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MODIFIED STEROID HORMONES—XXXV[1]

STEROIDAL ETHYNYL AMINES

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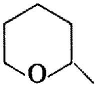
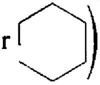
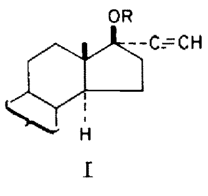
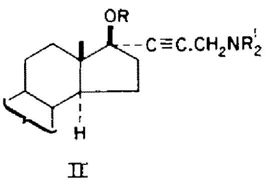
Abstract—Application of the Mannich reaction to a variety of steroidal 17α-ethynyl-17β-ols has yielded the corresponding propynylamines.

Terminal acetylenes have been shown[2] to undergo the Mannich reaction to yield the corresponding alk-2-ynyl-1-amines. α-Ethynyl carbinols gave very poor yields of products, but the condensation proceeded normally when the hydroxyl function was protected by acetylation.

We have now extended the Mannich reaction to steroidal 17α-ethynyl-17β-ols (I; R = H) in which the hydroxyl group was protected as the tetrahydropyran-2-yl ether (I; R = ). The Mannich condensations were carried out under basic conditions and, in general, required 2–6 days at 100° for completion. The protecting group was removed during the work-up procedure to give the corresponding 17α-(3′-dialkylaminoprop-1′-ynyl)-17β-ols (II; R = H, R^1 = Me or ). In one case in which the condensation was carried out on a 17β-acetoxy-17α-ethynyl steroid (I; R = Ac), the product (II; R = Ac, R^1 = Me) was an intractable gum which could only be obtained crystalline as a solvate.



I



II

Biological study of the products (II) and of their quaternary salts* failed to reveal significant activity.

EXPERIMENTAL

Rotations were determined on ca. 1% solutions in chloroform at room temp. U.V. absorption spectra were determined in ethanol.

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[1] Part XXXIV, *Tetrahedron* **20**, 1927 (1964).

[2] E. R. H. Jones, I. Marszak, and H. Bader, *J. Chem. Soc.* 1578 (1947).

General preparative procedure. The steroidal 17α-ethynyl-17β-ol (10 parts), dihydropyran (20 parts), phosphoryl chloride (0·25 parts) and dry benzene (100–250 parts) were stirred at room temp. for ca. 2 hr. The reaction mixture, diluted with ether, was poured into dil. Na_2CO_3 aq, washed with water, dried (Na_2SO_4) and evaporated to dryness under red. press. The crude product, which lacked hydroxyl absorption in the I.R., was kept at 100° in dioxan (100 parts) containing 30% aq dimethylamine, or other secondary amine, (10 parts) and *para*formaldehyde (2 parts) for 2–6 days, with daily additions of dimethylamine and *para*formaldehyde. Most of the dioxan was removed under red. press., the residue was diluted with ether and washed with 5 portions of dil. HCl.

The ether layer was washed with Na_2CO_3 aq and water. Evaporation of the dried (Na_2SO_4) extract afforded unchanged starting material, with the protecting group intact.

The acid wash was kept at room temp for 1–2 hr to ensure hydrolytic fission of the tetrahydropyranyl ether residue and then made alkaline with NaOH aq. The free amine was isolated by filtration or extraction and purified in the usual way.

3β,17β-Dihydroxy-17α-(3′-*dimethylaminoprop*-1′-*ynyl)androst*-5-*ene*, prepared from 3β,17β-dihydroxy-17α-ethynylandrost-5-ene, crystallized from acetone as needles, m.p. 179–181°, $[\alpha]_D$ −114·5°. (Found: C, 77·15; H, 9·85; N, 4·1. $C_{24}H_{37}NO_2$ requires: C, 77·55; H, 10·05; N, 3·75%).

The 3-*mono-acetate* (acetic anhydride–pyridine, 100°, 1 hr) formed needles from methanol aq., m.p. 135–137°, $[\alpha]_D$ −101·6°. (Found: C, 75·6; H, 9·35; N, 3·65. $C_{26}H_{39}NO_3$ requires: C, 75·5; H, 9·5; N, 3·4%).

The *methiodide* (methyl iodide–benzene, room temp, 2 hr) formed needles from methanol–ether, m.p. 259–261° dec. (Found: C, 58·5; H, 7·95; N, 2·65; I, 24·45. $C_{25}H_{40}NIO_2$ requires: C, 58·45; H, 7·85; N, 2·75; I, 24·7%).

The *tartrate* formed solvated needles from water, m.p. 165–168° dec. Satisfactory analytical data could not be obtained.

3,*17β-Dihydroxy*-17α-(3′-*dimethylaminoprop*-1′-*ynyl)oestra*-1,3,5(10)-*triene*, prepared from 17α-ethynyloestradiol, crystallized from methanol aq. as flakes, m.p. 210–212°, $[\alpha]_D$ −6·4°. (Found: C, 78·0; H, 8·6; N, 4·05. $C_{23}H_{31}NO_2$ requires: C, 78·15; H, 8·85; N, 3·95%).

The *hydrochloride* formed flakes from methanol–ether, m.p. 265–267° dec. (Found: C, 70·25; H, 8·1; N, 3·45; Cl, 8·95. $C_{23}H_{32}NClO_2$ requires: C, 70·85; H, 8·25; N, 3·6; Cl, 9·1%).

The *methobromide* formed flakes from ether–methanol, m.p. 252–254°. (Found: C, 63·95; H, 7·95; N, 3·05; Br, 17·65. $C_{24}H_{34}NBrO_2$ requires: C, 64·3; H, 7·65; N, 3·1; Br, 17·8%).

17β-Hydroxy-17α-(3′-*dimethylaminoprop*-1′-*ynyl) androst*-4-*en*-3-*one*, prepared from 3,3-ethylenedioxy-17α-ethynylandrost-5-en-17β-ol,[3] formed needles from aq. methanol, m.p. 154–156°, $[\alpha]_D$ +16·8°, λ_{max} 240 mμ (ε, 16,445). (Found: C, 77·75; H, 9·55; N, 3·57. $C_{24}H_{35}NO_2$ requires: C, 78·0; H, 9·55; N, 3·8%).

The *methobromide* formed needles from methanol–ether, m.p. 270–272° dec. (Found: 64·25; H, 8·5; N, 3·3; Br, 17·75. $C_{25}H_{38}NBrO_2$ requires: C, 64·65; H, 8·25; N, 3·0; Br, 17·2%).

17β-Hydroxy-17α-(3′-*piperidinoprop*-1′-*ynyl) androst*-4-*en*-3-*one*, prepared from 3,3-ethylenedioxy-17α-ethynylandrost-5-en-17β-ol,[3] formed plates from acetone, m.p. 174–175°, $[\alpha]_D$ +11·9°, λ_{max} 240 mμ (ε, 16,060). (Found: C, 79·3; H, 9·85; N, 3·0. $C_{27}H_{39}NO_2$ requires: C, 79·15; H, 9·6; N, 3·4%).

4-*Methyl*-17α-(3′-*dimethylaminoprop*-1′-*ynyl)oestra*-1,3,5(10)-*trien*-17β-*ol*, prepared from 17α-ethynyl-4-methyloestra-1,3,5(10)-trien-17β-*ol*, formed solvated needles from acetone–hexane, m.p. 127–128°, $[\alpha]_D$ −12°. (Found: C, 82·0; H, 9·2; N, 4·05. $C_{24}H_{33}NO$ requires: C, 82·0; H, 9·45; N, 4·0% after drying at 80° *in vacuo*).

17β-Acetoxy-17α-(3′-*dimethylaminoprop*-1′-*ynyl)oestr*-4-*en*-3-*one*, prepared from 17β-acetoxy-3,3-ethylenedioxy-17α-ethynyloestr-5-ene (total product obtained by ketalization of 17β-acetoxy-17α-ethynyloestr-4-en-3-one[4]) (omitting treatment with dihydropyran), was a gum which crystallized as an acetone solvate, needles, m.p. 57–60°, $[\alpha]_D$ −45°, λ_{max} 239 mμ (ε, 15,270), $\nu_{max}^{CCl_4}$ 1745 (−OAc), 1710 (Me_2CO), 1678 and 1620 cm^{-1} (4-en-3-one). (Found: C, 73·4; H, 8·95; N, 3·35. $C_{25}H_{35}NO_3 \cdot (CH_3)_2CO$ requires: C, 73·8; H, 9·0; N, 3·05%).

The *methobromide* crystallized from methanol–ether as needles, m.p. 241–242° dec. (Found: C, 62·95; H, 7·65; N, 2·8; Br, 16·1. $C_{26}H_{38}NBrO_3$ requires: C, 63·4; H, 7·8; N, 2·85; Br, 16·2%).

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[3] E. R. Squibb & Sons, *U.S. Pat* 2,288,854.

[4] J. Iriarte, C. Djerassi and H. J. Ringold, *J. Amer. Chem. Soc.* **81**, 436 (1959).