Steroids and Related Natural Products. Part XLI.[1] 14α-Methyl Œstranes

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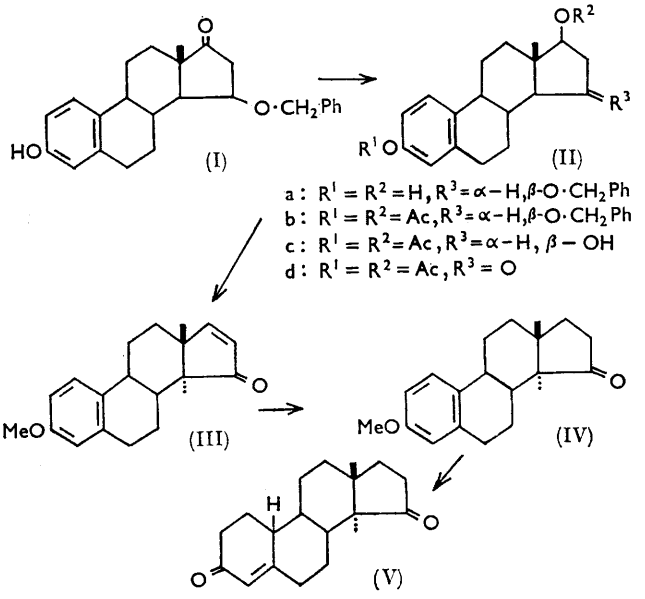
Œstrone has been converted into 14α-methylœstr-4-ene-3,15-dione (V) in 14 steps. Direct alkylation at position 14 (activated by a 15-oxo-group) proved convenient for introducing the angular methyl group. Configuration of the 14-methyl substituent was established by o.r.d. measurements.

ASSUMING that a defect or alternate pathway [2] in the biosynthetic [3] conversion of lanosterol into the hormonally active steroids might lead to 14α-methyl steroids, we synthesised 14α-methyltestosterone [4] and 14α-methylprogesterone.[5] We subsequently decided to complement the androgenic and progestational-type 14α-methyl steroids with several 14α-methyl œstranes and this led to the present study.

Our earlier syntheses of 14α-methyl steroids began from lanosterol as this is potentially one of the most abundant steroid precursors. Furthermore, degradation of lanosterol allowed ready access from common intermediates to both androstane and pregnane derivatives of known stereochemistry at the C/D ring juncture. The increasing availability of œstrone and derivatives by relatively simple total syntheses combined with new methods for easily obtaining 15-oxygenated œstranes [6] suggested that suitable transformation of œstrone could provide an attractive route to 14α-methyl œstranes. The feasibility of such an approach received further encouragement by a patent report describing the synthesis of 14α-methyl-11-oxoprogesterone based on alkylation of a 15-oxo-precursor,[7a] the 15-ol having been obtained by microbiological oxidation (cf. ref. 7*b*). Conversion of œstrone into the 14α-methyl œstranes (IV) and (V) illustrated the practicality of this route to certain 14α-methyl steroids.

Œstrone was converted into its 16β-benzyloxy-derivative (I) as previously reported.[6] Reduction of the 17-one (I) with sodium borohydride in ethanol gave the alcohol (IIa), and acetylation (acetic anhydride–pyridine) gave the diacetate (IIb). Cleavage of the benzyl protecting group by catalytic hydrogenolysis afforded the alcohol (IIc) which was subjected without further purification to oxidation with 8N-chromium trioxide in acetone solution. The resulting 15-one (IId) was obtained in reasonable yield [40% overall from ketone (I)]. Alkylation of the β-acetoxy-ketone (IId) in t-butyl alcohol containing potassium t-butoxide with methyl iodide gave the 14α-methylœstrane (III). Elimination of the β-acetoxy-group to yield the αβ-unsaturated ketone (III) proceeded with ease and only the olefin was isolated. Had elimination proceeded in part, the 17-acetoxy-counterpart would have been available as a useful precursor of, *e.g.*, 14α-methylœstrone. The



structure assigned to the 14α-methyl steroid (III) was substantiated by ^{1}H n.m.r. and o.r.d. studies. Sharp signals corresponding to the angular methyl groups appeared at δ 1·08 and 1·18 p.p.m. in the n.m.r. spectrum. The 16-olefin displayed two doublets (1H each) centred at δ 6·16 and 7·64 p.p.m. with a coupling constant (*J*) of 13 c./sec. Concomitant methylation of the 3-hydroxy-group was confirmed by appearance of three methoxy-protons at δ 3·78 p.p.m. Methylation of the phenol during alkylation was required to shorten the overall route to the œstrane (V).

The αβ-unsaturated ketone (III) was hydrogenated in the presence of 5% palladium on calcium carbonate. Reduction proceeded smoothly and led to formation of the ring-D saturated ketone (IV). The o.r.d. curve exhibited by ketone (IV) showed the positive Cotton effect characteristic of 14α-methyl-15-ones.[8] This

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[3] E. J. Corey, W. E. Russey, and P. R. Ortiz de Montellano, *J. Amer. Chem. Soc.*, 1966, **88**, 4750; E. E. van Tamelen, J. D. Willett, R. B. Clayton, and K. E. Lord, *ibid.*, p. 4752; D. H. R. Barton and G. P. Moss, *Chem. Comm.*, 1966, 261; R. B. Clayton, *Quart. Rev.*, 1965, **19**, 201.
[4] G. R. Pettit and P. Hofer, *Helv. Chim. Acta*, 1963, **46**, 2142.
[5] G. R. Pettit and P. Hofer, *J. Chem. Soc.*, 1963, 4439.
[6] E. W. Cantrall, R. Littell, and S. Bernstein, *J. Org. Chem.*, 1964, **29**, 64, 214; C. Djerassi, G. von Mutzenbecher, J. Fajkos, D. H. Williams, and H. Budzikiewicz, *J. Amer. Chem. Soc.*, 1965, **87**, 817; A. R. van Horn and C. Djerassi, *Steroids*, 1967, **9**, 163.
[7] (*a*) P. F. Beal, U.S.P. 3,166,528/1965 (*Chem. Abs.*, 1965, **62**, 10,495), and B. Bannister, U.S.P. 3,166,550/1965 (*Chem. Abs.*, 1965, **62**, 11,880); (*b*) R. Knuppen, O. Haupt, and H. Breuer, *Steroids*, 1966, **8**, 403.
[8] C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill, New York, 1960, p. 58; P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden Day, San Francisco, 1965, p. 129.

curve combined with evidence cited in ref. 7 allows assignment of the 14α-configuration. The terminal objective, the 14α-methyl-19-nor-steroid (V), was achieved by subjecting the aromatic derivative (IV) to a modified [9] Birch reduction procedure. Ketone (V) was formed in 49% yield. These experiments clearly demonstrate that œstrone can be readily converted into 14α-methyl-œstranes.

EXPERIMENTAL

All solvents were redistilled, and light petroleum refers to a fraction boiling at 65—66°. Tetrahydrofuran was distilled and passed through a column of activated alumina. Solvent extracts of aqueous solutions were dried over magnesium sulphate. Column chromatography was performed using 0·05—0·20 mm. silica gel (Merck), and t.l.c. plates were prepared using silica gel G (Merck). Thin-layer chromatograms (chloroform mobile phase unless otherwise noted) were developed by immersion in iodine vapour. Each analytical sample was colourless and displayed a single spot on t.l.c.

Melting points were recorded using a Kofler apparatus. Optical rotatory dispersion was measured by Miss K. Reimer using a JASCO ORD/UV-5 instrument and chloroform solution at 25°. ^{1}H N.m.r. measurements were conducted by P. A. Whitehouse using a Varian A-60 spectrometer ($CDCl_3$ as solvent) with tetramethylsilane as internal standard.

15β-*Benzyloxyœstra*-1,3,5(10)*trien*-3,17β-*diol* (IIa).—To 15β-benzyloxy-3-hydroxyœstra-1,3,5(10)trien-17-one (I) (0·046 g.) in ethanol (15 ml.) was added with stirring (at room temperature) sodium borohydride (0·15 g.). After 4 hr. solvent was removed *in vacuo* and the residue was treated with water followed by hydrochloric acid. The aqueous solution was extracted with chloroform and the combined extract was concentrated to a residue which crystallised from benzene to yield the *product* (0·030 g.) as plates, m. p. 118—120°; t.l.c., R_F 0·43 (95 : 5 chloroform–methanol); $\nu_{max.}$ (Nujol) 3450 and 3250 cm.$^{-1}$; $[\alpha]_{589}$ +19°, $[\alpha]_{450}$ +33°, $[\alpha]_{310}$ +109° (*c* 0·42) (Found: C, 79·45; H, 7·9. $C_{25}H_{30}O_3$ requires C, 79·35; H, 8·0%).

3,17β-*Diacetoxy*-15β-*benzyloxyœstra*-1,3,5(10)*triene* (IIb).—The diol (IIa) (0·11 g.) in pyridine (4 ml.) and acetic anhydride (0·3 ml.) was maintained for 1 hr. at 95°. Evaporation of solvent *in vacuo* gave a residue which was chromatographed in benzene on silica gel. The fraction eluted with benzene was the *diacetate* (IIb) (0·095 g.). Analytical sample, needles from benzene–light petroleum, m. p. 167—168°; t.l.c., R_F 0·46; $\nu_{max.}$ 1740 cm.$^{-1}$; $[\alpha]_{589}$ −35°, $[\alpha]_{450}$ −45°, $[\alpha]_{310}$ −84° (*c* 0·31) (Found: C, 75·15; H, 7·4; O, 17·55. $C_{29}H_{34}O_5$ requires C, 75·3; H, 7·4; O, 17·3%).

3,17β-*Diacetoxyœstra*-1,3,5(10)-*trien*-15-*one* (IId).—A mixture of the benzyl ether (IIb) (0·095 g.) in glacial acetic acid (4 ml.) and suspended 10% palladium–carbon (0·035 g.) was stirred under a slightly positive pressure of hydrogen at room temperature for 4 hr. Catalyst was collected, washed well with methanol, and the filtrate concentrated to dryness *in vacuo*. The colourless glass-like residue crystallised on scratching to yield alcohol (IIc) (0·075 g.). The product was shown homogeneous by t.l.c. and was used without further purification in the next step.

To a cold (ice-bath) rapidly stirred solution of alcohol (IIc) (0·070 g.) in acetone (4 ml.) was added (dropwise) 8N-chromium trioxide (0·09 ml.).[10] Approximately 5 min. later an excess of propan-2-ol was added followed by ice–water. The mixture was extracted with ethyl acetate. Following removal of solvent from the combined extract, a crystalline residue (0·066 g.) was obtained. Recrystallisation from benzene–light petroleum afforded a pure specimen of the *ketone* (II), m. p. 173—174°; t.l.c., R_F 0·23; $\nu_{max.}$ 1740 cm.$^{-1}$; $[\alpha]_{589}$ +90, $[\alpha]_{350}$ +54°, $[\alpha]_{313}$ +1860°, $[\alpha]_{294}$ 0, $[\alpha]_{280}$ −1360° (*c* 0·44) (Found: C, 71·2; H, 6·8. $C_{22}H_{26}O_5$ requires C, 71·35; H, 7·05%).

3-*Methoxy*-14α-*methylœstra*-1,3,5(10),16-*tetraen*-15-*one* (III).—Ketone (IId) (0·10 g.) was added to the solution obtained by dissolving potassium (0·50 g.) in t-butyl alcohol (15 ml.). The mixture was stirred under nitrogen for 1 hr. at room temperature. After cooling to approximately 15° methyl iodide (1·6 ml.) was added. During the first 5 min. a colourless solid separated and stirring was continued at room temperature for 4·5 hr. After dilution with water, the mixture was extracted with chloroform. Removal of solvent afforded a crystalline residue, a solution of which in benzene was chromatographed on silica gel. Elution with benzene–chloroform (4 : 1) gave the 14α-*methyl steroid* (III) (0·06 g.), m. p. 114—116° (from benzene–light petroleum); t.l.c., R_F 0·52; $\nu_{max.}$ 1690 cm.$^{-1}$; $[\alpha]_{589}$ +160°, $[\alpha]_{500}$ +233°, $[\alpha]_{381}$ +400°, $[\alpha]_{370}$ +333° (*c* 1·80); n.m.r. δ 1·08 (CH_3), 1·18 (CH_3), 3·78 (CH_3O), 6·5—7·2 complex (3 aromatic protons), 6·16 and 7·64 p.p.m. (2 vinyl protons, J = 13 c./sec.) (Found: C, 81·2; H, 7·95; O, 10·85. $C_{20}H_{24}O_2$ requires C, 81·05; H, 8·15; O, 10·8%).

3-Methoxyœstrone exhibits ^{1}H n.m.r. signals as follows: δ 0·89 (CH_3), 3·78 (CH_3O), and 6·5—7·2 p.p.m. complex (3 aromatic protons).

3-*Methoxy*-14α-*methylœstra*-1,3,5(10)*trien*-15-*one* (IV).—The ketone (III) (0·060 g.) in 95 : 5 methanol–water (5 ml.) containing suspended 5% palladium–calcium carbonate (0·060 g.) was stirred under a slightly positive pressure of hydrogen for 30 min. The solution was filtered and the catalyst washed with methanol. The filtrate was concentrated to dryness *in vacuo* and the residue dissolved in chloroform and dried. Removal of solvent gave a crystalline *product* as needles) (0·055 g.) (from aqueous methanol), m. p. 114—115°; t.l.c., R_F 0·72; $\nu_{max.}$ 1730 cm.$^{-1}$; $[\alpha]_D$ +69°, $[\alpha]_{400}$ +156°, $[\alpha]_{370}$ +168°, $[\alpha]_{335}$ 0°, $[\alpha]_{328}$ −118°, $[\alpha]_{324}$ 0° (*c* 1·60); n.m.r. δ 1·06 (CH_3), 1·25 (CH_3), 3·76 (CH_3O), 6·5—7·2 p.p.m. complex (3 aromatic protons) (Found: C, 80·1; H, 8·6; O, 11·1. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·8; O, 10·7%).

14α-*Methylœstra*-5-*ene*-3,15-*dione* (V).—Ether (IV) (0·050 g.) in tetrahydrofuran (5 ml.) and t-butyl alcohol (3 ml.) was slowly added to liquid ammonia (10 ml.) maintained at approximately −30°. Freshly cut lithium (0·10 g.) was added in 10 equal quantities during 0·5 hr. Stirring was continued for an additional 1·5 hr. while allowing the ammonia to evaporate. The residue was treated with absolute ethanol (5 ml.) followed by cautious addition of saturated aqueous sodium chloride. The resulting mixture was extracted with ether and the extract concentrated to a colourless crystalline solid (0·048 g.). The enol ether

[9] J. A. Cella, E. A. Brown, and R. R. Burtner, *J. Org. Chem.*, 1959, **24**, 743; G. R. Pettit, A. K. Das Gupta, and U. R. Ghatak, *Steroids*, 1963, **1**, 137.

[10] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 39.

intermediate displayed one spot on t.l.c. A solution of this intermediate in methanol (5 ml.) and hydrochloric acid (2 ml., 8%) was heated on a steam-bath for 20 min. Following dilution with saturated aqueous sodium chloride and extraction with ether, the combined extract was washed with water and concentrated (*in vacuo*) to dryness. The oily residue was subjected to Jones oxidation as described above for the preparation of ketone (IId) to give the *product* (V) as needles (0·025 g.), m. p. 149—150° (from ethanol), t.l.c., R_F 0·11 ($CHCl_3$); $\nu_{max.}$ 1730 and 1670 cm.$^{-1}$; $[\alpha]_{589}$ −38°, $[\alpha]_{380}$ −265°, $[\alpha]_{340}$ −1000°, $[\alpha]_{322}$ 0° (*c* 0·065) (Found: C, 79·5; H, 9·0. $C_{19}H_{26}O_2$ requires C, 79·7; H, 9·15%).

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