An Improved Stereospecific Total Synthesis of an Aromatic c-Ring Testosterone Analogue

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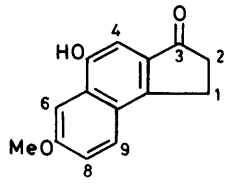
An improved stereospecific synthesis of 17β-hydroxy-11-methoxy-18-norandrosta-4,8,11,13-tetraen-3-one (12) from 5-hydroxy-7-methoxy-1*H*-benz[*e*]inden-3(2*H*)-one (1) is described. Higher yields were achieved in the Birch reduction step using 3,5-dihydroxy-7-methoxy-2,3-dihydro-1*H*-benz[*e*]inden-3-ol as the starting material. An interesting replacement reaction of the benzylic hydroxy by an alkoxy-group is described.

RECENT work [1] on the synthesis of 17α- and 17β-hydroxy-11-methoxy-18-norandrosta-4,8,11,13-tetraen-3-one and the observation that these compounds show a high degree of androgen binding *in vitro* have revived interest in the synthesis of aromatic c-ring steroids.

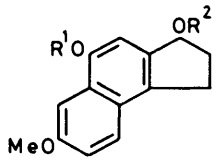
Previously, we reported [2] the synthesis of 17-hydroxy-11-methoxy-18-norandrosta-4,8,11,13-tetraen-3-one in moderate yields from 5,7-dimethoxy-1*H*-benz[*e*]inden-3(2*H*)-one. The stereochemistry of the 17-hydroxy-group was not assigned. It was also indicated that in the Birch reduction of the 2,3-dihydro-5,7-dimethoxy-1*H*-benz[*e*]inden-3-ol (3) only 2,3,6,9-tetrahydro-5,7-dimethoxy-1*H*-benz[*e*]inden-3-ol (7) is formed, under specific conditions, in low yields. Dalzell and his co-workers,[1] using a previously reported synthetic route,[3] improved significantly the metal–ammonia reduction of β-(4,6-dimethoxy-1-naphthyl)propionic acid, but without an obvious over-all advantage.

Herein we describe an improved stereospecific synthesis of 17β-hydroxy-11-methoxy-18-norandrosta-4,8,11,13-tetraen-3-one (12) starting from the easily available [4] 5-hydroxy-7-methoxy-1*H*-benz[*e*]inden-3(2*H*)-one (1). Sodium borohydride reduction of the ketone (1) in aqueous sodium hydroxide gave the 7-methoxy-1*H*-benz[*e*]indene-3,5-diol (2) in almost quantitative yield. 2,3,6,9-Tetrahydro-7-methoxy-1*H*-benz[*e*]indene-3,5-diol (6) was obtained exclusively (83%) by reduction of the dihydroxy-compound (2) with lithium in liquid ammonia. In the Birch reduction of compound (2) phenoxide ion formation at C-5 inhibited the hydrogenolysis of the benzylic hydroxy-group at C-3 to give the enol ether (6) in high yield. Previously,[2] it was pointed out that the Birch reduction of the methoxy-derivative (3) was complicated by a competing hydrogenolysis reaction. Relatively few examples of selective reduction based on salt formation are reported in the literature.[5] Methylation of the enol ether (6) with dimethyl sulphate in aqueous sodium hydroxide resulted in the formation, in good yield, of 2,3,6,9-tetrahydro-5,7-dimethoxy-1*H*-benz[*e*]inden-3-ol (7). Oxalic acid in tetrahydrofuran (THF) was found to hydrolyse the enol ether (7) to give 2,3,6,7,8,9-hexahydro-5-methoxy-7-oxo-1*H*-benz[*e*]-inden-3-ol (8) (yield 80%). The ketone (8) was alkylated *via* the pyrrolidine enamine,[6] with methyl iodide. 2,3,-6,7,8,9-Hexahydro-5-methoxy-6-methyl-7-oxo-1*H*-benz[*e*]inden-3-ol (10) was obtained in 70% yield after column chromatography on Florisil. The ^{1}H n.m.r. spectrum of (10) revealed a sharp C-6 methyl doublet.

The ketone (10) was annelated using the procedure of



(1)

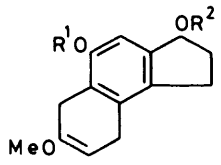


(2) $R^1 = R^2 = H$

(3) $R^1 = Me$, $R^2 = H$

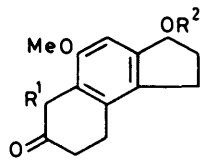
(4) $R^1 = R^2 = Me$

(5) $R^1 = Me$, $R^2 = Et$



(6) $R^1 = R^2 = H$

(7) $R^1 = Me$, $R^2 = H$

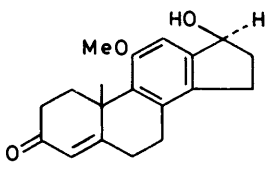


(8) $R^1 = R^2 = H$

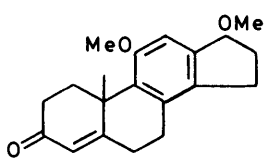
(9) $R^1 = H$, $R^2 = Me$

(10) $R^1 = Me$, $R^2 = H$

(11) $R^1 = R^2 = Me$



(12)



(13)

Robinson and Cornforth.[7] After column chromatography on Florisil followed by crystallisation from methanol, 17-hydroxy-11-methoxy-18-norandrosta-4,8,-11,13-tetraen-3-one, m.p. 183—185 °C, was isolated (yield 51%) (reported [1] m.p.s of the 17α- and 17β-

hydroxy-isomers are 193—196 and 172—174 °C, respectively). Both the ^1H and ^{13}C n.m.r. spectra revealed sharp C-10β-methyl signals indicating that the 17-hydroxy-compound is a single isomer. Assignment of β-stereochemistry to the 17-hydroxy-group is on the basis of a comparison of its mass spectrum with the spectra of authentic samples of 17α- and 17β-hydroxy-isomers and on the relative abundance of the $(M - H_2O)^+$ ion, which is more in the 17α- than in the 17β-isomer.

Hydrolysis of the enol ether (7) with oxalic acid in methanol at room temperature resulted not only in hydrolysis of the enol ether, but also in the replacement of the benzylic hydroxy- by a methoxy-group to furnish, in 75% yield, 2,3,6,7,8,9-hexahydro-3,5-dimethoxy-7-oxo-1*H*-benz[*e*]indene (9). The dihydroxy-compound (2) and its methoxy-derivative (3) were also found to undergo similar replacement reactions in methanol and ethanol solutions to give the corresponding alkoxy-derivatives in high yields. This interesting replacement reaction can be rationalised on the basis of the ease of formation of a benzylic cation. The ketone (9) was alkylated in benzene solution with methyl iodide and potassium dust [8] to give 2,3,6,7,8,9-hexahydro-3,5-dimethoxy-6-methyl-7-oxo-1*H*-benz[*e*]indene (11) in 76% yield. Compound (11) was annelated to obtain 11,17-dimethoxy-18-norandrosta-4,8,11,13-tetraen-3-one by the procedure described above (yield 55%).

The split C-6 methyl doublet in the ^1H n.m.r. spectrum of (11) showed that it is a mixture of the C-3α- and C-3β-methoxy-isomers. In the ^1H and ^{13}C n.m.r. spectra of (13) the split C-10β-methyl signal (1 : 2) suggested that it is a mixture of the 17α- and 17β-methoxy-isomers. The signals of the C-6, C-7, C-15, and C-16 methylene carbons were also found to be split.

Dalzell and his co-workers [1] reported differences in the shift of the C-10β-angular methyl signal in the ^1H n.m.r. spectrum of a mixture of 17α- and 17β-hydroxy-11-methoxy-18-norandrosta-4,8,11,13-tetraen-3-one induced by a europium shift reagent. They have assigned the high field C-10β-methyl signal to the 17β-isomer and the low field signal to the 17α-isomer. It is concluded, on the basis of the above observation, that (13) is a mixture of the 17α- and 17β-methoxy-isomers in the ratio 1 : 2. Hence, in the replacement reaction, the α- and β-methoxy-isomers of (9) are formed in the ratio (1 : 2). No attempt was made to separate the isomers.

EXPERIMENTAL

The compounds described are racemic. All m.p.s. are uncorrected. Light petroleum refers to the fraction with b.p. 60—80 °C. I.r. spectra were determined in chloroform (unless specified otherwise) using a Perkin-Elmer Infracord model 137E. ^1H N.m.r. spectra were recorded in CCl_4 (unless indicated otherwise) with tetramethylsilane (TMS) as internal reference on Varian T-60 and Bruker's WH-90 n.m.r. spectrometers. ^{13}C N.m.r. spectra were obtained in the Fourier mode on a Bruker WH-90 instrument in $CDCl_3$ solutions containing tetramethylsilane as internal reference. Mass spectra were recorded on a Du Pont 21-110B double-focussing mass spectrometer using a direct inlet system and an ionising voltage of 70 eV.

2,3-Dihydro-7-methoxy-1H-*benz*[e]*indene*-3,5-*diol* (2).—Sodium borohydride (3 g) was added to the ketone (1) (9 g) in 2% aqueous sodium hydroxide (350 ml) forming a yellow precipitate which dissolved on heating. The solution was heated on a steam-bath for 1 h, cooled, and acidified. The precipitated solid was filtered off, washed with water, and dried. Recrystallisation from acetone–benzene gave the dihydroxy-compound (2) (8.5 g), m.p. 162 °C; $\nu_{max.}$ (Nujol) 3 175 cm^{-1} (OH); *m/e* 230 (M^+), 212, 197, and 169 (Found: C, 73.1; H, 6.2. $C_{14}H_{14}O_3$ requires C, 73.02; H, 6.13%).

2,3,6,9-Tetrahydro-7-methoxy-1H-*benz*[e]*indene*-3,5-*diol* (6).—A solution of the dihydroxy-compound (2) (4.6 g) in anhydrous THF (85 ml) was added during 5 min to a stirred solution of lithium (1 g) in liquid ammonia (500 ml). More lithium (1.8 g) was added during a period of 15 min and stirring was continued for 1 h. Dry ethanol (100 ml) was added in drops and ammonia was allowed to evaporate. The residue was treated with ice cold water, acidified, and the precipitated solid was filtered off, washed with water, and dried. Crystallisation from methanol afforded the enol ether (6) (3.85 g), m.p. 184 °C; $\nu_{max.}$ 3 160 cm^{-1} (OH); *m/e* 232 (M^+), 214, 199, and 171 (Found: C, 72.65; H, 7.15. $C_{14}H_{16}O_3$ requires C, 72.39; H, 6.94%).

2,3,6,9-Tetrahydro-5,7-*dimethoxy*-1H-*benz*[e]*inden*-3-*ol* (7).—Dimethyl sulphate (3.8 g) was added to a solution of the enol ether (6) (3.5 g) in 5% aqueous sodium hydroxide (45 ml) and stirred at room temperature for 2 h. The precipitated solid was filtered off, washed, dried, and crystallised from ethyl acetate to yield the enol ether (7) (2.85 g), m.p. 131 °C; $\nu_{max.}$ 3 220 cm^{-1} (OH); δ($CDCl_3$) 1.8 (1 H, br s, OH), 2.0—3.65 (8 H, m, methylene H), 3.7 (3 H, s, enol OMe), 3.8 (3 H, s, OMe), 5.15 (1 H, br t, methine H), 5.75 (1 H, s, olefinic H), and 6.65 (1 H, s, ArH); *m/e* 246 (M^+), 228, 215, and 213 (Found: C, 73.4; H, 7.5. $C_{15}H_{18}O_3$ requires C, 73.14; H, 7.37%).

2,3,6,7,8,9-Hexahydro-5-*methoxy*-7-*oxo*-1H-*benz*[e]*inden*-3-*ol* (8).—An aqueous 10% oxalic acid (25 ml) was added to a solution of the enol ether (6) (2.5 g) in THF (100 ml) and stirred at room temperature for 12 h. Dilution with water followed by extraction with ethyl acetate and the usual work-up gave 2.3 g of the crude product. Recrystallisation from ether gave the pure ketone (8) (2.1 g), m.p. 137—138 °C; ν_{max} 3 400 (OH) and 1 710 cm^{-1} (C=O); δ($CDCl_3$) 1.8—3.1 (8 H, m, methylene H, 1 H at 2.2 exchanges with D_2O, OH), 3.5 (2 H, s, benzylic and α to keto-carbonyl), 3.85 (3 H, s, OMe), 5.7 (1 H, br t, methine H), and 6.85 (1 H, s, ArH) (Found: C, 72.5; H, 7.1. $C_{14}H_{16}O_3$ requires C, 72.39; H, 6.94%).

2,3,6,7,8,9-Hexahydro-5-*methoxy*-6-*methyl*-7-*oxo*-1H-*benz*[e]*inden*-3-*ol* (10).—To a solution of the ketone (8) (1.3 g) in dry thiophen-free benzene (50 ml) were added pyrrolidine (2 ml) and toluene-*p*-sulphonic acid (10 mg). The mixture was refluxed under nitrogen atmosphere for 3 h using a Dean–Stark water separator. The benzene and excess of pyrrolidine were removed under reduced pressure. The residue was dissolved in absolute methanol (30 ml) and refluxed for 1.5 h after the addition of methyl iodide (10 ml). The methyl iodide was removed under reduced pressure. A solution of sodium acetate (1 g) in water (20 ml) and acetic acid (1 ml) was added to the methanol solution and stirred overnight at room temperature. Dilution with water and extraction with ethyl acetate gave

a brown oily residue (1.3 g), which was purified by column chromatography on Florisil. Elution with ethyl acetate–light petroleum (1 : 9) gave the pure alkylated ketone (10) (0.9 g) as a thick liquid; $\nu_{max.}$ 3 400 (OH) and 1 710 cm^{-1} (C=O); δ 1.24 (3 H, d, *J* 8 Hz, Me), 1.90—3.0 (8 H, m, methylene H; 1 H at 2.25 exchanges with D_2O, OH), 3.5 (1 H, m, methine and α to keto-carbonyl), 3.7 (3 H, s, OMe), 4.9 (1 H, br t, methine H), and 6.5 (1 H, s, ArH); *m/e* 246 (M^+), 231, 204, and 203.

17β-*Hydroxy*-11-*methoxy*-18-*norandrosta*-4,8,11,13-*tetraen*-3-*one* (12).—Diethylaminobutan-3-one (0.7 g) was swirled gently with ice cooling whilst methyl iodide (1 ml) was added slowly. After continued cooling at this temperature for 30 min the crystalline methiodide formed was washed with dry ether and a solution of the ketone (10) (0.5 g) in dry thiophen-free benzene (15 ml) and potassium ethoxide (0.24 g of potassium in 7 ml of dry ethanol) were added under a nitrogen atmosphere. The mixture was stirred at 0—5 °C for 2 h and heated under reflux for 30 min. The dark red solution was cooled and acidified with dilute H_2SO_4. The benzene layer gave a thick oil (0.59 g) which was purified by column chromatography on Florisil. Elution with ethyl acetate–light petroleum (1 : 9) followed by crystallisation from methanol gave the pure compound (12) (0.31 g), m.p. 183—185 °C; ν_{max} 3 400 (OH) and 1 660 cm^{-1} (C=O); δ($CDCl_3$) 1.68 (1 H, s, Me), 1.8—3.3 (12 H, m, methylene H, 1 H at 2.25 exchanges with D_2O, OH), 3.86 (3 H, s, OMe), 5.25 (1 H, t, *J* 5 Hz, methine H), 5.83 (1 H, s, olefinic H), and 6.95 (1 H, s, ArH); *m/e* 298 (M^+), 283, 280, 265, and 255; ^{13}C n.m.r. δ 22.928 (10-Me), 28.192 (C-15), 29.102 (C-16), 31.051 (C-2), 33.066 (C-7), 34.626 (C-1), and 35.666 p.p.m.[9] (C-6) (Found: C, 76.7; H, 7.35. $C_{19}H_{22}O_3$ requires C, 76.48; H, 7.43%).

2,3,6,7,8,9-*Hexahydro*-3,5-*dimethoxy*-7-*oxo*-1H-*benz*[e]-*indene* (9).—Aqueous oxalic acid (10%) (50 ml) was added to a solution of the enol ether (7) (5 g) in methanol (150 ml) and the solution was stirred at room temperature for 24 h. Dilution with water followed by the usual work-up gave the crude product (4.6 g), which was purified by column chromatography on silica gel. Elution with ethyl acetate–light petroleum (1 : 19), followed by crystallisation from light petroleum gave the pure ketone (9) (3.75 g), m.p. 90 °C; ν_{max} 1 710 cm^{-1} (C=O); δ 1.95—3.1 (8 H, *m*, methylene H), 3.3 (3 H, s, benzylic OMe), 3.8 (3 H, s, OMe), 4.75 (1 H, br t, methine H), and 6.65 (1 H, s, ArH); *m/e* 246 (M^+), 215, 187, 173, and 159 (Found: C, 73.45; H, 7.4. $C_{15}H_{18}O_3$ requires C, 73.14; H, 7.37%).

2,3-*Dihydro*-3,5,7-*trimethoxy*-1H-*benz*[e]*indene* (4) *and* 3-*Ethoxy*-2,3-*dihydro*-5,7-*dimethoxy*-1H-*benz*[e]*indene* (5).—Treatment of compound (3) (2.5 g) with aqueous oxalic acid (10%) (5 ml) in methanol (100 ml) at room temperature for 1 h gave, on work-up, the 3-methoxy-compound (4) (2.4 g), recrystallised from light petroleum, m.p. 87 °C; δ 1.95—3.1 (4 H, m, methylene H), 3.25 (3 H, s, benzylic OMe), 3.8 (3 H, s, OMe), 3.9 (3 H, s, OMe), 4.8 (1 H, br t, methine H), 6.55 (1 H, s, ArH), and 6.8—7.45 (3 H, m, ArH).

Similar treatment in ethanolic solution gave the ethoxy-derivative (5) in quantitative yield, m.p. 79 °C; δ 1.2 (3 H, t, *J* 7 Hz, OCH_2CH_3), 2.0—3.2 (4 H, m, methylene H), 3.5 (2 H, q, *J* 7 Hz, OCH_2Me), 3.8 (3 H, s, OMe), 3.9 (3 H, s, OMe), 4.85 (1 H, t, *J* 6 Hz, methine H), 6.55 (1 H, s, ArH), and 6.7—7.4 (3 H, m, ArH).

2,3,6,7,8,9-*Hexahydro*-3,5-*dimethoxy*-6-*methyl*-7-*oxo*-1H-*benz*[e]*indene* (11).—The dimethoxy-ketone (9) was alkylated in benzene solution with methyl iodide and powdered potassium according to the procedure described by Grob and Jundt.[8] The product was purified by column chromatography on silica gel and eluted with ether–light petroleum (1 : 19) to give the methylated ketone (11) (76%) as a thick liquid; $\nu_{max.}$ 1 710 cm^{-1} (C=O); δ 1.3 (3 H, split d, *J* 8 Hz, Me), 1.95—3.15 (8 H, m, methylene H), 3.35 (3 H, s, benzylic OMe), 3.6 (1 H, q, *J* 8 Hz, methine H benzylic and α to keto carbonyl), 3.85 (3 H, s, OMe), 4.7 (1 H, br t, methine H), and 6.7 (1 H, s, ArH); *m/e* 260 (M^+), 245, 229, 217, and 201.

11,17-*Dimethoxy*-18-*norandrosta*-4,8,11,13-*tetraen*-3-*one* (13).—Compound (11) was annelated by the procedure described above. The unsaturated ketone (13) was obtained in 55% yield by column chromatography on silica gel. It was crystallised from ether–light petroleum, m.p. 131 °C; ν_{max} 1 665 cm^{-1} (C=O); δ 1.66 (3 H, split s, Me), 1.80—3.0 (12 H, m, methylene H), 3.43 (3 H, s, benzylic OMe), 3.83 (3 H, s, OMe), 4.77 (1 H, br t, methine H), 5.82 (1 H, s, olefinic H), and 6.84 (1 H, s, ArH); *m/e* 312 (M^+), 297, 284, 281, 270, 269, 266, and 255; ^{13}C n.m.r. δ 22.764 and 22.866 (10-Me), 28.430 and 28.561 (C-15), 29.100 and 29.187 (C-16), 31.066 (C-2), 31.139 and 31.284 (C-7), 32.799 and 32.974 (C-6), and 34.692 p.p.m. (C-1) (Found: C, 76.9; H, 7.8. $C_{20}H_{24}O_3$ requires C, 76.89; H, 7.74%).

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