Steroidal Analogues of Unnatural Configuration. Part 13.[1] Synthesis and Ring B Reactions of 4,4,9-Trimethyl-9β,10α-estr-5-ene

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The conversion of 17β-hydroxy-9-methyl-9β,10α-estr-4-en-3-one into 4,4,9-trimethyl-9β,10α-estr-5-ene is described, and certain ring B transformations of the latter compound are compared and contrasted with those carried out upon 4,4,14α-trimethyl-19(10 → 9β)*abeo*-10α-pregn-5-en-11-one in an earlier study. The stereochemical implications of these results are discussed.

DURING a recent investigation [2] into the reactions of 4,4,14α-trimethyl-19(10 → 9β)*abeo*-10α-pregn-5-en-11-one (1) and its 5β,6β-epoxide (2), evidence was presented for conformational abnormalities in the derived 6,11-diols (3)—(6). The respective roles of 6- and 11-functionality could not be clearly differentiated, and an attempt to ascertain the causes and extent of skeletal deformations in this series through selective reactions of the 6,11-diketone (7) was unsuccessful. Accordingly, attention was turned to the readily available 17β-hydroxy-9-methyl-9β,10α-estr-4-en-3-one [3] (8) as a possible source of a model 5-olefin (13) bearing the essential stereochemical features of (1). Such a model would serve as the starting material for comparative reactions in ring B and, in this way, the influence of ring C functionality and the 14α-methyl group upon conformational features in the curcurbitacin-derived 6,11-diols [2] (3)—(6) could be better defined.

The testosterone analogue (8) was subjected to forcing alkylation [4] with methyl iodide in the presence of potassium t-butoxide, to give the desired 4,4-dimethyl-Δ^5-3-ketone (11), in addition to minor products (9) and (10) of further alkylation. The structure of (11) followed unexceptionally from spectroscopic data. The Cotton effect of (11) ($\Delta\varepsilon_{295}$ −2.1) and of the minor products (9) and (10) compared closely with that of anhydrodihydrolitsomentone,[5] a triterpene derivative possessing identical functionality and stereochemistry in rings A and B.

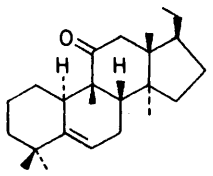
Notably, no evidence was seen for the formation of the 4,4-dimethyl-$\Delta^{5(10)}$-3-ketone during alkylation, despite the predilection of the Δ^4-bond of (8) for isomerisation toward the 5(10)- rather than the 5(6)-position.[6] This suggests that the deprotonation (or isomerisation) step leading to the 3,5-dien-3-olate of (8), is kinetically controlled under the reaction conditions and that successive methylations at C(4) are much faster than possible isomerisation involving abstraction of the hindered 10α-proton.

Oxidation of compound (11) with 8N-chromic acid in acetone at 0 °C gave the 3,17-diketone (12), which was cleanly reduced under Wolff–Kishner conditions to the desired 4,4-dimethyl-5-ene (13).

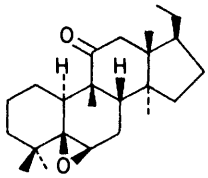
Epoxidation of the olefin (13) with *m*-chloroperbenzoic acid gave a single epoxide (14), whose n.m.r. signal for the 6-proton displayed coupling (doublet, *J* 6 Hz) characteristic of 5β,6β-epoxides in the 9β-alkyl-10α-series.[7] The high stereoselectivity of this addition to the Δ^5-bond of (13) is similar to that of (1). Similarly, *cis*-hydroxylation of compound (13) with osmium tetraoxide gave only the 5β,6β-diol (15). In this case, the

[1] Part 12, J. C. A. Boeyens, J. R. Bull, J. Floor, and A. Tuinman, *J.C.S. Perkin I*, 1978, 808.
[2] J. R. Bull and C. J. van Zyl, *Tetrahedron*, 1972, **28**, 3957.
[3] J. R. Bull and A. Tuinman, *Tetrahedron*, 1973, **29**, 1101.
[4] R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Chem. Soc.*, 1957, 1131.
[5] T. R. Govindachari, N. Viswanathan, and P. A. Mohamed, *Tetrahedron*, 1971, **27**, 4991.
[6] J. R. Bull, J. Floor, and A. Tuinman, *Tetrahedron*, 1975, **31**, 2157.
[7] J. R. Bull, *J.C.S. Perkin I*, 1972, 627.

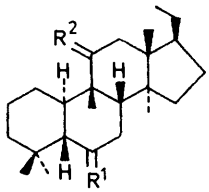
n.m.r. signal for the 6-proton appeared at δ 3.91 as a quartet (*J* 12 and 5 Hz), indicative of an axial proton in



(1)



(2)



(3) R^1 = β-OH, α-H; R^2 = β-H α-OH
(4) R^1 = R^2 = β-OH, α-H
(5) R^1 = β-H, α-OH; R^2 = β-OH, α-H
(6) R^1 = R^2 = β-H, α-OH
(7) R^1 = R^2 = O

an undeformed cyclohexane ring. Careful oxidation of (15) with chromium trioxide–pyridine afforded the 5β-hydroxy-6-ketone (16), which underwent ready dehydration in the presence of thionyl chloride in pyridine at −10 °C, to give the $\Delta^{5(10)}$-6-ketone (17). This reaction sequence parallels that carried out [7] upon the related olefin (1), for which comparable results were obtained. The weakly negative Cotton effect of the 6-oxo-group in (16) ($\Delta\varepsilon_{306}$ −0.2) accords qualitatively with the deduced net effect of that group in the related 5β-hydroxy-6,11-diketone.[7] However, the Cotton effect of the $n\rightarrow\pi^*$ transition in (17) is of opposite sign to that of the 6-oxo-group in the related $\Delta^{5(10)}$-6,11-diketone; in in view of evidence [7] for mutual perturbation of the chromophores in the latter compound, this discrepancy is probably not meaningful.

Reduction of the epoxide (14) with lithium in ethylamine [8] afforded the 5β-hydroxy-compound (18) (98%) together with traces of the 6β-hydroxy-compound (19) (see below), and prolonged treatment of (14) with lithium aluminium hydride in refluxing tetrahydrofuran gave only (18). These results contrast with the behaviour of (2),[2] and demonstrate the powerful steric influence of the 14α-methyl group.

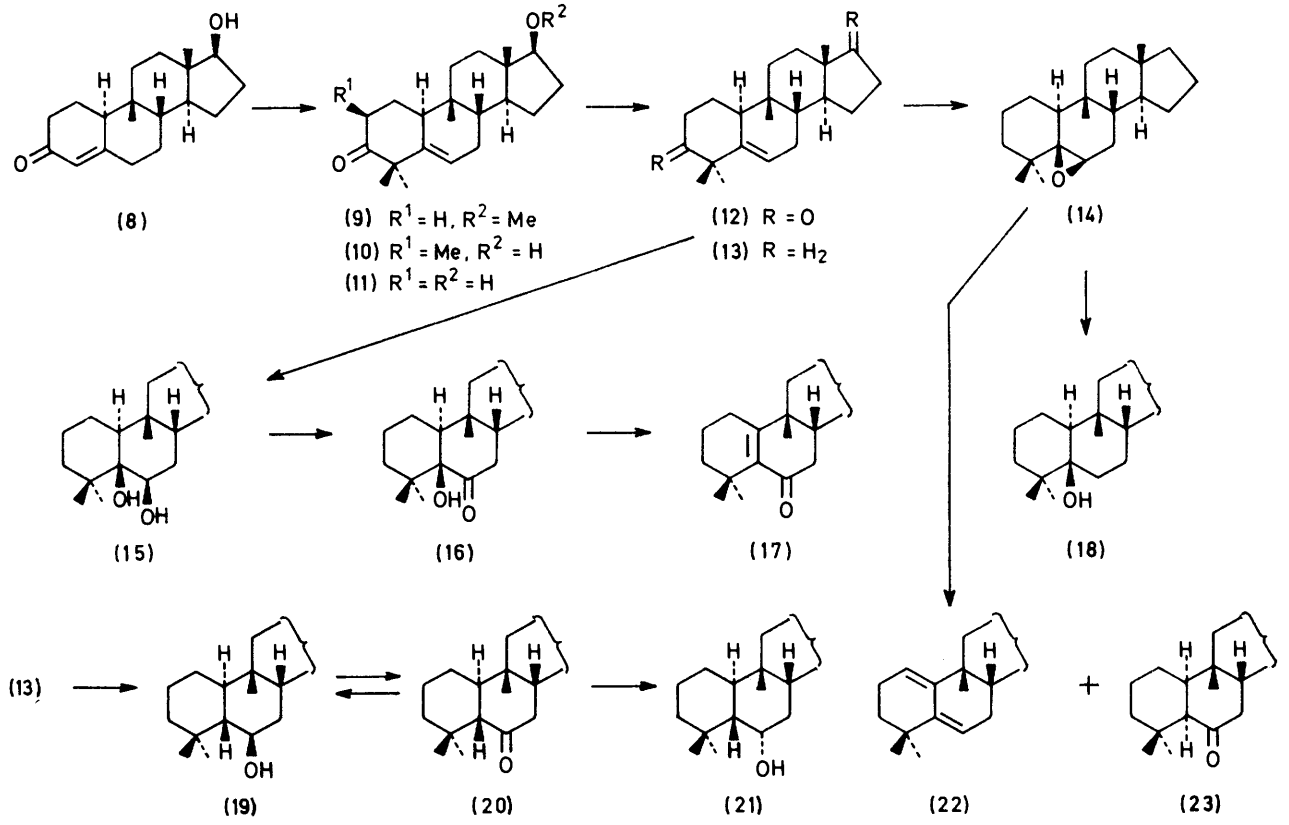
The failure of (14) to undergo significant C(5)–O bond cleavage necessitated using another route to the 6β-hydroxy-compound (19); this was achieved through hydroboration of the olefin (13) and subsequent alkaline peroxide oxidation to give a product (19) (68%), whose structure follows from the established stereoselectivity of addition to the Δ^5-bond in this series. Furthermore, the width (27 Hz) of the n.m.r. signal for the 6α-proton confirmed that the 6β-substituent is equatorial and hence, that ring B must be in a chair conformation.

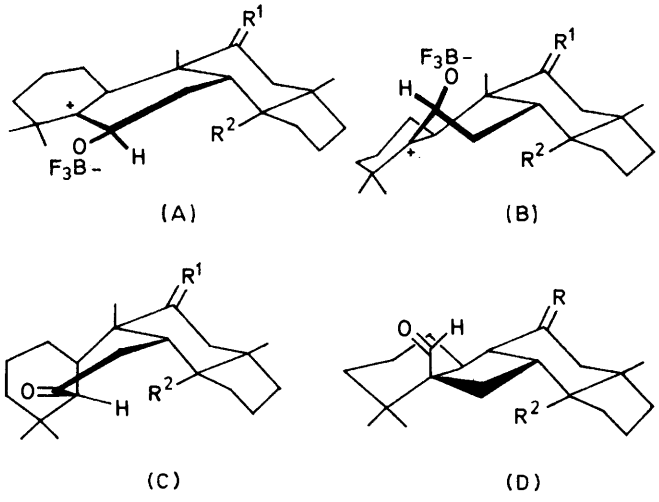
Oxidation of (19) afforded the 6-ketone (20), in which no conformational abnormalities could be detected spectroscopically. Reduction of (20) with lithium in liquid ammonia gave principally the 6β-hydroxy-compound (19) (95%), whereas treatment of (20) with lithium aluminium hydride resulted in almost exclusive formation of the 6α-hydroxy-compound (21) (98%). N.m.r. evidence showed that the 6-substituent in (21) is axial and it was reasonably assumed that ring B is also undeformed in this isomer. In both modes of reduction of (20), the stereoselectivity displayed by the respective reagents is similar to that found [2] toward the ring B functionality of the 6,11-diketone (7). However, the 6-ketone (20) and its reduction products (19) and (21) are conformationally ' normal ' in contrast [2,9] to the cucurbitacin-derived diols (3)—(6).

In a further experiment, the 5β,6β-epoxide (14) was treated with boron trifluoride–diethyl ether in benzene, to give the isomeric 6-ketone (23) as the major product (*ca.* 50%). The structure of (23) was demonstrated through treatment with methanolic potassium hydroxide, which resulted in quantitative conversion into the 5β-isomer (20). This accords with expectations based upon the relative stabilities of appropriate perhydrophenanthrenes,[10] and extrapolated to 5α,9β,10α- and 5β,9β,10α-steroids.[11] Several other products were detected (t.l.c.) in the crude rearrangement product but only one, the 1(10),5-diene (22) (20%) was isolated and identified. Traces of a further diene were found, but this and other minor components could not be purified and characterised. Nevertheless, the major rearrangement product (23) from (14) revealed that bond migration propensities differ markedly from those of (2), which gave mainly (80%) products of 7(6 ⟶ 5α)*abeo* rearrangement under the same reaction conditions.[2] An explanation was sought in the influence of substitution differences upon possible transition state geometries; thus, if it is reasonably assumed [12] that the substrate–Lewis acid complex will possess substantial ionic character at an advanced stage of C(5)–O bond breakage, then two relevant conformers (A) and (B) can be formulated. The groups most suitably aligned for migration are 6α-H in the $^7H_8$ conformer [13] (A) and C(7) in the $^{6,9}B$ conformer [13] (B). However, the former conformer (A) would be expected to preponderate, since it seems reasonable to assume that it will be of lower energy than (B); insofar as comparison can be made, such an assumption is compatible with experimental and theoretical findings (*X*-ray diffraction results and force-field calculations [9]) on ring B of comparable 6β-hydroxy-5β-compounds. In

[8] A. S. Hallsworth and H. B. Henbest, *J. Chem. Soc.*, 1957, 4604.
[9] J. C. A. Boeyens, J. R. Bull, A. Tuinman, and P. H. van Rooyen, in the press.
[10] N. L. Allinger, B. J. Gordon, I. J. Tyminski, and M. T. Wuesthoff, *J. Org. Chem.*, 1971, **36**, 739, and references cited therein.
[11] J. R. Bull, A. J. Hodgkinson, and A. Tuinman, *Tetrahedron*, 1973, **29**, 2415.
[12] D. N. Kirk and M. P. Hartshorn, ' Steroid Reaction Mechanisms ', Elsevier, Amsterdam, 1968, ch. 8.
[13] J. C. A. Boeyens, *J. Cryst. Mol. Struct.*, in the press.

the absence of other factors therefore, both epoxides (2) and (14) should rearrange mainly to the corresponding 6-oxo-5α-compounds. However, hydride migration will lead initially to a $B_{5,8}$ conformer [13] (C), which may subsequently undergo ring A inversion to give the most stable form of the product. The results show that the intermediate conformer (C) must be attainable in the case of (14), but impossible when R^2 = Me owing to severe steric compression on the α-face. Consequently, the pathway *via* conformer (A) is suppressed and participation by the higher-energy conformer (B), aligned for ring B contraction, is favoured in the case of (2).





These conclusions are supported by force-field calculations; [14] thus, heats of formation in the model series (R^1 = H_2, R^2 = H) [−90.7 and −86.7 kcal mol^{-1} for (C) and (D) respectively] favour the intermediate (C) derived from hydride migration, whereas those of the curcurbitacin-derived series (R^1 = O, R^2 = Me) [−122.5 and −125.9 kcal mol^{-1} for (C) and (D) respectively] reveal that the ring-contracted intermediate (D) is indeed the more stable.

The disparity in yields of products derived from the alternative mode of hydride migration from C(10) to C(5) in the two series may also be understood through consideration of reaction intermediates. Thus, in (14) initial hydride migration to give a 6β-hydroxy-$\Delta^{1(10)}$-intermediate, having a ring B conformation similar to (C), is reasonably competitive with the major reaction pathway, and leads ultimately to the diene (22) (20%). However, this pathway in (2) is inhibited by α-face steric compression, but not entirely prevented since a small proportion (5%) of the corresponding 1(10),5-diene is obtained.

The evidence presented here confirms that the 14α-methyl group in (1) and its derivatives plays a decisive role in the mechanistic and conformational aberrations displayed [2] by the series. In the light of these findings, a more detailed physicochemical examination of the

[14] N. L. Allinger, *QCPE*, 1975, **10**, 318.

6,11-diols (3)—(6) has been undertaken;[9] results hitherto available show that rings B and C do indeed adopt twist-boat conformations in certain cases. The results of this investigation will be the subject of a forthcoming publication.

EXPERIMENTAL

For general directions see ref. 1.

Alkylation of 17β-*Hydroxy*-9-*methyl*-9β,10α-*estr*-4-*en*-3-*one* (8).—A 1M-solution (20 ml) of potassium t-butoxide in t-butyl alcohol was added to a stirred solution of the enone (8) (2 g) in t-butyl alcohol (80 ml) at 40 °C under nitrogen. After 2 min methyl iodide (5 ml) was added and the mixture was stirred for 2 h at 25 °C, then acidified with aqueous acetic acid, diluted with water, and extracted with ethyl acetate. The usual work-up gave a product which was adsorbed on silica gel (200 g). Elution with ethyl acetate–hexane (1 : 1) gave 17β-*methoxy*-4,4,9-*trimethyl*-9β,10α-*estr*-5-*en*-3-*one* (9) (105 mg), m.p. 91—93 °C (from acetone–methanol), $[\alpha]_D$ +11° (*c* 0.8), $\nu_{max.}$ 1 703 cm^{-1}; $\Delta\varepsilon_{max.}$ −1.9 (294 nm); δ 0.78, 0.8, 1.19, and 1.2 (each 3 H, s, 4 × CH_3), 3.21 (1 H, t, *J* 8 Hz, 17α-H), 3.3 (3 H, s, 17β-OCH_3), and 5.52 (1 H, dt, *J* 6, 2, and 2 Hz, 6-H) (Found: C, 80.2; H, 10.25%; M^+, 330. $C_{22}H_{34}O_2$ requires C, 79.95; H, 10.4%; *M*, 330), followed by 17β-*hydroxy*-2β,4,4,9-*tetramethyl*-9β,10α-*estr*-5-*en*-3-*one* (10) (83 mg), m.p. 144—147 °C (from acetone–hexane), $[\alpha]_D$ +8° (*c* 0.6), $\nu_{max.}$ 3 602 and 1 705 cm^{-1}; $\Delta\varepsilon_{max.}$ −1.9 (295 nm); δ 0.79 (6 H, s, 2 × CH_3), 1.02 (3 H, d, *J* 6.5 Hz, 2β-CH_3), 1.19, and 1.22 (each 3 H, s, 2 × CH_3), 3.65 (1 H, q, *J* 8.5 and 7.5 Hz, 17α-H), and 5.48 (1 H, dt, *J* 6, 2, and 2 Hz, 6-H) (Found: C, 80.3; H, 10.3%; M^+, 330). Further elution afforded 17β-*hydroxy*-4,4,9-*trimethyl*-9β,10α-*estr*-5-*en*-3-*one* (11) (1.75 g), m.p. 171—173 °C (from dichloromethane–hexane), $[\alpha]_D$ +11° (*c* 0.8), $\nu_{max.}$ 3 604 and 1 705 cm^{-1}; $\Delta\varepsilon_{max.}$ −2.1 (295 nm); δ 0.79 and 0.83 (each 3 H, s, 2 × CH_3), 1.22 (6 H, s, 2 × CH_3), 3.64 (1 H, t, *J* 8 Hz, 17α-H), and 5.51 (1 H, dt, *J* 6, 2.5, and 2.5 Hz, 6-H) (Found: C, 79.9; H, 10.1%; M^+, 316. $C_{21}H_{32}O_2$ requires C, 79.7; H, 10.2%; *M*, 316).

4,4,9-*Trimethyl*-9β,10α-*estr*-5-*ene*-3,17-*dione* (12).—The alcohol (11) (1.65 g) in acetone (120 ml) was treated at 0 °C with 8N-chromic acid (1.5 ml) for 5 min. After addition of aqueous sodium disulphite (1%, 25 ml), the mixture was diluted with water and extracted with benzene to give the *diketone* (12) (1.65 g), m.p. 105—108 °C (from ethanol), $[\alpha]_D$ +90° (*c* 1.1), $\nu_{max.}$ 1 732 and 1 707 cm^{-1}; δ 0.87, 0.91, 1.19, and 1.21 (each 3 H, s, 4 × CH_3), and 5.57 (1 H, dt, *J* 6, 2, and 2 Hz, 6-H) (Found: C, 79.9; H, 9.7%; M^+, 314. $C_{21}H_{30}O_2$ requires C, 80.2; H, 9.6%; *M*, 314).

4,4,9-*Trimethyl*-9β,10α-*estr*-5-*ene* (13).—A mixture of the diketone (12) (1.4 g), hydrazine hydrate (85%, 2 ml), ethanol (3 ml), and diethylene glycol (100 ml) was refluxed (*ca.* 145 °C) for 1 h. Potassium hydroxide (1 g) was added and the volatile components were distilled until the temperature of the reaction mixture reached 220 °C. After 2.5 h at 220 °C the mixture was cooled, acidified, diluted with water, and extracted with benzene. The apparatus was rinsed with benzene to remove material which had distilled into the condenser, and the combined organic solution was worked up in the usual way to give material which was filtered through silica gel (45 g) to give the *olefin* (13) (780 mg), m.p. 53—56 °C (from acetone), $[\alpha]_D$ −3.4° (*c* 0.8), δ 0.72, 0.79, 0.98, and 1.04 (each 3 H, s, 4 × CH_3), and 5.34 (1 H, dt, *J* 6, 2, and 2 Hz, 6-H) (Found: C, 88.3; H, 12.0%; M^+, 286. $C_{21}H_{34}$ requires C, 88.0; H, 12.0%; *M*, 286).

5,6β-*Epoxy*-4,4,9-*trimethyl*-5β,9β,10α-*estrane* (14).—The olefin (13) (455 mg) in benzene (30 ml) was treated at 25 °C with *m*-chloroperbenzoic acid (70%, 450 mg) for 18 h to give, after work-up, the 5β,6β-*epoxide* (14) (460 mg), m.p. 111—113 °C (from acetone), $[\alpha]_D$ −39° (*c* 0.8); δ 0.66, 0.7, 0.89, and 1.07 (each 3 H, s, 4 × CH_3), and 3.08 (1 H, d, *J* 6 Hz, 6α-H) (Found: C, 83.65; H, 11.6%; M^+, 302. $C_{21}H_{34}O$ requires C, 83.4; H, 11.3%; *M*, 302).

4,4,9-*Trimethyl*-5β,9β,10α-*estrane*-5,6β-*diol* (15).—Osmium tetraoxide (100 mg) was added to the olefin (13) (100 mg) in dry pyridine (15 ml) at 25 °C. After 10 days, aqueous sodium disulphite (10%, 15 ml) was added and the mixture was stirred for 2 h and diluted with water. The product was isolated by extraction with chloroform and adsorbed on silica gel (15 g). Elution with ethyl acetate–hexane (1 : 4) afforded the 5β,6β-*diol* (15) (104 mg), m.p. 88—92 °C (from hexane), $[\alpha]_D$ −7° (*c* 0.7), $\nu_{max.}$ 3 575br cm^{-1}; δ 0.69 (3 H, s, CH_3), 1.0 (6 H, s, 2 × CH_3), 1.05 (3 H, s, CH_3), 2.24br (1 H, exch. by D_2O, O*H*), and 3.91 (1 H, q, *J* 12 and 5 Hz, 6α-H) (Found: C, 78.5; H, 11.4%; M^+, 320. $C_{21}H_{36}O_2$ requires C, 78.7; H, 11.3%; *M*, 320).

5-*Hydroxy*-4,4,9-*trimethyl*-5β,9β,10α-*estran*-6-*one* (16).—The diol (15) (85 mg) in pyridine (2 ml) was added dropwise to chromium trioxide (300 mg) in pyridine (5 ml) at 15 °C. After 2 h at 15 °C and 16 h at 25 °C, the mixture was poured into ice–water and extracted with benzene–ether (1 : 1). The extract was concentrated *in vacuo* and the residue was adsorbed on silica gel (10 g). Elution with ethyl acetate–hexane (1 : 9) afforded the *hydroxy-ketone* (16) (67 mg), m.p. 48—52 °C (from hexane), $[\alpha]_D$ −15° (*c* 0.7), $\nu_{max.}$ 3 595 and 1 710 cm^{-1}; $\Delta\varepsilon_{max.}$ −0.2 (306 nm); δ 0.73, 1.03, 1.19, and 1.22 (each 3 H, s, 4 × CH_3), 1.91 (1 H, q, *J* 12.5 and 3 Hz, 7α-H), and 3.41 (1 H, q, *J* 12.5 and 5 Hz, 7β-H) (Found: C, 79.1; H, 10.8%; M^+, 318. $C_{21}H_{34}O_2$ requires C, 79.2; H, 10.8%; *M*, 318).

4,4,9-*Trimethyl*-9β-*estr*-5(10)-*en*-6-*one* (17).—Thionyl chloride (250 μl) was added to the hydroxy-ketone (16) (50 mg) in dry pyridine (1.2 ml) at −10 °C. After being stirred at −10 °C for 1 h, the reaction was quenched with ice. The product was isolated by extraction with benzene and adsorbed on silica gel (10 g). Elution with ethyl acetate–hexane (1 : 19) afforded the *enone* (17) (30 mg), m.p. 79—83 °C (from hexane), $[\alpha]_D$ −112° (*c* 0.5), $\nu_{max.}$ 1 655 and 1 580 cm^{-1}; $\lambda_{max.}$ 255 nm (ε 9 370); $\Delta\varepsilon_{max.}$ −13.8 (251 nm) and +1.6 (329 nm); δ 0.75, 1.16, 1.18, and 1.23 (each 3 H, s, 4 × CH_3), 2.23 (1 H, q, *J* 17 and 2 Hz, 7β-H), and 2.72 (1 H, q, *J* 17 and 5 Hz, 7α-H) (Found: C, 84.0; H, 10.5%; M^+, 300. $C_{21}H_{32}O$ requires C, 83.9; H, 10.7%; *M*, 300).

Lithium–Ethylamine Reduction of the Epoxide (14).—Lithium (*ca.* 75 mg) was added in small portions to the epoxide (14) (260 mg) in ethylamine (25 ml, freshly distilled from lithium). After 90 min ammonium chloride was added, the ethylamine was allowed to evaporate, and water was added to the residue. The product was isolated by extraction with ethyl acetate and adsorbed on silica gel (30 g). Elution with chloroform–benzene (3 : 1) afforded 4,4,9-*trimethyl*-5β,9β,10α-*estran*-5-*ol* (18) (256 mg), m.p. 103—106 °C (from methanol), $[\alpha]_D$ −20° (*c* 0.6), $\nu_{max.}$ 3 618 cm^{-1}; δ 0.71, 0.83, 1.0, and 1.04 (each 3 H, s, 4 × CH_3), and 1.2 (1 H, s, exch. with D_2O, O*H*) (Found: C, 82.9; H, 12.3%; M^+, 304. $C_{21}H_{36}O$ requires C, 82.8; H, 11.9%;

M, 304), followed by a trace (*ca.* 4 mg) of the 6β-alcohol (19) (see following experiment).

4,4,9-*Trimethyl*-5β,9β,10α-*estran*-6β-*ol* (19).—Diborane in tetrahydrofuran (M; 4 ml) was added to the olefin (13) (300 mg) in tetrahydrofuran (3 ml) at 0 °C under nitrogen.

The mixture was kept at 0 °C for 4 h and overnight at 25 °C. Aqueous sodium hydroxide (10%; 4 ml) and hydrogen peroxide (30%; 4 ml) were added, and the mixture was refluxed for 1 h, acidified, and extracted with ethyl acetate. Chromatography of the product on silica gel (30 g) with chloroform–benzene (3 : 1) afforded the starting material (13) (60 mg), followed by the 6β-*alcohol* (19) (217 mg), m.p. 97—101 °C (from hexane), $[\alpha]_D$ −10° (*c* 0.9); $\nu_{max.}$ 3 600 cm^{-1}; δ 0.72, 0.91, 0.97, and 1.17 (each 3 H, s, 4 × CH_3), and 3.72br (1 H, $W_{\frac{1}{2}}$ *ca.* 27 Hz, 6α-H) (Found: C, 82.6; H, 12.1%; M^+, 304).

4,4,9-*Trimethyl*-5β,9β,10α-*estran*-6-*one* (20).—The alcohol (19) (130 mg) in acetone (10 ml) was treated with N-chromic acid at 0 °C for 20 min. Aqueous sodium sulphite (1%) was added and the mixture was extracted with benzene. The crude product was adsorbed on silica gel (25 g) and eluted with ethyl acetate–hexane (1 : 19) to give the *ketone* (20) (114 mg), m.p. 97—100 °C (from methanol), $[\alpha]_D$ −15° (*c* 0.9), $\nu_{max.}$ 1 705 cm^{-1}; $\Delta\varepsilon_{max.}$ −0.8 (296 nm); δ 0.71, 1.06, 1.08, and 1.11 (each 3 H, s, 4 × CH_3), 1.97 (1 H, q, *J* 12.5 and 4.5 Hz, 7α-H), 2.05 (1 H, d, *J* 8 Hz, 5β-H), and 2.66 (1 H, q, *J* 12.5 and 5.5 Hz, 7β-H) (Found: C, 83.3; H, 11.6%; M^+, 302. $C_{21}H_{34}O$ requires C, 83.4; H, 11.3%; *M*, 302).

Reduction of the 6-*Ketone* (20).—(*a*) A mixture of the ketone (20) (50 mg) and lithium aluminium hydride in dry tetrahydrofuran (5 ml) was refluxed for 1.5 h, the excess of reagent was destroyed with aqueous ammonium chloride, and the product was isolated by extraction with benzene. Crystallisation from methanol afforded 4,4,9-*trimethyl*-5β,9β,10α-*estran*-6α-*ol* (21) (16 mg), m.p. 107—109 °C, $[\alpha]_D$ −1.5° (*c* 0.5), $\nu_{max.}$ 3 625 cm^{-1}; δ 0.67, 0.86, 0.97, and 1.07 (each 3 H, s, 4 × CH_3), and 4.17 (1 H, m, $W_{\frac{1}{2}}$ 10 Hz, 6β-H) (Found: C, 83.0; H, 11.8%; M^+, 304). Chromatography of the mother liquor material on silica gel (10 g) with ethyl acetate–hexane (1 : 19) afforded further 6α-alcohol (21) (33 mg) and the 6β-alcohol (19) (*ca.* 1 mg), identified by comparison with authentic material.

(*b*) The ketone (20) (50 mg) in dry tetrahydrofuran (2 ml) and absolute ethanol (50 μl) was added dropwise to a stirred solution of lithium (*ca.* 50 mg) in liquid ammonia (*ca.* 10 ml, freshly distilled from sodium). After 20 min the excess of lithium was destroyed with ethanol and the ammonia was allowed to evaporate. The product was isolated by extraction with benzene and adsorbed on silica gel (10 g). Elution with ethyl acetate–hexane (1 : 9) gave the 6α-alcohol (21) (*ca.* 2 mg), followed by the 6β-isomer (19) (45 mg), both identified by comparison with authentic material.

Treatment of the Epoxide (14) *with Boron Trifluoride–Diethyl Ether*.—The epoxide (14) (140 mg) in dry benzene (15 ml) was treated at 25 °C under N_2 with boron trifluoride–diethyl ether (0.1 ml) for 15 min. The solution was diluted with benzene and washed successively with aqueous sodium hydrogen carbonate and sodium chloride. Evaporation of the solvent and chromatography of the residue on silica gel (35 g) with hexane gave a homogeneous oil (27 mg), $\lambda_{max.}$ 238 nm (ε 10 000), δ 0.74, 0.94, 1.04, and 1.25 (each 3 H, s, 4 × CH_3), 5.38, and 5.58 (each 1 H, m, $W_{\frac{1}{2}}$ 10 Hz, 1- and 6-H), *m/e* 284 (M^+), to which the 1(10),5-diene structure (22) was tentatively assigned, followed by a minor fraction (7 mg), *m/e* 284 (M^+), assumed to be an isomeric diene. Further elution with ethyl acetate–hexane (1 : 9) gave mixed fractions (105 mg) containing at least five components. Re-chromatography of the material on silica gel (25 g) afforded material (84 mg) which was crystallised from methanol to give 4,4,9-*trimethyl*-5α,9β,10α-*estran*-6-*one* (23) (70 mg), m.p. 113—115 °C, $[\alpha]_D$ +44° (*c* 0.5), $\nu_{max.}$ 1 709 cm^{-1}; $\Delta\varepsilon_{max.}$ +2.2 (289 nm); δ 0.74, 0.87, 0.92, and 1.03 (each 3 H, s, 4 × CH_3), and 2.79 (1 H, d, *J* 8.5 Hz, 5α-H) (Found: C, 83.1; H, 11.3%; M^+, 302).

Isomerisation of the 6-*Ketone* (23).—Treatment of the 5α-isomer (23) (5 mg) with methanolic 2N-potassium hydroxide (1 ml) at 25 °C for 24 h, followed by work-up and crystallisation of the product from methanol gave the 5β-isomer (20), identified by m.p., mixed m.p., and t.l.c.

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