969. *Modified Steroid Hormones. Part XXIX.*[1] *Some 17α-Chloroethynyl-17β-hydroxy-derivatives.*

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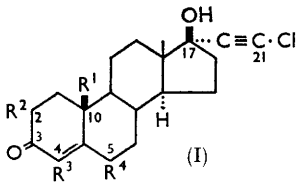
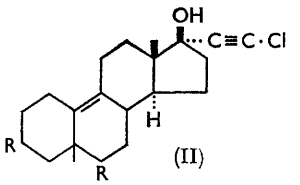
17α-Chloroethynyl-17β-hydroxy-steroidal derivatives have been prepared by reaction of 17-oxo-steroids with lithium chloroacetylide or, less conveniently, with sodium chloroacetylide in liquid ammonia.

Our earlier studies on 17α-ethynyl-17β-hydroxy-steroids had dealt with replacement of the terminal acetylenic hydrogen atom by hydroxymethyl [2] and by lower alkyl groups.[3] Hydroxymethyl had proved to be a disappointing substituent in that such compounds as 21-hydroxymethylethisterone were without apparent biological activity. A 21-methyl substituent, in contrast, enhanced several-fold the progestational activity of ethisterone, an observation which led to the preparation of 6α,21-dimethylethisterone.[3] The 21-methyl derivatives of 19-norethisterone and of the corresponding 5(10)-unsaturated derivative,[4] though somewhat less potent in the Clauberg assay than their ethynylic progenitors, were found by Dr. A. David and his colleagues of the B.D.H. Biological Department to have claudogenic [5] activity. In seeking more potent compounds of this type, we turned to related 21-chloro-structures (*e.g.*, I).

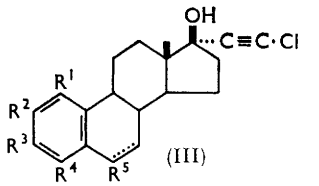
17α-Chloroethynyl-17β-hydroxy-steroids were prepared by condensation of the appropriate 17-ketones with (i) sodium chloroacetylide in liquid ammonia,[6] and (ii) lithium chloroacetylide under Grignard-type conditions.[7] Method (ii) proved the more convenient, in addition to giving somewhat higher yields of products, and was generally adopted.



(I)



(II)



(III)

Androstane Types.—Many of the 17-ketones required for this series have already been described in the literature (see Experimental section). The following are believed to be new. 3-Ethoxy-6-methylandrosta-3,5-dien-17-one prepared from 6α-methyl-androst-4-ene-3,17-dione [8] by reaction with ethyl orthoformate in dioxan in the presence of sulphuric acid as catalyst. Acid hydrolysis of the product resulting from condensation

[1] Part XXVIII, *J.*, 1962, 1223.
[2] Barton, Cooley, Ellis, and Petrow, *J.*, 1957, 5094.
[3] Barton, Burn, Cooley, Ellis, and Petrow, *J.*, 1959, 1957.
[4] Ellis, Petrow, Stansfield, and Weston, *J.*, 1960, 2389.
[5] Petrow, *J. Pharm. Pharmacol.*, 1960, **12**, 704.
[6] Viehe, *Chem. Ber.*, 1959, **92**, 1270.
[7] Viehe, *Chem. Ber.*, 1959, **92**, 1950.
[8] Ackroyd, Adams, Ellis, Petrow, and Stuart-Webb, *J.*, 1957, 4099.

with lithium chloroacetylide gave 17α-chloroethynyl-17β-hydroxy-6α-methylandrost-4-en-3-one (I; R^1 = Me, R^2 = R^3 = H, R^4 = α-Me). The 4-methyl analogue (I; R^1 = R^3 = Me, R^2 = R^4 = H) was similarly prepared from 3,3-ethylenedioxy-4-methylandrost-4-en-17-one,* itself derived from 4-methyltestosterone acetate.[9] 11β-Hydroxy-3-methoxyandrosta-3,5-dien-17-one was obtained from 11β-hydroxyandrost-4-ene-3,17-dione[10] after initial protection of the hydroxyl group by formylation. 3-Methoxy-5α-androst-2-en-17-one was prepared by partial catalytic reduction of 3-methoxyandrosta-3,5-dien-17-one. 3,3-Ethylenedioxy-2α-methyl-5α-androstan-17-one was prepared from 17β-hydroxy-2α-methylandrostan-3-one[11] by ketalisation followed by oxidation of the 17-hydroxyl group.

17α-Chloroethynyl-17β-hydroxyandrost-4-en-3-one was converted by alkaline hydrogen peroxide into the corresponding 4β,5β-epoxide, which passed into the 4-chloro-4-en-3-one (I; R^1 = Me, R^2 = R^4 = H, R^3 = Cl) on treatment with hydrochloric acid in acetic acid. The 3-enamine derived from 17α-chloroethynyl-17β-hydroxyandrost-4-en-3-one reacted with perchloryl fluoride to give the analogous 4-fluoro-derivative (I; R^1 = Me, R^2 = R^4 = H, R^3 = F). Condensation of 3β-acetoxy-6β-fluoro-5α-hydroxyandrostan-17-one with lithium chloroacetylide was unexpectedly accompanied by elimination of the elements of hydrogen fluoride with formation of 17α-chloroethynyl-5α,6α-epoxyandrostane-3β,17β-diol, which was isolated as the 3-acetate. The same diol was obtained by employing 5α,6α-epoxy-3β-hydroxyandrostan-17-one, its 3-acetate, or 3β,6β-diacetoxy-5α-hydroxyandrostan-17-one in the lithium chloroacetylide condensation.† 5β,6β-Epoxy-3β-hydroxyandrostan-17-one[13] similarly gave 17α-chloroethynyl-5β,6β-epoxyandrostane-3β,17β-diol. When the foregoing 5α,6α- or 5β,6β-epoxide was treated with periodic acid in aqueous acetone, 17α-chloroethynylandrostane-3β,5α,6β,17β-tetraol was obtained, the structure of which was confirmed by an alternative preparation from 3β,5α,6β-trihydroxyandrostan-17-one and lithium chloroacetylide. Oxidation of the tetraol in acetone with 4N-chromium trioxide–sulphuric acid[14] gave 17α-chloroethynyl-5α,17β-dihydroxyandrostane-3,6-dione, which passed into the corresponding 4-ene-3,6-dione on alkaline dehydration. The 6α-fluoro-derivative of 17α-chloroethynyl-17β-hydroxyandrost-4-en-3-one was finally obtained by reaction of 17α-chloroethynylandrost-5-ene-3β,17β-diol (see Experimental section) with hydrogen fluoride–*N*-bromoacetamide[15] to give the 5α-bromo-6β-fluoro-derivative, which was oxidised to the 3-ketone (not isolated), dehydrobrominated with potassium acetate in acetone, and epimerised to the required 6α-fluoro-derivative by hydrogen chloride in acetic acid.

19-*Nor-types*.—3-Methoxyœstra-2,5(10)-dien-17-one[16] condensed with lithium chloroacetylide to give 17α-chloroethynyl-3-methoxyœstra-2,5(10)dien-17β-ol, hydrochloric acid hydrolysis of which furnished the 4-en-3-one (I; R^1 = R^2 = R^3 = R^4 = H). Less drastic conditions of hydrolysis led to the formation of 17α-chloroethynyl-17β-hydroxyœstra-5(10)-en-3-one. These compounds have been prepared independently by Fried *et al.*[17] The now readily available 6α-methyl-19-norandrost-4-ene-3,17-dione[18] was

* The structure of this compound will be discussed in a forthcoming publication.

† The formation of an 5α,6α-epoxide by reaction of 3β,6β-diacetoxy-5α-hydroxyandrostan-17-one with vinylmagnesium bromide has been reported.[12]

[9] See Kirk and Petrow, *J.*, 1962, 1091.
[10] Brooks and Norymberski, *Biochem. J.*, 1953, **55**, 371.
[11] Ringold and Rosenkranz, *J. Org. Chem.*, 1956, **21**, 1333.
[12] Akhrem, Heřmánek, Syhora, and Zavel'skaya, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk* 1960, 1898; cf. *Chem. Abs.*, 1961, **55**, 15544.
[13] Davis and Petrow, *J.*, 1949, 2536.
[14] Cf. Djerassi, Engle, and Bowers, *J. Org. Chem.*, 1956, **21**, 1547, and references cited therein.
[15] Bowers, *J. Amer. Chem. Soc.*, 1959, **81**, 4107.
[16] Colten, Nysted, Riegel, and Raymond, *J. Amer. Chem. Soc.*, 1957, **79**, 1123.
[17] Fried, Bry, Oberster, Beyler, Windholz, Hannah, Sarett, and Steelman, *J. Amer. Chem. Soc.*, 1961 **83**, 4663.
[18] Villotti, Djerassi, and Ringold, *J. Amer. Chem. Soc.*, 1959, **81**, 4566.

converted into its 3-methyl enol ether with trimethyl orthoformate and toluene-*p*-sulphonic acid, and from it 17α-chloroethynyl-17β-hydroxy-6α-methyl-19-norandrost-4-en-3-one (I; $R^1 = R^2 = R^3 = H$, $R^4 = \alpha$-Me) was obtained. 17α-Chloroethynyl-5β-methyl-19-norandrost-9(10)-ene-3β,6β,17β-triol (II; R = β-OH) was prepared from the corresponding 17-ketone,[19] and was oxidised to the 3,6-diketone (II; R = :O).

Aromatic Types.—Œstra-1,3,5(10)-trien-17-one, the parent compound of aromatic types (III), was readily obtained by a minor modification of the method described in U.S.P. 2,947,763. 1-Methylœstra-1,3,5(10)-trien-17-one was prepared by oxidation of 1-methylœstra-1,3,5(10)-trien-17β-ol.[20] 1,4- and 2,4-Dimethylœstra-1,3,5(10)-trien-17-one were prepared from 17β-acetoxy-4-[21] and -2α-methylandrosta-1,4-dien-3-one,[22] respectively. These dienones were reduced with lithium aluminium hydride to the corresponding 3ξ,17β-diols, which were separately submitted to the dienol–benzene rearrangement to give 1,4- and 2,4-dimethylœstra-1,3,5(10)-trien-17β-ol (not isolated or characterised). Oxidation to the 17-ketones was accomplished with chromium trioxide and sulphuric acid in acetone. 2-Chloro-4 methylœstra-1,3,5(10)-trien-17-one was similarly prepared from 17β-acetoxy-2-chloroandrosta-1,4-dien-3-one, itself obtained by chlorination of 17β-acetoxyandrosta-1,4-dien-3-one.[23] These 17-ketones, as well as others referred to in the Experimental section, were readily converted by lithium chloroacetylide into the corresponding 17α-chloroethynyl-17β-hydroxy-derivatives in satisfactory yields.

Experimental

Optical rotations were measured for chloroform solutions (*ca.* 1% concentration) in a 1 dm. tube at temperatures between 20° and 25°, unless otherwise stated. Ultraviolet absorption spectra (in EtOH) were kindly determined by Mr. M. T. Davies, B.Sc. Infrared measurements were made for Nujol mulls with a Perkin-Elmer Infracord spectrophotometer; no calibration corrections were applied. All the 17α-chloroethynyl-17β-hydroxy-steroids described herein were characterised by a sharp band of medium intensity in the 2220 $cm.^{-1}$ region of the infrared spectrum; this band (the C≡C stretching mode) is considerably more intense than that exhibited by 17α-ethynyl-17β-hydroxy-steroids. Unless otherwise stated, " parts " are by vol. for liquids and by wt. for solids.

General Procedures for the Preparation of 17α-*Chloroethynyl*-17β-*hydroxy-steroids.*—*Method A.* Sodium (4 parts) and ferric nitrate (0·1 part) were added to liquid ammonia (300 parts), and the mixture was stirred under reflux until the blue colour disappeared. The mixture was cooled to −60°, and *trans*-dichloroethylene (8·5 parts by wt.) in anhydrous ether (25 parts) was added during 15 min. The cooling-bath was removed and the mixture stirred under reflux for 30 min. A solution or suspension of the 17-oxo-steroid (12·5 parts) in anhydrous tetrahydrofuran (150 parts) was added during 15 min., and the mixture stirred under reflux for 3 hr. Ammonium chloride (20 parts) was then introduced, the ammonia allowed to evaporate, and the steroidal product isolated from the residue by addition of water and extraction with ether. Purification was achieved by crystallisation from a suitable solvent. Yields were in the region of 70%.

Method B. Methyl iodide (57 parts by wt.) in anhydrous ether (100 parts) was slowly added to a stirred suspension of lithium (5·5 parts) in anhydrous ether (200 parts). The mixture was refluxed for a short time and then cooled to 0°. Nitrogen was passed through the apparatus, and *trans*-dichloroethylene (20 parts) in anhydrous ether (50 parts) was added during 30 min. The mixture was allowed to warm to room temperature, and stirring was continued for a further 1½ hr. To the resulting solution of lithium chloroacetylide, still under nitrogen, there was added during 30 min. a solution of the 17-oxo-steroid (14·5 parts) in anhydrous toluene (300 parts). The mixture was refluxed, with stirring, for 1½ hr., and then

[19] Davis and Petrow, *J.*, 1949, 2973.
[20] Dannenberg and Neumann, *Annalen*, 1961, **646**, 148.
[21] Sondheimer and Mazur, *J. Amer. Chem. Soc.*, 1957, **79**, 2906.
[22] B.P. 854,343.
[23] Joly, Warnant, Nominé, and Bertin, *Bull. Soc. chim. France*, 1958, 366.

cooled to −60°. Saturated aqueous ammonium chloride (25 parts) was added, and the stirred mixture was allowed to reach room temperature. The steroidal product was isolated with ether and purified by crystallisation from a suitable solvent. Yields were in the region of 80%.

In general, 17α-chloroethynyl-17β-hydroxy-derivatives of 3-enol ethers and 3,3-ethylenedioxy-compounds were not purified and isolated as such. In these cases, the steroidal product was treated with catalytic amounts of hydrochloric acid, toluene-*p*-sulphonic acid, or oxalic acid in aqueous methanol or ethanol in order to generate the parent ketone.

17α-*Chloroethynylandrost-5-ene*-3β,17β-*diol*, prepared from 3β-hydroxyandrost-5-en-17-one, crystallised from acetone in needles, m. p. 201·5°, $[\alpha]_D$ −126° (Found: C, 71·8; H, 8·2; Cl, 10·5. $C_{21}H_{29}ClO_2$ requires C, 72·3; H, 8·4; Cl, 10·2%). Treatment with acetic anhydride–pyridine for 18 hr. at room temperature gave the 3-*monoacetate*, plates (from aqueous ethanol), m. p. 178—180°, $[\alpha]_D$ −119° (Found: C, 70·7; H, 7·8. $C_{23}H_{31}ClO_3$ requires C, 70·7; H, 8·0%).

17α-*Chloroethynyl*-6-*methylandrost-5-ene*-3β,17β-*diol*, prepared from 3β-hydroxy-6-methylandrost-5-en-17-one,[24] crystallised from aqueous acetone in needles, m. p. 179—181°, $[\alpha]_D$ −104° (Found: C, 72·6; H, 8·4; Cl, 10·0. $C_{22}H_{31}ClO_2$ requires C, 72·9; H, 8·55; Cl, 9·8%). The 3-*monoacetate* crystallised from aqueous acetone in needles, m. p. 184°, $[\alpha]_D$ −107° (Found: C, 71·3; H, 8·5; Cl, 8·9. $C_{24}H_{33}ClO_3$ requires C, 71·2; H, 8·2; Cl, 8·8%).

17α-*Chloroethynyl*-17β-*hydroxyandrost*-4-*ene*-3,11-*dione*, prepared by reaction of 3-ethoxyandrosta-3,5-diene-11,17-dione [25] with lithium chloroacetylide followed by treatment of the crude product with hot aqueous methanol containing a catalytic amount of toluene-*p*-sulphonic acid, was purified from methanol to give crystals, m. p. 211—211·5°, $[\alpha]_D$ +88°, $\lambda_{max.}$ 237 mμ (log ε 4·17) (Found: C, 69·8; H, 7·0; Cl, 10·0. $C_{21}H_{25}ClO_3$ requires C, 69·9; H, 7·0; Cl, 9·8%).

17α-*Chloroethynyl*-17β-*hydroxyandrosta*-3,5-*diene*, prepared from androsta-3,5-dien-17-one,[26] crystallised from methanol in blades, m. p. 164—166°, $[\alpha]_D$ −272°, $\lambda_{max.}$ 228 mμ (log ε 4·26), 235 mμ (log ε 4·29), and 243·5 mμ (log ε 4·10) (Found: C, 76·3; H, 7·9. $C_{21}H_{27}ClO$ requires C, 76·2; H, 8·2%).

17α-*Chloroethynyl*-17β-*hydroxyandrost*-4-*ene*, prepared from androst-4-en-17-one,[27] crystallised from aqueous methanol in needles, m. p. 120·5—121°, $[\alpha]_D$ +11° (Found: C, 76·0; H, 8·6. $C_{21}H_{29}ClO$ requires C, 75·75; H, 8·8%).

17α-*Chloroethynyltestosterone* (I; R^1 = Me, R^2 = R^3 = R^4 = H), prepared by reaction of 3-ethoxyandrosta-3,5-dien-17-one [28] with lithium chloroacetylide followed by treatment of the product with aqueous methanolic toluene-*p*-sulphonic acid, was purified from acetone–hexane to give crystals, m. p. 183·5—184·5°, $[\alpha]_D$ +9°, $\lambda_{max.}$ 240·5 mμ (log ε 4·22) (Found: C, 72·6; H, 7·8; Cl, 10·8. $C_{21}H_{27}ClO_2$ requires C, 72·7; H, 7·85; Cl, 10·2%). The same compound was obtained by Oppenauer oxidation of 17α-chloroethynylandrost-5-ene-3β,17β-diol.

3-*Methoxyandrosta*-3,5-*dien*-17-*one*.—A mixture of androst-4-ene-3,17-dione (190 g.), dioxan (630 ml.), methyl orthoformate (70 ml.), methanol (5 ml.), and toluene-*p*-sulphonic acid (1·9 g.) was stirred for 45 min., then poured into aqueous sodium carbonate, and the solid was collected and air-dried. Purification from methylene dichloride–methanol–trace of pyridine gave the *enol ether* (60%), flakes, m. p. 167—173° (sinters at 161°) (Found: C, 79·3; H, 9·4. $C_{20}H_{28}O_2$ requires C, 79·95; H, 9·4%).

17α-*Chloroethynyl*-17β-*hydroxy*-3-*methoxyandrosta*-3,5-*diene*, prepared from the foregoing compound, separated from aqueous methanol in plates, m. p. 87—90°, $[\alpha]_D$ −220°, $\lambda_{max.}$ 240 mμ (log ε 4·26) (Found: C, 73·1; H, 8·2. $C_{22}H_{29}ClO_2$ requires C, 73·2; H, 8·1%).

3-*Ethoxy*-6-*methylandrosta*-3,5-*dien*-17-*one*.—Ethyl orthoformate (7·25 ml.) was added to 6α-methylandrost-4-ene-3,17-dione [8] (6 g.) in dioxan (29 ml.), followed by 5 drops of concentrated sulphuric acid in dioxan (15 ml.). The mixture was left at room temperature for 30 min., then poured into water (1 l.) containing pyridine (5 ml.). Crystallisation of the precipitate gave the *enol ether* as yellow plates (from aqueous ethanol) (65%), m. p. 137—138°, $[\alpha]_D$ −119° (Found: C, 80·8; H, 10·1. $C_{22}H_{32}O_2$ requires C, 80·4; H, 9·8%).

17α-*Chloroethynyl*-17β-*hydroxy*-6α-*methylandrost*-4-*en*-3-*one* (I; R^1 = Me, R^2 = R^3 = H, R^4 = α-Me), prepared by reaction of the foregoing compound with lithium chloroacetylide followed by treatment of the product with hot 2% ethanolic hydrochloric acid, crystallised

[24] Grenville, Patel, Petrow, Stuart-Webb, and Williamson, *J.*, 1957, 4105.
[25] Marshall, Ralls, Saunders, and Riegel, *J. Biol. Chem.*, 1957, **228**, 339.
[26] Rosenkranz, Kaufmann, and Romo, *J. Amer. Chem. Soc.*, 1949, **71**, 3689.
[27] Marke, *J. Amer. Chem. Soc.*, 1940, **62**, 223.
[28] Serini and Köster, *Chem. Ber.*, 1938, **71**, 1766.

from acetone–hexane in prisms, m. p. 152·5°, $[\alpha]_D$ +8°, $\lambda_{max.}$ 240 mμ (log ε 4·17) (Found: C, 73·5; H, 8·0; Cl, 9·5. $C_{22}H_{29}ClO_2$ requires C, 73·2; H, 8·1; Cl, 9·8%).

17β-*Acetoxy*-3,3-*ethylenedioxy*-4-*methylandrost*-4-*ene*.—A suspension of 4-methyltestosterone acetate [9] (7 g.) in ethylene glycol (150 ml.) to which toluene-*p*-sulphonic acid (0·35 g.) had been added, was slowly distilled at 50°/0·5 mm. for 2½ hr. The mixture was poured into aqueous sodium carbonate, and the precipitate purified from methanol–methylene dichloride containing a trace of pyridine. The *ketal* separated in needles, m. p. 187—189° (80%), $[\alpha]_D$ +100° (Found: C, 74·4; H, 9·2. $C_{24}H_{36}O_4$ requires C, 74·2; H, 9·35%).

3,3-*Ethylenedioxy*-17β-*hydroxy*-4-*methylandrost*-4-*ene*, prepared by saponification of the foregoing compound with hot methanolic potassium hydroxide, crystallised from aqueous methanol containing a trace of pyridine in needles, m. p. 196—198°, $[\alpha]_D$ +112°, $\nu_{max.}$ 3500 cm.$^{-1}$ (OH) (Found: C, 75·95; H, 9·85. $C_{22}H_{34}O_3$ requires C, 76·25; H, 9·9%).

3,3-*Ethylenedioxy*-4-*methylandrost*-4-*en*-17-*one*.—The foregoing compound (5·6 g.) in pyridine (56 ml.) was added to chromium trioxide (5·6 g.) in pyridine (56 ml.), and the mixture was set aside overnight. The product was isolated with ethyl acetate and purified from aqueous methanol, to give the *ketone* in needles (75%), m. p. 210—212°, $[\alpha]_D$ +178°, $\nu_{max.}$ 1730 cm.$^{-1}$ (C=O) (Found: C, 77·2; H, 9·2. $C_{22}H_{32}O_3$ requires C, 76·8; H, 9·35%).

17α-*Chloroethynyl*-17β-*hydroxy*-4-*methylandrost*-4-*en*-3-*one* (I; $R^1 = R^3 = Me$, $R^2 = R^4 =$ H), prepared by reaction of the foregoing compound with lithium chloroacetylide followed by treatment of the product with boiling methanol containing oxalic acid, separated from acetone–hexane in crystals, m. p. 198—200°, $[\alpha]_D$ +22° (in ethanol), $\lambda_{max.}$ 250 mμ (log ε 4·2) (Found: C, 72·9; H, 7·8; Cl, 10·15. $C_{22}H_{29}ClO_2$ requires C, 73·2; H, 8·1; Cl, 9·8%).

11β-*Formyloxyandrost*-4-*ene*-3,17-*dione*.—11β-Hydroxyandrost-4-ene-3,17-dione [10] (500 mg.) and toluene-*p*-sulphonic acid (100 mg.) in 98% formic acid (20 ml.) were kept for 2 days at room temperature. The mixture was diluted with water, then partially neutralised with aqueous sodium hydrogen carbonate, and the product was isolated with methylene dichloride. Crystallisation from ether–hexane gave the *formate*, needles (80%), m. p. 134—136°, $[\alpha]_D$ +203°, $\lambda_{max.}$ 237·5 mμ (log ε 4·21) (Found: C, 72·9; H, 7·5. $C_{20}H_{26}O_4$ requires C, 72·7; H, 7·9%).

11β-*Hydroxy*-3-*methoxyandrosta*-3,5-*dien*-17-*one*.—The foregoing compound (1 g.) was added to a solution of toluene-*p*-sulphonic acid (50 mg.) in dry dioxan (10 ml.), methyl orthoformate (1 ml.), and methanol (0·1 ml.). The mixture was kept at room temperature for 2 hr., then poured into very dilute aqueous pyridine, and the product was isolated with ether. A solution of this material in 2·5% methanolic potassium hydroxide (10 ml.) was heated under reflux for 1 hr., then treated with water, and the methanol was removed *in vacuo*. The crystalline product was purified from ether–hexane, to give 11β-*hydroxy*-3-*methoxyandrosta*-3,5-*dien*-17-*one* (65%), prisms, m. p. 184—187°, $[\alpha]_D$ −73°, $\lambda_{max.}$ 240 mμ (log ε 4·27), $\nu_{max.}$ 3500 (OH), 1730 cm^{-1}. (C=O) (Found: C, 75·9; H, 8·9. $C_{20}H_{28}O_3$ requires C, 76·45; H, 9·2%).

17α-*Chloroethynyl*-11β,17β-*dihydroxyandrost*-4-*en*-3-*one*, prepared by reaction of the foregoing compound with lithium chloroacetylide, followed by treatment of the product with cold 4% aqueous-methanolic oxalic acid, crystallised from ethanol in plates, m. p. 211—213°, $[\alpha]_D$ +40°, $\lambda_{max.}$ 241·5 mμ (log ε 4·19) (Found: C, 69·4; H, 7·5. $C_{21}H_{27}ClO_3$ requires C, 69·5; H, 7·2%).

3-*Methoxy*-5α-*androst*-2-*en*-17-*one*.—3-Methoxyandrosta-3,5-dien-17-one (13 g.) in ethyl acetate (400 ml.), ethanol (100 ml.), and pyridine (4 drops) was hydrogenated at room temperature in the presence of palladium–barium sulphate (3 g.) and palladium–calcium carbonate (0·5 g.) catalysts, until one equiv. of hydrogen had been absorbed. After removal of the catalysts by filtration, and of the solvents by distillation, the residue was purified from aqueous methanol containing a trace of pyridine, to give the *enol ether* (85%), needles, m. p. 96—98°, $[\alpha]_D$ +11° (in dioxan) (Found: C, 79·8; H, 9·6. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%). Hydrolysis with methanolic hydrochloric acid gave 5α-androstane-3,17-dione, m. p. and mixed m. p. 134—135°.

17α-*Chloroethynyl*-17β-*hydroxy*-5α-*androstan*-3-*one*, prepared from the foregoing compound, crystallised from aqueous methanol in needles, m. p. 209—211°, $[\alpha]_D$ −19° (Found: C, 72·15; H, 9·4; Cl, 10·35. $C_{21}H_{29}ClO_2$ requires C, 72·3; H, 8·3; Cl, 10·2%).

17α-*Chloroethynyl*-17β-*hydroxy*-4α-*methyl*-5α-*androstan*-3-*one*.—17β-Acetoxy-4α-methyl-5α-androstan-3-one [29] (5 g.), dioxan (15 ml.), methyl orthoformate (5 ml.), and toluene-*p*-sulphonic

[29] B.P. 874,142.

acid (50 mg.) were stirred together at room temperature for 30 min. After the addition of pyridine (2 ml.) and water, the product was isolated with ether and crystallised from methanol containing a trace of pyridine. The crude enol ether (m. p. 145—147°) so obtained was heated under reflux for 1 hr. with potassium hydroxide (2·5 g.) in methanol (300 ml.) and water (25 ml.). The product crystallised from aqueous methanol in needles, m. p. 173—175°, $\nu_{max.}$ 3480 cm.$^{-1}$ (OH). A pyridine (35 ml.) solution of this material (3·5 g.) was added to chromium trioxide (3·5 g.) in pyridine (35 ml.), and the mixture was left at room temperature for 24 hr. The product was isolated with ethyl acetate and crystallised from methanol–pyridine (trace), to give the crude 17-ketone, plates, m. p. 180—182°, $\nu_{max.}$ 1740 cm.$^{-1}$ (C=O). Reaction with lithium chloroacetylide gave 17α-*chloroethynyl*-17β-*hydroxy*-4α-*methyl*-5α-*androstan*-3-*one*, needles (from acetone), m. p. 206—206·5°, $[\alpha]_D$ −35° (Found: C, 72·75; H, 8·5; Cl, 9·7. $C_{22}H_{31}ClO_2$ requires C, 72·9; H, 8·6; Cl, 9·7%).

3,3-*Ethylenedioxy*-17β-*hydroxy*-2α-*methyl*-5α-*androstane*.—A mixture of 2α-methylandrostan-17β-ol-3-one [11] (5 g.), ethylene glycol (50 ml.), benzene (200 ml.), and toluene-*p*-sulphonic acid (0·5 g.) was refluxed for 24 hr. in an apparatus fitted with a water-separator. The mixture was washed with dilute aqueous alkali, the solvent was removed by distillation, and the residue purified from acetone–hexane. The *ketal* formed crystals (70%), m. p. 215—219°, $[\alpha]_D$ +10° (Found: C, 76·1; H, 10·1. $C_{22}H_{36}O_3$ requires C, 75·8; H, 10·4%).

3,3-*Ethylenedioxy*-2α-*methyl*-5α-*androstan*-17-*one*, prepared by oxidation of the foregoing compound with chromium trioxide–pyridine complex, crystallised from methylene dichloride–methanol in plates (80%), m. p. 228—232°, $[\alpha]_D$ +80°, $\nu_{max.}$ 1740 cm.$^{-1}$ (C=O) (Found: C, 76·1; H, 10·1. $C_{22}H_{34}O_3$ requires C, 76·3; H, 9·9%).

17α-*Chloroethynyl*-17β-*hydroxy*-2α-*methyl*-5α-*androstan*-3-*one*, prepared from the foregoing compound, crystallised from aqueous methanol in a solvated hydrated form, m. p. 125—130° (effervescence). Sublimation in a high vacuum at 150° gave the anhydrous compound, m. p. 101—103°, $[\alpha]_D$ −28° (Found: C, 72·4; H, 8·8; Cl, 10·0. $C_{22}H_{31}ClO_2$ requires C, 72·8; H, 8·6; Cl, 9·8%).

17α-*Chloroethynyl*-17β-*hydroxy*-4β,5β-*epoxyandrostan*-3-*one*.—An ice-cooled solution of 17α-chloroethynyltestosterone (1·85 g.) in methanol (100 ml.) was treated with 10% aqueous sodium hydroxide (5 ml.) and 30% hydrogen peroxide (3 ml.). The mixture was kept for 24 hr. at 0° then poured into water, and the product purified from aqueous methanol. The *epoxide* (75%) formed crystals, m. p. 183—185°, $[\alpha]_D$ +69° (Found: C, 69·9; H, 7·7; Cl, 9·6. $C_{21}H_{27}ClO_3$ requires C, 69·5; H, 7·5; Cl, 9·8%).

4-*Chloro*-17α-*chloroethynyltestosterone* (I; R^1 = Me, R^2 = R^4 = H, R^3 = Cl).—The foregoing epoxide (2·25 g.) in acetic acid (60 ml.) was treated with concentrated hydrochloric acid (3 ml.). After 5 min. at room temperature the mixture was poured into water, and the product was isolated and chromatographed on alumina (20 g.), with benzene–ether (1 : 1) as eluant. Purified from acetone–hexane, 4-*chloro*-17α-*chloroethynyltestosterone* (52%) separated in tablets, m. p. 105—106°, $[\alpha]_D$ +58°, $\lambda_{max.}$ 255 mμ (log ε 4·09) (Found: C, 66·4; H, 7·15. $C_{21}H_{26}Cl_2O_2$ requires C, 66·1; H, 6·9%).

17α-*Chloroethynyl*-17β-*hydroxy*-3-N-*pyrrolidylandrosta*-3,5-*diene*, prepared from 17α-chloroethynyltestosterone (2 g.) and pyrrolidine (2 ml.) in boiling methanol (10 ml.), crystallised from methylene dichloride–methanol in plates (70%), m. p. 204—205° (decomp.), $[\alpha]_D$ −193°, $\lambda_{max.}$ 279 mμ (log ε 4·27) (Found: C, 74·9; H, 8·7. $C_{25}H_{34}ClNO$ requires C, 75·1; H, 8·6%).

17α-*Chloroethynyl*-4-*fluorotestosterone* (I; R^1 = Me, R^2 = R^4 = H, R^3 = F).—The foregoing enamine (1·3 g.) in methanol (50 ml.) and water (5 ml.) was treated at −20° with perchloryl fluoride (1·4 g.) in methanol (85 ml.). The mixture was stirred at −20° for 15 min., allowed to warm to room temperature, then poured into water, and the product was isolated with ether. Chromatography on alumina (15 g.), with benzene–ether mixtures as eluants, gave a gum which crystallised from acetone–hexane. 17α-*Chloroethynyl*-4-*fluorotestosterone* (30%) formed prisms, m. p. 114—115°, $[\alpha]_D$ −1°, $\lambda_{max.}$ 247 mμ (log ε 4·13) (Found: C, 69·4; H, 7·3. $C_{21}H_{26}ClFO_2$ requires C, 69·1; H, 7·2%).

3β-*Acetoxy*-6β-*fluoro*-5α-*hydroxyandrostan*-17-*one*.—The boron trifluoride–ether complex (5 ml.) was added to 3β-acetoxy-5α,6α-epoxyandrostan-17-one (5 g.) in dry benzene, and the mixture set aside for 15 min. at room temperature. It was washed with aqueous sodium hydrogen carbonate, then with water, and dried, and the solvent removed. Crystallisation of the residue from benzene gave the *fluorohydrin* (60%), needles, m. p. 219—220°, $[\alpha]_D$ +22° (Found: C, 68·9; H, 8·7. $C_{21}H_{31}FO_4$ requires C, 68·8; H, 8·5%).

3β-*Acetoxy*-17α-*chloroethynyl*-5α,6α-*epoxy*-17β-*hydroxyandrostane*.—The foregoing compound was condensed with lithium chloroacetylide, and the crude product was treated with acetic anhydride–pyridine for 1 hr. at 100°. Crystallisation from aqueous acetone gave the *epoxide* (80%), needles, m. p. 219—221°, $[\alpha]_D$ −106° (Found: C, 67·7; H, 7·8. $C_{23}H_{31}ClO_4$ requires C, 67·8; H, 7·6%).

17α-*Chloroethynyl*-5α,6α-*epoxyandrostane*-3β,17β-*diol*, prepared by reaction of lithium chloroacetylide with 5α,6α-epoxy-3β-hydroxyandrostan-17-one or with 3β,6β-diacetoxy-5α-hydroxyandrostan-17-one, crystallised from aqueous acetone in needles (hydrated), m. p. 220—221°, $[\alpha]_D$ −117° (Found: C, 67·3, 67·4; H, 7·8, 8·1. $C_{21}H_{29}ClO_3,\frac{1}{2}H_2O$ requires C, 67·4; H, 7·8%). Acetylation in pyridine gave the 3β-acetate, m. p. 219—220°, identical with a sample prepared as described in the foregoing experiment.

17α-*Chloroethynyl*-5β,6β-*epoxyandrostane*-3β,17β-*diol*, prepared from 5β,6β-epoxy-3β-hydroxyandrostan-17-one,[13] crystallised from aqueous methanol in needles, m. p. 215—216°, $[\alpha]_D$ −58° (Found: C, 68·8; H, 8·1. $C_{21}H_{29}ClO_3$ requires C, 69·1; H, 8·0%).

17α-*Chloroethynylandrostane*-3β,5α,6β,17β-*tetraol*.—(*a*) A mixture of 17α-chloroethynyl-5α,6α-epoxyandrostane-3β,17β-diol (1 g.) and periodic acid (0·3 g.) in acetone (20 ml.) and water (3·5 ml.) was refluxed for 4 min. The product obtained on the addition of water was purified from aqueous acetone to give the *tetraol*, needles, m. p. 229—230°, $[\alpha]_D$ −55° (in dioxan) (Found: C, 64·2; H, 8·2; Cl, 8·7. $C_{21}H_{31}ClO_4,\frac{1}{2}H_2O$ requires C, 64·4; H, 8·2; Cl, 9·1%). The same compound was similarly obtained (75%) from 17α-chloroethynyl-5β,6β-epoxyandrostane-3β,17β-diol.

(*b*) Prepared by condensation of lithium chloroacetylide with 3β,5α,6β-trihydroxyandrostan-17-one and purified from acetone–hexane, it formed needles, m. p. 229°, not depressed in admixture with a specimen prepared by method (*a*) above.

3β-*Acetoxy*-17α-*chloroethynylandrostane*-5α,6β,17β-*triol*, prepared by treating 3β-acetoxy-17α-chloroethynyl-5α,6α-epoxyandrostan-17β-ol (1 g.) in acetone (20 ml.) and water (3·5 ml.) with periodic acid (0·3 g.) for 5 min. at the b. p., crystallised from aqueous methanol in needles (70%), m. p. 218°, $[\alpha]_D$ −64° (in dioxan) (Found: C, 65·0; H, 7·8; Cl, 8·55. $C_{23}H_{33}ClO_5$ requires C, 65·0; H, 7·7; Cl, 8·4%).

17α-*Chloroethynyl*-5α,17β-*dihydroxyandrostane*-3,6-*dione*.—4N-Chromium trioxide–sulphuric acid [14] (2·5 ml.) was added dropwise during 10 min. to a stirred solution of 17α-chloroethynylandrostane-3β,5α,6β,17β-tetrol (2 g.) in acetone (75 ml.). The mixture was poured into water, and the product collected and purified from acetone–hexane. The *dione* formed rods (77%), m. p. 250—251°, $[\alpha]_D$ −55° (in dioxan), $\nu_{max.}$ 1725 cm.$^{-1}$ (C=O) (Found: C, 66·6; H, 7·2. $C_{21}H_{27}ClO_4$ requires C, 66·6; H, 7·2%).

17α-*Chloroethynyl*-17β-*hydroxyandrost*-4-*ene*-3,6-*dione*.—A solution of the foregoing compound (0·7 g.) and potassium hydroxide (0·1 g.) in ethanol (20 ml.) was refluxed for 5 min. then poured into water, and the product isolated with ether. Chromatography on alumina (10 g.), with benzene as eluant, gave the unsaturated *dione* (45%), needles (from acetone–hexane), m. p. 232—233°, $[\alpha]_D$ −105°, $\lambda_{max.}$ 250·5 mμ (log ε 3·99) (Found: C, 70·1; H, 7·1. $C_{21}H_{25}ClO_3$ requires C, 69·9; H, 7·0%).

5α-*Bromo*-17α-*chloroethynyl*-6β-*fluoroandrostane*-3β,17β-*diol*.—17α-Chloroethynylandrost-5-ene-3β,17β-diol (7 g.), suspended in methylene dichloride (75 ml.), was added to anhydrous hydrogen fluoride (33 g.), tetrahydrofuran (55 g.), and *N*-bromoacetamide (3·1 g.) at −60°. The mixture was stirred at this temperature for 3 hr., then poured into ice–water and sodium hydrogen carbonate (100 g.). The product was isolated with methylene dichloride and crystallised from aqueous methanol, to give 5α-*bromo*-17α-*chloroethynyl*-6β-*fluoroandrostane*-3β,17β-*diol* (60%), needles, m. p. 198° (decomp.), $[\alpha]_D$ −75° (Found: C, 56·45; H, 6·35. $C_{21}H_{29}BrClFO_2$ requires C, 56·3; H, 6·5%).

17α-*Chloroethynyl*-6α-*fluoro*-17β-*hydroxyandrost*-4-*en*-3-*one* (I; R^1 = Me, R^2 = R^3 = H, R^4 = α-F).—A stirred suspension of the foregoing compound (4·5 g.) in acetone (70 ml.) was treated at 0° with 4N-chromium trioxide–sulphuric acid (2·5 ml.) added dropwise during 5 min. The crude product obtained by pouring the mixture into ice–water was heated with potassium acetate (8 g.) in acetone (50 ml.) under reflux for 3 hr. Addition of water gave a solid from which unchanged 5α-bromo-17α-chloroethynyl-6β-fluoroandrostane-3β,17β-diol (1·3 g.) was isolated by crystallisation from methanol. Chromatography of the mother-liquor material on silica (60 g.), with methylene dichloride–acetone (95 : 5) as eluant, gave a crude crystalline fraction (630 mg.) containing an αβ-unsaturated ketone [$\nu_{max.}$ 1680, 1610 cm.$^{-1}$ (3-oxo-4-ene)].

Its solution in acetic acid (30 ml.) was saturated with dry hydrogen chloride at room temperature, and the mixture was set aside for 5 hr. The product obtained by the addition of water was purified from acetone–hexane, to give 17α-*chloroethynyl*-6α-*fluoro*-17β-*hydroxyandrost*-4-*en*-3-*one*, prisms, m. p. 200—203° (decomp.), $[\alpha]_D$ +15°, $\lambda_{max.}$ 236 mμ (log ε 4·14) (Found: C, 68·8; H, 7·35. $C_{21}H_{26}ClFO_2$ requires C, 69·1; H, 7·2%).

17α-Chloroethynyl-17β-hydroxy-3-methoxycœstra-2,5(10)-diene, prepared from 3-methoxycœstra-2,5(10)-dien-17-one,[16] separated from methanol in soft crystals, m. p. 126—127°, $[\alpha]_D$ +68° (in dioxan) (Found: C, 72·25; H, 7·9; Cl, 9·8. Calc. for $C_{21}H_{27}ClO_2$: C, 72·7; H, 7·85; Cl, 10·2%). After storage for 6 months at room temperature, the m. p. of the analytical specimen fell to 116—117° {Fried *et al.*[17] give m. p. 112—115°, $[\alpha]_D$ +69° (in dioxan)}.

17α-*Chloroethynyl*-17β-*hydroxy*-19-*norandrost*-4-*en*-3-*one* (I; $R^1 = R^2 = R^3 = R^4 = H$), prepared by treating the foregoing compound (0·4 g.) in methanol (22 ml.) with 3N-hydrochloric acid (13·2 ml.) and maintaining the mixture for 15 min. at 60°, separated from ethyl acetate in crystals (70%), m. p. 194—195°, $[\alpha]_D$ −41°, $\lambda_{max.}$ 239 mμ (log ε 4·2) (Found: C, 72·0; H, 7·7; Cl, 11·1. Calc. for $C_{20}H_{25}ClO_2$: C, 72·2; H, 7·6; Cl, 10·65%) [Fried *et al.*[17] give m. p. 198—201°, $[\alpha]_D$ −49°, $\lambda_{max.}$ 240 mμ (ε 15,000)].

17α-*Chloroethynyl*-17β-*hydroxycœstr*-5(10)-*en*-3-*one*.—Anhydrous oxalic acid (0·78 g.) in water (15 ml.) was added to 17α-chloroethynyl-17β-hydroxy-3-methoxycœstra-2,5(10)-diene (1·04 g.) in methanol (250 ml.), and the mixture set aside for 1 hr. at room temperature. The product was isolated with ether and purified by chromatography on ethyl acetate-washed alumina (15 g.). Elution with benzene gave material which crystallised from ether. 17α-Chloroethynyl-17β-hydroxœstr-5(10)-en-3-one (45%) separated in crystals, m. p. *ca.* 158—160°, $[\alpha]_D$ +98° (Found: C, 71·7; H, 7·5; Cl, 10·95. Calc. for $C_{20}H_{25}ClO_2$: C, 72·2; H, 7·6; Cl, 10·65%) {Fried *et al.*[17] give m. p. *ca.* 160°, $[\alpha]_D$ +86° (in dioxan)}. The ultraviolet spectrum of the product showed the presence of <9% of conjugated material.

3-*Methoxy*-6-*methyl*-19-*norandrosta*-3,5-*dien*-17-*one*.—6α-Methyl-19-norandrost-4-en-3,17-dione [18] (3 g.), anhydrous dioxan (30 ml.), trimethyl orthoformate (3 ml.), and methanol (1 ml.) were stirred and treated with toluene-*p*-sulphonic acid (0·15 g.). After 45 min. pyridine (1 ml.) was added, followed by water, dropwise, until the product separated. Purification from aqueous methanol containing a trace of pyridine gave the *enol ether*, needles (55%), m. p. 153—155°, $[\alpha]_D$ −145° (in dioxan), $\lambda_{max.}$ 247 mμ (log ε 4·29) (Found: C, 79·6; H, 9·4. $C_{20}H_{28}O_2$ requires C, 79·95; H, 9·4%).

17α-*Chloroethynyl*-6α-*methyl*-19-*nortestosterone* (I; $R^1 = R^2 = R^3 = H$, R^4 = α-Me), prepared from the foregoing compound, crystallised from ethyl acetate in needles, m. p. 174—175°, $[\alpha]_D$ −77°, $\lambda_{max.}$ 240 mμ (log ε 4·19) (Found: C, 72·6; H, 8·1; Cl, 10·1. $C_{21}H_{27}ClO_2$ requires C, 72·7; H, 7·85; Cl, 10·2%).

17α-*Chloroethynyl*-5β-*methyl*-19-*norandrost*-9(10)-*ene*-3β,6β,17β-*triol* (II; R = β-OH), prepared from 3β,6β-diacetoxy-5β-methyl-19-norandrost-9(10)-en-17-one,[19] crystallised from aqueous ethanol, in plates, m. p. 173—174°, $[\alpha]_D$ +147° (in ethanol) (Found: Cl, 9·4. $C_{21}H_{29}ClO_3$ requires Cl, 9·7%).

17α-*Chloroethynyl*-17β-*hydroxy*-5β-*methyl*-19-*norandrost*-9(10)-*ene*-3,6-*dione* (II; R = :O).—4N-Chromium trioxide–sulphuric acid (0·75 ml.) was added dropwise during 10 min. to a stirred solution of the foregoing compound (0·5 g.) in acetone. The product obtained on the addition of water crystallised from acetone–hexane, to give the *dione* (60%), needles, m. p. 203·5°, $\nu_{max.}$ 1720 cm.$^{-1}$ (C=O) (Found: C, 69·7; H, 7·1; Cl, 10·2. $C_{21}H_{25}ClO_3$ requires C, 69·9; H, 7·0; Cl, 9·8%).

17α-*Chloroethynylœstra*-1,3,5(10)-*trien*-17β-*ol* (III; $R^1 = R^2 = R^3 = R^4 = R^5 = H$), prepared from œstra-1,3,5(10)-trien-17-one,[30] crystallised from aqueous methanol in plates, m. p. 59—60°, $[\alpha]_D$ −17°, $\lambda_{max.}$ 266, 274 mμ (ε 447, 472) (Found: C, 75·9; H, 7·7; Cl, 10·9. $C_{20}H_{23}ClO$ requires C, 76·3; H, 7·5; Cl, 11·3%).

1-*Methylœstra*-1,3,5(10)-*trien*-17-*one*, prepared by treating 1-methylœstra-1,3,5-(10)-trien-17β-ol [20] (2 g.) in acetone (60 ml.) with 4N-chromium trioxide–sulphuric acid (1·5 ml.), crystallised from aqueous methanol in laths (80%), m. p. 164—166°, $[\alpha]_D$ +268°, $\nu_{max.}$ 1735 cm.$^{-1}$ (C=O) (Found: C, 84·65; H, 8·8. $C_{19}H_{24}O$ requires C, 85·0; H, 9·0%).

17α-*Chloroethynyl*-1-*methylœstra*-1,3,5(10)-*trien*-17β-*ol* (III; R^1 = Me, $R^2 = R^3 = R^4 = R^5 = H$), prepared from the foregoing ketone, formed needles (from methanol), m. p. 71—74°

[30] U.S.P. 2,947,763.

(effervescence), $[\alpha]_D$ +28° (Found: C, 75·7; H, 7·25; Cl, 10·6. $C_{21}H_{25}ClO,\frac{1}{2}MeOH$ requires C, 75·3; H, 7·35; Cl, 10·35%).

1,4-*Dimethylœstra*-1,3,5(10)-*trien*-17-*one*.—A mixture of 17β-acetoxy-4-methylandrosta-1,4-dien-3-one [21] (2 g.) and lithium aluminium hydride (2 g.) in dry ether (300 ml.) was refluxed for 45 min. The excess of reagent was decomposed by addition of acetone, and the product, isolated with ether, was heated with acetic acid (15 ml.) and water (5 ml.) for 10 min. at 100°. The product was isolated with ether and crystallised from methanol, to give crude 1,4-dimethylœstra-1,3,5(10)-trien-17β-ol * (0·7 g.), $\nu_{max.}$ 3480 cm.$^{-1}$ (OH). Its solution in acetone (10 ml.) was treated with 4N-chromium trioxide–sulphuric acid (0·5 ml.). Crystallisation of the product from methanol gave the *ketone* (53%), needles, m. p. 126—128°, $[\alpha]_D$ +245°, $\nu_{max.}$ 1740 cm.$^{-1}$ (C=O) (Found: C, 85·3; H, 9·05. $C_{20}H_{26}O$ requires C, 85·05; H, 9·3%).

17α-*Chloroethynyl*-1,4-*dimethylœstra*-1,3,5(10)-*trien*-17β-*ol* (III; $R^1 = R^4 = Me$, $R^2 = R^3 = R^5 = H$), prepared from the foregoing compound, crystallised from aqueous methanol in needles, m. p. 86—89°, $[\alpha]_D$ +37° (Found: C, 76·7; H, 7·75; Cl, 10·75. $C_{22}H_{27}ClO$ requires C, 77·1; H, 7·95; Cl, 10·35%).

2,4-*Dimethylœstra*-1,3,5(10)-*trien*-17-*one*.—A mixture of 17β-acetoxy-2α-methylandrosta-1,4-dien-3-one [22] (5 g.) and lithium aluminium hydride (10 g.) in ether (400 ml.) was heated under reflux for 1 hr. The product, isolated with ether, was heated with acetic acid (20 ml.) and water (4 ml.) for 15 min. at 100°. The solid obtained on the addition of water was crystallised once from methanol, to give crude 2,4-dimethylœstra-1,3,5(10)-trien-17β-ol, m. p. 131—132°, $\nu_{max.}$ 3490 cm.$^{-1}$ (OH). Treatment of this material (2 g.) in acetone (20 ml.) with 4N-chromium trioxide–sulphuric acid (1·5 ml.) gave a product which crystallised from methanol, the *ketone* (75%) separating in flakes, m. p. 188—191°, $[\alpha]_D$ +148°, $\nu_{max.}$ 1740 cm.$^{-1}$ (C=O) (Found: C, 85·5; H, 10·0. $C_{20}H_{26}O$ requires C, 85·05; H, 9·3%).

17α-*Chloroethynyl*-2,4-*dimethylœstra*-1,3,5(10)-*trien*-17β-*ol* (III; $R^1 = R^3 = R^5 = H$, $R^2 = R^4 = Me$), prepared from the foregoing compound, separated from methanol in needles, m. p. 91·5—92·5°, $[\alpha]_D$ −30° (Found: C, 74·3; H, 7·8; Cl, 10·0. $C_{22}H_{27}ClO,MeOH$ requires C, 73·8; H, 8·35; Cl, 9·5%).

17β-*Acetoxy*-2-*chloroandrosta*-1,4-*dien*-3-*one*.—Chlorine (2·4 g.) in propionic acid (24 ml.) was added during 20 min. to a stirred solution of 17β-acetoxyandrosta-1,4-dien-3-one [23] (10 g.) in anhydrous ether (600 ml.) at −35°. The mixture was stirred at this temperature for 7 hr., and the product isolated with ether. Trituration with methanol gave a solid (3·5 g.), which was treated with pyridine (18 ml.) for 45 min. at room temperature. The product was isolated with ether and purified from methylene dichloride–hexane, to give 17β-*acetoxy*-2-*chloroandrosta*-1,4-*dien*-3-*one* (60%), needles, m. p. 185°, $[\alpha]_D$ −11°, $\lambda_{max.}$ 250·5 mμ (log ε 4·2) (Found: C, 69·1; H, 7·4. $C_{21}H_{27}ClO_3$ requires C, 69·3; H, 7·5%).

2-*Chloro*-4-*methylœstra*-1,3,5(10)-*trien*-17β-*ol*.—The foregoing compound (2·85 g.) in dry ether (200 ml.) was added during 15 min. to a stirred suspension of lithium aluminium hydride (2·9 g.) in ether (115 ml.). The mixture was heated for 10 min. under reflux, then cooled, and the product was isolated in the usual way. Its solution in acetic acid (450 ml.) and water (100 ml.) was refluxed for 1 min. and allowed to cool. The solid which separated was crystallised from methanol to give 2-*chloro*-4-*methylœstra*-1,3,5(10)-*trien*-17β-*ol* (65%), needles, m. p. 148°, $[\alpha]_D$ +88·5°, $\nu_{max.}$ 3500 cm.$^{-1}$ (OH) (Found: C, 75·1; H, 8·4; Cl, 11·3. $C_{19}H_{25}ClO$ requires C, 74·85; H, 8·3; Cl, 11·3%).

2-*Chloro*-4-*methylœstra*-1,3,5(10)-*trien*-17-*one*.—The foregoing compound (1 g.) in toluene (50 ml.) and cyclohexanone (10 ml.) was treated with aluminium isopropoxide (0·5 g.) in toluene (10 ml.), and the mixture refluxed under nitrogen for 1 hr. When it was cool, saturated aqueous Rochelle salt (15 ml.) was added, the solvents were removed by steam-distillation, and the product purified from acetone–hexane to give the *ketone* (70%), needles, m. p. 209—209·5°, $[\alpha]_D$ +145°, $\nu_{max.}$ 1740 cm.$^{-1}$ (C=O) (Found: C, 75·0; H, 7·3. $C_{19}H_{23}ClO$ requires C, 75·4; H, 7·7%).

2-*Chloro*-17α-*chloroethynyl*-4-*methylœstra*-1,3,5(10)-*trien*-17β-*ol* (III; $R^1 = R^3 = R^5 = H$, $R^2 = Cl$, $R^4 = Me$), prepared from the foregoing compound, was purified from aqueous methanol. It formed ill-defined crystals, indefinite m. p. 85—90°, $[\alpha]_D$ −32°, $\lambda_{max.}$ 272 and 280·5 mμ (ε 450 and 375) (Found: C, 69·5; H, 6·8; Cl, 20·35. $C_{21}H_{24}Cl_2O$ requires C, 69·45; H, 6·7; Cl, 19·5%).

* This compound has since been prepared by another route [20] and characterised.

17α-*Chloroethynyl*-4-*methylœstra*-1,3,5(10)-*trien*-17β-*ol* (III; $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = Me$), prepared from 4-methylœstra-1,3,5(10)-trien-17-one,[31] formed needles (from acetone–hexane), m. p. 132—132·5°, $[\alpha]_D$ −18·5° (Found: Cl, 10·95. $C_{21}H_{23}ClO$ requires Cl, 10·8%).

17α-*Chloroethynylœstra*-1,3,5(10)-*trien*-3,17β-*diol* (III; $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = OH$), prepared from œstrone, separated from benzene in crystals, m. p. 191°, $[\alpha]_D$ −15°, $\lambda_{max.}$ 281 and 287 mμ (ε 2120 and 1790) (Found: C, 72·8; H, 7·4; Cl, 10·65. $C_{20}H_{23}ClO_2$ requires C, 72·6; H, 7·0; Cl, 10·7%).

17α-*Chloroethynyl*-3-*methoxyœstra*-1,3,5(10)-*trien*-17β-*ol* (III; $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = OMe$), prepared from œstrone 3-methyl ether, crystallised from aqueous methanol in needles, m. p. 167°, $[\alpha]_D$ −14°, $\lambda_{max.}$ 278 and 287 mμ (ε 2050 and 1940) (Found: C, 73·0; H, 7·4. $C_{21}H_{25}ClO_2$ requires C, 73·1; H, 7·3%).

17α-*Chloroethynyl*-4-*methylœstra*-1,3,5(10)-*triene*-1,17β-*diol* (III; $R^1 = OH$, $R^2 = R^3 = R^5 = H$, $R^4 = Me$), prepared from 1-hydroxy-4-methylœstra-1,3,5(10)-trien-17-one,[32] crystallised from aqueous acetone in needles, m. p. 220—222°, $[\alpha]_D$ +44·5° (Found: C, 73·3; H, 7·3; Cl, 10·3. $C_{21}H_{25}ClO_2$ requires C, 73·1; H, 7·3; Cl, 10·3%).

17α-*Chloroethynyl*-1,6β-*dimethylœstra*-1,3,5(10)-*triene*-3,17β-*diol* (III; $R^1 = Me$, $R^2 = R^4 = H$, $R^3 = OH$, $R^5 = \beta$-Me), prepared from 3-hydroxy-1,6β-dimethylœstra-1,3,5(10)-trien-17-one,[33] formed needles (from aqueous acetone), m. p. 145—146°, $[\alpha]_D$ +2°, $\lambda_{max.}$ 286 mμ (ε 1660) (Found: C, 70·5; H, 7·7; Cl, 9·5. $C_{22}H_{27}ClO_2,H_2O$ requires C, 70·1; H, 7·8; Cl, 9·4%).

17α-*Chloroethynyl*-4,6α-*dimethylœstra*-1,3,5(10)-*triene*-1,17β-*diol* (III; $R^1 = OH$, $R^2 = R^3 = H$, $R^4 = Me$, $R^5 = \alpha$-Me), prepared from 1-hydroxy-4,6α-dimethylœstra-1,3,5(10)-trien-17-one,[33] crystallised from acetone in flakes, m. p. 110—112°, $[\alpha]_D$ +73°, $\lambda_{max.}$ 290 mμ (ε 1920) (Found: C, 73·1; H, 7·7; Cl, 10·2. $C_{22}H_{27}ClO_2$ requires C, 73·6; H, 7·6; Cl, 9·9%).

17α-*Chloroethynyl*-1,6-*dimethylœstra*-1,3,5(10),6-*tetraene*-3,17β-*diol* (III; $R^1 = R^5 = Me$, $R^2 = R^4 = H$, $R^3 = OH$), prepared from 3-hydroxy-1,6-dimethylœstra-1,3,5(10),6-tetraen-17-one,[33] separated in needles (from aqueous acetone), m. p. 190—193°, $[\alpha]_D$ −191°, $\lambda_{max.}$ 265 and 304·5 mμ (ε 7170 and 2080) (Found: C, 74·3; H, 7·1; Cl, 10·2. $C_{22}H_{25}ClO_2$ requires C, 74·0; H, 7·1; Cl, 9·9%).

CHEMICAL RESEARCH LABORATORIES, THE BRITISH DRUG HOUSES LTD.,
GRAHAM STREET, LONDON, N.1. [*Received, May 15th,* 1962.]

[31] Gentles, Moss, Herzog, and Hershberg, *J. Amer. Chem. Soc.*, 1958, **80**, 3702.
[32] Dreiding and Voltman, *J. Amer. Chem. Soc.*, 1954, **76**, 537.
[33] Burn, Petrow, and Weston, *J.*, 1962, 29.