petroleum),  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 728 (OAc), 1 608, 1 560, and 1 496 cm<sup>-1</sup> (extended styrene);  $\lambda_{\max}$  (EtOH) 315sh, 328.5, and 343.5 nm ( $\epsilon$  31 400, 41 500, and 31 300);  $\delta$ (CDCl<sub>3</sub>) 1.07 (3 H, s, 13-Me), 2.10 (3 H, s, OAc), 3.80 (3 H, s, OMe), 4.98 (1 H, t, *J* 3 Hz, 17a-H), 6.21br (1 H, s, 15-H), and 6.6–7.3 (3 H, m, ArH) (Found: C, 70.9; H, 6.9; S, 9.05%. C<sub>21</sub>H<sub>24</sub>O<sub>3</sub>S requires C, 70.75; H, 6.8; S, 9.0%). The 17 $\beta$ -ol (18a) had m.p. 140–141°,  $\nu_{\max}$  (dilute CCl<sub>4</sub>) 3 632 cm<sup>-1</sup> (free OH);  $\lambda_{\max}$  (EtOH) 317sh, 329, and 343.5 nm ( $\epsilon$  30 400, 39 700, and 30 400);  $\delta$ (CDCl<sub>3</sub>) 1.02 (3 H, s, 13-Me), 3.78 (3 H, s, OMe), 6.02br (1 H, s, 15-H), and 6.6–7.3 (3 H, m, ArH) (Found: C, 72.2; H, 7.05; S, 10.25%). The acetate (19a) was obtained as crystals, m.p. 162.5–164° (dichloromethane-ether),  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 744, 1 729 (OAc), 1 607, 1 559, and 1 496 cm<sup>-1</sup> (extended styrene);  $\lambda_{\max}$  (EtOH) 315sh, 328, and 343 nm ( $\epsilon$  29 900, 39 200, and 30 600);  $\delta$ (CDCl<sub>3</sub>) 1.10 (3 H, s, 13-Me), 2.10 (3 H, s, OAc), 3.79 (3 H, s, OMe), 5.06 (1 H, q, *J* 5 and 10.5 Hz, 17a-H), 6.06br (1 H, s, 15-H), and 6.6–7.3 (3 H, m, ArH) (Found: C, 70.55; N, 6.8; S, 9.1%).

From (12a) and (14a). (a) A solution of the seco-ketol (12a) (47.5 mg, 0.14 mmol) in methanol (5 ml) containing concentrated hydrochloric acid (0.5 ml) was heated under reflux for 3.5 h. The methanol was distilled off and the residue was extracted with dichloromethane. The usual work-up left the 17 $\alpha$ -ol (16a) (28.8 mg), identical with an authentic sample.

(b) A similar reaction was carried out with the seco-ketol (14a) (55.5 mg, 0.17 mmol) in methanol (5 ml) containing concentrated hydrochloric acid (0.5 ml), giving the 17 $\beta$ -ol (18a) (38.0 mg), identical with an authentic sample.

(c) In another experiment, a solution of the crude ketol mixture (100 mg, 0.3 mmol) obtained by partial reduction of the seco-dione (6a) in methanol (5 ml) and dichloromethane (10 ml) containing concentrated hydrochloric acid (0.1 ml) was heated under reflux for 3 h. The mixture was worked up as usual to give a viscous syrup which was purified by preparative t.l.c. [benzene-ethyl acetate (9 : 1)], giving the 17 $\alpha$ -ol (16a) (less polar) (33.8 mg) and 17 $\beta$ -ol (18a) (more polar) (41.7 mg). The product ratio is 1 : 1.2.

(d) The crude ketol mixture (75 mg) obtained above was acetylated with acetic anhydride-pyridine as usual. A solution of the crude acetate (85 mg) in dry benzene (2 ml) containing toluene-*p*-sulphonic acid (4 mg) was heated under reflux for 45 min. The cooled mixture was poured into cold aqueous sodium hydrogencarbonate solution and extracted with dichloromethane. After the usual work-up, there was obtained an oil (71 mg) which was purified by preparative t.l.c. (benzene with triple development), yielding the 17 $\beta$ -acetate (19a) (less polar) (31.5 mg) and 17 $\alpha$ -acetate (17a) (more polar) (27.4 mg). The product ratio (1.2 : 1) was consistent with that for the 17 $\alpha$ -ols obtained in (c).

3-Methoxy-16-oxa-D-homoestra-1,3,5(10),8,14-pentaen-17 $\alpha$ - (16b) and -17 $\beta$ -ol (18b) and their Acetates (17b) and

(19b).—From (8b). Lithium aluminium hydride (185 mg, 4.88 mmol) was added to a stirred solution of the pentaenone (8b) (2.89 g, 9.75 mmol) in dry tetrahydrofuran (60 ml). Stirring was continued for 1 h at room temperature. The mixture was quenched with a small amount of water. The inorganic salts were separated and filtered off. The filtrate was concentrated and extracted with ether–dichloromethane (4 : 1). The usual work-up gave a viscous syrup (2.9 g) which was purified by preparative t.l.c. [cyclohexane–ether (2 : 1) with triple development] to afford the 17a $\beta$ -ol (18b) (2.04 g, 70.2%), m.p. 134–136° (dichloromethane–ether); the 17a $\alpha$ -ol was not detected. The crystalline product was recrystallized from dichloromethane–ether, giving an analytical sample, m.p. 140.5–142°,  $\nu_{\max}$ . (dilute CCl<sub>4</sub>) 3 633 cm<sup>-1</sup> (free OH);  $\lambda_{\max}$ . (EtOH) 299sh, 311, and 323sh nm ( $\epsilon$  23 000, 27 900, and 21 300) (Found: C, 76.25; H, 7.45. C<sub>19</sub>H<sub>22</sub>O<sub>3</sub> requires C, 76.5; H, 7.45%). The acetate (19b) had m.p. 161–164° (dichloromethane–ether),  $\nu_{\max}$ . (CHCl<sub>3</sub>) 1 736 (OAc), 1 620, 1 563, and 1 493 cm<sup>-1</sup> (extended styrene);  $\lambda_{\max}$ . (EtOH) 299sh, 310.5, and 321sh nm ( $\epsilon$  24 300, 29 500, and 22 200);  $\delta$ (CDCl<sub>3</sub>) 1.13 (3 H, s, 13-Me), 2.11 (3 H, s, OAc), 3.79 (3 H, s, OMe), 5.00 (1 H, q, *J* 5 and 10 Hz, 17a-H), 6.58 (1 H, s, 15-H), and 6.6–7.3 (3 H, m, ArH) (Found: C, 73.85; H, 7.2. C<sub>21</sub>H<sub>24</sub>O<sub>4</sub> requires C, 74.1; H, 7.1%).

From (12b) and (14b). (a) A solution of the seco-ketol (12b) (52.6 mg) in dichloromethane (3 ml) and methanol (1.5 ml) containing concentrated hydrochloric acid (0.1 ml) was refluxed under nitrogen for 1 h. The mixture was poured into cold aqueous sodium hydrogencarbonate and extracted with dichloromethane. The usual work-up gave a viscous syrup (50.9 mg) which was crystallized from ether–pentane to furnish the 17a $\alpha$ -ol (16b) (27.2 mg), m.p. 112–115°. Recrystallization from dichloromethane–ether or acetone–ether gave an analytical specimen, m.p. 113–117°,  $\nu_{\max}$ . (dilute CCl<sub>4</sub>) 3 585 cm<sup>-1</sup> (bonded OH);  $\lambda_{\max}$ . (EtOH) 300sh, 312, and 325sh nm ( $\epsilon$  25 000, 30 700, and 23 200) (Found: C, 76.45; H, 7.4. C<sub>19</sub>H<sub>22</sub>O<sub>3</sub> requires C, 76.5; H, 7.45%). The acetate (17b) was obtained as in (c).

(b) A stirred solution of the seco-ketol (14b) (23.4 mg) in dichloromethane (2 ml) and methanol (1 ml) containing concentrated hydrochloric acid (0.05 ml) was refluxed under nitrogen for 1.5 h. After work-up as described above, the syrupy residue gave, on trituration with ether–pentane, the 17a $\beta$ -ol (18b) (12.3 mg), m.p. 137–140°, identical with an authentic sample.

(c) The crude ketol mixture (300 mg) obtained from the seco-dione (6b) was acetylated as usual. A solution of the crude acetate (350 mg) in dry benzene (10 ml) containing toluene-*p*-sulphonic acid (50 mg) was refluxed under nitrogen for 1.5 h. The cooled solution was poured into cold aqueous sodium hydrogencarbonate and extracted with ether. After the usual work-up, the crude product was purified by preparative t.l.c. [cyclohexane–ether (3 : 1) with double development] which separated the 17a $\beta$ -acetate (19b) (less polar) (26.9 mg) and 17a $\alpha$ -acetate (17b) (more polar) (148.4 mg); the product ratio is 1 : 5.5, similar to that for the starting ketols. The acetate (19b), m.p. 153–156° (ether–pentane), was identical with its authentic sample obtained above. The acetate (17b), m.p. 136–140° (ether–pentane), was recrystallized from dichloromethane–ether for analysis, m.p. 147–149°,  $\nu_{\max}$ . (CHCl<sub>3</sub>) 1 727 (OAc), 1 622, 1 603, 1 564, and 1 500 cm<sup>-1</sup> (extended styrene);  $\lambda_{\max}$ . (EtOH) 300sh, 311, and 324sh nm ( $\epsilon$  24 900, 30 100, and 22 400);  $\delta$ (CDCl<sub>3</sub>) 1.16 (3 H, s, 13-Me), 2.10

(3 H, s, OAc), 3.79 (3 H, s, OMe), 4.90 (1 H, t, *J* 2 Hz, 17a-H), 6.67br (1 H, s, 15-H), and 6.6–7.2 (3 H, m, ArH) (Found: C, 73.8; H, 7.1. C<sub>21</sub>H<sub>24</sub>O<sub>4</sub> requires C, 74.1; H, 7.1%). The structure was confirmed by hydride reduction to the corresponding alcohol (16b).

3-Methoxy-18-methyl-16-thia-D-homoestra-1,3,5(10),8,14-pentaen-17a $\alpha$ - (20a) and -17a $\beta$ -ol (22a) and their Acetates (21a) and (23a).—A solution of the pentaenone (9a) (931 mg, 2.85 mmol) in dry tetrahydrofuran (20 ml) was added dropwise over a 15 min period to an ice-cold stirred slurry of lithium aluminium hydride (54 mg, 1.4 mmol) in dry tetrahydrofuran (10 ml). The mixture was then stirred at room temperature for 1 h and decomposed with a little water. The inorganic precipitate was filtered off and the filtrate was evaporated *in vacuo*. The resulting residue was extracted with ether–chloroform (4 : 1). After the usual work-up, the crude product obtained (1 g) was purified by preparative t.l.c. [cyclohexane–ether (9 : 1) with triple development], yielding the 17a $\alpha$ -ol (20a) (less polar) (121.6 mg, 13.0%) and 17a $\beta$ -ol (22a) (more polar) (740 mg, 79.1%); the product ratio is 1 : 6.1. Two crystallizations from ether–pentane gave their analytical samples. The 17a $\alpha$ -ol (20a) had m.p. 112.5–114°,  $\nu_{\max}$ . (CHCl<sub>3</sub>) 1 607, 1 561, and 1 494 cm<sup>-1</sup> (extended styrene);  $\nu_{\max}$ . (dilute CCl<sub>4</sub>) 3 554 cm<sup>-1</sup> (bonded OH);  $\lambda_{\max}$ . (EtOH) 316sh, 330, and 345 nm ( $\epsilon$  27 000, 36 500, and 28 000) (Found: C, 72.9; H, 7.35; S, 9.8. C<sub>20</sub>H<sub>24</sub>O<sub>2</sub>S requires C, 73.15; H, 7.35; S, 9.75%). The acetate (21a) was prepared with acetic anhydride–pyridine as usual, foam,  $\nu_{\max}$ . (CHCl<sub>3</sub>) 1 728 (OAc), 1 608, 1 562, and 1 497 cm<sup>-1</sup> (extended styrene);  $\delta$ (CDCl<sub>3</sub>) 0.88 (3 H, t, *J* 7.5 Hz, 13-Me), 2.12 (3 H, s, OAc), 3.80 (3 H, s, OMe), 5.27 (1 H, t, *J* 3 Hz, 17a-H), 6.18br (1 H, s, 15-H), and 6.6–7.2 (3 H, m, ArH). The 17a $\beta$ -ol (22a), m.p. 100–101.5°,  $\nu_{\max}$ . (CHCl<sub>3</sub>) 1 607, 1 563, and 1 494 cm<sup>-1</sup> (extended styrene);  $\nu_{\max}$ . (dilute CCl<sub>4</sub>) 3 631 cm<sup>-1</sup> (free OH);  $\lambda_{\max}$ . (EtOH) 315sh, 329.5, and 344 nm ( $\epsilon$  27 700, 37 500, and 27 900) (Found: C, 72.9; H, 7.35; S, 10.0%). The acetate (23a) was prepared as above, m.p. 103–105° (dichloromethane–ether),  $\nu_{\max}$ . (CHCl<sub>3</sub>) 1 741 (OAc), 1 607, 1 563, and 1 501 cm<sup>-1</sup> (extended styrene);  $\delta$ (CDCl<sub>3</sub>) 0.97 (3 H, t, *J* 7.5 Hz, 13-Me), 2.10 (3 H, s, OAc), 3.79 (3 H, s, OMe), 5.12 (1 H, q, *J* 6 and 10.5 Hz, 17a-H), 6.06br (1 H, s, 15-H), and 6.6–7.2 (3 H, m, ArH).

3-Methoxy-18-methyl-16-oxa-D-homoestra-1,3,5(10),8,14-pentaen-17a $\beta$ -ol (22b) and its Acetate (23b).—In a manner similar to that described above, a stirred solution of the pentaenone (9b) (1.14 g, 3.67 mmol) in dry tetrahydrofuran (22 ml) was reduced with lithium aluminium hydride (69.5 mg, 1.83 mmol). The crude product obtained after usual work-up was purified through silica gel (Activity II; 8 g) by elution with benzene followed by dichloromethane to give, on crystallization from ether–pentane, the 17a $\beta$ -ol (22b) (1.03 g, 89.9%), m.p. 105.5–107°. Recrystallization from the same solvent gave an analytical sample, m.p. 105.5–107°,  $\nu_{\max}$ . (dilute CCl<sub>4</sub>) 3 632 cm<sup>-1</sup> (free OH);  $\lambda_{\max}$ . (EtOH) 300sh, 312, and 324sh nm ( $\epsilon$  23 700, 28 300, and 21 500) (Found: C, 76.65; H, 7.85. C<sub>20</sub>H<sub>24</sub>O<sub>3</sub> requires C, 76.9; H, 7.75%). The acetate (23b) was obtained in a usual manner, m.p. 104–106° (ether–pentane),  $\nu_{\max}$ . (CHCl<sub>3</sub>) 1 736 (OAc), 1 621, 1 607, 1 566, and 1 502 cm<sup>-1</sup> (extended styrene),  $\delta$ (CDCl<sub>3</sub>) 0.96 (3 H, t, *J* 7.5 Hz, 13-Me), 2.11 (3 H, s, OAc), 3.80 (3 H, s, OMe), 5.07 (1 H, q, *J* 6 and 10 Hz, 17a-H), 6.63br (1 H, s, 15-H), and 6.6–7.2 (3 H, m, ArH).

3-Methoxy-16-thia-D-homoestra-1,3,5(10),6,8,14-hexaen-17a-one (24a).—A solution of the pentaenone (8a) (5.7 g,



18.2 mmol) and chloranil (5.0 g, 20.3 mmol) in xylene (180 ml) was heated at reflux under nitrogen for 3.5 h. The mixture was concentrated *in vacuo*. The residual gummy product was directly purified through alumina (Activity II and III; 180 g) by elution with benzene. The crude product obtained was further decolorized by treating with active carbon in boiling acetone, giving on crystallization from acetone-ether the naphthalene (24a) (625 mg) as thin plates, m.p. 181–188°. The residue from the mother liquor (*ca.* 1.3 g) was rechromatographed on alumina (Activity II and III; 50 g). Elution with light petroleum-benzene (3 : 7) afforded additional crystalline compound (24a) (205 mg), m.p. 181–184° (acetone-ether). The total yield was 830 mg (14.7%). Recrystallization from dichloromethane-acetone gave an analytical sample, m.p. 190.5–191.5°,  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 711 (CO), 1 624, 1 601, and 1 501 (aromatic) cm<sup>-1</sup>;  $\lambda_{\max}$  (EtOH) 243.5, 271sh, 277, and 312 nm ( $\epsilon$  26 300, 21 300, 21 600, and 21 800);  $\delta$ (CDCl<sub>3</sub>) 1.35 (3 H, s, 13-Me), 3.90 (3 H, s, OMe), 6.60br (1 H, s, 15-H), and 7.0–7.9 (5 H, m, ArH); *m/e* 310 (*M*<sup>+</sup>) (Found: C, 73.2; H, 5.7; S, 10.6. C<sub>19</sub>H<sub>18</sub>O<sub>2</sub>S requires C, 73.5; H, 5.85; S, 10.35%).

**3-Methoxy-16-oxa-D-homoestra-1,3,5(10),6,8,14-hexaen-17a-one (24b).**—A stirred mixture of the pentaenone (8b) (296 mg, 1 mmol) and selenium dioxide (111 mg, 1 mmol) in acetic acid (8 ml) was refluxed under nitrogen for 15 min. The acetic acid was removed *in vacuo* and the residue was purified through alumina (Woelm; Activity I; 8 g) by eluting with benzene. The residue from combined eluates (183 mg) was subjected to preparative t.l.c. [cyclohexane-ether (2 : 1) with triple development] which furnished as major product, the naphthalene (24b) (111 mg, 37.8%), m.p. 125–130° (ether-pentane). Recrystallization from dichloromethane-ether gave an authentic sample, m.p. 128–131°,  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 725 (CO), 1 635sh, 1 626, 1 601, 1 573, 1 566, and 1 508 (aromatic) cm<sup>-1</sup>;  $\lambda_{\max}$  (EtOH) 221, 240sh, 250sh, 258, 266sh, and 284 nm ( $\epsilon$  17 400, 23 800, 30 600, 36 200, 33 500, and 16 400);  $\delta$ (CDCl<sub>3</sub>) 1.32 (3 H, s, 13-Me), 3.88 (3 H, s, OMe), 7.0–7.3 (4 H, m, 15-H and ArH), and 7.5–7.9 (2 H, m, ArH); *m/e* 294 (*M*<sup>+</sup>) (Found: C, 77.3; H, 6.2. C<sub>19</sub>H<sub>18</sub>O<sub>3</sub> requires C, 77.55; H, 6.15%).

**2-(6-m-Methoxyphenyl-3-oxohexyl)-2-methyl-5-thiacyclohexane-1,3-dione (26) and 3-Methoxy-9,10-seco-16-thia-D-homoestra-1,3,5(10),8(14)-tetraene-9,17a-dione (29).**—6-m-Methoxyphenylhex-1-en-3-one (25) was previously prepared from 6-m-methoxyphenylpropylmagnesium bromide by literature procedures.<sup>10,11</sup> A mixture of the dione (1a) (4.03 g, 0.028 mol), the vinyl ketone (25) (7.43 g, 0.036 mol), and dry toluene (22 ml) containing pyridine (2.2 ml) and hydroquinone (28 mg) was refluxed under nitrogen for 19 h. The solvent was evaporated to dryness and the residue was extracted with ether. The usual work-up gave the crude adduct (26) (9.8 g) as a viscous oil,  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 730 and 1 705 cm<sup>-1</sup> (CO), which was used as such for

subsequent reaction. The product was refluxed under nitrogen for 190 h in dry toluene (135 ml) containing benzoic acid (3.6 g) and triethylamine (3.4 ml) using a water separator. After the solvent was removed *in vacuo*, the residue was poured into cold aqueous sodium carbonate and extracted with ether-dichloromethane (4 : 1). The usual work-up gave a dark gummy product which was chromatographed on silica gel (Activity II; 125 g). After elution with benzene and benzene-dichloromethane (9 : 1), the successive fractions eluted with benzene-dichloromethane (4 : 1) and dichloromethane gave a viscous syrup (4.1 g). This product was further purified by preparative t.l.c. [benzene-ethyl acetate (9 : 1) with double development] to provide the unsaturated dione (2.15 g, 23.2%) which solidified on standing in a refrigerator. Trituration with ether-pentane gave an analytical specimen, m.p. 77–79°,  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 714 (CO), 1 672 (conjugated CO), 1 602, 1 582, and 1 486 (aromatic) cm<sup>-1</sup>;  $\lambda_{\max}$  (EtOH) 219, 250, 277sh, and 280sh nm ( $\epsilon$  11 400, 8 200, 5 400, and 4 700);  $\delta$ (CDCl<sub>3</sub>) 1.43 (3 H, s, 13-Me), 3.78 (3 H, s, OMe), and 6.7–7.3 (4 H, m, ArH); *m/e* 330 (*M*<sup>+</sup>) (Found: C, 68.9; H, 6.8; S, 9.6. C<sub>19</sub>H<sub>22</sub>O<sub>3</sub>S requires C, 69.05; H, 6.7; S, 9.7%).

**(4,9-Dioxo-5R-methyl-1R-2-thiabicyclo[3.3.1]nonane)-8R-spiro-1'-(6'-methoxy-1',2',3',4'-tetrahydronaphthalene) (27).**—A solution of the crude trione (26) obtained above (700 mg, *ca.* 1 mmol) in dry benzene (20 ml) was added to a stirred mixture of phosphoric acid (3 g) and phosphoric anhydride (1.2 g). Stirring was continued for 50 min at room temperature. The cooled mixture was poured into cold aqueous sodium hydrogencarbonate and extracted with ether. After the usual work-up, the residue was purified by preparative t.l.c. [cyclohexane-ether (9 : 1) with double development] which gave the pentaenone (8a) (95 mg), the bridged dione (27) (18.5 mg), and the starting material (26) (10.9 mg). The recovered material was repeatedly subjected to the above reaction with phosphoric acid (0.5 g) and phosphoric anhydride (0.2 g) in dry benzene (4 ml). After stirring at room temperature for 2.5 h, the mixture was then heated at 85–90° for an additional 1 h and worked up as described above. The crude product was purified similarly by preparative t.l.c. to afford the pentaenone (8a) (6 mg) and the dione (27) (25 mg) as second crops. The former compound (8) was identified with its authentic sample. The latter compound (27) (total 43.5 mg) was recrystallized from dichloromethane-ether for analysis, m.p. 179–180°,  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 731, 1 704, 1 698 (CO), 1 606, 1 570, and 1 495 (aromatic) cm<sup>-1</sup>;  $\lambda_{\max}$  (EtOH) 276 and 284 nm ( $\epsilon$  1 800 and 1 700);  $\delta$ (CDCl<sub>3</sub>) 1.23 (3 H, s, Me), 3.22 (2 H, s, CO-CH<sub>2</sub>-S), 3.77 (3 H, s, OMe), 3.96 (1 H, d, *J* 1.5 Hz, bridge H), and 6.6–7.6 (4 H, m, ArH); *m/e* 330 (*M*<sup>+</sup>) (Found: C, 68.75; H, 6.6; S, 9.6. C<sub>19</sub>H<sub>22</sub>O<sub>3</sub>S requires C, 69.05; H, 6.7; S, 9.7%).

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