482. *Modified Steroid Hormones. Part XV.* A New Route to 17α-Alkynyl-17β-hydroxy-steroids.*

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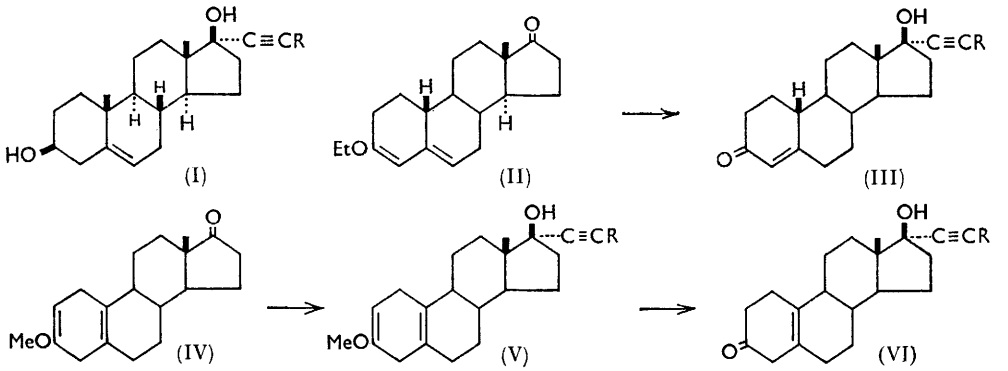
A general method for the conversion of 17-oxo-steroids into their 17α-alkynyl-17β-hydroxy-derivatives is reported. Its application to the preparation of some homologues of 17α-ethynyl-17β-hydroxyestr-4- (III; R = H) and -5(10)-en-3-one (VI; R = H) is described.

In Part XI [1] the preparation of 17α-prop-1′-ynyl- and 17α-but-1′-ynyl-17β-hydroxyandrost-4-en-3-one was reported. These compounds proved more active biologically [2] than the parent 17α-ethynyl-17β-hydroxyandrost-4-en-3-one (ethisterone), an observation which led us to extend the study to the partial synthesis of the corresponding homologues of 17α-ethynyl-17β-hydroxyestr-4- [3] (III; R = H) and -5(10)-en-3-one [4] (VI; R = H). The method used in Part XI, however, was clearly inapplicable to the preparation of the required 5(10)-ene derivatives (VI; R = alkyl), which fact led us to examine alternative routes to the required compounds.



Direct condensation of the model compound dehydroepiandrosterone with propyne in the presence of potassium t-butoxide proved wholly abortive. Slightly more encouraging results attended condensation of the lithium derivative of propyne with the steroidal ketone in tetrahydrofuran, when *ca.* 15% of the required product was obtained. Attention was finally directed to reaction with propynylmagnesium bromide, which was conveniently prepared by addition of the alkyne in cold tetrahydrofuran to ethylmagnesium bromide prepared in the same solvent (cf. the preparation of ethynylmagnesium bromide [5]). Reaction of this Grignard reagent with dehydroepiandrosterone in the boiling solvent readily furnished the known 17α-prop-1′-ynylandrost-5-ene-3β,17β-diol [1] (I; R = Me) in excellent yield. In addition, no significant reduction of the 17-oxo-group was observed such as occurs with ethyl- or n-propyl-magnesium halide.[6,7] Equally good results followed the use of butynyl- and hexynyl-magnesium bromide. The reaction, moreover, proved to be of general applicability and was successfully employed for the preparation of a range of 17α-alkynyl-17β-hydroxy-steroidal types (see Experimental section).

* Part XIV, preceding paper.

[1] Part XI, *J.*, 1959, 1957.
[2] David, Hartley, Millson, and Petrow, *J. Pharm. Pharmacol.*, 1957, **9**, 929.
[3] Djerassi, Miramontes, Rosenkranz, and Sondheimer, *J. Amer. Chem. Soc.*, 1954, **76** 4092.
[4] Colton, to G. D. Searle & Co., U.S.P. 2,725,389/1955.
[5] Jones, Skatteböl, and Whiting, *J.*, 1956, 4765.
[6] Butenandt, Schmidt-Thomé, and Paul, *Ber.*, 1938, **71**, 1313.
[7] Ruzicka and Rosenberg, *Helv. Chim. Acta*, 1936, **19**, 357.

Extension of this new method to 3-ethoxyestra-3,5-dien-17-one [3] (II), followed by cleavage of the 3-enol ether group with oxalic acid, furnished the required 17β-hydroxy-17α-prop-1′-ynylestr-4-en-3-one (III; R = Me). The higher homologues (III; R = Et, Pr^n, and Bu^n) were similarly prepared.

Partial synthesis of the estr-5(10)-enes (VI) proved more difficult. Reaction of 3-methoxyestra-2,5(10)-dien-17-one [8] (IV) with the alkynylmagnesium bromide gave the required 17α-alkynyl-17β-hydroxy-intermediates (V; R = alkyl), but these proved to be highly susceptible to acid treatment, being rapidly transformed into the corresponding 3-oxo-Δ^4-compounds (III; R = alkyl). It was ultimately found, however, that cautious treatment with aqueous-methanolic oxalic acid at room temperature for 30 min. furnished the required 17α-alkynyl-17β-hydroxyestr-5(10)-en-3-ones (VI; R = Me, Et, and Pr^n) essentially free from their Δ^4-isomers.

Experimental

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

17α-Prop-1′-ynylandrost-5-ene-3β,17β-diol (I; R = Me).—Ethylmagnesium bromide was prepared under nitrogen from magnesium (3·65 g.), ethyl bromide (16·3 g.), and anhydrous tetrahydrofuran (150 ml.). Propyne (8 g.) in tetrahydrofuran (60 ml.) at −60° was added rapidly with stirring and, when evolution of ethane had ceased (*ca.* 30 min.), dehydroepiandrosterone (4·3 g.) in tetrahydrofuran (100 ml.) was added dropwise, a gelatinous precipitate forming. The stirred mixture was heated under reflux for 2 hr., cooled, and treated with ammonium chloride (50 g.) in water (200 ml.), and the product isolated with ether. Purification from aqueous methanol gave 17α-prop-1′-ynylandrost-5-ene-3β,17β-diol in plates, m. p. 179—181°, not depressed in admixture with a specimen prepared by an earlier method.[1] Oppenauer oxidation (aluminium isoproproxide in ethyl methyl ketone and toluene) gave 17β-hydroxy-17α-prop-1′-ynylandrost-4-en-3-one, m. p. 177—179°. This compound was previously prepared by a slightly different route [1] and had m. p. 151—152°. After storage, this m. p. was found to have risen to 177—179°. The infrared spectra of the two higher-melting forms were identical.

17α-Hex-1′-ynylandrost-5-ene-3β,17β-diol (I; R = Bu^n), prepared similarly from dehydroepiandrosterone and hex-1-yne, crystallised from acetone–hexane in needles, m. p. 70—72° (after prolonged drying), $[\alpha]_D^{22}$ −114° (*c* 1·0) (Found: C, 81·1; H, 10·7. $C_{25}H_{38}O_2$ requires C, 81·1; H, 10·3%).

17β-Hydroxy-17α-prop-1′-ynylestr-4-en-3-one (III; R = Me).—Ethyl bromide (5 g.) was slowly added to magnesium (1·1 g.) in anhydrous tetrahydrofuran (50 ml.). The mixture was then refluxed under nitrogen for 30 min. and allowed to cool to room temperature. Propyne (3 g.) in tetrahydrofuran (30 ml.) at −60° was added with stirring, followed, 30 min. later, by 3-ethoxyestra-3,5-dien-17-one [3] (1·3 g.) in tetrahydrofuran (50 ml.). The mixture was refluxed for 2 hr. cooled somewhat, treated with N-aqueous oxalic acid (100 ml.), and heated under reflux with stirring for a further 1 hr. After removal of magnesium oxalate by filtration, the product was isolated with ether and crystallised from acetone–hexane. Further purification from aqueous methanol (charcoal) gave *17β-hydroxy-17α-prop-1′-ynylestr-4-en-3-one*, plates, m. p. 165—167°, $[\alpha]_D^{23}$ −37° (*c* 0·19), $\lambda_{max.}$ 241 mμ (log ε 4·21) (Found: C, 80·8; H, 8·9. $C_{21}H_{28}O_2$ requires C, 80·8; H, 9·0%).

17α-But-1′-ynyl-17β-hydroxyestr-4-en-3-one (III; R = Et), prepared similarly from the enol ether (II) and but-1-yne, crystallised from acetone–hexane in plates, m. p. 144—146°, $[\alpha]_D^{23}$ −46° (*c* 0·24), $\lambda_{max.}$ 240 mμ (log ε 4·23) (Found: C, 80·6; H, 9·1. $C_{22}H_{30}O_2$ requires C, 81·0; H, 9·2%).

17β-Hydroxy-17α-pent-1′-ynylestr-4-en-3-one (III; R = Pr^n) crystallised from acetone–hexane in plates, m. p. 100—102°, $[\alpha]_D^{23}$ −42° (*c* 0·78), $\lambda_{max.}$ 240 mμ (log ε 4·22) (Found: C, 80·9; H, 9·0. $C_{23}H_{32}O_2$ requires C, 81·2; H, 9·4%).

17α-Hex-1′-ynyl-17β-hydroxyestr-4-en-3-one (III; R = Bu^n) crystallised from acetone–hexane in prisms, m. p. 134—136°, $[\alpha]_D^{21}$ −40° (*c* 0·62), $\lambda_{max.}$ 240 mμ (log ε 4·24) (Found: C, 81·4; H, 9·6. $C_{24}H_{34}O_2$ requires C, 81·3; H, 9·7%).

[8] Colton, Nysted, Riegel, and Raymond, *J. Amer. Chem. Soc.*, 1957, **79**, 1123.

3-Methoxy-17α-prop-1′-ynylestra-2,5(10)-dien-17β-ol (V; R = Me).—Ethylmagnesium bromide was prepared under nitrogen from magnesium (1·2 g.), ethyl bromide (6 g.), and anhydrous tetrahydrofuran (50 ml.). Propyne (10 g.) in tetrahydrofuran (50 ml.) at −70° was added with stirring, followed after 30 min. by 3-methoxyestra-2,5(10)-dien-17-one [8] (1·4 g.) in the same solvent (50 ml.). The mixture was refluxed for 2 hr., cooled, and treated with aqueous ammonium chloride, and the product isolated with ether. After purification from aqueous methanol to which a drop of pyridine had been added, *3-methoxy-17α-prop-1′-ynylestra-2,5(10)-dien-17β-ol* formed needles, m. p. 177—179°, $[\alpha]_D^{23}$ +70° (*c* 0·68 in $CHCl_3$ containing a trace of pyridine) (Found: C, 80·7; H, 9·1. $C_{22}H_{30}O_2$ requires C, 80·9; H, 9·3%), after prolonged drying.

17β-Hydroxy-17α-prop-1′-ynylestr-5(10)-en-3-one (VI; R = Me).—The foregoing compound (250 mg.) in methanol (45 ml.) was treated with oxalic acid dihydrate (630 mg.) in water (5 ml.) for 30 min. at room temperature. The mixture was poured into water and extracted with ether, and the extract washed with aqueous sodium hydrogen carbonate, water, and dried. Removal of the solvent *in vacuo* gave a gum which crystallised from acetone–hexane. *17β-Hydroxy-17α-prop-1′-ynylestr-5(10)-en-3-one* formed plates, m. p. 153—155°, $[\alpha]_D^{22}$ +115° (*c* 0·72 in $CHCl_3$ and a trace of pyridine) (Found: C, 80·6; H, 9·2. $C_{21}H_{28}O_2$ requires C, 80·7; H, 9·0%).

17α-But-1′-ynyl-3-methoxyestra-2,5(10)-dien-17β-ol (V; R = Et), prepared from the enol ether (IV) and but-1-yne, crystallised from aqueous methanol–pyridine in needles, m. p. 68—70°, $[\alpha]_D^{22}$ +66° (*c* 0·41 in $CHCl_3$ and a trace of pyridine) (Found: C, 80·8; H, 9·4. $C_{23}H_{32}O_2$ requires C, 81·2; H, 9·4%).

17α-But-1′-ynyl-17β-hydroxyestr-5(10)-en-3-one (VI; R = Et), prepared from the foregoing compound by treatment with aqueous-methanolic oxalic acid at room temperature, crystallised from hexane in prisms, m. p. 114—115°, $[\alpha]_D^{23}$ +124° (*c* 0·98 in $CHCl_3$ and a trace of pyridine) (Found: C, 81·4; H, 8·9. $C_{22}H_{30}O_2$ requires C, 81·0; H, 9·2%).

3-Methoxy-17α-pent-1′-ynylestra-2,5(10)-dien-17β-ol (V; R = Pr^n), prepared from the enol ether (IV) and pent-1-yne, crystallised from aqueous methanol in needles, m. p. 95—96°, $[\alpha]_D^{22}$ +58° (*c* 0·98 in $CHCl_3$ and a trace of pyridine) (Found: C, 81·2; H, 9·6. $C_{24}H_{31}O_2$ requires C, 81·4; H, 9·6%).

17β-Hydroxy-17α-pent-1′-ynylestr-5(10)-en-3-one (VI; R = Pr^n), prepared from the foregoing compound, crystallised from hexane in prisms, m. p. 93—95°, $[\alpha]_D^{21}$ +112° (*c* 0·54 in $CHCl_3$ and a trace of pyridine) (Found: C, 81·3; H, 9·2. $C_{23}H_{32}O_2$ requires C, 81·2; H, 9·4%).

17α-Pent-1′-ynylestra-1,3,5(10)triene-3,17β-diol.—A solution of estrone acetate (4·1 g.) in tetrahydrofuran (100 ml.) was added dropwise in 20 min. to a stirred solution of pentynylmagnesium bromide (excess) prepared in tetrahydrofuran (200 ml.). The mixture was refluxed for 2 hr., cooled, and treated with aqueous ammonium chloride, and the product was isolated with ether. In order to ensure complete saponification, this material in methanol (90 ml.) was heated with potassium carbonate (2 g.) in water (10 ml.) for 3 hr. The product, isolated by dilution with water and extraction with ether, crystallised from acetone–hexane to give the *diol*, needles, m. p. 110—113°, $[\alpha]_D^{22}$ −5·5° (*c* 0·9) (Found: C, 81·6; H, 9·1. $C_{23}H_{30}O_2$ requires C, 81·7; H, 8·9%).

17α-Prop-1′-ynyl-3,5-cycloandrostane-6β,17β-diol, prepared from 6α-hydroxy-3,5-cycloandrostan-17-one,[9] separated from acetone–hexane in needles, m. p. 199—201°, $[\alpha]_D^{21}$ −12° (*c* 1·03) (Found: C, 80·4; H, 9·7. $C_{22}H_{32}O_2$ requires C, 80·5; H, 9·8%).

17α-But-1′-ynyl-3,5-cycloandrostane-6β,17β-diol crystallised from acetone–hexane in prisms, m. p. 172—174°, $[\alpha]_D^{22}$ −14·5° (*c* 0·92) (Found: C, 80·4; H, 10·0. $C_{23}H_{31}O_2$ requires C, 80·7; H, 9·9%).

17α-Pent-1′-ynyl-3,5-cycloandrostane-6β,17β-diol separated from aqueous methanol in blades, m. p. 146—148°, $[\alpha]_D^{22}$ −13° (*c* 1·04) (Found: C, 81·1; H, 9·9. $C_{23}H_{24}O_2$ requires C, 80·9; H, 10·1%).

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[9] Butenandt and Suranyi, *Ber.*, 1942, **75**, 591.