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THE ^{13}C -NMR SPECTRA OF 1,2,10-TRIOXYGENATED APORPHINES

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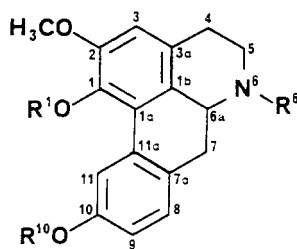
Since the appearance of the first studies on the ^{13}C -nmr spectra of aporphines (1,2), several tabulations of carbon chemical shifts have been published for a large number of aporphinoids (3-5). Some useful relationships between structure and chemical shifts are stated explicitly in these papers, and others can be deduced from the tables and from a more recent listing of the properties and occurrence of these compounds (6). Perusal of these tables reveals that out of more than 60 aporphinoid ^{13}C -nmr spectra reported only 9 represent the four possible ring-D monooxygenation patterns.

As a considerable amount of zenkerine [1] had been isolated a decade ago in our laboratory and partially characterized (7), we decided to attempt its purification from the remnants of the *Isolona zenkeri* (Annonaceae) fractions from which it was originally obtained with the hope of being able to determine at least the sign of its optical rotation and its ^{13}C -nmr spectrum. The successful purification of zenkerine allowed this modest goal to be reached, and also the ^{13}C analysis of the previously unknown O-

methylzenkerine [2], of pulchine (N-methylzenkerine) [3] isolated from *Ocotea pulchella* (Lauraceae) (8), and of 1,2,10-trimethoxyaporphine [4] isolated from *Thalictrum foliolosum* (Ranunculaceae) (9).

Although the free base of zenkerine is rather unstable and could only be obtained as a highly colored glass, it was possible to determine its optical rotation at 589 nm. It proved to be levorotatory, and its absolute configuration is, therefore, 6a(R) (10), establishing it as a biogenetic derivative of (R)-coclaurine presumably via crotsparine and sparsiflorine. Therefore, the N-methylcrotsparine which co-occurs with zenkerine in *I. zenkeri* (7) most probably belongs to the same stereochemical and biogenetic series.

The ^{13}C -nmr chemical shifts of compounds 1-4 are listed in Table 1. Resonances were assigned by correlation with published values (3,5) and by ^1H off-resonance decoupling experiments. On comparing the aromatic ring carbon resonance assignments given in the literature for 1-hydroxy-2-methoxyaporphines it became apparent that references (3) and (5) disagree with regard to the chemical shifts of C-1b and C-3a. Severini Ricca and Casagrande (3) based their attempted identification of the C-1b signal on the upfield shift expected for the carbon resonances upon protonation of the nitrogen atom. Unfortunately, these authors did not carry out any direct comparisons of the ^{13}C -nmr spectra of base-salt pairs, but relied on the spectra of four salts, two of which correspond to noraporphines, another to a dehydroaporphine, and the last to a 7-hydroxyaporphine. Considering all these structural variations with regard to the aporphine bases tabulated in their



	R ¹	R ⁶	R ¹⁰
1	H	H	CH ₃
2	CH ₃	H	CH ₃
3	H	CH ₃	CH ₃
4	CH ₃	CH ₃	CH ₃
5	H	CH ₃	H
6	CH ₃	CH ₃	H

TABLE 1. ^{13}C -nmr Chemical Shifts of Compounds **1-6** and of the Hydrochlorides of **1** and **4**

Atom	Compounds							
	5 ^a	6 ^a	1 ^b	2 ^b	3 ^b	4 ^b	1-HCl ^c	4-HCl ^c
C-1	141.6	144.3	141.5	145.0	141.4	145.1	142.9	147.3
C-2	146.5	151.3	145.9	152.0	145.7	152.0	148.1	152.9
C-3	110.2	111.6	110.1	111.8	109.5	111.3	110.9	112.2
C-3a	122.9	128.6 ^d	123.9	128.8 ^d	123.8	128.4 ^d	121.2 ^d	126.7 ^d
C-1a	119.4	125.9	119.1	126.4	119.3	126.8	119.0	125.9 ^d
C-1b	127.5	127.7 ^d	129.1 ^d	127.6 ^d	128.2 ^d	127.5 ^d	121.9	118.3
C-4	28.4	28.7	28.9	29.0	28.8	28.9	24.7	25.6
C-5	52.8	52.5	43.2	43.0	53.3	53.1	— ^g	51.4
C-6a	62.5	62.3	53.8	53.7	62.6	62.5	52.2	61.4
C-7	33.6	33.5	36.5	36.4	34.0	34.8	32.3	30.0
C-7a	126.0	126.6	128.7 ^d	128.2 ^d	127.9 ^d	127.8 ^d	125.1	125.9 ^d
C-8	127.9	128.4	128.1	128.2	128.2	128.4	128.7	129.3
C-9	113.2 ^e	114.0 ^e	112.4 ^e	113.2 ^e	112.4 ^e	113.1 ^e	112.1 ^e	113.5 ^e
C-10	155.3	155.7	159.2	158.4	158.2	158.5	158.2	158.6
C-11	115.4 ^e	114.5 ^e	114.1 ^e	113.5 ^e	114.0 ^e	113.7 ^e	115.1 ^e	113.5 ^e
C-11a	133.0	132.1	133.3	132.9	133.1	132.8	132.9	131.9
N-Me	43.5	43.5	—	—	43.8	43.6	—	— ^g
1-OMe	—	59.6	—	60.1	—	60.2	—	60.9
2-OMe	55.7	55.5	56.1 ^f	55.7 ^f	56.0 ^f	55.7 ^f	56.2 ^f	56.0 ^f
10-OMe	—	—	55.2 ^f	55.2 ^f	55.2 ^f	55.3 ^f	55.2 ^f	55.2 ^f

^aData from Severini Ricca and Casagrande (3), revised; 25.2 MHz, DMSO.^b20 MHz, CDCl₃.^c20 MHz, DMSO-*d*₆.^{d,e,f}Assignments interchangeable within columns.^gObscured by solvent signal.

study, we were unable to find any clear-cut distinction between the chemical shifts of C-1b and C-3a. On the other hand, Jackman *et al.* (5) used relaxation time measurements, selective irradiation experiments, and comparisons of the spectra of aporphines with different substitution patterns to obtain a coherent set of assignments that has generally been taken as a standard by the authors of more recent papers.

We have recorded the ^{13}C -nmr spectra of the hydrochlorides of **1** and **4** (Table 1) as examples of a 1-hydroxy-2-methoxynoraporphine and a 1,2-dimethoxyaporphine. The assignment of the C-7a resonance is reached unambiguously by considering relaxation times (5), and this atom, like C-3a, lies three bonds away from the nitrogen and belongs to an aromatic ring. Although both situations are not strictly identical, it seems reasonable to assume that the ^{13}C -nmr signals of C-3a and C-7a should

be displaced to a similar extent by *N*-protonation. In the cases of **1** and **4** we found that *N*-protonation shifts the C-7a resonance upfield by 3.6 and 1.9 ppm, respectively. Basing our assignments on reference (5), the C-3a signals appear shifted upfield by 2.7 and 1.7 ppm, in agreement with our assumption, while the C-1b peaks are much more strongly displaced 7.2 and 9.2 ppm upfield. If we use the work of Severini Ricca and Casagrande (3) as the basis of our assignments, the C-3a resonances undergo large upfield shifts and the signals attributed to C-1b are only weakly displaced. The report of Jackman *et al.* (5), therefore, leads to a much more reasonable distribution of protonation shifts. If the C-1 phenolic function is methylated, Jackman *et al.* (5) indicate that the *meta*-carbon signals (C-1b and C-3) are hardly displaced at all, and the *para*-carbon peak (C-3a) undergoes a downfield shift of 4.9 to 5.0 ppm. Severini Ricca and

Casagrande (3) suggest that the *para*-resonance should be practically unchanged as a result of *O*-methylation, and the two *meta*-carbon signals should be displaced downfield to very different degrees: C-3 by 0.9 to 1.8 ppm and C-1b by 5.1 to 6.0 ppm. We view such a situation as quite unlikely. Taking both *N*-protonation and *O*-1-methylation shifts into account, we believe that all the C-1b and C-3a assignments in Severini Ricca and Casagrande (3) for 1-hydroxy-2-methoxyaporphines (caaverine, lirinidine, apoglaziovine, isoboldine, and bracteoline) ought to be inverted. As apoglaziovine [5] and nuciferoline [6] share the 1,2,10-trioxxygenation pattern with compounds **1** to **4**, we have included the pertinent ^{13}C -nmr data in Table 1 for comparison.

It now becomes possible to analyze the changes produced in the ^{13}C -nmr spectra of this group of alkaloids by methylation of the phenol group at C-10. The *ipso*-(C-10) peak moves downfield by 2.8 to 2.9 ppm, both *ortho*-(C-9 and C-11) signals undergo upfield shifts of less than 2 ppm, the *meta*-(C-8 and C-11a) resonances are virtually unchanged, and the *para*-(C-7a) peak is displaced downfield by 0.9 to 2.2 ppm. A similar analysis of the *O*-methylation displacements in the ^{13}C -nmr spectra of aporphines with a single ring-D oxygen atom at C-9, although necessarily based on less data (6), suggests that the chemical shifts of these compounds are also rather insensitive to this structural change. It is worth noting that the *O*-methylation shifts predicted empirically for simple phenols are quite small, particularly at the *meta*- and *para*-positions (11,12). The ^{13}C -nmr behavior of the aporphines with ring-D monooxygenation at C-9 or C-10 would, thus, seem to be in line with that of relatively uncrowded phenols, as *O*-methylation should not introduce any major change in the conjugation of the oxygen atom with the aromatic ring. A similar situation can be predicted for aporphines with a single

oxygen atom on ring D at C-8 or C-11. On the contrary, downfield *O*-methylation shifts of several ppm should be expected for the ^{13}C resonances of the atoms *para* with regard to the hydroxyl group in the cases of 8-hydroxy-9-substituted, 3-hydroxy-2-substituted, and ring A- and D-trisubstituted aporphines. Here, replacement of the phenol hydrogen atom should result in torsion of the aryl-oxygen bond, and as a result of this, greater localization of the oxygen lone electron pairs, decreased electron density at the ring positions, and, therefore, relative deshielding of the carbon nuclei, particularly *ortho* and *para* with regard to the modified phenol function, as has already been suggested for 1-hydroxy-2-methoxy- and 11-hydroxy-10-methoxyaporphines (5). This hypothesis should clearly be checked experimentally and, in view of the pharmacological importance of some aporphine derivatives, points to the potential interest of quantum-chemical studies of the electronic structure of these compounds.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—

Analytical tlc was carried out on silica-gel pre-coated foils; preparative chromatography was effected on silica gel, either with pre-coated plates (0.5 mm thickness) or on "flash" columns; CH_2Cl_2 -MeOH- NH_4OH (90:9:1) was used as eluent in every case, saturating the tlc chamber with NH_3 vapor. ^1H -nmr spectra were recorded at 60 MHz in CDCl_3 with TMS as internal reference. ^{13}C -nmr spectra were recorded at 20 MHz in CDCl_3 or $\text{DMSO}-d_6$ (for the salts).

(-)-ZENKERINE [**1**].—Amorphous, purple-red solid, $[\alpha]^{23}_{\text{D}} -99^\circ$ ($c=0.10$ MeOH); ^1H nmr δ 3.80 s (3H, MeO-2 or -10), 3.86 s (3H, MeO-10 or -2), 6.57 s (1H, H-3), 6.73 dd $J=8.0$; 2.5 Hz (1H, H-9), 7.13 d $J=8.0$ Hz (1H, H-8), 8.02 d $J=2.5$ Hz (1H, H-11); ^{13}C nmr δ in Table 1.

(-)-*O*-METHYLZENKERINE [**2**].—Zenkerine, dissolved in MeOH, was methylated with CH_2N_2 in Et_2O at 5° . The major product was separated by column chromatography: dark brown, glassy solid; ^1H nmr δ 3.68 s (3H, MeO-1), 3.79 s (3H, MeO-2 or -10), 3.83 s (3H, MeO-10 or -2), 6.63 s (1H, H-3), 6.78 dd $J=8.0$; 2.5 Hz (1H, H-9), 7.16 d $J=8.0$ Hz (1H, H-8),

8.10 d $J=2.5$ Hz (1H, H-11); ^{13}C nmr δ in Table 1.

(-)-PULCHINE [3].—Zenkerine was *N*-methylated with HCHO-NaBH_4 in MeOH. The dark, glassy product was purified by column chromatography: $[\alpha]^{21}_{\text{D}} -130^\circ$ ($c=0.10$, MeOH); ^1H nmr δ 2.52 s (3H, N-Me), 3.81 s (3H, MeO-2 or -10), 3.84 s (3H, MeO-10 or -2), 6.59 s (1H, H-3), 6.79 dd $J=8.0$; 2.5 Hz (1H, H-9), 7.20 d $J=8.0$ Hz (1H, H-8), 8.06 d $J=2.5$ Hz (1H, H-11); ^{13}C nmr δ in Table 1.

(-)-1,2,10-TRIMETHOXYAPORPHINE [4]. *O*-Methylzenkerine was *N*-methylated with HCHO-NaBH_4 in MeOH. Glassy solid, $[\alpha]^{23}_{\text{D}} -169^\circ$ ($c=0.10$, MeOH); ^1H nmr δ 2.54 s (3H, N-Me), 3.68 s (3H, MeO-1), 3.82 s (3H, MeO-2 or -10), 3.87 s (3H, MeO-10 or -2), 6.63 s (1H, H-3), 6.81 dd $J=8.0$; 2.5 Hz (1H, H-9), 7.18 d $J=8.0$ Hz (1H, H-8), 8.03 d $J=2.5$ Hz (1H, H-11); ^{13}C nmr δ in Table 1.

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