Palladium-catalysed Spirocyclisation of 3-Acetoxy-1-(4-aminoalkyl)-cyclohexenes. Synthesis of (±)-Depentylperhydrohistrionicotoxin

William Carruthers* and S. Andrew Cumming

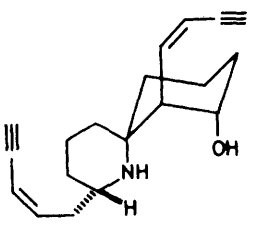
Department of Chemistry, The University of Exeter, Stocker Road, Exeter EX4 4QD, U.K.

Palladium(0)-catalysed cyclisation of 3-acetoxy-1-(4-aminoalkyl)cyclohexenes provides easy access to the 1-azaspiro[5.5]undecane ring system found in the histrionicotoxins; this has been exploited in a synthesis of (±)-depentylperhydrohistrionicotoxin.

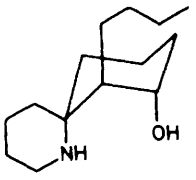
Histrionicotoxin (**1**) and several analogues were isolated[1] from the venom of the Colombian frog *Dendrobates histrionicus*, and both it and its perhydro and octahydro derivatives show great promise in the study of the phenomena involved in neuromuscular transmission;[2] similar properties have been found recently in the depentylperhydro compound (**2**).[3] Owing to this and the scarcity of the natural material, synthetic activity in this field has been widespread.[4] Several syntheses of (±)-perhydrohistrionicotoxin have been reported and the octahydro compound has also been made, but the syntheses are lengthy and none of the reported routes is readily adaptable to the synthesis of histrionicotoxin itself.

In our approach to compounds in this series we planned to set up the ring system (**4**) by a novel route employing palladium-catalysed cyclisation of suitably substituted 3-acetoxy-1-(4-aminoalkyl)cyclohexenes (**3**). Reaction of carbon nucleophiles with allylic acetates catalysed by Pd^0 complexes has been widely studied[5] and a few reactions leading to the formation of carbon–nitrogen bonds in bridged and fused-ring nitrogen heterocycles have been reported,[6] but no example of the formation of a spiro ring system by this procedure had been recorded when we took up this work. We have found that Pd^0-catalysed cyclisation of precursors of type (**3**, $R^2 = H$) provides easy access to the 1-azaspiro[5.5]undecane system found in the histrionicotoxins and we have used this reaction in a convenient and flexible synthesis of (±)-depentylperhydrohistrionicotoxin.

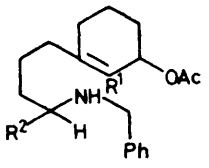
To test the viability of the route we studied first the cyclisation of the parent compound (**3**, $R^1 = R^2 = H$). Reaction of this with tetrakis(triphenylphosphine)palladium in boiling acetonitrile led to the spirocyclic compound (**4**, $R^1 = R^2 = H$) in over 80% yield. The structure was fully supported by the ^1H and



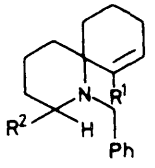
(1)



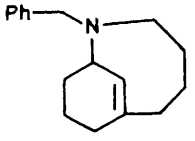
(2)



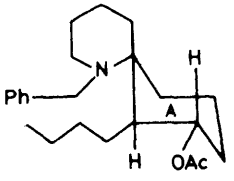
(3)



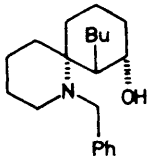
(4)



(5)



(6)



(7)

^{13}C n.m.r. spectra, which clearly eliminated the possible alternative structure (**5**). Similar results were reported by Godleski and his colleagues[7] while the present work was in progress. The butyl derivative (**3**, R^1=Bu^n, R^2=H), prepared by standard reactions from 2-butylcyclohexane-1,3-dione, was similarly converted into (**4**, R^1=Bu^n, R^2=H), although the yield here (60%) was smaller than that obtained from the parent compound, possibly because of the steric effect of the butyl substituent. The assigned structure for (**4**, R^1=Bu^n, R^2=H) is fully supported by the high resolution mass spectrum and ^{13}C and ^{1}H n.m.r. spectra. This compound has also been obtained very recently by Prof. A. J. Pearson by a different route using organoiron chemistry;[8] the properties of our compound agree closely with those of his.

Conversion of (**4**, R^1=Bu^n, R^2=H) into dependylperhydrohistrionicotoxin requires anti-Markovnikov hydration of the double bond, and we thought to effect this by hydroboration and oxidation, in the expectation that the nitrogen would direct attack of the hydroborating agent to give the required *cis*-axial orientation of the hydroxy substituent.[9] Hydroboration was readily effected with diborane in tetrahydrofuran, but oxidation of the crude alkylborane obtained, with alkaline hydrogen peroxide, gave only poor yields of a mixture of alcohols and a considerable amount of recovered alkylborane. Better results were obtained with trimethylamine oxide. Flash chromatography of the crude hydroboration product and oxidation of recovered (CH_2Cl_2) material with trimethylamine oxide[10] in boiling diglyme gave a mixture of alcohols (60%) whose acetates were readily separated by flash chromatography. The main component (90%) had ^{1}H and ^{13}C n.m.r. spectra and a high resolution mass spectrum fully consistent with the structure (**6**) of the desired acetate, in which the benzylamino part of the piperidine unit and the butyl and acetoxy substituents are all equatorial in ring A. The 400 MHz ^{1}H n.m.r. spectrum shows a signal for the C*H*OAc proton (t of d centred at δ 4.92) corresponding to coupling of an axial proton to two other axial protons (J 10.87 Hz) and to an equatorial proton (J 4.56 Hz); a very large non-equivalence of the benzylic protons (dd, δ 4.13, 3.04; J 14.34 Hz) is also observed. The ^{1}H n.m.r. spectrum of our acetate is very similar to that of an acetate obtained by Pearson[8] after troublesome oxidation of the alkylborane with alkaline hydrogen peroxide and to which he assigned structure (**6**).

The structure of (**6**) was confirmed by its conversion into dependylperhydrohistrionicotoxin (**2**). Hydrolysis of (**6**) with sodium hydroxide in warm methanol afforded the alcohol (**7**), whose 400 MHz ^{1}H n.m.r. spectrum showed a broad singlet for the C*H*OH proton at δ 3.99, possibly suggesting an equatorial disposition of this proton in contrast to that in the acetate, and two widely spaced doublets for the benzylic protons centred at δ 4.06 and 3.66 (J 12.69 Hz). Hydrogenolysis over palladised charcoal then led smoothly to dependylperhydrohistrionicotoxin (**2**), homogeneous by t.l.c. and h.p.l.c. The structure was fully supported by its 400 MHz ^{1}H and ^{13}C n.m.r. spectra and its high resolution mass spectrum. The ^{1}H n.m.r. spectrum agrees closely with that recently found by Pearson[8] and reported by Witkop *et al.*[3] The signal due to the C*H*OH proton now appears as a narrow quartet (δ 3.87) indicating an equatorial C*H*OH proton and suggesting that in the dependyl compound the hydroxy substituent is axial and possibly hydrogen-bonded to the amino group, as in histrionicotoxin itself.[1]

We thank the S.E.R.C. for a post-doctoral fellowship to S. A. C.

Received, 17th January 1983; Com. 083

References

1 J. W. Daly, I. Karle, C. W. Myers, T. Tokuyama, J. A. Waters, and B. Witkop, *Proc. Natl. Acad. Sci. USA*, 1971, **68**, 1870.
2 A. T. Elderfrawi, M. E. Elderfrawi, E. X. Albuquerque, A. C. Oliveira, N. Mansour, M. Adler, J. W. Daly, G. B. Brown, W. Burgermeister, and B. Witkop, *Proc. Natl. Acad. Sci. USA*, 1977, **74**, 2172.
3 K. Takahashi, B. Witkop, A. Brossi, M. A. Maleque, and E. X. Albuquerque, *Helv. Chim. Acta*, 1982, **65**, 252.
4 E. J. Corey, J. F. Arnett, and G. N. Widiger, *J. Am. Chem. Soc.*, 1975, **97**, 430; E. J. Corey and R. D. Balanson, *Heterocycles*, 1976, **5**, 445; M. Aratani, L. V. Dunkerton, T. Fukuyama, Y. Kishi, H. Kakoi, S. Sugiura, and S. Inoue, *J. Org. Chem.*, 1975, **40**, 2009; T. Fukuyama, L. V. Dunkerton, M. Aratani, and Y. Kishi, *ibid.*, 1975, **40**, 2011; E. Gössinger, R. Imhof, and H. Wehrli, *Helv. Chim. Acta*, 1975, **58**, 96; H. E. Schoemaker and W. N. Speckamp, *Tetrahedron Lett.*, 1978, 4841; D. A. Evans, E. W. Thomas, and R. E. Cherpeck, *J. Am. Chem. Soc.*, 1982, **104**, 3695; G. E. Keck and J. B. Yates, *J. Org. Chem.*, 1982, **47**, 3590.
5 Compare B. M. Trost, *Tetrahedron*, 1977, **33**, 2615.
6 B. M. Trost and J. P. Genet, *J. Am. Chem. Soc.*, 1976, **98**, 8516; B. M. Trost, S. A. Godleski, and J. L. Belletire, *J. Org. Chem.*, 1979, **44**, 2052.
7 S. A. Godleski, J. D. Meinhart, D. J. Miller, and S. Van Wallendael, *Tetrahedron Lett.*, 1981, **22**, 2247.
8 A. J. Pearson, personal communication.
9 A. J. Elliott and H. Guzik, *Tetrahedron Lett.*, 1982, **23**, 1983.
10 G. W. Kabalka and H. C. Hedgecock, *J. Org. Chem.*, 1975, **40**, 1776.