Tetrahedron, 1965, Vol. 21, pp. 1197 to 1202. Pergamon Press Ltd. Printed in Northern Ireland

MODIFIED STEROID HORMONES—XXXVII[1]

SOME 17α-BUTADIYNYL-17β-HYDROXY- AND 17α-(2'-THIENYL)-17β-HYDROXY-DERIVATIVES

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(*Received* 17 *November* 1964)

Abstract—17α-Butadiynyl-17β-hydroxy-steroids have been prepared by reaction of 17-oxo-steroids with monosodio-butadiyne and converted, by reaction with hydrogen sulphide, into 17α-(2'-thienyl) 17β-hydroxy-steroids.

EARLIER studies[2-4] on ω-substituted ethynyl steroids have now been extended to the preparation of the hitherto unknown ω-ethynyl types (—C≡C—C≡CH). These 17α-butadiynyl-17β-hydroxy-steroids were prepared by condensing the appropriate 17-ones with monosodio-butadiyne in liquid ammonia. The acetylenic reagent was conveniently prepared[5,6] *in situ* by reacting 1,4-dichlorobut-2-yne with sodamide. Typical 17-ones treated in this way included D.H.A. and its 6-methyl derivative, substituted oestratrienes and 3-methoxy-oestra-2,5(10)-dien-17-one, and gave the corresponding 17α-butadiynyl-17β-hydroxy-steroids, (I, R = H; I, R = Me; II, R^1 = OMe, R^2 = H; II, R^1 = OH, R^2 = H; II, R^1 = H, R^2 = H; II, R^1 = H, R^2 = Me and III). 17α-Butadiynyl-3-methoxy-oestra-2,5(10)-dien-17β-ol (III) was converted by mild acid hydrolysis into 17α-butadiynyl-19-norandrost-4-en-17β-ol-3-one (IV, R = H). 3-Ethoxy-androsta-3,5-dien-17-one, on treatment with the reagent followed by mild acid hydrolysis, similarly gave 17α-butadiynyl-androst-4-en-17β-ol-3-one (IV, R = Me).

In the androstane and 19-norandrostane series, the 17α-butadiynyl-17β-hydroxy-steroids were stable in the solid state on prolonged storage at room temperature. Stability was, in general, lower in the oestrane series and marked discolouration and decomposition were found in some samples stored for 2–3 months. All these compounds decomposed when heated to moderate temperatures, so that m.p. and temperatures of decomposition were often ill-defined and dependent upon the rate of heating. They were accordingly of little value as criteria of identity and purity. During purification, it was necessary to avoid lengthy heating of solutions and some difficulty was experienced in recrystallization of the oestrane derivatives due to their

[1] Part XXXVI, D. Burn, G. Cooley, M. T. Davies, A. K. Hiscock, D. N. Kirk, V. Petrow and D. M. Williamson, *Tetrahedron* **21**, 569 (1965).
[2] S. P. Barton, G. Cooley, B. Ellis and V. Petrow, *J. Chem. Soc.* 5094 (1957).
[3] S. P. Barton, D. Burn, G. Cooley, B. Ellis and V. Petrow, *J. Chem. Soc.* 1957 (1959).
[4] C. Burgess, D. Burn, J. W. Ducker, B. Ellis, P. Feather, A. K. Hiscock, A. P. Leftwick, J. S. Mills and V. Petrow, *J. Chem. Soc.* 4995 (1962).
[5] F. Bohlmann, *Ber. Dtsch. Chem. Ges.* **84**, 785 (1951).
[6] J. B. Armitage, E. R. H. Jones and M. C. Whiting, *J. Chem. Soc.* 1993 (1952).

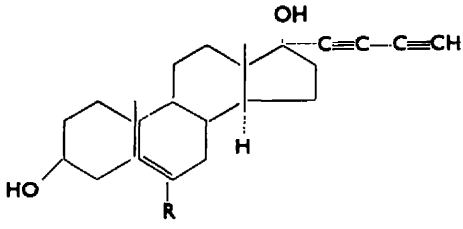
decomposition under these experimental conditions. In particular, satisfactory analyses could not be obtained for 17α-butadiynyloestra-1,3,5(10)-trien-17β-ol (II, $R^1 = H$, $R^2 = H$) and 17α-butadiynyl-4-methyl-oestra-1,3,5(10)-trien-17Δ-ol (II, $R^1 = H$, $R^2 = Me$). Identity was established in all cases by spectroscopic examination.

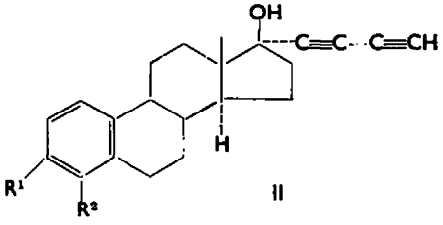
Treatment of the 17α-butadiynyl-17β-hydroxy derivatives of androst-5-en-3β-ol, 3-methoxy-oestra-1,3,5(10)-triene, androst-4-en-3-one and 19-norandrost-4-en-3-one with hydrogen sulphide in the presence of alkali[7] led to the formation of the corresponding 17β-hydroxy-17α-thienyl steroids (V, R = H; VI; VII, R = Me and VII, R = H). 17α-(2′-Thienyl)-androst-4-en-17β-ol-3-one (VII, R = Me) was also prepared by Oppenauer oxidation of the 5-en-3β-ol (V, R = H).

Attempted acetylation of 17α-(2′-thienyl)-androst-5-en-3β,17β-diol (V, R = H) led to dehydration with formation of 3β-acetoxy-17-(2′-thienyl)-androsta-5,16-diene (VIII). This result is rather surprising as attempts to dehydrate 17α-ethynyl and 17α-alkyl-17β-ols generally lead to the production of significant quantities of the Wagner-Meerwein rearrangement products.

3β,17β-Dimethoxy-17α-(2′-thienyl)-androst-5-ene (V, R = Me) was prepared by methylating the diol (V, R = H) with sodamide and methyl iodide in liquid ammonia.[8]

Inter alia we observed that hydration of 17α-butadiynyl-androst-5-en-3β,17β-diol (I, R = H) with dilute sulphuric acid in presence of mercuric ions gave, in small yield, 17α-but-1′-yn-3′-onyl-androst-5-en-3β,17β-diol (IX).





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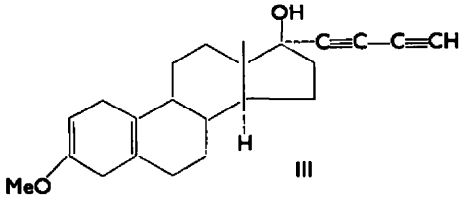

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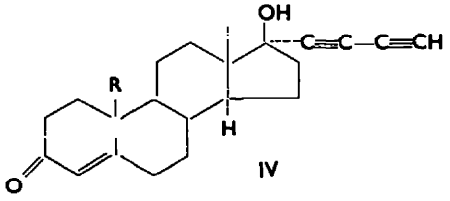
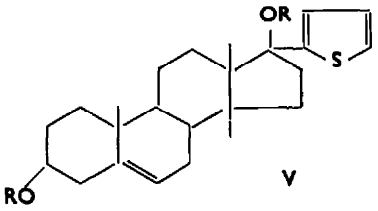


IV

[7] K. E. Schulte, J. Reisch and L. Hörner, *Ber. Dtsch. Chem. Ges.* **95**, 1943 (1962).
[8] Ger. Patents 1062698 and 1117572; Belg. Patent 636603.



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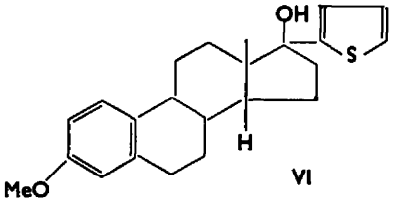

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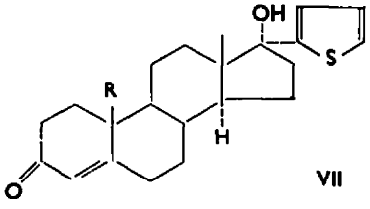

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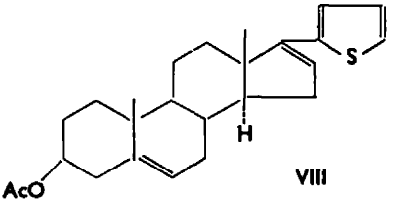

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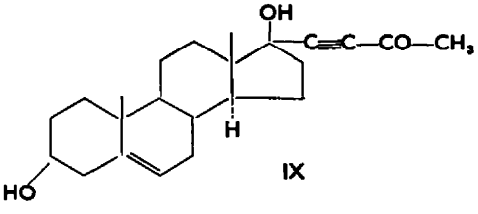

IX

EXPERIMENTAL

Optical rotations were measured at temp between 20° and 25°, using dioxan as solvent (unless otherwise stated) at concentrations of approximately 1%. The PMR spectra were recorded upon solutions in $CDCl_3$ at 40 Mcs/sec. UV absorption spectra, IR absorption spectra, PMR spectra and optical rotations were determined under the supervision of Mr. M. T. Davies, B.Sc., F.R.I.C. Unless otherwise stated, "parts" are parts by wt. (g) for solids and parts by volume (ml) for liquids.

General procedure for the preparation of 17α-*butadiynyl*-17β-*hydroxy-steroids*

Sodium (2·3 parts) and $Fe(NO_3)_3$ (0·05 part) were added to liquid ammonia (133 parts) and the mixture was stirred under reflux until the blue colour disappeared. 1,4-Dichlorobut-2-yne[9] (4·1 parts by wt.) was added dropwise and after a further 5 min a solution of the 17-oxo-steroid (9·4 parts) in anhydrous tetrahydrofuran (67 parts) was added. The mixture was stirred under reflux for 1½ hr, solid NH_4Cl was added and the NH_3 was allowed to evaporate. The steroidal product was isolated from the residue by addition of water and extraction with ether. Purification was achieved by crystallization from a suitable solvent. Yields were in the range 30–60%. All the 17α-butadiynyl-17β-hydroxy-steroids described herein were characterized by a pair of sharp bands of medium

[9] W. Reppe *et al.*, *Liebigs Ann.* **596**, 78 (1955).

intensity in the region of 3600 and 3300 cm^{-1} and a pair of weaker bands in the region of 2050 and 2225 cm^{-1}. In the UV, the diacetylene chromophore has been reported[10] to show characteristic bands in the regions of 229 mμ, 237 mμ and 251 mμ. The steroidal derivatives in general showed dominant bands in the regions of 240–241·5 mμ and 249–256 mμ, but the results were complicated by absorption by other chromophores in the molecule and by an observed instability of the compounds when exposed to UV irradiation.

17α-*Butadiynyl-androst-5-en-3β,17β-diol* (I, R = H), prepared from androst-5-en-3β-ol-17-one, crystallized from MeOH in colourless needles, m.p. 209° (dec); $[\alpha]_D$ −170°; λ_{max}^{EtOH} 229·5 mμ (ε, 314), 241 mμ (ε, 338·5), 254 mμ (ε, 213); ν_{max}^{Nujol} 3585, 3156 cm^{-1} (OH); 3366 cm^{-1} (≡CH); 2219, 2050 cm^{-1} (—C≡C—C≡C—). (Found: C, 81·7; H, 8·7. $C_{23}H_{30}O_2$ requires: C, 81·6; H, 8·9%.)

17α-*Butadiynyl-6-methyl-androst-5-en-3β,17β-diol* (I, R = Me),* prepared from 6-methyl-androst-5-en-3β-ol-17-one, crystallized from aqueous MeOH in colourless needles, m.p. 191°(dec). $[\alpha]_D$ −126°; λ_{max}^{EtOH} 240·5–241 mμ (ε, 377), 249 mμ (ε, 254), 272 mμ (ε, 52·5), 289 mμ (ε, 50·4), 307 mμ (ε, 38·8); λ_{inf}^{EtOH} 251–252 mμ (ε, 251); ν_{max}^{Nujol} 3570, 3180 cm^{-1} (OH); 3325 cm^{-1} (≡CH); 2220, 2045 cm^{-1} (—C≡C—C≡C—). (Found: C, 81·5; H, 9·0. $C_{24}H_{32}O_2$ requires: C, 81·8; H, 9·15%.)

17α-*Butadiynyl-androst-4-en-17β-ol-3-one* (IV, R = Me), prepared by reaction of 3-ethoxy-androsta-3,5-dien-17-one with monosodio-butadiyne followed by treatment of the crude product (0·5 g) in MeOH (20 ml) with 3 N HCl (10 drops), allowing the mixture to stand for 1 hr at room temp, was purified from aqueous MeOH and acetone–hexane in colourless needles, m.p. 160° (dec); $[\alpha]_D$ −32°; λ_{max}^{EtOH} 240–241 mμ (ε, 16555);ν_{max}^{Nujol} 3400 cm^{-1} (OH); 3218 cm^{-1} (≡CH); 2205, 2045 cm^{-1} (—C≡C—C≡C—). (Found: C, 81·4; H, 8·45. $C_{23}H_{28}O_2$ requires: C, 82·1; H, 8·4%.)

17α-*Butadiynyl-3-methoxy-oestra-2,5(10)-dien-17β-ol* (III), prepared from 3-methoxy-oestra-2,5(10)-dien-17-one, crystallized from MeOH containing a trace of pyridine in colourless needles, m.p. 130–150° (dec); $[\alpha]_D^{22\cdot5}$ +68°; λ_{max}^{EtOH} 252 mμ (ε, 397), 255 mμ (ε, 394); λ_{inf}^{EtOH} 240 mμ (ε, 501), 262·5 mμ (ε, 201); ν_{max} 3607 cm^{-1} (OH); 3313 cm^{-1} (≡CH); 2226, 2055 cm^{-1} (—C≡C—C≡C—); 1697, 1666 cm^{-1} (Δ2,5[10]). (Found: C, 81·4; H, 8·1. $C_{23}H_{28}O_2$ requires: 82·1; H, 8·4%.)

17α-*Butadiynyl-19-norandrost-4-en-17β-ol-3-one* (IV, R = H), prepared from 17α-butadiynyl-3-methoxy-oestra-2,5(10)-dien-17β-ol (0·8 g) by treatment in MeOH (48 ml) with 3 N HCl (32 ml) maintaining the mixture at 60° for 15 min, was purified from MeOH in colourless needles, 0·59 g = 77%, m.p. 186° (dec); $[\alpha]_D$ −93·5°; λ_{max} 240 mμ (ε, 17090); $\nu_{max}^{CCl_4}$ 3606 cm^{-1} (OH); 3309 cm^{-1} (≡CH); 2227, 2055 cm^{-1} (—C≡C—C≡C—); 1678 cm^{-1} (CO); 1620 cm^{-1} (Δ4). (Found: C, 81·45; H, 8·1. $C_{22}H_{26}O_2$ requires: C, 81·9; H, 8·1%.)

17α-*Butadiynyl-3-methoxy-oestra-1,3,5(10)-trien-17β-ol* (II, R^1 = OMe, R^2 = H), prepared from oestrone 3-methyl ether, crystallized from aqueous MeOH in colourless needles containing MeOH of crystallization which was removed by adding and evaporating benzene, leaving an amorphous white solid, m.p. 72–82° (dec); $[\alpha]_D$ −42° (in EtOH); λ_{max}^{EtOH} 256 mμ (ε, 528), 278·5 mμ (ε, 1930), 287·5 mμ (ε, 1830); $\nu_{max}^{CCl_4}$ 3609 cm^{-1} (—OH); 3317 cm^{-1} (≡CH); 2246, 2055 cm^{-1} (—C≡C—C≡C—); NMR 2·5–3·6τ (Ring A 3-proton multiplet); 6·26, 7·79 and 9·13τ (singlets) correspond to aromatic —OMe, ≡CH and 13-CH_3 protons respectively. (Found: C, 82·7; H, 7·8. $C_{23}H_{26}O_2$ requires: C, 82·6; H, 7·8%.)

17α-*Butadiynyl-oestra-1,3,5(10)-trien-3,17β-diol* (II, R^1 = OH, R^2 = H), prepared from oestrone, crystallized from benzene–ether in colourless prisms, m.p. 134–137° (dec); $[\alpha]_D$ −41° (in $CHCl_3$); λ_{max}^{EtOH} 249·5 mμ (ε, 397); 255 mμ (ε, 516); λ_{inf}^{EtOH} 262 mμ (ε, 561); 281 mμ (ε, 1880); $\nu_{max}^{CH_2Cl_2}$ 3593 cm^{-1} (OH), 3300 cm^{-1} (≡CH); ν_{max}^{Nujol} 2215, 2050 cm^{-1} (—C≡C—C≡C—). (Found: C, 83·3; H, 7·8. $C_{22}H_{24}O_2$ requires: C, 82·5; H, 7·5%.)

17α-*Butadiynyl-oestra-1,3,5(10)-trien-17β-ol* (II, R^1 = H, R^2 = H), prepared from oestra-1,3,5(10)-trien-17-one,[11] crystallized from aqueous acetone in colourless needles, m.p. 100–102° (dec); $[\alpha]_D$ −35° (in $CHCl_3$); λ_{max} 241·5 mμ (ε, 377), 255·5 mμ (ε, 426), 266·5 mμ (ε, 460), 274 mμ (ε, 417); $\nu_{max}^{CCl_4}$ 3604 cm^{-1} (OH), 3311 cm^{-1} (≡CH), 2230, 2061 cm^{-1} (—C≡C—C≡C—). (Found: C, 84·5; H, 8·3. $C_{22}H_{24}O$ requires: C, 86·8; H, 7·95%.)

17α-*Butadiynyl-4-methyl-oestra-1,3,5(10)-trien-17β-ol* (II, R^1 = H, R^2 = Me), prepared from

* Preparation by Mr. J. V. Syms of this Department.

[10] J. B. Armitage, C. L. Cook, N. Entwistle, E. R. H. Jones and M. C. Whiting, *J. Chem. Soc.* 1998 (1952).

[11] U.S. Patent 2947763.

4-methyl-oestra-1,3,5(10)-trien-17-one[12], crystallized from MeOH in felted needles, m.p. 145–147° (dec); $[\alpha]_D$ −38° (in $CHCl_3$); λ_{max}^{EtOH} 241 mμ (ε, 404), 255 mμ (ε, 391); λ_{max}^{EtOH} 261 mμ (ε, 290), 268 mμ (ε, 279) $\nu_{max}^{CCl_4}$ 3590 cm^{-1} (OH); 3300 cm^{-1} (≡CH); 2225, 2055 cm^{-1} (—C≡C—C≡C—). (Found: C, 84·8; H, 8·3. $C_{23}H_{26}O$ requires: C, 86·7; H, 8·2%.)

General procedure for the preparation of 17α-(2′-*thienyl*)-17β-*hydroxy-steroids*

Hydrogen sulphide was passed steadily into a solution (heated under reflux) of the appropriate 17α-butadiynyl-17β-hydroxy-steroid (2 parts) in a mixture of EtOH (75 parts) and N NaOH (7·5 parts) for 6–7 hr. The reaction mixture was poured into water and the steroidal product was isolated by extraction with ether. Purification was achieved by crystallization from a suitable solvent and, when necessary, by chromatography. Yields were in the range 30–50%.

The UV absorption of 2-methyl-thiophen was reported[13] as λ_{max} 232 mμ (ε, 7413). 2-Substituted thiophen was reported[14] to show, in the IR, bands at approximately 1523, 1422, 1354, 1231, 1081, 1042, 925, 853 and 830 cm^{-1}.

17α-(2′-*Thienyl*)-*androst-5-en*-3β,17β-*diol* (V, R = H), prepared from 17α-butadiynyl-androst-5-en-3β,17β-diol, crystallized from benzene in hexagonal plates, m.p. 173·5–174°; $[\alpha]_D$ −28°; λ_{max}^{EtOH} 237·5 mμ (ε, 7460); $\nu_{max}^{CH_2Cl_2}$ 3615 cm^{-1}; ν_{max}^{Nujol} 1244, 1056, 1018, 1005, 692, 670 cm^{-1}. (Found: C, 73·5; H, 8·6; S, 8·5. $C_{23}H_{32}O_2S$ requires: C, 74·2; H, 8·7; S, 8·6%.)

17α-(2′-*Thienyl*)-*androst*-4-*en*-17β-*ol*-3-*one* (VII; R = Me). (a) This was prepared from 17α-butadiynyl-androst-4-en-17β-ol-3-one, and crystallized from MeOH in colourless needles, m.p. 219°; $[\alpha]_D$ +86°; λ_{max}^{EtOH} 239 mμ (ε, 24050); $\nu_{max}^{CH_2Cl_2}$ 3590, 1670, 1615 cm^{-1}; ν_{max}^{Nujol} 1230, 1010, 715 cm^{-1}. (Found: C, 74·3; H, 8·3; S, 8·8. $C_{23}H_{30}O_2S$ requires: C, 74·6; H, 8·2; S, 8·6%.)

(b) Aluminium isopropoxide (2·0 g) in anhydrous toluene (40 ml) was added to 17α-(2′-thienyl)-androst-5-en-3β,17β-diol (2·5 g) in toluene (100 ml) and cyclohexanone (30 ml) and the mixture was heated under reflux for 2 hr and cooled. A saturated aqueous solution of Rochelle salt was added, and the mixture was steam-distilled to remove organic solvents. After cooling, the solid product was collected and purified from MeOH, affording 17α-(2′-thienyl)-androst-4-en-17β-ol-3-ene, identical in m.p., rotation and UV spectrum with the product described in (a) above.

17α-(2′-*thienyl*)-19-*norandrost*-4-*en*-17β-*ol*-3-*one* (VII, R = H). This was prepared from 17α-butadiynyl-19-norandrost-4-en-17β-ol-3-one, and crystallized from benzene–pet. ether in needles, m.p. 172–172·5°; $[\alpha]_D$ +36°; λ_{max}^{EtOH} 239 mμ (ε, 20600); $\nu_{max}^{CCl_4}$ 3608, 1677, 1621 cm^{-1}; $\nu_{max}^{CS_2}$ 1260, 695, 669 cm^{-1}. (Found: C, 74·3; H, 7·7; S, 9·0. $C_{22}H_{28}O_2S$ requires: C, 74·1; H, 7·9; S, 9·0%.)

3-*Methoxy*-17α-(2′-*thienyl*)-*oestra*-1,3,5(10)-*trien*-17β-*ol* (VI). This was prepared from 17α-butadiynyl-3-methoxy-oestra-1,3,5(10)-trien-17β-ol, and crystallized from benzene in minute grains, m.p. (182–182·5°); $[\alpha]_D$ +76·4°; λ_{max}^{EtOH} 278 mμ (ε, 2100), 287·5 mμ (ε, 2010), 231 mμ (ε, 13800) $\nu_{max}^{CH_2Cl_2}$ 3575, 1607, 1571, 1497 cm^{-1}; $\nu_{max}^{CS_2}$ 1255, 1237, 1040, 692 cm^{-1}. (Found: C, 74·5; H, 7·6; S, 9·1. $C_{23}H_{28}O_2S$ requires: C, 74·9; H, 7·7; S, 8·7%.)

3β-*Acetoxy*-17-(2′-*thienyl*)-*androsta*-5,16-*diene* (VIII). A solution of 17α-(2′-thienyl)-androst-5-en-3β,17β-diol (2·09 g) in a mixture of acetic anhydride (25 ml) and pyridine (5 ml) was refluxed for 3 hr, cooled, and poured into water. Ether extraction gave an oil which was crystallized from MeOH in colourless plates, m.p. 142·5°; $[\alpha]_D$ −41°; λ_{max}^{EtOH} 279 mμ (ε, 11400); $\nu_{max}^{CCl_4}$ 1735 cm^{-1}; $\nu_{max}^{CS_2}$ 1371, 1361, 1242, 1033, 797, 685 cm^{-1}. (Found: C, 75·5; H, 8·0; S, 8·5. $C_{25}H_{32}O_2S$ requires: C, 75·7; H, 8·1; S, 8·1%.)

3β,17β-*Dimethoxy*-17α-(2′-*thienyl*)-*androst*-5-*ene* (V, R = Me). To liquid NH_3 (150 ml) at −60° was added Na (1·27 g) and a trace of $Fe(NO_3)_3$ and the mixture was stirred until the blue colour disappeared. 17α-(2′-Thienyl)-androst-5-en-3β,17β-diol (5·04 g) in anhydrous tetrahydrofuran (80 ml) was added and the mixture was stirred for 1½ hr. MeI (7·6 g) in tetrahydrofuran (25 ml) was added and stirring was continued for a further 3 hr. The mixture was poured onto ice and the steroidal product was extracted with ether and purified by chromatography on alumina, eluting with benzene, and by crystallization from benzene–MeOH as colourless needles, yield 2·72 g (50%), m.p. 151–152°; $[\alpha]_D$ −54°; λ_{max}^{EtOH} 236 mμ (ε, 4690); $\nu_{max}^{CS_2}$ 1376, 1262, 1248, 1099, 1062, 947, 821, 739, 693 cm^{-1}; NMR 2·6–3·3τ (heteroaromatic ABX system); 6·68, 6·81 and 9·02τ (singlets) correspond to 3-OMe, 17β-OMe and (coincident) 10-Me and 13-Me protons respectively. A single-proton

[12] M. J. Gentles, J. B. Moss, H. L. Herzog and E. B. Hershberg, *J. Amer. Chem. Soc.* **80**, 3702 (1958).
[13] E. Campaigne and J. L. Diedrich, *J. Amer. Chem. Soc.* **73**, 5240 (1951).
[14] A. R. Katritzky and A. J. Boulton, *J. Chem. Soc.* 3500 (1959).

multiplet at ca. 4·6τ (6-H) completes the analysis. (Found: C, 74·4; H, 9·1; S, 8·0. $C_{25}H_{36}O_2S$ requires: C, 75·0; H, 9·1; S, 8·0%.)

17α-But-1'-yn-3'-onyl-androst-5-en-3β,17β-diol (IX). 17α-Butadiynyl-androst-5-en-3β,17β-diol (2·0 g) was added to MeOH (40 ml) containing 10% H_2SO_4aq (40 ml) and $HgSO_4$ (1·0 g) and the mixture was refluxed for 2½ hours, cooled and diluted with water. The precipitate was collected and purified by partition chromatography on a Celite column containing 60% aqueous MeOH (80%), eluting with hexane–benzene mixtures. Crystallization from aqueous acetone gave a colourless solid, yield 0·24 g (11%), m.p. 191°; $[\alpha]_D$ −141° (in $CHCl_3$); ORD (in dioxan, 0·3%) plain negative curve, $[\phi]$ 500 mμ (−0·78°); 400 mμ (−1·45°); 290 mμ (−3·56°); λ_{max}^{EtOH} 227 mμ (ε, 7201); $\nu_{max}^{CH_2Cl_2}$ 3605 cm^{-1} (OH); 1676 cm^{-1} (CO); ν_{max}^{Nujol} 2170 cm^{-1} (—C≡C—). (Found: C, 77·6; H, 9·2. $C_{22}H_{32}O_2$ requires: C, 77·5; H, 9·05%.)