17β-OESTRADIOL 17-METHYL ETHER

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Received October 13, 1965

17β-Methoxyoestra-1,3,5(10)-trien-3-ol has been prepared from oestrone through catalytic hydrogenation in methanolic hydrogen chloride (1). Similar hydrogenation of oestrone methyl ether gave the known 3,17β-dimethoxyoestra-1,3,5(10)-triene (2,3) which was also obtained from the 17-monomethyl ether upon further methylation with dimethyl sulphate.

Evidence has been obtained that the hydrogen iodide demethylation product of oestradiol dimethyl ether, previously reported by Urushibara and Nitta (2) and represented as oestradiol 17-methyl ether, is identical with oestradiol 17-acetate (4). The product arises through acid-catalysed esterification of oestradiol. A convenient preparative method for oestradiol 17-monoacetate is described.

Reported melting points of oestradiol 17-acetate derivatives

	This work	Urushibara and Nitta(2)
oestradiol 17-acetate:	217-218°	213.5-214.5°
——— 3-benzoate:	166-167°	165.5-166.5°
—— 3-p-toluensulphonate:	123.5-124.5°	124.5-125.5°

EXPERIMENTAL

17β-Methoxyoestra-1,3,5(10)-trien-3-ol

Oestrone (4.95 g.) in methanol (650 ml.) containing hydrogen chloride (45.7 g.) was stirred with platinum oxide catalyst (494 mg.) under hydrogen for 18 hr. The solution was worked up by conventional methods yielding a white residue (5.38 g.) which was boiled with methanol (20 ml.). The insoluble oestradiol 17-methyl ether was collected and recrystallised from chloroform-methanol, forming prisms (2.7 g.) m.p. 244.5-245°, $[\alpha]_D^{21}$ + 51.3° (c = 0.26 in chloroform-methanol, 3:2); Anal. Calcd. for $C_{19}H_{26}O_2$: C,79.7; H,9.15%. Found: C,79.8; H,9.0%.

The 17-methyl ether formed a 3-acetate, m.p. 93-95°, $[\alpha]_D^{24}$ + 58.8° (c = 0.30 in chloroform); Anal. Calcd. for $C_{21}H_{28}O_3$: C,76.8; H,8.6%. Found: C,76.8; H,8.65%; $\nu_{max.}^{CS_2}$ 1775, 1210 cm $^{-1}$. (phenolic acetate). The 3-benzoate had m.p. 170-171°, $[\alpha]_D^{23}$ + 52.5° (c = 0.26 in chloroform). Anal. Calcd. for $C_{26}H_{30}O_3$: C,79.95; H,7.75%. Found: C,79.9; H,8.1%

3,17β-Dimethoxyoestra-1,3,5(10)-triene. -

(a) 17β-Methoxyoestra-1,3,5(10)-trien-3-ol (1.83 g.) in ethanol (200 ml.) and aqueous sodium hydroxide (1N; 300 ml.) was methylated with dimethyl sulphate in the normal way to give the dimethoxy derivative, m.p. 161-162° (lit., (2,3) 161-162°), $[\alpha]_D^{24}$ + 69.0° (c = 0.30 in chloroform). Anal. Calcd. for $C_{20}H_{28}O_2$: C,79.75; H,9.65%. Found: C,79.95; H,9.4%. P.M.R. spectrum, τ = 9.20 (18-Me), 6.61 (17-OMe), 6.24 (3-OMe).

(b) 3-Methoxyoestra-1,3,5(10)-trien-17-one (3.38 g.) in methanolic hydrogen chloride was hydrogenated as described above. Chromatography on alumina of the crude product (3.39 g.) afforded the pure dimethyl ether (2.29 g.), identical with a sample prepared by method (a).

Hydrogen iodide demethylation of 3,17β-dimethoxy-oestra-1,3,5(10)-triene. -

The dimethyl ether (2.29 g.) in glacial acetic acid (30 ml.) was treated with hydriodic acid (sp. gr. 1.7; 30 ml.) and heated at 100° for 30 min. After dilution with water, the solution was worked up conventionally; chromatographic separation of the crude product gave unchanged starting material (721 mg.), oestradiol (565 mg.) and also oestradiol 17-monoacetate (617 mg.) m.p. 217-218°, identified by m.p., mixed m.p., and infrared spectrum with an authentic sample.

Treatment of oestradiol with hydrogen iodide-acetic acid. - Oestradiol was treated with hydriodic acid as for the demethylation of its dimethyl ether.

Two components only were detected in the crude product by thin layer chromatography on silica gel; the R_F-values corresponded to those of oestradiol ($R_F = 0.3$) and oestradiol 17-acetate ($R_F = 0.7$)(system: benzene: ethyl acetate, 4:1).

Oestradiol 17-monoacetate. - Oestradiol (554 mg.) with p-toluenesulphonic acid (647 mg.) was heated under reflux in ethyl acetate (60 ml.), the condensate being allowed to pass over molecular sieve (Union Carbide type 13X; 15 g.) contained in a soxhlet apparatus. After 24 hr. the solution was washed free of acid, dried and evaporated to dryness. The chromatographically homogeneous residue of *oestradiol 17-monoacetate* (640 mg.) crystallised from methanol as needles, m.p. 216-218° $[\alpha]_D^{23}$ + 44.7° ($c = 0.22$ in chloroform)(lit. (4), m.p. 217-218°, $[\alpha]_D^{22}$ + 45.5°. *Anal.* Calcd. for $C_{20}H_{26}O_3$: C,76.4; H,8.35% . Found: C,76.35; H,8.2%. $\nu_{max.}^{CS_2}$ 3600 (OH), 1740, 1246 cm^{-1} . (aliphatic acetate).

Oestradiol 17-acetate 3-p-toluensulphonate had m.p. 123.5-124.5°, $[\alpha]_D^{23}$ + 28.3° ($c = 0.27$ in chloroform). *Anal.* Calcd. for $C_{27}H_{32}O_5S$: C,69.2; H,6.9%. Found: C,69.3; H,7.0% .

Oestradiol 17-acetate 3-benzoate had m.p. 166-167°, $[\alpha]_D^{23}$ + 34.4° ($c = 0.22$ in chloroform). *Anal.* Calcd. for $C_{27}H_{30}O_4$: C,77.5; H,7.25%. Found: C,77.55; H,7.4%.

ACKNOWLEDGEMENT

We thank Mr. D.M. Carr and Mr. J.F. Richards for technical help and for the microanalyses.

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