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STUDIES ON HISTRIONICOTOXIN: REARRANGEMENT OF THE SPIROCYCLIC HISTRIONICOTOXIN CARBON SKELETON INTO THE FUSED PUMILIOTOXIN SKELETON

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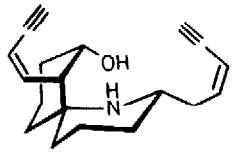
Summary: On treatment with acid the spirocyclic ketoamine 5 undergoes a retro-Mannich reaction followed by recondensation to give the unsaturated imine 8, thus converting the histrionicotoxin carbon skeleton into the pumiliotoxin C skeleton.

In recent years a substantial number of interesting alkaloids have been isolated from the Columbian frog Dendrobates histrionicus and Dendrobates pumilio.[1] Histrionicotoxin 1 and pumiliotoxin C 2 have attracted most interest from the synthetic view point,[2] because of their unique properties as cholinolytic and antagonists of specific ionic channels in electrogenic membranes. More recently another member of this class of alkaloids, gephyrotoxin 3 has attracted attention.[3]



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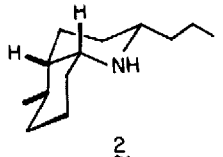

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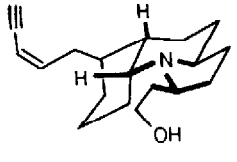

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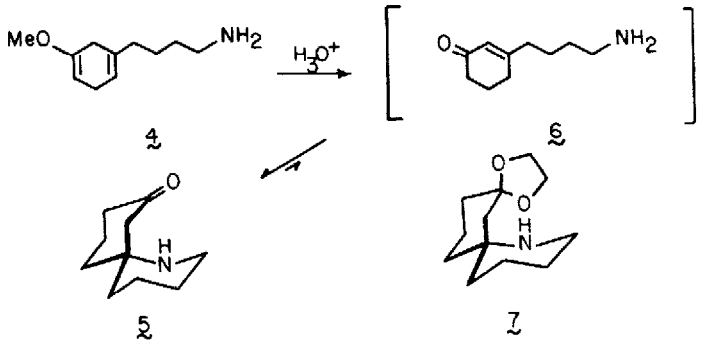
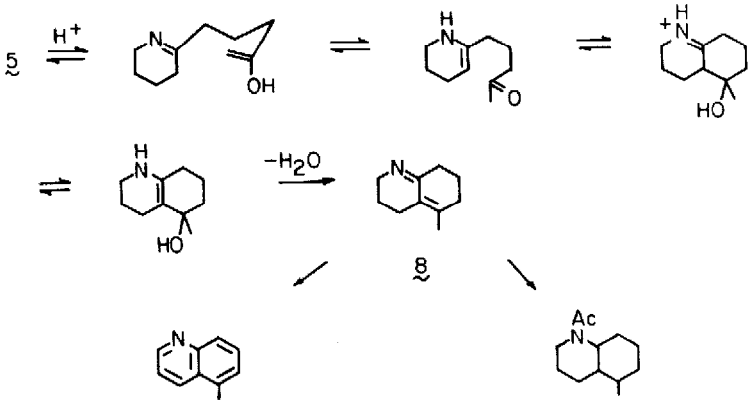


We have been studying approaches to the total synthesis of histrionicotoxin, and report here an unexpected rearrangement that relates the carbon skeleton of the spirocyclic framework of histrionicotoxin to that of pumiliotoxin C and gephyrotoxin.

Birch reduction of 4-(3'-methoxyphenyl)butylamine hydrochloride ($Li/NH_3/EtOH$) gave the enol ether 4 (75%), which was directly hydrolysed (2NHCl/THF) to give the spirocyclic amine 5, νmax 3290, 2920, 1710 cm^{-1}, ^{13}C NMR 210.6 (s), 55.9 (s), 51.9 (t), 40.9, 40.6, 36.9 (t), 34.7 (t), 26.7 (t), 20.7, 20.13, (94%). We have not been able to detect the enone 6 in this hydrolysis, although the ^1H NMR spectrum of 5 in trifluoroacetic acid indicated that, under these strongly acidic conditions, approximately 5% of 6 to be present as the trifluoroacetate salt.[4]



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When the spirocyclic ketoamine 5, having the same carbon skeleton as histrionicotoxin (without the C_4 and C_5 side chains), was exposed to standard ketalization (ethylene glycol/benzene/p-toluenesulfonic acid catalysis heated at reflux for 20 h.) with the expectation of preparing 7,[5] a single compound was formed which had no carbonyl absorption (IR) but also had no ketal protons (NMR) These data, νmax 2930, 1680, 1630, 1615, 1435, 1380, 960 cm^{-1}. ^1H NMR (δ) 3.43 (2H, t J=6Hz), 2.40-2.00 (6H, m), 2.00-1.13 (4H, m), 1.73 (3H, s). ^{13}C NMR 164.9 (s), 141.3 (s), 123.5 (s), 49.0 (t), 35.1 (t), 32.6 (t), 24.1, 22.4, 22.1, 19.1 indicate a deep seated rearrangement had taken place to give the α,β-unsaturated imine 8 (84%). Confirmation of this structure was further obtained by dehydrogenation (10% Pd/C/p-cymene) to give 5-methylquinoline, and hydrogenation (10% $Pd/C/H_2$) followed by acetylation to give 9.[6]

Naturally the ethylene glycol plays no part in this rearrangement since its omission from the above reaction does not alter its course. Apparently 5 prefers to undergo a retro-Mannich reaction rather than a retro-Michael reaction.[7]

While there has been biosynthetic speculations concerning the formation of the Dendrobates alkaloids 1, 2 and 3,[1] the transformation 5 → 8 represents the first experimental demonstration that the spirocyclic carbon skeleton can be readily converted into the fused carbon skeleton found in pumiliotoxin C, and gephyrotoxin.

Acknowledgements. The National Institute of Health is gratefully thanked for their support of this study.

References

1. For a comprehensive list of these alkaloids see - J. W. Daly, G. B. Brown, M. Mensah-Dwumah, and C. W. Myers, Toxicon, 163 (1978); B. Witkop, Experientia, 27, 1121 (1971); J. W. Daly, I. Karle, W. Myers, T. Tokuyama, J. A. Waters, and B. Witkop, Proc. Nat. Acad. Sci., 68, 1870 (1971), T. Tokuyama, K. Uenoyama, G. Brown, J. W. Daly, and B. Witkop, Helv. Chim. Acta., 57, 2597 (1974); I. Karle, J. Am. Chem. Soc., 95, 4936 (1973); Pumiliotoxin - J. W. Daly, T. Tokuyama, G. Habermehl, I. L. Karle, and B. Witkop, Justus Liebigs Am. Chem., 729, 198 (1969).

2. Synthesis of pumiliotoxin C. W. Oppolzer, and E. Flaskamp, Helv. Chim. Acta., 60, 204 (1977); L. E. Overman, and P. J. Jessup, J. Am. Chem. Soc., 100, 5179 (1978); Perhydrohistrionicotoxin - E. J. Corey, J. F. Arnett, and G. N. Widiger, J. Am. Chem. Soc., 97, 430 (1975); E. J. Corey and R. D. Balanson, Heterocycles, 5, 445 (1976); H. E. Schoemaker, and W. N. Speckamp, Tetrahedron, 36, 951 (1980); E. J. Corey, M. Petrzilka, and Y. Ueda, Helv. Chim. Acta., 60, 2294 (1977); D. A. Evans, and E. W. Thomas, Tetrahedron Letters, 411 (1979); T. Fukuyama, L. V. Dunkerton, M. Aratani, and Y. Kishi, J. Org. Chem., 40, 2011 (1975); M. Aratani, L. V. Dunkerton, T. Fukuyama, Y. Kishi, H. Kakoi, S. Sugiura, and S. Inoue, Ibid., 40, 2009 (1975).

3. J. W. Daly, B. Witkop, T. Tokuyama, T. Nishikawa, and I. L. Karle, Helv. Chim. Acta., 60, 1128 (1977).

4. E. Winterfeldt, Heterocycles, 12, 1631 (1979) describes similar routes to spirocyclic amines related to histrionicotoxin.

5. This should be contrasted with similar spirocyclic ketoamines which readily form ketals without rearrangement T. A. Bryson, and C. A. Wilson, Synthetic Comm., 6 (7), 521 (1976).

6. J. A. Su, E. Siew, E. V. Brown, and S. L. Smith, Org. Mag. Resonance, 10, 122 (1977).

7. C. A. Grob and P. W. Schiess, Angew. Chem. Int. Ed., 6, 1 (1967).

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