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CLEAVAGE OF RING A IN 5β-STEROIDS

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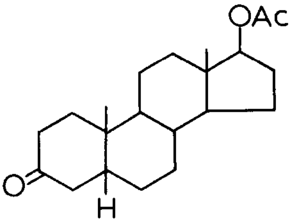
Recently we required a method to effect the unsymmetric cleavage of the 2,3-bond in 17β-acetoxy-5β-androstan-3-one (1). Schmidt reaction of 1 and Beckmann rearrangement of the oximes from 1 gave a mixture of the two isomeric products 2 and 3 (X = NH) in a ratio of ca. 1:1.[2] Since these reactions produced less than 50% of the desired isomer 2 and also because of the difficulty in separating large amounts of 2 and 3 (X = NH),[3] we sought other methods to cleave the 2,3-bond in 1. The syn and anti oximes of 1 have also been separated and each oxime undergoes a stereospecific Beckmann rearrangement to 2 or 3 (X = NH).[4] But again the delicate chromatographic separation of the oximes[4a] was not amenable to large scale preparations. Baeyer-Villiger oxidation of 1 also gave a mixture of 2 and 3 (X = O) with the undesired 3 predominating.[5] Next we investigated the possible synthesis of 2-substituted derivatives of 1 by direct substitution. But a literature search quickly indicated that this possibility was not hopeful, since all reported reactions of 3-keto-5β-steroids gave predominantly, if not exclusively, 4-substituted products[5b,6] except for formation of the 2-hydroxymethylene derivative. No doubt this is due to the preferential enolization of 3-keto-5β-steroids towards carbon 4.[7] It should be noted that ozonolysis of the 2-hydroxymethylene derivative of 1 leads to cleavage of ring A between carbons 2 and 3 but in a symmetric fashion to yield a diacid.[5b]



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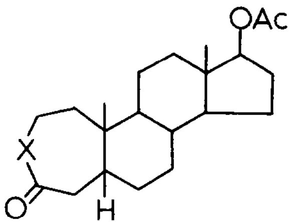

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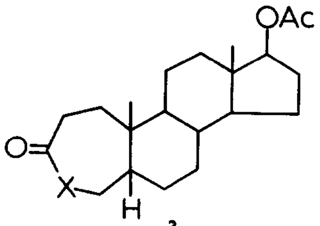

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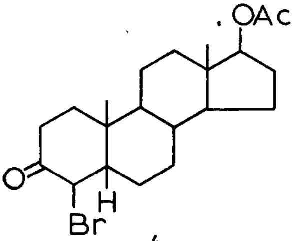
Takahashi, *et al.*,[8] have found that refluxing 4β-bromo-5β-cholestan-3-one in acetic acid containing sodium acetate gives 2β-acetoxy-5β-cholestan-3-one in high yield. We have now extended this reaction to the bromoketone 4[6a] which on treatment with sodium acetate in refluxing acetic acid gives 2β,17β-diacetoxy-5β-androstan-3-one (5) in good yield.[9] The salient features in the nmr spectrum of 5 are a double doublet (J = 6 and 14 Hz) at δ 5.15 which is assigned to the 2α-hydrogen, a broad triplet (J = 13 Hz) at δ 2.81 due to the 4α-hydrogen, and a double doublet (J = 5 and 13 Hz) at *ca.* δ 2.2 due to the 4β-hydrogen. This product was not unexpected in light of previous substitution reactions of steroidal bromoketones;[8,10] and we[11] and others[12] have been concerned with the mechanism of this transformation. Zinc-acetic acid reduction of 5 gives 1, which indicates that no acyloxy-ketone exchange had occurred.[13] Furthermore, bromination of 5 with bromine in acetic acid gives a bromodiacetoxyketone. The nmr spectrum of this compound has a double doublet (J =5 and 13 Hz) at δ 5.21 due to the 2α-hydrogen and a doublet (J = 13 Hz) at δ 4.98 due to the 4α-hydrogen. These data are consistent only with structure 5 for the diacetoxyketone.



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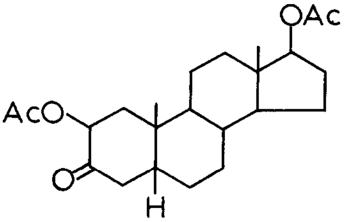

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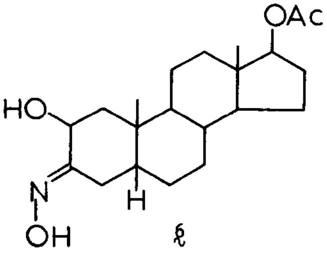
Treatment of 5 with hydroxylamine hydrochloride in methanol-sodium acetate gives the hydroxyoxime 6, mp 213-215°, in 70-80% yield. The nmr spectrum of 6 confirmed that the ring A acetate had been hydrolyzed and that the hydroxyl was still at carbon 2 - double doublet at δ 4.20 (J = 5 and 13 Hz) assigned to the 2α-hydrogen and a second double doublet at δ 2.90 (J =



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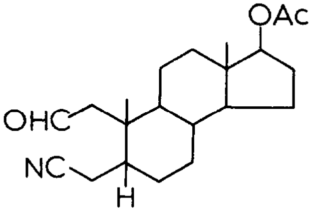

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4 and 14 Hz) which is assigned to the 4β-hydrogen,[4a] suggesting that the oxime has the stereochemistry shown in **6**.[14] Beckmann fragmentation[15] of crude **6** with thionyl chloride and aqueous potassium hydroxide[16] gives the cyanoaldehyde **7**, mp 110-112°, which could be isolated in greater than 70% yield. This aldehyde was converted into its 2,4-DNP derivative, mp 238-240°, for analysis. The nmr spectrum of **7** has a double doublet (J = 1 and 3 Hz) at δ 9.8 due to the aldehyde proton which is coupled to the two adjacent diastereotopic protons.[17] An INDOR analysis of this aldehydic signal confirmed that the CH_2-CHO moiety was isolated by a quaternary carbon as required by structure **7**.[18] Thus we had achieved the desired cleavage of ring A in a 5β-steroid.[19]

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