Biogenetically Modelled Synthesis of a Samandarine-type Alkaloid

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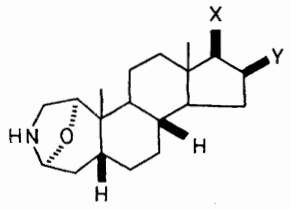
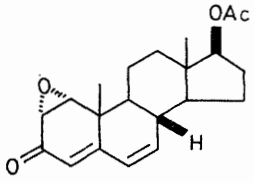
Summary The 3-aza-4-oxo-lactam produced by Schmidt rearrangement of 17β-acetoxy-1α-hydroxy-5β-androstan-3-one was reduced to yield a samandarine-type salamander alkaloid.

AN interest in the physiological properties[1] of samandarine (**1**) led us to examine synthetic routes for the construction of the characteristic oxazolidine system, *i.e.* the partial synthesis of 1α,4α-epoxy-3-aza-A-homo-5β-steroids.

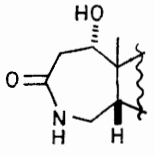
Of the syntheses so far attempted,[2] the two successful ones have involved multi-step transformations of 2,3-seco-steroid intermediates.[2a,c] We felt that a more direct approach, which might approximate to the biosynthesis, would be to carry out a controlled reduction of the 1α-hydroxy-3-aza-4-oxo-A-homo-steroid obtainable by Beckmann-type ring-A expansion of the appropriate 1α-hydroxy-3-oxo-5β-steroid. We report here the application of this scheme to the synthesis of (**2**), an alkaloid produced by *Cryptobranchus maximus* Stanley.[3]



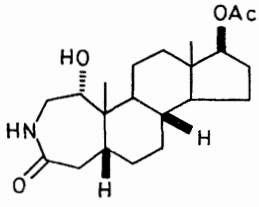
(1) X = H, Y = OH
(2) X = OH, Y = H



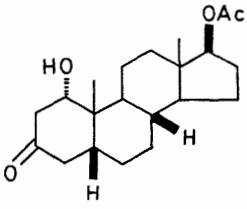
(3)



(6)



(5)



(4)

Monoepoxidation of 17β-acetoxyandrosta-1,4,6-trien-3-one gave the 1α,2α-epoxide (**3**),[4] which was hydrogenated (5% Pd–$CaCO_3$/propan-2-ol)[5] to afford 17β-acetoxy-1α-hydroxy-5β-androstan-3-one (**4**),‡ m.p. 185—188° (49%). A Schmidt reaction on (**4**) gave a mixture of lactams which could be separated by preparative-layer chromatography (1 : 3 : 3 v/v methanol–chloroform–ether; silica gel PF_{254}) thus providing (**5**), m.p. 222—224° (38%) and (**6**), m.p. 322—325° (decomp.) (18%).

Analogous to the electrochemical reduction of amides in ethanol–methylamine,[6] (**5**) was reduced with lithium–ethylamine–2-methylpropan-2-ol to give (**2**), m.p. 191—192° (40%) (lit. m.p. 191—193°[2a]). The identity of (**2**) was confirmed by comparison (mixed m.p., i.r., g.l.c., and m.s.) with authentic material.

This approach should be directly applicable to the synthesis of other salamander alkaloids, and in a formal sense the synthesis of (**2**) also constitutes one of samandarine, samandarone, and samandaridine; since (**2**) has been transformed into (**1**),[2a] and this into the other two alkaloids.[1,7]

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‡ All new compounds were characterized by n.m.r., i.r., o.r.d., and mass spectra. Purity was established by t.l.c. and/or g.l.c., and microanalyses, or high-resolution mass measurements.

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