Synthesis of 17α-Ethynyl-7α,11β-dihydroxyestra-1,3,5(10)-triene-3,17β-diol

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17α-Ethynyl-7α,11β-dihydroxyestradiol (9) was synthesized starting from androsta-1,4,6-triene-3,11,17-trione (1). Compound (1) was acetalized selectively at C-17 with ethylene glycol to give the ethylene acetal (4). Selective reduction of the 11-oxo-group in compound (4), followed by aromatization of ring A with zinc and acetylation gave the diacetate (6b) which, on epoxidation followed by reduction with lithium aluminium hydride and subsequent hydrolysis, gave the 7α,11β-dihydroxy-derivative (8) which was ethynylated to give the title compound (9). The diol (9) shows a poorer separation of postcoital antifertility activity from uterotropic activity in the rat than do either the 7α- or 11β-monohydroxy-analogues.

Modification of 17-ethynylestradiol by a single substitution with either a 7α-hydroxy-[1] or 11β-hydroxy-group [2] greatly reduced estrogenicity without significantly affecting the postcoital antifertility potency in rats (Table). Therefore, it was expected that a compound with hydroxy-substituents at both 7α- and 11β-positions might further increase postcoital antifertility activity or decrease estrogenicity. This prompted us to undertake the synthesis of 17α-ethynyl-7α,11β-dihydroxyestradiol † (9).

In our initial approach, androsta-1,4,6-triene-3,11,17-trione [3] (1) was treated with *m*-chloroperbenzoic acid [4] to give the 6α,7α-epoxide (2). Treatment of the epoxide (2) with hydrobromic acid followed by reaction with zinc and ethanol gave the 7α-hydroxy-derivative (3). Attempts to prepare the 17-ethylene acetal derivative of compound (3) by heating a solution of the ketone (3) with ethylene glycol and toluene-*p*-sulphonic acid in benzene resulted, however, in the elimination of the 7α-hydroxy-group and compound (4) was obtained. We then investigated an alternative method which was successful (Scheme). Compound (1) was first converted into its 17-ethylene acetal (4) by reaction with ethylene glycol and toluene-*p*-sulphonic acid in benzene solution. Reduction of the 11-ketone (4) with lithium tri(t-butoxy)-aluminium hydride in tetrahydrofuran (THF) gave the 11β-alcohol (5). Aromatization of compound (5) using activated zinc [5] in refluxing dimethylformamide (DMF) [6] gave the 6-olefin (6a) which, on acetylation with pyridine and acetic anhydride, gave the diacetate (6b). Epoxidation of the diacetate using *m*-chloroperbenzoic acid in dichloromethane gave the 6α,7α-epoxide (7). Reduction of compound (7) with lithium aluminium hydride in THF, followed by mild, acidic hydrolysis, gave 3,7α,11β-trihydroxy-derivative (8). Reaction of the ketone (8) with lithium acetylide–ethylenediamine complex in dimethyl sulphoxide (DMSO) yielded 17α-ethynylestra-1,3,5(10)-triene-3,7α,11β,17β-tetraol (9).

Using protocols previously published,[7] compound (9) was assayed by the oral route for both uterotropic activity and postcoital antifertility activity in rats against 17α-ethynylestradiol, 17α-ethynyl-7α-hydroxyestradiol, and 17α-ethynyl-11β-hydroxyestradiol. These results are summarized in the Table.

The data in the Table indicate that compound (9) is effective as a postcoital antifertility agent at a dose of 2 mg kg^{-1} day^{-1}, yet exhibits only 0.14% of the uterotropic activity of 17α-ethynylestradiol in rats, yielding a 91-fold separation of uterotropic from postcoital antifertility activity relative to 17α-ethynylestradiol. More significantly, however, compound (9) is less potent than either 17α-ethynyl-7α- or 17α-ethynyl-11β-hydroxyestradiol in the postcoital antifertility assay without offering any advantage in terms of reduced estrogenicity, and this is reflected in the comparative separations of postcoital from uterotropic activity.

† Estradiol is estra-1,3,5(10)-triene-3,17β-diol.

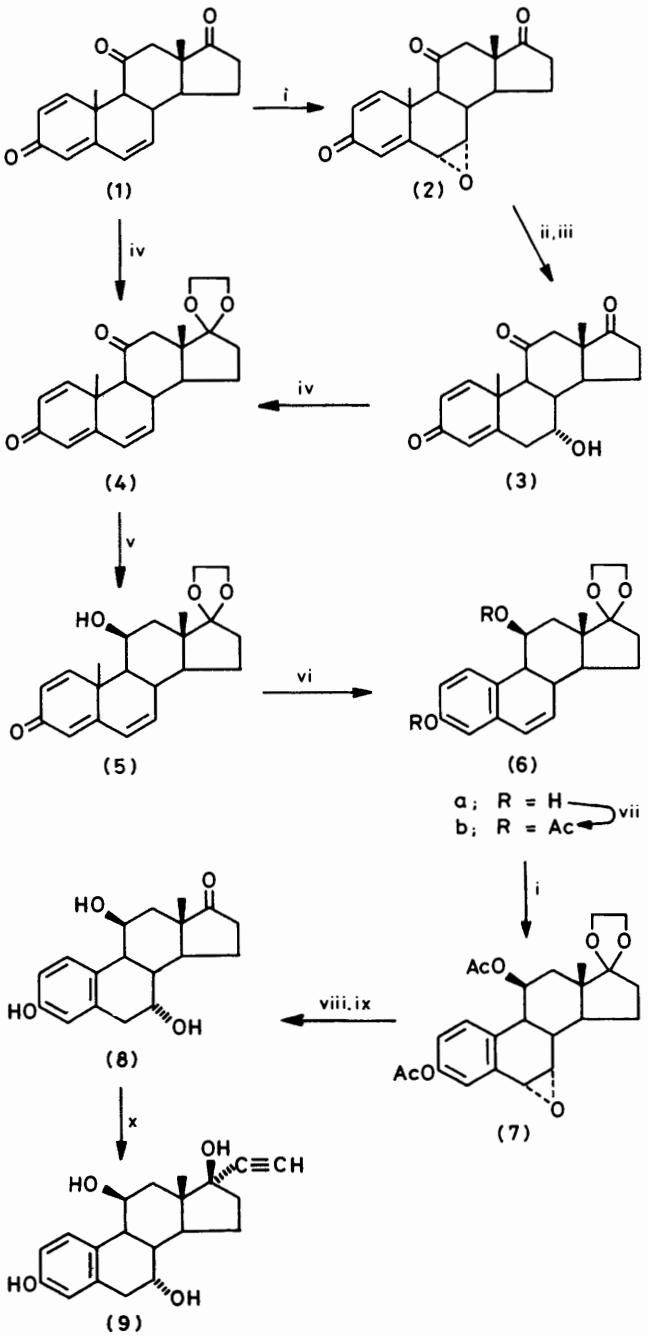
Experimental

Unless otherwise stated, m.p.s were determined with a Thomas–Hoover Model 6406-H apparatus and are not corrected; i.r. spectra were recorded as KBr pellets with a Perkin–Elmer 467 spectrophotometer; ^{1}H n.m.r. spectra were measured in $CDCl_3$ (unless otherwise stated), using tetramethylsilane as internal standard, with a Varian EM-390 90 MHz or A-60 60 MHz spectrometer; microanalyses were obtained by MicroTech Laboratories, Inc., Skokie, Illinois; mass spectra were recorded on a Finigan quadrupole mass spectrometer at the Southwest Research Institute, San Antonio, Texas. Light petroleum was purified and distilled in the range b.p. 40—60 °C.

6α,7α-*Epoxyandrosta*-1,4-*diene*-3,11,17-*trione* (2).—To a stirred, ice-cooled solution of androsta-1,4,6-triene-3,11,17-trione (1) (2 g) in dichloromethane (120 ml) under nitrogen at 0 °C was added dropwise a solution of *m*-chloroperbenzoic acid (1.4 g) in dichloromethane (25 ml). The mixture was removed from the ice-bath and was stirred at room temperature under nitrogen for 3 d. An additional solution of *m*-chloroperbenzoic acid (350 mg) in dichloromethane (10 ml) was added to the ice-cooled mixture. The mixture was then stirred at room temperature for an further 2 d and was then poured into ice-cold aqueous sodium hydrogen carbonate. The organic phase was separated and was washed in turn with aqueous sodium hydrogen carbonate, water, and brine, and was then dried (Na_2SO_4). The epoxide (2) (1.3 g, 62%) was obtained after crystallizing from acetone–hexane, m.p. 229—231 °C (decomp.); $\nu_{max.}$ 1 740, 1 710, 1 660, 1 630, and 1 595 cm^{-1}; δ 0.97 (3 H, s, 13-Me), 1.44 (3 H, s, 10-Me), 3.64 (1 H,

Table. Uterotropic and postcoital antifertility activity

Compound	Oral postcoital antifertility activity in the rat (ED_{100}/ μg kg^{-1} day^{-1})	Oral uterotropic activity relative to that of 17α-ethynylestradiol in the rat (%)	Separation of postcoital antifertility activity from uterotropic activity
17α-Ethynylestradiol	256	100.0	1
17α-Ethynyl-7α-hydroxyestradiol	250	0.1	1 024
17α-Ethynyl-11β-hydroxyestradiol	100	0.86	298
17α-Ethynyl-7α,11β-dihydroxyestradiol	2 000	0.14	91



Scheme. *Reagents*: i, *m*-chloroperbenzoic acid, CH_2Cl_2; ii, HBr; iii, Zn, Et*OH*; iv, $HOCH_2CH_2OH$, H^+; v, $LiAl(OBu^t)_3H$, THF; vi, Zn, DMF; vii, Ac_2O, pyridine; viii, $LiAlH_4$, THF; ix, H^+, CH_3OH; x, $LiC{\equiv}CH{-}H_2NCH_2CH_2NH_2$, DMSO

d, 6- or 7-H), 3.78 (1 H, d, 7- or 6-H), 6.25 (1H, dd, *J* 2 and 10 Hz, 2-H), 6.53 (1 H, d, 4-H), and 7.80 (1 H, d, *J* 10 Hz 1-H).

7α-Hydroxyandrosta-1,4-diene-3,11,17-trione (3).—A solution of the epoxide (2) (1.3 g) in chloroform (75 ml) and 48% hydrobromic acid (25 ml) was shaken in a separatory funnel several times over a period of 20 min. The organic layer was separated, washed in turn with water and brine, and dried (Na_2SO_4). The solvent was evaporated off under reduced pressure to give the crude bromohydrin (1.5 g); $\nu_{max.}$ 3 360, 1 740, 1 705, 1 660, 1 615, and 1 595 cm^{-1}. The presence of bromine was indicated by the Beilstein test.[8]

To a mixture of the crude bromohydrin (1.5 g) in ethanol (450 ml) and water (75 ml) was added activated zinc and the mixture was stirred at room temperature for 5.5 h. The mixture was filtered and the zinc was washed well with ethanol. The combined filtrate and washings were evaporated to remove ethanol, water was added, and the aqueous mixture was extracted with ethyl acetate. The extract was washed in turn with water and brine and was then dried (Na_2SO_4). Chromatography on dry-column silica gel with diethyl ether–ethyl acetate (1 : 1) as eluant gave after work-up, a product (500 mg), crystallization of which from acetone–diethyl ether gave the alcohol (3) (300 mg, 23%), m.p. 209—215 °C; $\nu_{max.}$ 3 340 and 1 740 cm^{-1}; δ 0.89 (3 H, s, 13-Me), 1.45 (3 H, s, 10-Me), 4.23 (1 H, m, 7-H), 5.83 (1 H, m, 4-H), 5.92 (1 H, m, 2-H), and 7.70 (1 H, d, 1-H).

Attempted Acetalization of Compound (3).—A mixture of the trione (3) (240 mg), benzene (60 ml), ethylene glycol (2 ml), and toluene-*p*-sulphonic acid (50 mg) was heated at reflux for 85 min using a Dean–Stark trap. The mixture was cooled, treated with aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The extract was washed in turn with aqueous sodium hydrogen carbonate, water, and brine, and was then dried (Na_2SO_4). Evaporation of the solvent gave a residue which was crystallized from diethyl ether to give the triene-acetal (4) (140 mg, 54%); $\nu_{max.}$ 1 705, 1 650, 1 600, and 1 580 cm^{-1}; δ 0.95 (3 H, s, 13-Me) and 1.38 (3 H, s, 10-Me). The compound was identical to the product obtained by acetalization of compound (1) (see below).

17-Ethylenedioxyandrosta-1,4,6-triene-3,11-dione (4) *by Acetalization of Compound* (1).—To a solution of the trione (1) (4 g) in benzene (400 ml) were added in turn ethylene glycol (3.5 ml) and toluene-*p*-sulphonic acid (400 mg) and the mixture was heated under reflux under nitrogen atmosphere for 2 h using a Dean–Stark apparatus. The reaction mixture was cooled, poured into ice-cold aqueous sodium hydrogen carbonate, and the benzene layer was separated. The aqueous phase was extracted with ethyl acetate and the extract was combined with the benzene solution. The combined organic phases were washed in turn with aqueous sodium hydrogen carbonate, water, and brine, and were then dried

(Na_2SO_4). The solvent was evaporated off under reduced pressure and the residue was triturated with a mixture of diethyl ether–acetone–hexane; the resultant crystals were filtered off and dried to give the *acetal* (4) (2.97 g, 65%). Dry-column chromatography of the mother liquors in silica gel with diethyl ether–ethyl acetate (1 : 1) as eluant gave an additional crop of the *acetal* (1 g). Two recrystallizations from acetone–hexane gave an analytical sample, m.p. 172.5—173 °C; $\nu_{max.}$ 1 705, 1 650, 1 600, and 1 575 cm^{-1}; δ 0.94 (3 H, s, 13-Me), 1.39 (3 H, s, 10-Me), 3.82 (4 H, m, 17-acetal), 6.00 (2 H, m), 6.22 (2 H, m), and 7.64 (1 H, d, *J* 10 Hz, 1-H); *m/z* 340 (M^+) (Found: C, 74.15; H, 7.3. $C_{21}H_{24}O_4$ requires C, 74.09; H, 7.11%).

17-*Ethylenedioxy*-11β-*hydroxyandrosta*-1,4,6-*trien*-3-*one* (5).—To a solution of lithium tri(t-butoxy)aluminium hydride (14 g) in anhydrous THF (100 ml) under nitrogen was added dropwise a solution of the dione (4) (6.8 g) in THF (100 ml) and the mixture was stirred under nitrogen for 20.5 h at room temperature. THF (100 ml), diethyl ether (50 ml), water (1.5 ml), 20% aqueous sodium hydroxide (1.5 ml), and water (9 ml) were then added in turn and the solution was stirred for 1.5 h under nitrogen. The mixture was filtered through a sintered glass funnel and the precipitate was washed with ethyl acetate. The filtrate was concentrated to dryness under reduced pressure and the residue was dissolved in ethyl acetate, the solution was treated under reflux with charcoal and then filtered through Celite to give the crude alcohol (5) (7 g) which was further purified by dry-column chromatography on silica gel with diethyl ether–ethyl acetate (8 : 2) as eluant. Work-up and crystallization of the product so obtained from acetone–hexane and diethyl ether–light petroleum gave the pure *alcohol* (5) (3 g, 44%), m.p. 180—182 °C. An additional crop (0.5 g) was obtained from the mother liquors. An analytical sample was obtained by crystallization from diethyl ether–light petroleum and had m.p. 181—182 °C; $\nu_{max.}$ 3 450, 1 645, and 1 595 cm;'; δ 1.21 (3 H, s, 13-Me), 1.48 (3 H, s, 10-Me), 3.83 (4 H, m, 17-acetal), 4.45 (1 H, m, 11-H), 6.00 (1 H, m), 6.22 (3 H, m), and 7.25 (1 H, d, *J* 10 Hz, 1-H); *m/z* 342 (M^+) (Found: C, 73.65; H, 8.0. $C_{21}H_{26}O_4$ requires C, 73.66; H, 7.65%).

17-*Ethylenedioxy*-3,11β-*dihydroxyestra*-1,3,5(10),6-*tetraene* (6a).—*Activated zinc*. Zinc (40 g) was added to a mixture of concentrated sulphuric acid (160 ml) and fuming nitric acid (several drops) and the mixture was heated in an oil-bath for 30 min at 100 °C. The mixture was allowed to cool and the acid was decanted. Ice-water (1 000 ml) was added to the residue and the mixture left for 1 min. The water was decanted and the zinc was washed with water until the washings were neutral to pH paper. The zinc was then washed twice with 95% ethanol and twice with acetone and was then oven-dried at 100—120 °C for 40 min. The zinc was used immediately in the following reaction.

The trienone (5) (1 g) was dissolved in DMF (40 ml) containing water (0.2 ml) and activated zinc (20 g) was added. The mixture was stirred and heated under reflux under nitrogen for 4 h. The mixture was cooled, filtered, and the zinc was washed with ethyl acetate. The combined filtrate and washings were evaporated to dryness under reduced pressure and the residue was chromatographed on a dry column of silica gel with diethyl ether–ethyl acetate (8 : 2) as eluant to give, after work-up, a product (500 mg, 52%), trituration of which with diethyl ether–light petroleum yielded a crystalline product. Further crystallization from diethyl ether and acetone–hexane gave the *phenol* (6a), m.p. 209—210 °C (micro); $\nu_{max.}$ 3 500, 3 240, 1 630, 1 610, and 1 570 cm^{-1}; δ ([$^2H_6$]acetone) 1.12 (3 H, s, 13-Me), 3.80 (4 H, s, 17-acetal), 5.86 (1 H, d, *J* 9 Hz, 7-H), 6.31br (1 H, d, *J* 9 Hz, 6-H), 6.48 (1 H, s, 4-H), 6.55 (1 H, dd, *J* 2.5 and 8 Hz, 2-H), and 7.12 (1 H, d, *J* 8 Hz, 1-H); *m/z* 328 (M^+) (Found: C, 73.35; H, 7.35. $C_{20}H_{24}O_4$ requires C, 73.15; H, 7.37%).

3,11β-*Diacetoxy*-17-*ethylenedioxyestra*-1,3,5(10),6-*tetraene* (6b).—A mixture of the diol (6a) (2 g), pyridine (10 ml), and acetic anhydride (10 ml) was heated at 70—80 °C for 6.5 h. The reagents were evaporated off under reduced pressure and the residue was crystallized from methanol to give the *diacetate* (6b) (2.12 g, 84%), m.p. 126—127 °C. An analytical sample was crystallized from methanol, m.p. 127—128.5 °C; $\nu_{max.}$ 1 765, 1 730, 1 245, and 1 210 cm^{-1}; δ 1.01 (3 H, s, 13-Me), 1.97 (3 H, s, COMe), 2.23 (3 H, s, COMe), 3.83 (4 H, m, 17-acetal), 5.84 (1 H, m, 11α-H), 6.03 (1 H, d, *J* 10 Hz, 6-H), 6.47 (1 H, dd, *J* 2 and 10 Hz, 7-H), and 6.87 (3 H, m, ArH); *m/z* 412 (M^+) (Found: C, 69.85; H, 6.95. $C_{24}H_{28}O_6$ requires C, 69.89; H, 6.84%).

3,11β-*Diacetoxy*-6α,7α-*epoxy*-17-*ethylenedioxyestra*-1,3,5(10)-*triene* (7).—To a stirred solution of the olefin (6b) (2.7 g) in dichloromethane (130 ml) under nitrogen atmosphere at 0 °C was added dropwise a solution of *m*-chloroperbenzoic acid (1.6 g) in dichloromethane (45 ml). The mixture was set aside at room temperature overnight and was then poured into ice-cold aqueous sodium hydrogen carbonate and was then extracted with ethyl acetate. The extract was washed in turn with aqueous sodium hydrogen carbonate, water, and brine, and was then dried (Na_2SO_4) and the solvent was partially evaporated off under reduced pressure. Treatment (reflux) with charcoal and concentration under reduced pressure gave a product which, on crystallization from dichloromethane–diethyl ether, gave the *epoxide* (7) (2.36 g, 84%), m.p. 154—157 °C; an analytical sample was crystallized from dichloromethane–diethyl ether, m.p. 156—157 °C; $\nu_{max.}$ 1 760, 1 725, 1 240, and 1 210 cm^{-1}; δ 1.03 (3 H, s, 13-Me), 1.92 (3 H, s, COMe), 2.26 (3 H, s, COMe), 3.59 (1 H, d, *J* 3.5 Hz, 6- or 7-H), 3.80 (1 H, d, *J* 3.5 Hz, 7- or 6-H), 3.85 (4 H, s, 17-acetal), 5.81 (1 H, m, 11-H), 6.71 (2 H, d, ArH), 7.08 (1 H, m, ArH); *m/z* 428 (M^+) (Found: C, 67.65; H, 6.65. $C_{24}H_{28}O_7$ requires C, 67.28; H, 6.59%).

3,7α,11β-*Trihydroxyestra*-1,3,5(10)-*trien*-17-*one* (8).—A solution of compound (7) (500 mg) in anhydrous THF (10 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (270 mg) in anhydrous THF under nitrogen. The mixture was heated at reflux for 3.3 h and was then cooled in an ice-bath. Water was added cautiously and the mixture was then acidified (hydrochloric acid). Additional water was added, the mixture was extracted with ethyl acetate, and the extract was washed in turn with water and brine and was then dried (Na_2SO_4). The solvent was evaporated off under reduced pressure, the residue was dissolved in methanol containing 0.4N HCl (1 ml) and the mixture was heated at 60 °C for 7 min. The solvent was evaporated off and the residue was dried by azeotropic distillation with benzene. The residue was dissolved in acetone, charcoal was added, and the mixture was heated under reflux and then filtered through Celite. Evaporation of the filtrate gave a residue which was crystallized from acetone to give the *ketone* (8) (176 mg, 50%), m.p. 278 °C. Recrystallization from acetone–hexane gave an analytical sample, m.p. 283—284 °C (vacuum capillary); $\nu_{max.}$ 3 510, 3 320, 3 220, and 1 730 and 1 710 cm^{-1} (split C=O); δ ([$^2H_6$]acetone) 1.11 (3 H, s, 13-Me), 4.28 (1 H, m, 7β-H), 4.87 (1 H, m, 11α-H), 6.52 (1 H, s, 4-H), 6.60 (1 H, dd, *J* 3 and 9 Hz, 2-H), and 7.13 (1 H, d, *J* 9 Hz, 1-H) (Found: C, 71.45; H, 7.45. $C_{18}H_{22}O_4$ requires C, 71.50; H, 7.33%).

17α-*Ethynyl*-3,7α,11β,17β-*tetrahydroxyestra*-1,3,5(10)-*triene* (17α-*Ethynyl*-7α,11β-*dihydroxyestradiol*) (9).—A solution of the crude ketone (8) (1 g) in dry DMSO (85 ml) under nitrogen was treated with lithium acetylide–ethylenediamine complex (4 g) and the mixture was stirred for 4.25 h at room temperature. The mixture was poured into ice-water, acidified with hydrochloric acid, and extracted with ethyl acetate. The extract was washed in turn with water and brine and was then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the residue was dissolved in a mixture of ethanol (50 ml) and acetic acid (5 ml) and Girard ' P ' reagent (1.25 g) was added. The mixture was heated at reflux for 2 h, cooled, and concentrated under reduced pressure. Water was added to the residue and the mixture was extracted with ethyl acetate. Normal work-up, followed by treatment (reflux) with charcoal and crystallization from ethanol, gave the *ethynyl derivative* (9) (210 mg, 19%), m.p. 271—272 °C (vacuum capillary); $\nu_{max.}$ 3 280 and 1 610 cm^{-1}; δ [[$^2H_6$]acetone–[$^2H_4$]methanol (1 : 1)] 1.13 (3 H, s, 13-Me), 2.94 (1 H, s, C≡CH), 6.54 (1 H, s, 4-H), 6.61 (1 H, dd, *J* 3 and 8 Hz, 2-H), 7.20 (1 H, d, *J* 8 Hz, 1-H) (Found: C, 73.25; H, 7.35. $C_{20}H_{24}O_4$ requires C, 73.15; H, 7.3%).

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