MACROCENTRINE: AN UNUSUAL DITERPENOID ALKALOID

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Abstract - Macrocentrine, a new diterpenoid alkaloid from Delphinium macrocentrum Oliv., has been shown to possess an unusual dictyzine-like structure.

We have investigated the alkaloids of Delphinium macrocentrum Oliv., a plant native to Kenya, and isolated by conventional chromatographic procedures a new and unusual diterpenoid alkaloid which we have named macrocentrine.

This alkaloid, which crystallized from EtOH-H_2O in colourless tablets, mp 207-209°C, gave an ei-ms which contained as the base-peak an apparent molecular ion of composition $C_{22}H_{35}NO_5$ (found m/z 393.2511, calcd. 393.2516) with high-mass fragment ions at m/z 376 (21) and 362 (35) amu. The ir spectrum had ν_{max} (KBr) 3400 cm^{-1} (br s, OH), but was devoid of absorptions attributable to carbonyl or olefinic functionalities. The 200 MHz ^{1}H-nmr spectrum (CD_3OD, TMS) revealed, inter alia, the presence of a quaternary methyl (δ 0.81, 3H, s) and an ethyl unit (δ 1.11, 3H, t J=7Hz), and the absence of methoxyl or methylenedioxy groups.

Delphinium alkaloids usually conform to two main groups of diterpenoids[1]: those with a C_{19} lycoctonine/aconitine-type skeleton (1); and those derived from a C_{20} atisine-type one (2). The former is usually methoxylated but not the latter, which is, however, often olefinic. The C_{22} formulation of macrocentrine taken together with the absence of methoxyl or methylenedioxy groups excluded a structure based on lycoctonine and we therefore turned to consideration of hexacyclic derivatives of the C_{20} skeleton carrying an N-Et function.

The 50.4 MHz ^{13}C-nmr spectra of macrocentrine in pyridine-d_5, or CD_3OD-$CDCl_3$ revealed resonances for 22 C (see Table), in accord with the molecular composition deduced from the ms evidence; and, together with the ir spectrum, excluded olefinic and carbonyl functions. We hypothesised that the formation of the m/z 362 amu fragment-ion corresponded to the loss of a CH_2OH unit and that this was present in the molecule as a result of the conversion of the exocyclic methylene functionality,

Table: ^{13}C nmr data for dictyzine (3) and macrocentrine (5).

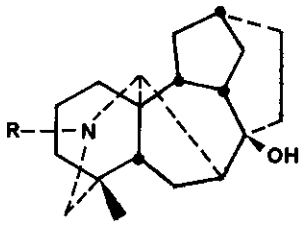
	3[3]	5[c]	5[d]
C-1	40.2 t	31.9 t	33.0 t
2	20.8 t	69.0 d	70.1 d
3	27.7 t[a]	67.5 d	68.5 d
4	34.4 s	38.7 s	39.3 s
5	44.2 d	39.6 d	41.0 d
6	26.6 t[a]	27.5 t	28.7 t
7	36.2 d	35.7 d	36.1 d
8	42.0 s	41.9 s	42.4 s
9	52.8 d	51.5 d	52.5 d
10	45.6 s	45.4 s	46.0 s
11	21.9 t	21.5 t	22.8 t[a]
12	42.8 d	42.7 d	43.6 d
13	23.1 t	23.3 t	24.4 t
14	26.6 t[a]	22.2 t	22.6 t[a]
15	86.7 d	86.0 d	86.4 d
16	79.8 s	79.2 s	80.4 s
17	59.8 t[b]	67.3 t	67.3 t
18	23.6 q	21.7 q	22.8 q
19	67.8 t[b]	48.7 t	50.1 t
20	73.5 d	75.9 d	76.8 d
NCH_2	-	49.7 t	49.4 t
CH_3	-	12.2 q	12.7 q

[a] These values may be interchanged within a column.

[b] We suggest that these assignments be reversed.

[c] In CD_3OD.

[d] In Py-d_5.



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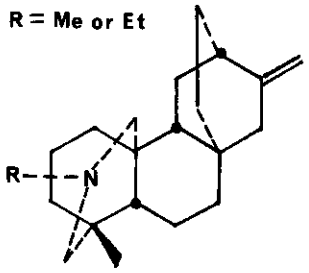

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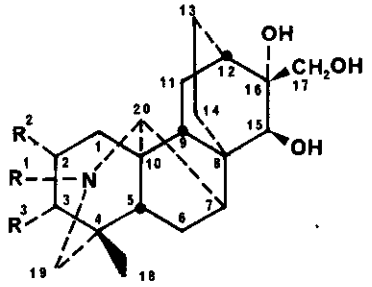
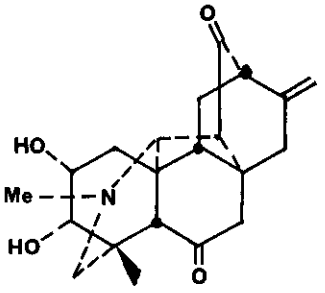


3 R^1 = Me, R^2 = R^3 = H

5 R^1 = Et, R^2 = R^3 = OH



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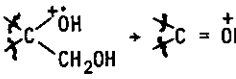
typical of the C_{20}-alkaloids, into a vic.-diol system, i.e. we visualised the fragmentation process as being  .

Looking for models for such a system we encountered dictyzine (3)[2], and were struck by the very close correspondence of the ^{13}C-nmr resonances attributed to the C/D ring system, and pendant hydroxymethyl group, of this alkaloid[3] with those found for macrocentrine (see Table). Thus we deduced that macrocentrine was a dihydroxy N-ethyl homologue of dictyzine.

Placement of the two additional hydroxyl groups was more problematical. We excluded sites on rings C and D in order to preserve the correspondence of the ^{13}C-nmr data, and considered attachments to rings A and B. Returning to the ^{1}H-nmr spectrum of macrocentrine, we observed that there were signals for 5 protons in the region 3.5-5 ppm: an AB pair, δ 4.00 and 3.52 (each J = 11.5 Hz); a singlet at δ 3.90; a rather broad multiplet at δ 3.76 ($w^1/_2$ = ca. 10 Hz); and a doublet at δ 3.19 (J = 4.5 Hz). We attributed these to the diastereotopic hydroxymethyl function, the isolated H-15, and the "extra" diol group respectively. Selective decouplings revealed that irradiation at δ 3.80 collapsed the doublet at δ 3.19 to a singlet and also simplified a multiplet at δ 1.88 ppm; while irradiation at δ 1.88 ppm converted the multiplet at δ 3.76 to a clean doublet (J = 4.3 Hz). We concluded that the two "extra" hydroxyl groups formed a vic.-diol unit of the type $CH_nCH(OH)CH(OH)$-C≤. This then had to be accommodated in ring A, and we thought that the relatively low abundance of an (M-17) ion in the ms of macrocentrine excluded a hydroxyl at C-1[4], thus leading us to a 2,3-diol. The magnitude of the observed coupling between the carbinyl protons indicated that these could not be in an axial-axial orientation. As 2α-hydroxylation of C-20 diterpenoids is relatively common[1,5] we were inclined to make this stereochemical assignment and, guided by the precedent provided by hetidine (4)[6], to construct a cis-diol with a 3α-OH. We had thus arrived at structure 5 for macrocentrine, but without definite proof for the geometry of the diol system.

We therefore resorted to an X-ray crystallographic analysis of the alkaloid. This revealed[7] macrocentrine to indeed have the structure and relative stereochemistry depicted in 5.

Macrocentrine is, to-date, an unusual alkaloid: to our knowledge it is only the second example, after dictyzine, of a C_{20} alkaloid in which the unit usually present as an exocyclic methylene group has been converted to a vic.-diol. This suggests a biosynthetic generation, via epoxidation and subsequent ring-opening of the oxirane, and prompts the thought that these alkloids may be clues to the construction of their C_{19}-relatives, i.e. that this hydroxylation paves the way for detachment of C-17 from the C_{20} system while, as originally suggested more than 30 years ago[8], a 15β-OH may provide the site for a leaving group which results in a rearrangement to the C_{19}-aconitine/lycoctonine ring system.

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