940. 2-*Hydroxy-œstrogens. Part II.** *Synthesis of* 2,3-*Dihydroxy-œstra*-1,3,5(10)-*trien*-17-*one and Œstra*-1,3,5(10)-*triene*-2,3,16α,17β-*tetraol.*

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A convenient new method is described for the synthesis of the 2-hydroxy-derivatives named in the title from œstra-1,3,5(10)-triene-2,3,17β-triol.

EARLIER[1] we reported the synthesis of œstra-1,3,5(10)-triene-2,3,17β-triol (2-hydroxy-œstradiol-17β) from 19-nortestosterone and showed[2] that this triol-17β is converted *in vivo* into 2-methoxyœstrone, with significant quantities of other phenolic steroid metabolites. Presumptive evidence was obtained for the presence of 2,3-dihydroxyœstra-1,3,5(10)-trien-17-one (2-hydroxyœstrone) and -1,3,5(10)-triene-2,3,16α,17β-tetraol (2-hydroxy-œstriol) among these metabolites. However, to substantiate these findings it was necessary to synthesise authentic samples and we now report a practical and convenient

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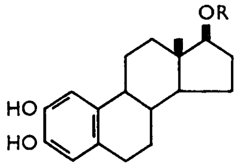
* Part I, *Tetrahedron*, 1960, **10**, 144.

[1] Rao and Axelrod, *Chem. and Ind.*, 1959, p. 1454; *Tetrahedron*, 1960, **10**, 144.

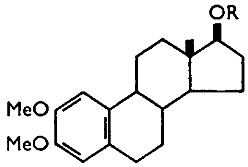
[2] Axelrod, Rao, and Goldzieher, *Arch. Biochem. Biophys.*, 1960, **87**, 152.

method for preparing these two compounds from the 2,3,17β-triol. Other syntheses, by a different route, have been recently reported.[3,4]

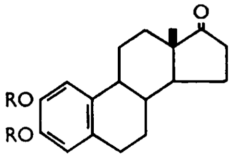
17β-Acetoxy-œstra-1,3,5(10)-triene-2,3-diol (Ia), an intermediate in our earlier synthesis[1] of the triol, with methyl sulphate and anhydrous potassium carbonate in boiling acetone gave 17β-acetoxy-2,3-dimethoxyœstra-1,3,5(10)-triene (IIa) in excellent yield. Alkaline hydrolysis then gave 2,3-dimethoxyœstra-1,3,5(10)-triene-17β-ol (IIb), which was also obtained in high yield by direct methylation of the triol[1] (Ib) as above. Oxidation of the 17β-alcohol (IIb) with 8N-chromic acid[5] gave rather low yields of 2,3-dimethoxyœstra-1,3,5(10)-trien-17-one (IIIa), besides other unidentifiable oxidation products, but Oppenauer oxidation gave consistently high yields of this ketone. Compound (IIIa) was then smoothly demethylated by pyridine hydrochloride at 200°, to give 2,3-dihydroxyœstra-1,3,5(10)-trien-17-one (IIIb) in excellent yield.



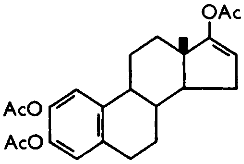
(I) a: R = Ac
b: R = H



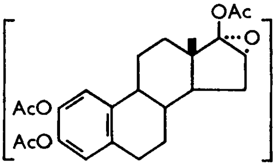
(II) a: R = Ac
b: R = H



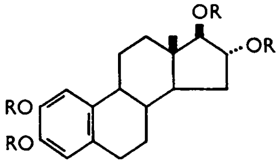
(III) a: R = Me. b: R = H
c: R = Ac



(IV)



(V)



(VI) a: R = H. b: R = Ac

The tetraol (VIa) was thence synthesised by the method of Leeds, Fukushima, and Gallagher.[6] The derived diacetate (IIIc) with isopropenyl acetate in the presence of a catalytic amount of toluene-*p*-sulphonic acid monohydrate gave 2,3,17-triacetoxyœstra-1,3,5(10),16-tetraene (IV) in satisfactory yield. This enol acetate with perbenzoic acid gave the epoxy-acetate (V), which was not isolated but was directly reduced with lithium aluminium hydride[6] in tetrahydrofuran to œstra-1,3,5(10)-triene-2,3,16α,17β-tetraol (VIa) in good yield.

TABLE 1.

Molecular rotation differences between œstrogens and 2-hydroxy-œstrogens.

Compound	$[M]_D$	$[M_D]$ 2-Hydroxy-deriv.	$\Delta[M]_D$ (2-OH)
Œstrone	+433° [a]	+477° [d]	+44°
Œstradiol-17β	+215 [b]	(MeOH) +267 [e]	+52
Œstriol	+196 [c]	(2·5-MeOH) +307 [d]	+111

[a] Fieser and Fieser, " Steroids," Reinhold Publ. Corp., New York, 1959, p. 463. [b] *Op. cit.*, p. 466. [c] *Op. cit.*, p. 477. [d] This paper. [e] Rao and Axelrod, *Chem. and Ind.*, 1959, 1454; *Tetrahedron*, 1960, **10**, 144.

The correctness of structure (VIa) was supported by a comparison of the molecular rotatory differences of 2-hydroxy-œstrogens shown in Table 1. Further, the ultraviolet absorption maximum at 288 mμ was typical of 2-hydroxy-œstrogens.[3,4] The infrared

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[3] Fishman, Tomasz, and Lehman, *J. Org. Chem.*, 1960, **25**, 585.

[4] Coombs, *Nature*, 1960, **188**, 317.

[5] Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, p. 39; Bowers, Halsall, Jones, and Lemin, *J.*, 1953, p. 2548; Djerassi, Engel, and Bowers, *J. Org. Chem.*, 1956, **21**, 1547.

[6] Leeds, Fuhushima, and Gallagher, *J. Amer. Chem. Soc.*, 1954, **76**, 2943.

TABLE 2.

Molecular rotation data of 2-hydroxy-œstrogen acetates.

Compound	$[M]_D$	$\Delta[M]_D$ (2-OAc)
2,3-Diacetoxyœstra-1,3,5(10)-trien-17-one	+467° [a]	+12° [d]
3-Acetoxyœstra-1,3,5(10)-trien-17-one	+455 [b]	
2,3,17β-Triacetoxyœstra-1,3,5(10)-triene	+217 [c]	+71
3,17β-Diacetoxyœstra-1,3,5(10)-triene	+146 [b]	
2,3,16α,17β-Tetra-acetoxyœstra-1,3,5(10)-triene	−19 [a]	+63
3,16α,17β-Triacetoxyœstra-1,3,5(10)-triene	−82 [b]	

[a] This paper. [b] Determined in our laboratories. [c] Rao and Axelrod, *Chem. and Ind.*, 1959, 1454; *Tetrahedron*, 1960, **10**, 144. [d] Although the reported value for œstrone 3-acetate (Velliuz and Muller, U.S.P. 2,773,886, $[M]_D$ + 400°) yields a 2-acetoxy-contribution more in agreement ($\Delta[M]_D$ +67°) with the other acetates reported in this paper, an analytical sample of 3-acetoxyœstrone gave a higher value of the molecular rotation in our hands.

spectrum included peaks similar to those for the other 2-hydroxy-œstrogens between 1650 and 1400 cm.$^{-1}$ (aromatic ring).[7] Unequivocal proof was provided by preparing the formation of a tetra-acetate (VIb). The molecular rotatory differences for the acetates of 2-hydroxy-œstrogens are shown in Table 2 and are in good agreement within experimental error. As expected, the tetraol (VIa) was more polar than œstriol and other 2-hydroxy-œstrogens, as indicated by paper partition chromatography. The physical constants of our compound (VIa) are in agreement with those reported by Coombs,[4] except that we obtained a higher value of $[\alpha]_D$.

EXPERIMENTAL

Microanalyses were performed by Messrs. Micro-Tech Laboratories, Skokie, Illinois, U.S.A. M. p.s were determined on samples dried under a high vacuum at 60° for 24 hr. Ultraviolet absorption spectra were determined for methanol solutions with a Cary recording spectrophotometer (model 11 MS). The infrared spectra were determined for potassium bromide discs on a Perkin-Elmer (model 21) infrared spectrometer. Rotations were determined for chloroform solutions unless otherwise stated, with a Zeiss–Winkel polarimeter. Merck " Reagent grade " aluminium oxide, " Suitable for chromatographic adsorption," treated with ethyl acetate and then activated to give Brockmann activity II—III, was used in chromatography. Light petroleum used was that of Mallinckrodt " Analytical Reagent grade " and b. p. 30—60°.

17β-*Acetoxy*-2,3-*dimethoxyœstra*-1,3,5(10)-*triene* (IIa).—17β-Acetoxy-1,3,5(10)-triene-2,3-diol (Ia) (4 g.) was heated in anhydrous acetone (430 ml.) with anhydrous potassium carbonate (123 g.) and dimethyl sulphate (43 ml.) for 6 hr. (ferric chloride–potassium ferricyanide test[8] negative), then the excess of methyl sulphate was decomposed by water (20 ml.) and warming on a water bath. Most of the acetone was evaporated under a vacuum at 40° and the residue was treated with water (500 ml.) and then extracted with ethyl acetate. The extract was washed with water until neutral, then dried (Na_2SO_4) and evaporated. The residue crystallised from methanol to give (3·6 g., 83%) 17β-acetoxy-2,3-dimethoxyœstra-1,3,5(10)-triene, m. p. 180—181°, $[\alpha]_D^{29}$ +59° (*c* 0·51), $\lambda_{max.}$ 282 mμ (ε 4843), $\lambda_{min.}$ 252 mμ (ε 1132), $\nu_{max.}$ 1726, 1608, and 1512 cm.$^{-1}$ (Found: C, 73·6; H, 8·2. Calc. for $C_{22}H_{30}O_4$: C, 73·7; H, 8·4%) (lit.,[3] m. p. 179—182°, $[\alpha]_D^{27}$ +53°).

2,3-*Dimethoxyœstra*-1,3,5(10)-*trien*-17β-*ol* (IIb).—Compound (IIa) (3·4 g.) was heated in 5% methanolic potassium hydroxide (300 ml.) for 2 hr. The usual working up gave 2,3-dimethoxyœstra-1,3,5(10)-trien-17β-ol (2·9 g.) that, crystallised from acetone–light petroleum, had m. p. 130—132°, $[\alpha]_D^{23\cdot5}$ +82° (*c* 0·78), $\lambda_{max.}$ 285 mμ (ε 3828), $\lambda_{min.}$ 255 mμ (ε 561), $\nu_{max.}$ 3500, 1613, and 1515 cm.$^{-1}$ (Found: C, 75·9; H, 9·0. Calc. for $C_{20}H_{28}O_3$: C, 75·9; H, 8·9%) (lit.,[3] m. p. 131—133°, $[\alpha]_D^{27}$ +85°).

Compound (IIb) was also obtained by a similar methylation of the triol (Ib), as above, in 80% yield and crystallised from acetone–light petroleum (m. p. and mixed m. p. 130—132°; correct infrared spectrum).

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[7] Bellamy, " The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, 1959, p. 64.

[8] Barton, Evans, and Gardner, *Nature*, 1952, **170**, 249.

2,3-*Dimethoxyœstra*-1,3,5(10)-*trien*-17-*one* (IIIa).—(*a*) To a cold solution (10—15°) of the triol (IIb) (290 mg.) in acetone (30 ml.; distilled from permanganate) in an atmosphere of nitrogen, 8N-chromium trioxide[5] was added dropwise till the reddish-brown colour persisted. After an additional 2 minutes' stirring, the mixture was diluted with water (500 ml.) and extracted with ethyl acetate. The extract was washed with water, saturated sodium hydrogen carbonate solution, and with water until neutral. The product (287 mg.) was then chromatographed on alumina (8·5 g.). Elution with light petroleum–benzene (1 : 1) gave 2,3-dimethoxyœstra-1,3,5(10)-trien-17-one (115 mg., 39%) which, crystallised from acetone, had m. p. 170—172°, $[\alpha]_D^{24}$ +161° (*c* 0·63), $\lambda_{max.}$ 285 mμ (ε 4024), $\lambda_{min.}$ 255 mμ (ε 753), $\nu_{max.}$ 1720, 1605, and 1515 cm.$^{-1}$ (Found: C, 76·0; H, 8·2. Calc. for $C_{20}H_{26}O_3$: C, 76·4; H, 8·3%) (lit.,[3] m. p. 173—176°).

Further elution of the column with benzene and benzene–ether (8 : 2) gave a product (160 mg.) which resisted crystallisation, $\nu_{max.}$ 1730, 1710, and 1665 cm.$^{-1}$ (C=O), that was not further investigated.

(*b*) To the triol (IIb) (2·89 g.) in dry toluene (600 ml.) cyclohexanone (28 ml.) and aluminium isopropoxide (6 g.) were added, and the whole heated under reflux for 4 hr., then washed with 10% sulphuric acid, water, saturated hydrogen carbonate solution, and water until neutral. Toluene and most of the excess of cyclohexanone were removed under reduced pressure and the residue was chromatographed on alumina (100 g.). The ketone (IIIa), m. p. 170—172° (1·9 g., 68%), eluted with light petroleum–benzene (1 : 1), was identical (mixed m. p.; infrared spectrum) with that obtained as in (*a*). Further elution of the column with benzene and benzene–ether (1 : 1) gave unoxidised product (IIb) (700 mg.), m. p. 129—131°.

2,3-*Dihydroxyœstra*-1,3,5(10)-*trien*-17-*one* (IIIb).—The ether (IIIa) (2·5 g.) and freshly distilled pyridine hydrochloride (5 g.) were heated for 1 hr. at 200° under nitrogen, then diluted with water and the precipitated 2,3-dihydroyxœstra-1,3,5(10)-trien-17-one (IIIb) was filtered off. It (2·2 g., 90%) crystallised from acetone–light petroleum and had m. p. 194—195°, $[\alpha]_D^{24}$ +166° (*c* 0·5 in EtOH), $\lambda_{max.}$ 288 mμ (ε 3796), $\lambda_{min.}$ 254 mμ (ε 366), $\nu_{max.}$ 3370b, 1722, 1610, and 1515 cm.$^{-1}$ (Found: C, 75·2; H, 7·9. Calc. for $C_{18}H_{22}O_3$: C, 75·5; H, 7·8%) (cf. refs. 3 and 4).

The 2,3-diacetate was prepared with pyridine and acetic anhydride in the cold and crystallised from methanol in needles, m. p. 164—166°, $[\alpha]_D^{29}$ +126° (*c* 0·75), $\lambda_{max.}$ 278 (ε 1390), 271 mμ (ε 1390), $\lambda_{min.}$ 274 (ε 1269), 249 mμ (ε 315), $\nu_{max.}$ 1770, 1730, and 1505 cm.$^{-1}$ (Found: C, 71·2; H, 7·2. Calc. for $C_{22}H_{26}O_5$: C, 71·3; H, 7·1%) (lit.,[4] m. p. 170—171°).

2,3,17-*Triacetoxyœstra*-1,3,5(10),16-*tetraene* (IV).—To a solution of diacetate (IIIc) (1·95 g.) in isopropenyl acetate (75 ml.), toluene-*p*-sulphonic acid monohydrate (700 mg.) was added and the whole was refluxed for 15 min. The isopropenyl acetate was then distilled off during 6 hr., being replaced by fresh reagent to maintain the volume constant. The mixture was then cooled and diluted with ether. The ether solution was washed with ice-cold 5% sodium hydrogen carbonate solution and water until neutral, dried, and evaporated. The residue was chromatographed on a short column of alumina (70 g.). The combined material (775 mg., 35%), m. p. 160—162°, eluted with light petroleum-benzene (1 : 1) and benzene, crystallised from acetone–light petroleum, giving 2,3,17-*triacetoxyœstra*-1,3,5(10),17-*tetraene*, m. p. 166—168°, $[\alpha]_D^{26}$ +82° (*c* 0·51), $\lambda_{max.}$ 273 (ε 1432), 278 mμ (ε 1469), $\lambda_{min.}$ 276 (ε 1344), 253 mμ (ε 828), $\nu_{max.}$ 1765, 1630, 1505, and 1375 cm.$^{-1}$ (Found: C, 69·8; H, 6·8. $C_{24}H_{28}O_6$ requires C, 69·9; H, 6·8%).

Œstra-1,3,5(10)-*triene*-2,3,16α,17β-*tetraol* (IVa).—To a solution of the enol acetate (IV) (1 g., 0·0025 mole) in benzene (20 ml.), a 0·33M-solution (18·8 ml.) of perbenzoic acid in chloroform was added and the whole was set aside for 20 hr., then diluted with benzene (100 ml.) and washed with 2% ice-cold sodium hydroxide solution and water until neutral.

The residue (1 g.) obtained on evaporation was added in dry tetrahydrofuran (100 ml.) with stirring to lithium aluminium hydride (1·25 g.) in tetrahydrofuran (50 ml.) in 15 min., then the mixture was heated under reflux for 2 hr. The excess of reagent was destroyed by ethyl acetate. The hydride complex was decomposed with 5% ice-cold hydrochloric acid and then extracted with a large quantity of ethyl acetate. The ethyl acetate solution was washed with water, 5% sodium hydrogen carbonate solution, and water until neutral. After drying and evaporation the residue (700 mg.) was a gum which, crystallised from dilute methanol, had m. p. 253—256° (decomp.). Two additional crystallisations from 80% methanol and one finally from absolute methanol gave the pure tetraol with constant m. p. 262—263° (vac.), $[\alpha]_D^{29}$ +80° (*c* 0·79 in

MeOH), $\lambda_{max.}$ 288 mμ (ε 3968), $\lambda_{min.}$ 253 mμ (ε 599), $\nu_{max.}$ 3440b, 1613, 1515, and 1450 cm.$^{-1}$. The material, despite drying at 60° in a high vacuum, retained solvent tenaciously (Found: C, 64·2; H, 8·4. Calc. for $C_{18}H_{24}O_4,2\frac{1}{2}CH_3{\cdot}OH$: C, 64·0; H, 8·8%) (cf. ref. 4).

The tetraol (300 mg.), pyridine (10 ml.), and acetic anhydride (6 ml.) at 70° (3 hr.) gave the *tetra-acetate*, needles (from aqueous methanol), m. p. 96—100°, $[\alpha]_D^{28}$ −4° (*c* 0·5), $\lambda_{max.}$ 268 (ε 1815), 277 mμ (ε 1579), $\lambda_{min.}$ 257 (ε 795), 275 mμ (ε 1517), $\nu_{max.}$ 1773, 1743, 1505, and 1375 cm.$^{-1}$ (Found: C, 65·7; H, 6·7. $C_{26}H_{32}O_8$ requires C, 66·0; H, 6·8%).

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