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THE EPIMERIC 1-CYANO-5α-CHOLESTAN-3-ONES

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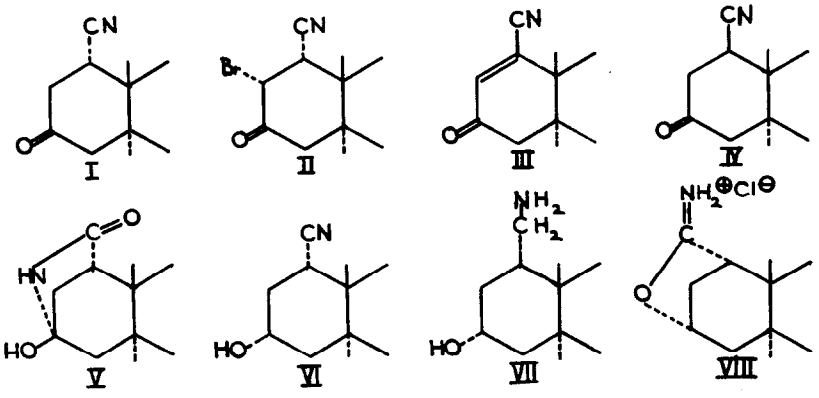
The introduction of cyano substituents into the steroid nucleus has been reported by several groups,(1) and recently, two publications (2) have been concerned with cyanation at C_1. As our work also involves steroids containing a cyano substituent at C_1, we wish to report our findings.

We prepared 1α-cyano-5α-cholestan-3-one (I), m.p. 168°, $[\alpha]_D$ + 56° ($CHCl_3$), $\nu_{max.}$ 2245 cm.$^{-1}$ (CN) and 1724 cm.$^{-1}$ (CO) from 5α-cholest-1-en-3-one, potassium cyanide and ammonium chloride, and our constants agree with those reported by Julia (2).



Bromination of the 1α-cyanoketone in acetic acid, gives the 2α-bromoketone (II), m.p. 210-212° (dec), $[\alpha]_D$ + 14° ($CHCl_3$), $\nu_{max.}$ 2245 $cm.^{-1}$ (CN), 1740 $cm.^{-1}$ (CO), which on dehydrobromination with lithium chloride (3) gives the unsaturated cyanoketone (III), m.p. 190°, $[\alpha]_D$ + 28° ($CHCl_3$), $\lambda^{EtOH}_{max.}$ 236 mμ (ε = 11,000) $\nu_{max.}$ 2237 $cm.^{-1}$ (CN), 1690 $cm.^{-1}$ (CO) 1575 $cm.^{-1}$ (C=C). Hydrogenation of the unsaturated ketonitrile (III) in ethyl acetate containing palladised charcoal gave 1β-cyano-5α-cholestan-3-one (IV), m.p. 144°, $[\alpha]_D$ + 17° ($CHCl_3$) and having an infrared spectrum identical to the 1α-cyanoketone (I).

The N.M.R. spectra of the cyanoketones (I and IV) were interpreted by Dr. P. Bladon, to whom we express our thanks. The 1α-cyanoketone (I) shows a doublet centred at τ =7.36 (J = 4.1 c.p.s) and a triplet centred at τ =6.83 (J = 4 c.p.s.). These values are consistent with the C_1-β hydrogen being equally coupled to both C_2 hydrogens. The C_{18} methyl group shows at τ =9.31 and the C_{19} methyl at τ =8.9. The 1β-cyanoketone (IV) shows a single peak at τ =7.31 (area = 3H) due to the 1α, 2α and 2β hydrogens. Because of the identical chemical shift of these three hydrogens no measurable coupling is discernable. The C_{18} methyl shows at τ =9.31, but the C_{19} methyl now appears at τ =8.73, the low field shift being due to the magnetic anisotropy of the -C≡N group.

The 1α-cyanoketone (I) with ethanolic potassium hydroxide yields the lactam (V), m.p. 252-254°, $[\alpha]_D$ + 82° ($CHCl_3$), $\nu_{max.}$ 1708 $cm.^{-1}$ (lactam CO), 1677 $cm.^{-1}$ (associated lactam CO). Treatment of the 1β-cyanoketone (IV) with ethanolic potassium hydroxide (1%) causes epimerisation to the axial 1α-cyanoketone (I), so that both ketones (I and IV) when hydrolysed with ethanolic potassium hydroxide (5%) afford the same lactam (V).

Reduction of the 1α-cyanoketone (I) either by a rapid Meerwein-Ponndorf procedure (4) or with sodium borohydride in isopropanol leads to the formation of 1α-cyano-3α-hydroxy-5α-cholestane (VI), m.p. 153-155°, $[\alpha]_D$ + 53° ($CHCl_3$), $\nu_{max.}^{CCl_4}$ 3663 $cm.^{-1}$ (OH) 2245 $cm.^{-1}$ (CN) which on further reduction with lithium aluminium hydride leads to 1α-aminomethyl-3α-hydroxy-5α-cholestane (VII), m.p. 186-187°, $[\alpha]_D$ + 38° ($CHCl_3$), $\nu_{max.}$ 1590 $cm.^{-1}$ (NH def.). We assign the 1α,3α-configuration to the amine (VII) as the infrared spectrum in carbon tetrachloride shows a band at 3650 $cm.^{-1}$ (OH) denoting a frequency shift ($\Delta\nu$) of 13 cm^{-1} in OH absorption and the doublet which is normally associated with a primary amine is replaced by a broad band at 3571-3300 $cm.^{-1}$ indicative of intramolecular hydrogen bonding. Moreover treatment of the hydroxynitrile (VI) in anhydrous ether with dry hydrogen chloride(5)yields the iminoether hydrochloride (VIII), m.p. 133-140°, $\nu_{max.}$ 1670 $cm.^{-1}$ (C=NH), thus establishing the cis relationship of the substituents at C_1 and C_3. It is interesting to note that Julia (2) reports that the reduction of the ethylene ketal of (I) with lithium aluminium hydride in tetrahydrofuran leads to replacement of the cyano substituent by hydroxyl with formation of the ethylene ketal of 1α-hydroxy-5α-cholestan-3-one.

Since alkaline hydrolysis of the saturated cyanoketones (I and IV) leads to lactam formation, it was of interest to observe the behaviour of 1-cyano-5α-cholest-1-en-3-one (III) to acidic and basic hydrolysis. The compound (III) is unaffected when refluxed with ethanolic hydrogen chloride, whereas aqueous ethanolic potassium hydroxide converts it in good yield to the known 5α-cholestan-1,3-dione (6), m.p. 166-168°, $[\alpha]_D$ + 100°

($CHCl_3$), $\lambda_{max.}^{EtOH}$ 255 mμ (ε = 16,000), $\lambda_{max}^{EtOH/NaOH}$ 285 mμ (ε = 19,000), $\nu_{max.}$ 1736, 1710 $cm.^{-1}$. Bromination of the dione gave the known 2,2-dibromo-5α-cholestan-1,3-dione.

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