Total Synthesis of a Ring-C-aromatic 18-Nor-steroid

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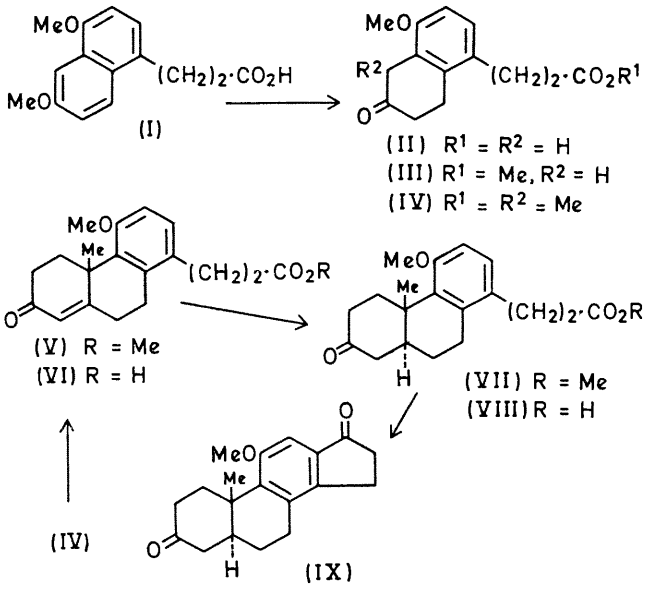
Summary The total synthesis of 11-methoxy-18-nor-5α-androsta-8(9),11,13(14)-triene-3,17-dione is reported

IN view of the recent interest[1] in C-ring-aromatic steroids, we report our work on the total synthesis of such a compound



Reduction† of the known acid (I)[2] with sodium and alcohol in liquid ammonia, followed by mild acid hydrolysis, furnished a mixture of products Chromatography of this mixture afforded the crystalline acid‡ (II) (64%), m p 126—127°, λ_{max} 275 and 283 nm (ε 1995 and 1963), ν_{max} 1712 cm^{-1}, τ ($CDCl_3$) 6 77—7 57 (8H), 6 45 (2H, s), 6 22 (3H, s), and 3 12 (2H, q, *J* 8 Hz) The keto-acid (II) furnished a methyl ester (III), m p 84°, λ_{max} 276 and 283 nm (ε 1905 and 1928), ν_{max} 1720 cm^{-1}, τ ($CDCl_3$) 6 81—7·57 (8H), 6 46 (2H, s), 6 32 (3H, s), 6 20 (3H, s), and 3 17 (2H, q, *J* 8 6 Hz) The enamine, m p 98—99°, ν_{max} 1728, 1611, and 1568 cm^{-1}, prepared from (III) was alkylated with methyl iodide in methanolic solution The alkylated product, obtained as a liquid, was purified by evaporative distillation The resulting homogeneous (t l c and column chromatography) product provided a crystalline semicarbazone (91%), m p 203—204° The structure (IV) for this product is supported from its spectral characteristics λ_{max} 276 and 283 nm (ε 1905 and 1950), ν_{max} (film) 1711 and 1733 cm^{-1}, τ (CCl_4) 8 74 (3H, d, *J* 7·5 Hz), 7 00—7 80 (9H), 6 41 (3H, s), 6 23 (3H, s), and 3 25 (2H, q, *J* 7 2 Hz)

The reaction of the keto-ester (IV) with the methiodide of 1-diethylaminobutan-3-one furnished a higher-boiling product which was characterised as (V) from elemental analyses and spectral properties, λ_{max} 229, 278, and 284 nm (ε 21,880, 3236, and 3199), ν_{max} 1715 and 1660 cm^{-1}, τ (CCl_4) 8 32 (3H, s), 6 95—8 22 (12H), 6 37 (3H, s), 6 18 (3H, s), 4 32 (1H, s), and 3 20 (2H, q, *J* 8 4 Hz), 2,4-dinitrophenylhydrazone, m p 182—183°, λ_{max} ($CHCl_3$) 390 nm (ε 34,040), semicarbazone, m p 239—240° Alkaline hydrolysis of (V) produced a noncrystalline acid, characterised as (VI) by its crystalline semicarbazone, m p 243—244° Birch reduction of (VI) followed by esterification (CH_2N_2) furnished the crystalline methyl ester (VII), m p 89°, λ_{max} 275 and 282 nm (ε 1938 and 1945), ν_{max} 1723 and 1705 cm^{-1} This ester, on alkaline hydrolysis, afforded the corresponding acid (VIII), m p 140°, λ_{max} 276 and 283 nm (ε 1823 and 1833), ν_{max} 1705 cm^{-1} (broad) The *trans*-structure (VIII) for the acid is assigned by analogy with the well-known stereochemical course of the Birch reduction Polyphosphoric acid cyclisation of (VIII) furnished in excellent yield the crystalline C-aromatic compound (IX), m p 172°, λ_{max} 264 and 319 nm (ε 15,490 and 6542), ν_{max} 1704 cm^{-1} (broad)

As far as we know, this is the first synthesis of a ring-C-aromatic steroid with an angular methyl group at C-10 and an oxygen function at C-11

† The reaction conditions for this reduction are critical, slight change in the conditions produces β-(1,2 3 4-tetrahydro 8-methoxy-5-naphthyl)propionic acid as the main product of the reduction

‡ All compounds described herein gave expected elemental analyses. U v spectra were taken in ethanol solution, and i r spectra were measured in chloroform solution unless otherwise stated

The structure recently established[3] for the mould metabolite, viridin, is the first naturally occurring c-aromatic steroid.

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