Synthesis of the ABC Ring System of the Steroid Batrachotoxin

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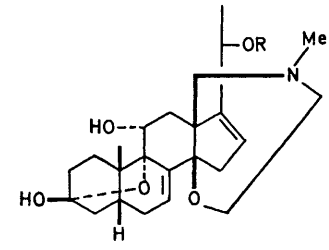
Summary Cholic acid has been converted into methyl 3β-methoxy-3α,9α-oxido-11α-acetoxy-Δ⁷-cholenate (**13**), an intermediate embodying the ABC ring system of batrachotoxin.

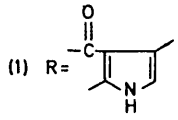
BATRACHOTOXIN (**1**),[1] the rare potent poison of the Colombian arrow frog, is a valuable neurophysiological tool.[2] Substantial progress towards the partial synthesis of batrachotoxinin A (**2**) has recently been made.[3] We now report an efficient conversion of cholic acid into the ester (**13**), an intermediate embodying the ABC ring system of batrachotoxin and possessing an entry to the CDE ring system *via* well-established side chain degradation procedure.

Cholic acid was transformed by the method of Fieser[4] into diacetate (**3**) (43% overall). Desulphurization of the corresponding ethylene dithioacetal with Raney nickel afforded the olefin ester (**4**),‡ (75%) m.p. 114—115°. Selective removal, (i) K_2CO_3, (ii) CH_2N_2, of the C-3 acetate group followed by oxidation (K_2CrO_4) gave the acetate (**5**)‡ (90%) as a colourless oil. Treatment of (**5**) with osmium tetroxide in pyridine led in 50% yield to the corresponding 9α,11α-osmate ester, m.p. 168° (decomp.), obtained as a white crystalline dipyridine adduct after chromatography over silica gel.§

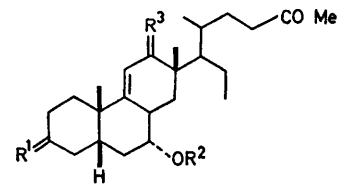
Cleavage of the osmate ester of (**5**) with H_2S–aq.NH_4Cl produced the hemiacetal (**7**)‡ (98%) m.p. 117—119°. Removal (MeO^-, MeOH) of the C-7 acetate group of (**7**) produced the 7α-11α-diol hemiacetal (**8**)‡ (82%) m.p. 185—185·5°. These last two substances readily formed acetals (**9**)‡ (79%, oil) and (**10**)‡ (85%), m.p. 154—155°, respectively, upon treatment with acidic methanol.[5]

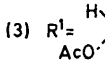
The C-7 acetate group of (**9**) was inert towards cleavage with methoxide ion in methanol. Similarly, acetylation of (**10**) gave exclusively the C-11 acetate (**11**). The acetate alcohol (**11**)‡ (quant., oil) thus formed (Ac_2O, pyridine) upon dehydration with $POCl_3$ in pyridine smoothly led to the desired methyl 3β-methoxy-3α,9α-oxido-11α-acetoxy-Δ⁷-cholenate (**13**)‡ (90%, oil).

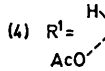


(1) R= 

(2) R = H

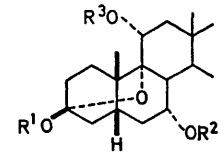


(3) R¹=  ,R²=Ac,R³=O

(4) R¹=  ,R²=Ac,R³=H,H

(5) R¹=O, R²=Ac, R³=H,H

(6) R¹=O, R²=H, R³=H,H



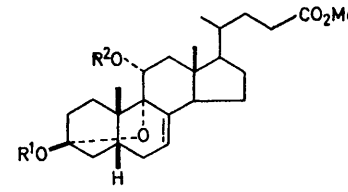
(7) R¹=R³=H, R²=Ac

(8) R¹=R²=R³=H

(9) R¹=Me, R²=Ac, R³=H

(10) R¹=Me, R²=R³=H

(11) R¹=Me, R²=H, R³=Ac



(12) R¹=R²=H

(13) R¹=Me, R²=Ac

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‡ A satisfactory C and H analysis and/or an exact molecular ion mass determination was obtained for this substance. N.m.r.[6] and i.r. spectra were also consistent with the structure shown.

§ Whereas acetate (**5**) reacted only slowly with osmium tetroxide in pyridine (7 days), the free alcohol (**6**),‡ m.p. 127—128°, gave after one day its corresponding osmate ester in 98% yield.

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[2] See *inter alia*, T. Narahashi, E. X. Albuquerque, and T. Deguchi, *J. Gen. Physiol.*, 1971, **58**, 54.
[3] W. Graf, E. Gössinger, R. Imhof, and H. Wehrli, *Helv. Chim. Acta*, 1971, **54**, 2789 and references therein; U. Kerb, H.-D. Berndt, U. Eder, R. Wiechert, P. Buchschacher, A. Furlenmeier, A. Fürst, and M. Müller, *Experientia*, 1971, **27**, 759.
[4] L. F. Fieser, S. Rajagopalan, E. Wilson, and M. Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 4133.
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[6] R. F. Zurcher, *Helv. Chim. Acta*, 1963, **46**, 2054.