A Simple Route to 17-Aza-5α-androstan-16-one

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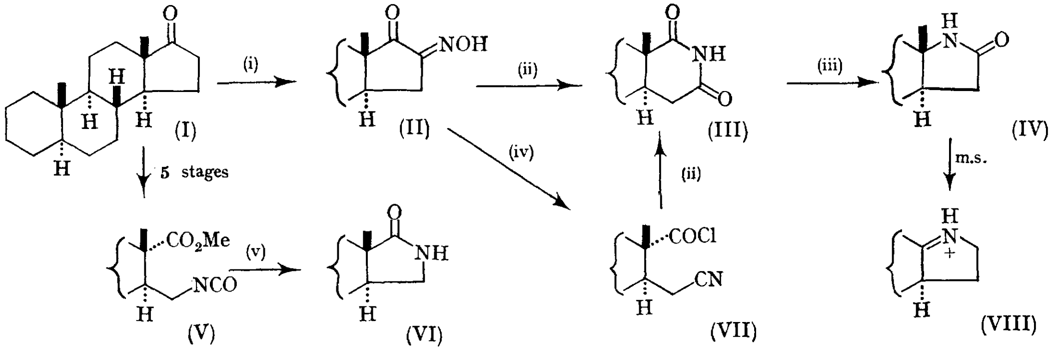
IN connection with work on 5α-androstan-16-one,[1] we wished to study the corresponding 17-azasteroid (IV). Related compounds, such as 3β-acetoxy-17-aza-androst-5-en-16-one, have been prepared *via* 17a-aza-D-homosteroids by a sequence of seven efficient stages, giving an overall yield of *ca.* 20%.[2] In developing the more direct, three-stage synthesis shown below, which gives the 17-aza-androstanone (IV) in 48% yield, light has been thrown on some transformations which were obscure.



Reagents: i, KOBu^t–RONO; ii, H_2SO_4–AcOH–H_2O; iii, Br_2–NaOMe–MeOH; iv, $SOCl_2$; v, NaOMe–MeOH. m.s. = mass spectral examination.

The key stage is the Hofmann reaction of the imide (III), which could, in principle, lead to the 16- or the 17-aza-system. N.m.r. and m.s. examination [notably the high intensity of the $M - 15$ peak[3] arising from the stabilised immonium ion (VIII)] indicated a 17-aza-structure for the product: the 16-aza-isomer (VI), synthesised unambiguously by a route similar to that used recently for other 16-azasteroids,[4] was different. Thus the 13—17a bond migrates preferentially during ring contraction of the imide (III).

Beckmann rearrangement of the hydroximino-ketone (II)[5] to the imide (III) is best achieved (76%) with sulphuric acid in moist acetic acid, conditions used for converting γ-cyano-acids to glutarimides.[6] Acetylation of the 3β-hydroxy-Δ^5-derivative of (II) and treatment with thionyl chloride is reported[7] to give the 3β-acetoxy-Δ^5-compound corresponding to imide (III). (The literature is too confusing for an adequate account to be given here.) We find that reaction of the hydroximino-ketone (II) with thionyl chloride affords the cyano-chloride (VII) accompanied by up to 20% of the imide (III), the relative proportions of the products being very sensitive to minor variations in the experimental conditions. The cyano-chloride is converted to the imide (III) in high yield under the acidic conditions used for the rearrangement of the hydroximino-ketone (II).

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[3] 3β-Methoxy-17-aza-5α-androstan-16-one (preparation not yet described) behaves similarly (H. Budzikiewicz, C. Djerassi and D. H. Williams, "Mass Spectrometry of Organic Compounds", Holden-Day, San Francisco, 1967).

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