Chiloenamine and Chiloenine: Two Unusual Isoquinoline derived Alkaloids. A New Insight into the Catabolism of Aporphines

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A study of *Berberis buxifolia* and *B. actinacantha* (Berberidaceae) has yielded the novel alkaloids chiloenamine (**1**) and chiloenine (**4**) which are catabolic oxidation products of aporphines.

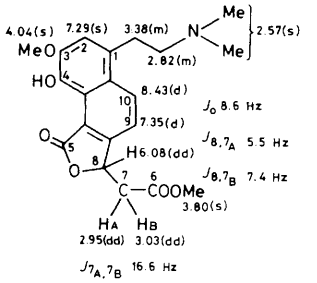
As part of a programme of investigation of the chemical constituents of Chilean barberries, we studied the alkaloids of *Berberis buxifolia* Lam. and *B. actinacantha* Mart. ex Schult. (Berberidaceae).† From both these plants, the yellow, amorphous, and optically inactive base chiloenamine (**1**) was obtained, whose u.v. spectrum, λ_{max} (MeOH) 215, 269, 327, 341, and 387 nm (log ϵ 4.49, 4.32, 3.22, 3.25, and 3.45) is appreciably different from that of any known isoquinoline alkaloid.

The mass spectrum of chiloenamine (**1**) shows a small molecular ion peak at *m/z* 373 consistent with the formula $C_{20}H_{23}O_6N$, and a dominant base peak at *m/z* 58 representing the iminium cation $CH_2{=}\overset{+}{N}Me_2$. This cation indicates the presence of a dimethylaminoethyl side chain in the alkaloid. The most intense peak next to the base peak is at *m/z* 241, due to the ion (**2**).‡

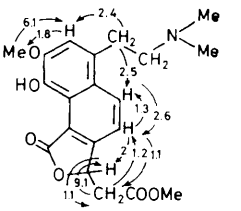
Details of the 360 MHz $CDCl_3$ ^1H n.m.r. spectrum of chiloenamine are given in formula (**1**). A telling feature is the well defined aliphatic ABX pattern representing the protons at C-7 and C-8. The protons 7_A-H and 7_B-H each appear as doublets of doublets at δ 2.95 and 3.03, while 8-H is represented by a doublet of doublets centred at δ 6.08.

The ^1H n.m.r. chemical shift assignments were confirmed not only by appropriate spin decoupling experiments, but also by a nuclear Overhauser enhancement (n.O.e.) difference study.[1] This was carried out on a 360 MHz instrument, and the results are given in formula (**1A**). It is important to bear in mind that reciprocal n.O.e's for two neighbouring protons or sets of protons are not necessarily equal, but depend upon the magnitude of the relaxation times T_1. Thus, irradiation of a fast relaxing proton close to a slow relaxing one will result in a larger n.O.e. for the slow relaxing proton than when the reverse operation is carried out. With chiloenamine (**1A**), irradiation of the fast relaxing C-3 methoxy protons at δ 4.04 leads to an appreciable n.O.e. of 6.1% for 2-H, whereas irradiation of the slow relaxing 2-H at δ 7.29 produces a small n.O.e. of 1.8% for the C-3 methoxy protons.

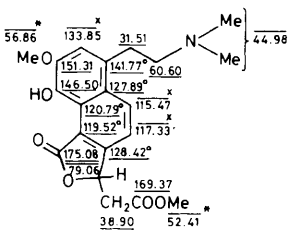
Since the structure of chiloenamine is unusual, a ^{13}C n.m.r. spectrum of the alkaloid was obtained as confirmatory evidence, and the data are given in formula (**1B**) (in p.p.m.) It was critical at this stage to employ off-resonance decoupling to determine the first-order multiplicities, and hence the number of protons bound to each carbon. However, the amount of chiloenamine available was insufficient to carry out such an operation efficiently. We, therefore, turned to the recently developed gated spin echo (GASPE) technique, in which one observes the evolution of a carbon spin with a time which is dependent upon the magnitude of the carbon–hydrogen coupling and the multiplicity. As a result, quaternary and methylene carbon signals appear above an arbitrary line, while methine and methyl carbon signals are found below that line.[2] The GASPE results proved to be in agreement with the structural assignments, and have been summarized in formula (**1B**) in which signals appearing above the line are



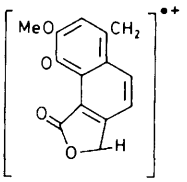
(1)



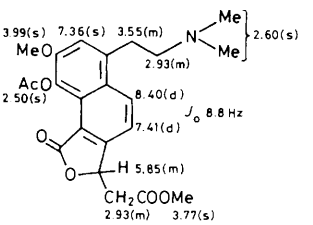
(1A)



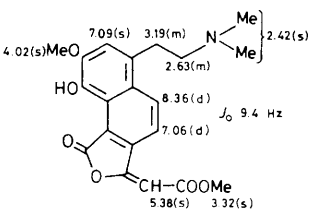
(1B)



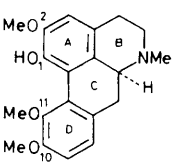
(2)



(3)



(4)



(5)

† *B. buxifolia* was collected near Punta Arenas (8 kg, whole plant, no leaves), and gave 5 mg of (**1**). *B. actinacantha* was gathered near Santiago (17 kg, branches without leaves) and gave 12.5 mg of (**1**), 1 mg of (**4**), and 3 mg of (**5**).

‡ Chiloenamine (**1**), *m/z* 373 $(M)^+$ (0.3), 329 (0.2), 315 $(M-58)^+$ (0.4), 300 (0.3), 241 (0.7), 227 (0.2), and 58 (100%). Molecular weight confirmed by chemical ionisation mass spectrometry (c.i.m.s.). I.r. ν_{max} ($CHCl_3$) 1710 and 1740 cm^{-1}. In formula (**1B**), chemical shifts with identical superscripts are interchangeable. T.l.c. R_f 0.19 on Merck Silica Gel F-254 plates, using $CHCl_3$–MeOH–NH_4OH (95 : 5 : 0.5).

underlined, and those below the line are marked by a bar over them.

The presence of a phenolic function in chiloenamine (**1**) was substantiated by acetylation of the alkaloid using acetic anhydride in pyridine at room temperature. Details of the ^{1}H n.m.r. spectrum of the resulting *O*-acetylchiloenamine (**3**), $C_{22}H_{15}O_7N$, are given in formula (**3**).§

A minor alkaloid accompanying chiloenamine in *B. actinacantha* is the optically inactive and amorphous yellow–orange chiloenine (**4**), $C_{20}H_{21}O_6N$. The mass spectrum of (**4**) shows a small molecular ion at *m/z* 371, and base peak at *m/z* 58, again representing $CH_2{=}\overset{+}{N}Me_2$. The ^{1}H n.m.r. $CDCl_3$ spectrum proved easier to interpret than that of chiloenamine, and details have been summarized in formula (**4**).¶

§ *O*-Acetylchiloenamine (**3**), λ_{max} (MeOH) 217, 233, 253, 288, 307, 320, and 349 nm (log ϵ 4.52, 4.33, 4.46, 3.76, 3.77, 3.79, and 3.79); *m/z* 415 $(M)^+$ (1.5), 371 (0.3), 355 (0.5), 329 (0.3), 324 (1.2), 315 (0.6), 255 (0.4), 241 (0.8), and 58 (100%); ν_{max} ($CHCl_3$) 1765 cm^{-1} (br).

¶ Chiloenine (**4**), λ_{max} (MeOH) 204, 230 sh, 290, and 377 nm (log ϵ 4.19, 4.02, 3.49, and 3.14); *m/z* 371 $(M)^+$ (0.8), 356 (0.5), 340 (0.6), 326 (1.8), 269 (0.4), 256 (0.8), and 58 (100%). Molecular weight confirmed by c.i.m.s. I.r. ν_{max} ($CHCl_3$) 1670 and 1735 cm^{-1} (br.). T.l.c. R_f 0.70 on Merck Silica Gel F-254 plates, using MeCN–C_6H_6–$MeCO_2Et$–MeOH–NH_4OH (40 : 30 : 20 : 5 : 5).

Chiloenamine (**1**) is, in all likelihood, the product of an *in vivo* degradative route for the aporphines, in which ring D of an aporphine is oxidized and cleaved at the C-10 to C-11 bond. Such a process could occur either through Hofmann elimination of the appropriate aporphine salt followed by oxidative fission of the lower ring of the resulting phenanthrene system, or by initial oxidation of ring D of the aporphine, followed by Hofmann elimination. Chiloenine (**4**) would then be the product of a further oxidation of chiloenamine (**1**). It is unlikely that chiloenine (**4**) is formed on isolation since chiloenamine (**1**) could be recovered unchanged after standing in methanol solution in an air atmosphere overnight. Significantly, we have also found that the known aporphine alkaloid (+)-corydine (**5**) accompanies chiloenamine (**1**) and chiloenine (**4**) in *B. actinacantha*.

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