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SYNTHESIS OF SAMANINE TYPE ALKALOIDS

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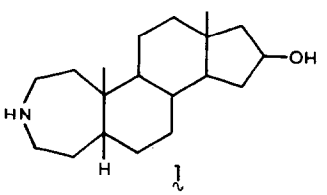
The venomous nature of the European salamander, Salamandra maculosa, has been known for years. Over a century ago the toxic substance was extracted from the skin glands of these salamanders.[2] Later it was found that this extract was a mixture of steroidal alkaloids.[3] One of the constituents of this mixture, samanine, was very recently found to have structure 1.[3a,4] This is one of the very few naturally occurring steroidal alkaloids in which the nitrogen is incorporated into the steroidal skeleton. Habermehl and Haaf also reported a synthesis of 1 from 16β-hydroxy-5β-cholestan-3-one (2) along with the original structural work.[4] The crucial step in this synthesis was the Beckmann rearrangement of the oximes from ketone 2 and the subsequent delicate chromatographic separation of the two resulting lactams. At about the same time, Oka and Hara reported a similar synthesis of 1.[5]



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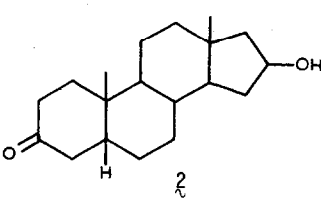

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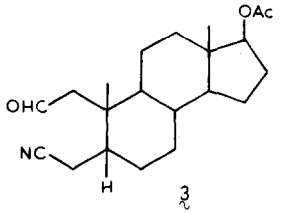
However, this synthesis required a chromatographic separation of the two oximes from 2 followed by a Beckmann rearrangement of one of the oximes to give only the desired 3-aza-A-homo compound. Since samanine was available in only small quantities from either the salamanders or synthesis, a detailed evaluation of its biological properties is not known.[3]

The other salamander alkaloids have been found to exhibit novel cardioactive properties.[3,6]

Recently, we reported a facile route to 2,3-seco 5β-steroids,[7] and this appeared to be a more direct route to samanine and related alkaloids. Our method involves cleavage of a 5β-cholestan-3-one to give the cyanoaldehyde 3.[7] Previously we had also converted 3 into the cyclic product 4; however, we encountered some difficulty in cleaving the sulfonamide and retaining a functional group at C-17.[8] Reduction of 3 with sodium borohydride



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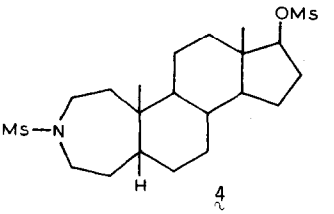

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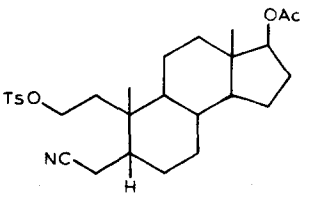
and tosylation gave the tosylate 5 in high yield. The nitrile in 5 was reduced with diborane and cyclized with one equivalent of benzoic anhydride in pyridine to give the amide 6 in ca. 40-50% yield. A similar cyclization with acetic anhydride - pyridine gave the corresponding



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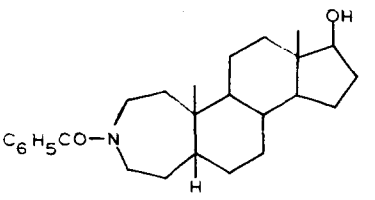

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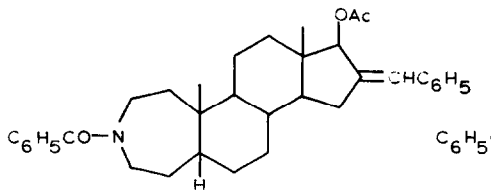
acetamide which was identical to that prepared by Oka and Hara by a different route.[9] This cyclization requires one equivalent of anhydride and the uncyclized amide is not an intermediate in the reaction. The details of the mechanism of this cyclization, which are in accord with these observations, is under study.

The next task was to transpose the C-17 hydroxyl to C-16. This was achieved by Jones' oxidation[10] of 6 followed by benzylidene formation using benzaldehyde and methanolic KOH. After experiencing some difficulty in reducing the benzylidene ketone directly with dichloroaluminium hydride,[11] the ketone was reduced with sodium borohydride and acetylated to give 7 in good yield. Compound 7 was treated with ozone followed by mild zinc reduction to give an acetoxy ketone in ca. 90% yield. This was further reduced with zinc and anhydrous hydrogen bromide in methylene chloride to yield 8. Ketone 8 has all of the skeletal features of samanine (1) and the C-16 ketone has been reduced to the 16β-hydroxy compound.[4] In



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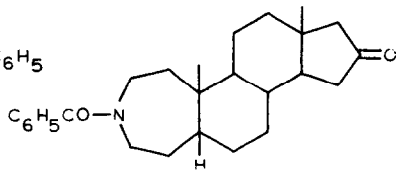

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addition intermediate 8 also provides a handle to allow us to alter the functionality in the D-ring of samanine and related compounds.[12]

(1) Address correspondence to this author.

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(3) For details see (a) G. Habermehl, "Progress in Organic Chemistry," Butterworth and Co., London, 1968, volume VII, p 35; (b) G. Habermehl in "The Alkaloids," R.H.F. Manske, ed., Academic Press, New York, N.Y., 1967, volume IX, p 427.

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(9) We are grateful to Professor Oka for this comparision; K. Oka and S. Hara, Tetrahedron Letters, 1189 (1969).

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(12) We are grateful to the British Columbia Heart Foundation for support of this work.