523. *Modified Steroid Hormones. Part XVI.* The Preparation of Some 6-Ethynyl-steroids.*

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3β-Acetoxy-6-oxo-steroids (I) and their 5α-hydroxy-derivatives (VI) have been converted into unsaturated 6-ethynyl derivatives (III) and (XI) [or (XIII)], respectively.

6-Oxo-3,5-cyclo-steroids (IV) passed smoothly into 6ξ-ethynyl-6ξ-hydroxy-derivatives (V), but rearrangement into a 3β-acetoxy-Δ^5-steroid was accompanied by hydration of the acetylenic group and formation of a 3β-acetoxy-6-acetyl-Δ^5-steroid of type (III).

Exploratory studies carried out intermittently during 1956—58 into the preparation of 6-ethynyl-steroids are reported herein.

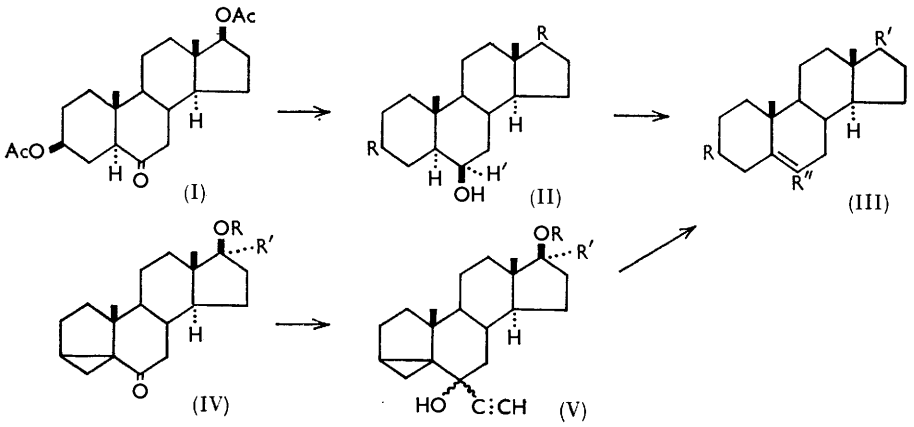
Reaction of 3β,17β-diacetoxyandrostan-6-one [1] (I) with ethynylmagnesium bromide, followed by acetylation of the product, furnished 3β,17β-diacetoxy-6α-ethynylandrostan-6β-ol (II; R = OAc, ··· H; R′ = C:CH) in low yield. The configuration of the hydroxyl and the ethynyl group at position 6 is assumed by analogy with the formation of 6β-hydroxy-6α-methyl derivatives from 6-oxo-steroids such as (I) and methylmagnesium halide.[2] The same compound (II) was later obtained in much greater yield by using lithium acetylide [3] in place of the Grignard reagent. On treatment with thionyl chloride in pyridine the foregoing diacetate passed smoothly into 3β,17β-diacetoxy-6-ethynylandrost-5-ene (III; R = R′ = OAc, ··· H; R″ = C:CH) which was strongly dextrorotatory and had $\lambda_{max.}$ 232 mμ (ε 14,000). With methanolic potassium carbonate it furnished the unsaturated diol (III; R = R′ = OH, ··· H; R″ = C:CH), which passed on oxidation with chromic acid–pyridine [4] into 6-ethynyl-3β-hydroxyandrost-5-en-17-one (III; R = OH, ··· H; R′ = :O; R″ = C:CH), characterised as the 3-acetate. Alkaline hydrolysis of the parent diacetate (II) to the corresponding diol, followed by oxidation with chromic acid–pyridine, gave the diketone (II; R = :O, R′ = C:CH). In contrast to the parent diacetate (II; R = OAc, ··· H; R′ = C:CH), however, the last compound failed to dehydrate normally with Darzens's reagent, the non-crystalline product obtained showing only very low ultraviolet absorption at 232 mμ.

The foregoing ethynylation was extended to 17β-acetoxy-3,5-cycloandrostan-6-one [5] (IV; R = Ac, R′ = H). In this case, however, ethynylmagnesium bromide [6] proved superior to lithium acetylide by furnishing a higher yield of a product regarded as 17β-acetoxy-6ξ-ethynyl-3,5-cycloandrostan-6ξ-ol (V; R = Ac, R′ = H). Rearrangement of this cyclo-steroid with acetic acid–sulphuric acid led unexpectedly to a product,

* Part XV, *J.*, 1960, 2389.

[1] Grenville, Patel, Petrow, Stuart-Webb, and Williamson, *J.*, 1957, 4105.
[2] Fieser and Rigaudy, *J. Amer. Chem. Soc.*, 1951, **73**, 4660; Fried, Arth, and Sarett, *ibid.*, 1959, **81**, 1235; see, however, Sneen, *ibid.*, 1958, **80**, 3971, 3982.
[3] Cf. Inhoffen and Weissermel, *Chem. Ber.*, 1954, **87**, 187.
[4] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.
[5] Butenandt and Suránvi, *Ber.*, 1942, **75**, 591.
[6] Jones, Skatteböl, and Whiting, *J.*, 1956, 4765.

$C_{25}H_{36}O_5$, possessing an αβ-unsaturated ketonic residue [$\lambda_{max.}$ 243 mμ (ε 3200)] and lacking an ethynyl group (infrared data). This product is regarded as 3β,17β-diacetoxy-6-acetylandrost-5-ene (III; R = R′ = OAc, • • • H; R″ = COMe), a formulation supported by its conversion on modified Wolff–Kishner reduction [7] into 3β,17β-diacetoxy-6-ethylandrost-5-ene (III; R = R′ = OAc, • • • H; R″ = Et). The structure of the last



compound was established by its independent preparation from 3β,17β-diacetoxyandrostan-6-one (I); this was treated with ethylmagnesium bromide and the product acetylated, to give 3β,17β-diacetoxy-6α-ethylandrostan-6β-ol (II; R = OAc, • • • H; R′ = Et), which passed into the foregoing 6-ethyl derivative on dehydration with thionyl chloride and pyridine.

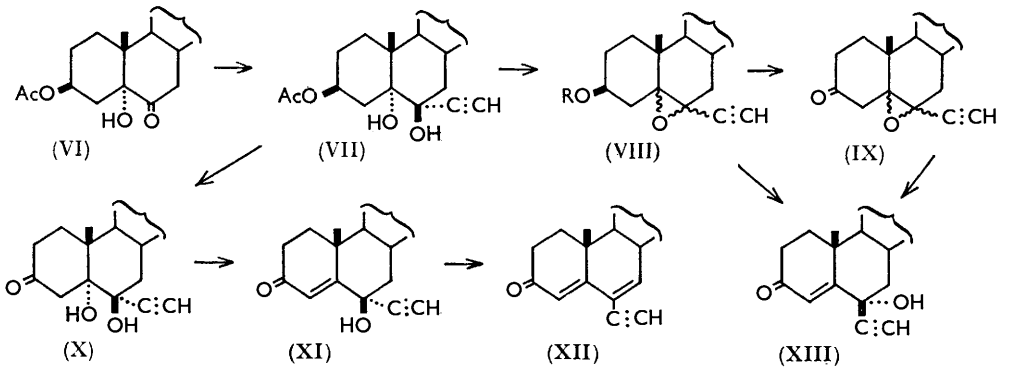
A Grignard reaction between 17α-ethynyl-17β-hydroxy-3,5-cycloandrostan-6-one [1] (IV; R = H, R′ = C:CH) and ethynylmagnesium bromide similarly afforded 6ξ,17α-diethynyl-3,5-cycloandrostane-6ξ,17β-diol (V; R = H, R′ = C:CH), which was not isolated but was directly rearranged with acetic and sulphuric acid to 3β-acetoxy-6-acetyl-17α-ethynylandrost-5-en-17β-ol (III; R = OAc, • • • H; R′ =OH, • • • C:H; R″ = COMe). The stability of the 17α-ethynyl-17β-hydroxy-system to the acidic rearrangement conditions employed has been previously established.[1]

Further studies involved ethynylation of 3β-acetoxy-5α-hydroxycholestan-6-one [8] (VIa) with lithium acetylide, followed by acetylation of the product: 3β-acetoxy-6α-ethynylcholestane-5α,6β-diol (VIIa) was obtained in moderate yield. The configuration assigned to the groups at position 6 follows from the presently described transformation of the compound. Its attempted dehydration to a 4,6-diene by thionyl chloride in pyridine surprisingly furnished a product, $C_{31}H_{48}O_3$, which is formulated as 3β-acetoxy-5ξ,6ξ-epoxy-6ξ-ethynylcholestane (VIIIa; R = Ac) on the basis of (i) the absence from its spectrum of significant ultraviolet absorption above 220 mμ, (ii) its failure to give a colour with trichloroacetic acid, and (iii) its infrared spectrum which revealed the presence of acetoxyl and ethynyl groups and the absence of hydroxyl or oxo-functions. This structure (VIIIa; R = Ac) is supported by the observation that hot aqueous-acetonic periodic acid [9] effected fission of the epoxide ring, albeit in low yield, with regeneration of the parent diol (VIIa). This result is additionally significant in that it provides evidence for the configuration of the groups attached to $C_{(6)}$ in the diol (VIIa). Hydrolysis of 5,6-epoxides is known to result in the formation of *trans*-diaxial diols.[10] As the 5-hydroxyl group is already

[7] Huang-Minlon, *J. Amer. Chem. Soc.*, 1949, **71**, 3301.
[8] (*a*) Pickard and Yates, *J.*, 1908, **93**, 1678: (*b*) Fieser and Rajagopalan, *J. Amer. Chem. Soc.*, 1949, **71**, 3938.
[9] Cf. ref. 8 (*b*).
[10] Cf. Barton, *J.*, 1953, 1027.

known to have the α-configuration, it follows that the 6-hydroxyl group must be β-oriented as shown in (VIIa).

Saponification of the triol monoacetate (VIIa), followed by oxidation of the product with chromium trioxide–pyridine, furnished 5α,6β-dihydroxy-6α-ethynylcholestan-3-one



("a" series: cholestane; "b" series: 17β-hydroxy-17α-methylandrostane)

(Xa) (characterised as the oxime). On treatment with hot methanolic sodium hydroxide this suffered dehydration to yield 6α-ethynyl-6β-hydroxycholest-4-en-3-one (XIa) ($\lambda_{max.}$ 239 mμ, ε 12,500).

5ξ,6ξ-Epoxy-6ξ-ethynylcholestan-3β-ol (VIIIa; R = H), derived from its acetate by alkaline hydrolysis, was oxidised by chromium trioxide in sulphuric acid–acetone [11] to 5ξ,6ξ-epoxy-6ξ-ethynylcholestan-3-one (IXa), converted by cold methanolic potassium hydroxide into an αβ-unsaturated ketone ($\lambda_{max.}$ 239·5 mμ, ε 13,800), isomeric with the product (XIa); to this ketone the constitution of 6β-ethynyl-6α-hydroxycholest-4-en-3-one (XIIIa) is assigned. The same compound was obtained directly from the alcohol (VIIIa; R = H) by Oppenauer oxidation. Attempts to effect dehydration of either epimer (XIa or XIIIa) by heating it with 1% ethanolic hydrochloric acid proved unsuccessful. Elimination of the elements of water from the 6β-hydroxy-isomer (XIa) [but not from the 6α-hydroxy-steroid (XIIIa)] was eventually achieved by treating its solution in acetic acid–acetic anhydride with a catalytic quantity of perchloric acid, 6-ethynylcholesta-4,6-dien-3-one (XIIa) ($\lambda_{max.}$ 291 mμ, ε 18,600) being then obtained in low yield.

3β-Acetoxy-5α,17β-dihydroxy-17α-methylandrostan-6-one (VIb), prepared by oxidation of 3β-acetoxy-17α-methylandrostane-5α,6β,17β-triol,[12] was similarly converted by lithium acetylide into 3β-acetoxy-6α-ethynyl-17α-methylandrostane-5α,6β,17β-triol (VIIb). Saponification gave the corresponding tetrol which passed into 6α-ethynyl-5α,6β,17β-trihydroxy-17α-methylandrostan-3-one (Xb) on oxidation with chromium trioxide–pyridine. Treatment with methanolic alkali effected smooth dehydration to the required 6α-ethynyl-6β,17β-dihydroxy-17α-methylandrost-4-en-3-one (XIb) ($\lambda_{max.}$ 238 mμ, ε 12,200).

Experimental

Optical rotations were measured for chloroform solutions in a 1 dm. tube unless otherwise stated. Ultraviolet and infrared absorption spectra were kindly determined by Mr. M. T. Davies, B.Sc. B.D.H. chromatographic alumina was used.

3β,17β-Diacetoxy-6α-ethynylandrostan-6β-ol (II; R = OAc, • • • H; R′ = C:CH).—A solution of 3β,17β-diacetoxyandrostan-6-one [1] (2 g.) in dry dioxan (100 ml.) was added in 30 min. to a stirred solution of lithium acetylide (from 1 g. of lithium) in liquid ammonia (500 ml.) at −37°. Thereafter, the mixture was stirred for 5 hr. at −33°, cooled, and treated with ammonium chloride (10 g.), and the ammonia was allowed to evaporate overnight. The product,

[11] Cf. Djerassi, Engle, and Bowers, *J. Org. Chem.*, 1956, **21**, 1547 and references cited therein.
[12] Julia and Heusser, *Helv. Chim. Acta*, 1952, **35**, 2080.

isolated with methylene dichloride, was treated with acetic anhydride (10 ml.)–pyridine (10 ml.) for 18 hr. at room temperature, and the solid obtained by pouring the mixture into water was purified from acetone–hexane. 3β,17β-*Diacetoxy*-6α-*ethynylandrostan*-6β-*ol* separated in needles, m. p. 200°, $[\alpha]_D^{23}$ +12° (*c* 0·76) (Found: C, 70·5; H, 8·8. $C_{25}H_{36}O_5,\frac{1}{2}H_2O$ requires C, 70·5; H, 8·8%).

3β,17β-*Diacetoxy*-6-*ethynylandrost*-5-*ene* (III; R = R′ = OAc, ··· H; R″ = C:CH).—Purified thionyl chloride (1·5 ml.) was added dropwise in 5 min. to a stirred solution of the foregoing compound (2 g.) in pyridine (10 ml.) at 0°. After 20 min. at 0°, the mixture was poured on crushed ice, and the product isolated with ether. Crystallisation from methanol gave 3β,17β-*diacetoxy*-6-*ethynylandrost*-5-*ene*, pale yellow needles or prisms, m. p. 182—183° (decomp.), $[\alpha]_D^{20}$ −112° (*c* 0·34), $\lambda_{max.}$ 232 mμ (ε 14,000) in EtOH (Found: C, 74·9; H, 8·7. $C_{25}H_{34}O_4$ requires C, 75·3; H, 8·6%).

6-*Ethynyl*-3β,17β-*dihydroxyandrost*-5-*ene* (III; R = R′ = OH, ··· H; R″ = C:CH), formed by hydrolysis of the foregoing compound with aqueous-methanolic potassium carbonate (1 hr. under reflux), crystallised from acetone–hexane in needles, m. p. 212—213° (decomp.), $[\alpha]_D^{21}$ −94° (*c* 0·54) (Found: C, 80·5; H, 9·6. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%).

6-*Ethynyl*-3β-*hydroxyandrost*-5-*en*-17-*one* (III; R = OH, ··· H; R′ = :O, R″ = C:CH) (with Mrs. S. P. Hall, B.Sc.).—The foregoing diol (2·2 g.) in pyridine (22 ml.) was added to chromium trioxide (2·2 g.) in pyridine (22 ml.). The mixture was set aside for 18 hr., and the product isolated with benzene. Purification from methanol gave the *ketone* as needles, m. p. 185—187° (decomp.), $[\alpha]_D^{21}$ −22° (*c* 0·7), $\nu_{max.}$ 3590 (OH) and 1746 cm.$^{-1}$ (5-membered ring C=O) in CCl_4 (Found: C, 80·85; H, 9·0. $C_{21}H_{28}O_2$ requires C, 80·7; H, 9·3%). The 3β-*acetate* crystallised from acetone–hexane in blades, m. p. 155—157°, $[\alpha]_D^{22}$ −52° (*c* 0·86), $\nu_{max.}$ 1746 cm.$^{-1}$ in CCl_4 (Found: C, 77·7; H, 8·9. $C_{23}H_{30}O_3$ requires C, 77·9; H, 8·5%).

6α-*Ethynyl*-6β-*hydroxyandrostane*-3,17-*dione* (II; R = :O, R′ = C:CH).—A solution of 3β,17β-diacetoxy-6α-ethynylandrostan-6β-ol (0·82 g.) in methanol (25 ml.) and water (5 ml.) containing potassium carbonate (0·5 g.) was heated under reflux for 1 hr. The product was isolated by the addition of water, and separated (0·53 g.) from chloroform in needles, m. p. 255°. It was oxidised overnight with chromium trioxide (1 g.) in pyridine (10 ml.). The *product*, isolated with benzene, separated from acetone in plates, m. p. 255—257° (decomp.), $[\alpha]_D^{23}$ +85° (*c* 0·47) (Found: C, 76·4; H, 8·4. $C_{21}H_{28}O_3$ requires C, 76·8; H, 8·6%).

17β-*Acetoxy*-6ξ-*ethynyl*-3,5-*cycloandrostan*-6ξ-*ol* (V; R = Ac, R′ = H).—A suspension of ethynylmagnesium bromide was prepared by gradually adding a solution of ethylmagnesium bromide (from 1·66 g. of magnesium and 8·3 g. of ethyl bromide) in tetrahydrofuran (50 ml.) to a stirred solution of acetylene in tetrahydrofuran (50 ml.) through which a stream of purified acetylene was being passed.[6] The suspension was cooled to 0°, and 17β-acetoxy-3,5-cycloandrostan-6-one [5] (2·3 g.) in tetrahydrofuran (25 ml.) was added. The mixture was allowed to reach room temperature, stirred for 4½ hr., then set aside overnight. An excess of saturated aqueous ammonium chloride was carefully added, with stirring, the organic layer was separated, and the aqueous phase extracted with chloroform. The combined organic phases were washed with aqueous ammonium chloride and dried, the solvents were removed, and the residue was acetylated in pyridine for 18 hr. at room temperature. A solution of the product in benzene was passed through a short column of alumina (15 g.) to give a solid which crystallised from hexane. 17α-*Acetoxy*-6ξ-*ethynyl*-3,5-*cycloandrostan*-6ξ-*ol* separated in needles, m. p. 124° $[\alpha]_D^{24}$ +35° (*c* 0·55) (Found: C, 77·6; H, 9·0. $C_{23}H_{32}O_3$ requires C, 77·5; H, 9·05%). The compound showed no significant ultraviolet absorption and failed to give a colour with tetranitromethane. The infrared spectrum indicated the presence of ethynyl, hydroxyl, and acetoxyl groups.

3β,17β-*Diacetoxy*-6-*acetylandrost*-5-*ene* (III; R = R′ = OAc, ··· H, R″ = COMe).—The foregoing compound (1·9 g.) in acetic acid (20 ml.) was treated with sulphuric acid (0·8 ml.) in acetic acid (20 ml.) and set aside for 18 hr. The product was isolated by dilution with water and extraction with ether. Its solution in benzene was passed through a short column of alumina (15 g.), giving 3β,17β-*diacetoxy*-6-*acetylandrost*-5-*ene* which crystallised from hexane as needles, m. p. 131—132°, or plates, m. p. 137°, $[\alpha]_D^{23}$ −39° (*c* 0·49), $\lambda_{max.}$ 243 mμ (ε 3300) in EtOH (Found: C, 72·3; H, 8·5. $C_{25}H_{36}O_5$ requires C, 72·1; H, 8·7%). The compound gave a yellow colour with tetranitromethane and an orange precipitate when warm with Brady's solution. The infrared spectrum indicated the presence of two acetoxyl groups and an αβ-unsaturated ketonic residue, and confirmed the absence of hydroxyl and ethynyl groups.

Wolff–Kishner Reduction[7] *of Compound* (III; R = R′ = OAc, ··· H; R″ = COMe).—The foregoing compound (1 g.) in ethanol (5 ml.) and diethylene glycol (20 ml.) was heated with 85% hydrazine hydrate (4 ml.) under reflux for 5 hr. Sodium hydroxide (2 g.) in water (2 ml.) was added, the condenser was removed, and the temperature raised to 195—200°; then the condenser was replaced and the temperature maintained at this level for 6 hr. When cool, the mixture was poured into water, and the product isolated with ether and acetylated in pyridine. The resulting material was chromatographed on alumina (30 g.). Elution with benzene–hexane (1 : 1) gave a low yield of solid which crystallised from methanol. 3β,17β-*Diacetoxy*-6-*ethyl*-*androst*-5-*ene* separated in plates, m. p. 139—140°, $[\alpha]_D^{20}$ −66·5° (*c* 0·89) (Found: C, 74·9; H, 9·8. $C_{25}H_{38}O_4$ requires C, 74·6; H, 9·5%).

3β,17β-*Diacetoxy*-6α-*ethylandrostan*-6β-*ol* (II; R = OAc, ··· H; R′ = Et).—3β,17β-Diacetoxyandrostan-6-one[1] (8 g.) in tetrahydrofuran (200 ml.) was added to a stirred solution of Grignard reagent prepared from ethyl bromide (29 g.) and magnesium (5·8 g.) in tetrahydrofuran (300 ml.). The mixture was stirred for 6 hr., then left overnight. After treatment with aqueous ammonium chloride, the product was isolated in the usual way, acetylated in pyridine, and chromatographed on alumina (100 g.). Elution with benzene and ether–benzene (1 : 9) gave material which crystallised from acetone–hexane. 3β,17β-*Diacetoxy*-6α-*ethyl*-*androstan*-6β-*ol* formed needles or prisms, m. p. 119—120°, $[\alpha]_D^{25}$ −11° (*c* 0·52) (Found: C, 71·5; H, 9·3. $C_{25}H_{40}O_5$ requires C, 71·4; H, 9·6%).

3β,17β-*Diacetoxy*-6-*ethylandrost*-5-*ene* (III; R = R′ = OAc, ··· H; R″ = Et).—Thionyl chloride (1·8 ml.) was added dropwise with shaking to an ice-cooled solution of the foregoing compound (2 g.) in pyridine (20 ml.). After 20 min. at 0°, the mixture was poured into ice-water, and the product collected and purified from methanol. 3β,17β-Diacetoxy-6-ethylandrost-5-ene separated in plates, m. p. 139—140°, not depressed in admixture with a specimen prepared as described above.

3β-*Acetoxy*-6-*acetyl*-17α-*ethynylandrost*-5-*en*-17β-*ol* (III; R = −OAc, ··· H; R′ = −OH, ··· C≡CH; R″ = COMe).—17α-Ethynyl-17β-hydroxy-3,5-cycloandrostan-6-one (1 g.) in tetrahydrofuran (10 ml.) was added to a cooled stirred suspension of ethynylmagnesium bromide[6] (prepared from 0·72 g. of magnesium, 3·6 g. of ethyl bromide, and acetylene) in tetrahydrofuran (20 ml.). The mixture was stirred for 4 hr., then set aside overnight at room temperature. After decomposition with aqueous ammonium chloride, the product was isolated with chloroform, and its solution in acetic acid (10 ml.) was treated for 18 hr. with sulphuric acid (0·4 ml.) in acetic acid (10 ml.). The product was isolated with ether, and its solution in benzene chromatographed on alumina (30 g.). Elution with ether–benzene (1 : 1) gave 3β-*acetoxy*-6-*acetyl*-17α-*ethynylandrost*-5-*en*-17β-*ol*, needles (from hexane), m. p. 188°, $[\alpha]_D^{25}$ −74° (*c* 0·52), $\lambda_{max.}$ 241 mμ (ε 3400) in EtOH (Found: C, 75·3; H, 8·8. $C_{25}H_{34}O_4$ requires C, 75·3; H, 8·6%). The infrared spectrum indicated the presence of ethynyl, hydroxyl, and acetoxyl groups and an αβ-unsaturated ketonic residue.

3β-*Acetoxy*-6α-*ethynylcholestane*-5α,6β-*diol* (VIIa).—3β-Acetoxy-5α-hydroxycholestan-6-one[8] (23 g.) in ether (1·8 l.) was added in 1 hr. to a stirred solution of lithium acetylide (from 7 g. of lithium) in liquid ammonia (2 l.). The mixture was stirred for 5 hr. at −33°, cooled, and treated with ammonium chloride (60 g.), and the ammonia allowed to evaporate overnight. After isolation with methylene dichloride and acetylation in pyridine, the product crystallised from acetone, to give the *diol*, needles, m. p. 228—229°, $[\alpha]_D^{23}$ −21° (*c* 0·96) (Found: C, 76·1; H, 10·2. $C_{31}H_{50}O_4$ requires C, 76·5; H, 10·4%).

3β-*Acetoxy*-5ξ,6ξ-*epoxy*-6ξ-*ethynylcholestane* (VIIIa; R = Ac).—Thionyl chloride (4·5 ml.) was added dropwise during 10 min. to a stirred solution of the foregoing diol (4·5 g.) in pyridine (55 ml.) at 0°. After a further 10 min. at 0°, the mixture was poured into ice-water, and the product isolated with ether. Crystallisation from methanol gave the *epoxide*, needles, m. p. 106—107°, $[\alpha]_D^{22}$ −43° (*c* 0·43) (Found: C, 79·4; H, 10·0. $C_{31}H_{48}O_3$ requires C, 79·4; H, 10·3%). The compound occasionally separated as prisms, m. p. 116—118°, $[\alpha]_D^{26}$ −42·5°. It was recovered unchanged after being heated with acetic acid for 5 hr. at 100°.

Reaction of Compound (VIIIa; R = Ac) *with Periodic Acid.*—The foregoing epoxide (0·6 g.) in acetone (20 ml.) was heated under reflux for 30 min. with periodic acid dihydrate (0·4 g.) in water (2 ml.). The product, isolated with chloroform and crystallised from acetone, gave some unchanged epoxide. Material deposited from the mother-liquor and purified from acetone–hexane gave, in low yield, needles of 3β-acetoxy-6α-ethynylcholestane-5α,6β-diol, m. p. 224—227°, not depressed in admixture with a specimen prepared as described above.

6α-*Ethynyl*-5α,6β-*dihydroxycholestan*-3-*one* (Xa).—A mixture of the diol (VIIa) (10 g.) and potassium carbonate (2·2 g.) in methanol (200 ml.) and water (12 ml.) was refluxed for 1·5 hr. The solution was concentrated to half its bulk, water was added, and the crude 6α-ethynylcholestane-3β,5α,6β-triol was collected, washed with water, and dried. Its solution in pyridine (100 ml.) was treated for 18 hr. with chromium trioxide (10 g.) in pyridine (100 ml.), and the product isolated with benzene. Chromatography on alumina (100 g.), with ether–benzene (1 : 1) as eluant, gave the *ketone*, m. p. 221—223° (needles from acetone–hexane), $[\alpha]_D^{22}$ −2° (*c* 0·54) (Found: C, 78·5; H, 10·35. $C_{29}H_{46}O_3$ requires C, 78·7; H, 10·5%). The *oxime* separated from ethanol in irregular crystals, m. p. 252° (decomp.) (Found: C, 75·8; H, 10·0. $C_{29}H_{47}O_3N$ requires C, 76·1; H, 10·35%).

6α-*Ethynyl*-6β-*hydroxycholest*-4-*en*-3-*one* (XIa).—A mixture of the foregoing ketone (3·4 g.) and sodium hydroxide (0·4 g.) in methanol (170 ml.) and water (20 ml.) was heated under reflux for 45 min. Water (500 ml.) was added to the cooled solution, and the product was collected, washed, dried, and purified from hexane. 6α-*Ethynyl*-6β-*hydroxycholest*-4-*en*-3-*one* separated in needles, m. p. 173—174°, $[\alpha]_D^{21}$ +25·5° (*c* 0·54), $\lambda_{max.}$ 239 mμ (ε 12,500) in EtOH (Found: 81·9; H, 10·2. $C_{29}H_{44}O_2$ requires C, 82·0; H, 10·4%).

5ξ,6ξ-*Epoxy*-6ξ-*ethynylcholestan*-3β-*ol* (VIIIa; R = H), prepared by alkaline saponification of the acetate (VIIIa; R = Ac), crystallised from methanol in needles, m. p. 154°, $[\alpha]_D^{23}$ −29° (*c* 0·59) (Found: C, 79·8; H, 10·9. $C_{29}H_{46}O_2,\frac{1}{2}H_2O$ requires C, 79·95; H, 10·9%).

5ξ,6ξ-*Epoxy*-6ξ-*ethynylcholestan*-3-*one* (IXa).—Chromic acid in aqueous 4·03N-sulphuric acid [11] (0·29 ml.) was added dropwise to a stirred, cooled solution of the foregoing compound (0·5 g.) in acetone (75 ml.). After 5 min. the mixture was poured into ice-water, and the precipitate was collected and dried. Purification from acetone–hexane and then from hexane gave the *ketone*, prisms, m. p. 139—140°, $[\alpha]_D^{20}$ −52° (*c* 0·84) (Found: C, 81·7; H, 10·45. $C_{29}H_{44}O_2$ requires C, 82·0; H, 10·4%). The infrared spectrum indicated the presence of an ethynyl and an oxo-group.

6β-*Ethynyl*-6α-*hydroxycholest*-4-*en*-3-*one* (XIIIa).—(*a*) A solution of the foregoing compound (200 mg.) in methanol (5 ml.) containing potassium hydroxide (100 mg.) was left for 1 hr. at room temperature. The product was isolated with ether and crystallised from hexane. 6β-*Ethynyl*-6α-*hydroxycholest*-4-*en*-3-*one* separated in prismatic needles, m. p. 110—111°, $[\alpha]_D^{25}$ +25° (*c* 0·52), $\lambda_{max.}$ 239·5 mμ (ε 13,800) (Found: C, 82·2; H, 10·6. $C_{29}H_{44}O_2$ requires C, 82·0; H, 10·4%).

(*b*) A solution of 5ξ,6ξ-epoxy-6ξ-ethynylcholestan-3β-ol (5 g.) in cyclohexanone (33 ml.) and toluene (20 ml.) was distilled until 5 ml. of distillate had collected. Aluminium t-butoxide (5 g.) was then added and the mixture refluxed for 1 hr. When cool, it was washed with aqueous Rochelle salt, and the solvents were removed by steam-distillation. The dark residue was isolated with methylene dichloride and chromatographed on alumina (70 g.). Elution with ether–benzene (1 : 3) gave 6β-ethynyl-6α-hydroxycholest-4-en-3-one, needles (from hexane), m. p. 110°, not depressed on admixture with a specimen prepared by method (*a*) above.

6-*Ethynylcholesta*-4,6-*dien*-3-*one* (XIIa).—6α-Ethynyl-6β-hydroxycholest-4-en-3-one (0·5 g.) in acetic acid (10 ml.) and acetic anhydride (2·5 ml.) was treated with perchloric acid (0·1 ml.). After 1 hr. at room temperature, the mixture was poured into water, and the product isolated with ether and crystallised from hexane at 0°. The *dienone* formed prismatic needles, m. p. 123—124°, $[\alpha]_D^{21}$ +52° (*c* 0·5), $\lambda_{max.}$ 291 mμ (ε 18,600) (Found: C, 86·2; H, 10·5. $C_{29}H_{42}O$ requires C, 85·7; H, 10·4%).

3β-*Acetoxy*-5α,17β-*dihydroxy*-17α-*methylandrostan*-6-*one* (VIb).—3β-Acetoxy-17α-methylandrostane-5α,6β,17β-triol [12] (10 g.) in pyridine (150 ml.) was added to chromium trioxide (10 g.) in pyridine (100 ml.). After 24 hr. the product was isolated with benzene and crystallised from acetone–hexane, giving the *ketone* in plates, m. p. 207—208°, $[\alpha]_D^{24}$ −98° (*c* 0·96) (Found: C, 69·4; H, 9·05. $C_{22}H_{34}O_5$ requires C, 69·8; H, 9·05%).

3β-*Acetoxy*-6α-*ethynyl*-17α-*methylandrostane*-5α,6β,17β-*triol* (VIIb).—The foregoing ketone (20 g.) in tetrahydrofuran (1·6 l.) was added during 1 hr. to a stirred solution of lithium acetylide (from 10 g. of lithium) in liquid ammonia (2 l.) at −37°. The mixture was stirred for 3 hr. at −33°, cooled, and treated with ammonium chloride (100 g.), and the ammonia was allowed to evaporate. The product, isolated with chloroform, was acetylated in pyridine and purified from acetone–hexane. The *triol* crystallised in plates, m. p. 225—227°, $[\alpha]_D^{20}$ −53° (*c* 0·61) (Found: C, 70·8; H, 8·7. $C_{24}H_{36}O_5$ requires C, 71·25; H, 9·0%).

6α-*Ethynyl*-17α-*methylandrostane*-3β,5α,6β,17β-*tetraol*, prepared by saponification of the

foregoing compound, crystallised from aqueous methanol in prisms or plates, m. p. indefinite between 260° and 285° (effervescence), $[\alpha]_D^{20}$ −27° (*c* 0·5) in EtOH (Found: C, 69·5; H, 9·5. $C_{22}H_{34}O_4,H_2O$ requires C, 69·4; H, 9·5%).

6α-*Ethynyl*-5α,6β,17β-*trihydroxy*-17α-*methylandrostan*-3-*one* (Xb).—The foregoing compound (7·6 g.) in pyridine (76 ml.) was added to chromium trioxide (7·6 g.) in pyridine (80 ml.), and the mixture kept for 18 hr. at room temperature. The product was isolated with benzene and crystallised from acetone–hexane, to give the *ketone* in prismatic needles, m. p. 253—256° (decomp.), $[\alpha]_D^{21}$ −26° (*c* 0·72) (Found: C, 73·4; H, 8·9. $C_{22}H_{32}O_4$ requires C, 73·3; H, 8·95%).

6α-*Ethynyl*-6β,17β-*dihydroxy*-17α-*methylandrost*-4-*en*-3-*one* (XIb).—The foregoing ketone (3·3 g.) and sodium hydroxide (0·33 g.) in methanol (150 ml.) and water (16 ml.) were refluxed for 45 min. The mixture was just acidified with acetic acid, then concentrated somewhat, water was added and the product collected and crystallised from acetone. 6α-*Ethynyl*-6β,17β-*dihydroxy*-17α-*methylandrost*-4-*en*-3-*one* separated in needles, m. p. 243—244°, $[\alpha]_D^{25}$ +1° (*c* 0·85), $\lambda_{max.}$ 238 mμ (ε 12,200) in EtOH (Found: C, 76·7; H, 9·1. $C_{22}H_{30}O_3$ requires C, 77·1; H, 8·8%).

We thank the Directors of The British Drug Houses Ltd. for permission to publish these results.

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[*Received, November 23rd*, 1959.]