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SYNTHESIS OF 17-AZAPROGESTERONE

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A recent communication (1) described the synthesis of 3β-acetoxy-5α-17-azapregnan-20-one and reported a method for the elimination of carbon 17 in order to make a 5-membered D-lactam. In continuation of that work, we wish to report the synthesis of 17-azaprogesterone.

The known 3β-acetoxy-17a-aza-D-homoandrost-5-en-17-one I (2), which served as starting material, was benzoylated under Schotten-Baumann conditions to give the N-benzoyl lactam II, m.p. 205-207°. Formylation of II with ethyl formate under the usual conditions (3) have in high yield the 16-hydroxymethylene-N-benzoyl lactam III, m.p. 135-138°. Oxidative cleavage of III with hydrogen peroxide in base (4) gave the expected 3β-hydroxy-13α-benzoylamino-13,16-seco-17-norandrost-5-en-16-oic acid IV, m.p. 232-234° in a yield of 70%. The ring closure to the imide V, m.p. 238-240°, was effected by heating the acid IV with acetic anhydride and pyridine on a steam bath. When the imide V was refluxed with hydrazine hydrate (5,6) in ethanol for 16 hours, debenzoylation occurred and 3β-acetoxy-17-azaandrost-5-en-16-one VI, m.p. 185-187° was obtained. Reduction of this γ-lactam VI with lithium aluminum hydride in refluxing dioxan for 70 hrs. yielded 17-azaandrost-5-en-3β-ol VII, m.p. 217-219°. Acetylation of VII with acetic anhydride in pyridine at room temperature gave 3β-acetoxy-17-azapregn-5-en-20-one VIII, m.p. 205-206°, which upon partial hydrolysis with potassium carbonate in methanol yielded 3β-hydroxy -17-azapregn-5-en-20-one IX, m.p. 256-257°. IX could also be obtained by treating the amine

VII with acetic anhydride at room temperature for 5 minutes. Finally, 17-azapregn-4-ene-3,20-dione X, m.p. 179-181°, (Anal.calcd.for $C_{20}H_{29}O_2N$: C,76.15; H, 9.27; N, 4.44. Found: C, 75.99; H, 9.41; N, 4.56.$\lambda_{max}^{methanol}$ 240 mμ, ε = 16,500. ν_{max}^{KBr} 1680 (Δ^4 -3-ketone), 1645 (N-acetyl), 1620 (c=c of Δ^4-3-ketone) cm^{-1}.) was obtained in approximately 70% yield by Oppenauer oxidation of 3β-hydroxy-17-azapregn-5-en-20-one VIII.

For all intermediates satisfactory elemental analysis were obtained.

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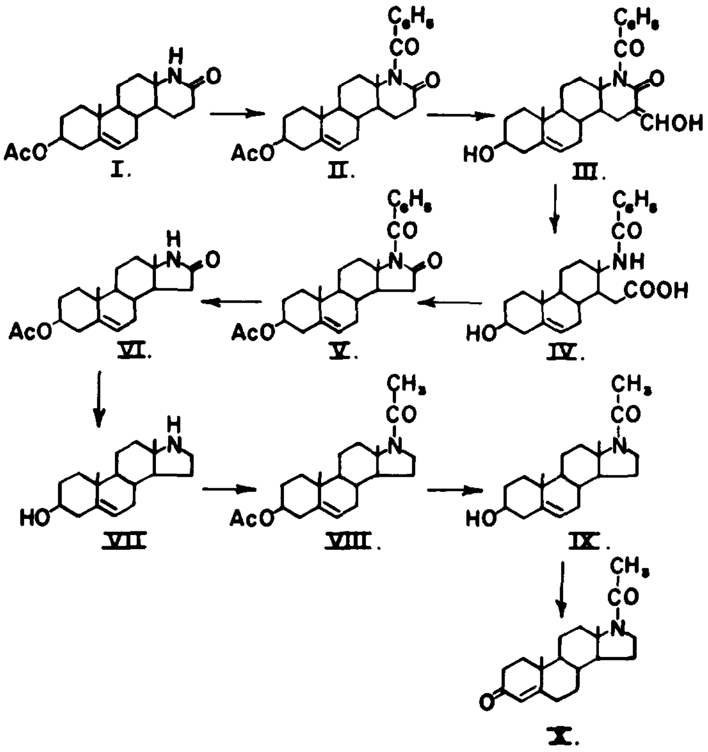
I.
II.
III.
IV.
V.
VI.
VII
VIII.
IX.
X.
AcO
HO
C_6H_5
CO
CHOH
COOH
NH
CH_3