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SYNTHESIS AND CHARACTERS OF 1-SUBSTITUTED A-NORSTEROIDS

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It would be expected that a substituent at C-1 of the steroid nucleus is more hindered sterically than at the other positions except C-11. We wish to report about the synthesis of A-norsteroids which have a side chain at C-1, and describe about some characteristic features of these compounds.

A-Nortestosterone (I) (1) was condensed with ethyl formate in the presence of sodium hydride to form 1-hydroxymethylene-A-nortestosterone (II), m.p. 200-202°, λ_{max}^{EtOH} mμ(log ε): 254(4.25), 290(3.99), $\lambda_{max}^{0.01N\text{-KOH-EtOH}}$: 235(4.37), 340(4.24), which easily produced the enamines with primary or secondary amines. By the hydrogenation with 5% paradium charcoal as catalyst, II absorbed one mole equivalent of hydrogen to form 3,5-dihydro compound (III), m.p. 217-219°, λ_{max}^{EtOH}: 278(3.99), $\lambda_{max}^{0.01N\text{-KOH-EtOH}}$: 310 (4.43), of which 5β configuration was deduced from the investigation described bellow.

Deformylation of III directly or *via* its morpholinoenamine (IV) with 10% sodium hydroxide solution followed by acetylation afforded 17β-acetoxy-A-norandrostan-2-one (V), m.p. 146-148°, which was identified with authentic 5β isomer (2,3) by the aid

of IR spectroscopy and gas chromatography. Authentic 5α (3,4) and 5β samples showed the retention time of 13.1 and 12.4 mins., respectively (2% SE-30, 180 cm×4 mm i.d., 210°; N_2 45 ml/min.).

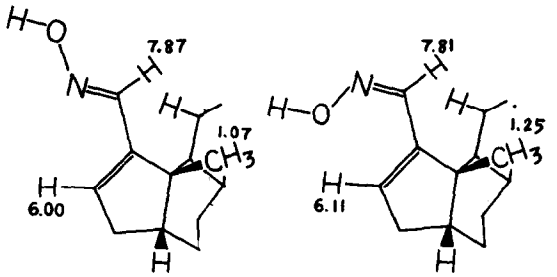
On the other hand, the formylation described above specifically converted 17β-hydroxy-5β-A-norandrostan-2-one (VI) (1) to 3-formyl derivative (VII), m.p. 242-243°, λ_{max}^{EtOH}: 311 (4.02), $\lambda_{max}^{0.01N\text{-KOH-EtOH}}$: 311(4.24), rather than 1-formyl compound (III).

1-Formyl ketone (III) was refluxed in benzene with cyclohexanol and p-toluenesulfonic acid to form the cyclohexyl ether (VIII), λ_{max}^{EtOH}: 279(4.67), which was reduced with sodium borohydride and then treated with 2N hydrochloric acid to give α,β-unsaturated aldehyde (IX), λ_{max}^{EtOH}: 243(3.96), ν_{max}^{KBr} cm^{-1}: 3441, 2718, 1682, 1595.

With the use of the silica gel liquid-chromatography, the oxime prepared from IX was able to be resolved into two compounds Xa, m.p. 205-208°, λ_{max}^{EtOH}: 242(4.22), ν_{max}^{KBr}: 3281, 1621, 971, NMR $\delta_{TMS}^{CDCl_3}$: 0.75(s, 18-CH_3), 1.07(s, 19-CH_3), 3.61(t, 17-H), 6.00(t, C=C-H), 7.87p.p.m.(s, N=C-H), and Xb, m.p. 185-187°, λ_{max}^{EtOH}: 242(4.14), ν_{max}^{KBr}: 3259, 1612, 926, NMR $\delta_{TMS}^{CDCl_3}$: 0.76(s, 18-CH_3), 1.25(s, 19-CH_3), 3.58(t, 17-H), 6.11(t, C=C-H), 7.81 p.p.m.(s, N=C-H), the ratio of Xa and Xb being 1 : 10. These two compounds should be the syn and anti isomers of the oxime on the basis of the following consideration.

It has been reported (5) that an azomethine proton cis to hydroxyl group of aldoxime resonates at a lower magnetic field than the proton of trans form. The Dreiding model of Xb shows that the rotation of aldoximino group is hindered by the angular

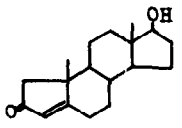
methyl group and the equatorial hydrogen atom at C-11. Thus, the oxygen atom of oximino group and the olefinic proton being very likely to form an intramolecular hydrogen bond, the signal of olefinic proton of the anti oxime should appear at a lower magnetic field than the proton of syn oxime. A similar example appears in reference (6). The discrepancy in chemical shift between 19-methyl groups of Xa and Xb is also due to the different anisotropic effects of the oxygen atoms. These considerations derive that Xa must be the syn form and Xb the anti form.



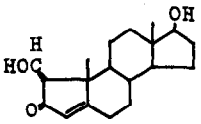
syn Xa anti Xb

Reduction of Xa with lithium aluminium hydride followed by acetylation with acetic anhydride and pyridine afforded the α,β-unsaturated acetoamide (XI), m.p. 161-163°, ν_{max}^{KBr}: 3313, 1741, 1643, NMR $\delta_{TMS}^{CDCl_3}$: 3.86(m, N-CH_2), 4.56(qa, 17-H), 5.46(m, C=C-H), 5.62p.p.m.(broad, N-H). On the other hand, the same treatment of Xb formed the acetoenamide (XII), m.p. 205-207°, λ_{max}^{EtOH}: 241 (3.16), ν_{max}^{KBr}: 3292, 1738, 1640, NMR $\delta_{TMS}^{CDCl_3}$: 3.89(m, C=C-CH_2), 4.50(qa, 17-H), 5.54(m, C=C-H), 5.62(broad, N-H). UV absorption band at 241 mμ for XII indicates the presence of N-C=C system

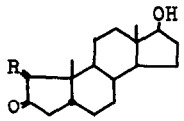
(7). Gas chromatographical analysis of the reaction products showed that the syn and anti isomers of the oxime produced specifically XI and XII, respectively (retention time of crude product: 9.40 and 10.05 mins. 1% SE-30, 210°). Consequently, it seems that the migration of C=C double bond has occurred in course of the reduction in the case of anti oxime (Xb).



I



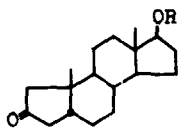
II



III R=CHOH

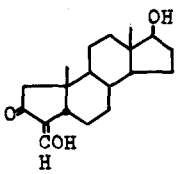
IV R=CHN⬡O

VIII R=CHO-⬡

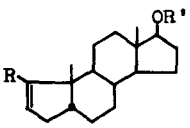


V R=$COCH_3$

VI R=H



VII



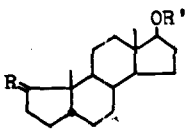
IX R=CHO, R'=H

Xa R=$^{HO}N{=}C^{H}$, R'=H

Xb R=$_{HO}N{=}C^{H}$, R'=H

XI R=$CH_2NHCOCH_3$, R'=$COCH_3$

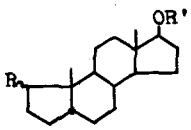
XIII R=C≡N, R'=$COCH_3$



XII

R=$CHNHCOCH_3$

R'=$COCH_3$



XIV

R=$CH_2NHCOCH_3$

R'=$COCH_3$

Furthermore, dehydration of Xb with acetic anhydride and pyridine afforded the α,β-unsaturated nitrile (XIII), m.p. 141-142°, λ_{max}^{EtOH}: 222(3.74), ν_{max}^{KBr}: 2231, 1738, 1605, which was treated with lithium aluminium hydride followed by acetylation to form the saturated acetoamide (XIV), m.p. 170-193°, ν_{max}^{KBr}: 3336, 1735, 1652. According to the NMR spectrum [$\delta_{TMS}^{CDCl_3}$: 0.94, 1.02p.p.m. (s, 19-CH_3)], this acetoamide is the 3 : 2 mixture of 1α and 1β derivatives.

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