Coyhaiquine: An Oxidized Proaporphine–Benzylisoquinoline Alkaloid

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The study of the n.m.r. spectrum of (+)-coyhaiquine (**1**), the first known oxidized proaporphine–benzylisoquinoline, has led to a simple method for the assignment of stereochemistry at C-13 for the proaporphines.

We report the novel alkaloid (+)-coyhaiquine (**1**), $C_{26}H_{27}O_5N$, isolated and characterized as a result of a continuing chemical investigation of *Berberis empetrifolia* Lam. (Berberidaceae).[1] The free base exhibits λ_{max} (MeOH) 210, 231sh, and 283 nm (log ϵ 4.44, 4.24, and 3.63). The mass spectrum contains a molecular ion peak m/z 433, which is also the base peak. Another important peak, m/z 416, is due to loss of hydroxyl from the molecular ion. The 360 MHz (Fourier transform) n.m.r. spectrum of coyhaiquine in $CDCl_3$ is explicit, and has been outlined around formula (**1**).†

Acid catalysed rearrangement of (**1**) produced the *C*-1,2,9,10-tetrasubstituted aporphine (−)-(**2**) whose c.d. curve shows a negative trough at 239 nm indicating the *R*-configuration at C-6a.[2]‡ It follows that coyhaiquine (**1**) incorporates the identical configuration at C-6a.

In order to determine the relative stereochemistry about the C-13 spiro centre, an n.m.r. nuclear Overhauser effect (n.O.e.) study of the alkaloid was undertaken. The chemical shifts for 6a-H [δ 3.43 (J_1 6.2, J_2 10.8 Hz)], 7β-H [δ 2.41 (J_1 5.8, J_2 12 Hz)], and 7α-H [δ 2.17 (J_1 10.7, J_2 11.6 Hz)], were first assigned by decoupling experiments. Irradiation of 8-H (δ 6.14) caused n.O.e.s of 1% for the C-1 methoxy resonance (δ 3.64), of 3% for the 3′,5′-H signal (δ 7.08), and of 3% for 7α-H (δ 2.17). Additionally, irradiation of the C-1 methoxy

† (+)-Coyhaiquine (**1**): mass spectrum m/z 433 (M^+) (100), 432 (85), 416 (30), 404 (58), 310 (32); c.d. $\Delta\epsilon$(nm), MeOH, +5.2(270), +1.3(246), +6.5(229); $[\alpha]_D^{25}$ +28° (*c* 0.02, MeOH). 20 kg *B. empetrifolia* (dry) furnished 16 mg of (**1**).

‡ (−)-Aporphine (**2**): λ_{max} (MeOH) 217, 227, and 304 nm (log ϵ 4.36, 3.99, and 3.84); m/z 433 (M^+, $C_{26}H_{27}O_5N$) (21), 416 (16), 310 (4), 204 (100); c.d. $\Delta\epsilon$(nm), MeOH, +1.9(300), +4.2(274), −23(239), positive tail (210); $[\alpha]_D^{25}$ −29° (*c* 0.04, MeOH).

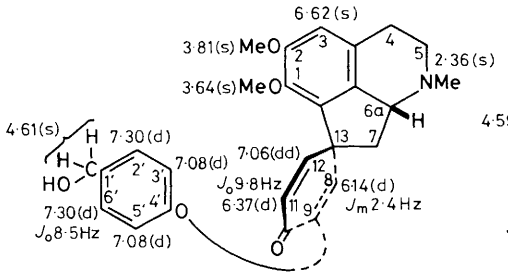
resonance (δ 3.64) led to n.O.e.s of 2% for 8-H (δ 6.14), and 2% for the 3′,5′-H signal (δ 7.08). On the other hand, irradiation of 12-H (δ 7.06) resulted in an 8% n.O.e. of 11-H (δ 6.37), while irradiation of 11-H (δ 6.37) produced a 5% n.O.e. of 12-H (δ 7.06). These data show that in coyhaiquine (**1**) 6a-H and the two vicinal vinylic hydrogens of ring D (*i.e.* 11-H and 12-H) are on the same side. This arrangement corresponds to the *syn*-stereochemistry.

A counter-clockwise rotation of the dienone moiety of (**1**) must, therefore, have taken place during the acid catalysed dienone–phenol rearrangement to (**2**), so that the aryl ring A migrates to that terminal of the dieone conjugated system which is *syn* to 6a-H.[1]

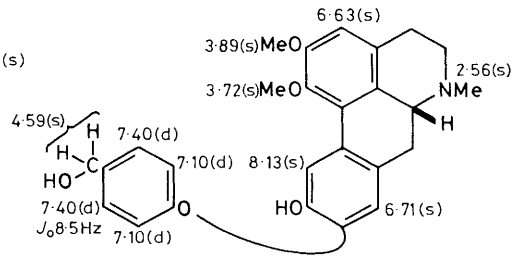
Coyhaiquine is an oxidized proaporphine–benzylisoquinoline. It is probably the result of *in vivo* oxidation of a proaporphine–benzylisoquinoline alkaloid of the *syn*-series such as (+)-pakistanamime (**3**) or (+)-patagonine (**4**), although it could also be the product of the oxidation of a *syn*-phenolic dimer such as (+)-valdivianine (**5**) or (+)-valdiberine (**6**),[1] followed by methylation of the C-1 phenolic function.

We then tried to establish a simple method for differentiating between proaporphines of the *syn*-series, as represented by (+)-coyhaiquine (**1**), (+)-pakistanamine (**3**), (+)-patagonine (**4**), (+)-valdivianine (**5**), and (+)-valdiberine (**6**); and proaporphines of the *anti*-series, as exemplified by (+)-epivaldiberine (**7**) and (−)-orientalinone (**8**) in which the two vicinal vinylic hydrogens of ring D lie on the side opposite 6a-H.[1] For this purpose, it was noted that in the *syn*-series, the two adjacent vinylic hydrogens of ring D which lie *syn* to 6a-H have a relatively large difference in chemical shifts of about 0.70 p.p.m. [*e.g.* for coyhaiquine (**1**), δ 7.06 − 6.37 = 0.69 p.p.m.; and for pakistanamine (**3**), δ 7.05 − 6.35 = 0.70 p.p.m.]. However, with proaporphines of the *anti*-configuration, the two adjacent vinylic hydrogens, which are now *anti* to 6a-H, are represented by peaks which are separated by only *ca.* 0.44 p.p.m. as in epivaldiberine (**7**), δ 6.89 − 6.46 = 0.43 p.p.m.; and in orientalinone (**8**), δ 6.88 − 6.43 = 0.45 p.p.m.

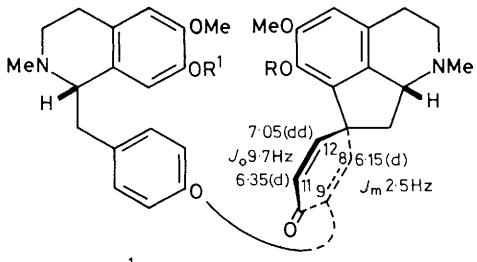
The aforementioned results allowed us to carry out for the first time a complete analysis of the n.m.r. spectra of the simple monomeric proaporphines (±)-pronuciferine (**9**) and (−)-glaziovine (**10**), as summarized with the formulae (**9**) and (**10**). The 360 MHz ($CDCl_3$) spectra of (**9**) and (**10**), supported by appropriate spin decouplings, show a set of two adjacent vinylic protons with a relatively large difference in



(1)

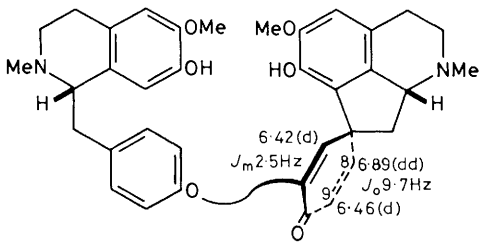


(2)



(3) R = R¹ = Me
(4) R = Me, R¹ = H
(5) R = H, R¹ = Me
(6) R = R¹ = H

N.m.r. chemical shifts are for (**3**).



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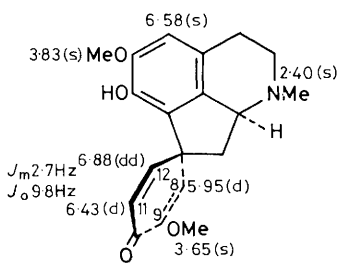

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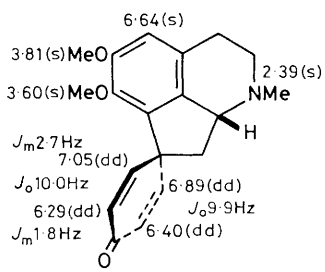
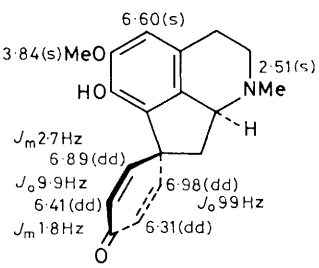


(9)



(10)

chemical shifts [*e.g.* for (**9**), δ 7.05 − 6.29 = 0.76 p.p.m.; and for (**10**), δ 6.98 − 6.31 = 0.67 p.p.m.] which must lie *syn* to 6a-H. The corresponding pairs of vinylic protons *anti* to 6a-H are represented by peaks which are separated by only *ca.* 0.49 p.p.m.

We conclude that it is presently not necessary to carry out an n.m.r. n.O.e. analysis to establish the relative configuration of a proaporphine substituted in ring D. Rather, simple subtraction of the chemical shift values for the two adjacent vinylic protons of the dienone will indicate whether the proaporphine belongs to the *syn*- or the *anti*-series.

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