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STEREOSPECIFIC TOTAL SYNTHESIS OF RAC. 5α-PREGNAN-3β-OL-20-ONE[*1]

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THE total synthesis of several steroids (1,2) has previously been reported from this laboratory. In this communication a straightforward total synthesis of rac. 5α-pregnan-3β-ol-20-one (XIIIa) is reported.

The tricyclic ketone II was prepared from 6-methoxy-1-tetralone (I) (3) through three steps in essentially the same manner as that described in the literature (4), but with a substantially improved yield (40 %) (4). Compound II was subjected to the modified Birch reduction of Wilds and Nelson (5) using lithium and alcohol in liquid ammonia to give the dienol ether III,[*2] m.p. 133~135°,[*3] λ_{max}^{EtOH} 208.5 mμ (ε 4480), $\nu_{max}^{CHCl_3}$ 3525, 3423, 1693, 1661 cm^{-1}, in 74 % yield. Acid hydrolysis of the latter compound gave the conjugated ketone IVa (6), m.p. 123~124°, λ_{max}^{EtOH} 242 mμ (ε 17200), $\nu_{max}^{CHCl_3}$ 3525, 3410, 1655, 1616 cm^{-1}, which was then converted into the benzoyl derivative IVb, m.p. 178.5~180°, λ_{max}^{EtOH} 235.5 mμ (ε 29600), $\nu_{max}^{CHCl_3}$ 1712, 1660, 1618, 1589, 1493 cm^{-1}. The overall yield of IVb from the dienol ether III was 89.4 % (6).

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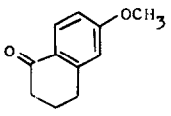
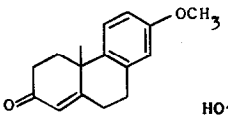
*1 Studies on Total Syntheses of Steroids XIII.

*2 All compounds reported gave satisfactory analyses.

*3 All melting points were measured on Kofler block and corrected.



I



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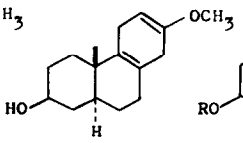

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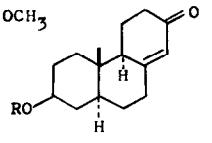
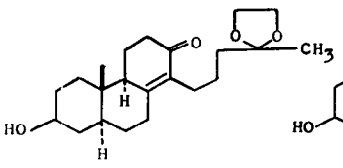
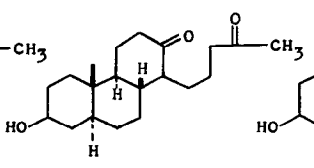


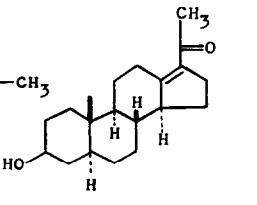
IVa R=H
IVb R=COC_6H_5



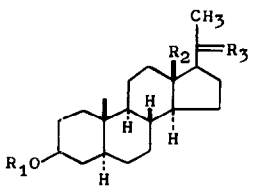
V



VI



VII



VIII R_1=H, R_2=CN, R_3=O
IX R_1=H, R_2=CN, R_3= 
X R_1=H, R_2=CH=NH, R_3= 
XI R_1=H, R_2=CHO, R_3= 
XII R_1=H, R_2=CH_3, R_3= 
XIIIa R_1=H, R_2=CH_3, R_3=O
XIIIb R_1=$COCH_3$, R_2=CH_3, R_3=O

Construction of ring D was carried out in a way similar to that reported in the total synthesis of dl-19-nor-pregna-1,3,5(10)-trien-3-ol-20-one (1b). Condensation of the benzoyl derivative IVb with 5-bromopentan-2-one ethylene ketal (1b) in boiling xylene in the presence of sodium hydride, followed by alkaline hydrolysis gave the product V, λ_{max}^{EtOH} 250 mμ, $\nu_{max}^{CHCl_3}$ 1660, 1610 cm^{-1}. This was converted without purification into the saturated diketone VI, $\nu_{max}^{CHCl_3}$ 1710 cm^{-1}, by reduction with lithium in liquid ammonia and by subsequent deketalization. Ring closure of the crude diketone was effected by warming it at 85° with dilute alcoholic sodium hydroxide to give the tetracyclic conjugated ketone VII (7), m.p. 157-158°, λ_{max}^{EtOH} 258 mμ (ε 13340), $\nu_{max}^{CHCl_3}$ 1670, 1643, 1615 cm^{-1}. The overall yield of VII from the tricyclic

conjugated ketone IVb was 52 %.

Introduction of a methyl group into the angular position, 13, was achieved by the method employed in the foregoing total synthesis of steroids (1). On hydrocyanation (2) using hydrogen cyanide and triethyl aluminum in tetrahydrofuran, the tetracyclic conjugated ketone VII was transformed in 80 % yield into the 13β-cyano ketone VIII, m.p. 166.5~167°, $\nu_{max}^{CHCl_3}$ 3600, 3460, 2240, 1713 cm^{-1}, accompanied with a small amount of the 13α-isomer. The 13β-cyano ketone VIII was converted in excellent yield into the ethylene ketal IX, m.p. 189~191°, $\nu_{max}^{CHCl_3}$ 3596, 3466, 2236 cm^{-1}, which was then reduced with an excess of lithium aluminum hydride in tetrahydrofuran at room temperature to afford the crude imino methyl derivative X, m.p. 185~201°, $\nu_{max}^{CHCl_3}$ 3594, 3400~3250, 1635 cm^{-1}. Hydrolysis of the latter compound with acetic acid in aqueous methanol-tetrahydrofuran buffered with sodium acetate gave the 13β-formyl derivative XI, m.p. 186~192°, $\nu_{max}^{CHCl_3}$ 3611, 3456, 2786, 1709 cm^{-1}, in excellent yield. Huang-Minlon reduction of compound XI reduced the formyl group and gave in 88 % yield the 13β-methyl compound XII, m.p. 182~183°, $\nu_{max}^{CHCl_3}$ 3595, 3430 cm^{-1}, which was then deketalized to the final product, rac. 5α-pregnan-3β-ol-20-one (XIIIa), m.p. 191~192°, $\nu_{max}^{CS_2}$ 3615, 1705 cm^{-1}. The last four reactions were carried out successively without purification of the products and the overall yield of XIIIa, based upon the 13β-cyano ketone ketal IX, was 65.6 %. The infra-red spectra of XIIIa and its acetate XIIIb, m.p. 132~134°, $\nu_{max}^{CS_2}$ 1736, 1704 cm^{-1}, were identical with those of authentic samples of the natural steroids (8). All reactions employed in this work proceeded in the desired stereochemical sense and no tedious procedures were necessary. The overall yield of the final product XIIIa from the tricyclic ketone II was 16.2 %.

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