14-Methyl Steroids. Part 2.[1,2] Total Synthesis of (±)-14α-Methyl-19-norsteroids

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trans-1,6-Dimethylbicyclo[4.3.0]nonane-2,7-dione (1) is converted, *via* regiospecific homologation at C-2, into *trans*-1,6-dimethyl-2-methylenebicyclo[4.3.0]nonane-3,7-dione (6). Conjugate alkylation of (6) with *m*-methoxybenzylmagnesium chloride followed by acid treatment, affords a mixture of (±)-3-methoxy-14-methyl-14α-estra-1,3,5(10),9(11)-tetraen-17-one (8) and the corresponding Δ^8-isomer (9). The stereoselectivity of reductions of the $\Delta^{9(11)}$- and Δ^8-bonds in (8) and (9) and the derived 17-acetals is examined, and an efficient synthesis of (±)-3-methoxy-14-methyl-14α-estra-1,3,5(10)-trien-17-one (13) is described.

Earlier investigations have shown that 3-methoxyestra-1,3,5(10)-trien-15-one, and related compounds bearing additional functionality in ring D, undergo highly stereoselective 14β-methylation in the presence of base and methyl iodide,[1] whereas the additional presence of a Δ^8-bond causes a reversal of stereoselectivity.[3] Attempts to use these findings to advantage in developing a stereoselective partial synthesis of 14α-methyl-19-norsteroids from estrone have hitherto been thwarted by difficulties in preparing suitable substrates bearing latent C-17 functionality,[4] and in modifying or transposing ring D functionality after introduction of the 14α-methyl group. Increased steric hindrance around ring D results in substantially diminished reactivity of the 15-oxo-group; although progress has been made toward solving aspects of this problem, the number of steps involved in regenerating C-17 functionality from 14α-methyl-15-ketones, renders such routes impractical.

Accordingly, attention was turned to totally synthetic methods for preparing 14α-methylestrone and related compounds. One such approach is suggested by the differing reactivity of the carbonyl groups in *trans*-1,6-dimethylbicyclo[4.3.0]nonane-2,7-dione (1).[5] It was envisaged that the formal attachment of a 3-methoxyphenethyl moiety to C-2 of the diketone (1) would furnish the elements of the desired skeleton directly. A prerequisite for such an approach would be concomitant functionalisation of C-9 (steroid numbering) for subsequent 9,10-bond formation. Preliminary attempts to alkylate the vinyl anion derived from n-butyl-lithium treatment of the 2-tosylhydrazone of (1) were unsuccessful.

An alternative approach, which has been used with success in the total synthesis of estrone and related 19-norsteroids,[6] entails prior conversion of (1) into the 2-methylene-3,6-diketone (6), for conjugate addition of a 3-methoxybenzyl moiety. Initially, the approach involving sequential 2-methylation, dehydration to a 2-methyl-Δ^2-compound, and photosensitised oxygenation was examined.[7] Reaction of (1) with methylmagnesium iodide gave the expected [5] product of regiospecific 2-methylation; however acidic dehydration furnished an inseparable mixture of endo- and exo-cyclic olefins (n.m.r.), further elaboration of which proved to be impractical.

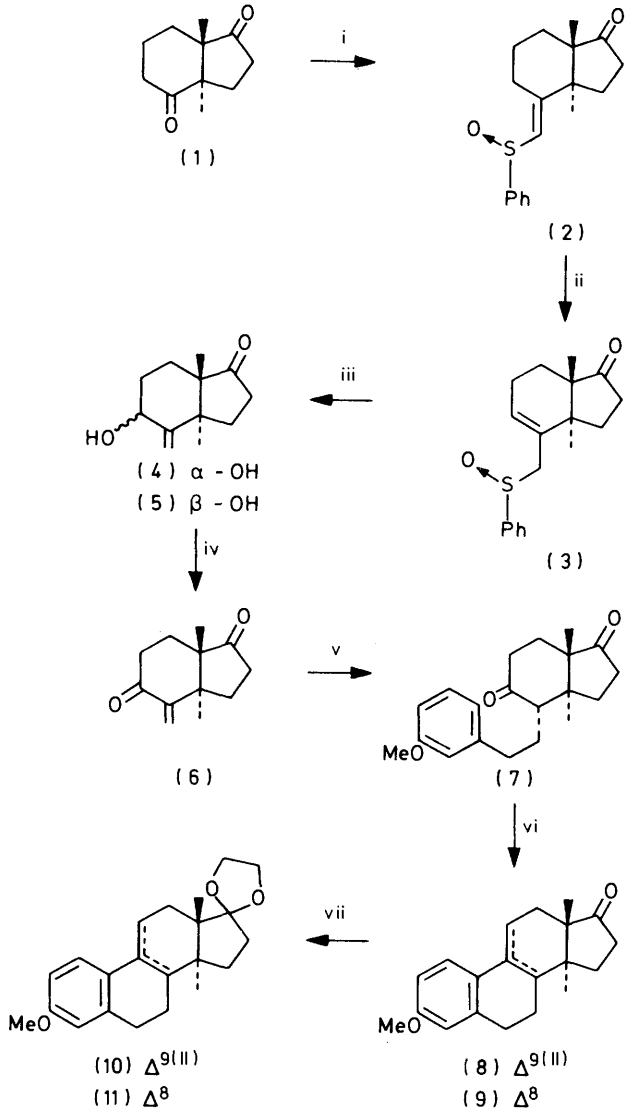
Attention was turned to a recently described [8] reaction sequence for converting carbonyl compounds into homologated allylic alcohols. Treatment of (1) with α-lithiated diethyl (phenylsulphinyl)methylphosphonate in tetrahydrofuran afforded the 2-(phenylsulphinyl)methylene derivative (2) (56%), the spectroscopic properties of which demonstrated that the expected [5] regiospecificity had prevailed. No other addition products were detected. Compound (2) was smoothly isomerised to the allylic sulphoxide (3) (71%) in the presence of potassium hydride in tetrahydrofuran; the n.m.r. spectrum of the product (3) displayed a two-proton singlet at 3.53 p.p.m. for the methylene protons adjacent to the sulphinyl group and a triplet (*J* 3 Hz) at 5.48 p.p.m. for the C(3)-proton.

The sulphoxide (3) underwent a [2,3] sigmatropic rearrangement [8,9] in the presence of trimethyl phosphite and dimethylamine in absolute methanol at 60 °C, to give an inseparable mixture of the 2-methylene-3-alcohols (4) and (5) (95%). N.m.r. analysis of the mixture revealed that the ratio of 3-axial (4) and 3-equatorial (5) isomers was *ca.* 1 : 2; the normal preference for formation of an axial hydroxy-group in conformationally rigid systems [10] may be suppressed in this instance by the 1,3-diaxial relationship of the incoming C–O bond with the 1-methyl group.

Oxidation of the mixture of alcohols (4) and (5) with pyridinium chlorochromate in dichloromethane at 20 °C afforded the 2-methylene-3,7-diketone (6); the crystalline product failed to melt sharply, but careful chromatographic analysis and examination of spectroscopic data did not reveal the presence of impurities.

With the desired synthon for rings C and D in hand, conjugate addition of a 3-methoxybenzyl moiety was examined. Direct addition [7] of *m*-methoxybenzylmagnesium chloride resulted only in 1,2-addition but, although the reaction carried out in the presence of copper(II) acetate proved to be capricious, careful exclusion of moisture and oxygen and control of the reaction temperature, followed by rapid reverse quenching of the reaction mixture afforded the 9,10-seco-steroid (7) in good yield. Initial preparations gave a non-crystalline product, containing *ca.* 10% of an isomeric impurity, presumably the 8-epimer of (7).[6] Accordingly, the crude alkylation product was treated briefly with methanolic sodium hydroxide, to give a pure isomer (7), the structure of which was confidently assigned 8β-configuration.[6]

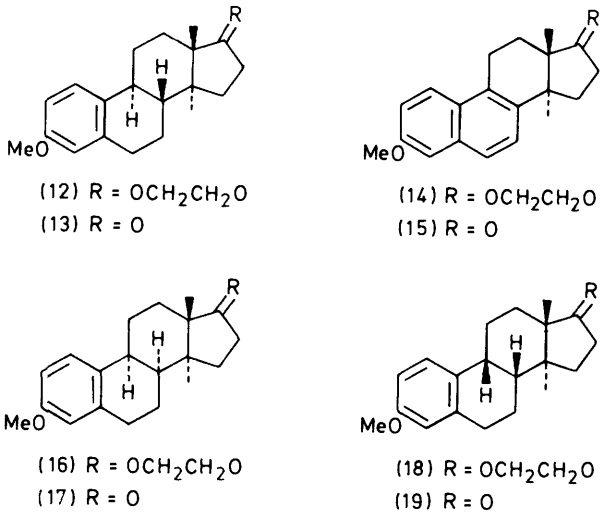
Closure of ring B in related 9,10-seco-compounds has been carried out using methanolic hydrochloric acid,[6] but similar treatment of (7) led to complex mixtures containing, in addition to the desired cyclised products, artefacts which appeared to have suffered subsequent dehydrogenation. However, treatment of (7) with toluene-*p*-sulphonic acid in refluxing benzene proceeded slowly but in excellent yield (89%) to a mixture of the $\Delta^{9(11)}$- and Δ^8-isomers (8) and (9); n.m.r. examination showed an isomer ratio of *ca.* 1 : 1. Since it is known that the $\Delta^{9(11)}$-isomer is thermodynamically favoured in C,D-*trans*-steroids,[11] the mixture was subjected to more prolonged acidic treatment; however, the proportions of (8) and (9) remained constant. This implies that the 14α-methyl group



Reagents: i, $PhS(O)CH_2P(O)(OEt)_2$, Bu^nLi, THF; ii, KH, THF; iii, $P(OMe)_3$, Me_2NH, MeOH, 60 °C; iv, $C_5H_5\overset{+}{N}HCrO_3Cl^-$, CH_2Cl_2; v, 3-$MeOC_6H_4CH_2MgCl$, $Cu(OAc)_2 \cdot H_2O$, THF; vi, *p*-TsOH, C_6H_6, heat; vii, $(CH_2OH)_2$, $C_6H_5CH_3$, *p*-TsOH, heat

plays a role in disturbing the equilibrium which obtains in the analogous dehydroestrone derivatives, possibly through slightly increased puckering of ring D[11] in response to steric interactions with 1,3-disposed axial C–H bonds.

Separation of the $\Delta^{9(11)}$- and Δ^8-isomers (8) and (9) proved difficult, but pure samples were obtained by careful column chromatography and p.l.c., and the isomers were readily distinguished by their spectroscopic properties. In practice, the isomers were more efficiently separated after acetalisation; thus prolonged treatment of the mixture of (8) and (9) with ethylene glycol and toluene-*p*-sulphonic acid in refluxing toluene, resulted in *ca.* 75% conversion into a mixture of the 17,17-ethylenedioxy-compounds (10) and (11), which could be separated with relatively little overlap of fractions by conventional column chromatography on silica gel. It is noteworthy that the unchanged ketone mixture (8) + (9) recovered from the acetalisation reaction retained a *ca.* 1 : 1 ratio of isomers, whereas the Δ^8-17-acetal (11) was the major product (*ca.* 66%) of derivatisation; it is reasoned that the factor responsible for ring D puckering in the ketone (9) is reinforced by the sp^3 hybridisation at C-17 and that the equilibrium is thus shifted in favour of the Δ^8-isomer during acetalisation.



In order to complete the synthetic sequence to 14α-methylestrone analogues, selective reduction of the $\Delta^{9(11)}$- and Δ^8-bonds of the respective isomers was examined. Thus, reduction of the $\Delta^{9(11)}$-17-acetal (10) with lithium in liquid ammonia–tetrahydrofuran at −50 °C afforded only the 'natural' 8β,9α-isomer (12), which was converted into the 14α-methyl analogue (13) of estrone methyl ether upon treatment with trifluoroacetic acid in aqueous tetrahydrofuran. The structure of (13) was readily deduced from a comparison of ^{13}C and ^1H n.m.r. spectra with those of estrone methyl ether. Furthermore, the properties of (13) correspond closely with those recently reported [12] for material prepared by an unrelated synthetic route.

In a similar experiment, the Δ^8-17-acetal (11) was treated with lithium in liquid ammonia–tetrahydrofuran at −50 °C. N.m.r. examination of the crude reduction product revealed that it consisted mainly of the 8β,9α-isomer (12) (*ca.* 90%), and that the remaining material comprised a *ca.* 1 : 1 mixture of the two *cis*-isomers (16) and (18). Attempted chromatographic separation failed, but slightly contaminated (12) could be obtained through crystallisation of the mixture.

Clearly, the method of choice for preparing the pure estrone analogues (12) and (13) is *via* reduction of the $\Delta^{9(11)}$-isomer (10), but the favourable stereochemical outcome of reduction of (11) also implies that a practical synthesis of (12) is possible without prior separation of the isomeric precursors, since material of sufficient purity for further elaboration can be thus obtained.

It was also of interest to compare the stereoselectivity of catalytic hydrogenation of compounds prepared in this work, with that observed for analogous estrone derivatives.[13,14] It was expected that the presence of a 14α-methyl group would increase the proportions of dihydro-products arising from β-face hydrogenation and thus provide a practical route to 9β-isomers of 14α-methylestrone. Indeed, an analogous manipulation of stereoselectivity has been reported [15] for related 14α,17α-disubstituted steroids. A variety of hydrogenation catalysts and conditions was examined but, since few major differences in product ratios were observed, all of the experiments reported here were carried out at 25 °C and 1 atm of hydrogen, using 10% palladium on carbon.

Hydrogen uptake by the Δ^8-17-ketone (9) proceeded slowly, and the product comprised a significant amount (36%) of the equilenin analogue (15), the structure of which was

readily ascertained by n.m.r. spectroscopy. The remaining material consisted of an oily mixture of dihydro-compounds, which failed to separate upon chromatography. However, n.m.r. examination of the product indicated the presence of a *ca.* 18 : 26 : 56 mixture of three isomers. The minor component (18%) was identified as the 8β,9α-isomer (13), by comparison with n.m.r. signals of authentic material, and the major component (56%) was assigned the 8β,9β-structure (19); this was based upon the exceptionally high-field position (δ 0.32 p.p.m.) of one of the methyl signals. Examination of models reveals that the 14α-methyl group of the 8β,9β-isomer (19) lies uniquely within the shielding zone of the aromatic ring. The remaining component (26%) of the mixture was accordingly assigned the 8α,9α-structure (17).

This result differs substantially from that observed for hydrogenation of Δ^8-estrone derivatives, which leads primarily to 8α,9α-isomers,[14] and demonstrates the sterically directing role of the 14α-methyl group. Formation of the B,C-*trans*-isomer (13) during hydrogenation may be ascribed to isomerisation of the olefin or equilibration of a ' half-hydrogenated ' state [16] under the reaction conditions.

Attempted hydrogenation of the Δ^8-17-acetal (11) resulted mainly in formation of the corresponding equilenin derivative (14) (74%), together with approximately equal amounts of two dihydro-compounds, tentatively assigned 8α,9α- and 8β,9β-structures (16) and (18). This reaction was not further investigated in view of the inefficient conversion into dihydro-products.

The ready formation of equilenin derivatives during hydrogenation of the Δ^8-compounds (9) and (11) may be attributable to the slow uptake of hydrogen by the relatively hindered olefinic bond, thus allowing the familiar palladium-mediated dehydrogenation [17] to compete under the mild reaction conditions.

The tendency for preferred β-face hydrogenation was sustained in the $\Delta^{9(11)}$-isomers (8) and (10). Thus, hydrogenation of the $\Delta^{9(11)}$-17-ketone (8) led to an inseparable mixture of the 8β,9α-(13) and 8β,9β-(19) isomers (*ca.* 25 and 75% respectively; estimated by appropriate n.m.r. signals). No equilenin analogue (15) was detected in the reaction product. It has been reported [13] that hydrogenation of $\Delta^{9(11)}$-estrone methyl ether leads mainly to the ' natural ' 8β,9α-isomer, accompanied by minor amounts of the 8β,9β-isomer, but that hydrogenation of the corresponding 17,17-ethylenedioxy-derivative affords a *ca.* 1 : 1 mixture of 8β,9α- and 8β,9β-isomers. However, the same functional change at C-17 in the 14α-methyl system failed to improve the β-face stereoselectivity further. Indeed, n.m.r. examination of the crystalline product obtained through hydrogenation of (10) showed that the 8β,9β-isomer (18) comprised *ca.* 60% of the mixture. Although the mixture was chromatographically inseparable, crystallisation afforded essentially pure 8β,9α-isomer (12); the non-crystalline residue derived from the mother-liquor comprised *ca.* 90% 8β,9β-isomer (18).

The disappointing conclusion of the foregoing hydrogenation experiments is that, although a trend favouring formation of 8β,9β-isomers is evident, no practically useful methods for their synthesis have hitherto been uncovered, owing to the difficulties encountered in attempting to separate isomeric mixtures. This problem is receiving further attention.

Experimental

M.p.s were determined on a Kofler hot-stage apparatus. Unless otherwise stated, spectra were recorded as follows: i.r., Perkin-Elmer 257, chloroform solutions; u.v., Unicam SP8-100, ethanol solutions; ^{1}H n.m.r., Varian EM-390, deuteriochloroform solutions with tetramethylsilane as internal standard; mass (electron impact), Varian MAT 212. Silica gel for column chromatography refers to Kieselgel 60. Steroidal structures are depicted and named as the enantiomers having 13β,14α-configuration.

trans-1,6-*Dimethyl*-2-(*phenylsulphinyl*)*methylenebicyclo*-[4.3.0]*nonan*-7-*one* (2).—n-Butyl-lithium in hexane (1.6 M; 26 ml) was added dropwise to diethyl (phenylsulphinyl)methylphosphonate (11.04 g) in anhydrous tetrahydrofuran (60 ml) at −78 °C under nitrogen. After 1 h at −78 °C, a solution of the diketone (1) (3.6 g) in anhydrous tetrahydrofuran (30 ml) was added dropwise, and the mixture was stirred at −78 °C for 1 h and at 25 °C for 48 h. Saturated aqueous ammonium chloride (50 ml) was added, and the mixture was concentrated under reduced pressure then extracted with chloroform. The organic phase was washed with water, dried over anhydrous magnesium sulphate, and concentrated to give a semi-crystalline residue. Crystallisation from benzene gave the *vinyl sulphoxide* (2) (2.5 g), m.p. 184—190 °C. A recrystallised sample of (2) had m.p. 192—193 °C (from benzene); *m/z* 302 (M^+) and 285 ($M^+ - OH$); $\nu_{max.}$ 1 735 (CO) and 1 030 cm^{-1} (SO); δ 1.11 and 1.24 (1- and 6-Me), 6.23 (1 H, d, *J* 2 Hz, C:CH), and 7.4—7.8 (5 H, m, C_6H_5) (Found: C, 71.5; H, 7.4; S, 10.5. $C_{18}H_{22}O_2S$ requires C, 71.5; H, 7.3; S, 10.6%).

Chromatography of the mother-liquor residue on silica gel with ethyl acetate–benzene (1 : 1) afforded further vinyl sulphoxide (2) (0.87 g) and unchanged diketone (1) (0.58 g).

trans-1,6-*Dimethyl*-2-(*phenylsulphinyl*)*methylbicyclo*[4.3.0]-*non*-2-*en*-7-*one* (3).—Potassium hydride (50% suspension in oil; 2 g) was added to a solution of the vinyl sulphoxide (2) (3.365 g) in anhydrous tetrahydrofuran (200 ml). The mixture was stirred at 25 °C for 5 h, then cooled to 0 °C and quenched with saturated aqueous ammonium chloride. The mixture was then concentrated under reduced pressure and the product (3.5 g) isolated by extraction with chloroform. Two crystallisations from benzene–hexane afforded the *allylic sulphoxide* (3) (2.1 g), m.p. 132—135 °C, and chromatography of the combined mother-liquor residues on silica gel with ethyl acetate–benzene (1 : 1) gave further (3) (0.29 g).

An analytical sample of (3) had m.p. 134—135 °C (from benzene–ethyl acetate); *m/z* 286.138 ($M^+ - O$); $\nu_{max.}$ 1 735 (CO), 1 035, and 1 020 cm^{-1} (SO); δ 1.06 and 1.09 (1- and 6-Me), 3.53 [2 H, s, S(O)CH_2], 5.48 (1 H, t, *J* 3 Hz, 3-H), and 7.5—7.8 (5 H, m, C_6H_5) (Found: C, 71.5; H, 7.3; S, 10.5. $C_{18}H_{22}O_2S$ requires C, 71.5; H, 7.3; S, 10.6%).

Rearrangement of the Allylic Sulphoxide (3).—The sulphoxide (3) (2.114 g) in tetrahydrofuran (10 ml) was added to trimethyl phosphite (4.7 g) and dimethylamine hydrochloride (3.75 g) in absolute methanol (20 ml), and the resultant mixture was kept at 60 °C for 24 h. Saturated aqueous sodium hydrogen carbonate was added and the product was isolated by extraction with chloroform, and chromatographed on silica gel (200 g) with ethyl acetate–benzene (1 : 1) to give gummy crystalline material (1.3 g) which, after sublimation at 60 °C under vacuum, furnished an inseparable mixture of 3α- and 3β-*hydroxy*-trans-1,6-*dimethyl*-2-*methylenebicyclo*-[4.3.0]*nonan*-7-*one* (4) and (5), m.p. 45—150 °C; *m/z* 194 (M^+) and 179 ($M^+ - Me$); $\nu_{max.}$ 3 650 (OH),1 740 (CO), and 915 cm^{-1} (C:C); δ(4) 0.87 and 1.63 (1- and 6-Me), 4.45 (1 H, br, $W_{\frac{1}{2}}$ 10 Hz, 3β-H), and 4.97 and 5.2 (each 1 H, br s, $W_{\frac{1}{2}}$ 2.5 Hz, C:CH_2), and δ(5) 0.96 and 1.07 (1- and 6-Me), 4.55 (obsc.) (1 H, br, $W_{\frac{1}{2}} > 20$ Hz, 3α-H), and 4.87 and 5.31 (each 1 H, br s, $W_{\frac{1}{2}}$ 4 Hz, C:CH_2) (Found: C, 74.5; H, 9.9. $C_{12}H_{18}O_2$ requires C, 74.2; H, 9.3%). The relative intensities of n.m.r. signals of the mixture revealed that the ratio of 3-isomers (4) and (5) was *ca.* 1 : 2.

trans-1,6-*Dimethyl*-2-*methylenebicyclo*[4.3.0]*nonane*-3,7-*dione* (6).—Pyridinium chlorochromate (2.5 g) was added to a stirred solution of the 3-hydroxy-compounds (4) and (5) (1.3 g) in dry dichloromethane (100 ml) at 20 °C. After 2 h at 20 °C, further reagent (0.5 g) was added, and stirring was continued until no starting material was detected on t.l.c. (*ca.* 1 h). Aqueous sodium hydrogen sulphite was added, the organic layer worked up, and the crystalline residue (1.3 g) chromatographed on silica gel (130 g) with ethyl acetate–benzene (2 : 3) to give the diketone (6) (1.075 g), m.p. 130—156 °C (from benzene–hexane); *m/z* 192 (M^+) and 177 (M^+ − Me); $\nu_{max.}$ 1 740 (7-CO), 1 690 (3-CO), and 1 625 cm^{-1} (C:C); δ 1.06 and 1.09 (1- and 6-Me), and 5.22 and 6.05 (each 1 H, d, *J* 1 Hz, C:CH_2) (Found: C, 74.6; H, 8.5. $C_{12}H_{16}O_2$ requires C, 75.0; H, 8.5%).

3-*Methoxy*-14-*methyl*-9,10-*seco*-14α-*estra*-1,3,5(10)-*triene*-9,17-*dione* (7).—*m*-Methoxybenzyl chloride (13.15 g) in dry tetrahydrofuran (120 ml) was added dropwise during 1 h to magnesium turnings (2.53 g) in dry tetrahydrofuran (25 ml) under nitrogen. The mixture was then stirred for 10 min at 50 °C, and cooled to 0 °C. Pulverised copper(II) acetate monohydrate (4.2 g) was added. After 5 min at 0 °C, the dark green solution was cooled to −20 °C and the methylene-diketone (6) (2 g) in dry tetrahydrofuran (50 ml) was added dropwise during 45 min. The stirred mixture was then maintained at −20 °C for 20 min and −10 °C for 20 min. The mixture, under nitrogen, was poured into cold aqueous 2M-sulphuric acid (500 ml). The product was isolated by extraction with ether and refluxed for 2 min in methanolic 0.1M-sodium hydroxide. The mixture was neutralised with solid CO_2 and concentrated under reduced pressure. The oily residue was suspended in water and the product isolated by extraction with chloroform. Chromatography on silica gel (300 g) with ethyl acetate–benzene (1 : 9) afforded the 9,10-*seco-compound* (7) (2.55 g), m.p. 78—79 °C (from aqueous methanol); *m/z* 314 (M^+) and 299 (M^+ − Me); $\nu_{max.}$ 1 735 (17-CO) and 1 700 cm^{-1} (9-CO); δ 0.78 and 1.29 (13β- and 14α-Me), 3.88 (OMe), 6.70—6.95 (3 H, m, ArH), and 7.15—7.4 (1 H, m, ArH) (Found: C, 76.35; H, 8.5. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.3%).

Acid-catalysed Cyclisation of the 9,10-*Seco-compound* (7).—A solution of compound (7) (550 mg) and toluene-*p*-sulphonic acid (300 mg) in dry benzene (100 ml) was refluxed under nitrogen in a Dean–Stark apparatus for 20 h. The reaction mixture was cooled, treated with sodium hydrogen carbonate, and the organic layer worked up to give a crystalline product which was adsorbed on silica gel (50 g). Elution with ethyl acetate–benzene (1 : 19) afforded material (452 mg), shown by n.m.r. to comprise a 1 : 1 mixture of the $\Delta^{9(11)}$- and Δ^8-steroids (8) and (9).

A portion (280 mg) of this material was chromatographed on a long column of silica gel (50 g) with benzene, to give 3-*methoxy*-14-*methyl*-14α-*estra*-1,3,5(10),9(11)-*tetraen*-17-*one* (8) (60 mg), m.p. 178—179 °C (from benzene–hexane); *m/z* 296 (M^+) and 281 (M^+ − Me); $\nu_{max.}$ 1 730 (CO), 1 640, and 1 610 cm^{-1}; $\lambda_{max.}$ 264 nm (log ε 4.29); δ 0.79 (14α-Me); 0.98 (13β-Me), 3.78 (OMe), 6.22 (1 H, br m, $W_{\frac{1}{2}}$ 6 Hz, 11-H), 6.54—6.82 (2 H, m, 2- and 4-H), and 7.62 (1 H, d, *J* 9 Hz, 1-H) (Found: C, 81.1; H, 8.3. $C_{20}H_{24}O_2$ requires C, 81.0; H, 8.2%), followed by fractions of (8) and (9) containing successively increasing amounts of (9). Those fractions enriched (>90%) in (9), were combined (50 mg) and separated by multiple development on p.l.c. with benzene, to give pure 3-*methoxy*-14-*methyl*-14α-*estra*-1,3,5(10),8-*tetraen*-17-*one* (9) (20 mg), m.p. 163—164 °C (from benzene–hexane); *m/z* 296 (M^+) and 281 (M^+ − Me); $\nu_{max.}$ 1 730 (CO) and 1 610 cm^{-1}; $\lambda_{max.}$ 275 nm (log ε 4.24); δ 1.01 (13β-Me), 1.08 (14α-Me), 3.8 (OMe), 6.6—6.86, and 7.07—7.27 (3 H, m, 1-, 2-, and 4-H) (Found: C, 80.8; H, 8.05%).

Acetalisation of the $\Delta^{9(11)}$- *and* Δ^8-17-*Ketones* (8) *and* (9).—A mixture (1 : 1; 2 g) of the $\Delta^{9(11)}$- and Δ^8-ketones (8) and (9) in toluene (500 ml) was treated with ethylene glycol (20 ml) and toluene-*p*-sulphonic acid (2 g). The resultant mixture was heated to boiling point and a portion of the solvent (*ca.* 100 ml) was slowly distilled over 6 h. Although t.l.c. revealed the presence of some starting material after 6 h, more extended treatment failed to force the reaction to completion. The mixture was cooled to 5 °C and washed successively with aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue (2.5 g) was chromatographed on silica gel (250 g) with benzene to give 17,17-*ethylenedioxy*-3-*methoxy*-14-*methyl*-14α-*estra*-1,3,5(10),9(11)-*tetraene* (10) (369 mg), m.p. 146—148 °C (from hexane); *m/z* 340 (M^+) and 325 (M^+ − Me); δ 0.93 (14α-Me), 0.97 (13β-Me), 3.76 (OMe), 3.7—4.0 (4 H, m, OCH_2CH_2O), 6.22 (1 H, br m, $W_{\frac{1}{2}}$ 8 Hz, 11-H), 6.53—6.82 (2 H, m, 2- and 4-H), and 7.62 (1 H, d, *J* 9 Hz, 1-H) (Found: C, 77.1; H, 8.35. $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.3%), followed by mixed fractions (507 mg), and 17,17-*ethylenedioxy*-3-*methoxy*-14-*methyl*-14α-*estra*-1,3,5(10),8-*tetraene* (11) (795 mg), m.p. 104—105 °C (from hexane); *m/z* 340 (M^+) and 325 (M^+ − Me); δ 1.02 (13β-Me), 1.25 (14α-Me), 3.8 (OMe), 3.8—4.0 (4 H, m, OCH_2CH_2O), 6.64—6.8 (2 H, m, 2- and 4-H), and 7.14 (1 H, d, *J* 9 Hz, 1-H) (Found: C, 78.3; H, 8.3%). Further elution with ethyl acetate–benzene (1 : 49) afforded a mixture of the unchanged ketones (8) and (9) (493 mg). Rechromatography of the mixed acetal fractions afforded further (10) (125 mg), mixed fractions (200 mg), and (11) (176 mg).

17,17-*Ethylenedioxy*-3-*methoxy*-14-*methyl*-14α-*estra*-1,3,5(10)-*triene* (12).—(a) The $\Delta^{9(11)}$-17-acetal (10) (50 mg) in dry tetrahydrofuran (4.5 ml) was added during 3 min to lithium (120 mg) in liquid ammonia (distilled from sodium; *ca.* 50 ml) at −50 °C. After a further 30 min at −50 °C, the reaction mixture was quenched with ammonium chloride, and the ammonia was evaporated in a stream of nitrogen. Extraction of the residue with chloroform afforded the *dihydro-compound* (12) (50 mg), m.p. 145—146 °C (from hexane); *m/z* 342 (M^+); δ 1.0 (13β-Me), 1.08 (14α-Me), 3.78 (OMe), 3.8—3.95 (4 H, br m, OCH_2CH_2O), and 6.59—7.2 (3 H, m, 1-, 2-, and 4-H) (Found: C, 77.05; H, 8.9. $C_{22}H_{30}O_3$ requires C, 77.2; H, 8.8%).

(b) The Δ^8-17-acetal (11) (50 mg) was treated with lithium in liquid ammonia at −50 °C for 1 h, as described in the foregoing experiment. Chromatography of the product on silica gel (5 g) with benzene afforded impure (12) (36 mg), m.p. 136—138 °C (from hexane). N.m.r. analysis of the product revealed that it contained *ca.* 10% of the 8α,9α- and 8β,9β-isomers (16) and (18) (see later).

3-*Methoxy*-14-*methyl*-14α-*estra*-1,3,5(10)-*trien*-17-*one* (13).—The acetal (12) (54 mg) was dissolved in aqueous tetrahydrofuran (80%; 2.4 ml) containing trifluoroacetic acid (0.2 ml). After 16 h at 25 °C, sodium hydrogen carbonate was added, and the mixture was concentrated under reduced pressure. Water was added and the product was isolated by extraction with chloroform, and adsorbed on silica gel (10 g). Elution with ethyl acetate–benzene (1 : 49) afforded the 17-ketone (13) (32 mg), m.p. 134—135 °C (from benzene–hexane); *m/z* 298 (M^+) and 283 (M^+ − Me); $\nu_{max.}$ 1 735 cm^{-1} (CO); δ 0.9 (14α-Me), 1.03 (13β-Me), 3.78 (OMe), and

6.65—7.35 (3 H, m, 1-, 2-, and 4-H) (Found: C, 80.5; H, 9.0. Calc. for $C_{20}H_{26}O_2$: C, 80.5; H, 8.8%) (lit.,[12] m.p. 129—130 °C).

Hydrogenation of the Δ^8*-Compounds* (9) *and* (11).—(a) The Δ^8-17-ketone (9) (50 mg) in ethyl acetate (10 ml) was hydrogenated in the presence of pre-reduced palladium on carbon (10%; 30 mg). After 16 h, hydrogen uptake ceased, and the filtered reaction mixture was concentrated and chromatographed on silica gel (5 g). Elution with ethyl acetate–benzene (1 : 49) afforded 3-*methoxy*-14-*methyl*-14α-*estra*-1,3,5(10),6,8-*pentaen*-17-*one* (15) (18 mg), m.p. 186—187 °C (from benzene–hexane); *m/z* 294 (M^+) and 279 ($M^+ - 15$); $\nu_{max.}$ 1 735 cm^{-1} (CO); $\lambda_{max.}$ 229 nm (log ε 4.80); δ 0.88 (13β-Me), 1.13 (14α-Me), 3.9 (OMe), and 7.1—7.95 (5 H, m, 1-, 2-, 4-, 6-, and 7-H) (Found: C, 81.4; H, 7.5. $C_{20}H_{22}O_2$ requires C, 81.6; H, 7.5%), followed by an oily mixture of (13), (17), and (19) (30 mg), *m/z* 298 and 283; $\nu_{max.}$ 1 735 cm^{-1} (CO); δ[8β,9α-isomer (13); *ca.* 18%] 0.88 (14α-Me), 1.01 (13β-Me), 3.76 (OMe), and 6.6—7.2 (3 H, m, 1-, 2-, and 4-H); δ[8α,9α-isomer (17); *ca.* 26%] 0.98 (14α-Me), 1.13 (13β-Me), 3.76 (OMe), and 6.6—7.2 (3 H, m, 1-, 2-, and 4-H); δ[8β,9β-isomer (19); *ca.* 56%] 0.32 (14α-Me), 1.13 (13β-Me), 3.76 (OMe), and 6.6—7.2 (3 H, m, 1-, 2-, and 4-H). Attempted separation of the mixture by further column chromatography and p.l.c. failed.

(b) The Δ^8-17-acetal (11) (50 mg) in ethyl acetate (10 ml) was hydrogenated in the presence of pre-reduced palladium on carbon (10%; 20 mg) until hydrogen uptake ceased (*ca.* 20 h). The filtered reaction mixture was concentrated and chromatographed on silica gel (5 g) with benzene to give 17,17-*ethylenedioxy*-3-*methoxy*-14-*methyl*-14α-*estra*-1,3,5(10),6,8-*pentaene* (14) (29 mg), m.p. 158—159 °C (from hexane); *m/z* 338 (M^+) and 323 ($M^+ - Me$); δ 0.88 (13β-Me), 1.31 (14α-Me), 3.93 (OMe), 3.85—4.06 (4 H, m, OCH_2CH_2O), and 7.1—7.92 (5 H, m, 1-, 2-, 4-, 6-, and 7-H) (Found: C, 78.2; H, 7.6. $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.75%), followed by the 8α,9α-dihydro-compound (16) (5 mg), *m/z* 342 (M^+) and 327 ($M^+ - Me$); δ 1.13 (13β-Me), 1.3 (14α-Me); 3.78 (OMe), 3.7—4.0 (4 H, m, OCH_2CH_2O), and 6.56—7.2 (3 H, m, 1-, 2-, and 4-H), and the 8β,9β-dihydro-compound (18) (5 mg), *m/z* 342 (M^+) and 327 ($M^+ - Me$); δ 0.47 (14α-Me), 1.13 (13β-Me), 3.78 (OMe), 3.78—3.93 (4 H, m, OCH_2CH_2O), and 6.63—7.2 (3 H, m, 1-, 2-, and 4-H). The small amounts of (16) and (18) precluded further characterisation.

Hydrogenation of the $\Delta^{9(11)}$*-Compounds* (8) *and* (10).—(a) The $\Delta^{9(11)}$-17-ketone (8) (20 mg) in ethyl acetate (6 ml) was hydrogenated in the presence of pre-reduced palladium on carbon (10%; 10 mg) until hydrogen uptake ceased (1.5 h). The filtered reaction mixture was concentrated to give an oily mixture of (13) and (19) (18 mg), *m/z* 298 and 283; $\nu_{max.}$ 1 730 cm^{-1} (CO); δ[8β,9α-isomer (13); *ca.* 25%] 0.9 (14α-Me), 1.02 (13β-Me), 3.78 (OMe), and 6.65—7.35 (3 H, m, 1-, 2-, and 4-H); δ[8β,9β-isomer (19); *ca.* 75%] 0.32 (14α-Me), 1.13 (13β-Me), 3.78 (OMe), and 6.65—7.35 (3 H, m, 1-, 2-, and 4-H), which failed to separate on chromatography.

(b) The $\Delta^{9(11)}$-17-acetal (10) (28 mg) in ethyl acetate (5 ml) was hydrogenated in the presence of pre-reduced palladium on carbon (10; 20 mg) for 20 h. The filtered reaction mixture was concentrated and chromatographed on silica gel (4 g) with benzene. Crystallisation of the product (25 mg) from hexane afforded the 8β,9α-isomer (12) (7 mg), m.p. 138—140 °C, the spectroscopic properties of which were identical with those of authentic material. N.m.r. analysis of the oily mother-liquor residue (18 mg) showed that it comprised *ca.* 90% of the 8β,9β-isomer (18).

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