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14-METHYL STEROIDS. PART 3.[1] SYNTHESIS OF (±)-14α-METHYL-9β-ESTRADIOL AND RELATED 14α-METHYL-19-NORSTEROIDS

KARL BISCHOFBERGER and JAMES R BULL *

National Chemical Research Laboratory, Council for Scientific and Industrial Research, P.O. Box 395, PRETORIA 0001, Republic of South Africa

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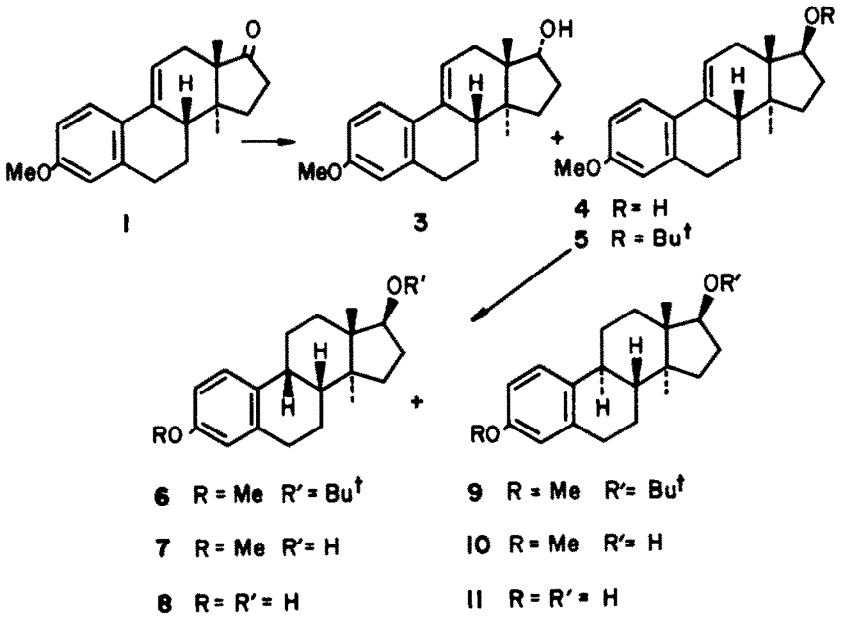
Abstract - Catalytic hydrogenation of a totally synthetic mixture of (±)-3-methoxy-14-methyl-14α-estra-1,3,5(10),9(11)-tetraen-17-one(1) and the corresponding 1,3,5(10),8-tetraen-17-one(2) gives a mixture of 14α-methyl-8β,9β-, -8α,9α-, and -8β,9α-estrones, which is converted into the 17β-hydroxy-mixtures. t-Butylation gives a separable mixture of the three isomers, of which (±)-17β-t-butoxy-3 methoxy-14-methyl-9β,14α-estra-1,3,5(10)-triene(6) is the major component. The corresponding 14α-methylestradiols are prepared. A practical synthesis of (±)-14-methyl-14α-estra-1,3,5(10),6,8-pentaene-3,17β-diol(25) is described, and it is shown that DDQ dehydrogenation of 1,3,5(10),9(11)-tetraenes in this series leads exclusively to the corresponding 1,3,5(10),6,8,11-hexaenes, whereas that of 1,3,5(10),8-tetraenes gives only 1,3,5(10),6,8-pentaenes.

We have recently described an efficient total synthesis of (+)-3-methoxy-14-methyl-14α-estra-1,3,5(10)-trien-17-one,[1] in which the penultimate step entails lithium-liquid ammonia reduction of 17,17-ethylenedioxy-derivatives of the corresponding $\Delta^{9(11)}$and Δ^{8}-compounds (1) and (2). However, catalytic hydrogenation of either of these compounds, or their respective 17-acetals, afforded inseparable mixtures of 8,9-dihydro-isomers. Accordingly, it was not possible to prepare pure 14α-methyl-8α- and 14α-methyl-9β-analogues of estrone methyl ether by this route, and alternative pathways to this objective were sought through modification of the 17-functionality of (1) and (2).

Ideally, a practical approach would entail modification of a mixture of (1) and (2), since prior separation can only be achieved with difficulty or indirectly.[1] However, initial experiments were carried out upon the pure $\Delta^{9(11)}$-isomer (1), in order to optimise the reaction sequences and conditions, and to ascertain whether the expected[1] mixture of only two dihydro-isomers could be separated. It was reasoned that conversion of the 17-oxo-group into a 17β-t-butoxy-group, via sequential reduction and etherification, would diminish the overall polarity of the products to a level where their distinctive skeletal features would enable them to be separated chromatographically.

Treatment of the $\Delta^{9(11)}$-17-ketone (1) with sodium in refluxing isopropanol-toluene afforded a readily-separable mixture of 17α- and 17β-hydroxy-compounds (3) and (4); as expected,[2] the latter isomer was preponderant

(ca 76%). Treatment of (4) with isobutene in the presence of phosphoric acid and boron trifluoride-etherate[3] gave the corresponding 17β-t-butyl ether (5) (88%); there was no evidence of concomitant isomerisation of the $\Delta^{9(11)}$-bond during this step. Hydrogenation of (5) in the presence of 10% palladium on charcoal proceeded slowly (20 h) to give a two-component mixture [R_F 0.35 and 0.18 in benzene-hexane (1:1)], which was readily separated by column chromatography. The less-polar minor isomer (34%) was assigned 9β-configuration (6),



on the basis of the diagnostic up-field chemical shift (δ 0.2 p.p.m.) of the 14α-methyl protons,[1] and accordingly, the major product (58%) was assigned the structure (9) having 'natural' configuration.

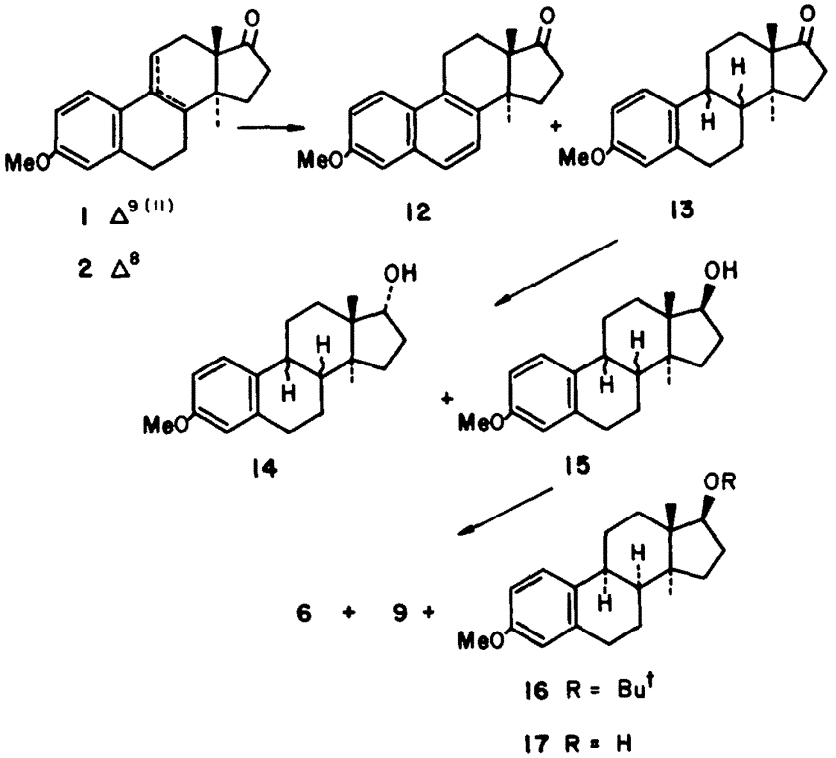
The respective hydrogenation products (6) and (9) were converted into the corresponding 17β-hydroxy-compounds (7) and (10), through treatment with toluene-p-sulphonic acid in refluxing benzene. Boron tribromide treatment[4] of (7) and (10) in dichloromethane at 0°C gave, in turn, (±)-14-methyl-9β,14α-estra-1,3,5(10)-triene-3,17β-diol (8) and (±)-14-methyl-14α-estra-1,3,5(10)-triene-3,17β-diol (11) respectively. The properties of (10) and (11) corresponded to those of material prepared by an independent synthesis,[2] and thereby confirmed the configurational assignments given to the hydrogenation products (6) and (9).

The stereoselectivity of catalytic hydrogenation of the 17β-t-butyl ether (5) differs markedly from that of the corresponding 17-ketone (1) and its 17,17-ethylenedioxy-derivative,[1] both of which afforded the respective 9β-isomers as major products. Although it is not obvious how the 17β-t-butoxy-group can exert a direct effect upon the stereochemical outcome of hydrogenation of the $\Delta^{9(11)}$-bond, it may be responsible for buttressing the 13β-methyl group in (5) or altering the ring D conformation to an extent which increases the puckering of ring C, and hence, the steric shielding upon the β-face about the $\Delta^{9(11)}$-bond.

Although the successful separation of the isomers (6) and (9) demonstrated the feasibility of this route to the hitherto inaccessible 9β-series of 14α-methylestrone analogues, the unfavourable stereoselectivity of $\Delta^{9(11)}$-bond hydrogenation, in the presence of a 17β-t-butoxy-group, necessitated a change in

the reaction sequence. Furthermore, it was necessary to ascertain whether the 8α-series, detected as minor products of hydrogenation of Δ^8-precursors,[1] could also be isolated via a unified process starting from the mixture of estratetraenes (1) and (2).

Accordingly, the 1:1 mixture of (1) and (2), obtained during the cyclodehydration step in the total synthesis,[1] was hydrogenated in the presence of 10% palladium on charcoal, to give a mixture of products, which was chromatographically separated into the 14α-methylequilenin analogue (12) (13%) and an oily fraction (84%) comprising the three possible 8,9-dihydro-compounds (13). As expected from hydrogenations carried out upon the respective pure estratetraenes (1) and (2),[1] the major component (65%) of the mixture was shown by n.m.r. (relative intensity of the 14α-methyl signal at 0.32 p.p.m.) to be the 9β-isomer; the 'natural' isomer comprised ca 25% and the 8α-isomer, ca 10%.



Reduction of the dihydro-mixture (13) with sodium in refluxing isopropanol-toluene gave a complex mixture, which was separated chromatographically into two main fractions, comprising the mixtures of 17α-hydroxy-compounds (14) (7%) and 17β-hydroxy-compounds (15) (86%). These fractions did not display significant differences in the proportions of their component 8,9-dihydro-isomers, as evidenced by n.m.r. The latter fraction was t-butylated in the usual way. Chromatography of the resultant mixture on silica gel afforded two very minor products, which were shown by mass spectrometry to contain two t-butyl residues (see below), followed by the pure 9β-isomer (6) (56%), an intermediate fraction (9%), and the pure 'natural' isomer (9) (22%). The intermediate fraction was shown by n.m.r. to comprise the 8α-isomer (16) contaminated with the $\Delta^{9(11)}$-compound (5). The origin of the contaminant is uncertain, but it may have arisen through a small amount of residual tetraene from incomplete hydrogenation, which escaped detection during the intermediate stages of the reaction sequence.

Treatment of this fraction with m-chloroperbenzoic acid in dichloromethane at 0°C resulted in conversion of the contaminant, via the labile 9,11-epoxide, into polar decomposition products. Chromatography of the resultant mixture afforded the pure 8α-isomer (16), which was deprotected with toluene-p-sulphonic acid in refluxing benzene to give (±)-14-methyl-8α,14α-estra-1,3,5(10)-triene-3,17β-diol 3-methyl ether (17). Scarcity of material precluded preparation and characterisation of the parent diol.

The foregoing unified method of preparation thus afforded access to the three families of isomers, in relative yields dictated by the stereoselectivity of hydrogenation of the estratetraene mixtures (1) and (2). The preponderance of 9β-products makes the method complementary to that described earlier,[1] in which the 'natural' isomers are obtained stereoselectively.

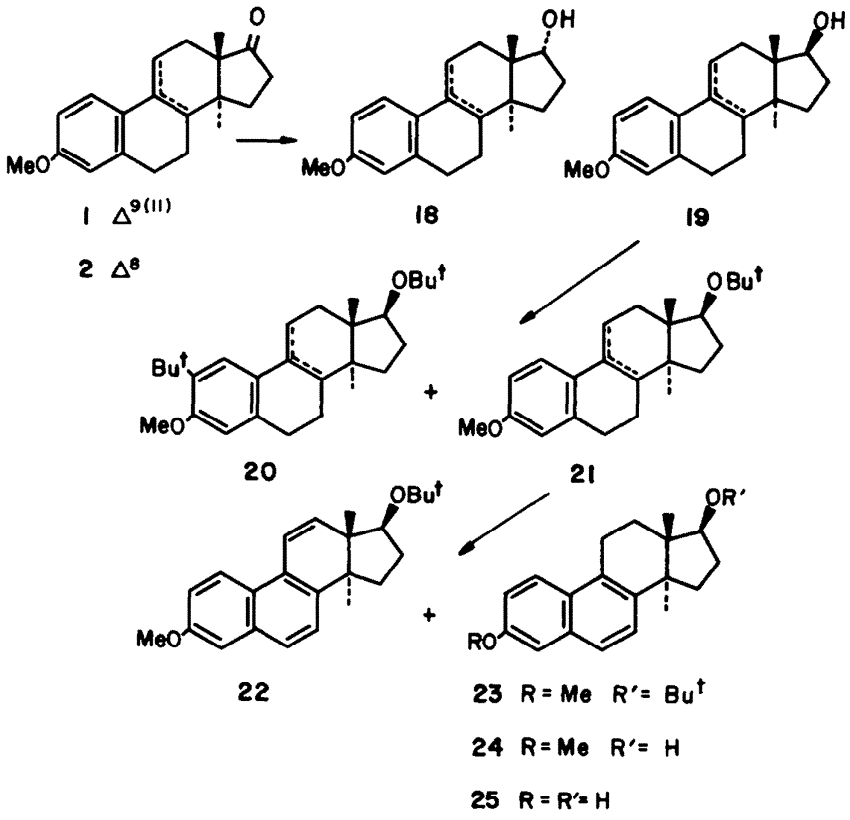
In order to complete the synthesis of comparable compounds in this series, an efficient method was sought for preparing 14-methyl-14α-estra-1,3,5(10),6,8-pentaene-3,17β-diol (25). It was not expected that direct hydride reduction of the 14α-methylequilenin analogue (12) would favour formation of the 17β-hydroxy-compound, owing to the steric effect of the 14α-methyl group.[5] Indeed, a small-scale reduction of (12) with lithium aluminium hydride revealed that the desired isomer comprised only ca 20% of the product (t.l.c.). Furthermore, the attempted reduction of (12) with sodium in isopropanol led to complex mixtures arising from concomitant reduction of ring A. In view of the small amount of (12) available as a by-product of the hydrogenation sequence, an alternative route to (24) and (25) was investigated.

Thus, the 1:1 mixture of estratetraenes (1) and (2) was reduced with sodium in refluxing isopropanol-toluene to give mainly the expected 1:1 mixture of $\Delta^{9(11)}$ and Δ^{8}-17β-alcohols (19) (86%), which was readily separated from the minor fraction (11%) comprising a comparable mixture of 17α-alcohols (18). t-Butylation of (19), under standard conditions for 65h, gave an inseparable mixture of $\Delta^{9(11)}$- and Δ^{8}-17β-t-butyl ethers (21)(61%). A significant by-product (ca 28%) was formed under these reaction conditions, but could be almost completely suppressed by carrying out the t-butylation of (19) for shorter periods. The by-product mixture was assigned the 2-t-butyl-17β-t-butoxy-structure (20), since n.m.r. examination showed two pairs of one-proton singlets in the aromatic region (6.58-7.67 p.p.m.). Interestingly, the n.m.r. spectrum also revealed that the ratio of $\Delta^{9(11)}$- and Δ^{8}-isomers in (20) was ca 35:65, whereas that of the 17β-t-butoxy-mixture (21) showed that the ratio of $\Delta^{9(11)}$- and Δ^{8}-isomers was ca 60:40. This implies that C-alkylation of the Δ^{8}-component of the olefinic mixture proceeds more rapidly than that of the $\Delta^{9(11)}$-component.

Treatment of (21) with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in refluxing benzene resulted in smooth formation of two readily-separable products, the hexaene (22) and the pentaene (23), in proportions similar to those of the $\Delta^{9(11)}$- and Δ^{8}-isomers in the starting material. The pentaene (23) failed to undergo further dehydrogenation in the presence of DDQ in refluxing benzene.

The dehydrogenation products (22) and (23) were readily identified with the aid of their distinctive spectroscopic properties. The ultraviolet spectrum of the pentaene (23) was dominated by absorption at 229 nm (log ε 4.83), with a complex pattern of less intense bands between 259 and 339 nm; comparable absorption is reported for equilenin and its 3-methyl ether.[6] In the hexaene (22), the main absorption occurred at 242 nm (log ε 4.79), and all the secondary bands appeared to be shifted to longer wavelength in relation to the pentaene (23).

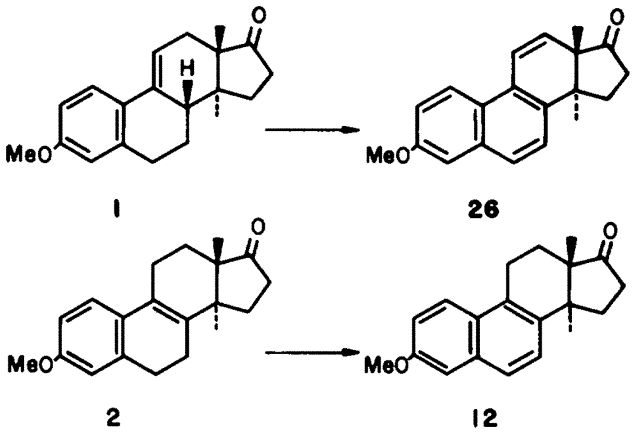
The 90 MHz n.m.r. spectra of (22) and (23) were not clearly resolved but,



at 500 MHz, the aromatic proton signals could all be distinguished. Thus, the spectrum of the hexaene (22) displayed the familiar pattern of ring A proton signals, together with doublets centred at δ 7.6 and 7.17 (J 8.2Hz) for 6- and 7-H, and at δ 7.06 and 6.31 (J 9.7Hz) for 11- and 12-H. Signals for 6- and 7-H in the pentaene (23) occurred at δ 7.55 and 7.17 (d, J 8.3Hz). Interestingly, the signals assigned to the 14α-methyl group in (22) and (23) displayed long-range coupling (J ca 1Hz), presumably to 15β-H, whereas that assigned to the 13β-methyl group in the pentaene (23) also displayed coupling (J 0.6Hz) to 12α-H.
In practice, the overall efficiency of the dehydrogenation reaction could be improved to ca 91% through catalytic hydrogenation of the hexaene (22), which cleanly saturated the Δ^{11}-bond, to give further pentaene (23). Stepwise deprotection of (23) afforded the 17β-alcohol (24) and hence, (±)-14-methyl-14α-estra-1,3,5(10),6,8-pentaene-3,17β-diol (25).

In order to obtain further insight into the foregoing dehydrogenation, a similar experiment was carried out with DDQ upon the 1:1 mixture of $\Delta^{9(11)}$- and Δ^{8}-17-ketones (1) and (2) in refluxing benzene. As before, the proportions of the derived hexaene (26) and pentaene (12) were similar to those of the starting material mixture. Accordingly, separate experiments were carried out upon pure (1) and (2), which confirmed that the $\Delta^{9(11)}$-isomer (1) gave only the hexaene (26), whereas the Δ^{8}-isomer (2) gave only the pentaene (12).

It is therefore evident that the first step in dehydrogenation of the $\Delta^{9(11)}$-compound (1) entails loss of hydride from C(12), and that the resultant 3-oxonium species undergoes rearrangement with loss of the C(8) proton to form a transient 1,3,5(10),8,11-pentaene. The failure to detect such an intermediate



suggests that formation of the hexaene (26) through subsequent loss of a C(7) hydride is rapid, in contrast to the reported[7] dehydrogenation of 3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one, in which such a pentaene is isolated.

In the case of the Δ^8-isomer (2), a similarly rapid loss of C(7) hydride leads directly to the equilenin analogue (12), which is incapable of undergoing further dehydrogenation in ring C. The dehydrogenations of (1) and (2) are remarkably efficient, and contrast with the capricious DDQ-mediated reactions of certain estrone derivatives.[8]

The spectroscopic properties of (26) and (12) were similar to those of the comparable 17β-t-butyl ethers (22) and (23). A notable difference in the n.m.r. was the smaller magnitude of long-range coupling between the 14α-methyl group and 15β-H(J ca 0.6Hz) in (26) and (12) probably as a result of flattening of ring D.

EXPERIMENTAL

For general instructions, see ref. 1. Compounds are depicted and named as the enantiomers having 13β-configuration.

Sodium-Isopropanol Reduction of the $\Delta^{9(11)}$-17-Ketone (1)

Sodium (500 mg) was added in small portions during 2h to a refluxing solution of 3-methoxy-14-methyl-14α-estra-1,3,5(10),9(11)-tetraen-17-one (1)(222 mg) in toluene (40 ml) and isopropanol (4 ml). After a further 6h at 90-100°C, the mixture was cooled to 0°C and quenched with 0.5M-sulphuric acid (to pH 6-7). The organic phase was separated and washed with saturated aqueous sodium hydrogencarbonate and water, then dried ($MgSO_4$) and evaporated under reduced pressure. The residue (240 mg) was chromatographed on silica gel (50 g) with ethyl acetate-benzene (1:10) to give 3-methoxy-14-methyl-14α-estra-1,3,5(10),9(11)-tetraen-17α-ol (3)(19 mg) as an oil, ν_{max} 3610 cm^{-1} (OH); m/z 298 (M^+) and 283 (M^+-Me); δ 0.8 (13β-Me), 1.03(14α-Me), 3.8 (OMe), ca 3.95 obsc (1H, m, W ca 18Hz, 17β-H), 6.3br (1H, m, W 6Hz, 11-H), 6.57-6.83 (2H, m, 2- and 4-H), and 7.65 (1H, d, J 9Hz, 1-H), and 3-methoxy-14-methyl-14α-estra-1,3,5(10),9(11)-tetraen-17β-ol (4)(169 mg), m.p. 145-147°C (from benzene-hexane); ν_{max} 3610 cm^{-1}(OH); m/z 298 (M^+) and 283 (M^+-Me); δ 0.8 (14α-Me), 0.88 (13β-Me), 3.8 (OMe), 4.27 (1H, m, W 16Hz, 17α-H), 6.24 br (1H, m, W 6Hz, 11-H), 6.56-6.8 (2H, m, 2- and 4-H), and 7.62 (1H, d, J 9Hz, 1-H)(Found: C, 80.4; H, 8.8. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.8%).

17β-t-Butoxy-3-methoxy-14-methyl-14α-estra-1,3,5(10),9(11)-tetraene (5)

The 17β-hydroxy-compound (4)(140 mg) in dry dichloromethane (3 ml) under nitrogen was cooled to -78°C in a pressure vessel, and 100% phosphoric acid (0.08 ml) and boron trifluoride etherate (0.08 ml) were added with stirring, followed by liquid isobutene (4 ml). The vessel was sealed and stirred at 25°C for 65h. The valve was opened with care and the excess isobutene was allowed to evaporate. Aqueous sodium hydrogencarbonate (4 ml) was added and the organic layer was

followed by the 17β-t-butyl ether (5)(146 mg), m.p. 138-140°C (from chloroform-methanol); m/z 354 (M^+), 339 (M^+-Me), and 297 (M^+-Bu^t); δ 0.8 (14α-Me), 0.86 (13β-Me), 1.15 (OBu^t), 3.8 (OMe), 3.96 (1H, m, W ca 16Hz, 17α-H), 6.23 (1H, m, W 6Hz,11-H), 6.56-6.8 (2H, m, 2- and 4-H), and 7.65 (1H, d, J 9Hz, 1-H)(Found: C, 81.7; H, 9.7. $C_{24}H_{34}O_2$ requires C,81.3; H, 9.7%).

Catalytic Hydrogenation of the 17β-t-Butyl Ether (5)

The 17β-t-butyl ether (5)(50 mg) in ethyl acetate (10 ml) was hydrogenated in the presence of palladium on carbon (10%; 50 mg) for 20h. The filtered reaction mixture was concentrated and chromatographed on silica gel (10 g) with benzene-hexane (1:1) to give 17β-t-butoxy-3-methoxy-14-methyl-9β,14α-estra-1,3,5(10)-triene (6)(17 mg), m.p. 112-114°C (from dichloromethane-methanol); m/z 356 (M^+) and 299 (M^+-Bu^t); δ 0.2(14α-Me), 1.0 (13β-Me), 1.12 (OBu^t), 3.73 obsc (1H, m, W >15Hz, 17α-H), 3.8 (OMe), 6.65-6.82 (2H, m, 2- and 4-H), and 7.2 (1H, d, J 8Hz, 1-H)(Found: C, 80.8; H, 10.3. $C_{24}H_{36}O_2$ requires C, 80.85; H, 10.2%), and 17β-t-butoxy-3-methoxy-14-methyl-14α-estra-1,3,5(10)-triene (9)(29 mg), m.p. 95-97°C (from dichloromethane-methanol); m/z 356 (M^+) and 299 (M^+-Bu^t); δ 0.86 and 0.88 (13β- and 14α-Me), 1.12 (OBu^t), 3.78 (OMe), ca 3.84 obsc (1H, m, 17α-H), 6.57-6.8 (2H, m, 2- and 4-H), and 7.2 (1H, d, J 8Hz, 1-H)(Found: C, 80.8; H, 10.4%).

14-Methyl-9β,14α- and -14α-estra-1,3,5(10)-triene-3,17β-diol 3-Methyl Ethers (7) and (10)

(a) A solution of the t-butyl ether (6)(400 mg) and toluene-p-sulphonic acid (370 mg) in benzene (90 ml) was refluxed for 2h under nitrogen. Aqueous sodium hydrogencarbonate was added to the cooled solution, and the organic layer was separated, washed with water, and dried ($MgSO_4$). The residue obtained after evaporation of the solvent was filtered through silica gel (30 g) with ethyl acetate-benzene (1:10), to give the 17β-alcohol (7) as a glass (324 mg), ν_{max} 3620 (OH) cm^{-1}; m/z 300 (M^+) and 285 (M^+-Me); δ 0.2 (14α-Me), 1.02 (13β-Me), 3.78 (OMe), 4.02 br (1H, dd, J 9 and 6Hz, 17α-H), 6.6-6.83 (2H, m, 2- and 4-H), and 7.2 (1H, d, J 9Hz, 1-H)(Found: M^+, 300.2089. $C_{20}H_{28}O_2$ requires M, 300.2088). The compound failed to give reproducible microanalytical results, owing to tenacious retention of solvent.

(b) Similar treatment of the t-butyl ether (9)(214 mg) afforded the corresponding 17β-alcohol (10)(145 mg), m.p. 133-135°C (from benzene-hexane); ν_{max} 3620 (OH) cm^{-1}; m/z 300 (M^+)and 285 (M^+-Me); δ 0.89 (6H, s, 13β- and 14α-Me), 3.78 (OMe), 4.15 (1H, dd, J 8.5 and 6Hz, 17α-H), 6.58-6.8 (2H, m, 2- and 4-H), and 7.22 (1H, d, J 8Hz, 1-H)(Tit.,[2] m.p. 130-132°C).

14-Methyl-9β,14α- and -14α-estra-1,3,5(10)-triene-3,17β-diols (8) and (11)

(a) A solution of boron tribromide (280 mg) in dichloromethane (0.55 ml) was added to the 3-methyl ether (7) (220 mg) in dry dichloromethane (10 ml) at -78°C. After 2h at 0°C, the reaction mixture was quenched through addition of aqueous sodium hydrogencarbonate. After 20 min, the precipitate was collected, washed in turn with water and dichloromethane, and crystallised from aqueous ethanol, with charcoal treatment, to give the 3,17β-diol (8)(148 mg) as slightly discoloured needles, m.p. 239-240°C; m/z 286 (M^+)(Found: C, 79.8; H, 9.4. $C_{19}H_{26}O_2$ requires C, 79.7; H, 9.15%).

(b) Similar treatment of the 3-methyl ether (10)(82 mg) afforded the 3,17β-diol (11)(60 mg), m.p. 237-239°C (from aqueous ethanol); m/z 286 (M^+)(Found: C, 79.8; H, 9.2%)(lit.,[2] m.p. 230-231°C).

Preparation of the 14α-Methyl-8β,9β-,-8α,9α-, and -8β,9α-isomers (6),(9), and (16) from the Estratetraen-17-one Mixture (1) and (2)

A 1:1 mixture (1.6 g) of 3-methoxy-14-methyl-14α-estra-1,3,5(10),9(11)- and -1,3,5(10),8-tetraen-17-ones (1) and (2) in ethyl acetate (150 ml) was hydrogenated in the presence of palladium on carbon (10%; 320 mg) until hydrogen uptake ceased (ca 18h). The filtered reaction mixture was concentrated and chromatographed on silica gel (150 g) with ethyl acetate-benzene (1:49) to give 3-methoxy-14-methyl-14α-estra-1,3,5(10),6,8-pentaen-17-one (12) (214 mg), m.p. 186-187°C (from benzene-hexane); λ_{max} 229 (log ε 4.8), 265 (3.74), 276 (3.76), 287 (3.58), 321 (3.27), and 336 (3.37) nm; δ (500 MHz) 0.89 (3H, s, 13β-Me), 1.13 (3H, d, J 0.6Hz, 14α-Me), 3.9 (3H, s, OMe), 7.12 (1H, d, J 2.7Hz, 4-H), 7.16 (1H, dd, J 9.2 and 2.7Hz, 2-H), 7.26 (1H, d, J 8.4Hz, 7-H), 7.62 (1H, d, J 8.4Hz, 6-H), and 7.86 (1H, d, J 9.2Hz, 1-H) (lit.,[1] m.p. 186-187°C), followed by an isomeric mixture of 8,9-dihydro-compounds (13)(1.35 g), m/z 298 (M^+). This mixture (13) was treated with sodium in refluxing toluene-isopropanol, as described in a previous experiment, and the product was chromatographed on silica gel (150 g) with ethyl acetate-benzene (1:10) to give an oily fraction (97 mg), comprising the 8,9-dihydro-17α-hydroxy-isomers (14), ν_{max} 3620 cm^{-1} (OH); m/z 300 (M^+) and 285

(M^+-Me); the estimated proportions of the 8β,9β-, 8α,9α-, and 8β,9α-isomers were ca 65:10:25 (n.m.r.).

The mixture (15) was t-butylated, as described in a previous experiment, and the product was chromatographed on silica gel (120 g) with benzene-hexane (2:3). Early fractions afforded two minor products (19 and 10 mg resp.), having m/z 412 (M^+), which were not further characterised. Further elution with the same solvent gave the 8β,9β-dihydro-compound (6)(750 mg), m.p. and mixed m.p. 112-114°C (from dichloromethane-methanol), followed successively by an impure oily fraction (122 mg) and the 8β,9α-dihydro-compound (9)(305 mg), m.p. and mixed m.p. 96-97°C (from dichloromethane-methanol). The impure fraction was homogeneous on t.l.c. but had m/z 356 (M^+) and 354, and n.m.r. examination revealed that it contained ca 70% of the desired product (16), contaminated with the $\Delta^{9(11)}$-compound (5). The fraction was treated with m-chloroperbenzoic acid (50 mg) in dichloromethane at 0°C for 3h. Aqueous sodium hydrogencarbonate was added and the organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The crystalline residue was chromatographed on silica gel (10 g) with benzene-hexane (1:1) to give 17β-t-butoxy-3-methoxy-14-methyl-8α,14α-estra-1,3,5(10)-triene (16)(54 mg), m.p. 119-120°C (from dichloromethane-methanol); m/z 356 (M^+) and 300 ($M^+-C_4H_8$); δ 0.97 (14α-Me), 1.1 (13β-Me), 1.13 (OBu^t), 3.74 obsc (1H, m, 17α-H), 3.78 (OMe), 6.57-6.8 (2H, m, 2- and 4-H), and 7.1 (1H, d, J 8Hz, 1-H)(Found: C, 80.9; H, 10.0. $C_{24}H_{36}O_2$ requires C, 80.85; H, 10.2%).

14-Methyl-8α,14α-estra-1,3,5(10)-triene-3,17β-diol 3-Methyl Ether (17)

The t-butyl ether (16)(36 mg) was treated with toluene-p-sulphonic acid in refluxing benzene under nitrogen for 3.5h and the product was chromatographed on silica gel (3g) with ethyl acetate-benzene (1:10) to give the 17β-alcohol (17)(26 mg), m.p. 140-141°C (from aqueous methanol); m/z 300 (M^+)and 285 (M^+-Me); δ 0.98 (14α-Me), 1.08 (13β-Me), 3.78 (OMe), 4.01 (1H, dd, J 8.5 and 6Hz, 17α-H), 6.54-6.8 (2H, m, 2-, and 4-H), and 7.09 (1H, d, J 8Hz, 1-H)(Found: C, 80,15; H, 9.5. $C_{20}H_{28}O_2$ requires C, 80,0; H, 9.4%).

17β-t-Butoxy-3-methoxy-14-methyl-14α-estra-1,3,5(10),9(11)- and -1,3,5(10),8-tetraenes (21)

A 1:1 mixture (500 mg) of 3-methoxy-14-methyl-14α-estra-1,3,5(10),9(11)- and -1,3,5(10),8-tetraen-17-one (1) and (2) was treated with sodium in refluxing toluene-isopropanol, as described in a previous experiment, and the product was chromatographed on silica gel (50 g) with ethyl acetate-benzene (1:10). The first fraction (55 mg) comprised an inseparable 1:1 mixture of $\Delta^{9(11)}$- and Δ^{8}-17α-alcohols (18), ν_{max} 3620 cm^{-1} (OH); m/z 298 (M^+) and 283 m(M^+-Me); δ($\Delta^{9(11)}$-component) 0.78 (13β-Me), 1.02 (14α-Me), 3.8 (OMe), ca 3.98 br (1H, m, 17β-H), 6.3 br (1H, m, $W_{\frac{1}{2}}$ 6Hz, 11-H), 6.58-6.8 (2H, m, 2- and 4-H), and 7.65 (1H, d, J 9Hz, 1-H); δ(Δ^{8}-component) 0.78 (13β-Me), 1.26 (14α-Me), 3.8 (OMe), ca 3.98 br (1H, m, 17β-H), 6.58-6.8 (2H,m, 2- and 4-H), and 7.14 (1H, d, J 9Hz, 1-H). Further elution with the same solvent gave an inseparable 1:1 mixture (430 mg) of the $\Delta^{9(11)}$- and Δ^{8}-17β-alcohols (19), ν_{max} 3620 cm^{-1} (OH); m/z 298 (M^+)and 283 (M^+-Me); δ($\Delta^{9(11)}$-component) 0.78 (14α-Me), 0.86 (13β-Me), 3.7 (OMe), 4.12 br (1H, m, 17α-H), 6.24 br (1H, m, $W_{\frac{1}{2}}$ 6Hz), 11-H, 6.45-6.8 (2H, m, 2- and 4-H), and 7.62 (1H), d, J 9Hz, 1-H); δ(Δ^{8}-component) 0.88 (13β-Me), 1.02 (14α-Me), 3.7 (OMe), 4.12 br (1H, m, 17α-H), 6.45-6.8 (2H ,m, 2- and 4-H), 7.0-7.3 (1H, m, 1-H).

The mixture of 17β-alcohols (19) was t-butylated, as described in a previous experiment, and the product was chromatographed on silica gel with benzene-hexane (1:1) to give an inseparable mixture of products (164 mg), formulated as the 17β-t-butoxy-2-butyl-$\Delta^{9(11)}$- and -Δ^{8}-compounds (20), m.p. 120-123°C; m/z 410 (M^+) and 395 (M^+-Me); δ($\Delta^{9(11)}$-component; ca 35%) 0.8 (14α-Me), 0.85 (13β-Me), 1.16 (OBu^t), 1.37 (2-Bu^t), 3.82 (OMe), 3.9 obsc (1H, m, 17α-H), 6.27 (1H, m, $W_{\frac{1}{2}}$ Hz, 11-H), 6.58 (1H, s, 4-H), and 7.67 (1H, s, 1-H); δ(Δ^{8}-component; ca 65%) 0.85 (13β-Me), 1.02 (14α-Me), 1.16 (OBu^t), 1.37 (2-Bu^t), 3.82 (OMe), 3.9 br (1H, m, 17α-H), 6.68 (1H, s, 4-H), and 7.17 (1H, s, 1-H). Further elution with the same solvent gave an inseparable mixture of 17β-t-butoxy-$\Delta^{9(11)}$- and -Δ^{8}-compounds (21)(312 mg); m/z 354 (M^+) and 339 (M^+-Me); δ($\Delta^{9(11)}$-component; ca 60%) 0.8 (14α-Me), 0.85 (13β-Me), 1.15 (OBu^t), 3.78 (OMe), 3.94 br (1H, m, 17α-H), 6.23 br (1H, m, W 6Hz, 11-H), 6.55-6.8 (2H, m, 2- and 4-H), and 7.65 (1H, d, J 9Hz, 1-H); δ(Δ^{8}-component; ca 40%) 0.85 (13β-Me), 1.02 (14α-Me), 1.15 (OBu^t), 3.78 (OMe), 3.95 br (1H, m, 17α-H), 6.55-6.8 (2H, m, 2- and 4-H), and 7.13 (1H, d, J 9Hz, 1-H).

17β-Butoxy-3-methoxy-14-methyl-14α-estra-1,3,5(10),6,8-pentaene (23)

(a) The 3:2 mixture (270 mg) of the 17β-t-butoxy-$\Delta^{9(11)}$- and -Δ^{8}-compounds (21) was refluxed with 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ)(454 mg) in dry benzene (90 ml) under nitrogen for 4h. Aqueous sodium hydrogencarbonate was added, and the organic layer was separated and washed with water, dried ($MgSO_4$), and evaporated to give a crystalline residue (280 mg), which was chromatographed

on silica gel (30 g). Elution with benzene-hexane (1:1) afforded 17β-t-butoxy-3-methoxy-14-methyl-14α-estra-1,3,5(10),6,8,11-hexaene (22)(161 mg), m.p. 148-150°C (from dichloromethane-methanol); λ_{max} 243 (log ε 4.75), 284 (3.64), 297 (3.62), 316 (3.62), and 343 (3.52) nm; m/z 350 (M^+), and 293 (M^+-Bu^t); δ (500 MHz), 0.84 (3H, s, 13β-Me), 1.17 (3H, d, J 1.2Hz, 14α-Me), 1.22 (9H, s,t-Bu), 3.89 (3H, s, OMe), 4.26 (1H, dd, J 8.7 and 6Hz, 17α-H), 6.31 (1H, J 9.7 Hz, 12-H), 7.06 (1H, d, J 9.7Hz, 11-H), 7.08 (1H, d, J 2.6Hz, 4-H), 7.13 (1H, dd, J 9.2 and 2.6Hz, 2-H), 7.17 (1H, d, J 8.2Hz, 7-H), 7.6 (1H, d, J 8.2Hz, 6-H), and 7.91 (1H, d, J 9.2Hz, 1-H)(Found: C, 82.1; H, 8.7. $C_{24}H_{30}O_2$ requires C, 82.2; H, 8.6%). followed by 17β-t-butoxy-3-methoxy-14-methyl-14α-estra-1,3,5(10),6,8-pentaene (23)(99 mg), m.p. 132-134°C (from dichloromethane-methanol; λ_{max} 229 (log ε 4.83), 266 (3.68); 277 (3.72), 287 (3.55), 322 (3.3), and 337 (3.42) nm; m/z 352 (M^+) and 337 (M^+-Me); δ (500 MHz), 0.73 (1H, d, J 0.6Hz, 13β-Me), 1.1 (1H, d, J, 1.04 Hz, 14α-Me), 1.19 (9H, s, t-Bu), 3.89 (3H, s, OMe), 3.99 (1H, dd, J 8.9 and 6.4Hz,17α-H), 7.09 (1H, d, J 2.7Hz, 4-H), 7.13 (1H, dd, J 9.2 and 2.7Hz, 2-H), 7.17 (1H, d, J , 8.3 Hz, 7-H), 7.55 (1H, d, J 8.3Hz, 6-H), and 7.86 (1H, d, J 9.2Hz, 1-H)(Found: C, 81.2; H, 9.1. $C_{24}H_{32}O_2$ requires C, 81.8; H, 9.15%).

(b) The hexaene (22)(135 mg) in ethyl acetate (10 ml) was hydrogenated in the presence of palladium on charcoal (5%; 40 mg) for 2h, and the filtered solution was evaporated. The crystalline residue was filtered through silica gel (15 g) with benzene-hexane (1:1) to give the pentaene (23)(123 mg), m.p. and mixed m.p. 132-134°C (from dichloromethane-methanol).

14-Methyl-14α-estra-1,3,5(10),6,8-pentaene-3,17β-diol 3-Methyl Ether (24)

Treatment of the 17β-t-butyl ether (23)(140 mg) with toluene-p-sulphonic acid (50 mg) in refluxing benzene, as described in previous experiments,followed by filtration of the product through silica gel with ethyl acetate-benzene (1:10), gave the 17β-alcohol(24)(110 mg), m.p. 133-134°C (from benzene-hexane); ν_{max} 3610 cm^{-1} (OH); m/z 296 (M^+) and 281 (M^+-Me); δ 0.78 (13β-Me), 1.1 (14α-Me), 3.92 (OMe), 4.32 (1H, dd, J 8.5 and 6Hz, 17α-H), 7.1-7.3 (3H, m, 2-, 4-, and 7-H), 7.6 (1H, d, J 8Hz, 6-H), and 7,92 (1H, d, J 10Hz, 1-H)(Found: C,80.8; H, 8.2. $C_{20}H_{24}O_2$ requires C, 81.0; H, 8.2%).

14-Methyl-14α-estra-1,3,5(10),6,8-pentaene-3,17β-diol (25)

The methyl ether (24)(60 mg) was hydrolysed with boron tribromide as described in previous experiments. The product (45 mg) was crystallised twice from chloroform-ethanol to give the diol (25), m.p. 140-145°C; λ_{max} 229 (log ε 4.77), 259 (3.45),268 (3.6), 279 (3.66, 290 (3.51), 326 (3.28), and 339 (3.35) nm (Found: M^+, 282.1620. $C_{19}H_{22}O_2$ requires M, 282.1619). Attempted removal of solvent of crystallisation under high vacuum resulted in decomposition of the compound.

Dehydrogenation of the Estratetraen-17-ones (1) and (2)

(a) The 1:1 mixture (29.6 mg) of $\Delta^{9(11)}$- and Δ^8-17-ketones (1) and 2) was refluxed with DDQ (50 mg) in dry benzene (10 ml) under nitrogen for 4h. The product was worked up and chromatographed on silica gel (3g) with ethyl acetate-benzene (1:49) to give 3-methoxy-14-methyl-14α-estra- 1,3,5(10),6,8,11-hexaen-17-one (26)(14 mg), m.p. 166-167°C (from benzene-hexane); ν_{max} 1740 cm^{-1} (CO); λ_{max} 242 (log ε 4.79), 292 (3.68),303 (3.85), 316 (3.95), 340 (3.53), and 355 (3.57); m/z 292 (M^+) and 277 (M^+-Me); δ (500 MHz) 0.98 (3H, s, 13β-Me), 1.18 (3H, d, J 0.7 Hz, 14α-Me), 3.91 (1H, s, OMe), 6.47 (1H, d, J 9.7 Hz, 12-H), 7.11 (1H, d, J 2.6Hz, 4-H), 7.162 obsc (1H, d, J ca 9.7Hz, 11-H), 7.164 (1H, dd, J 9.3 and 2.6Hz, 2-H), 7.28 (1H, d, J 8.2Hz 7-H), 7.69 (1H, d, J 8.2Hz, 6-H), and 7.99 (1H, d, J 9.3Hz, 1-H)(Found: C, 82.0; H, 7.0. $C_{20}H_{20}O_2$ requires C, 82.2; H, 6.9%). Further elution with ethyl acetate-benzene (1:19) gave the pentaene (12) 15 mg), m.p. and mixed m.p. 184-186°C (from benzene-hexane).

(b) Dehydrogenation of the $\Delta^{9(11)}$-compound (1)(3 mg) with DDQ,as described in (a), afforded the pure hexaene (26)(3 mg) m.p. and mixed m.p. 166-167°C, uncontaminated with (12).

(c) Similar dehydrogenation of the Δ^8-compound (2)(6 mg) afforded only the pentaene (12)(5 mg), m.p. and mixed 184-186°C.

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