Tetrahedron, 1966, Vol. 22, pp. 2829 to 2836. Pergamon Press Ltd. Printed in Northern Ireland

MODIFIED STEROID HORMONES—XLVI[1]
SOME 17α-ETHYNYL AND 17α-VINYL DERIVATIVES

C. BURGESS, D. BURN, P. FEATHER, M. HOWARTH and V. PETROW
Chemical Research Department, The British Drug Houses Ltd., Graham Street, London

(*Received* 5 *March* 1966)

Abstract—Novel 17α-bromoethynyl, 17α-chloroethynyl, 17α-iodoethynyl, 17α-trifluoropropynyl, 17α-vinyl and 17α-trifluorovinyl-17β-hydroxy (and/or 17β-alkoxy)-steroids have been prepared for biological examination.

IN EARLIER studies[2–6] we have shown that modification of the ethynyl group in 17α-ethynyl-17β-hydroxy-steroids can lead to both qualitative and quantitative changes in biological activity. In view of the importance of such compounds as antifertility agents, we have now extended our studies to include certain novel 17α-chloroethynyl, 17α-trifluoropropynyl and 17α-trifluorovinyl-17β-hydroxy-steroids. Many of the novel 17β-hydroxy derivatives as well as some previously reported[5] have also been converted into their alkyl ethers. Additionally we have prepared novel 17α-bromoethynyl, 17α-iodoethynyl and 17α-vinyl-17β-alkoxy-steroids. All the compounds have been screened for claudogenic activity and the results will be published elsewhere.

Chloroethynyl steroids. These were prepared by treating the corresponding 17-one with alkali-metal chloroacetylides.[5,7] Yields were generally good. For preparation of the corresponding 3-alkoxy-oestra-2,5(10)-dien derivatives, the appropriate 3-alkoxy-oestra-1,3,5(10)-triene was reduced to the 1,4-dihydro derivative by sodium in iron-free liquid ammonia.[8] The resulting 17β-ol was converted by Oppenauer oxidation into the 17-one, which was condensed with the alkali-metal chloroacetylide.

Conversion of the foregoing 17α-chloroethynyl-17β-hydroxy-steroids into the 17β-methyl ethers was achieved by reaction with sodamide in liquid ammonia to obtain the sodio-derivative, followed by metathesis with methyl iodide.[9] The process gave consistently good yields and is preferred, especially for large-scale working, to earlier procedures[10] which employ silver oxide and methyl iodide. The apparent resistance of the chloroethynyl group to attack by sodamide is noteworthy in view of the facility with which it reacts with such reagents as lithium alkyls.[11]

[1] Part XLV, G. Cooley, B. Ellis and V. Petrow, *Tetrahedron* Professor Stephen, Memorial issue, in the press.
[2] S. P. Barton, G. Cooley, B. Ellis and V. Petrow, *J. Chem. Soc.* 5094 (1957).
[3] S. P. Barton, D. Burn, G. Cooley, B. Ellis and V. Petrow, *J. Chem. Soc.* 1957 (1959).
[4] B. Ellis, V. Petrow, M. Stansfield and G. Weston, *J. Chem. Soc.* 2389 (1960).
[5] C. Burgess, D. Burn, J. W. Ducker, B. Ellis, P. Feather, A. K. Hiscock, A. P. Leftwick, J. S. Mills and V. Petrow, *J. Chem. Soc.* 4995 (1962).
[6] C. Burgess, D. Burn, P. Feather, M. Howarth and V. Petrow, *Tetrahedron* **21**, 1197 (1965).
[7] H. G. Viehe, *Chem. Ber.* **92**, 1270 and 1950 (1959).
[8] H. L. Dryden, Jr., G. M. Webber, R. R. Burtner and J. A. Cella, *J. Org. Chem.* **26**, 3237 (1961).
[9] German Patents 1062698 and 1117572.
[10] U.S. Patents 3067214, 3092623 and 3100204.
[11] H. G. Viehe, *Chem. Ber.* **92**, 3064 (1959).

The above procedure could be adopted for the preparation of ethyl ethers providing a longer reaction time with the alkyl halide was allowed. Attempts to prepare n-propyl and cyclopentyl ethers were unsuccessful. No difficulty was experienced in preparing benzyl and diethylaminoethyl ethers.

In a modification of the above process, the 17-oxo steroid was treated with sodium chloroacetylide in liquid ammonia and, when reaction was complete, an excess of methyl iodide was added and the mixture stirred for a further 2–3 hours. Isolation of the product in the usual way yielded the 17α-chloroethynyl-17β-methoxy derivative directly. This process was particularly convenient with such starting materials as equilenin 3-methyl ether and 9(11)-dehydro-oestrone 3-methyl ether which were only available in limited quantities.

17β-Alkoxy-17α-chloroethynyl-19-norandrost-4-en-3-ones and an oestr-5(10)-en-3-one derivative were obtained by hydrolysis of appropriate 3-methoxy-oestra-2,5(10)-diene derivatives. A 19-norandrost-5-en-3ζ-hydroxy derivative was obtained by reduction of the corresponding 4-en-3-one.

Trifluorovinyl steroids. These were prepared by reaction of the 17-oxo-steroid with trifluorovinyl magnesium bromide.[12,13] One of the resulting 17β-hydroxy compounds was methylated by treatment with sodamide and methyl iodide in liquid ammonia.

Vinyl steroids. Methylation of 17α-vinyl-oestra-1,3,5(10)-trien-3,17β-diol[14] by the foregoing procedure gave the 3,17β-dimethyl ether in low yield, in a single stage.

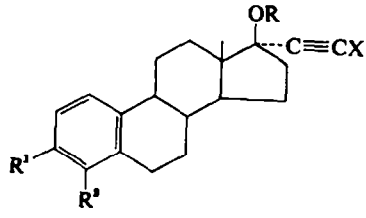
Trifluoropropynyl steroids. 3,3,3-Trifluoropropyne (prepared by the method of Finnegan and Norris[15]) was converted into a Grignard reagent by treatment with ethyl magnesium bromide[13,16] in ether, and condensed directly with oestrone 3-methyl ether in tetrahydrofuran. Methylation to the resulting 17α-trifluoropropynyl-17β-hydroxy derivative was achieved with sodamide and methyl iodide in liquid ammonia, under somewhat milder conditions than in previous preparations to minimise degradation of the trifluoropropynyl group.

In subsequent preparations of 17α-trifluoropropynyl steroids from oestrone and 4-methyl-oestra-1,3,5(10)-trien-17-one, we employed an alternative procedure in which the 3,3,3-trifluoropropyne was passed into lithamide in liquid ammonia and the resulting lithio-acetylene used for the reaction. The success of this method contrasts with the observation of Henne and Nager[16] that sodamide, in place of lithamide, converted 3,3,3-trifluoropropyne into a tar.

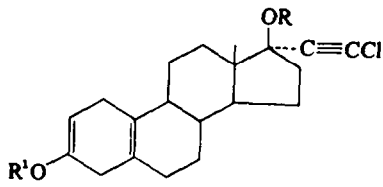
Bromoethynyl and iodoethynyl steroids. These were prepared by direct halogenation of the corresponding 17α-ethynyl-17β-methoxy-steroid. The bromo-analogue was obtained by the method of Fried *et al.*[13] whereby the ethyne is treated with potassium t-butoxide in t-butanol and the resulting potassium derivative reacted with N-bromo-succinimide. The iodo-analogue was prepared by iodination with the morpholine/iodine adduct.[17]

[12] I. L. Knunyants, R. N. Sterlin, R. D. Yatsenko and L. N. Pinkina, *Izvest. Akad. Nauk S.S.S.R. Otdel. khim. Nauk.* **11**, 1345 (1958).
[13] J. H. Fried, T. S. Bry, A. E. Oberster, R. E. Beyler, T. B. Windholz, J. Hannah, L. H. Sarett and S. L. Steelman, *J. Amer. Chem. Soc.* **83**, 4663 (1961).
[14] C. Djerassi and C. R. Scholz, *J. Amer. Chem. Soc.* **71**, 3962 (1949).
[15] W. G. Finnegan and W. P. Norris, *J. Org. Chem.* **28**, 1139 (1963).
[16] A. L. Henne and M. Nager, *J. Amer. Chem. Soc.* **74**, 650 (1952).
[17] P. L. Southwick and J. R. Kirchner, *J. Org. Chem.* **27**, 3305 (1962).

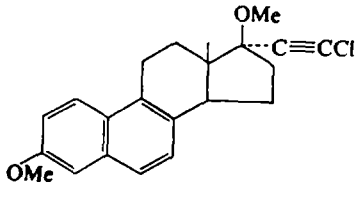
The bromoethynyl and iodoethynyl steroid proved to be reasonably stable in the absence of light.



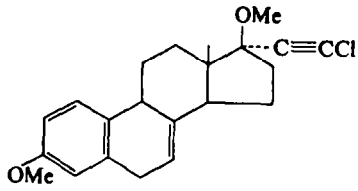
I



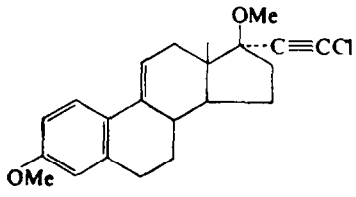
II



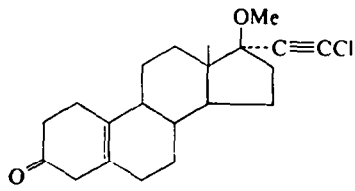
III



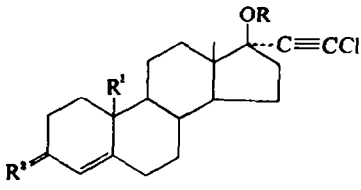
IV



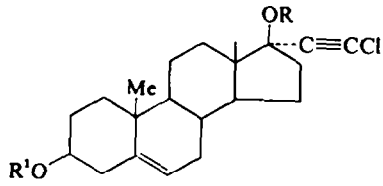
V



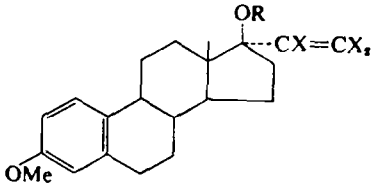
VI



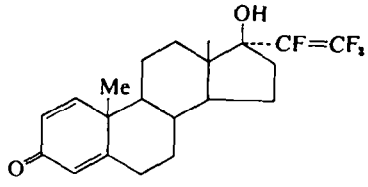
VII



VIII



IX



X

EXPERIMENTAL

UV absorption spectra (in EtOH), IR absorption spectra and optical rotations were determined under the supervision of Mr. M. T. Davies, B.Sc., F.R.I.C.

17α-Chloroethynyl-17β-hydroxy steroids were prepared from 17-oxo steroids by the general procedures described by Viehe[7] and in our previous publication,[8] employing lithium chloroacetylide in ether or sodium chloroacetylide in liquid ammonia.

17β-Alkoxy steroids, except when otherwise stated, were prepared from the corresponding 17β-hydroxy steroids according to the general procedure described here. Sodium (1–4 gram-atoms per

mole of steroid) and a trace of ferric nitrate were added to liquid ammonia (20–50 ml per g of steroid) and the mixture was stirred under reflux until the blue colour disappeared. The mixture was cooled to about −60° (bath temp), the 17β-hydroxy steroid in anhydrous tetrahydrofuran (THF) (10–20 ml per g of steroid) was added and stirring was continued for 15–60 min. The necessary alkyl halide (in quantity equivalent to the Na or a slight excess) in anhydrous tetrahydrofuran (2–8 ml per g of steroid) was added, stirring was continued at about −60° for a time appropriate to the alkyl halide used (2–3 hr for MeI, benzyl bromide or diethylaminoethyl bromide; 13 hr for EtI) and the mixture was poured on to ice. The steroidal product was collected by filtration or by extraction with ether.

17α-Chloroethynyl-17β-methoxy steroids were alternatively prepared directly from the 17-ketones without isolation of the 17β-hydroxy derivatives by the following general procedure. *trans*-1,2-Dichloroethylene (0·5 mole per gram-atom of Na) in anhydrous ether (20–25 ml per g of steroid) was added slowly to $NaNH_2$, prepared as above from Na (0·7–1·0 g per g of steroid) in liquid ammonia (50 ml per g of steroid), and the mixture was stirred under reflux for 1 hr. The 17-oxo steroid in anhydrous THF (20–25 ml per g of steroid) was added slowly and the mixture was stirred for a further 2 hr. MeI (0·5 mole per gram-atom of Na, or a slight excess) in anhydrous ether (15–25 ml per g of steroid) was added slowly and the mixture was stirred for a further 2 hr and poured on to ice. The steroidal product was collected by filtration.

17α-Chloroethynyl-3-ethoxy-oestra-1,3,5(10)-trien-17β-ol (I, R = H, R^1 = OEt, R^2 = H, X = Cl), prepared from oestrone 3-ethyl ether[18] and lithium chloroacetylide, crystallized from aqueous MeOH in needles (yield = 50%), m.p. 148–151°. (Found: C, 73·3; H, 7·8; Cl, 9·85. $C_{22}H_{27}ClO_2$ requires: C, 73·6; H, 7·6; Cl, 9·9%.)

17α-Chloroethynyl-3-n-propoxy-oestra-1,3,5(10)-trien-17β-ol (I, R = H, R^1 = OPr^n, R^2 = H, X = Cl), prepared from oestrone 3-n-propyl ether[19] and sodium chloroacetylide, crystallized from aqueous EtOH in needles (yield = 58%), m.p. 127–127·5°; $[\alpha]_D^{24}$ −9·0° (*c*, 0·82 in dioxan); λ_{max} 287 mμ (ε, 1760), 279 mμ (ε, 1876), 221 mμ (ε, 8577); ν_{max}^{Nujol} 3600 cm^{-1} (OH), 2208 cm^{-1} (C≡C). (Found: C, 73·8; H, 7·8; Cl, 10·0. $C_{23}H_{29}ClO_2$ requires: C, 74·1; H, 7·8; Cl, 9·5%.)

17α-Chloroethynyl-3-ethoxy-17β-methoxy-oestra-1,3,5(10)-triene (I. R = Me, R^1 = OEt, R^2 = H, X = Cl) crystallized from MeOH in minute grains (yield = 67%), m.p. 124·5°; $[\alpha]_D^{25}$ −18° (*c*, 1·04 in dioxan); λ_{max} 288 mμ (ε, 1690), 279 mμ (ε, 1810); $\nu_{max}^{CCl_4}$ 2210 cm^{-1} (C≡C). (Found: C, 74·6; H, 7·9; Cl, 9·2. $C_{23}H_{29}ClO_2$ requires: C, 74·1; H, 7·8; Cl, 9·5%.)

17α-Chloroethynyl-17β-methoxy-3-n-propoxy-oestra-1,3,5(10)-triene (I; R = Me, R^1 = OPr^n, R^2 = H, X = Cl) crystallized from MeOH in needles (yield = 65%), m.p. 115·5–116°; $[\alpha]_D^{26}$ −20° (*c*, 0·9 in dioxan); λ_{max} 287 mμ (ε, 1784), 279 mμ (ε, 1947); ν_{max}^{Nujol} 2210 cm^{-1} (C≡C), 1100 cm^{-1} (—OMe). (Found: C, 74·0; H, 8·05; Cl, 9·6. $C_{24}H_{31}ClO_2$ requires: C, 74·5; H, 8·1; Cl, 9·2%.)

3-n-Propoxy-oestra-2,5(10)-dien-17-one. 3-n-Propyl ether of oestrone[19] (19·6 g) in a mixture of anhydrous THF (300 ml) and t-butanol (300 ml) was added slowly to stirred, redistilled iron-free liquid ammonia[8] (2·5 ml) at −70°. Na (50 g) was added in portions during 30 min and the mixture was stirred at reflux temp for 4½ hr. MeOH (300 ml) was added cautiously to discharge the blue colour and the ammonia was allowed to evaporate, through a Hg trap to exclude air. Water (600 ml) was added, the organic solvents were distilled off at reduced press below 40°, more water (600 ml) was added, and the precipitate was collected, washed with water and recrystallized from MeOH containing a trace of pyridine, affording 3-n-propoxy-oestra-2,5(10)-dien-17β-ol (15·8 g = 82%) sufficiently pure for the next stage.

Aluminium isopropoxide (15·1 g) in anhydrous toluene (200 ml) was added to an anhydrous solution of the foregoing 17β-ol (14·7 g) in a mixture of toluene (600 ml) and cyclohexanone (150 ml) and the mixture was refluxed for 2 hr under N_2, cooled and treated with saturated Rochelle salt solution (200 ml). After removal of organic solvents by steam-distillation under N_2, the steroidal product was collected and purified from MeOH containing a trace of pyridine, giving the 17-one as needles (9·2 g = 63%), m.p. 135·5–136°; $[\alpha]_D^{24}$ +176·5° (*c*, 0.87 in dioxan); no significant UV absorption; $\nu_{max}^{CCl_4}$ 1744 cm^{-1} (CO), 1695, 1666 cm^{-1} {Δ2,5(10)}. (Found: C, 80·0; H, 9·5. $C_{21}H_{30}O_2$ requires: C, 80·2; H, 9·6%.)

17α-Chloroethynyl-3-n-propoxy-oestra-2,5(10)-dien-17β-ol (II, R = H, R^1 = Pr^n, prepared from the foregoing compound and lithium chloroacetylide, crystallized from MeOH containing a trace of

[18] R. Courrier, L. Velluz, J. J. Alloiteau and G. Rousseau, *Compt. Rend. Soc. Biol.* **139**, 128 (1945).
[19] U.S. Patent 2855412.

pyridine in needles (yield = 72%), m.p. 149·5°; $[\alpha]_D^{24}$ +64° (*c*, 1·06 in dioxan); no significant UV absorption; $\nu_{max}^{CCl_4}$ 3615 cm^{-1} (OH), 2210 cm^{-1} (C≡C), 1695, 1665 cm^{-1} {Δ2,5(10)}. (Found: C, 74·0; H, 8·4; Cl, 9·4. $C_{33}H_{31}ClO_2$ requires: C, 73·7; H, 8·3; C, 9·4%.)

17α-*Chloroethynyl*-3-n-*propoxy*-17β-*methoxy-oestra*-2,5(10)-*diene* (II, R = Me, R^1 = P_r^n) crystallized from MeOH containing a trace of pyridine as minute grains (yield = 78%), m.p. 135°; $[\alpha]_D^{25}$ +50·5° (*c*, 1·06 in dioxan); no significant UV absorption; $\nu_{max}^{CCl_4}$ 2200 cm^{-1} (C≡C), 1696, 1666 cm^{-1} {Δ2,5(10)}. (Found: C, 74·4; H, 8·6; Cl, 8·5. $C_{24}H_{33}ClO_2$ requires: C, 74·1; H, 8·6; Cl, 9·1%.)

17α-*Chloroethynyl*-3,17β-*dimethoxy-oestra*-2,5(10)-*diene* (II, R = Me, R^1 = Me) crystallized from MeOH containing a trace of pyridine in needles (yield = 49%), m.p. 101·5–102°; $[\alpha]_D^{27}$ +59° (*c*, 1·65 in dioxan); no significant UV absorption. (Found: C, 73·1; H, 8·2; Cl, 9·8. $C_{23}H_{29}ClO_2$ requires: C, 73·2; H, 8·1; Cl, 9·8%.)

17α-*Chloroethynyl*-3,17β-*dimethoxy-oestra*-1,3,5(10)-*triene* (I, R = Me, R^1 = OMe, R^2 = H, X = Cl). (a) Preparation from the 17β-ol[5] (I, R = H, R^1 = OMe, R^2 = H, X = Cl) gave plates (yield 87·5%), m.p. 114–114·5°; $[\alpha]_D^{27}$ −20° (*c*, 0.90 in dioxan); λ_{max} 287 mμ (ε, 2000), 278 mμ (ε, 2115); $\nu_{max}^{CCl_4}$ 2200 cm^{-1} (C≡C); $\nu_{max}^{CS_2}$ 1099 cm^{-1} (17β-OMe). (Found: C, 73·4; H, 8·0; Cl, 10·2. $C_{23}H_{27}ClO_2$ requires: C, 73·6; H, 7·6; Cl, 9·9%.) (b) Preparation directly from oestrone 3-methyl ether gave a product (yield = 63%) identical with that recorded in (a) above.

17α-*Chloroethynyl*-17β-*ethoxy*-3-*methoxy-oestra*-1,3,5(10)-*triene* (I, R = Et, R^1 = OMe, R^2 = H, X = Cl) crystallized from MeOH in plates (yield = 74%), m.p. 96°; $[\alpha]_D^{25}$ −13·5° (*c*, 1·02 in dioxan); λ_{max} 287·5 mμ (ε, 1820), 279 mμ (ε, 1910); $\nu_{max}^{CCl_4}$ 2200 cm^{-1} (C≡C) $\nu_{max}^{CS_2}$ 1091 cm^{-1} (—OEt). (Found: C, 73·5; H, 8·1; Cl, 9·6. $C_{23}H_{29}ClO_2$ requires: C, 74·1; H, 7·8; Cl, 9·5%.)

17β-*Benzyloxy*-17α-*chloroethynyl*-3-*methoxy-oestra*-1,3,5(10)-*triene* (I, R = $C_6H_5{\cdot}CH_2$, R^1 = OMe, R^2 = H, X = Cl) crystallized from MeOH in needles (yield = 36%). m.p. 125·5–126°; $[\alpha]_D^{25\cdot5}$ −6° (*c*, 0·82 in dioxan); λ_{max} 287 mμ (ε, 1927), 278 mμ (ε, 1992); $\nu_{max}^{CCl_4}$ 2200 cm^{-1} (C≡C); 1609, 1574 and 1499 cm^{-1} (aromatic rings). (Found: C, 77·4; H, 7·4; Cl, 8·2. $C_{28}H_{31}ClO_2$ requires: C, 77·3; H, 7·2; Cl, 8·15%.)

17α-*Chloroethynyl*-17β-*diethylaminoethoxy*-3-*methoxy-oestra*-1,3,5(10)-*triene hydrochloride* (I, R = $[Et_2NHC_2H_4]^+Cl^-$, R^1 = OMe, R^2 = H, X = Cl). Diethylaminoethyl bromide was prepared[20] and distilled immediately before use. The basic steroidal product was dissolved in anhydrous ether and the hydrochloride precipitated by passing in HCl, collected and recrystallized from MeOH–EtOAc as fine needles, m.p. 229–229·5°; $[\alpha]_D^{22}$ −8° (*c*, 1·00 in EtOH); λ_{max} 287 mμ (ε, 1920), 278 mμ (ε, 2020). (Found: C, 67·9; H, 8·3; Cl, 14·2; N, 3·0. $C_{27}H_{39}Cl_2NO_2$ requires: C, 67·5; H, 8·2; Cl, 14·8; N, 2·85%.)

17α-*Chloroethynyl*-17β-*methoxy-oestra*-1,3,5(10)-*triene* (I, R = Me, R^1 = H, R^2 = H, X = Cl)* crystallized from hexane in needles (yield = 75%), m.p. 110·5–111°; $[\alpha]_D^{27}$ −34° (*c*, 1·10 in $CHCl_3$); ν_{max}^{Nujol} 2220 cm^{-1} (C≡C), 1095 cm^{-1} (—OMe). (Found: C, 77·05; H, 7·6; Cl, 11·4. $C_{21}H_{25}ClO$ requires: C, 76·7; H, 7·65; Cl, 10·8%.)

17α-*Chloroethynyl*-17β-*methoxy*-4-*methyl-oestra*-1,3,5(10)-*triene* (I, R = Me, R^1 = H, R^2 = Me, X = Cl) crystallized from MeOH as minute grains (yield = 64%), m.p. 109·8–110·2°; $[\alpha]_D^{20}$ −27° (*c*, 0·97 in dioxan); λ_{max} 269·5 mμ (ε, 172), 263 mμ (ε, 229); $\nu_{max}^{CCl_4}$ 2220 cm^{-1} (C≡C), $\nu_{max}^{CS_2}$ 1101 cm^{-1} (—OMe). (Found: C, 76·8; H, 7·7; Cl, 10·4. $C_{23}H_{27}ClO$ requires: C, 77·05; H, 7·9; Cl, 10·3%.)

17α-*Chloroethynyl*-3,17β-*dimethoxy-oestra*-1,3,5(10),6,8-*pentaene* (III) prepared directly from equilenin 3-methyl ether, crystallized from Et_2O–MeOH in needles (yield = 65%), m.p. 123–123·5°; $[\alpha]_D^{24}$ −177° (*c*, 0·45 in $CHCl_3$); λ_{max}^{EtOH} 238 mμ (ε, 52800). (Found: C, 73.35; H, 6·65; Cl, 10·25. $C_{23}H_{23}ClO_2$ requires: C, 74·5; H, 6·45; Cl, 10·0%.)

17α-*Chloroethynyl*-3,17β-*dimethoxy-oestra*-1,3,5(10),7-*tetraene* (IV), prepared directly from equilin 3-methyl ether, was purified by chromatography on an alumina column, eluting with pet. ether, and by crystallization from Et_2O–MeOH, as rods (yield = 46%), m.p. 82°; $[\alpha]_D^{24}$ +12° (*c*, 0·75 in $CHCl_3$); λ_{max} 228 mμ (ε, 18000). (Found: C, 73·6; H, 7·2; Cl, 10·2. $C_{23}H_{25}ClO_2$ requires: C, 74·05; H, 7·05; Cl, 9·95%.)

17α-*Chloroethynyl*-3,17β-*dimethoxy-oestra*-1,3,5(10),9(11)-*tetraene* (V), prepared directly from 9(11)-dehydro-oestrone 3-methyl ether,[21] crystallized from CH_2Cl_2–MeOH in flakes (yield = 79%),

* Preparation by Mr. A. K. Hiscock, B.Sc.

[20] K. H. Meyer and H. Hopff, *Ber. Dtsch. Chem. Soc.* **54**, 2274 (1921).

[21] B. J. Magerlein and J. A. Hogg, *J. Amer. Chem. Soc.* **80**, 2220 (1958).

m.p. 132°; $[\alpha]_D^{25}$ +101° (*c*, 1·1 in $CHCl_3$); λ_{max} 262 mμ (ε, 20400). (Found: C, 73·85; H, 6·95; Cl, 9·95. $C_{22}H_{29}ClO_2$ requires: C, 74·05; H, 7·05; Cl, 9·95%.)

17α-*Chloroethynyl*-17β-*methoxy-oestra*-5(10)-*en*-3-*one* (VI). Oxalic acid (14 g anhydrous) in water (140 ml) was added to II (R = Me, R^1 = Me) in MeOH (750 ml) and the mixture stirred at room temp for 45 min. Ether was added and the ethereal solution was washed with $NaHCO_3$aq and with water, dried over Na_2SO_4, and the solvent was evaporated at reduced press. Purification by chromatography on a neutral alumina column, eluting with benzene and by crystallization from MeOH containing a trace of pyridine gave minute grains, (3·29 g = 58%), m.p. 116–116·5°; $[\alpha]_D^{25}$ +103·5° (*c*, 0·6 in dioxan); λ_{max} 289–278 mμ (ε, 55) corresponds to not more than 3% ring A aromatic impurity, no significant 4-en-3-one. (Found: C, 72·2; H, 7·7; Cl, 9·9. $C_{21}H_{27}ClO_2$ requires: C, 72·7; H, 7·85; Cl, 10·2%.)

17α-*Chloroethynyl*-17β-*methoxy*-19-*norandrost*-4-*en*-3-*one* (VII, R = Me, R^1 = H, R^2 = O), prepared from II (R = Me, R^1 = Me; 3·74 g) by treatment in MeOH (180 ml) with 3N HCl (120 ml) at 60° for 15 min, was purified by chromatography on an alumina column, eluting with pet. ether–benzene mixtures, and by crystallization from MeOH as needles (2·20 g = 61%), m.p. 105·5–106°; $[\alpha]_D^{25}$ −58° (*c*, 1·03 in dioxan); λ_{max} 239–240·5 mμ (ε, 16620); $\nu_{max}^{CCl_4}$ 2200 cm^{-1} (C≡C,) 1678 cm^{-1} (CO), 1619 cm^{-1} (Δ4); $\nu_{max}^{CS_2}$ 1098 cm^{-1} (—OMe). (Found: C, 73·3; H, 7·9; Cl, 10·0. $C_{21}H_{27}ClO_2$ requires: C, 72·7; H, 7·85; Cl, 10·2%.)

17α-*Chloroethynyl*-17β-*methoxy*-19-*norandrost*-5-*en*-3ζ-*ol*.* Sodium borohydride (1·25 g) was added in portions during 3½ hr to stirred solution of the foregoing compound (2·60 g) in MeOH (100 ml) containing water (0·1 ml) at room temp.[22] The mixture was allowed to stand overnight, diluted with water, the steroidal product was recovered by extraction with ether and purified by chromatography on an alumina column, eluting with benzene, and by crystallization from hexane as needles (1·37 g = 53%), m.p. 129–129·5°; $[\alpha]_D^{25}$ −52° (*c*, 1·05 in dioxan); ORD plain negative curve, at 290 mμ $[\phi]$ = −1610° (*c*, 0·61 in dioxan at 30°); $\nu_{max}^{CCl_4}$ 3600 cm^{-1} (OH), 2200 cm^{-1} (C≡C), 1660 cm^{-1} (Δ4); $\nu_{max}^{CS_2}$ 1096 cm^{-1} (—OMe). (Found: C, 72·0; H, 8·2; Cl, 10·35. $C_{21}H_{29}ClO_2$ requires: C, 72·5; H, 8·1; Cl, 10·2%.)

17α-*Chloroethynyl*-17β-*methoxy-androst*-5-*en*-3β-*ol* (VIII, R = Me, R^1 = H), prepared by the general procedure from the 17β-ol (VIII, R = H, R^1 = H)[5] (3·36 g), employing sodamide from Na (0·22 g) and MeI (0·60 ml), was crystallized from aqueous MeOH in needles (2·55 g = 73%), m.p. 144°; $[\alpha]_D^{27}$ −128° (*c*, 0·81 in dioxan); $\nu_{max}^{CCl_4}$ 3620 cm^{-1} (OH), 2206 cm^{-1} (C≡C), 1666 cm^{-1} (Δ5); $\nu_{max}^{CS_2}$ 1096 cm^{-1} (—OMe). (Found: C, 72·3; H, 8·6; Cl, 9·9. $C_{22}H_{31}ClO_2$ requires: C, 72·8; H, 8·6; Cl, 9·8%.) Acetylation with Ac_2O–pyridine at 100° afforded 17α-*chloroethynyl*-17β-*methoxy-androst*-5-*en*-3β-*ol acetate* (VIII, R = Me, R^1 = Ac) which crystallized from aqueous MeOH as plates, m.p. 110–110·5°; $[\alpha]_D$ −121° (*c*, 0·96 in dioxan). (Found: C, 70·8; H, 8·0; Cl, 9·6. $C_{24}H_{33}ClO_3$ requires: C, 71·15; H, 8·2; Cl, 8·8%.)

17α-*Chloroethynyl*-17β-*diethylaminoethoxy*-19-*norandrost*-4-*en*-3-*one* (VII, R = $Et_2NHC_2H_4$, R^1 = H, R^2 = O). Compound II (R = H, R^1 = Me;[5] 4·0 g) was converted by the general procedure, employing freshly prepared and distilled diethylaminoethyl bromide,[20] into II (R = Et_2N C_2H_4, R^1 = Me), which resisted crystallization and was treated in MeOH (500 ml) with 3N HCl (140 ml) at 60° for 15 min. An ethereal solution of the steroidal product was extracted with 2N HCl and the product was recovered from the aqueous layer by the addition of an excess of alkali followed by extraction with ether. Crystallization from aqueous MeOH gave the 4-en-3-one plates (0·64 g = 12%), m.p. 115–115·5°; $[\alpha]_D^{25}$ −34·5° (*c*, 0·37 in dioxan); λ_{max} 238 mμ (ε, 16730); $\nu_{max}^{CCl_4}$ 2200 cm^{-1} (C≡C), 1677 cm^{-1} (CO), 1623 cm^{-1} (Δ4); $\nu_{max}^{CS_2}$ 1095 cm^{-1} (—$OC_6H_4NEt_2$). (Found: C, 72·4; ¹H 9·2; Cl, 8·2; N, 3·4. $C_{26}H_{38}ClNO_2$ requires: C, 72·3; H, 8·9; Cl, 8·2; N, 3·2%.)

17α-*Chloroethynyl*-17β-*methoxy-androst*-4-*en*-3-*one* (VII, R = Me, R^1 = Me, R^2 = O). 17α-Chloroethynyl-3-methoxy-androsta-3,5-dien-17β-ol[5] was methylated by the general procedure, and the crude reaction product (6·1 g) in MeOH (250 ml) was refluxed for 1 hr with *p*-toluenesulphonic acid in water (10 ml). After cooling, the mixture was diluted with water, the steroidal product recovered by extraction with ether and purified by crystallization from acetone and from MeOH as plates (yield = 27%), m.p. 147–147·5°; $[\alpha]_D^{22}$ −6·4° (*c*, 0·94 in dioxan); λ_{max} 240·5 mμ (ε, 15880); $\nu_{max}^{CCl_4}$ 2210 cm^{-1} (C≡C), 1679 cm^{-1} (CO), 1618 cm^{-1} (Δ4); $\nu_{max}^{CS_2}$ 1096 cm^{-1} (—OMe). (Found: C, 72·65; H, 8·2; Cl, 9·8. $C_{22}H_{29}ClO_2$ requires: C, 73·2; H, 8·1; Cl, 9·8%.)

* Our ORD evidence indicates that the double bond is in the Δ5 position.

[22] F. Sondheimer and Y. Klibansky, *Tetrahedron* **5**, 15 (1959).

3-Methoxy-17α-trifluorovinyl-oestra-1,3,5(10)-trien-17β-ol (IX, R = H, X = F). Trifluorobromoethylene (13 g) was passed into anhydrous THF (100 ml), containing Mg turnings (4·0 g) and a crystal of I_2, under N_2, at room temp with exclusion of moisture, in a flask fitted with a dry-ice reflux condenser. A vigorous reaction began after a short induction period, and was controlled by cooling the flask in a dry-ice–alcohol bath. The mixture was then stirred at room temp for 30 min, cooled to −20 to −25°, and treated with oestrone 3-methyl ether (5·0 g) in anhydrous THF (200 ml). Stirring was continued at −20 to −25° for 4 hr, and then at reflux temp for 6 hr. The mixture was cooled to room temp, treated with excess of sat NH_4Claq and then with dil HCl. The steroidal product was recovered by ether extraction and purified by chromatography on an alumina column, eluting with benzene–ether mixtures and by crystallization from MeOH, affording minute crystals (3·18 g = 49%), m.p. 108°; $[\alpha]_D^{25}$ +53° (*c*, 0·52 in dioxan); λ_{max} 287 mμ (ε, 1880), 278 mμ (ε, 1970); λ_{inf} 229 mμ (ε, 6850), 220 mμ (ε, 8250); $\nu_{max}^{CCl_4}$ 3630 cm^{-1} (OH), 1775 cm^{-1} (CF_2=CF); $\nu_{max}^{CS_2}$ 1148 cm^{-1} (CF). (Found: C, 68·2; H, 6·9; F, 15·8. $C_{21}H_{25}F_3O_2$ requires: C, 68·8; H, 6·9; F, 15·6%.)

3,17β-Dimethoxy-17α-trifluorovinyl-oestra-1,3,5(10)-triene (IX, R = Me, X = F) crystallized from MeOH as needles (yield = 69%), m.p. 146–149°; $[\alpha]_D^{25}$ +58° (*c*, 0·29 in dioxan); λ_{max} 287 mμ (ε, 1910), 278 mμ (ε, 1990); λ_{inf} 229 mμ (ε, 7190), 220 mμ (ε, 8640); $\nu_{max}^{CH_2Cl_2}$ 1770 cm^{-1}(CF_2=CF); $\nu_{max}^{CS_2}$ 1272 and 1147 cm^{-1} (CF); 1097 cm^{-1} (—OMe). (Found: C, 68·8; H, 7·4; F, 14·8. $C_{22}H_{27}F_3O_2$ requires: C, 69·4; H, 7·2; F, 15·0%.)

17α-Trifluorovinyl-androst-5-en-3β,17β-diol. Treatment of androst-5-en-3β-ol-17-one with trifluorovinyl magnesium bromide by the above procedure afforded 17α-trifluorovinyl-androst-5-en-3β,17β-diol, purified by chromatography on an alumina column, eluting with benzene–ether mixtures and with ether, and by crystallization from acetone–hexane as needles (yield = 37%), m.p. 198·5°; $[\alpha]_D^{25}$ −58° (*c*, 0·92 in dioxan). (Found: C, 67·9; H, 8·05; F, 15·4. $C_{21}H_{29}F_3O_2$ requires: C, 68·1; H, 7·9; F, 15·4%.)

17α-Trifluorovinyl-androst-4-en-17β-ol-3-one. Aluminium isopropoxide (3·9 g) in anhydrous toluene (11 ml) was added to an anhydrous solution of the foregoing compound (2·2 g) and EtCOMe (17·5 ml) in toluene (110 ml) and the mixture was refluxed for 2 hr, cooled, washed with dil H_2SO_4, $NaHCO_3$aq and water, and freed from solvent by steam-distillation. The residue was purified by chromatography on an alumina column, eluting with benzene–ether mixtures, and by crystallization from acetone–hexane as needles (0·89 g = 41%), m.p. 187–188°; λ_{max} 239–240 mμ (ε, 16060). (Found: C, 68·4; H, 7·6. $C_{21}H_{27}F_3O_2$ requires: C, 68·5; H, 7·4%.)

17α-Trifluorovinyl-androst-1,4-dien-17β-ol-3-one (X). A mixture of the foregoing compound (0·49 g), 2,3-dichloro-5,6-dicyanobenzoquinone[23] (0·49 g) and anhydrous benzene (10 ml) was refluxed for 16 hr, cooled, and poured into a solution of sodium hydroxide (2 g) in water (40 ml). The steroidal product was recovered by extraction with ether and purified by chromatography on an alumina column, eluting with ether, and by crystallization from acetone–hexane as needles (0·33 g = 67%), m.p. 126·5°; $[\alpha]_D^{24}$ −1·6° (*c*, 0·53 in dioxan); λ_{max} 244 mμ (ε, 13810); $\nu_{max}^{CCl_4}$ 3626 cm^{-1} (OH), 1772 cm^{-1} (CF_2=CF), 1666 cm^{-1} (CO), 1628 and 1606 cm^{-1} (Δ1,4). (Found: C, 69·1; H, 7·0. $C_{21}H_{25}F_3O_2$ requires: C, 68·8; H, 6·9%.)

3,17β-Dimethoxy-17α-vinyl-oestra-1,3,5(10)-triene (IX, R = Me, X = H). Methylation of 17α-vinyl-oestra-1,3,5(10)-trien-3,17β-diol[14] by the general procedure afforded a mixture from which the 3,17β-dimethyl ether was isolated by chromatography on an alumina column, eluting with petroleum ether–benzene mixtures. Purification from acetone–hexane afforded needles (yield = 21%), m.p. 143°; $[\alpha]_D^{25}$ +63·5° (*c*, 0·63 in dioxan); λ_{max} 286 mμ (ε, 1940), 277·5 mμ (ε, 2030); λ_{inf} 219 mμ (ε, 8550). (Found: C, 80·6; H, 8·9. $C_{22}H_{30}O_2$ requires: C, 80·9; H, 9·3%.)

3-Methoxy-17α-trifluoropropynyl-oestra-1,3,5(10)-trien-17β-ol (I, R = H, R^1 = OMe, R^2 = H, X = CF_2). EtMgBr was prepared from Mg (0·94 g) and EtBr (3·0 ml) in anhydrous ether (15 ml) under N_2, and cooled to −70°. 3,3,3-Trifluoropropyne, prepared[15] from 1,1,2-trichloro-3,3,3-trifluoropropene (50 g) was distilled in, and the mixture was stirred and refluxed under a dry-ice reflux condenser for 1½ hr and cooled to room temp. Oestrone 3-methyl ether (4·0 g) in anhydrous THF (100 ml) was added, followed by anhydrous ether (25 ml), and the mixture was stirred at room temp for 16 hr. Water was added cautiously and the steroidal product was isolated by extraction with ether. Crystallization from MeOH gave unchanged oestrone 3-methyl ether (1·9 g), m.p. 167–168°, and the residue recovered from the mother-liquor was chromatographed on an alumina column,

[23] D. Burn, D. N. Kirk and V. Petrow, *Proc. Chem. Soc.* 14 (1960).

eluting oestrone 3-methyl ether (0·22 g) with benzene and the 17α-trifluoropropynyl-17β-ol with benzene–ether mixtures. Purification from aqueous MeOH afforded minute crystals (1·13 g = 35%), m.p. 167·5–168·5°; $[\alpha]_D$ −5·6° (*c*, 1·01 in dioxan); λ_{max} 286 mμ (ε, 1910), 278 mμ (ε, 1990); λ_{inf} 219 mμ (ε, 8330); $\nu_{max}^{CCl_4}$ 3620 cm^{-1} (OH), 2250 cm^{-1} (C≡C); $\nu_{max}^{CS_2}$, 1275 1147 cm^{-1} (CF). (Found: C, 69·5; H, 6·9. $C_{22}H_{25}F_3O_2$ requires: C, 69·8; H, 6·7%.)

3,17β-*Dimethoxy*-17α-*trifluoropropynyl-oestra*-1,3,5(10)-*triene* (I, R = Me, R^1 = OMe, R^2 = H, X = CF_3). The foregoing compound (3·32 g) in anhydrous THF (105 ml) was added to sodamide, prepared as above from Na (0·40 g) in liquid ammonia (250 ml), at −70°, during 10 min, and the mixture was stirred for a further 10 min. MeI (5·0 g) in anhydrous THF (50 ml) was added during 5 min, the mixture was stirred at −70 to −60° for 3 hr and poured on to ice. The steroidal product was isolated by extraction with ether and purified from MeOH, affording the 17β-methyl ether as needles, (2·34 g = 68%), m.p. 80–80·5°; $[\alpha]_D^{25}$ −11° (*c*, 1·6 in dioxan); λ_{max} 286 mμ (ε, 1900), 277·5 mμ (ε, 2000); λ_{inf} 227·5 mμ (ε, 7650), 220 mμ (ε, 8700); $\nu_{max}^{CCl_4}$ 2250 cm^{-1} (C≡C); $\nu_{max}^{CS_2}$ 1275, 1146 cm^{-1} (CF). (Found: C, 70·1; H, 7·3. $C_{23}H_{27}F_3O_2$ requires: C, 70·4; H, 6·9%.)

17α-*Trifluoropropynyl-oestra*-1,3,5(10)-*trien*-3,17β-*diol* (I, R = H, R^1 = OH, R^2 = H, X = CF_3). 3,3,3-Trifluoropropyne, prepared[15] from 1,1,2-trichloro-3,3,3-trifluoropropene (20 g) was distilled into liquid ammonia (250 ml) containing lithamide, prepared from Li (0·37 g), at −70°, and the mixture was stirred for a further 10 min. Oestrone (5·0 g) in anhydrous THF (225 ml) was added during 20 min and the mixture was stirred at −50° for 2 hr and finally at reflux temp for 1½ hr. NH_4Cl was added and the ammonia allowed to evaporate. The steroidal product was recovered by extraction with ether and purified by chromatography on an alumina column, eluting with ether, and by crystallization from benzene as grains, m.p. 100·5–102°, containing benzene of crystallization. Removal of benzene *in vacuo* at 70° afforded the diol as an amorphous solid (2·64 g = 39%), m.p. 170·3°; $[\alpha]_D^{26}$ −7·0° (*c*, 0·97 in dioxan); λ_{max} 286 mμ (ε, 1895), 280 mμ (ε, 2110); ν_{max}^{Nujol} 3410 and 3330 cm^{-1} (OH), 2260 cm^{-1} (C≡C). (Found: 68·8; H, 6·4. $C_{21}H_{23}F_3O_2$ requires: C, 69·2; H, 6·4%.)

4-*Methyl*-17α-*trifluoropropynyl-oestra*-1,3,5(10)-*trien*-17β-ol (I, R = H, R^1 = H, R^2 = Me, X = CF_3) was prepared from the 17-one[24] (0·92 g) by the above procedure and purified by chromatography on an alumina column, eluting with toluene–ether mixtures, and by crystallization from aqueous MeOH as small grains (0·80 g = 64%), m.p. 128–128·5°; $[\alpha]_D^{26}$ −15° (*c*, 0·93 in dioxan); λ_{max} 269·5 mμ (ε, 169), 262·5 mμ (ε, 222); λ_{inf} 258 mμ (ε, 192), 219 mμ (ε, 8840); $\nu_{max}^{CCl_4}$ 3603 cm^{-1} (OH), 2258 cm^{-1} (C≡C); $\nu_{max}^{CH_2Cl_2}$ 1603·5, 1583 cm^{-1} (aromatic ring). (Found F, 15·45. $C_{22}H_{25}F_3O$ requires: F, 15·7%.)

17α-*Bromethynyl*-3,17β-*dimethoxy-oestra*-1,3,5(10)-*triene* (I, R = Me, R^1 = OMe, R^2 = H, X = Br). To a stirred solution of 17α-ethynyl-3,17β-dimethoxy-oestra-1,3,5(10)-trien (15·0 g) in t-butanol (375 ml) was added a solution of potassium t-butoxide prepared by dissolving K (1·45 g) in t-butanol (75 ml), and the mixture was refluxed for 1 hr cooled to room temp, treated with N-bromosuccinimide (17·2 g) and stirred for 18 hr. Water was added, the steroidal product was recovered by extraction with ether and purified by chromatography on an alumina column, eluting with pet. ether, and by crystallization from MeOH as plates (4·70 g = 27%), m.p. 131·5–132°; $[\alpha]_D^{25}$ −34° (*c*, 0·99 in $CHCl_3$); λ_{max} 287 mμ (ε, 1950), 278 mμ (ε, 2020); λ_{inf} 218 mμ (ε, 9760); $\nu_{max}^{CCl_4}$ 2180 cm^{-1} (C≡C); $\nu_{max}^{CS_2}$ 1099 cm^{-1} (—OMe). (Found: C, 65·1; H, 6·8; Br. 20·25. $C_{22}H_{27}BrO_2$ requires: C, 65·5; H, 6·7; Br, 19·8%.)

17α-*Iodoethynyl*-3,17β-*dimethoxy-oestra*-1,3,5(10)-*triene* (I, R = Me, R^1 = OMe, R^2 = H, X = I). A mixture of 17α-ethynyl-3,17β-dimethoxy-oestra-1,3,5(10)-triene (1·60 g), I_2 (2·50 g), morpholine (3·50 g) and MeOH (100 ml) was heated briefly to the b.p. and then allowed to stand in the dark at room temp for 2 days. Water was added, the steroidal product was recovered by extraction with ether and purified from MeOH as needles, m.p. 120°; $[\alpha]_D$ −30° (*c*, 1·42 in $CHCl_3$); λ_{max} 286 mμ (ε, 1980), 278 mμ (ε, 2100); $\nu_{max}^{CCl_4}$ 2173 cm^{-1} (C≡C); $\nu_{max}^{CS_2}$ 1098 cm^{-1} (—OMe). (Found: C, 58·7; H, 6·4; I, 28·8. $C_{22}H_{27}IO_2$ requires: C, 58·65; H, 6·0; I, 28·2%.)

[24] J. Schmitt, J. J. Panouse, P. J. Cornu, A. Hallot, H. Pluchet and P. Comoy, *C. R. Acad. Sci. Paris* **259**, 1652 (1964).