# Cycloaddition Route to 14,17-Ethano- and 14-Alkyl-19-norsteroids

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Cycloaddition of phenyl vinyl sulphone to 14,16-dien-17-yl acetates derived from estrone proceeds regio- and stereo-selectively to give intermediates for conversion into 14,17α-ethenoestra-1,3,5(10)-triene-3,17β-diol derivatives and related ring D bridged 19-norsteroids. Oxidative cleavage of the 14α,17α-etheno bridge leads to 14α,17α-diformyl-17β-acetates and to 14α-formyl-17-ketones. Aspects of the chemistry of the 14α-formyl compounds are discussed, and methods are described for their conversion into 14α-methyl-and 14-hydroxymethyl-19-norsteroids.

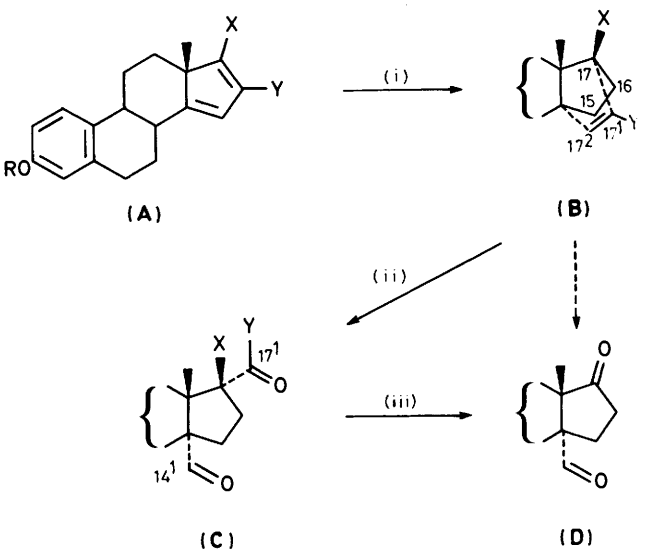
Numerous pathways to 14α-alkyl steroids have been described, based upon degradation of natural products,[1] base-mediated alkylation of 15-ketones,[2] and total synthesis.[3,4] In a programme directed toward the synthesis of 14-alkyl-19-norsteroids, we have found that stereoselectivity of ring-junction alkylation of steroidal 15-ketones is strongly influenced by surrounding structural features.[2] Furthermore, subsequent restoration of appropriate ring D functionality sometimes entails cumbersome transposition methodology.[5]

Although efficient total syntheses of 14-methyl-19-norsteroids have now been developed,[3,4] they are of limited generality for the elaboration of modified hormone analogues, owing partly to diminished ring D reactivity and stereoselectivity, attendant upon the presence of the 14-methyl group.

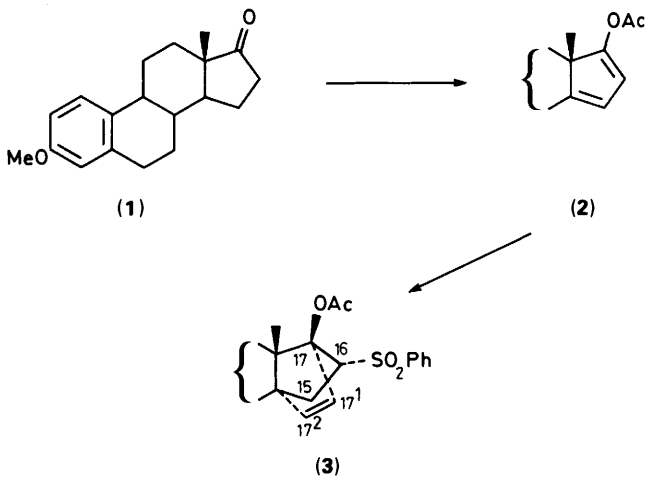
In an effort to develop a more versatile synthetic approach to 14-alkyl-19-norsteroids, we sought a method which would ensure the desired stereoselectivity and, at the same time, generate functionality at C-14 and C-17 which could be elaborated in different ways. Our conceptual approach (Scheme 1) was based upon Diels–Alder addition of an ethylene equivalent to a steroidal 14,16-diene (**A**), followed by oxidative cleavage of the residual olefinic bond in the cycloadduct (**B**).[6] In this way, the ring D system (**C**) could be restored, with concomitant introduction of a 14α-formyl group, and with 17-substitution patterns determined by the choice of 16- and 17-substituents in the starting diene. Implicit in the approach was that an oxygen function at C-17 would also allow extended oxidative cleavage, leading to the 14α-formyl-17-ketone (**D**).

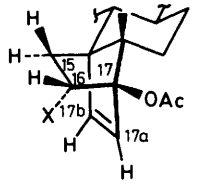
We were encouraged in this approach by the evidence of highly stereoselective cycloadditions to steroidal 14,16-dienes, in the extensive work of Solo *et al.*,[7] and by precedent[8] for oxidative cleavage of analogous ring D bridged steroids. Furthermore, it appeared that phenyl vinyl sulphone would meet our need for an effective ethylene equivalent in the cycloaddition step.[9]

In the first phase of the work, estrone 3-methyl ether (**1**) was readily converted into the dienyl acetate (**2**), using a three-step sequence without purification of intermediates. Treatment of (**2**) with phenyl vinyl sulphone in benzene at 145 °C for 90 h resulted in formation of a single cycloadduct (**3**) (92%), the structure of which was assigned by analogy[7] and by subsequent transformations. Although a 500 MHz $^1$H n.m.r. spectrum of (**3**) did not yield irrefutable evidence for the regiochemistry or the overall stereochemistry of the product, the signals were fully assigned by comparison with those rigorously assigned to estrone 3-methyl ether (**1**) and its 14α-methyl derivative,[10] and are consistent with the proposed structure. The pattern of signals for the protons of the ring-bridge was distinctive, and revealed that the magnitude of the larger vicinal coupling ($J$ 8.6 Hz) on the β-bridge is consonant with an *exo-exo* rather than an *endo-endo* disposition of the protons, thereby supporting the expected *endo* orientation of the 16-phenylsulphonyl group.[11] This was further borne[11] out by n.m.r. examination of the derived 17$^1$, 17$^2$-dihydro compound (**4**), in which the analogous

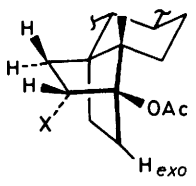



**Scheme 1.** Cycloaddition–oxidative cleavage route to 14α-alkyl-19-norsteroids: i, β-face cycloaddition by ethylene equivalent; ii, oxidative cleavage of C(17$^1$)–C(17$^2$), iii, oxidative cleavage of C(17)–C(17$^1$)



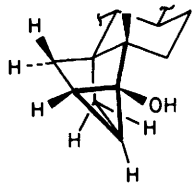


(3) X = $SO_2Ph$



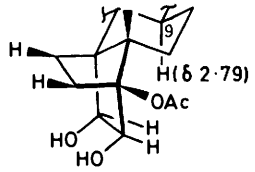
(4) X = $SO_2Ph$

$J_{15\beta,15\alpha}$ 12.6 Hz $J_{15\beta,15\alpha}$ 12.8 Hz $J_{15\beta,16\beta}$ 11.7 Hz
$J_{15\beta,16\beta}$ 8.6 Hz $J_{15\alpha,16\beta}$ 4.9 Hz $^4J_{16\beta,17^1exo}$ 11.7 Hz
$J_{15\alpha,16\beta}$ 5.0 Hz

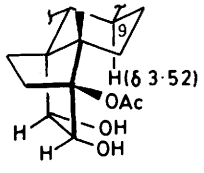


(9)

$J_{15\beta,15\alpha} = J_{17^2exo,17^2endo}$ 10 Hz
$J_{15\alpha,16\beta} = J_{17^1,17^2endo}$ 1.2 Hz
$J_{15\beta,16\beta} = J_{17^1,17^2exo} = {}^4J_{15\beta,17^2exo}$ 1.5 Hz
$J_{16\beta,17^1}$ 10 Hz



(16)



(17)

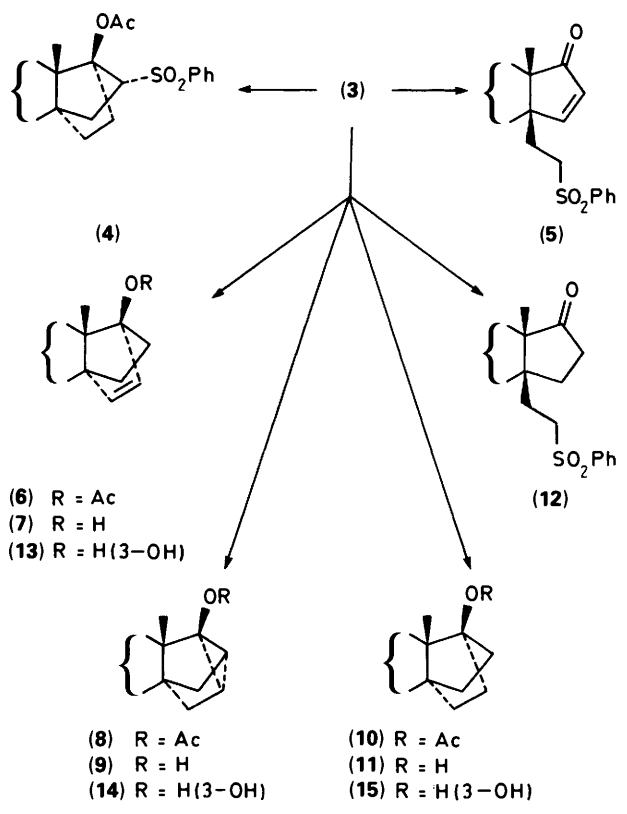
$J_{17^1exo,17^2exo}$ 9.4 Hz $J_{17^1endo,17^2endo}$ 7.4 Hz
$^4J_{17^1exo,16\beta} = {}^4J_{17^2exo,15\beta}$ 1.9 Hz

**Scheme 2.** Diagnostic $^1H$ n.m.r. properties of the ring D bridged compounds (**3**), (**4**), (**9**), (**16**), and (**17**) (at 500 MHz in $CDCl_3$)

signal for 16β-H showed a larger vicinal coupling ($J$ 11.7 Hz) and was further split by a four-bond W-coupling ($J$ 2.9 Hz) with the $17^1$-*exo*-proton (Scheme 2); these features are characteristic of 2-*endo*-substituted bicyclo[2.2.1]heptanes.

Further evidence for the structural assignment was obtained through alkaline treatment of the cycloadduct (**3**) to give the 14β-(2-phenylsulphonylethyl)-$\Delta^{15}$-17-one (**5**), the spectroscopic properties of which clearly demonstrated the presence of the cyclopentenone subunit. In contrast to an analogous retrograde reaction implicated in alkaline treatment of a related cycloadduct,[12] the conversion of (**3**) into (**5**) proceeded cleanly and in high yield. The reaction must proceed through the intermediacy of the bridgehead alkoxide, followed by cleavage of the 16,17-bond, and conclusively demonstrates the assigned regiochemistry of the cycloadduct (**3**).

Desulphonylation of the cycloadduct (**3**) was carried out according to the procedure developed by Trost *et al.*[13] The compound (**3**) was treated with sodium amalgam (6%) and disodium hydrogen phosphate in tetrahydrofuran–methanol at −20 °C until starting material had been consumed. The resulting mixture (t.l.c.), arising from reduction and some concomitant hydrolysis of the bridgehead acetoxy group, was treated with acetic anhydride and toluene-*p*-sulphonic acid.



(**6**) R = Ac
(**7**) R = H
(**13**) R = H(3−OH)

(**8**) R = Ac
(**9**) R = H
(**14**) R = H(3−OH)

(**10**) R = Ac
(**11**) R = H
(**15**) R = H(3−OH)

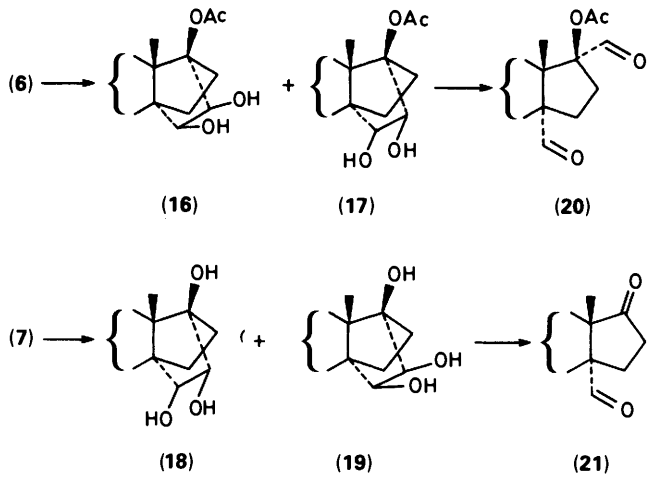
Crystallisation of the resultant crude product afforded 14,17α-etheno-3-methoxyestra-1,3,5(10)-trien-17β-yl acetate (**6**) (93%). Although the crude product appeared to be chromatographically homogeneous, it contained small amounts of an impurity (**8**), which was only detected in subsequent experiments carried out with unrecrystallised material. Thus, hydrolysis of the acetoxy olefin (**6**) [containing (**8**)] gave the expected hydroxy olefin (**7**) [containing (**9**)], from which the pure compound (**7**) was obtained after crystallisation. However, catalytic hydrogenation of the total hydrolysis product (**7**) [containing (**9**)] gave a chromatographically separable mixture comprising the expected 14,17α-ethano compound (**11**) (95%) and the 16α,17a-cyclo-14,17α-ethano compound (**9**) (5%). By contrast, catalytic hydrogenation of recrystallised hydroxy olefin (**7**) resulted in exclusive formation of (**11**).

The structure of (**9**) was deduced largely from 500 MHz n.m.r. data; the $^{13}C$ n.m.r. spectrum showed two high-field doublets (δ 15.2 and 12.9) assigned to the cyclopropyl carbon atoms C-16 and C-17a, whereas the $^1H$ spectrum revealed a closed spin system which was assigned (Scheme 2) with the aid of connectivity and n.O.e. experiments. The spectroscopic properties of the derived acetate (**8**) were comparable and self-consistent.

The formation of the cyclo compound (**8**) during desulphonylation of (**3**) is reminiscent of a participation reaction carried out upon a skeletally related but functionally dissimilar bridged steroid,[14] and suggests that the reaction conditions permit some competing interception of the presumed radical intermediate by the olefinic bond. Nevertheless, it is surprising that the analagous process was not observed during desulphonylation of 2-(phenylsulphonyl)bicyclo[2.2.1]heptane.[9]

The amounts of (**8**) formed during desulphonylation of (**3**) were variable, but never exceeded *ca.* 6% in our experiments. It is suspected that very small variations in concentration and temperature control may account for these differences.

The need for close adherence to optimum conditions for sodium amalgam reduction of (**3**) was further demonstrated in




an experiment, in which the temperature was maintained initially at −20 °C, then allowed to rise to 0 °C. In this case the overall yield of (**6**) [+(**8**)], isolated after acetylation of the crude product, diminished to *ca.* 54%, and was accompanied by the corresponding dihydro compound (**10**) (14%). Furthermore, at temperatures exceeding 0 °C, the reaction course was influenced by the basicity of the medium, and the hydroxy olefin (**7**) was a minor product (18%), accompanied by the 14β-(2-phenylsulphonylethyl)-17-one (**12**) (31%). The structure of (**12**) was shown by its identity with the product obtained through catalytic hydrogenation of the enone (**5**) in the presence of palladium–calcium carbonate.

The 17-alcohols (**7**), (**9**), and (**11**), obtained through alkaline hydrolysis of the desulphonylation products (**6**), (**8**), and (**10**) respectively, were readily converted into their respective estradiol analogues (**13**), (**14**), and (**15**), by treatment with di-isobutylaluminium hydride in refluxing toluene.

With the bridged olefins (**6**) and (**7**) in hand, attention was turned to oxidative cleavage of the $\Delta^{17^1}$-bond. Preliminary experiments, in which (**6**) or (**7**) were subjected to ozonolysis under a variety of conditions, gave erratic results; variable amounts of the desired products were accompanied by numerous by-products. It was suspected that the primary cleavage products might be susceptible to decomposition during work-up, and accordingly, a stepwise sequence was adopted, in which *cis*-hydroxylation was followed by glycol cleavage.

Treatment of the acetoxy olefin (**6**) with osmium tetraoxide in dry pyridine at 25 °C for 20 h gave a readily separable mixture of the (17$^1$*S*,17$^2$*S*)- and (17$^1$*R*,17$^2$*R*)-diols (**16**) (31%) and (**17**) (59%). The isomers were readily distinguished by n.m.r.; thus, the signals for the bridged methine protons of (**16**) appeared as double doublets (*J* 9.4 and 1.9 Hz, after $D_2O$ exchange), whereas those of (**17**) appeared as doublets (*J* 7.4 Hz, after $D_2O$ exchange) (Scheme 2), demonstrating their *exo,exo*-orientation in the former case, through the larger magnitude of the vicinal coupling and the four-bond W-coupling to the 15β- and 16β-protons.[11] Another useful diagnostic feature of the spectra of (**16**) and (**17**) was the chemical shift difference in the signal for the 9α-proton. In the case of (**16**) it appeared in the 'usual' region (δ 2.79),[10] but suffered a substantial downfield shift to δ 3.52 in (**17**), presumably under the influence of the proximate *exo*-orientated 17$^2$-hydroxy group. A similar effect upon the 12α-proton would be expected, but this was obscured by signal overlap in the high-field region.

Hydroxylation of the hydroxy olefin (**7**) with osmium tetraoxide in dry pyridine at 25 °C for 20 h gave (in order of chromatographic elution) the (17$^1$*R*,17$^2$*R*)- and (17$^1$*S*,17$^2$*S*)-17β,17$^1$,17$^2$-triols (**18**) (24%) and (**19**) (66%), the structures of which were assigned by comparative spectroscopic data and by chemical correlation with the respective 17β-acetoxy-17$^1$,17$^2$-diols (**17**) and (**16**).

For practical purposes, large-scale hydroxylations of (**6**) and (**7**) were carried out in tetrahydrofuran (THF) using catalytic amounts of osmium tetraoxide in the presence of 4-methylmorpholine-4-oxide. The reactions proceeded rather slowly by comparison with stoichiometric osmylations, but gave generally satisfactory yields (in excess of 80% overall conversion).

A striking feature of the hydroxylations of (**6**) and (**7**) was the influence of the bridgehead substituent upon the stereochemical outcome; thus, *exo*-directed osmylation predominates in the case of the acetoxy olefin (**6**), but is the disfavoured course in the hydroxy olefin (**7**). Since the purely steric factors are comparable in both substrates, the result suggests a directing effect reminiscent of the trend observed by Kishi *et al.*[15] in osmylation of allylic OR compounds. Thus, *endo*-attack here, corresponding to *anti*-approach by the reagent, is assisted by the presence of a free 17β-hydroxy group, but is sterically impeded or the effect partially negated when a 17β-acetoxy group is present.

Treatment of the individual 17β-acetoxy-17$^1$,17$^2$-diols (**16**) or (**17**) with sodium periodate in aqueous ethanol furnished the 17β-acetoxy-14α,17α-dicarbaldehyde (**20**) in practically quantitative yield. Larger scale preparations were conveniently conducted upon the hydroxylation mixture [(**16**) + (**17**)], obtained by rapid filtration chromatography to remove unrelated impurities. The structure of the product (**20**) was evident from the presence of two low-field n.m.r. signals (δ 9.38 and 9.99) for the aldehydic protons.

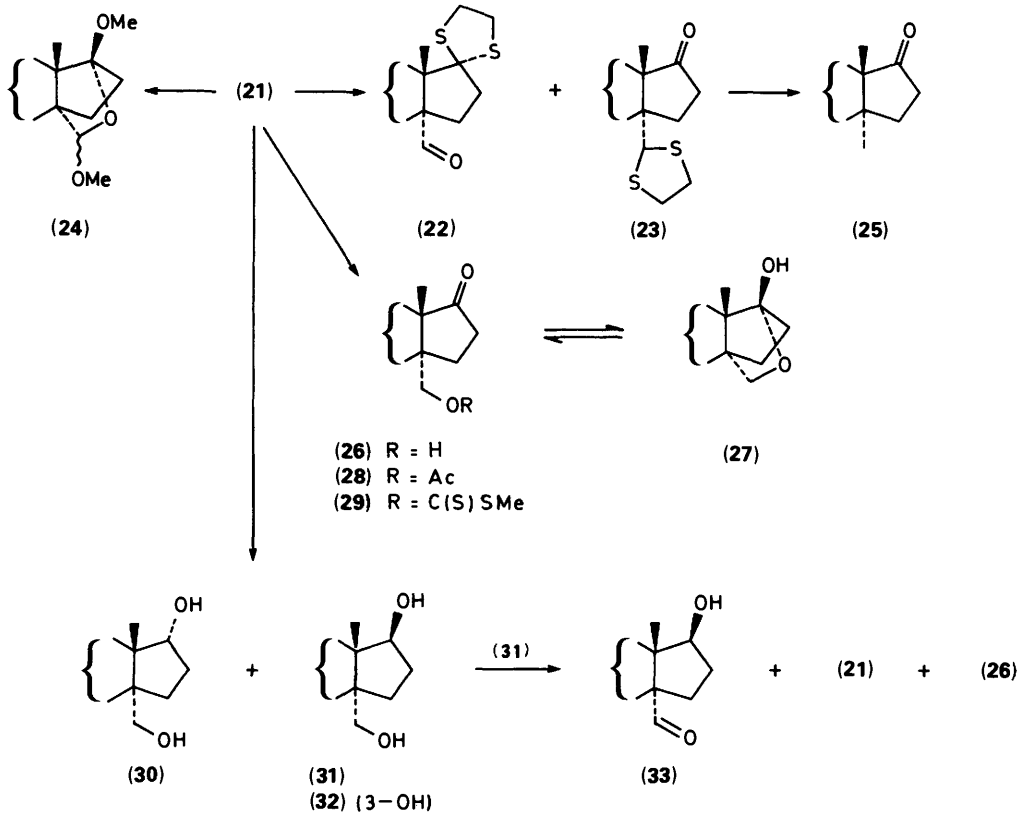
The triols (**18**) and (**19**) (individually or as a mixture) underwent double oxidative cleavage smoothly, to give 14-formylestrone 3-methyl ether (**21**). The compound displayed the expected infrared ($\nu_{max.}$ 1 742 and 1 714 cm$^{-1}$), $^1$H n.m.r. (1 H, s, C*H*O, at δ 9.9), and $^{13}$C [δ 215.8 (s, C-17) and 203.5 (d, C-14$^1$)] characteristics for the carbonyl groups, but an anomalous, bisignate c.d. spectrum [apparent $\Delta\varepsilon_{max.}$ −1.56 (315 nm) and +0.69 (273 nm)], associated perhaps with some chromophoric interaction.

It is estimated that the overall conversion of estrone 3-methyl ether (**1**) into this essential intermediate for further elaboration, proceeds in *ca.* 34% yield, and with most satisfactory stereo- and regio-control.

Among the initial objectives in the programme, the synthesis of 14-methylestrone analogues enjoyed some priority, and the conversion of (**21**) into the corresponding 14α-methyl compound (**25**) was therefore of interest, as was the chemoselectivity of reactions of the 14$^1$- and 17-oxo-groups.

Thioacetalisation of (**21**) in acetic acid, with ethane-1,2-dithiol in the presence of boron trifluoride–diethyl ether displayed reasonable selectivity to give the undesired minor isomer (**22**) (16%), accompanied by the 14$^1$,14$^1$-dithioacetal (**23**) as the major product (73%). In a mistaken attempt to modify the reaction rate and perhaps the selectivity further, an experiment was carried out in methanol, to give a product formulated as (**24**).

Treatment of the dithioacetal (**23**) with Raney nickel in ethanol at 25 °C gave a satisfactory yield (63%) of 3-methoxy-14-methylestra-1,3,5(10)-trien-17-one (**25**), the comparable spectroscopic properties of which were identical with those recorded for the known racemic material,[4,16] and quite different from those of the corresponding 14β-isomer.[5] Furthermore, a c.d. spectrum of (**25**) in methanol ($\Delta\varepsilon_{max.}$ 2.5 at 298 nm) revealed that the 14-methyl group makes a dissignate contribution ($\Delta\Delta\varepsilon$ *ca.* −0.8, by comparison with estrone 3-methyl ether) to the Cotton effect, consonant with the assignment of 14α-configuration.[17] Consequently, the configuration assigned to the primary cycloadduct (**3**) and all the derived intermediates was confirmed.




In further attempts to differentiate the carbonyl groups in the formyl ketone (**21**), various selective hydride reductions were performed, the most successful of which was found to be lithium tri(sec-butyl)borohydride ('L-Selectride'), which furnished the 14α-hydroxymethyl-17-one (**26**) in essentially quantitative yield. The spectroscopic properties of (**26**) revealed that it exists in a state of equilibrium in solution with the corresponding hemiacetal (**27**). An i.r. spectrum of (**26**) in pyridine displayed both hydroxyl and carbonyl absorption, whereas only hydroxyl absorption was observed in a mineral oil film, Similarly, the n.m.r. spectrum of (**26**) in [$^2H_5$]pyridine revealed doubling of several signals in a *ca.* 40:60 ratio, favouring the hemiacetal (**27**). An interesting feature of the latter form was an unusually large W-coupling (*J* 4.1 Hz) between 14$^1$-$H_{exo}$ and 15β-H.

The hydroxy ketone (**26**) was readily converted into the corresponding acetoxy (**28**) and methyl xanthate (**29**) derivatives, which displayed the expected spectroscopic properties. The latter derivative was prepared in order to explore the scope for an improved reductive route[18] to the 14α-methyl compound (**25**). However, treatment of (**29**) with tributyltin hydride gave impure material comprising the desired product (**25**) and inseparable impurities; consequently, the route was abandoned.

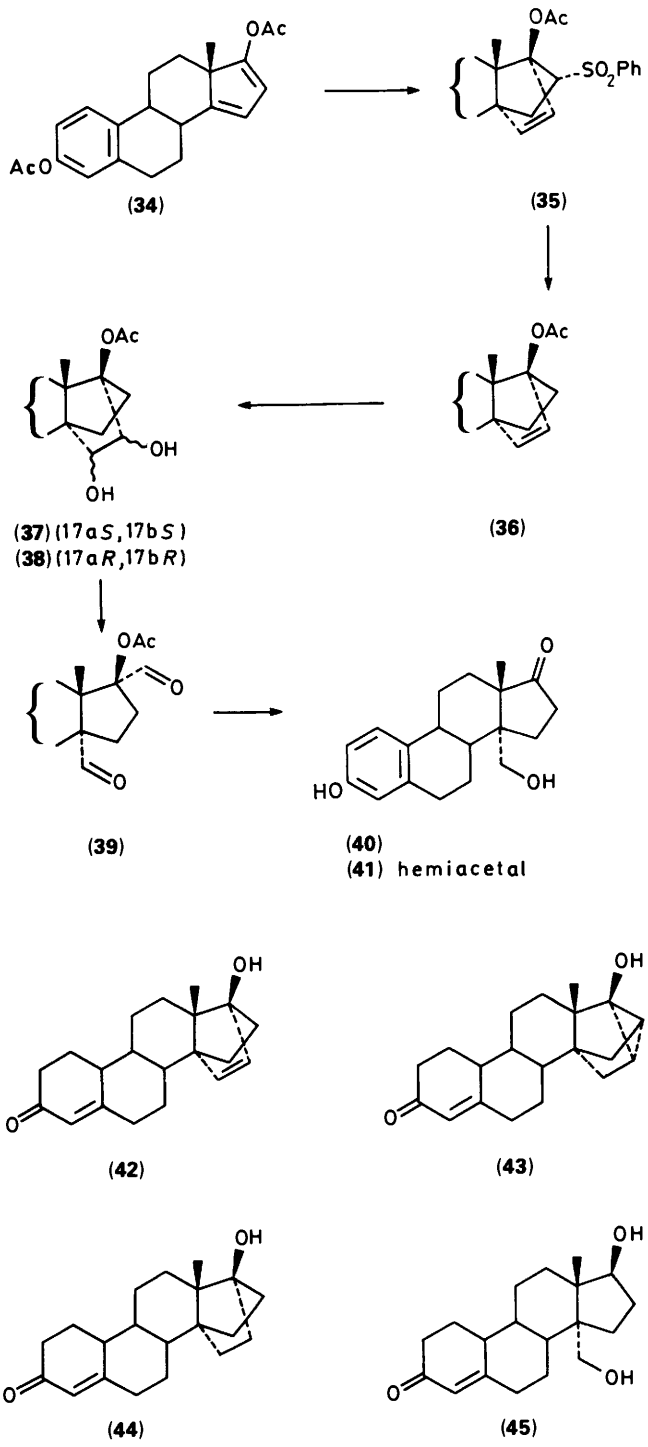
Forcing reduction of the formyl ketone (**21**) or further reduction of the 14-hydroxymethyl ketone (**26**) with lithium aluminium hydride gave a 1:3 ratio of the 14$^1$,17α- and 14$^1$,17β-diols (**30**) and (**31**). The isomers were readily differentiated by characteristic n.m.r. signals for the respective 17-protons. It is probable that α-face hydride delivery is assisted in this case by the 14$^1$-hydroxy group, hence the favoured formation of (**31**). The major isomer (**31**) was demethylated with di-isobutylaluminium hydride to give the 14α-hydroxymethyl analogue (**32**) of estradiol.

Attempted selective oxidation of the 14$^1$,17β-diol (**31**) with pyridinium chlorochromate gave the 14α-formyl-17β-alcohol (**33**) as the major product (41%), accompanied by the product (**21**) of overoxidation (32%), and the 14α-hydroxymethyl-17-ketone (**26**) (16%). The reaction was not optimised, but demonstrated that access to 14α-formyl analogues of estradiol is possible. A modified Swern-type oxidation of (**33**) was less successful.

The cycloaddition–cleavage sequence was also carried out on the 3-*O*-acetyl system in order to provide access to intermediates susceptible to mild base-mediated ring A deprotection. Thus, the dienyl acetate (**34**) underwent cycloaddition with phenyl vinyl sulphone to give the cycloadduct (**35**), which was characterised as before and converted into the acetoxy olefin (**36**). In this case, the by-products of reduction were not investigated, and the primary product (**36**) was recrystallised to provide pure material for subsequent steps. Osmylation of (**36**) afforded a *ca.* 1:2 mixture of the diols (**37**) and (**38**); predictably, the proportions and distinctive characteristics of (**37**) and (**38**) were similar to those of the corresponding 3-methoxy compounds (**16**) and (**17**).

Periodate cleavage of a mixture of (**37**) and (**38**) gave the dialdehyde (**39**). Treatment of (**39**) with lithium aluminium hydride gave a crude product, which was not characterised but assumed to be the 3,14$^1$,17β,17$^1$-tetraol. Indeed, periodate cleavage of this material afforded the 14α-hydroxymethyl analogue (**40**) of estrone. This product displayed characteristics similar to those of (**26**), in that the solution state of the material revealed an equilibrium with the corresponding hemiacetal (**41**).

Finally, a series of Birch reductions was performed on the 3-methyl ethers of skeletally modified estradiol analogues prepared here, in order to ascertain the scope for synthesis of the corresponding 19-nortestosterone analogues. For example, treatment of the hydroxy olefin (**7**) in THF–liquid ammonia–ethanol at −78 °C with lithium, followed by acid treatment of




the product, afforded the corresponding $\Delta^4$-3-one (**42**). The spectroscopic properties of (**42**) showed that the ring D structure was unaffected by the reaction sequence. Similar treatment of (**9**), (**11**), and (**31**) afforded the corresponding 19-nortestosterone analogues (**43**), (**44**), and (**45**).

## Experimental

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. Unless otherwise stated, spectra were recorded as follows: i.r., Perkin-Elmer 257, chloroform solutions; $^1$H n.m.r., Varian EM-390 (tetramethylsilane as internal standard) (90 MHz) or Bruker WM-500 (500 MHz), deuteriochloroform solutions; $^{13}$C n.m.r., Varian CFT-20 (20 MHz), Bruker AM-300 (75 MHz), or Bruker WM-500 (125 MHz), deuteriochloroform solutions; mass (electron impact), Varian MAT 212; c.d., Jasco J-20, methanol solutions. Optical rotations were measured for chloroform solutions at 20 °C with a Perkin-Elmer 241 polarimeter.

Silica gel for column chromatography refers to Merck Kieselgel 60: 70—230 mesh for gravity columns, and 230—400 mesh for flash chromatography.

*3-Methoxyestra-1,3,5(10),14,16-pentaen-17-yl Acetate* (**2**).—Copper(II) bromide (70 g, 0.313 mol) was added to a warm solution of estrone 3-methyl ether (**1**) (35 g, 0.123 mol) in benzene (280 ml) and methanol (280 ml), and the mixture was heated under reflux for 1 h. The hot mixture was filtered, and the filtrate was poured into a mixture of chloroform (1 750 ml) and water (1 750 ml). The mixture was shaken vigorously and refiltered through a Celite pad. The organic layer was washed with water (2 × 1 000 ml) and brine (1 000 ml), dried ($Na_2SO_4$), and concentrated under reduced pressure to give the crude 16α-bromo-derivative (45.6 g) as a crystalline residue. A deoxygenated solution of this product, lithium bromide (70 g), and lithium carbonate (60 g) in anhydrous *N,N*-dimethylformamide (DMF) (430 ml) was refluxed under argon for 4 h. The cooled solution was poured into a mixture of acetic acid (430 ml) and water (2 160 ml), and the product was extracted with ether (4 × 750 ml). The combined organic phase was washed successively with water (3 × 750 ml), aqueous sodium hydrogen carbonate (4 × 750 ml), and brine (750 ml), dried ($Na_2SO_4$), and concentrated under reduced pressure to give a crude mixture (t.l.c.) of 3-methoxyestra-1,3,5(10),14-tetraen-17-one and 3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-one, as a dark red gum (35.2 g).

A solution of the mixture and toluene-*p*-sulphonic acid monohydrate (14.4 g) in acetic anhydride (360 ml) and isopropenyl acetate (360 ml) was heated under reflux for 4 h. The cooled solution was poured into ice-water, and stirred for 1.5 h, while the liberated acetic acid was neutralised by additions of solid sodium hydrogen carbonate. Extraction with ether, and crystallisation of the product (24.63 g; 62%) from acetone–hexane gave the dienyl acetate (**2**), m.p. 123—125 °C (lit.,[19] m.p. 123—125 °C); $\delta_H$ 1.1 (3 H, s, 13β-Me), 2.23 (3 H, s, 17-OAc), 3.78 (3 H, s, 3-OMe), 5.87 (1 H, m, 15-H), 6.16 (1 H, d, *J* 2.5 Hz, 16-H), and 6.6—7.32 (3 H, m, 1-, 2-, and 4-H).

*3-Methoxy-16α-phenylsulphonyl-14,17α-ethenoestra-1,3,5(10)-trien-17β-yl Acetate* (**3**).—(*a*) A mixture of the dienyl acetate (**2**) (4.0 g, 12.33 mmol) and phenyl vinyl sulphone (6.23 g, 37.0 mmol) in anhydrous benzene (15 ml), in a sealed tube, was heated at 145 °C for 90 h. The reaction mixture was cooled to 25 °C and chromatographed directly on silica gel (500 g), using benzene–ethyl acetate (19:1) as eluant. This gave unreacted phenyl vinyl sulphone (4.24 g) followed by the *cycloadduct* (**3**) (5.57 g, 92%), m.p. 180—181.5 °C (from benzene–hexane); $[\alpha]_D$ + 100° (*c* 0.98); $\nu_{max.}$ 1 745, 1 318, and 1 149 cm$^{-1}$; $\delta_H$(500 MHz) 0.88 (3 H, s, 13β-Me), 1.11 (1 H, ddd, *J* 13.5, 4.0, and 2.6 Hz, 12β-H), 1.23 (1 H, dddd, *J* 13.6, 13.3, 12.3, and 4.0 Hz, 11β-H), 1.39 (1 H, ddd, *J* 12.0, 11.6, and 2.6 Hz, 8β-H), 1.64 (3 H, s, 17β-OAc), 1.68 (1 H, dddd, *J* 12.3, 12.0, 9.9, and 7.7 Hz, 7α-H), 1.85 (1 H, dddd, *J* 12.3, 4.1, 3.6, and 2.6 Hz, 7β-H), 1.99 (1 H, dd, *J* 12.6 and 5.0 Hz, 15α-H), 2.03 (1 H, dd, *J* 12.6 and 8.6 Hz, 15β-H), 2.21 (1 H, dddd, *J* 13.3, 3.8, 3.7, and 2.6 Hz, 11α-H), 2.3 (1 H, ddd, *J* 13.6, 13.5, and 3.8 Hz, 12α-H), 2.51 (1 H, ddd, *J* 12.3, 11.6, and 3.7 Hz, 9α-H), 2.86 (2 H, m, 6α- and 6β-H), 3.75 (3 H, s, 3-OMe), 4.17 (1 H, dd, *J* 8.6 and 5.0 Hz, 16β-H), 6.16 and 6.4 (each 1 H, d, *J* 6.1 Hz, 17$^1$- and 17$^2$-H), 6.61 (1 H, d, *J* 2.8 Hz, 4-H), 6.68 (1 H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.15 (1 H, d, *J* 8.6 Hz, 1-H), 7.56 (2 H, m, *m*-H × 2 of $PhSO_2$), 7.64 (1 H, m, *p*-H of

$PhSO_2$), and 7.89 (2 H, m, *o*-H × 2 of $PhSO_2$) (Found: C, 70.8; H, 6.8; S, 6.2%; $M^+$, 492. $C_{29}H_{32}O_5S$ requires C, 70.7; H, 6.55; S, 6.5%; *M*, 492).

(*b*) A mixture of the dienyl acetate (**2**) (17 g, 52.4 mmol) and phenyl vinyl sulphone (10.58 g, 62.9 mmol) in anhydrous xylene (30 ml) was heated in a sealed tube at 145 °C for 72 h. The reaction mixture was cooled to 25 °C, whereupon the product crystallised. Recrystallisation from benzene–hexane gave the product (**3**) (13.61 g, 52.7%), identical to that obtained in the foregoing experiment. The mother liquor residue was combined with the filtrate and chromatographed on silica gel (950 g) using toluene–ethyl acetate (19:1) as eluant to give further (**3**) (10.19 g, 39.5%).

3-*Methoxy*-16α-*phenylsulphonyl*-14,17α-*ethanoestra*-1,3,5-(10)-*trien*-17β-*yl Acetate* (**4**).—A solution of the cycloadduct (**3**) (49.2 mg, 0.1 mmol) in ethyl acetate (5 ml) was hydrogenated in the presence of palladium on charcoal (5%, 25 mg) at 25 °C and atmospheric pressure. The catalyst was removed by filtration, after hydrogen consumption had ceased (±8 h). The filtered catalyst was washed with ethyl acetate and the combined organic phase was concentrated under reduced pressure. Chromatography of the residue (51 mg) on silica gel (5 g), using toluene–ethyl acetate (19:1) as eluant, gave the *dihydro compound* (**4**) (48 mg; 97%); m.p. 199—200 °C (from benzene–hexane); $[\alpha]_D$ −12° (*c* 1.03); $\nu_{max.}$ 1 738, 1 315, and 1 147 $cm^{-1}$; $\delta_H$(500 MHz) 0.91 (3 H, s, 13β-Me), 1.66 (3 H, s, 17β-OAc), 1.81 (1 H, dt, *J* 2 × 12.5, and 3.9 Hz, 12α-H), 2.29 (1 H, dd, *J* 12.8 and 4.9 Hz, 15α-H), 2.74 (1 H, dt, *J* 2 × 11.3, and 3.3 Hz, 9α-H), 2.83 (2 H, m, 6α- and 6β-H), 3.75 (3 H, s, 3-OMe), 4.37 (1 H, ddd, *J* 11.7, 4.9, and 2.9 Hz, 16β-H), 6.60 (1 H, d, *J* 2.7 Hz, 4-H), 6.68 (1 H, dd, *J* 8.6 and 2.7 Hz, 2-H), 7.16 (1 H, d, *J* 8.6 Hz, 1-H), 7.55 (2 H, m, *m*-H × 2 of $PhSO_2$), 7.61 (1 H, m, *p*-H of $PhSO_2$), and 7.92 (2 H, m, *o*-H × 2 of $PhSO_2$) (Found: C, 70.45; H, 7.0; S, 6.5%; $M^+$, 494. $C_{29}H_{34}O_5S$ requires C, 70.4; H, 6.9; S, 6.5%; *M*, 494).

3-*Methoxy*-14-(2-*phenylsulphonylethyl*)-14β-*estra*-1,3,5(10),-15-*tetraen*-17-*one* (**5**).—Methanolic M-potassium hydroxide (10 ml) was added to a stirred solution of the cycloadduct (**3**) (1 g, 2.03 mmol) in anhydrous THF (5 ml) at 25 °C under argon. The reaction mixture was stirred for 16 h, then poured into water (50 ml). The aqueous layer was acidified with dilute hydrochloric acid to pH 5, then extracted with ethyl acetate (4 × 50 ml). The combined organic phase was washed once with brine, dried ($Na_2SO_4$), and concentrated under reduced pressure. The product (950 mg) was filtered through a short column of silica gel, using benzene–ethyl acetate (19:1) as eluant, to give the *enone* (**5**) (870 mg; 95%), m.p. 148—149.5 °C (from methanol); $[\alpha]_D$ +96.8° (*c* 1.01); $\lambda_{max.}$ 219 nm (ε 22 086); $\nu_{max.}$ 1 701, 1 312, and 1 147 $cm^{-1}$; $\Delta\varepsilon_{max.}$ −0.897 (240 nm); $\delta_H$ 0.91 (3 H, s, 13β-Me), 3.77 (3 H, s, 3-OMe), 6.23 (1 H, d, *J* 7 Hz, 16-H), 6.57—7.17 (3 H, m, 1-, 2-, and 4-H), 7.33 (1 H, d, *J* 7 Hz, 15-H), and 7.53—8.1 (5 H, m, $SO_2Ph$) (Found: C, 72.0; H, 6.6; S, 7.0%; $M^+$, 450. $C_{27}H_{30}O_4S$ requires C, 72.0; H, 6.7; S, 7.1%; *M*, 450).

3-*Methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*yl Acetate* (**6**).—(*a*) Sodium amalgam (6%; 31.5 g) was added to a stirred solution of the 17β-acetoxy sulphone (**3**) (2 g, 4.06 mmol) and anhydrous disodium hydrogen phosphate (2.33 g, 15.4 mmol) in anhydrous methanol–THF (4:1) (50 ml) at −20 °C under argon. The reaction mixture was stirred at −20 °C for 3 h, then quenched by the addition of water (40 ml). The solution was decanted and the amalgam was washed successively with water and ethyl acetate. Extraction of the combined solution and washings with ethyl acetate gave a crude product (1.42 g), which was was stirred with toluene-*p*-sulphonic acid (50 mg) in acetic anhydride (15 ml) at 25 °C for 16 h, then quenched by the addition of ice and solid sodium hydrogen carbonate. The mixture was extracted with benzene, and the extract was washed with saturated aqueous sodium hydrogen carbonate (3 × 50 ml) and water, dried ($Na_2SO_4$), and evaporated under reduced pressure to give 3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*yl acetate* (**6**) (1.19 g, 83%), m.p. 119—121 °C (from methanol); $[\alpha]_D$ +95.7° (*c* 1.11); $\nu_{max.}$ 1 720 $cm^{-1}$; $\delta_H$(500 MHz) 0.91 (3 H, s, 13β-Me), 1.22 (1 H, ddd, *J* 13.2, 3.9, and 3.3 Hz, 12β-H), 1.3 (1 H, ddt, *J* 2 × 13.1, 12.2, and 3.9 Hz, 11β-H), 1.42 (1 H, ddd, *J* 11.5, 11.4, and 2.5 Hz, 8β-H), 2.08 (3 H, s, 17β-OAc), 2.08 (1 H, ddd, *J* 13.2, 13.1, and 3.9 Hz, 12α-H), 2.21 (1 H, dddd, *J* 13.1, 3.9, 3.5, and 3.3 Hz, 11α-H), 2.45 (1 H, ddd, *J* 12.2, 11.4, and 3.5 Hz, 9α-H), 2.86 (2 H, m, 6α- and 6β-H), 3.76 (3 H, s, 3-OMe), 5.98 and 6.28 (each 1 H, d, *J* 6.1 Hz, $17^1$- and $17^2$-H), 6.62 (1 H, d, *J* 2.8 Hz, 4-H), 6.7 (1 H, dd, 8.6 and 2.8 Hz, 2-H), and 7.2 (1 H, d, *J* 8.6 Hz, 1-H); $\delta_C$ (125 MHz) 170.8 (s, 17β-O*C*OCH$_3$), 157.4 (s, C-3), 137.9 (s, C-5), 133.2 and 133.1 (each d, C-$17^1$ and C-$17^2$), 132.5 (s, C-10), 127.0 (d, C-1), 113.7 (d, C-4), 111.7 (d, C-2), 94.2 (s, C-17), 58.4 (s, C-13), 55.15 (q, 3-OCH$_3$), 54.7 (s, C-14), 40.2 and 39.5 (each d, C-8 and C-9), 30.2, 29.7, 28.6, 28.4, 27.2, and 23.9 (each t, C-6, C-7, C-11, C-12, C-15, and C-16), 21.5 (q, 17β-OCO*C*H$_3$), and 14.5 (q, C-18) (Found: C, 78.55; H, 8.3%; $M^+$, 352. $C_{23}H_{28}O_3$ requires C, 78.4; H, 8.0%; *M* 352). Chromatography of the mother liquor residue on silica gel (15 g) with benzene–ethyl acetate (19:1) gave further (**6**) (146 mg, 10.2%) followed by unreacted material (**3**) (20 mg, 1%).

Treatment of (**6**) (5.23 g) in THF (30 ml) with methanolic M-potassium hydroxide (100 ml) for 1 h at 25 °C gave 3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*ol* (**7**) (4.42 g; 96%), m.p. 151—152 °C (from benzene–hexane); $[\alpha]_D$ +143° (*c* 1.09); $\nu_{max.}$ 3 590 and 3 430br $cm^{-1}$; $\delta_H$(500 MHz) 0.88 (3 H, s, 13β-Me), 1.64 (1 H, m, exch. by $D_2O$, 17β-OH), 2.45 (1 H, dt, *J* 2 × 11.6, and 3.8 Hz, 9α-H), 2.85, (2 H, m, 6α- and 6β-H), 3.76 (3 H, s, 3-OMe), 5.91 and 5.95 (each 1 H, d, *J* 6.1 Hz, $17^1$- and $17^2$-H), 6.62 (1 H, d, *J* 2.9 Hz, 4-H), 6.7 (1 H, dd, *J* 8.6 and 2.9 Hz, 2-H), and 7.21 (1 H, d, *J* 8.6 Hz, 1-H) (Found: C, 81.4; H, 8.7%; $M^+$, 310. $C_{21}H_{26}O_2$ requires C, 81.25; H, 8.4%; *M*, 310). The mother-liquor residue was adsorbed on silica gel (23 g), and elution with benzene–ethyl acetate (19:1) gave further (**7**) (130 mg, 2.8%). The mother-liquor residue contained compound (**9**) as an impurity, which could not be detected or separated chromatographically, but was isolated in subsequent experiments carried out with the total chromatographic fraction of (**6**) + (**8**).

(*b*) Sodium amalgam (6%, 3.1 g) was added to a stirred solution of the sulphone (**3**) (200 mg, 0.406 mmol) and anhydrous disodium hydrogen phosphate (233 mg, 1.64 mmol) in anhydrous methanol–THF (4:1) (5 ml) at −20 °C under argon. The reaction mixture was stirred at −20 °C for 3 h, then quenched by the addition of water (5 ml). The solution was decanted and the amalgam residue was washed successively with water and ethyl acetate. Extraction with ethyl acetate gave a crude product (140 mg), which was chromatographed on silica gel (15 g), with toluene–ethyl acetate as eluant, to give the acetate (**6**) [+(**8**)] (133 mg) and the derived alcohol (**7**) [+(**9**)] (6 mg).

(*c*) Sodium amalgam (6%, 17.5 g) was added to a stirred solution of the sulphone (**3**) (794 mg, 1.61 mmol) and disodium hydrogen phosphate (915 mg, 6.45 mmol) in anhydrous ethanol (140 ml) at −20 °C under argon. After 2 h at −20 °C, further sodium amalgam (6%; 3.5 g) was added to the reaction mixture, which was stirred at −20 °C for a further 1 h and then at 0 °C for 21 h. Water (140 ml) was added and the mixture was stirred at 20 °C for 0.5 h and then decanted. The amalgam was washed successively with water and ethyl acetate, and the product was isolated by extraction with ethyl acetate. The residue (503 mg) was treated with acetic anhydride (9 ml) and toluene-*p*-sulphonic acid (100 mg) at 25 °C for 16 h. Ice and solid sodium

hydrogen carbonate were added, and the product was isolated by extraction with benzene, and chromatographed on silica gel (60 g), with benzene–ethyl acetate (19:1) as eluant, to give the 17β-acetate (**6**) [+(**8**)] (308 mg, 54%), followed by mixed fractions (61 mg) and 3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*yl acetate* (**10**) (81 mg, 14%), m.p. 122—124 °C(from methanol); $[\alpha]_D$ +34° (*c* 0.97); $\nu_{max.}$ 1 720 $cm^{-1}$; $\delta_H$(500 MHz) 0.92 (3 H, s, 13β-Me), 2.0 (3 H, s, 17β-OAc), 2.61 (1 H, dt, *J* 2 × 11.6, and 4.3 Hz, 9α-H), 2.83 (2 H, m, 6α- and 6β-H), 3.75 (3 H, s, 3-OMe), 6.61 (1 H, d, *J* 2.8 Hz, 4-H), 6.7 (1 H, dd, *J* 8.5 and 2.8 Hz, 2-H), and 7.21 (1 H, d, *J* 8.5 Hz, 1-H) (Found: C, 77.6; H, 8.8%; $M^+$, 354. $C_{23}H_{30}O_3$ requires C, 77.9; H, 8.5%; *M*, 354).

Treatment of (**10**) (450 mg, 1.27 mmol) in THF (3 ml) with methanolic 1M-potassium hydroxide (13 ml) at 25 °C under argon for 16 h, followed by extraction of the acidified reaction mixture with ethyl acetate gave a product (424 mg), which was crystallised from methanol to give 3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*ol* (**11**) (330 mg; 83%), m.p. 120.5—121 °C; $[\alpha]_D$ +46° (*c* 0.99); $\nu_{max.}$ 3 395br $cm^{-1}$; $\delta_H$(500 MHz) 0.89 (3 H, s, 13β-Me), 2.6 (1 H, dt, *J* 2 × 11.6, and 4.3 Hz, 9α-H), 2.83 (2 H, m, 6α- and 6β-H), 3.76 (3 H, s, 3-OMe), 6.61 (1 H, d, *J* 2.9 Hz, 4-H), 6.7 (1 H, dd, *J* 8.6 and 2.9 Hz, 2-H), and 7.21 (1 H, dd, *J* 8.6 and 0.6 Hz, 1-H) (Found: C, 80.7; H, 9.1%; $M^+$, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0%; *M*, 312). Chromatography of the mother-liquor residue on silica gel (4.5 g) with benzene–ethyl acetate (9:1) gave further (**11**) (56 mg, 14%).

(*d*) The sulphone (**3**) (200 mg; 0.4 mmol) was reduced with sodium amalgam as described in (*a*), but at 25 °C. Chromatography of the product on silica gel (20 g), with benzene–ethyl acetate (19:1) as eluant, gave the 14,17α-etheno-17β-ol (**7**) [+(**9**)] (23 mg, 18%), followed by 3-*methoxy*-14-(2-*phenylsulphonylethyl*)-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**12**) (57 mg; 31%), m.p. 81—83 °C (from ether–hexane); $[\alpha]_D$ +20° (*c* 0.76); $\nu_{max.}$ 1 728, 1 312, and 1 150 $cm^{-1}$; $\delta_H$ 0.87 (3 H, s, 13β-Me), 3.77 (3 H, s, 3-OMe), 6.58—7.34 (3 H, m, 1-, 2-, and 4-H), and 7.5—8.05 (5 H, m, $SO_2Ph$) (Found: C, 71.8; H, 7.3; S, 6.9%; $M^+$, 452. $C_{27}H_{32}O_4S$ requires C, 7.17; H, 7.1; S, 7.1%; *M*, 452).

*Catalytic Hydrogenation of Compound* (**7**) [+(**9**)]; *Isolation of the* 16α,17¹-*Cyclo Compound* (**9**).—The 14,17α-etheno compound (**7**) [+(**9**)] (61.2 mg, 0.2 mmol) in ethyl acetate (6 ml) was shaken in hydrogen in the presence of palladium–charcoal (5%, 20 mg) at 25 °C, until hydrogen uptake ceased (*ca.* 2 h). The filtered mixture was evaporated under reduced pressure, and the residue was chromatographed on silica gel (7 g), with benzene–ethyl acetate (9:1) as eluant, to give the 16α,17¹-cyclo compound (**9**) (3 mg) followed by the 14,17α-ethano compound (**11**) (56 mg). (17¹*R*)-3-*Methoxy*-14,17α-*ethano*-16α,17¹-*cycloestra*-1,3,5(10)-*trien*-17β-*ol* (**9**) had m.p. 133—134 °C (from benzene–hexane); $[\alpha]_D$ +104° (*c* 0.95); $\nu_{max.}$ 3 600, 3 430br, 3 055, 1 030, and 850 $cm^{-1}$; $\delta_H$(500 MHz) 0.9 (3 H, s, 13β-Me), 1.03 and 1.28 (each 1 H, ddd, *J* 6.1, 1.5, and 1.2 Hz, 16- and 17¹-H), 1.45 and 1.49 (each 1 H, dd, *J* 10.0 and 1.2 Hz, 15α- and *endo*-17²-H), 1.54 (1 H, s, exch. by $D_2O$, 17-OH), 1.77 and 1.84 (each 1 H, dt, *J* 10.0, and 2 × 1.5 Hz, 15β- and *exo*-17²-H), 2.28 (1 H, m, 9α-H), 2.8 (2 H, m, 6α- and 6β-H), 3.76 (3 H, s, 3-OMe), 6.6 (1 H, d, *J* 2.8 Hz, 4-H), 6.71 (1 H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.28 (1 H, d, *J* 8.6 Hz, 1-H); $\delta_C$ (125 MHz) 157.4 (s, C-3), 137.9 (s, C-5), 132.5 (s, C-10), 126.7 (d, C-1), 113.8 (d, C-4), 111.65 (d, C-2), 80.6 (s, C-17), 55.2 (q, 3-$OCH_3$), 43.2 (s, C-14), 43.0 (d, C-9), 37.0 (s, C-13), 35.4 (d, C-8), 36.9, 34.9, 29.9, 28.5, 27.1, and 23.6 (each t, C-6, C-7, C-11, C-12, C-15, and C-17²), 15.2 and 12.9 (each d, C-16 and C-17¹), and 14.4 (q, C-18) (Found: C, 81.2; H, 8.7%; $M^+$, 310. $C_{21}H_{26}O_2$ requires C, 81.25; H, 8.4%; *M*, 310).

Treatment of compound (**9**) with toluene-*p*-sulphonic acid (5 mg) in acetic anhydride (2 ml) afforded the corresponding 17β-*acetate* (**8**), m.p. 106—107 °C (from methanol); $[\alpha]_D$ +86.4° (*c* 1.0); $\nu_{max.}$ 3 050, 1 730, 1 073, and 857 $cm^{-1}$; $\delta_H$(500 MHz) 0.93 (3 H, s, 13β-Me), 1.1 and 1.33 (each 1 H, ddd, *J* 6.2, 1.5, and 1.2 Hz, 16- and 17¹-H), 1.12 (1 H, dddd, *J* 12.7, 12.2, 11.8, and 5.9 Hz, 11β-H), 1.75 and 1.89 (each 1 H, dt, *J* 10.2, and 2 × 1.5 Hz, 15β- and *exo*-17²-H), 1.83 (1 H, dt, *J* 2 × 11.4, and 2.3 Hz, 8β-H), 2.01 (3 H, s, 17β-OAc), 2.15 and 2.16 (each 1 H, dd, *J* 10.2 and 1.2 Hz, 15α- and *endo*-17²-H), 2.28 (1 H, ddd, *J* 11.8, 11.4, and 3.9 Hz, 9α-H), 2.36 (1 H, dddd, 12.7, 3.9, 3.5, and 2.7 Hz, 11α-H), 2.8 (2 H, m, 6α- and 6β-H), 3.76 (3 H, s, 3-OMe), 6.61 (1 H, d, *J* 2.8 Hz, 4-H), 6.71 (1 H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.23 (1 H, d, *J* 8.6 Hz, 1-H); $\delta_C$(125 MHz), 170.7 (s, 17β-O*C*OCH$_3$), 157.45 (s, C-3), 137.9 (s, C-5), 132.4 (s, C-10), 126.7 (d, C-1), 113.8 (d, C-4), 111.7 (d, C-2), 85.2 (s, C-17), 55.2 (q, 3-$OCH_3$), 44.8 (s, C-14), 42.9 and 35.0 (each d, C-8 and C-9), 32.7 (s, C-13), 33.1, 30.5, 29.9, 29.3, 27.1, and 23.7 (each t, C-6, C-7, C-11, C-12, C-15, and C-17²), 21.6, (q, 17β-OCO*C*H$_3$), 14.8 and 14.7 (each d, C-16 and C-17¹), and 13.2 (q, C-18) (Found: C, 78.2; H, 7.9%; $M^+$, 352. $C_{23}H_{28}O_3$ requires C, 78.4; H, 8.0%; *M*, 352).

*Deprotection of the* 3-*Methyl Ethers* (**7**), (**9**), *and* (**11**).—(*a*) Di-isobutyl aluminium hydride (1.2M in toluene; 1.2 ml, 1.44 mmol) was added to a stirred solution of the 3-methyl ether (**7**) (124 mg, 0.4 mmol) in anhydrous toluene (6 ml) under argon, and the mixture was refluxed for 24 h. Hydrochloric acid (10%; 5 ml) was added to the cooled mixture, and the product was isolated by extraction with ethyl acetate. Chromatography of the residue (120 mg) on silica gel (10 g), with chloroform–methanol (19:1) as eluant, gave starting material (**7**) (5.4 mg; 4.4%) followed by 14,17α-*ethenoestra*-1,3,5(10)-*triene*-3,17β-*diol* (**13**) (107 mg; 91%), m.p. 228—229 °C (from benzene–ethyl acetate); $[\alpha]_D$ +140° (*c* 0.92, THF); $\nu_{max.}$(Nujol) 3 320br $cm^{-1}$ (Found: C, 81.0; H, 8.5%; $M^+$, 296. $C_{20}H_{24}O_2$ requires C, 81.0; H, 8.2%; *M*, 296).

(*b*) Similar treatment of the 3-methyl ether (**9**) (124.2 mg, 0.4 mmol), followed by chromatography of the product on silica gel (15 g), with benzene–ethyl acetate (4:1) as eluant, gave starting material (**9**) (5.6 mg; 4.5%) followed by (17¹*R*)-14,17α-*ethano*-16α,17¹-*cycloestra*-1,3,5(10)-*triene*-3,17β-*diol* (**14**) (108 mg; 91%), m.p. 239.5—240 °C (from benzene–ethyl acetate); $[\alpha]_D$ +124.5° (*c* 0.54, THF); $\nu_{max.}$(Nujol) 3 450 and 3 330br $cm^{-1}$ (Found: C, 80.9; H, 8.2%; $M^+$, 296. $C_{20}H_{24}O_2$ requires C, 81.0; H, 8.2%; *M*, 296).

(*c*) Similar treatment of the 3-methyl ether (**11**) (129 mg, 0.41 mmol), followed by chromatography of the product on silica gel (10 g), with chloroform–methanol (19:1) as eluant, gave starting material (5.8 mg, 4.5%) followed by 14,17α-*ethanoestra*-1,3,5(10)-*triene*-3,17β-*diol* (**15**) (111 mg; 90%), m.p. 240—241 °C (from chloroform–methanol); $[\alpha]_D$ +46° (*c* 1.02, THF); $\nu_{max.}$(Nujol) 3 450 and 3 320br $cm^{-1}$ (Found: C, 80.75; H, 8.9%; $M^+$, 298. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.8%; *M*, 298).

*Hydroxylation of the* 14,17α-*Etheno-compounds* (**6**) *and* (**7**).—(*a*) Osmium tetraoxide (500 mg, 1.97 mmol) was added to a stirred solution of the compound (**6**) [containing unseparated (**8**)] (554.6 mg, 1.57 mmol) in anhydrous pyridine (30 ml), and the mixture was stirred at 25 °C for 20 h. Aqueous sodium hydrogen sulphite (10%; 70 ml) was added slowly (15 min) to the cooled (*ca.* 2 °C) reaction mixture, and stirring was continued for 2 h. Extraction with ethyl acetate gave a crude product (697 mg), which was chromatographed on deactivated silica gel (70 g), with benzene–ethyl acetate (1:1) as eluant, to give the 16α,17²-cyclo compound (**8**) (39 mg, 7%), followed by (17¹S,-17²S)-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-17β,17¹,-17²-*triol* 17-*acetate* (**16**) (189.5 mg; 31.2%), m.p. 169—171 °C (from dichloromethane–hexane); $[\alpha]_D$ +35° (*c* 1.0); $\nu_{max.}$ 3 410 and 1 708 $cm^{-1}$; $\delta_H$(500 MHz) 1.01 (3 H, s, 13β-Me), 2.1 (3 H, s, 17β-OAc), 2.79obsc. (1 H, m, 9α-H), 2.8 (2 H, m, 6α- and 6β-H), 3.34 (1 H, d, *J* 4.7 Hz, exch. by $D_2O$, 17¹-OH), 3.76 (3 H, s, 3-OMe), 4.27 (1 H, dd, *J* 9.4 and 1.9 Hz, 17²-H), 4.49 [1 H, ddd, *J* 9.4, 4.7 (exch.), and 1.9 Hz, 17¹-H), 5.11 (1 H, s, exch. by $D_2O$,

17²-OH), 6.61 (1 H, d, *J* 2.7 Hz, 4-H), 6.69 (1 H, dd, *J* 8.4 and 2.7 Hz, 2-H), and 7.17 (1 H, d, *J* 8.4 Hz, 1-H) (Found: C, 71.2; H, 7.8%; $M^+$, 386. $C_{23}H_{30}O_5$ requires C, 71.5; H, 7.8%; *M*, 386) and (17¹*R*, 17²*R*)-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-17β,17¹,17²-*triol* 17-*acetate* (**17**) (357 mg; 58.7%), m.p. 187—189 °C (from ether–hexane); $[\alpha]_D$ +25° (*c* 1.0); $\nu_{max.}$ 3 400br and 1 720 $cm^{-1}$; $\delta_H$(500 MHz) 0.94 (3 H, s, 13β-Me) 2.11 (3 H, s, 17β-OAc) 2.87 (2 H, m, 6α- and 6β-H), 2.98 (1 H, d, *J* 5.9 Hz, exch. by $D_2O$, 17¹-OH), 3.1 (1 H, d, *J* 5.5 Hz, exch. by $D_2O$, 17²-OH), 3.52 (1 H, dt, *J* 2 × 11.7, and 4.9 Hz, 9α-H), 3.75 (3 H, s, 3-OMe), 4.08 [1 H, dd, *J* 7.4 and 5.5(exch.) Hz, 17²-H)], 4.57 [1 H, dd, *J* 7.4 and 5.9 (exch.) Hz, 17¹-H], 6.62 (1 H, d, *J* 2.7 Hz, 4-H), 6.68 (1 H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.15 (1 H, d, *J* 8.6 Hz, 1-H) (Found: C, 71.4; H, 8.0%; $M^+$, 386. $C_{23}H_{30}O_5$ requires C, 71.5; H, 7.8%; *M*, 386).

(*b*) Compound (**7**) [containing unseparated (**9**)] (1,5 g, 4.83 mmol) in dry pyridine (190 ml) was treated with osmium tetraoxide (1.5 g, 5.9 mmol) for 20 h at 25 °C. The product was worked up, as described in the foregoing experiment, and chromatographed on silica gel (180 g), with benzene–ethyl acetate (1:3) as eluant, to give the 16α,17¹-cyclo compound (**9**) (69 mg, 4.6%) followed by (17¹R,17²R)-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-17β,17¹,17²-*triol* (**18**) (398 mg, 24%), m.p. 205—207 °C (from aqueous acetonitrile); $[\alpha]_D$ +49° (*c* 1.1 in THF); $\nu_{max.}$ 3 350br $cm^{-1}$; $\delta_H$(500 MHz), 0.92 (3 H, s, 13β-Me), 1.63br (2 H, m, exch. by $D_2O$, 17¹- and 17²-OH), 2.84br (1 H, m, exch. by $D_2O$, 17β-OH), 3.45 (1 H, dt, *J* 2 × 11.6, and 4.9 Hz, 9α-H), 3.75 (3 H, s, 3-OMe), 3.77 and 4.09 (each 1 H, d, *J* 7.3 Hz, 17¹- and 17²-H), 6.62 (1 H, d, *J* 2.8 Hz, 4-H), 6.68 (1 H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.15 (1 H, d, *J* 8.6 Hz, 1-H) (Found: C, 72.9; H, 8.1%; $M^+$, 344. $C_{21}H_{28}O_4$ requires C, 73.2; H, 8.1%; *M*, 344), and (17¹S,17²S)-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-17β,17¹,17²-*triol* (**19**) (1.09 g, 65.5%), m.p. 217—219 °C (from aqueous acetonitrile); $[\alpha]_D$ + 49° (*c* 1.0 in THF); $\nu_{max.}$ 3 360br $cm^{-1}$; $\delta_H$(500 MHz) 0.99 (3 H, s, 13β-Me), 1.60br (2 H, m, exch. by $D_2O$, 17¹- and 17²-OH), 2.52br (1 H, m, exch. by $D_2O$, 17β-OH), 2.69 (1 H, dt, *J* 2 × 11.4, and 4.7 Hz, 9α-H), 3.75 (3 H, s, 3-OMe), 4.14 (1 H, dd, *J* 9.3 and 2.2 Hz, 17²-H), 4.39 (1 H, dd, *J* 9.4 and 1.1 Hz, 17¹-H), 6.6 (1 H, d, *J* 2.8 Hz, 4-H), 6.69 (1 H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.19 (1 H, d, *J* 8.6 Hz, 1-H) (Found: C, 73.0; H, 8.2%; $M^+$, 344. $C_{21}H_{28}O_4$ requires C, 73.2; H, 8.2%; *M*, 344).

(*c*) Osmium tetraoxide (0.5 g, 1.97 mmol) was added to a stirred solution of compound (**7**) (6.08 g, 19.6 mmol) and 4-methylmorpholine-4-oxide monohydrate (5.325 g, 39.4 mmol) in THF (100 ml) and water (10 ml) at 25 °C. After 5 days, further 4-methylmorpholine-4-oxide monohydrate (5.325 g, 39.4 mmol) and osmium tetraoxide (0.1 g, 0.4 mmol) were added. After a further 5 days, water (10 ml) was added followed by solid sodium hydrogen sulphite (4.5 g), and stirring was continued for 0.75 h. Extraction of the mixture with ethyl acetate, and chromatography of the product (8.6 g) on silica gel (550 g), with toluene–ethyl acetate (1:1 ⟶ 1:3) as eluant, gave compounds (**9**) (293 mg, 4.8%), (**18**) (1.496 g, 22.6%), and (**19**) (4.1 g, 60%).

17β-*Acetoxy*-3-*methoxyestra*-1,3,5(10)-*triene*-14,17α-*dicarbaldehyde* (**20**).—Aqueous sodium periodate (6%; 40 ml) was added to a stirred solution of the 17β-acetoxy-17¹,17²-diols (**16**) and (**17**) (923 mg, 2.39 mmol) in absolute ethanol (90 ml), and the reaction mixture was stirred at 25 °C for 45 min. Extraction with chloroform gave a crystalline residue, which was recrystallised from chloroform–hexane to give 17β-*acetoxy*-3-*methoxyestra*-1,3,5(10)-*triene*-14,17α-*dicarbaldehyde* (**20**) (914 mg, 99.5%), m.p. 155—157 °C; $[\alpha]_D$ +41° (*c* 0.9); $\nu_{max.}$ 1 715br $cm^{-1}$; $\delta_H$ 1.23 (3 H, s, 13β-Me), 2.07 (3 H, s, 17β-OAc), 3.74 (3 H, s, 3-OMe), 6.50—7.27 (3 H, m, 1-, 2-, and 4-H), 9.38 (1 H, s, 17α-CHO), and 9.99 (1 H, s, 14α-CHO) (Found: C, 72.0; H, 7.5%; $M^+$, 384. $C_{23}H_{28}O_5$ requires C, 71.85; H, 7.3%; *M* 384).

3-*Methoxy*-17-*oxoestra*-1,3,5(10)-*triene*-14-*carbaldehyde* (**21**).—Aqueous sodium periodate (6%; 126 ml) was added to a stirred solution of the 17β,17¹,17²-triols (**18**) and (**19**) (2.53 g, 7.35 mmol) in absolute ethanol (200 ml) and the reaction mixture was stirred at 25 °C for 1 h. Extraction with ethyl acetate gave a crystalline residue which was recrystallised from methanol to give 3-*methoxy*-17-*oxoestra*-1,3,5(10)-*triene*-14-*carbaldehyde* (**21**) (1.17 g, 51%), m.p. 171—173 °C; $[\alpha]_D$ +140° (*c* 1.0); $\nu_{max.}$ 1 742 and 1 714 $cm^{-1}$; $\Delta\varepsilon_{max.}$ −1.556 (315 nm) and +0.685 (273 nm); $\delta_H$(500 MHz) 1.03 (3 H, s, 13β-Me), 1.77 (1 H, ddd, *J* 13.8, 4.9, and 2.2 Hz, 12β-H), 2.92 (2 H, m, 6α- and 6β-H), 3.77 (3 H, s, 3-OMe), 6.63 (1 H, d, *J* 2.8 Hz, 4-H), 6.72 (1 H, dd, *J* 8.5 and 2.8 Hz, 2-H), 7.18 (1 H, d, *J* 8.5 Hz, 1-H), and 9.9 (1 H, s, 14α-CHO); $\delta_C$(125 MHz) 215.8 (s, C-17), 203.5 (d, C-14¹), 157.9 (s, C-3), 137.3 (s, C-5), 131.2 (s, C-10), 127.1 (d, C-1), 113.8 (d, C-4), 112.0 (d, C-2), 59.5 (s, C-14), 55.15 (q, 3-$OCH_3$), 50.4, (s, C-13), 40.4 and 40.2 (each d, C-8 and C-9), 32.0 (t, C-16), 30.6, 26.6, 23.0, and 22.55 (each t, C-6, C-7, C-11, C-12, and C-15), and 17.5 (q, C-18) (Found: C, 76.8; H, 7.7%; $M^+$, 312. $C_{20}H_{24}O_3$ requires C, 76.9; H, 7.7%; *M*, 312). The mother-liquor residue was adsorbed on silica gel (100 g), and elution with benzene–ethyl acetate (9:1) gave further (**21**) (550 mg, 24%).

*Thioacetalisation of the* 14-*Formyl*-17-*ketone* (**21**).—(*a*) Boron trifluoride–diethyl ether (141 μl, 1.2 mmol) was added to a stirred solution of the formyl ketone (**21**) (312.5 mg, 1.0 mmol) and ethane-1,2-dithiol (841.1 μl, 10 mmol) in glacial acetic acid (10 ml) at 25 °C under argon. The reaction mixture was stirred for 30 h, then quenched by addition of water (10 ml). The mixture was extracted with ethyl acetate, and the extract was washed with saturated aqueous sodium hydrogen carbonate (2 × 50 ml), dried ($Na_2SO_4$), and evaporated under reduced pressure. Chromatography of the residue (409 mg) on silica gel (50 g), with benzene and benzene–ethyl acetate (19:1) as eluants, gave 17,17-(*ethylenedithio*)-3-*methoxyestra*-1,3,5(10)-*triene*-14-*carbaldehyde* 17,17-*ethylenedithioacetal* (**22**) (62 mg, 16%), m.p. 219—220 °C (from benzene–hexane); $[\alpha]_D$ −81.2° (*c* 0.97); $\nu_{max.}$ 1 695 $cm^{-1}$; $\delta_H$ 1.21 (3 H, s, 13β-Me), 3.77 (3 H, s, 3-OMe), 6.53—7.4 (3 H, 1-, 2-, and 4-H), and 10.56br (1 H, s, $W_{\frac{1}{2}}$ 3 Hz, 14¹-H) (Found: C, 68.2; H, 7.2; S, 16.3%; $M^+$, 388. $C_{22}H_{28}O_2S_2$ requires C, 68.0; H, 7.3; S, 16.5%; *M*, 388) followed by 14-[14′,14′-(*ethylenedithio*)*methyl*]-3-*methoxyestra*-1,3,5-(10)-*trien*-17-*one* as a colourless foam (285 mg, 73.3%), $[\alpha]_D$ +135° (*c* 0.99); $\nu_{max.}$ 1 726 $cm^{-1}$; $\Delta\varepsilon_{max.}$ +0.5 (303 nm), −1.695 (264 nm), and +2.137 (240 nm); $\delta_H$ 1.13 (3 H, s, 13β-Me), 3.78 (3 H, s, 3-OMe), 5.26 (1 H, s, 14¹-H), and 6.57—7.33 (3 H, m, 1-, 2-, and 4-H) (Found: C, 68.2; H, 7.5; S, 16.2%; $M^+$ 388. $C_{22}H_{28}O_2S_2$ requires C, 68.0; H, 7.3; S, 16.5%; *M*, 388).

(*b*) Boron trifluoride–diethyl ether (25 μl, 0.24 mmol) was added to a stirred solution of the formyl ketone (**21**) (100 mg, 0.32 mmol) and ethane-1,2-dithiol (33 μl, 0.38 mmol) in dry methanol at 25 °C under argon. The mixture was stirred for 22 h, water was added, and the product was isolated by extraction with ethyl acetate. Chromatography on silica gel (10 g), with benzene–ethyl acetate (49:1) as eluant, gave 3,14¹ξ,17β-*trimethoxy*-17α,14-*epoxymethanoestra*-1,3,5(10)-*triene* (**24**) (83 mg, 72.5%), m.p. 143—144 °C (from methanol); $[\alpha]_D$ +17.6° (*c* 0.97); $\delta_H$ 0.97 (3 H, s, 13β-Me), 3.5 and 3.52 (each 3 H, s, 14¹- and 17-OMe), 3.81 (3 H, s, 3-OMe), 5.39br (1 H, s, $W_{\frac{1}{2}}$ 4 Hz, 14¹-H), and 6.6—7.42 (3 H, m, 1-, 2-, and 4-H); $\delta_C$(125 MHz) 157.5 (s, C-3), 137.7 (s, C-5), 132.5 (s, C-10), 126.6 (d, C-1), 113.8 (d, C-4), 113.35 (s, C-17), 111.6 (d, C-2), 104.4 (d, C-14¹), 56.3 and 53.0 (each q, 14¹- and 17β-$OCH_3$), 55.1 (q, 3-$OCH_3$), 52.1 and 50.5 (each s, C-13 and C-14), 39.3 and 38.1 (each d, C-8 and C-9), 30.5, 30.2, 27.3, 26.4, 24.9, and 23.3 (each t, C-6, C-7, C-11, C-12, C-15, and C-16), and 15.3 (q, C-18) (Found: C, 73.4; H, 8.5%; $M^+$, 358. $C_{22}H_{30}O_4$ requires C, 73.3; H, 8.4%; *M*, 358).

3-*Methoxy*-14-*methylestra*-1,3,5(10)-*trien*-17-*one* (**25**).—A solution of the $14^1,14^1$-ethylenedithioacetal (**23**) (368.4 mg, 0.948 mmol) and Raney nickel (5 ml of a suspension in ethanol) in absolute ethanol (20 ml) was stirred at 25 °C for 1 h. The mixture was filtered, and the Raney nickel was thoroughly washed with ethyl acetate and methanol. The combined filtrate was concentrated under reduced pressure, and the residue (280 mg) was chromatographed on silica gel (30 g), with toluene–ethyl acetate (99:1) as eluant, to give 3-*methoxy*-14-*methylestra*-1,3,5(10)-*trien*-17-*one* (**25**) (178 mg, 63%), m.p. 139—141 °C (from benzene–hexane); $[\alpha]_D$ +113° (*c* 0.9); $\nu_{max.}$ 1 732 $cm^{-1}$; $\Delta\varepsilon_{max.}$ +2.46 (298 nm); $\delta_H$(500 MHz) 0.88 and 1.01 (each 3 H, s, 13β- and 14α-Me), 3.76 (3 H, s, 3-OMe), 6.62 (1 H, d, *J* 2.7 Hz, 4-H), 6.7 (1 H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.18 (1 H, dd, *J* 8.6 and 0.8 Hz, 1-H) (Found: C, 80.6; H, 8.9%; $M^+$, 298. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.8%; *M*, 298) followed by the 14-formyl-17-ketone (**21**) (27 mg; 9.2%).

14-*Hydroxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* (**26**) *and* (**27**).—Lithium tri(s-butyl)borohydride (M in THF; 11.2 ml) was added to a stirred solution of the formyl ketone (**21**) (2.91 g, 9.3 mmol) in anhydrous THF (150 ml) at 0 °C under argon. After 1 h at 0 °C, water (50 ml) was added, followed by a cold (0 °C) hydrogen peroxide (30%; 75 ml) and 6M sodium hydroxide (50 ml), and the mixture was stirred for a further 2 h. The product was extracted with ethyl acetate, and the extract was washed with aqueous sodium hydrogen carbonate, dried ($Na_2SO_4$), and evaporated under reduced pressure to give a crystalline residue, which was recrystallised from acetone–hexane to give 14-*hydroxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* (**26**) and (**27**) (2.804 g; 96%), m.p. 164—166 °C; $[\alpha]_D$ +73° (*c* 0.95 in THF); $\nu_{max.}$(pyridine) 3 170br and 1 730 $cm^{-1}$; $\nu_{max.}$(Nujol) 3 310br $cm^{-1}$; $\delta_H$(500 MHz; [$^2H_5$]pyridine) 1.07 ['1.2 H', s, 13β-Me of (**26**)], 1.14 ['1.8 H', s, 13β-Me of (**27**)], 3.65 ['0.6 H', d, *J* 7.3 Hz, *endo*-$14^1$-H of (**27**)], 3.79 (3 H, s, 3-OMe), 3.93 and 4.14 [each '0.4 H', d, *J* 11.2 Hz, $14^1$-$H_2$ of (**26**)], 4.32 ['0.6 H', dd, *J* 7.3 and 4.1 Hz, *exo*-$14^1$-H of (**27**)], 6.85 ['0.4 H', d, *J* 2.6 Hz, 4-H of (**26**)], 6.87 ['0.6 H', d, *J* 2.6 Hz, 4-H of (**27**)], 7.01 (1 H, dd, *J* 8.6 and 2.6 Hz, 2-H), 7.31 ['0.4 H', d, *J* 8.6 Hz, 1-H of (**26**)], and 7.35 ['0.6 H', d, *J* 8.6 Hz, 1-H of (**27**)] (Found: C, 76.4; H, 8.6%; $M^+$, 314. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.3%; *M*, 314).

14-*Acetoxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* (**28**).—A solution of the 14α-hydroxymethyl-17-ketone (**26**) (94.3 mg, 0.3 mmol) and acetic anhydride (2.84 ml, 30 mmol) in dry pyridine (3 ml) was stirred at 25 °C for 2 h. Ice and solid sodium hydrogen carbonate were added, and the product was extracted with ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate (3 × 10 ml), dried ($Na_2SO_4$), and evaporated to give 14-*acetoxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* (**28**) (102.4 mg, 96%), m.p. 149—150 °C (from methanol); $[\alpha]_D$ +91° (*c* 0.94); $\nu_{max.}$ 1 738br $cm^{-1}$; $\Delta\varepsilon_{max.}$ 1.67 (195 nm); $\delta_H$(500 MHz) 1.05 (3 H, s, 13β-Me), 2.01 (3 H, s, $14^1$-OAc), 3.76 (3 H, s, 3-OMe), 4.11 and 4.3 (each 1 H, d, *J* 12.1 Hz, $14^1$-$H_2$), 6.6 (1 H, d, *J* 2.8 Hz, 4-H), 6.7 (1 H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.16 (1 H, d, *J* 8.6 Hz, 1-H); $\delta_C$(125 MHz) 217.35 (s, C-17), 170.4 (s, $14^1$-O*C*OCH$_3$), 157.5 (s, C-3), 137.1 (s, C-5), 132.6 (s, C-10), 126.6 (d, C-1), 113.7 (d, C-4), 111.6 (d, C-2), 65.2 (t, C-$14^1$), 55.1 (q, 3-O*C*H$_3$), 51.8 and 45.95 (each s, C-13 and C-14), 41.8 and 37.3 (each d, C-8 and C-9), 33.9, 30.9, 26.1, 25.5, 24.9, and 24.4 (each t, C-6, C-7, C-11, C-12, C-15, and C-16), 20.8 (q, $14^1$-OCO*C*H$_3$), and 18.3 (q, C-18) (Found: C, 74.2; H, 7.8%; $M^+$, 356. $C_{22}H_{28}O_4$ requires C, 74.1; H, 7.9%; *M*, 356).

14-*Hydroxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* $14^1$-*methyl xanthate* (**29**).—Carbon disulphide (1.04 ml) was added to a stirred solution of the 14α-hydroxymethyl-17-ketone (**26**) (104.3 mg, 0.332 mmol) and 1,5-diazabicyclo[4.3.0]non-5-ene (160 μl, 1.35 mmol) in anhydrous DMF (1.04 ml). The reaction mixture was stirred for 30 min at 25 °C, methyl iodide (2.08 ml) was added, and stirring was continued for a further 30 min. Water was added, and the product was isolated by extraction with ethyl acetate and filtered through silica gel (10 g) with benzene–ethyl acetate (19:1) to give 14-*hydroxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* $14^1$-*methyl xanthate* (**29**) (130 mg; 97%), m.p. 148—149.5 °C (from methanol–diethyl ether); $[\alpha]_D$ +101° (*c* 1.05); $\nu_{max.}$ 1 737 and 1 068 $cm^{-1}$; $\delta_H$(500 MHz) 1.08 (3 H, s, 13β-Me), 2.55 (3 H, s, –SMe), 2.86 (2 H, m, 6α- and 6β-H), 3.76 (3 H, s, 3-OMe), 4.37 and 4.99 (each 1 H, d, *J* 12.0 Hz, $14^1$-$H_2$), 6.61 (1 H, d, *J* 2.9 Hz, 4-H), 6.7 (1 H, dd, *J* 8.6 and 2.9 Hz, 2-H), and 7.17 (1 H, d, *J* 8.6 Hz, 1-H) (Found: C, 65.0; H, 7.1; S, 15.6%; $M^+$, 404. $C_{22}H_{28}O_3S_2$ requires C, 65.3; H, 7.0; S, 15.7%; *M*, 404).

*Lithium Aluminium Hydride Reduction of the* 14α-*Formyl*-17-*ketone* (**21**).—Lithium aluminium hydride (486.4 mg, 12.8 mmol) was added in one portion to a stirred solution of the formyl ketone (**21**) (2.0 g, 6.4 mmol) in anhydrous THF (100 ml) at −10 °C under argon. The reaction mixture was allowed to warm to 25 °C over 3 h, then ethyl acetate was added, followed by water. The mixture was acidified and extracted into ethyl acetate. The extract was washed with water, dried ($Na_2SO_4$), and evaporated under reduced pressure, to give a product (2.2 g) which was chromatographed on silica gel (200 g), with benzene–ethyl acetate (1:1) as eluant, to give 14-*hydroxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17α-*ol* (**30**) (526 mg, 26%), m.p. 230—231 °C (from benzene–ethyl acetate); $[\alpha]_D$ +80° (*c* 0.98 in THF); $\nu_{max.}$(Nujol) 3 100br $cm^{-1}$; $\delta_H$(500 MHz; [$^2H_5$]pyridine) 0.92 (3 H, s, 13β-Me), 3.78 (3 H, s, 3-OMe), 4.03 and 4.63 (each 1 H, d, *J* 12.0 Hz, $14^1$-$H_2$), 4.19 (1 H, dd, *J* 7.1 and 1.3 Hz, 17β-H), 4.96br (1 H, m, exch. by $D_2O$, $14^1$-OH), 6.26br (1 H, m, exch. by $D_2O$, 17α-OH), 6.83 (1 H, d, *J* 2.8 Hz, 4-H), 6.96 (1 H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.35 (1 H, d, *J* 8.6 Hz, 1-H) (Found: C, 75.6; H, 8.8%; $M^+$, 316. $C_{20}H_{28}O_3$ requires C, 75.9; H, 8.9%; *M*, 316), followed by 14-*hydroxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17β-*ol* (**31**) (1.456 g, 72%), m.p. 192—194 °C (from benzene); $[\alpha]_D$ +99° (*c* 1.06 in THF); $\nu_{max.}$ 3 350br $cm^{-1}$; $\delta_H$(500 MHz; [$^2H_5$]pyridine) 1.3 (3 H, s, 13β-Me), 3.77 (3 H, s, 3-OMe), 4.03 and 4.24 (each 1 H, d, *J* 11.6 Hz, $14^1$-$H_2$), 4.8 (1 H, dd, *J* 8.8 and 6.8 Hz, 17α-H), 4.94br (1 H, m, exch. by $D_2O$, $14^1$-OH), 5.83br (1 H, m, exch. by $D_2O$, 17β-OH), 6.84 (1 H, d, *J* 2.8 Hz, 4-H), 6.97 (1 H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.38 (1 H, d, *J* 8.6 Hz, 1-H) (Found: C, 75.8; H, 8.7%; $M^+$, 316. $C_{20}H_{28}O_3$ requires C, 75.9; H, 8.9%; *M*, 316).

14-*Hydroxymethylestra*-1,3,5(10)-*triene*-3,17β-*diol* (**32**).—Diisobutylaluminium hydride (1.2M in toluene; 3.0 ml, 3.6 mmol) was added to a stirred solution of the 3-methyl ether (**31**) (108.5 mg, 0.34 mmol) in dry toluene (5 ml) under argon, and the mixture was refluxed for 40 h, cooled to room temperature, and quenched by the addition of hydrochloric acid (10%; 10 ml). Extraction with ethyl acetate and crystallisation of the residue from benzene–ethyl acetate gave 14-*hydroxymethylestra*-1,3,5(10)-*triene*-3,17β-*diol* (**32**) (76 mg, 73%), m.p. 243—245 °C; $[\alpha]_D$ +104° (*c* 0.51 in THF); $\nu_{max.}$(Nujol) 3 292br $cm^{-1}$ (Found: C, 75.2; H, 8.7%; *M*, 302. $C_{19}H_{26}O_3$ requires C, 75.5; H, 8.7%; *M*, 302). The mother-liquor residue was adsorbed on silica gel (4.5 g), and elution with benzene–ethyl acetate (1:1) gave further (**32**) (24 mg, 23%).

*Attempted Selective Oxidation of the* 14-*Hydroxymethyl*-17β-*ol* (**31**).—(*a*) Pyridinium chlorochromate (194 mg, 0.9 mmol) was added in portions during 1 h to a stirred suspension of the diol (**31**) (189.6 mg, 0.6 mmol) in anhydrous dichloromethane (19 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, then quenched by addition of propan-2-ol (0.2 ml). The reaction

mixture was filtered through a short column of silica gel and the filtrate was concentrated under reduced pressure. Chromatography of the residue (210 mg) on silica gel (30 g), with toluene–ethyl acetate (9:1) as eluant, gave, in order of elution, the 14-formyl-17-one (**21**) (63.5 mg; 34%), 17β-*hydroxy*-3-*methoxyestra*-1,3,5(10)-*triene*-14-*carbaldehyde* (**33**) (77 mg, 41%), m.p. 146—148 °C (from benzene–hexane); $[\alpha]_D$ +44° (*c* 0.96); $\nu_{max.}$ 3 600, 3 460br, and 1 705 $cm^{-1}$; $\Delta\varepsilon_{max.}$ −0.715 (310 nm); $\delta_H$(500 MHz) 0.99 (3 H, s, 13β-Me), 1.56 (1 H, s, exch. by $D_2O$, 17β-OH), 1.73 (1 H, ddt, *J* 13.1, 2 × 13.0, and 5.0 Hz, 11β-H), 1.96 (1 H, dt, *J* 2 × 12.3, and 2.5 Hz, 8β-H), 2.2 (1 H, dt, *J* 2 × 13.1, and 4.7 Hz, 12α-H), 2.52 (1 H, ddt, *J* 13.0, 2 × 4.7, and 2.2 Hz, 11α-H), 2.83 (3 H, m, 6α-, 6β-, and 9α-H), 3.76 (3 H, s, 3-OMe), 3.87 (1 H, t, *J* 7.8 Hz, 17α-H), 6.59 (1 H, d, *J* 2.7 Hz, 4-H), 6.71 (1 H, dd, *J* 8.6 and 2.7 Hz, 2-H), 7.2 (1 H, d, *J* 8.6 Hz, 1-H), and 10.15 (1 H, s, 14α-CHO) (Found: C, 76.3; H, 8.4%; $M^+$, 314. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.3%; *M*, 314), and the 14-hydroxymethyl-17-one (**26**) (31 mg, 16%).

(*b*) To a stirred solution of oxalyl chloride (18.3 μl, 0.21 mmol) in anhydrous THF (1 ml) at −78 °C, was added dimethyl sulphoxide (15.5 μl, 0.22 mmol). The solution was allowed to warm up to −35 °C for 3 min and then recooled to −78 °C. A solution of the diol (**31**) (63.3 mg, 0.2 mmol) in anhydrous THF was added to the reaction mixture. The resulting solution was allowed to warm to −35 °C for 30 min and to −20 °C for 30 min. Triethylamine (0.14 ml, 1 mmol) was added and the mixture was warmed to 25 °C, then quenched by the addition of water. The product was isolated by extraction with ethyl acetate and chromatographed on silica gel (10 g), with toluene–ethyl acetate (9:1) ⟶ (1:1) as eluant, to give, in order of elution, the 14-formyl-17-one (**21**) (15 mg, 24%), the 14-formyl-17β-ol (**33**) (13 mg, 21%), the 14-hydroxymethyl-17-one (**26**) (22 mg, 35%), and starting material (**31**) (8 mg, 12%).

16α-(*Phenylsulphonyl*)-14,17α-*ethenoestra*-1,3,5(10)-*triene*-3,17β-*diyl diacetate* (**35**).—A mixture of estra-1,3,5(10),14,16-pentaene-3,17-diyl diacetate (**34**)[20] (1.23 g, 3.49 mmol) and phenyl vinyl sulphone (1.77 g, 10.5 mmol) in dry benzene (4.6 ml) was heated in a sealed tube at 145 °C for 90 h. The reaction mixture was cooled to 25 °C and chromatographed directly on silica gel (180 g), with benzene–ethyl acetate (19:1) as eluant, to give 16α-(*phenylsulphonyl*)-14,17α-*ethenoestra*-1,3,5(10)-*triene*-3,17β-*diyl diacetate* (**35**) (1.5 g, 82.5%), m.p. 196—197 °C (from acetone–hexane); $[\alpha]_D$ +96° (*c* 0.95); $\nu_{max.}$ 1 748, 1 320, and 1 149 $cm^{-1}$; $\delta_H$ 0.91 (3 H, s, 13β-Me), 1.66 (3 H, s, 17β-OAc), 2.27 (3 H, s, 3-OAc), 4.23 (1 H, t, *J* 7 Hz, 16β-H), 6.19 and 6.46 (each 1 H, d, *J* 6 Hz, $17^1$- and $17^2$-H), 6.75—7.31 (3 H, m, 1-, 2-, and 4-H), and 7.46—8.05 (5 H, m, $PhSO_2$) (Found: C, 69.3; H, 6.2; S, 6.2%; $M^+$, 520. $C_{30}H_{32}O_6S$ requires C, 69.2; H, 6.2; S, 6.2%; *M*, 520).

14,17α-*Ethenoestra*-1,3,5(10)-*triene*-3,17β-*diyl diacetate* (**36**).—The sulphone (**35**) (1.045 g; 2.01 mmol) was treated with sodium amalgam, as described in the reduction of (**3**) [exp. (*a*)]. The crude product (690 mg) was treated with toluene-*p*-sulphonic acid (50 mg) in acetic anhydride (10 ml) at 20° for 16 h. Ice and solid sodium hydrogen carbonate were added and the product was extracted into benzene. The extract was washed with aqueous sodium hydrogen carbonate (3 × 50 ml), dried ($Na_2SO_4$), and evaporated. Chromatography of the residue on silica gel (100 g), with benzene–ethyl acetate (19:1) as eluant, gave 14,17α-*ethenoestra*-1,3,5(10)-*triene*-3,17β-*diyl diacetate* (**36**), m.p. 102—103.5 °C (from acetone–hexane); $[\alpha]_D$ +92° (*c* 0.95); $\nu_{max.}$ 1 750 and 1 735 $cm^{-1}$; $\delta_H$ 0.91 (3 H, s, 13β-Me), 2.08 (3 H, s, 17β-OAc), 2.27 (3 H, s, 3-OAc), 2.83 (2 H, m, 6α- and 6β-H), 5.96 and 6.29 (each 1 H, d, *J* 6 Hz, $17^1$- and $17^2$-H), and 6.66—7.4 (3 H, m, 1-, 2-, and 4-H) (Found: C, 75.8; H, 7.5%; $M^+$, 380. $C_{24}H_{28}O_4$ requires C, 75.8; H, 7.4%; *M*, 380).

*Hydroxylation of the* 14,17α-*Etheno-compound* (**36**).—Osmylation of compound (**36**) (2.24 g, 5.89 mmol), as described in previous experiments, followed by reductive work-up and chromatography of the product on silica gel (300 g), with benzene–ethyl acetate (4:1) as eluant, gave ($17^1$S,$17^2$S)-14,17α-*ethanoestra*-1,3,5(10)-*triene*-3,17β,$17^1$,$17^2$-*tetraol* 3,17β-*diacetate* (**37**) (654 mg; 27%), m.p. 195—197 °C (from acetone–hexane); $[\alpha]_D$ +31° (*c* 1.0); $\nu_{max.}$ 3 425br, 1 748, and 1 710 $cm^{-1}$; $\delta_H$ 1.04 (3 H, s, 13β-Me), 2.13 (3 H, s, 17β-OAc), 2.27 (3 H, s, 3-OAc), 2.88 (3 H, m, 6α-, 6β-, and 9α-H), 3.37 (1 H, d, *J* 5 Hz, exch. by $D_2O$, −OH), 4.31 and 4.51 (each 1 H, d, *J* 10 Hz, $17^1$- and $17^2$-H), 5.14 (1 H, s, exch. by $D_2O$, -OH), and 6.75—7.43 (3 H, m, 1-, 2-, and 4-H) (Found: C, 69.25; H, 7.0%; $M^+$, 414. $C_{24}H_{30}O_6$ requires C, 69.55; H, 7.3%; *M*, 414), followed by ($17^1$R,$17^2$R)-14,17α-*ethanoestra*-1,3,5(10)-*triene*-3,17β,$17^1$,$17^2$-*tetraol* 3; 17β-*diacetate* (**38**) (1.37 g, 56%), m.p. 199—200 °C (from acetone–hexane); $[\alpha]_D$ +22° (*c* 0.99); $\nu_{max.}$ 3 440br and 1 740 $cm^{-1}$; $\delta_H$ 0.96 (3 H, s, 13β-Me), 2.13 (3 H, s, 17β-OAc), 2.27 (3 H, s, 3-OAc), 2.93 (2 H, m, 6α- and 6β-H), 3.2 (2 H, m, exch. by $D_2O$, $17^1$- and $17^2$-OH), 3.62 (1 H, m, 9α-H), 4.1 and 4.6 (each 1 H, d, *J* 7.5 Hz, $17^1$- and $17^2$-H), and 6.77—7.41 (3 H, m, 1-, 2-, and 4-H) (Found: C, 69.55; H, 7.4%; $M^+$, 414. $C_{24}H_{30}O_6$ requires C, 69.55; H, 7.3%; *M* 414).

3,17β-*Diacetoxyestra*-1,3,5(10)-*triene*-14,17-*dicarbaldehyde* (**39**).—Aqueous sodium periodate (6%; 52 ml) was added to a stirred solution of the diols (**37**) and (**38**) (1.37 g, 3.31 mmol) in absolute ethanol (100 ml), and the reaction mixture was stirred at 25 °C for 1 h. Extraction with chloroform gave a crystalline residue, which was recrystallised from acetone–hexane to give 3,17β-*diacetoxyestra*-1,3,5(10)-*triene*-14,17-*dicarbaldehyde* (**39**) (839 mg, 62%), m.p. 184—185 °C; $[\alpha]_D$ +40° (*c* 1.0); $\nu_{max.}$ 1 740 $cm^{-1}$; $\delta_H$ 1.19 (3 H, s, 13β-Me), 2.03 (3 H, s, 17β-OAc), 2.27 (3 H, s, 3-OAc), 6.7—7.2 (3 H, m, 1-, 2-, and 4-H), 9.3 (1 H, s, 17α-CHO), and 9.93 (1 H, d, *J* 1 Hz, 14α-CHO) (Found: C, 70.1; H, 6.8%; $M^+$, 412. $C_{24}H_{28}O_6$ requires C, 69.9; H, 6.8%; *M*, 412).

3-*Hydroxy*-14-*hydroxymethylestra*-1,3,5(10)-*trien*-17-*one* (**40**) *and* (**41**).—A solution of the dialdehyde (**39**) (568 mg; 1.42 mmol) in anhydrous THF (20 ml) was added over 5 min to a stirred suspension of lithium aluminium hydride (539 mg; 14.2 mmol) in anhydrous THF (30 ml) at 0 °C under argon. The reaction mixture was stirred at 0 °C for 15 min, then at 25 °C for 6 h. Ethyl acetate was added, followed by water. The mixture was acidified and extracted with ethyl acetate to give the crude 14,17-bis(hydroxymethyl)-3,17β-diol as a crystalline residue (512 mg), $\nu_{max.}$(Nujol) 3 300br $cm^{-1}$ (Found: $M^+$, 332.1986. $C_{20}H_{28}O_4$ requires *M*, 332.1988). A solution of the product in absolute ethanol (40 ml) at 25 °C was treated with aqueous sodium metaperiodate (6%; 25 ml) for 1 h. Water was added and the product was isolated by extraction with ethyl acetate, and chromatographed on silica gel (46 g), with chloroform–methanol (49:1) as eluant, to give 3-*hydroxy*-14-*hydroxymethylestra*-1,3,5(10)-*trien*-17-*one* (**40**) and (**41**) (281 mg, 66%), m.p. 243—245 °C (from chloroform–methanol); $[\alpha]_D$ +74° (*c* 0.97 in THF); $\nu_{max}$ 3 450sh, 3 310br, and 1 720 $cm^{-1}$; $\delta_H$(500 MHz; [$^2H_5$]pyridine) 1.06 ['1.2 H', s, 13β-Me of (**40**)], 1.13 ['1.8 H', s, 13β-Me of (**41**)], 3.65 ['0.6 H', d, *J* 7.3 Hz, *endo*-$14^1$-H of (**41**)], 3.95 ['0.4 H', d, *J* 11.3 Hz, $14^1$-H of (**40**)], 4.15 ['0.4 H', d, *J* 11.3 Hz, $14^1$-H of (**40**)] 4.34 ['0.6 H', dd, *J* 7.3 and 4.0 Hz, *exo*-$14^1$-H of (**41**)], 5.06 (1 H, m, exch. by $D_2O$, 3-OH), 6.38 (1 H, m, exch. by $D_2O$, $14^1$-OH). 7.06 (1 H, d, *J* 1.2 Hz, 4-H), 7.16 (1 H, dd, *J* 8.5 and 1.2 Hz, 2-H), 7.31 ['0.4 H', d, *J* 8.5 Hz, 1-H of (**40**)] and 7.36 ['0.6 H', d, *J* 8.5 Hz, 1-H of (**41**)] (Found: C, 75.9; H, 8.2%; $M^+$, 300. $C_{19}H_{24}O_3$ requires C, 76.0; H, 8.05%; *M*, 300).

*Birch Reduction of the* 3-*Methyl Ethers* (**7**), (**9**), (**11**), *and* (**31**).—(*a*) A solution of the 3-methyl ether (**7**) (124.2 mg, 0.4

mmol) in anhydrous THF (12 ml) was added to stirred, anhydrous liquid ammonia (12 ml) (freshly distilled from sodium) at −78 °C under argon. Lithium metal (85 mg, 0.12 mmol) was added in small pieces. After 10 min, dry ethanol (0.72 ml) was added to this solution over 3 min, and the blue solution was stirred at −78 °C for a further 15 min. Ammonium chloride (800 mg) was added in portions, and the reaction mixture was stirred at −78 °C until it became colourless. The cooling bath was removed, and the ammonia was allowed to evaporate. The residue was extracted with ethyl acetate to give a product (143 mg), which was dissolved in methanol (20 ml), cooled to 0 °C, and treated with conc. HCl (0.5 ml) for 2 h. Aqueous sodium hydrogen carbonate (20 ml) was added, and the methanol was evaporated under reduced pressure. The residue was extracted with ethyl acetate to give a product (135 mg), which was chromatographed on silica gel (20 g), with benzene–ethyl acetate (2:1) as eluant, to give 14,17α-*etheno*-17β-*hydroxyestr*-4-*en*-3-*one* (**42**) (92 mg, 77%), m.p. 226—228 °C (from chloroform–ethyl acetate); $[\alpha]_D$ +112.5° (*c* 1.05); $\lambda_{max.}$ 240 nm (ε 16 752); $\nu_{max.}$ 3 600, 3 390br, and 1 652 $cm^{-1}$; $\Delta\varepsilon_{max.}$ −1.88 (316 nm); $\delta_H$(500 MHz) 0.86 (3 H, s, 13β-Me), 5.8 (1 H, s, 4-H), and 5.8 and 5.85 (each 1 H, d, *J* 5.9 Hz, $17^1$- and $17^2$-H); $\delta_C$(125 MHz) 199.9 (s, C-3), 166.5 (s, C-5), 136.4 and 132.75 (each d, C-$17^1$ and C-$17^2$), 124.4 (d, C-4), 90.0 (s, C-17), 57.6 and 56.0 (each s, C-13 and C-14), 46.0, 42.9, and 41.2 (each d, C-8, C-9, and C-10), 36.3, 35.5, 31.7, 28.3, 27.1, 26.75, and 26.5 (each t, C-1, C-2, C-6, C-7, C-11, C-12, C-15, and C-16), and 14.0 (q, C-18) (Found: C, 80.6; H, 8.8%; $M^+$, 298. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.8%; M, 298).

(*b*) Similar treatment of compound (**9**) (248 mg, 0.8 mmol) gave ($17^1R$)-17β-hydroxy-14,17α-ethano-16α,$17^1$-cycloestr-4-en-3-one (**43**) (133 mg, 56%), m.p. 197—199 °C (from chloroform–ethyl acetate); $[\alpha]_D$ +54° (*c* 0.95); $\lambda_{max.}$ 240 nm (ε 16 580); $\nu_{max.}$ 3 605, 3 420br, 3 055, 1 655, 1 065, and 880 $cm^{-1}$; $\Delta\varepsilon_{max.}$ −1.83 (316 nm); $\delta_H$ 0.93 (3 H, s, 13β-Me), and 5.83br (1 H, s, $W_{\frac{1}{2}}$ 4 Hz, 4-H); $\delta_C$(125 MHz) 199.8 (s, C-3), 166.4 (s, C-5), 125.2 (d, C-4), 80.3 (s, C-17), 48.4 (d, C-10), 43.0 (s, C-14), 42.6 (d, C-9), 36.75 (s, C-13), 36.75 (d, C-8), 36.4, 35.2, 34.7, 28.0, 26.8, 26.7, and 26.5 (each t, C-1, C-2, C-6, C-7, C-11, C-12, C-15, and C-$17^2$), 14.9 and 13.2 (each d, C-16 and C-$17^1$), and 14.2 (q, C-18) (Found: C, 80.2; H, 8.8%; $M^+$, 298. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.8%; *M*, 298).

(*c*) Similar treatment of compound (**11**) (125 mg, 0.4 mmol) gave 17β-hydroxy-14,17α-ethanoestr-4-en-3-one (**44**) (94 mg, 78%), m.p. 213—215 °C (from chloroform–ethyl acetate); $[\alpha]_D$ +35.5° (*c* 1.05); $\lambda_{max.}$ 243 nm (ε 17 615); $\nu_{max.}$ 3 600, 3 410br, and 1 655 $cm^{-1}$; $\Delta\varepsilon_{max.}$ −1.94 (316 nm); $\delta_H$ 0.92 (3 H, s, 13β-Me), and 5.89br (1 H, s, $W_{\frac{1}{2}}$ 4 Hz, 4-H); $\delta_C$(75 MHz) 199.8 (s, C-3), 166.6 (s, C-5), 124.35 (d, C-4), 83.6 (s, C-17), 46.9 and 46.6 (each s, C-13 and C-14), 43.8, 43.1, and 42.7 (each d, C-8, C-9, and C-10), 36.3, 35.7, 35.1, 32.6, 32.3, 26.8, 26.4, and 26.0 (each t, C-1, C-2, C-6, C-7, C-11, C-12, C-15, C-16, C-$17^1$, and C-$17^2$), and 13.5 (q, C-18) (Found: C, 79.9; H, 9.7%; $M^+$, 300. $C_{20}H_{28}O_2$ requires C, 80.0; H, 9.4%; *M*, 300).

(*d*) Similar treatment of compound (**31**) (127 mg, 0.4 mmol), and chromatography of the product on silica gel (16 g), with benzene–ethyl acetate (1:19) as eluant, gave 17β-*hydroxy*-14-*hydroxymethylestr*-4-*en*-3-*one* (**45**) (88 mg, 72%), m.p. 188—190 °C (from aqueous methanol); $[\alpha]_D$ +64.5° (*c* 0.3 in THF); $\lambda_{max.}$ 241 nm (ε 16 667); $\nu_{max.}$ 3 350br and 1 655 $cm^{-1}$; $\Delta\varepsilon_{max.}$ −1.89 (317 nm); $\delta_H$(500 MHz; [$^2H_4$]methanol) 0.98 (3 H, s, 13β-Me), 3.46 and 3.72 (each 1 H, d, *J* 12.2 Hz, $14^1$-$H_2$), 4.14 (1 H, dd, *J* 9.2 and 6.6 Hz, 17α-H), 4.79 and 5.08 (each 1 H, br m, exch. by $D_2O$, 17β- and $14^1$-OH), and 5.76 (1 H, s, 4-H); $\delta_C$(125 MHz; [$^2H_4$]methanol) 202.8 (s, C-3), 170.75 (s, C-5), 124.55 (d, C-4), 78.6 (d, C-17), 62.5 (t, C-$14^1$), 51.1 and 48.4 (each s, C-13 and C-14), 46.2, 45.7, and 44.4 (each d, C-8, C-9, and C-10), 37.7, 37.3, 31.2, 29.9, 29.8, 27.8, 27.6, and 27.3 (each t, C-1, C-2, C-6, C-7, C-11, C-12, C-15, and C-16), and 15.8 (q, C-18) (Found: C, 74.8; H, 9.3%; $M^+$, 304. $C_{19}H_{28}O_3$ requires C, 75.0; H, 9.3%; *M*, 304).

## Acknowledgement

We thank Professor Dr. R. Wiechert (Schering AG, Berlin) for a generous gift of estrone.

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*Received 6th January* 1989; *Paper* 9/00110G