Tetrahedron Letters,Vol.25,No.49,pp 5705-5708,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

PROXIMITY EFFECTS IN 1-AZASPIROCYCLO[5.5]UNDECANES. X-RAY STRUCTURE DETERMINATION OF A DIOL DERIVATIVE

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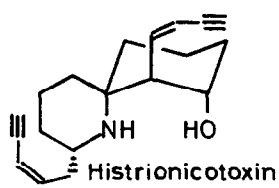
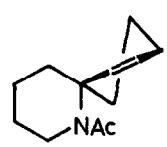
Summary: Neighbouring group participation is used to control bromination of the alkene **(1)** to give the bromo-acetate **(3)** which is converted into the diol **(6a)** [characterised by X-ray structure determination of the cyclic carbamate **(8)**] and the epoxide **(2)**.

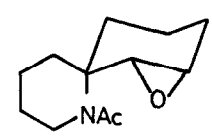
In view of the ready availability of the alkene **(1)**,[1] we wished to explore nucleophilic opening of the corresponding epoxide **(2)** as part of a general strategy[2] towards the synthesis of histrionicotoxin derivatives.[3] All attempts at direct epoxidation of **(1)** were unsuccessful,[4] but an indirect method involving N-acetyl participation[5,6] in the addition of bromine to the double bond was effective. Treatment of the alkene **(1)** with N-bromosuccinimide in acetic acid, followed by neutralisation to pH7, gave the aminobromo-acetate **(3)**.§ The trans-relationship of the bromine and acetoxy substituents in **(3)** was clearly evident from the observed vicinal coupling constant (10.5 Hz) for H_a and H_b in the ^1H n.m.r. spectrum. The stereochemical relationship between nitrogen and oxygen in **(3)** was deduced by conversion (i, Bu_3SnH; ii, Ac_2O) of **(3)** into **(4)**, a compound which we had previously prepared from the ethanol solvolysis (followed by acetylation) of **(5)**.[1]



Histrionicotoxin



1



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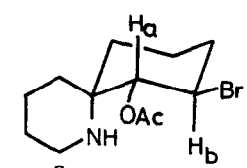
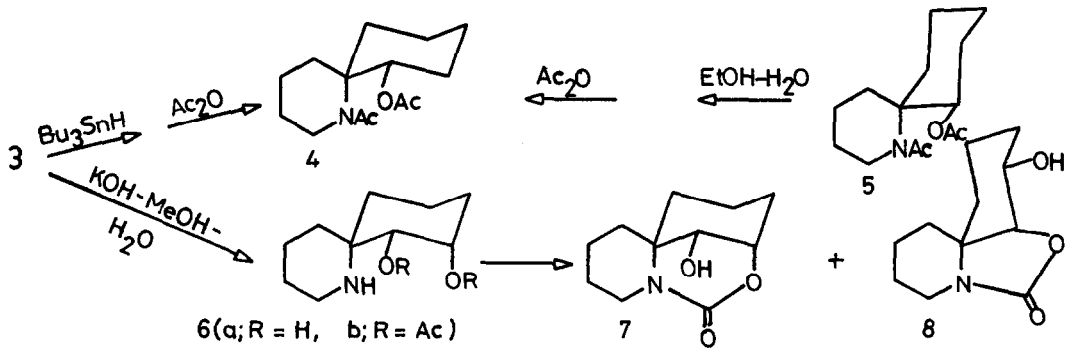
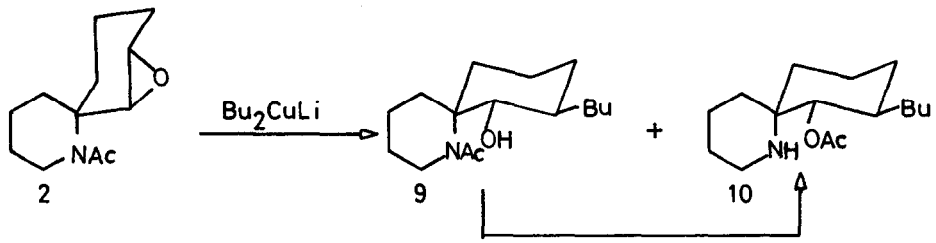


3

§ All new compounds exhibited spectroscopic and analytical data consistent with the structure assigned.



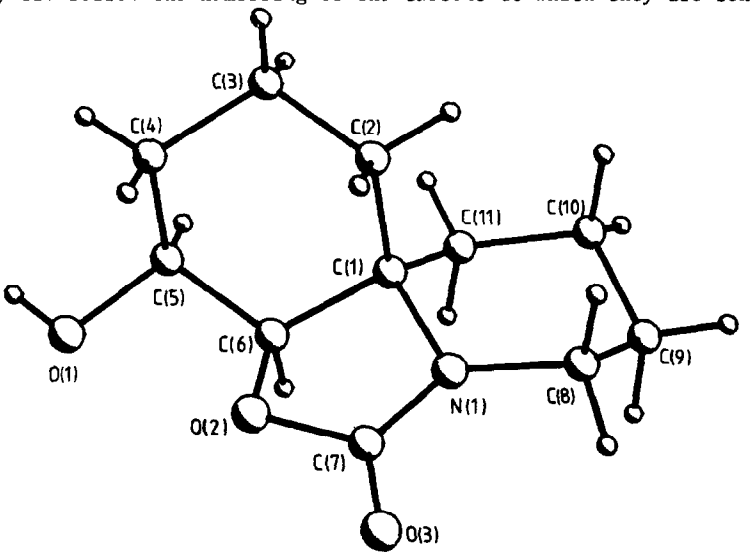
Treatment of the bromo-acetate **(3)** with oxygen bases gave little of the epoxide **(2)**. Surprisingly, the use of KOH in aqueous methanol gave the cis-diol **(6a)**[§] in high yield. This was characterised both as the diacetate **(6b)**[§] and as the cyclic carbamate derivatives **(7)**[§] and **(8)**[§] which were formed together on treatment of **(6a)** with carbonyldiimidazole in refluxing THF. The mixture of carbamates could be equilibrated in the presence of KOH in aqueous methanol to the five-membered compound **(8)**, m.p. 164-165 °C, whose structure was determined by X-ray analysis (see **Figure**).



A modest yield (33%) of the epoxide **(2)** was obtained using KOH in aqueous DMSO. However, by far the most effective reagent was 4-lithio-1-trimethylsilylbuta-1,3-diyne[7] in DMSO/THF, which produced **(2)**[§] in 69% yield. Lithium acetylide ethylene diamine complex in DMSO was also a reasonable reagent for the transformation (59%). The epoxide **(2)** was singularly unreactive to attack by acetylenic nucleophiles. It did react with lithium dibutylcuprate in THF at -20 °C to give a mixture of two compounds, **(9)**[§] and **(10)**.[§] On silica gel **(9)** was converted into **(10)**. These compounds arise by nucleophilic attack of cuprate at the remote carbon of the epoxide **(2)** rather than at the internal carbon atom. This observation is consistent with the results obtained in a study of a closely related compound by Kishi,[2] and is further support for a growing body of observations that nucleophilic opening of epoxides is not only controlled by conformational factors, but also by electronic effects.[8] A solution to the histrionicotoxin problem by the epoxide route will depend on the development of a reagent which can control the balance of these effects.

Figure[1]

Molecular Structure of (8) showing the atom numbering scheme; the hydrogens have not been labelled for clarity but follow the numbering of the carbons to which they are bonded.



[1] Crystal data: **(8)** $C_{11}H_{17}NO_3$, M = 211.1208, monoclinic, space group $P2_1/c$, a = 9.058(3), b = 13.451(4), c = 8.603(3) Å, β = 91.01(2)°, U = 1048.0 $Å^3$, Z = 4, D_c = 1.338 gcm^{-3}, F(000) = 456, λ(Mo-K_α) = 0.71069 Å, μ(Mo-K_α) = 0.58 cm^{-1}, R = 0.033 and R_w = 0.031 for 1084 unique diffractometer data with $5<2\theta<45°$ and $F>3\sigma(F)$; all non-hydrogen atoms refined anisotropically, H atoms refined freely with individual isotropic temperature factors.

Bond Lengths: C(1)-C(2) 1.537(3), C(1)-C(11) 1.525(3), C(2)-C(3) 1.520(3), C(4)-C(5) 1.508(3), C(5)-O(1) 1.426(2), C(7)-N(1) 1.342(2), C(7)-O(3) 1.218(2), C(8)-N(1) 1.449(2), C(10)-C(11) 1.530(3), C(1)-C(6) 1.530(3), C(1)-N(1) 1.475(2), C(3)-C(4) 1.514(3), C(5)-C(6) 1.504(3), C(6)-O(2) 1.463(2), C(7)-O(2) 1.361(2), C(8)-C(9) 1.518(3), C(9)-C(10) 1.527(3)Å. Bond Angles: C(2)-C(1)-C(6) 111.5(2), C(6)-C(1)-C(11) 114.5(2), C(6)-C(1)-N(1) 97.5(1), C(1)-C(2)-C(3) 112.9(2), C(3)-C(4)-C(5) 109.9(2), C(4)-C(5)-O(1) 112.9(2), C(1)-C(6)-C(5) 117.2(2), C(5)-C(6)-O(2) 110.9(1), N(1)-C(7)-O(3) 129.7(2), C(9)-C(8)-N(1) 108.9(2), C(9)-C(10)-C(11) 111.8(2), C(1)-N(1)-C(7) 111.0(1), C(7)-N(1)-C(8) 125.1(2), C(2)-C(1)-C(11) 113.3(2), C(2)-C(1)-N(1) 109.9(2), C(11)-C(1)-N(1) 109.0(2), C(2)-C(3)-C(4) 110.1(2), C(4)-C(5)-C(6) 112.8(2), C(6)-C(5)-O(1) 107.6(2), C(1)-C(6)-O(2) 102.9(1), N(1)-C(7)-O(2) 109.3(1), O(2)-C(7)-O(3) 121.0(2), C(8)-C(9)-C(10) 111.5(2), C(1)-C(11)-C(10) 111.7(2), C(1)-N(1)-C(8) 120.5(1), C(6)-O(2)-C(7) 107.4(1)°. The atomic coordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K. Any request should be accompanied by the full literature citation for this communication.

We thank the S.E.R.C., Gallaher Limited (CASE award), and Churchill College for generous financial support.

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(Received in UK 21 September 1984)