391. *Modified Steroid Hormones. Part XI.* Some Ethisterone Homologues.*

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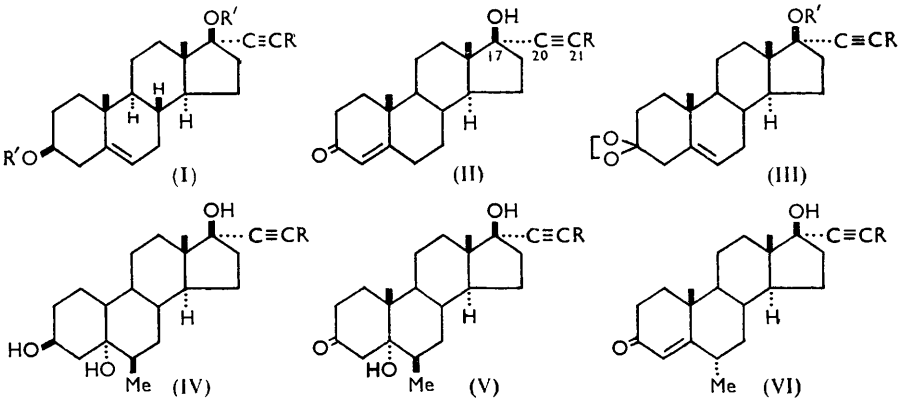
A method for the conversion of 17α-ethynyl-17β-hydroxy-derivatives of androstane into the $C_{(21)}$-alkyl derivatives is described. Its application to the preparation of the potent progestational agents 21-methyl- † (VI; R = Me) and 21-ethyl-6α-methylethisterone (VI; R = Et) is reported.

Our studies on alkylated steroid hormones [1] are herein extended to some 21-alkyl derivatives of 17α-ethynyl-17β-hydroxyandrost-4-en-3-one (ethisterone) (II; R = H) and its 6α-methyl homologue (VI; R = H).

Initial attempts to prepare the $C_{(21)}$-alkyl derivatives of ethisterone (II; R = H) employed 17α-ethynylandrost-5-ene-3β : 17β-diol (I; R = R′ = H) as starting material. Protection of the two hydroxyl groups was achieved by condensing the diol with 2 : 3-dihydropyran to give the bistetrahydropyranyl ether (I; R = H, R′ = C_5H_9O) as a mixture of isomers which was used directly for alkylation. Conversion of a tertiary hydroxyl group into a tetrahydropyranyl ether has been recorded previously.[2] The bis-ether (I; R = H, R′ = C_5H_9O) with lithamide in liquid ammonia readily gave the 21-metallo-derivative which passed smoothly into a 21-alkyl intermediate on treatment with an alkyl



halide. Regeneration of the 3β- and 17β-hydroxyl groups with ethanolic toluene-*p*-sulphonic acid furnished the 21-alkyl derivatives (I; R = alkyl, R′ = H) which passed into the required 21-alkylethisterones (II; R = alkyl) on Oppenauer oxidation. The 21-methyl, -ethyl, -propyl and -octyl derivatives of 17α-ethynyl-17β-hydroxy-5α-androst-4-en-3-one were obtained in this way. Their biological study [3] revealed that the 21-methyl and the 21-ethyl homologue are superior to the parent steroid (II; R = H) as progestational agents administered by the oral route. The preparation of these compounds was therefore studied further, and an alternative, and in some respects more convenient, reaction sequence developed.

Ethisterone (II; R = H) was converted into its 3 : 3-ethylenedioxy-derivative [4] (III; R = R′ = H) and thence by reaction with 2 : 3-dihydropyran into 3 : 3-ethylenedioxy-17α-ethynyl-17β-(tetrahydro-2-pyranyloxy)androst-5-ene (III; R = H, R′ = C_5H_9O). Alkylation of the ethynyl group by lithamide in liquid ammonia followed by an alkyl

* Part X, *J.*, 1959, 788.

† The nomenclature in the Introductory section is based upon the use of the trivial name "ethisterone" for (II; R = H).

[1] Part VII, *J.*, 1957, 4112.

[2] Elphimoff-Felkin, *Bull. Soc. chim. France*, 1955, 784.

[3] David, Hartley, Millson, and Petrow, *J. Pharm. Pharmacol.*, 1957, **9**, 929.

[4] U.S.P. 2,288,854.

halide, and by removal of the 3- and 17-protecting groups by hot alcoholic oxalic acid, furnished the 21-alkylated ethisterone (II; R = alkyl). In view of the ready availability of the ketone (II; R = H), this route may be preferred as a preparative method.

While this work was in progress, we learnt that 6α-methylethisterone [5] (VI; R = H) is about six times as potent as ethisterone as a progestational agent when tested in the Clauberg assay. Consequently we prepared some 21-alkyl-6α-methylethisterones in the hope that the enhancing effects of 6α- and 21-alkylation on biological activity might prove additive. This was achieved in the following ways.

17α-Prop-1′-ynylandrost-5-ene-3β : 17β-diol (I; R = Me, R′ = H) was oxidised with monoperphthalic acid to the corresponding 5α : 6α-epoxide admixed with some 5β : 6β-epoxide. The former oxide with methylmagnesium iodide furnished 6β-methyl-17α-prop-1′-ynyl-5α-androstane-3β : 5α : 17β-triol (IV; R = Me) which passed into the 3-ketone (V; R = Me) on oxidation with chromium trioxide–pyridine. Treatment of this β-hydroxy-ketone with catalytic amounts of hydrochloric acid in hot ethanol led to dehydration and concomitant epimerisation of the 6β-methyl group (cf. ref. 5) with the formation of 17β-hydroxy-6α-methyl-17α-prop-1′-ynylandrost-4-en-3-one (6α : 21-dimethylethisterone) (VI; R = Me). The higher homologues (VI; R = Et and Pr) were similarly prepared from 17α-but-1′-ynyl- and 17α-pent-1′-ynylandrost-5-ene-3β : 17β-diol, respectively. A second convenient method of obtaining the intermediate triols (IV; R = Me, Et and Pr) involved condensing 17α-ethynyl-6β-methyl-5α-androstane-3β : 5α : 17β-triol [5] (IV; R = H) with 2 : 3-dihydropyran, alkylating the product at $C_{(21)}$ and subsequently removing the protecting groups.

Simple variations of the foregoing routes to 21-alkyl derivatives of 6α-methylethisterone were explored. Thus, 17α-ethynyl-5α : 17β-dihydroxy-6β-methyl-5α-androstan-3-one [5] (V; R = H) was transformed into its 3 : 3-ethylenedioxy-derivative, and the product, after reaction with 2 : 3-dihydropyran, treated with lithamide in liquid ammonia followed by ethyl iodide. Removal of the protecting groups furnished 17α-but-1′-ynyl-5α : 17β-dihydroxy-6β-methyl-5α-androstan-3-one (V; R = Et), from which 21-ethyl-6α-methylethisterone may be obtained (see above). In addition, the immediate precursor (V; R = Pr) of 6α-methyl-21-propylethisterone (VI; R = Pr) was prepared from 3 : 3-ethylenedioxy-17α-pent-1′-ynyl-17β-(tetrahydro-2-pyranyloxy)androst-5-ene (III; R = Pr, R′ = C_5H_9O) by conversion into the corresponding 5α : 6α-epoxide followed by reaction with methylmagnesium iodide and regeneration of the 3- and 17-oxygen functions. Finally, 21-methylation of 17α-ethynyl-6-methylandrost-5-ene-3β : 17β-diol [6] gave 6-methyl-17α-prop-1′-ynylandrost-5-ene-3β : 17β-diol which passed into 6α : 21-dimethylethisterone on Oppenauer oxidation.

Biological study of the foregoing ethisterone homologues revealed that 6α : 21-dimethylethisterone (VI; R = Me) is about twelve times as potent as ethisterone in the Clauberg assay.[3]

Experimental

Rotations were determined in a 1 dm. tube in chloroform unless otherwise stated. Ultraviolet absorption spectra (in ethanol) were kindly determined by Mr. M. T. Davies, B.Sc. B.D.H. alumina (chromatography grade) was used throughout.

17α-Ethynyl-3β : 17β-bis(tetrahydro-2-pyranyloxy)androst-5-ene (I; R = H, R′ = C_5H_9O).—17α-Ethynylandrost-5-ene-3β : 17β-diol (10 g.) in tetrahydrofuran (85 ml.) and 2 : 3-dihydropyran (25 ml.) was treated with phosphorus oxychloride (0·2 ml.). After 3 hr., the mixture was poured into water and the product collected, washed, and crystallised once from aqueous acetone containing 2 drops of pyridine. The *bis-ether* was obtained as a mixture of isomers, needles, m. p. 154—156°, repeated crystallisation of which gave material of m. p. 174°, $[\alpha]_D^{21}$ −120° (*c* 0·6) (Found: C, 77·2; H, 9·8. $C_{31}H_{46}O_4$ requires C, 77·1; H, 9·5%).

17α-Prop-1′-ynylandrost-5-ene-3β : 17β-diol (I; R = Me, R′ = H).—The foregoing compound (4·1 g.) in dry ether (165 ml.) was added during 1 hr. to a stirred solution of ferric nitrate

[5] Part V, *J.*, 1957, 4099.
[6] Part VI, *J.*, 1957, 4105.

(200 mg.) and lithium (0·45 g.) in freshly redistilled liquid ammonia (100 ml.) maintained between −40° and −35°. After a further 2½ hours stirring, methyl iodide (11 ml.) in dry ether (50 ml.) was added in 30 min. and the stirring continued for a further 3 hr. Ammonium chloride (4 g.) was added, the ammonia allowed to evaporate, and the product, isolated with ether, heated under reflux for 30 min. with toluene-*p*-sulphonic acid (0·6 g.) in ethanol (60 ml.). The solid obtained on the addition of water was purified from aqueous methanol to give 17α-*prop*-1′-*ynyl-androst*-5-*ene*-3β : 17β-*diol*, needles, m. p. 179—181°, $[\alpha]_D^{21}$ −121° (*c* 0·98) (Found: C, 76·4; H, 9·7. $C_{22}H_{32}O_2,H_2O$ requires C, 76·3; H, 9·9%). The compound was dried *in vacuo* at 100°, the m. p. remaining unchanged (Found: C, 79·9; H, 9·7. $C_{22}H_{32}O_2$ requires C, 80·4; H, 9·8%). Acetylation in pyridine (18 hr. at 20°) gave the 3β-*monoacetate*, plates (from aqueous ethanol), m. p. 201—202°, $[\alpha]_D^{23}$ −118° (*c* 0·68) (Found: C, 77·6; H, 9·2. $C_{24}H_{34}O_3$ requires C, 77·8; H, 9·25%).

17α-*But*-1′-*ynylandrost*-5-*ene*-3β : 17β-*diol* (I; R = Et, R′ = H), prepared similarly, formed needles (from acetone–hexane), m. p. 78—81°, $[\alpha]_D^{24}$ −121° (*c* 0·83) (Found: C, 81·0; H, 10·2. $C_{23}H_{34}O_2$ requires C, 80·7; H, 9·9%). The 3β-*monoacetate* formed needles (from acetone–hexane), m. p. 134—135°, $[\alpha]_D^{21}$ −116° (*c* 0·67) (Found: C, 77·7; H, 9·3. $C_{25}H_{36}O_3$ requires C, 78·1; H, 9·4%).

17α-*Pent*-1′-*ynylandrost*-5-*ene*-3β : 17β-*diol* (I; R = Pr, R′ = H) formed needles (from acetone–hexane), m. p. 70—71°, $[\alpha]_D^{23}$ −120° (*c* 0·97) (Found: C, 80·5; H, 10·5. $C_{24}H_{36}O_2$ requires C, 80·8; H, 10·2%). The 3β-*monoacetate* formed needles (from ether–light petroleum), m. p. 98—101°, $[\alpha]_D^{20}$ −112° (*c* 1·0) (Found: C, 78·2; H, 9·9. $C_{26}H_{38}O_3$ requires C, 78·3; H, 9·6%).

17α-*Dec*-1′-*ynylandrost*-5-*ene*-3β : 17β-*diol* (I; R = octyl, R′ = H) formed crystals (from acetone–hexane), m. p. 117°, $[\alpha]_D^{21}$ −107° (*c* 0·97) (Found: C, 81·4; H, 10·5. $C_{29}H_{46}O_2$ requires C, 81·6; H, 10·9%).

3 : 3-*Ethylenedioxy*-17α-*ethynylandrost*-5-*en*-17β-*ol* (III; R = R′ = H).—17α-Ethynyl-17β-hydroxyandrost-4-en-3-one (10 g.) and toluene-*p*-sulphonic acid (200 mg.) in benzene (220 ml.) and ethylene glycol (12 ml.) were heated under reflux for 4 hr. in an apparatus fitted with a water-separator. The product crystallised on cooling, and was purified from aqueous pyridine to give the ketal, plates, m. p. 258—259°, $[\alpha]_D^{25}$ −69° (*c* 0·75 in pyridine) (Found: C, 77·35; H, 9·2. Calc. for $C_{22}H_{32}O_3$: C, 77·5; H, 9·05%) (lit.,[4] m. p. 252—254°, $[\alpha]_D$ −90°).

3 : 3-*Ethylenedioxy*-17α-*ethynyl*-17β-(*tetrahydro*-2-*pyranyloxy*)*androst*-5-*ene* (III; R = H, R′ = C_5H_9O).—The foregoing ketal (3·8 g.) in dry tetrahydrofuran (200 ml.) and 2 : 3-dihydropyran (10 ml.) was treated with phosphorus oxychloride (0·08 ml.). After 2½ hr., the mixture was poured into a large volume of dilute aqueous sodium hydrogen carbonate, and the precipitate collected and crystallised once from aqueous acetone to which a few drops of pyridine had been added. The ketal-ether separated as an intimate mixture of blades and needles, m. p. 170—174°, $[\alpha]_D^{23}$ −92° (*c* 0·76 in pyridine) (Found: C, 76·6; H, 8·7. $C_{28}H_{40}O_4$ requires C, 76·3; H, 9·15%), which on fractionation gave *isomer A*, blades, m. p. 184—186°, $[\alpha]_D^{24}$ −107·5° (*c* 1·07 in pyridine) (Found: C, 76·8; H, 8·9%), and a minor proportion of *isomer B*, needles, m. p. 144—145°, $[\alpha]_D^{22}$ −54° (*c*, 0·73 in pyridine) (Found: C, 76·4; H, 8·85%).

17β-*Hydroxy*-17α-*prop*-1′-*ynylandrost*-4-*en*-3-*one* (II; R = Me).—(*a*) A solution of 17α-prop-1′-ynylandrost-5-ene-3β : 17β-diol (1·2 g.) in toluene (100 ml.) and *cyclo*hexanone (40 ml.) was distilled until the distillate became clear. After the addition of aluminium *iso*propoxide (5 g.) in toluene (15 ml.), the mixture was refluxed for 1 hr., cooled, and washed with dilute sulphuric acid, and the solvents were removed in steam. The product, isolated with ether, was purified by passage of its benzene solution through a short column of alumina. Crystallisation from acetone–hexane gave 17β-*hydroxy*-17α-*prop*-1′-*ynylandrost*-4-*en*-3-*one*, needles, m. p. 151—152°, $[\alpha]_D^{25}$ +11° (*c* 0·53 in ethanol), $\lambda_{max.}$ 240 mμ (log ε 4·2) (Found: C, 80·4; H, 9·3. $C_{22}H_{30}O_2$ requires C, 80·9; H, 9·3%).

(*b*) The product (III; R = H, R′ = C_5H_9O) (4 g.; mixed isomers) in tetrahydrofuran (100 ml.) was added dropwise in 1 hr. to a stirred solution of ferric nitrate (0·2 g.) and lithium (1·55 g.) in liquid ammonia (400 ml.) at −40° to −35°. After this had been stirred for a further 2½ hr., a solution of methyl iodide (11 ml.) in ether (50 ml.) was added during 30 min., and the stirring continued for a further 3 hr. Ammonium chloride (5 g.) was added, the ammonia allowed to evaporate, and the product isolated with ether. Its solution in ethanol (200 ml.) was treated with 2% aqueous oxalic acid (100 ml.), and the mixture refluxed for 45 min. Dilution with water gave a solid which crystallised from acetone–hexane in needles, m. p. 151—152°, not depressed in admixture with a sample prepared by method (*a*) above.

17α-*But*-1′-*ynyl*-17β-*hydroxyandrost*-4-*en*-3-*one* (II; R = Et).—(*a*) 17α-But-1′-ynylandrost-5-ene-3β : 17β-diol was oxidised by the Oppenauer method (see previous preparation), and the product chromatographed on alumina. Elution with benzene gave 17α-*but*-1′-*ynyl*-17β-*hydroxyandrost*-4-*en*-3-*one*, plates (from acetone–hexane), m. p. 118—120°, $[\alpha]_D^{23}$ +12° (*c* 0·74 in ethanol), $\lambda_{max.}$ 240·5 mμ (log ε 4·2) (Found: C, 80·6; H, 9·8. $C_{23}H_{32}O_2$ requires C, 81·1; H, 9·5%).

(*b*) The product (III; R = H, R′ = C_5H_9O) was treated with lithamide and then with ethyl iodide under conditions similar to those described above, to give 17α-*but*-1′-*ynyl*-3 : 3-*ethylenedioxy*-17β-(*tetrahydro*-2-*pyranyloxy*)*androst*-5-*ene* (III; R = Et, R′ = C_5H_9O), needles (from acetone containing a trace of pyridine), m. p. 120—121°, $[\alpha]_D$ −125·5° (*c* 0·97) (Found: C, 76·4; H, 9·4. $C_{30}H_{44}O_4$ required C, 76·9; H, 9·5%). Treatment with hot aqueous-ethanolic oxalic acid, as described above, then gave 17α-but-1′-ynyl-17β-hydroxyandrost-4-en-3-one, plates (from acetone–hexane), m. p. 118—120°, not depressed in admixture with a sample prepared by method (*a*).

17β-*Hydroxy*-17α-*pent*-1′-*ynylandrost*-4-*en*-3-*one* (II; R = Pr),, prepared by (*a*) Oppenauer oxidation of the diol (I; R = Pr, R′ = H) and (*b*) propylation of the product (III; R = H, R′ = C_5H_9O) to give the *derivative* (III; R = Pr, R′ = C_5H_9O), m. p. 104—106°, $[\alpha]_D^{25}$ −136° (*c* 1·07) (Found: C, 77·5; H, 9·55. $C_{31}H_{46}O_4$ requires C, 77·1; H, 9·6%) followed by treatment with aqueous-ethanolic oxalic acid, separated in prisms (from acetone–hexane), m. p. 86—87°, $[\alpha]_D^{23}$ +8° (*c* 0·72 in ethanol), $\lambda_{max.}$ 241 mμ (log ε 4·2) (Found: C, 81·1; H, 9·4. $C_{24}H_{34}O_2$ requires C, 81·3; H, 9·7%).

17α-*Hex*-1′-*ynyl*-17β-*hydroxyandrost*-4-*en*-3-*one* (II; R = Bu), prepared by butylation of the product (III; R = H, R′ = C_5H_9O) followed by removal of the protecting groupings, separated from ether–light petroleum in prisms, m. p. 80—81°, $[\alpha]_D^{21}$ +2° (*c* 1·0 in ethanol), $\lambda_{max.}$ 241 mμ (log ε 4·2) (Found: C, 81·6; H, 10·0. $C_{25}H_{36}O_2$ requires C, 81·5; H, 9·85%). The 2 : 4-*dinitrophenylhydrazone* formed needles (from chloroform–ethanol), m. p. 156—158° (Found: C, 67·8; H, 7·0; N, 10·2. $C_{31}H_{40}O_5N_4$ requires C, 67·9; H, 7·35; N, 10·2%).

17α-*Dec*-1′-*ynyl*-17β-*hydroxyandrost*-4-*en*-3-*one* (II; R = octyl), prepared by Oppenauer oxidation of the diol (I; R = octyl, R′ = H), separated from acetone–hexane in needles, m. p. 97—99°, $[\alpha]_D^{20}$ +9° (*c* 1·05), $\lambda_{max.}$ 241 mμ (log ε 4·17) (Found: C, 81·6; H, 10·5. $C_{29}H_{44}O_2$ requires C, 82·0; H, 10·4%).

Epoxides derived from 17α-*Prop*-1′-*ynylandrost*-5-*ene*-3β : 17β-*diol*.—The diol (I; R = Me, R′ = H) (10 g.) in tetrahydrofuran (150 ml.) was treated with monoperphthalic acid (10 g.) in ether (120 ml.), and the mixture kept overnight and then poured into 1% aqueous sodium hydroxide (1·5 l.). Most of the ether was removed by aeration, and the solids were collected, washed, and fractionated from aqueous ethanol. The 5α : 6α-*epoxide* formed needles, m. p. 200—201°, $[\alpha]_D^{24}$ −121° (*c* 0·98) (Found: C, 73·3; H, 9·4. $C_{22}H_{32}O_3,H_2O$ requires C, 72·9; H, 9·45%). The anhydrous *material* (Found: C, 76·7; H, 9·4. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·4%) was obtained after drying *in vacuo* at 140°. The 5β : 6β-*epoxide* separated in plates, m. p. between 180° and 200° depending upon the rate of heating, $[\alpha]_D^{22}$ −58° (*c* 0·78) (Found: C, 72·7; H, 9·0. $C_{22}H_{32}O_3,H_2O$ requires C, 72·9; H, 9·45%). The anhydrous *material* (Found: C, 76·9; H, 9·6%) was obtained after drying *in vacuo* at 140°.

3β-*Acetoxy*-5α : 6α-*epoxy*-17α-*prop*-1′-*ynyl*-5α-*androstan*-17β-*ol* separated from chloroform–methanol in prisms, m. p. 245—247°, $[\alpha]_D^{23}$ −110° (*c* 1·0) (Found: C, 74·2; H, 8·9. $C_{24}H_{34}O_4$ requires C, 74·6; H, 8·9%).

3β-*Acetoxy*-5β : 6β-*epoxy*-17α-*prop*-1′-*ynyl*-5α-*androstan*-17β-*ol* formed needles (from aqueous ethanol), m. p. 192—193°, $[\alpha]_D^{22}$ −74° (*c* 1·02) (Found: C, 74·1; H, 8·9%).

5α : 6α-*Epoxy*-3β-*propionoxy*-17α-*prop*-1′-*ynyl*-5α-*androstan*-17β-*ol* crystallised from aqueous methanol in needles, m. p. 206—207°, $[\alpha]_D^{21}$ −104° (*c* 0·9) (Found: C, 74·8; H, 9·1. $C_{25}H_{36}O_4$ requires C, 75·0; H, 9·1%).

5β : 6β-*Epoxy*-3β-*propionoxy*-17α-*prop*-1′-*ynyl*-5α-*androstan*-17β-*ol* separated from aqueous methanol in needles, m. p. 158—160°, $[\alpha]_D^{24}$ −52° (*c* 1·16) (Found: C, 74·8; H, 8·85%).

17α-*But*-1′-*ynyl*-5α : 6α-*epoxy*-5α-*androstane*-3β : 17β-*diol*, obtained by oxidation of the diol (I; R = Et, R′ = H) with monoperphthalic acid in ether–chloroform, separated from acetone–hexane in needles, m. p. 121—123°, $[\alpha]_D^{24}$ −116° (*c* 0·55) (Found: C, 76·6; H, 9·9. $C_{23}H_{34}O_3$ requires C, 77·05; H, 9·6%).

5α : 6α-*Epoxy*-17α-*pent*-1′-*ynyl*-5α-*androstane*-3β : 17β-*diol*, obtained from the diol (I; R = Pr, R′ = H), crystallised from acetone–hexane in needles, m. p. 147—148°, $[\alpha]_D^{22}$ −93° (*c* 1·03) (Found: C, 77·3; H, 10·1. $C_{24}H_{36}O_3$ requires C, 77·4; H, 9·7%).

6β-*Methyl*-17α-*prop*-1′-*ynyl*-5α-*androstane*-3β : 5α : 17β-*triol* (IV; R = Me).—(*a*) 5α : 6α-Epoxy-3β-propionoxy-17α-prop-1′-ynyl-5α-androstan-17β-ol (5 g.) in benzene (150 ml.) was added to a reagent prepared from magnesium (3·4 g.), methyl iodide (10 ml.), and ether (45 ml.). The mixture was stirred, and some solvent (70 ml.) removed by distillation. After being heated under reflux for 5 hr., the mixture was cooled and acidified with dilute hydrochloric acid, and the organic layer washed neutral. Removal of the solvent gave a solid which was purified from ethyl acetate and then from aqueous ethanol. The *triol* formed needles, m. p. 219—221°, $[\alpha]_D^{21}$ −63° (*c* 0·88) (Found: C, 76·7; H, 9·9. $C_{23}H_{36}O_3$ requires C, 76·6; H, 10·1%). The compound frequently separated in a solvated (? hydrated) form and melted (with effervescence) anywhere between 140° and 200°. The 3β-*monoacetate* separated from acetone–hexane in blades, m. p. 185—187°, $[\alpha]_D^{20}$ −57° (*c*, 0·91) (Found: C, 75·1; H, 9·6. $C_{25}H_{38}O_4$ requires C, 74·6; H, 9·5%.

(*b*) Phosphorus oxychloride (0·8 ml.) was added to a stirred suspension of 17α-ethynyl-6β-methyl-5α-androstane-3β : 5α : 17β-triol (12 g.) in dry ether (400 ml.) and 2 : 3-dihydropyran (12 ml.). Dissolution was complete in 30 min. The mixture was set aside overnight, then washed with aqueous sodium hydrogen carbonate and water and dried ($CaCl_2$ for several hours), and the solvent was removed *in vacuo*. The product, a sticky solid, was used without further purification.

Ferric nitrate (0·4 g.) and lithium (2·4 g.) were added to liquid ammonia (400 ml.) at −30° to −40°, and the mixture stirred for 30 min. The foregoing sticky solid (10 g.) in a mixture of tetrahydrofuran (20 ml.) and ether (80 ml.) was added during 45 min., and, after a further 2½ hours' stirring, methyl iodide (21 ml.) in ether (100 ml.) was added during 30 min. Stirring was continued for a further 3 hr., ammonium chloride (20 g.) was added, and the ammonia allowed to evaporate. The product was isolated with ether and heated under reflux for 1 hr. with oxalic acid (10 g.) in methanol (100 ml.) and water (10 ml.). Concentration gave crystals which were purified from aqueous ethanol. The triol formed needles, identical with a specimen prepared by method (*a*) above.

17α-*But*-1′-*ynyl*-6β-*methyl*-5α-*androstane*-3β : 5α : 17β-*triol* (IV; R = Et), prepared from 17α-but-1′-ynyl-5α : 6α-epoxy-5α-androstane-3β : 17β-diol by method (*a*) above, and from 17α-ethynyl-6β-methyl-5α-androstane-3β : 5α : 17β-triol by method (*b*) above, crystallised from acetone–hexane in dimorphic forms, m. p. 110—112° and 168—170°, respectively, $[\alpha]_D$ −53° (*c* 0·72) (Found: C, 73·2; H, 10·1. $C_{24}H_{38}O_3,H_2O$ requires C, 73·4; H, 10·3%). The anhydrous *triol* (Found: C, 77·5; H, 10·0. $C_{24}H_{38}O_3$ requires C, 77·0; H, 10·2%) was obtained after drying for several days *in vacuo* at 50°. The 3β-*monoacetate* crystallised from aqueous methanol in needles, m. p. 191—193°, $[\alpha]_D^{22}$ −63° (*c* 0·91) (Found: C, 74·2; H, 9·4. $C_{26}H_{40}O_4$ requires C, 74·9; H, 9·7%).

6β-*Methyl*-17α-*pent*-1′-*ynyl*-5α-*androstane*-3β : 5α : 17β-*triol* (IV; R = Pr), prepared by methods (*a*) and (*b*) above, crystallised from acetone–hexane in dimorphic forms, m. p. 92—94° and 177—179°, $[\alpha]_D^{22}$ −47° (*c* 0·82) (Found: C, 75·7; H, 10·2. $C_{25}H_{40}O_3,\frac{1}{2}H_2O$ requires C, 75·5; H, 10·4%). Satisfactory analyses for anhydrous material could not be obtained even after drying for several days *in vacuo*. Similar difficulties in analogous series have been reported.[7] The 3β-*monoacetate* crystallised from aqueous methanol in prisms, m. p. 189—191°, $[\alpha]_D$ −56° (*c* 0·79) (Found: C, 75·1; H, 9·6. $C_{27}H_{42}O_4$ requires C, 75·3; H, 9·8%).

5α : 17β-*Hydroxy*-6β-*methyl*-17α-*prop*-1′-*ynyl*-5α-*androstan*-3-*one* (V; R = Me).—The triol (IV; R = Me) (3·4 g.) in pyridine (35 ml.) was added to the complex prepared from chromium trioxide (3 g.) and pyridine (30 ml.), and the mixture kept overnight at room temperature. Benzene (250 ml.) was added, insoluble material removed, and the filtrate washed successively with water, dilute hydrochloric acid, water, dilute aqueous sodium carbonate, and water. Removal of the solvent gave a solid which crystallised from acetone–hexane. The *ketone* formed needles, m. p. 248—250° (decomp.), $[\alpha]_D^{25}$ −45° (*c* 0·82) (Found: C, 76·8; H, 9·5. $C_{23}H_{34}O_3$ requires C, 77·1; H, 9·6%).

17α-*But*-1′-*ynyl*-5α : 17β-*dihydroxy*-6β-*methyl*-5α-*androstan*-3-*one* (V; R = Et), prepared by similar oxidation of the triol (IV; R = Et), crystallised from aqueous methanol in needles, m. p. 225—227° (decomp.), $[\alpha]_D^{18}$ −44·5° (*c* 0·89) (Found: C, 77·6; H, 9·7. $C_{24}H_{36}O_3$ requires C, 77·4; H, 9·7%).

5α : 17β-*Dihydroxy*-6β-*methyl*-17α-*pent*-1′-*ynyl*-5α-*androstan*-3-*one* (V; R = Pr), obtained by oxidation of the triol (V; R = Pr), separated from aqueous methanol in flakes, m. p. 180—182°, $[\alpha]_D^{20}$ −41° (*c* 0·78) (Found: C, 77·1; H, 9·8. $C_{25}H_{38}O_3$ requires C, 77·7; H, 9·9%).

[7] Ushakow and Madaeva, *J. Gen. Chem., U.S.S.R.*, 1939, **9**, 436; Ringold, Batres, and Rosenkranz, *J. Org. Chem.*, 1957, **22**, 99; Campbell, Babcock, and Hogg, *J. Amer. Chem. Soc.*, 1958, **80**, 4717.

17β-*Hydroxy*-6α-*methyl*-17α-*prop*-1′-*ynylandrost*-4-*en*-3-*one* (VI; R = Me).—A solution of the ketone (V; R = Me) (1·5 g.) in ethanol (45 ml.), to which 4 drops of concentrated hydrochloric acid had been added, was heated under reflux for 1 hr. The mixture was carefully diluted with water and kept overnight at 0° to give a solid which crystallised from aqueous methanol. 17β-*Hydroxy*-6α-*methyl*-17α-*prop*-1′-*ynylandrost*-4-*en*-3-*one* formed plates, m. p. 99—102°, $[\alpha]_D^{24}$ +12° (*c* 1·0), $\lambda_{max.}$ 241 mμ (log ε 4·16) (Found: C, 77·2; H, 9·6. $C_{23}H_{32}O_2,H_2O$ requires C, 77·1; H, 9·6%). The anhydrous *ketone* (Found: C, 80·7; H, 9·4. $C_{23}H_{32}O_2$ requires C, 81·1; H, 9·5%) was obtained after drying over P_2O_5 for 24 hr. at 50°/1 mm. It was hygroscopic.

17α-*But*-1′-*ynyl*-17β-*hydroxy*-6α-*methylandrost*-4-*en*-3-*one* (VI; R = Et), obtained from the ketone (V; R = Et) by the foregoing procedure, crystallised from aqueous methanol in blades, m. p. 74—76°, $[\alpha]_D^{22}$ +17° (*c* 1·02), $\lambda_{max.}$ 241 mμ (log ε 4·16) (Found: C, 77·7; H, 9·95. $C_{24}H_{34}O_2,H_2O$ requires C, 77·35; H, 9·75%). The anhydrous *ketone* (Found: C, 80·8; H, 10·1. $C_{24}H_{34}O_2$ requires C, 81·3; H, 9·7%) was obtained after drying *in vacuo* at 55°.

17β-*Hydroxy*-6α-*methyl*-17α-*pent*-1′-*ynylandrost*-4-*en*-3-*one* (VI; R = Pr), obtained from the ketone (V; R = Pr), crystallised from aqueous methanol in needles, m. p. 83—87°, $[\alpha]_D^{18}$ +10·8° (*c* 0·57), $\lambda_{max.}$ 240·5 mμ (log ε 4·13) (Found: C, 80·4; H, 9·9. $C_{25}H_{36}O_2$ requires C, 81·5; H, 9·85%). There was insufficient material for further purification.

3 : 3-*Ethylenedioxy*-17α-*ethynyl*-6β-*methyl*-5α-*androstane*-5α : 17β-*diol*, obtained by the method used for the preparation of the ketal (III; R = R′ = H), separated from aqueous methanol containing a trace of pyridine, in blades, m. p. 216—217°, $[\alpha]_D^{20}$ −64° (*c* 1·0) (Found: C, 73·9; H, 8·8. $C_{24}H_{36}O_4$ requires C, 74·0; H, 9·3%).

3 : 3-*Ethylenedioxy*-17α-*ethynyl*-6β-*methyl*-17β-(*tetrahydro*-2-*pyranyloxy*)-5α-*androstan*-5α-*ol* crystallised from aqueous acetone containing a trace of pyridine, in plates, m. p. 157—158°, $[\alpha]_D^{21}$ −66° (*c* 0·98) (Found: C, 73·6; H, 9·1. $C_{29}H_{44}O_5$ requires C, 73·7; H, 9·4%). Ethylation in liquid ammonia followed by treatment of the product with hot aqueous ethanolic oxalic acid gave 17α-but-1′-ynyl-5α : 17β-dihydroxy-6β-methyl-5α-androstan-3-one (V; R = Et), identified by mixed m. p. determination and by conversion into 17α-but-1′-ynyl-17β-hydroxy-6α-methyl-5α-androst-4-en-3-one (VI; R = Et).

5α : 17β-*Dihydroxy*-6β-*methyl*-17α-*pent*-1′-*ynyl*-5α-*androstan*-3-*one* (V; R = Pr).—The ketal (III; R = Pr, R′ = C_5H_9O) (2·6 g.) in chloroform (75 ml.) was treated for 18 hr. at 0° with monoperphthalic acid (1·7 g.) in ether (30 ml.). The wax-like product in ether (35 ml.) was added to the reagent prepared from magnesium (2·4 g.), methyl iodide (7 ml.), and ether (50 ml.), and the mixture was stirred at room temperature for 7 hr. and then set aside overnight. The product, isolated with ether as a yellow gum, was heated under reflux ror 1 hr. with oxalic acid (1·4 g.) in ethanol (100 ml.) and water (50 ml.). The product in benzene was chromatographed on alumina to give the ketone, identical with a specimen prepared by an alternative route (above).

17α-*Ethynyl*-6-*methyl*-3β : 17β-*bis*(*tetrahydro*-2-*pyranyloxy*)*androst*-5-*ene* crystallised from acetone containing a trace of pyridine, in needles, m. p. 178—180°, $[\alpha]_D^{20}$ −122° (*c* 0·45) (Found: C, 77·0; H, 9·5. $C_{32}H_{48}O_4$ requires C, 77·4; H, 9·7%).

6-*Methyl*-17α-*prop*-1′-*ynylandrost*-5-*ene*-3β : 17β-*diol*.—The foregoing compound was methylated, to give material which crystallised from acetone in needles, m. p. 161°. Treatment of this substance with hot aqueous ethanolic oxalic acid gave the *diol*, needles (from acetone–hexane), m. p. 111—112° or 135—137°, $[\alpha]_D^{20}$ −103° (*c* 0·6) (Found: C, 81·0; H, 10·1. $C_{22}H_{34}O_2$ requires C, 80·65; H, 10·0%).

17β-*Hydroxy*-6α-*methyl*-17α-*prop*-1′-*ynylandrost*-4-*en*-3-*one* (VI; R = Me) (with Mr. M. Stansfield, A.R.I.C.).—A solution of the foregoing diol (1 g.) in toluene (75 ml.) and *cyclo*hexanone (15 ml.) was distilled until the distillate became clear. Aluminium *iso*propoxide (1 g.) in toluene (15 ml.) was then added, and the mixture heated under reflux for 2 hr. After addition of concentrated aqueous Rochelle salt, the mixture was steam-distilled for several hours, and the product isolated with ether. Crystallisation from aqueous methanol gave plates of 17β-hydroxy-6α-methyl-17α-prop-1′-ynylandrost-4-en-3-one, identical in every respect with a sample prepared by the previously described route.

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