767. *Modified Steroid Hormones. Part XIII.* Some Propargyl Derivatives.*

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The preparation of the 2α- (I; R = α-CH_2·C:CH, R′ = H) and 6α-propargyl (IV; R = OH, R′ = H) derivatives of testosterone and the 6α-propargyl derivatives of progesterone (IV; R = Ac, R′ = H) and 17α-acetoxyprogesterone (IV; R = Ac, R′ = OAc) is reported.

Work on methylated steroid hormones [1,2] is herein extended to the preparation of some propargyl derivatives.

Condensation of testosterone with ethyl formate [3] in the presence of sodium hydride afforded 2-formyltestosterone (I; R = CHO, R′ = H), which was treated without purification with propargyl bromide. Elimination of the formyl group from the intermediate (I; R = CHO, R′ = CH_2·C:CH) with sodium hydroxide led to the required 2α-propargyltestosterone (I; R = α-CH_2·C:CH, R′ = H) (characterised as the 17-acetate). The structure assigned to the last compound was supported by the infrared spectrum which (in CCl_4) showed bands at 3312 (:C·H), 2104 (C:C), 1736 (OAc), 1675, and 1619 cm.$^{-1}$ (Δ^4-3-one).

Preparation of 6α-propargyltestosterone (IV; R = OH, R′ = H) was achieved by extension of the general method developed in Part VII.[2] 5α,6α-Epoxy-3,3-ethylenedioxy-5α-androstan-17β-ol [2] (II; R = OH, R′ = H) with propargylmagnesium bromide furnished

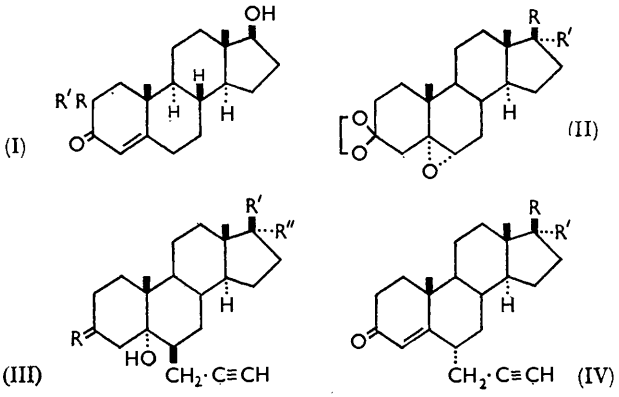
* Part XII, *J.*, 1959, 3595, which paper was incorrectly numbered Part XI (cf. *J.*, 1959, 788).

[1] Burn, Ellis, Petrow, Stuart-Webb, and Williamson, *J.*, 1957, 4092; Ackroyd, Adams, Ellis, Petrow, and Stuart-Webb, *ibid.*, p. 4099.

[2] Cooley, Ellis, Kirk, and Petrow, *J.*, 1957, 4112; B.P. 809,465/1959; cf. Campbell, Babcock, and Hogg, *J. Amer. Chem. Soc.*, 1958, **80**, 4717.

[3] Quartey, *J.*, 1958, 1710.

3,3-ethylenedioxy-6β-propargyl-5α-androstane-5α,17β-diol (III; R = ethylenedioxy, R′ = OH, R″ = H) which passed smoothly into the corresponding ketone (III; R = O, R′ = OH, R″ = H) on treatment with aqueous acetic acid. Dehydration with ethanolic hydrochloric acid afforded a product regarded as 6α-propargyltestosterone (IV; R = OH, R′ = H) by analogy with the formation of 6α-methylated steroid hormones under similar experimental conditions.[1,2] No attempt was made to prepare the 6β-isomer as, in general, 6β-alkylated hormones are less potent biologically than their 6α-alkyl analogues. Application of the same reaction sequence to 3,3:20,20-bisethylenedioxy-5α,6α-epoxy-5α-pregnane[3] (II; R = 1,1-ethylenedioxyethyl, R′ = H) led to the intermediates (III; R = ethylenedioxy, R′ = 1,1-ethylenedioxyethyl, R′ = H) and (III; R = O, R′ = Ac,



R″ = H) and thence to 6α-propargylprogesterone (IV; R = Ac, R′ = H). Evidence for the α-configuration of the propargyl group was obtained from the *R*-band spectrum. It has been shown[4] that 6β-substitution by halogen and acyloxy-groups produces a bathochromic shift of *ca.* 15 mμ of the fine-structure bands of steroidal Δ^4-3-ones, whilst 6α-substitution produces a negligible shift. We find[5] the same pattern of behaviour to apply to 6-methyl substituents although in this case the shifts are somewhat smaller. As the *R*-band spectrum of 6α-propargylprogesterone (IV; R = Ac, R′ = H) is virtually identical with that of progesterone it seems reasonable to conclude that, in this compound too, the 6-substituent has the α-configuration. Unfortunately, extension of such measurements to the other 6-propargyl steroids described herein did not prove possible owing to their limited solubility in suitable organic solvents.

Finally, attention was directed to the preparation of the 6α-propargyl analogue of the progestationally active substance, 17α-acetoxy-6α-methylprogesterone.[6,7] 3,3:20,20-Bisethylenedioxy-5α,6α-epoxy-5α-pregnan-17α-ol[6] (II; R = 1,1-ethylenedioxyethyl, R′ = OH) was treated with propargylmagnesium bromide, and the resulting product (III; R = ethylenedioxy, R′ = 1,1-ethylenedioxyethyl, R″ = OH) was hydrolysed with aqueous-methanolic oxalic acid, to yield 5α,17α-dihydroxy-6β-propargyl-5α-pregnane-3,20-dione (III; R = O, R′ = Ac, R″ = OH). Dehydration with ethanolic hydrochloric acid afforded 17α-hydroxy-6α-propargylprogesterone (IV; R = Ac, R′ = OH) which passed into the required 17α-acetoxy-6α-propargylprogesterone (IV; R = Ac, R′ = OAc) on forced acetylation.[8]

Biological results will be reported elsewhere.

[4] Bird, Cookson, and Dandegaonker, *J.*, 1956, 3675.
[5] With Mr. M. T. Davies, B.Sc., unpublished work.
[6] Babcock, Gutsell, Herr, Hogg, Stuki, Barns, and Dulin, *J. Amer. Chem. Soc.*, 1958, **80**, 2904.
[7] Sala, Camerino, and Cavallero, *Acta Endocrinol.*, 1958, **29**, 508.
[8] Turner, *J. Amer. Chem. Soc.*, 1953, **75**, 3489.

Experimental

M. p.s are corrected. Optical rotations were determined for chloroform solutions. Ultraviolet (in ethanol) and infrared spectra were kindly determined by Mr. M. T. Davies, B.Sc., and Miss D. F. Dobson, B.Sc.

2α-Propargyltestosterone (; R = α-CH_2·C:CH, R′ = H).—A solution of testosterone (5·75 g.) in ethyl formate (5 ml.) and dry benzene (100 ml.) containing sodium hydride (1·5 g.) was stirred under nitrogen at room temperature for 2 days. Dilution with water and extraction with ether yielded unchanged testosterone (1 g.). Ether-extraction of the acidified aqueous phase yielded 2-formyltestosterone as a gum (4·1 g.) which was treated in dry acetone (200 ml.) containing propargyl bromide (4 ml.) with potassium carbonate (1·2 g.). The mixture was then refluxed under nitrogen for 14 hr. The product (I; R = CHO, R′ = CH_2·C:CH) (5·4 g.), obtained by dilution with water and extraction in ether, was kept overnight under nitrogen at room temperature in methanol (100 ml.) and water (5 ml.) containing sodium hydroxide (4 g.). The product was isolated with ether and filtered in benzene solution through a short column of alumina (15 g.). Crystallisation from aqueous methanol yielded *2α-propargyltestosterone* as needles, m. p. 137—139°, $[\alpha]_D^{26}$ +60·7° (*c* 0·8), $\lambda_{max.}$ 241 mμ (log ε 4·19) (Found: C, 81·2; H, 9·55. $C_{22}H_{30}O_2$ requires C, 81·0; H, 9·25%). The *acetate* crystallised from aqueous methanol in rods, m. p. 141—143°, $[\alpha]_D^{25}$ +50·9° (*c* 0·8), $\lambda_{max.}$ 241 mμ (log ε 4·18) (Found: C, 77·7; H, 8·8. $C_{24}H_{32}O_3$ requires C, 78·2; H, 8·75%).

3,3-Ethylenedioxy-6β-propargyl-5α-androstane-5α,17α-diol.—A solution of the ketal epoxide [3] (II; R = OH, R′ = H) (3 g.) in dry benzene (100 ml.) was added to the Grignard reagent prepared from propargyl bromide (7 ml.) and magnesium (2 g.) in dry ether (75 ml.) with mercuric chloride [9] as initiator. It was necessary to add the steroid as soon as the Grignard reagent had been prepared since the latter was unstable. After the mixture had been kept at room temperature overnight, aqueous ammonium chloride was added to the cooled (0°) solution, and the product was isolated with ether. Chromatography on alumina (60 g.) in benzene gave the *ketal monohydrate* as needles [from ether–light petroleum (b. p. 40—60°)], m. p. 204°, $[\alpha]_D^{21}$ −70·5° (*c* 0·65) (Found: C, 70·65; H, 9·25. $C_{24}H_{36}O_4,H_2O$ requires C, 70·9; H, 9·4%). Prolonged drying of this material *in vacuo* at 150° yielded the hemihydrate (Found: C, 72·15; H, 9·75. $C_{24}H_{36}O_4,\frac{1}{2}H_2O$ requires C, 72·5; H, 9·4%).

5α,17β-Dihydroxy-6β-propargyl-5α-androstan-3-one (III; R = O, R′ = OH, R″ = H).—The foregoing ketal (1·08 g.) was kept at room temperature overnight in acetic acid (35 ml.) and water (1 ml.). The product was isolated with ether and crystallised from acetone–hexane to give the *ketone* as laths, m. p. 194—195°, $[\alpha]_D^{20}$ −50·8° (*c* 0·59) (Found: C, 76·3; H, 9·3. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·35%). The *acetate* crystallised from aqueous methanol in needles, m. p. 175—177°, $[\alpha]_D^{22}$ −42·1° (*c* 0·36) (Found: C, 74·2; H, 8·8. $C_{24}H_{34}O_4$ requires C, 74·6; H, 8·9%).

6α-Propargyltestosterone (IV; R = OH, R′ = H).—The ketone (III; R = O, R′ = OH, R″ = H) (0·17 g.) in ethanol (20 ml.) containing concentrated hydrochloric acid (0·1 ml.) was heated under reflux for 20 min. Dilution with water and recrystallisation of the product from aqueous ethanol gave *6α-propargyltestosterone* as needles, m. p. 163—165°, $[\alpha]_D^{20}$ +94·8° (*c* 0·8), $\lambda_{max.}$ 239·5 mμ (log ε 4·19) $\nu_{max.}$ (in CCl_4) 3634 (OH), 3327 (:C·H), 2121 (C:CH), 1688, 1616 $cm.^{-1}$ (Δ^4-3-one) (Found: C, 81·3; H, 9·5. $C_{22}H_{30}O_2$ requires C, 80·9; H, 9·3%).

5α-Hydroxy-6β-propargyl-5α-pregnane-3,20-dione (III; R = O, R′ = Ac, R″ = H).—The bis-ketal epoxide [3] (II; R = 1,1-ethylenedioxyethyl, R′ = H) (10 g.) in dry benzene (300 ml.) was added with stirring to the Grignard reagent prepared from propargyl bromide (10 ml.) and magnesium (3 g.) in dry ether (100 ml.), and the mixture was kept overnight at room temperature. The bisethylenedioxy-alcohol (14 g.), isolated in the usual way, was kept for 1 hr. at room temperature in methanol (150 ml.) and water (30 ml.) containing oxalic acid dihydrate (7 g.). The solid obtained on dilution with water recrystallised from chloroform–ethanol, to give *5α-hydroxy-6β-propargyl-5α-pregnane-3,20-dione* as prisms, m. p. 231—233°, $[\alpha]_D^{22}$ +29·5° (*c* 0·95) (Found: C, 77·4; H, 9·2. $C_{24}H_{34}O_3$ requires C, 77·8; H, 9·25%).

6α-Propargylprogesterone (IV; R = Ac, R′ = H).—The foregoing hydroxy-diketone (4·65 g.) was refluxed for 1 hr. in ethanol (100 ml.) containing concentrated hydrochloric acid (0·4 ml.). *6α-Propargylprogesterone* was precipitated with water and crystallised from aqueous ethanol as plates, m. p. 130—131°, $[\alpha]_D^{20}$ +177·6° (*c* 1·03), $\lambda_{max.}$ 240 mμ (log ε 4·17), $\lambda_{max.}$ (in cyclohexane) 323

[9] Cf. Renaud, *Bull. Soc. chim. France*, 1950, 1044.

(ε 43), 338 (ε 41), 351 (ε 30) and 369 mμ (ε 10), [progesterone in cyclohexane shows $\lambda_{max.}$ 321 (ε 41), 338 (ε 38), 351 (ε 28) and 367 mμ (ε 11)], $\nu_{max.}$ (in CCl_4) 3315 (≡C·H), 2117 (·C≡CH), 1713 (20-one), 1686 and 1614 cm.$^{-1}$ (Δ^4-3-one) (Found: C, 81·8; H, 9·0. $C_{24}H_{32}O_2$ requires C, 81·8; H, 9·15%).

5α,17α-*Dihydroxy*-6β-*propargyl*-5α-*pregnane*-3,20-*dione* (III; R = O, R′ = Ac, R″ = OH).—The bis-ketal epoxide [6] (II; R = 1,1-ethylenedioxyethyl, R′ = OH) (11 g.) in dry benzene (350 ml.) was added with stirring to the Grignard reagent prepared from propargyl bromide (14 ml.) and magnesium (4 g.) in dry ether (150 ml.), and the mixture kept overnight at room temperature. The bisethylenedioxy-alcohol (14·2 g.), isolated in the usual way, was kept for 2 hr. at room temperature in methanol (200 ml.) and water (25 ml.) containing oxalic acid dihydrate (7 g.). 5α,17α-*Dihydroxy*-6β-*propargyl*-5α-*pregnane*-3,20-*dione* was precipitated with water and crystallised from dichloromethane–methanol as plates, m. p. 213—215°, $[\alpha]_D^{25}$ −61·1° (*c* 1·02), $\nu_{max.}$ (in Nujol) 3576, 3425 (OH), 3278 (≡C·H), 1712 (3- and 20-one), and 1690 cm.$^{-1}$ (17-OH, 20-one) * (Found: C, 74·0; H, 9·1. $C_{24}H_{34}O_4$ requires C, 74·5; H, 8·9%).

17α-*Hydroxy*-6α-*propargylprogesterone* (IV; R = Ac, R′ = OH).—The foregoing dihydroxy-diketone (4·3 g.) was refluxed for 1 hr. in ethanol (100 ml.) containing concentrated hydrochloric acid (0·4 ml.). The *product* was precipitated with water and crystallised from aqueous methanol as prisms, m. p. 164—166°, $[\alpha]_D^{23}$ +75·1° (*c* 1·79), $\lambda_{max.}$ 240 mμ, log ε 4·17, $\nu_{max.}$ (in Nujol) 3445 (OH), 3250 (≡C·H), 1700 (20-one), 1644 and 1599 cm.$^{-1}$ (Δ^4-3-one), $\nu_{max.}$ (in CH_2Cl_2) 1668, and 1608 cm^{-1} (Found: C, 78·1; H, 8·4. $C_{24}H_{32}O_3$ requires C, 78·2; H, 8·75%).

This compound (1·75 g.) in acetic acid (90 ml.) and acetic anhydride (20 ml.) containing toluene-*p*-sulphonic acid (0·8 g.) was stirred at room temperature for 4 hr. with initial cooling. The *acetate*, isolated with ether, was crystallised from aqueous methanol as prisms, m. p. 180—182°, $[\alpha]_D^{22}$ +66·8° (*c* 1·8), $\lambda_{max.}$ 239 mμ, log ε 4·18, $\nu_{max.}$ (in Nujol) 3301 (≡C·H), 2112 (C≡CH) 1741, 1246 (OAc), 1722 (20-one), 1671 and 1614 cm.$^{-1}$ (Δ^4-3-one) (Found: C, 75·6; H, 8·3. $C_{26}H_{34}O_4$ requires C, 76·1; H, 8·35%).

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* Compounds containing the 17α-hydroxy-20-ketone system often show an " extra " carbonyl band around 1690 cm.$^{-1}$ due to hydrogen-bonding.[10]

[10] Jones, Humphries, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2820.