The Structure of the Steroid Toad Venom Constituent Bufotoxin[1]

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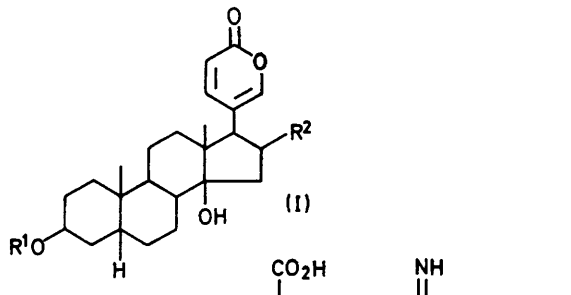
Summary Bufotalin 3-suberate has been prepared and the mixed carbonic anhydride derivative of the half ester has been condensed with arginine monohydrochloride to yield bufotoxin (Ia); this partial synthesis of bufotoxin (Ia) provides unequivocal support for recent structure proposals.

EARLY biological[2] and chemical[3] studies of bufotoxin (Ia) type toad venom constituents culminated in the bufotalin 14-suberylarginine structure for bufotoxin in 1941.[4] Structural evidence[5] has been accumulating that bufotoxin is in fact the 3-suberylarginine derivative of bufotalin. We now report a synthesis of bufotoxin (Ia) from bufotalin which unequivocally supports the 3-suberylarginine proposal of Kamano and Meyer.[5]

Treatment of bufotalin with suberic α-anhydride in pyridine gave bufotalin 3-suberate (Ib).[5] A solution of the half ester in tetrahydrofuran containing triethylamine was condensed (at −10°) with isobutyl chloroformate. To the resulting mixed carbonic anhydride was added arginine monohydrochloride in methanol–water. Bufotoxin (Ia) was isolated as granular crystals, m.p. 209—212° (64%), by preparative t.l.c. and was found to be identical to an authentic specimen of vulgarobufotoxin (Ia)[6] kindly provided by Professor Meyer. This particular interconversion further supports the view that bufotoxin (Ia) and vulgarobufotoxin are one and the same. In an analogous series of experiments, resibufogenin was converted into resibufogenin 3-suberylarginate (II), m.p. 189—197° (now designated resibufotoxin), and also bufalin was converted into bufalin 3-suberylarginate (Ic), m.p. 204—211° (herein named bufalitoxin).

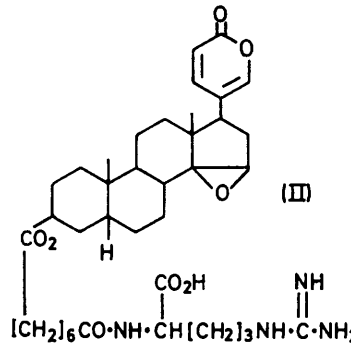
The preceding experiments should provide a useful model for synthesis of related toad poison toxins.



a; $R^1 = CO[CH_2]_6CO{\cdot}NH{\cdot}CH[CH_2]_3NH{\cdot}C{\cdot}NH_2$, $R^2 = OAc$

b; $R^1 = CO[CH_2]_6CO_2H$, $R^2 = OAc$

c; $R^1 = CO[CH_2]_6CO{\cdot}NH{\cdot}CH[CH_2]_3NH{\cdot}C{\cdot}NH_2$, $R^2 = H$



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[1] For preceding contribution see G. R. Pettit, Y. Kamano, F. Bruschweiler, and P. Brown, *J. Org. Chem.*, 1971, **36**, in the press.
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