Journal of Natural Products
Vol. 46, No. 6, pp. 881-883, Nov-Dec 1983

THREE NEW CULARINE ALKALOIDS: CULACORINE, NORCULARICINE, AND OXOCULARINE

DAOVI P. ALLAIS and HÉLÈNE GUINAUDEAU*[1]

Faculté de Médicine et de Pharmacie, Université de Limoges, 87032 Limoges Cedex, France

ABSTRACT.—*Corydalis claviculata* (L.) DC (Fumariaceae) has yielded the new alkaloids (+)-culacorine (**8**), (+)-norcularicine (**10**), and oxocularine (**11**).

The cularines are a relatively small group of isoquinoline alkaloids that incorporate an oxepine system. Six cularines have been recognized; namely, (+)-cularine (**1**), (+)-cularimine (**2**), (+)-cularidine (**3**), and (+-cularicine (**4**), which bear oxygenated functions at C-7, C-3′, and C-4′ (1); and (+)-sarcocapnine (**5**) and oxosarcocapnine (**6**, which are oxygenated at C-7, C-4′, and C-5′ and are sometimes called isocularines (2).

Typically, cularines are produced by plants belonging to the botanical family Fumariaceae. Alkaloids **1-4** are found in the genera *Dicentra* and *Corydalis*, while isocularines **5** and **6** have been obtained from a *Sarcocapnos* species. To this listing of cularine alkaloids must be added the interesting and recently characterized gouregine (**7**), which has an unusual oxygenation pattern and bears two methyl substituents at C-α (3). Gouregine originates in a member of the Annonaceae family, *Guatteria ourego* Dun., and its biogenesis has been correctly suggested to proceed by oxidation of a 1,2,3,9-tetraoxygenated aporphine.

We now wish to describe three amorphous new cularines from *Corydalis claviculata* (L.) DC, a tendril-climbing annual herb that had originally been investigated by Manske and has been found to contain cularine (**1**), cularidine (**3**), and cularicine (**4**), as well as protopine and stylopine (4). The site of collection of *C. claviculata* by Manske has not been specified, but our plant was gathered in the vicinity of Limoges, France.

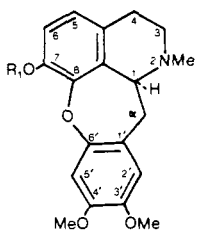
Culacorine (**8**), $C_{18}H_{19}O_4N$, is the first diphenolic cularine to be characterized, if one excludes the unusual gouregine (**7**). Its uv spectrum, with a maximum at 285 nm, is characteristic of many isoquinoline alkaloids, and shows a bathochromic shift upon addition of base.

The nmr spectrum has been outlined for **8**. There is only one methoxyl singlet at δ 3.89. The H-5 and H-6 absorptions appear as a two-proton singlet at δ 6.81, and the H-2′ and H-5′ singlet resonances are at δ 6.64 and 6.67.

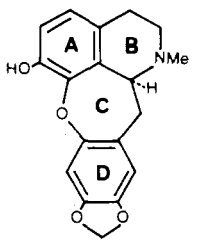
Mass spectroscopy is a particularly useful tool in the structural elucidation of the cularines. If a methoxyl group is present at C-3′, *para* to the oxepine oxygen, the base base peak will correspond to the $(M-15)^+$ ion due to facile loss of a methyl from that methoxyl and formation of a stabilized *p*-quinonium ion (1). In the case of culacorine (**8**), however, no easy loss of a methyl is observed, and the molecular ion peak *m/z* 313 is also the base peak, indicating that a phenolic function is present at C-3′. Also visible in the mass spectrum is the important peak *m/z* 161, corresponding to species **9**, *i.e.*, to the upper half of the alkaloid, thus pointing to the fact that the second phenolic function is attached to ring A.

Like all known cularines, culacorine (**8**) is strongly dextrorotatory, and its *O*-methylation with diazomethane yielded (+)-cularine (**1**) of known absolute configuration (5).

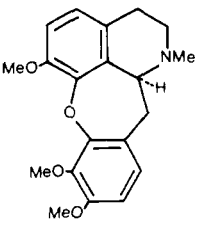
[1]Alternate address: ERA 317, UER de Chimie Thérapeutique, Centre d'Etudes Pharmaceutiques, 92290 Chatenay-Malabry, France.



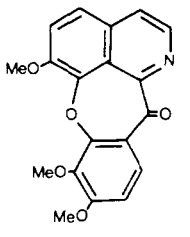
1, R=R_1=Me
2, R=H; R_1=Me
3, R=Me; R_1=H



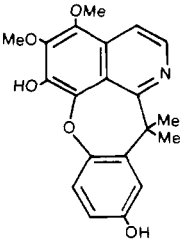
4



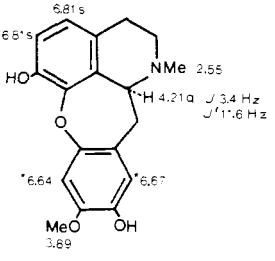
5



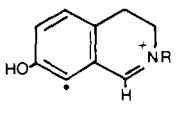
6



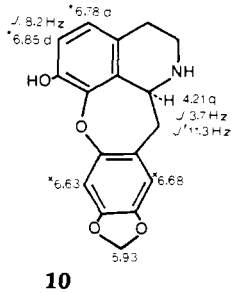
7



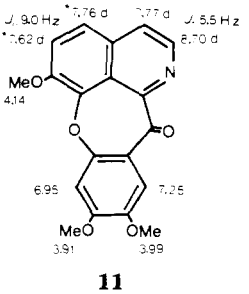
8



9, R=Me
11, R=H



10



11

Chemical shifts with identical superscripts are interchangeable.

Characterization of the second alkaloid as the monophenolic (+)-norcularicine (**10**), $C_{17}H_{15}O_4N$, did not present any particular difficulty. The nmr spectrum, as described for **10**, is quite straightforward. The mass spectrum shows molecular ion *m/z* 297, which is also the base peak. There is also a strong *m/z* 147 peak representing species **11**. As expected, the alkaloid turned out to be a appreciably dextrorotatory, and its *N*-methylation by the Eschweiler-Clarke procedure furnished (+)-cularicine (**4**).

If oxosarcocapnine (**6**) is the first oxoisocularine known, then our third alkaloid, the yellow non-phenolic oxocularine (**11**), $C_{19}H_{15}O_5N$, may be considered the first oxo derivative of a cularine. The nmr spectrum is well defined and is summarized in **11**. Readily noticeable are the two sets of aromatic doublets of doublets representing H-3 and H-4 on the one hand, and H-5 and H-6 on the other. Additionally, two aromatic proton singlets are present, as well as three methoxy singlets. The mass spectrum of oxocularine shows a molecular ion *m/z* 337, which is also the base peak.

In order to relate chemically oxocularine (**11**) to a known cularine base, (+)-curlarine (**1**) was oxidized with lead tetraacetate in glacial acetic acid (2). The product, obtained albeit in the relatively low yield of 10%, proved to be oxocularine (**11**).

It should be noted in conclusion that the chief genera of the family Fumariaceae are *Dicentra, Corydalis, Sarcocapnos, Rupicapnos,* and *Fumaria*. Cularines have been found in *Dicentra, Corydalis* and *Sarcocapnos* species, but never in *Fumaria* species. The genus

Rupicapnos, found mostly in Spain and north Africa, does not seem to have been studied extensively.

EXPERIMENTAL

SPECTROSCOPIC DATA.—All nmr data were obtained using a Brüker 200 MHz Supercon (FT) spectrometer. Spectra are for $CDCl_3$ solutions, with TMS as internal standard. Mass spectra were collected on an AEI MS-902 instrument; uv spectra were recorded in MeOH solution.

EXTRACTION AND CHROMATOGRAPHY.—The dry plant (0.5 kg) was extracted first with petroleum ether and then with ethanol. The ethanolic extract, following evaporation of the solvent, was dissolved in 0.5 N hydrochloric acid. The acidic solution was basified with ammonium hydroxide and extracted with chloroform to give 4.2 g of crude alkaloids. This material was placed on a column of silica gel for tlc and eluted with a mixture of cyclohexane-acetone-methanol (40:50:10 v/v). Two main fractions were collected.

The early fraction from the chromatogram (895 mg) was further fractionated on a column of silica gel for tlc using the system chloroform-methanol (98:2) to afford 480 mg of cularine (**1**), 40 mg of cularidine (**3**), and 12 mg of oxocularine (**11**).

The late fraction provided 240 mg of protopine. Further chromatography of the residue on silica gel tlc plates, using benzene-ethyl acetate-acetone (40:20:40) in an atmosphere saturated with ammonia led to the isolation of 20 mg of culacorine (**8**) and 3 mg of norcularicine (**10**).

Culacorine (**8**): λ max (MeOH) 209, 225 sh, 285, 296 sh nm (log ε 4.50, 4.19, 3.80, 3.64); ms *m/z* 313 (M^+, 100), 312 (7), 298 (75), 296 (42), 270 (16), 161 (4); cd MeOH Δε (nm) +0.45 (290), −1.9 (274), −3 (232), 0 (228), positive tail (217); $[\alpha]^{25}D$ +188° (0.08, MeOH).

Norcularicine (**10**): λ max (MeOH) 206, 224 sh, 287 nm (log ε 4.57, 4.23, 3.79); ms *m/z* 297 (M^+, 100), 297 (62), 280 (51), 267 (20), 147 (23); cd (MeOH) Δε (nm) −0.7 (273), −0.5 (232), (228), positive tail (215); $[\alpha]^{25}D$ +216° (0.06, MeOH).

Oxocularine (**11**): λ max (MeOH) 214, 254, 302 sh, 402 nm (log ε 4.53, 4.40, 3.62, 3.71), λ max (MeOH-H^+) 224, 267, 331 sh, 345 sh, 486 nm (4.47, 4.37, 3.70, 3.60, 3.61); ν max ($CHCl_3$) 1665 cm^{+1}; ms *m/z* 337 (M^+, 100), 294 (54), 279 (8).

N-Methylation of Norcularicine (**10**): Two mg of **10** were dissolved in 0.5 ml of formic acid and 0.5 ml of formaldehyde. After 4 h under reflux, the solution was basified using ammonium hydroxide and extracted with chloroform to supply 1.5 mg of cularicine (**4**). The product was identified by means of its ^1H-nmr, ms, and uv spectra, as well as by its specific rotation.

Oxidation of Cularine (**1**): Cularine (**1**) (30 mg) was dissolved in 5 ml of acetic acid and the solution added to 120 mg of lead tetraacetate in 5 ml of acetic acid. After 12 h at room temperature, excess methanol was added, and the solvent evaporated. The residue was dissolved in water, basified with ammonium hydroxide, and extracted with chloroform. Purification by tlc on silica gel using the system chloroform-ethyl acetate-methanol (50:45:5) afforded 3 mg (10%) of oxocularine (**11**).

O-Methylation of 8: Compound **8** (1½ mg) was dissolved in methanol, and the solution was treated with diazomethane for 72 h. Work-up gave rise to 1.2 mg of cularine, identical with an authentic sample.

LITERATURE CITED

1. M. Shamma, "The Isoquinoline Alkaloids, Chemistry and Pharmacology," Academic Press, New York, 1972, pp 153-164.
2. M.J. Campello, L. Castedo, J.M. Saá, R. Suau, and M.C. Vidal, *Tetrahedron Lett.*, **23**, 239 (1981).
3. M. Leboeuf, D. Cortes, R. Hocquemiller, A. Cavé, A. Chiaroni, and C. Riche, *Tetrahedron*, **38**, 2889 (1982).
4. R.H.F. Manske, *Can. J. Res.*, **18B**, 97 (1940); *ibid.*, **16B**, 81 (1938); and *Can. J. Chem.*, **43**, 989 (1965).
5. J. Kunitomo, K. Morimoto, K. Yamamoto, Y. Yoshikawa, K. Azuma, and K. Fujitani, *Chem. Pharm. Bull.*, **19**, 2197 (1971).

Received 20 January 1983