Synthesis of the Steroid (±)-17α-Ethynyl-17β-hydroxy-13β-allylgon-4-en-3-one

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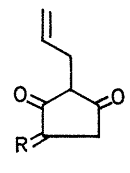
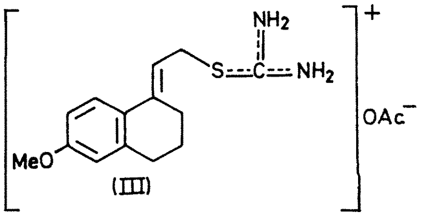
Summary The title compound was synthesized using various methods of protecting the C-13 allyl group from reducing agents.

REACTION[1] of diethyl oxalate with allylacetone in the presence of sodium ethoxide and subsequent treatment of the product with acid gave compound (I), m.p. 43—45°, which was converted with $NaBH_4$ into (II), m.p. 124—126·5°. Condensation of (II) with the isothiouronium salt (III)[2] yielded (IV), m.p. 81—83°. By the conventional method, cyclization of the product (m.p. 68—69°) obtained after reduction of the C-15 double bond with Zn dust and AcOH yielded (V), m.p. 73—76°, λ_{max} 314 nm (ϵ 30,900), which was reduced with $NaBH_4$ in MeOH to (VI), ν_{max} 3350—3500 cm^{-1} (OH). Treatment of (VI) with conc. HCl in MeOH gave (VII), m.p. 129—132°. A sequence of reactions (*e.g.* partial hydrogenation in the presence of Raney-Ni and reduction with potassium in liquid ammonia and tetrahydrofuran) afforded (VIII), m.p. 125—128°, λ_{max} 278 (ϵ 1890) and 286 nm (1780). Treatment[3] of (VIII) with acetic anhydride and toluene *p*-sulphonic acid at 80° for 1·5 h gave (IX) as the major product in 26% yield, m.p. 113—117°. Hydrolysis of (IX) with KOH in MeOH gave (X), m.p. 140—142°, ν_{max} 3400 cm^{-1} (OH), which was converted into the tetrahydropyranyl ether (XI), m.p. 97—98°, so that the allyl group might not be reduced in subsequent reactions. Birch reduction of (XI) with lithium in liquid ammonia, tetrahydrofuran, and EtOH followed by acid treatment yielded (XII), m.p. 150—151°, λ_{max} 240 nm (ϵ 16,200). Compound (XII) was oxidized with CrO_3-C_5H_5N to (XIII), m.p. 167—168°, ν_{max} 1740 cm^{-1} (CO). The C-3 enol-ether of (XIII) was treated with lithium acetylide in ethylenediamine, and then, with acid to yield (±)-17α-ethynyl-17β-hydroxy-13β-allylgon-4-en-3-one (XIV), m.p. 144—145°, ν_{max} 3400 (OH), 3300 (C≡CH), 2100 (C≡C), 3100, 1620, 910 (CH_2=CH–), 1670, and 1630 cm^{-1} (C=C–CO), M^+ 324. The progestational activity of (XIV) was as potent as that of Norgestrel[4] (McPhail test).

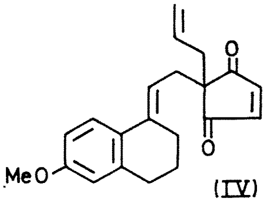


(I) R = O

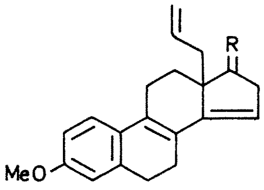
(II) R = $<^{\mathrm{OH}}_{\mathrm{H}}$



(III)

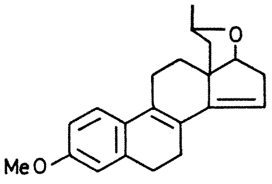


(IV)

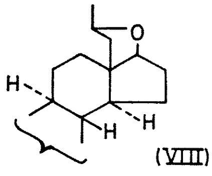


(V) R = O

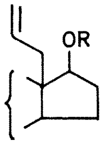
(VI) R = $<^{\mathrm{OH}}_{\mathrm{H}}$



(VII)

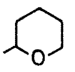


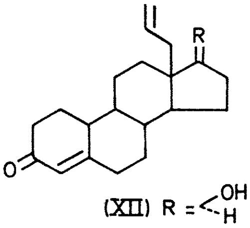
(VIII)



(IX) R = Ac

(X) R = H

(XI) R = 



(XII) R = $<^{\mathrm{OH}}_{\mathrm{H}}$

(XIII) R = O

(XIV) R = $<^{\mathrm{OH}}_{\mathrm{C\equiv CH}}$

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