NEW ISOQUINOLINE ALKALOIDS FROM CORYDALIS CLAVICULATA

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Abstract — The alkaloids (+)-crassifoline (6), (+)-claviculine (9) and (+)-norcularidine (12) have been obtained from Corydalis claviculata. (+)-Crassifoline possesses the S configuration at C-1. The phenolic groups in (+)-claviculine are at C-7 and C-3'. (+)-Norcularidine is a new natural product.

The cularines are a small group of alkaloids incorporating a dihydrooxepine system, and are found mainly among plants of the botanical family Fumariaceae. Typical cularine bases are (+)-cularine (1) and the recently characterized (+)-sarcocapnine (2).[1]

No studies using labeled precursors have been carried out to elucidate the biogenesis of the cularines. It is logical to assume, however, that they are formed from 7,8,3',4'-tetraoxygenated tetrahydrobenzylisoquinolines of type 3. Intramolecular oxidative coupling could proceed in either a para or an ortho mode with formation of cularine (1) or sarcocapnine (2) analogs.[2] The main drawback of this hypothesis has been that although about 100 benzylisoquinoline alkaloids are known, at the initiation of our studies none were recognized to possess the required 7,8,3',4' substitution pattern. Conscious of this lacuna, we decided to study the alkaloidal profile of Corydalis claviculata (L.) DC, a small herbaceous annual belonging to the family Fumariaceae. This plant had been originally investigated by Manske, and had been shown to produce (+)-cularine (1), (+)-cularidine (4) and (+)-cularicine (5).[3] C. claviculata is relatively common in France, and our sample was collected in the Monts d'Ambazac near Limoges.

We now report the isolation and characterization of the diphenolic and amorphous (+)-crassifoline (6), $C_{19}H_{23}O_4N$, the first naturally occurring tetrahydrobenzylisoquinoline oxygenated at the required C-7, 8, 3' and 4' sites, and thus of pivotal importance in the biogenesis of the cularines.

The UV spectrum of crassifoline (6) shows a maximum at 282 nm, typical of many tetrahydrobenzylisoquinolines; and a bathochromic shift in base denotes the presence of at least one phenolic function. The mass spectrum includes a weak (M - 1) ion m/z 328, while the base peak m/z 192 is due to rings A and B resulting from benzylic fission of the C-1 to C-α bond. One of the phenolic groups is thus located on ring A, while the other is attached to ring C.

The NMR spectrum of crassifoline at 360 MHz in $CDCl_3$ is given around expression 6. In particular, in the aromatic region, the two-proton doublet of doublets as well as the three-proton ABX system, define the substitution pattern of the aromatic rings.

In order to establish conclusively the location of the two phenolic functions in crassifoline (6), the NMR spectrum was recorded in DMSO-d_6 (6A) and then again in DMSO-d_6 + NaOD (6B). Under such conditions, aromatic protons para to a phenolic function will show upfield shifts in basic solution greater than 0.55 ppm, while protons ortho or meta to the phenol will experience smaller upfield shifts.[4] The observed upfield shifts (6B) of 0.77 ppm for H-5 and of 0.57 ppm for H-6' clearly indicate that phenolic hydroxyls are located at C-8 and C-3', so that the methoxyl substituents must be positioned at C-7 and C-4'.

Crassifoline is slightly dextrorotatory, $\alpha_D^{25°}$ +17° (0.18, MeOH), and its CD curve shows a positive tail near 215 nm so that it must possess the S configuration as indicated.[5]

The racemic form of crassifoline was actually synthesized by Kametani and coworkers in 1971,[2] and by Jackson in 1974,[6] and their NMR spectral data are in agreement with those reported here. Very recently, and following completion of our experimental work, (+)-crassifoline, isolated from Sarcocapnos crassifolia, has been described independently.[7] The structural proof, however, rested on a simple comparison of the natural product with the synthetic racemate. Such comparison may not, however, be sufficient as structural proof since it would be ambiguous to differentiate between structure 6 and alternate structure 7 for crassifoline either by TLC or by simple NMR spectral comparison. However, the present NMR study in DMSO-d_6 and DMSO-d_6 + NaOD conclusively proves the validity of structure 6 for crassifoline.

Finally, in our hands, diazomethane O-methylation of (+)-crassifoline (6) provided (+)-O,O-dimethylcrassifoline (8), whose NMR spectrum, summarized around expression 8, clearly shows four methoxyl singlets.

A second compound we have found in C. claviculata is the diphenolic cularine-type alkaloid (+)-claviculine (9), $C_{18}H_{19}O_4N$, which crystallized from methanol, mp 112° C. The UV spectrum with a shoulder at 275 nm and a maximum at 281 nm is congruent with a cularine structure, and again a bathochromic shift in base denotes the presence of at least one phenolic group. The NMR spectrum ($CDCl_3$) has been summarized around expression 9. The key feature of this spectrum is the two closely packed sets of aromatic doublets of doublets, one centered at δ 6.58 and the

other at δ 6.81. These represent H-2' and H-3' on the one hand, and H-5 and H-6 on the other. In order to establish conclusively the provenance of the two aromatic doublets of doublets, the methoxyl singlet at δ 3.85 was irradiated. The resulting 20% NOE of the δ 6.58 doublet of doublets proved that this absorption represents H-2' and H-3'. Conversely, irradiation of the δ 6.58 band caused a 3% NOE of the δ 3.85 signal. The logical conclusion was thus that the δ 6.81 absorption is due to H-5 and H-6.

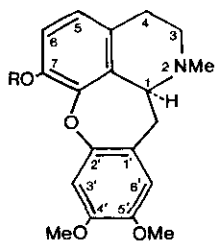
The mass spectrum of (+)-claviculine (9) incorporates molecular ion m/z 313 which is also the base peak. Another significant peak is m/z 161 due to ion 10 which indicates the presence of a hydroxyl at C-7 in species 9.

Claviculine (9) is strongly dextrorotatory, $\alpha_D^{25°}$ +208° (0.54, MeOH), so that it possesses the S configuration.[8] As expected, its O-methylation with diazomethane engendered (+)-sarcocapnine (2).

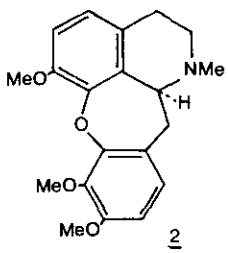
It is interesting to note that (+)-claviculine (9) is the first cularine type alkaloid substituted at C-4' and C-5' which has been obtained from a Corydalis species; the only two other known cularines possessing this kind of substitution pattern having been isolated from the genus Sarcocapnos.

As with crassifoline (6), claviculine (9) has very recently been described by a Spanish group.[7] But their structural proof although adequate, cannot be considered completely conclusive. In particular, the alternate structure 11 for claviculine was considered and rejected simply because it incorporates a catecholic system. Our present structural proof for claviculine (9), relying on NMR NOEDS as well as on mass spectral measurements clearly shows that a methoxyl substituent must be situated at C-4'. It follows that only one phenolic substituent is attached to ring D.

The third alkaloid we wish to describe is the completely new and amorphous (+)-norcularidine (12),[9] $C_{18}H_{19}O_4N$, whose UV spectrum includes a shoulder at 279 nm and a maximum at 285 nm, with a bathochromic shift in base. The alkaloid is a secondary base lacking an N-methyl singlet absorption in the NMR spectrum. This spectrum has been outlined around expression 12. It will be noted that O-methyl singlets are present at δ 3.84 and 3.88. Very significantly, the two-proton doublet of doublets absorption due to H-5 and H-6 shows almost the same characteristics as the corresponding one for claviculine (9), indicating that a phenol is located at H-7. The mass spectrum shows molecular ion m/z 313, while the base peak m/z 298 is due to loss of a methyl group. A telling feature of the mass spectrum is the small peak m/z 147 due to ion 13, so that the phenolic group is indeed at C-7. As a final structure proof, Clarke-Eschweiler N-methylation of (+)-norcularidine (12) furnished the known (+)-cularidine (4) which we have also found in C. claviculata.[9]



1 R·Me
4 R H



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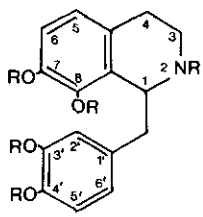

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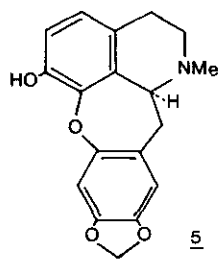

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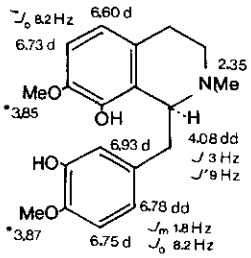

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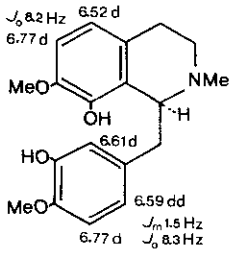
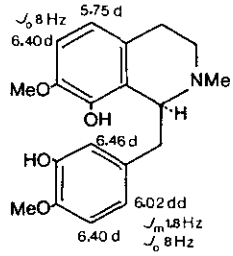
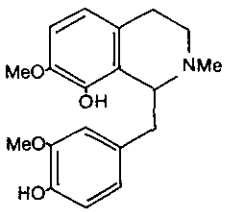


6A



6B



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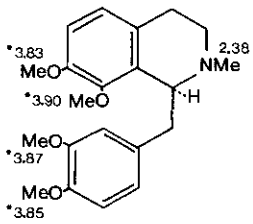
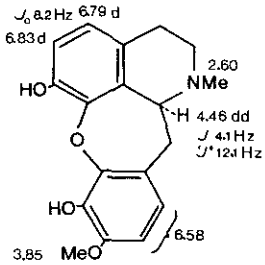
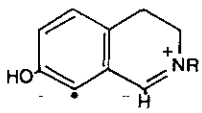


5 aromatic H at 6.75–6.82

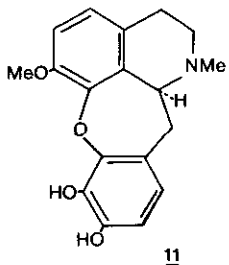
8



9



10 R Me
13 R H



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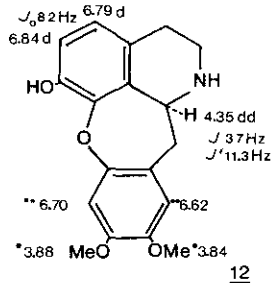

12

The above results buttress the thesis that 7,8,3',4'-tetrasubstituted tetrahydrobenzylisoquinoline analogs of crassifoline (6) may act as precursors to the cularines, so that a species such as 3 could undergo either para or ortho coupling to lead to cularines with the 3',4' or 4',5' substitution patterns, as exemplified in the present context by the alkaloids (+)-norcularidine (12) and (+)-claviculine (9), respectively.

Table of Spectral Data for the Alkaloids and Their Derivatives

(+)-Crassifoline (6): λ max (MeOH) 228 sh, 282 nm (log ε 4.67, 4.26); λ max (MeOH-OH^-) 237 sh, 287, 294 sh nm (log ε 4.59, 4.25, 4.23). Mass spectrum m/z 328 $(M-1)^+$ (0.2), 192 (100), 177 (14). CD (MeOH) Δε (nm) 0(290), -4.2(274), -11.5(236), 0(224), positive tail near 215 nm.

(+)-O,O-Dimethylcrassifoline (8): $C_{21}H_{27}O_4N$; mass spectrum m/z 357 $(M)^+$ (0.1), 206 (100), 191 (5), 190 (11). $\alpha_D^{25°}$ +13° (0.075, MeOH).

(+)-Claviculine (9): λ max (MeOH) 227 sh, 275 sh, 281 nm (log ε 4.08, 3.48, 3.52); λ max (MeOH-OH^-) 244 sh, 290 nm (log ε 4.00, 2.74). Mass spectrum m/z 313 $(M)^+$ (100), 298 (62), 270 (22), 255 (4), 252 (7), 176 (4), 174 (13), 161 (14). CD (MeOH) Δε (nm) 0(300), -1.6(274), 0(250), -3.1(233), 0(227), positive tail near 215 nm.

(+)-Sarcocapnine (2), from O-methylation of 9: $C_{20}H_{23}O_4N$; CD (MeOH) Δε (nm) 0(290), -1.5(278), -6.7(236), 0(227), positive tail near 215 nm.

(+)-Norcularidine (12): λ max (MeOH) 228 sh, 279 sh, 285, 293 sh nm (log ε 4.06, 3.70, 3.78, 3.60); λ max (MeOH-OH^-) 246 sh, 289 nm (log ε 3.89, 3.79). Mass spectrum m/z 313 $(M)^+$ (92), 298 (100), 283 (15), 147 (3). CD (MeOH) Δε (nm) 0(300), -3.2(277), -1.5(235), 0(229), positive tail near 215 nm. $\alpha_D^{25°}$ +216° (0.06, MeOH).

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8. Ref. 7 above reports α_D +443° for 9. This value is too large and is, therefore, suspect.
9. C. claviculata (500 g) supplied 13 mg of 6, 620 mg of 9, and 6 mg of 12.

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