THE CARBON-13 NMR SPECTRA OF APORPHINE ALKALOIDS[1, 2]

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ABSTRACT.—The ^{13}C spectra of twenty-one aporphine alkaloids have been analyzed and assigned by means of spin-spin multiplicities, coupling constant and virtual coupling data, selective and single frequency off-resonance double irradiation techniques, and spin lattice relaxation times.

The chemical shifts of the twelve aromatic carbon atoms have been correlated with the types of oxygen substitution.

The aporphines constitute a recurring theme in isoquinoline alkaloid chemistry. Together with the bisbenzylisoquinolines, they form the most numerous group of isoquinoline alkaloids. Several aporphines exhibit pronounced pharmacological activity. In particular, apomorphine, derived from the acid catalyzed rearrangement of morphine, is easily the most thoroughly investigated dopamine agonist and has been the subject of a large number of pharmacological investigations (3, 4). Although known aporphine alkaloids presently number over 130, new members of this group are still being isolated from plants. The present investigation was, therefore, initiated with a view towards establishing carbon-13 nmr spectroscopy as a standard tool in the characterization and structural elucidation of new aporphines.

There have been a number of investigations of the ^{13}C nmr spectra of alkaloids (5), including several synthetic and natural aporphines (6). In the present study we have undertaken careful analyses of the spectra of twenty-one representative members of the aporphine group. A detailed description of the assignment of the spectrum of glaucine is first presented, which will serve as the archetype for the remaining members of the group. Finally, some generalizations regarding the relation between chemical shifts and various substitution patterns are presented.

In general, the assignment of the resonances of the sp^3 hybridized carbon atoms of rings B and C is trivial, being based on the multiplicities associated with one bond coupling constants and on highly characteristic chemical shifts. The more difficult and important problem concerns the assignments of the absorptions of the twelve aromatic carbons, which of course reflect the wide variety of oxygenation patterns found in this group of alkaloids. These twelve resonances usually can be classified as belonging to one of three groups depending on whether they arise from unsubstituted carbon atoms which show large splittings due to one bond couplings, oxygen bearing carbon atoms which are usually strongly deshielded, or the five carbon atoms at the ring junctions. In arriving at assignments for the individual resonances within each of these three groups, we have made minimal appeal to arguments based on chemical shift correlations. Rather, we have chosen,

wherever possible, to use the less equivocal evidence available from spin-spin and virtual coupling data, a variety of double irradiation techniques, and the values of spin lattice relaxation times (T_1) (5b).

EXPERIMENTAL SECTION

The ^{13}C nmr spectra were obtained on either a JEOL PS-100-FT, Varian CFT-20, or a Varian XL-100-15 spectrometer. Where possible, spectra were obtained with solutions of the alkaloids in deuteriochloroform and with tetramethylsilane as an internal reference. Some of the free phenols as well as the quaternary salts were too insoluble in this solvent and had to be examined in dimethyl sulfoxide-d_6, in which case the solvent signals were used as an internal reference. A comparison of the chemical shifts for boldine in the two solvents is included in table 1. Relaxation measurements were made using the standard 180-τ-90° sequence on carefully degassed solutions (0.7-1M). The PS-100-FT spectrometer used in these experiments has a 90° pulse width of 20 μsec. Recovery times of five times the longest T_1 were used. The relaxation times were calculated by fitting the two parameter equation by the method of nonlinear least squares.

The normal spectra were obtained using noise or square wave modulation of the proton decoupler. Undecoupled spectra were recorded by gating off the decoupler during data acquisition.

ANALYSES OF SPECTRA

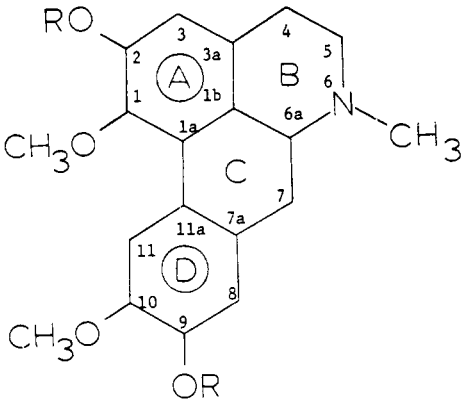
GLAUCINE (**1**).—Chemical shifts and relaxation times for the carbon atoms of glaucine (**1**) are listed in Table 1.

TABLE 1. Chemical shifts (ppm) and spin lattice relaxation time, T_1 (sec) for carbon atoms in glaucine and boldine.

	Glaucine (**1**)		Boldine (**4**)			
	δ^a	T_1	δ^a	δ^b	T_1	R[c]
1	144.2	18.7	142.0	142.6	7.3	2.6
1a	126.8	15.1	126.8	126.2	7.1	2.1
1b	127.2	7.9	125.9	125.5	3.5	2.3
2	151.8	9.4	148.1	149.1	2.3	4.1
3	110.4	0.27	113.3	114.1		
3a	128.8	4.3	129.9	128.7	1.9	2.3
4	29.2	0.16	28.9	28.5		
5	53.3	0.15	53.5	52.8		
6(CH_3)	43.4	0.45	44.0	43.7		
6a	62.5	0.33	62.5	62.3		
7	34.5	0.15	34.2	33.7		
7a	129.3	4.3	130.2	129.5	1.9	2.3
8	110.9	0.29	114.2	115.2		
9	148.0	9.8	145.1	145.7	2.3	4.3
10	147.4	9.7	145.6	146.0	3.6	2.7
11	111.6	0.29	110.1	111.8		
11a	124.4	8.9	123.6	122.8	4.0	2.3

[a]$CDCl_3$.
[b]Dimethylsulfoxide-d_6.
[c]T_1(glaucine)/T_1(boldine).

With the exception of the methoxyl carbon atoms, all sp^3 hybridized carbon atoms can be assigned either by their multiplicities in the gated noise irradiated spectrum or by chemical shifts. Thus, the NCH_3 absorption appears as a quartet and that of the 6a carbon as a doublet. The three methylene carbon atoms give triplets, of which one is at considerably lower field than the other two and is accordingly assigned to C(5). Distinction between the two benzylic methylene carbon atoms is made on the basis of the similarity of the chemical shift of C(4)



1 R=CH_3
4 R=H

to that (δ=29.2) of the similarly constituted α-carbon atoms of tetralin, and because the chemical shift of this absorption remains unaltered in the 7-oxygenated aporphines (see below). Of the four absorptions due to the methoxyl carbon atoms, three almost overlap (δ=55.6, 55.7, 55.8 ppm), whereas the fourth is considerably deshielded (δ=60.0 ppm). This last absorption is assigned to the sterically hindered methoxyl carbon at C(1) since it is absent in the spectrum of thaliporphine (**2**) (table 2).

The three unsubstituted aromatic carbon atoms are identified with the three absorptions in the region 110–112 ppm which are doublets (J~160 Hz) in the

TABLE 2. Carbon-13 chemical shifts for aporphine alkaloids in $CDCl_3$ (unless otherwise stated).

Compound Number	Compound Name	Substitution							
		1	2	3	6	7	9	10	11
1	Glaucine	OCH_3	OCH_3	H	CH_3	H	OCH_3	OCH_3	H
2	Thaliphorphine[a]	OH	OCH_3	H	CH_3	H	OCH_3	OCH_3	H
3	Predicentrine	OCH_3	OH	H	CH_3	H	OCH_3	OCH_3	H
4	Boldine[f]	OCH_3	OH	H	CH_3	H	OH	OCH_3	H
5	Isoboldine[a]	OH	OCH_3	H	CH_3	H	OH	OCH_3	H
6	Nantenine	OCH_3	OCH_3	H	CH_3	H	O—CH_2—O		H
7	Domesticine[a]	OH	OCH_3	H	CH_3	H	O—CH_2—O		H
8	Dicentrine	O—CH_2—O		H	CH_3	H	OCH_3	OCH_3	H
9	Oliveridine[e]	O—CH_2—O		H	CH_3	OH	OCH_3	H	H
10	Oliverine[e]	O—CH_2—O		H	CH_3	OCH_3	OCH_3	H	H
11	Nuciferine	OCH_3	OCH_3	H	CH_3	H	H	H	H
12	N-Methylasimilobine	OCH_3	OH	H	CH_3	H	H	H	H
13	Oliveroline[e]	O—CH_2—O		H	CH_3	OH	H	H	H
14	Pachypodanthine[e]	O—CH_2—O		H	H	OCH_3	H	H	H
15	Guatterine[e]	O—CH_2—O		OCH_3	CH_3	OH	H	H	H
16	Isocorydine Methiodide[a, g]	OCH_3	OCH_3	H	$(CH_3)_2$	H	H	OCH_3	OH
17	Corydine Methiodide[a, g]	OH	OCH_3	H	$(CH_3)_2$	H	H	OCH_3	OCH_3
18	Apomorphine Dimethyl Ether	H	H	H	CH_3	H	H	OCH_3	OCH_3
19	Isocorydine	OCH_3	OCH_3	H	CH_3	H	H	OCH_3	OH
20	Thaliphorphine Acetate[b]	OAc	OCH_3	H	CH_3	H	OCH_3	OCH_3	H
21	Boldine Diacetate	OCH_3	OAc	H	CH_3	H	OAc	OCH_2	H

TABLE 2. Continued.

Compound Number	Compound Name	Chemical Shifts (δ)								
		1	1a	1b	2	3	3a	4	5	6(CH_3)
1	Glaucine	144.2	126.8	127.2	151.8	110.4	128.8	29.2	53.3	43.4
2	Thaliphorphine[a]	140.7	119.5	127.2	145.8	108.7	123.9	29.0	53.5	44.0
3	Predicentrine	142.3	126.3	125.9	148.2	113.5	129.6	28.7	53.3	43.8
4	Boldine[f]	142.0	126.8	125.9	148.1	113.3	129.9	28.9	53.5	44.0
5	Isoboldine[a]	140.8	119.6	126.7	146.5	109.3	123.1	28.6	53.1	43.8
6	Nantenine	144.0	126.4	127.0	151.4	110.3	128.2	29.0	52.9	43.6
7	Domesticine[a]	141.2	119.7	127.2	146.6	110.0	123.2	28.6	53.3	43.9
8	Dicentrine	141.7	116.6	126.4	146.6	106.1	126.6	29.2	53.6	44.0
9	Oliveridine[e]	141.6	116.3	122.5	146.5	106.3	126.9	23.2	49.8	39.5
10	Oliverine[e]	141.4	116.0	123.5	146.4	106.5	127.4	25.3	52.0	40.7
11	Nuciferine	144.6	126.3	127.5	151.4	110.9	128.1	28.9	52.8	43.5
12	N-Methylasimilobine	143.0	125.6	126.9	148.1	114.2	129.6	28.6	53.2	43.7
13	Oliveroline[e]	142.4	116.5	123.4	146.8	107.4	127.6	22.8	48.9	40.6
14	Pachypodanthine[e]	141.8	114.8	124.7	146.7	107.9	127.2	29.1	42.7	—
15	Guatterine[e]	143.9	110.7	124.1	134.9	139.5	119.3	17.2	49.3	39.0
16	Isocorydine Methiodide[a, g]	144.0	124.6	121.2	150.2	111.6[d]	124.5	23.2	59.6	[c]
17	Corydine Methiodide[a, g]	143.0	118.3	120.8	149.0	112.1	119.1	23.0	59.9	[c]
18	Apomorphine Dimethyl Ether	126.2	132.6	134.9	126.5	127.9	131.5	29.2	53.0	44.0
19	Isocorydine	141.7	125.4	129.8[d]	150.8	110.8	128.8[d]	29.1	52.4	43.6
20	Thaliphorphine Acetate[b]	134.9	127.4	127.4	150.6	110.3	130.6	27.8	52.2	42.3
21	Boldine Diacetate	147.1	129.1	133.9	143.1	122.0	129.8	28.8	52.9	43.9

Compound Number	Compound Name	Chemical Shifts (δ)							
		6a	7	7a	8	9	10	11	11a
1	Glaucine	62.5	34.5	129.3	110.9	148.0	147.4	111.6	124.4
2	Thaliphorphine[a]	62.7	34.5	128.9	110.9	147.6	147.1	112.0	124.8
3	Predicentrine	62.5	34.2	129.2	110.7	148.1	147.6	110.0	124.1
4	Boldine[f]	62.5	34.2	130.2	114.2	145.1	145.6	110.1	123.6
5	Isoboldine[a]	62.6	33.9	129.2	115.1	145.4[d]	145.2	113.7	123.6
6	Nantenine	62.1	34.9	130.4	107.8	146.0[d]	145.9[d]	108.4	125.1
7	Domesticine[a]	62.5	34.0	130.1	108.2	145.4	145.3	108.8	126.0
8	Dicentrine	62.4	34.3	128.3	110.5	148.2	147.6	111.2	123.4
9	Oliveridine[e]	64.3	70.0	141.3	109.0	159.1	112.5	127.8	121.4
10	Oliverine[e]	63.4	81.5	139.4	109.3	159 0	112.2	128.0	122.2
11	Nuciferine	61.9	34.8	135.9	127.7[d]	126.7[d]	126.4[d]	127.3[d]	131.6
12	N-Methylasimilobine	62.2	34.7	136.0	127.8[d]	127.2[d]	127.2[d]	127.2[d]	131.7
13	Oliveroline[e]	64.6	69.8	138.8	123.8	127.6[d]	127.8[d]	127.0	128.6
14	Pachypodanthine[e]	60.4	83.2	136.4	123.1	127.4	127.4	126.7	129.6
15	Guatterine[e]	64.2	69.7	138.7	123.6	126.9	126.9	125.7	128.7
16	Isocorydine Methiodide[a, g]	68.1	29.8	125.8	118.3	111.2[d]	148.4	143.7	118.3
17	Corydine Methiodide[a, g]	67.9	29.6	125.8	123.3	110.6	152.0	144.8	124.2
18	Apomorphine Dimethyl Ether	62.5	34.7	129.8	123.3	111.4	152.0	147.0	127.8
19	Isocorydine	62.6	35.6	129.6[d]	118.6	110.7	149.0	143.6	119.8
20	Thaliphorphine Acetate[b]	61.8	33.5	129.6	110.9	148.7	147.7	111.3	123.4
21	Boldine Diacetate	62.4	33.5	129.8	122.0	138.8	149.8	112.4	130.0

[a]Solvent is DMSO-d_6. [b]Acetate salt. [c]53.0 and 43.0 ppm. [d]Cannot be unequivocally assigned.

[e]The C–7 substituent and H–6a are cis to each other.

[f]The spectrum of boldine has been assigned previously[6b] on the basis of chemical shift arguments and the findings agree with those reported here except for the 3a and 7a resonances which were not assigned.

[g]Chemical shifts have been reported[6b] for N-methylisocorydinium chloride in $CDCl_3/CH_3OH$ and for N-methylcorydinium chloride in $CDCl_3$. Significant differences from the values reported here for DMSO solutions are observed making comparisons of many of the assignments difficult.

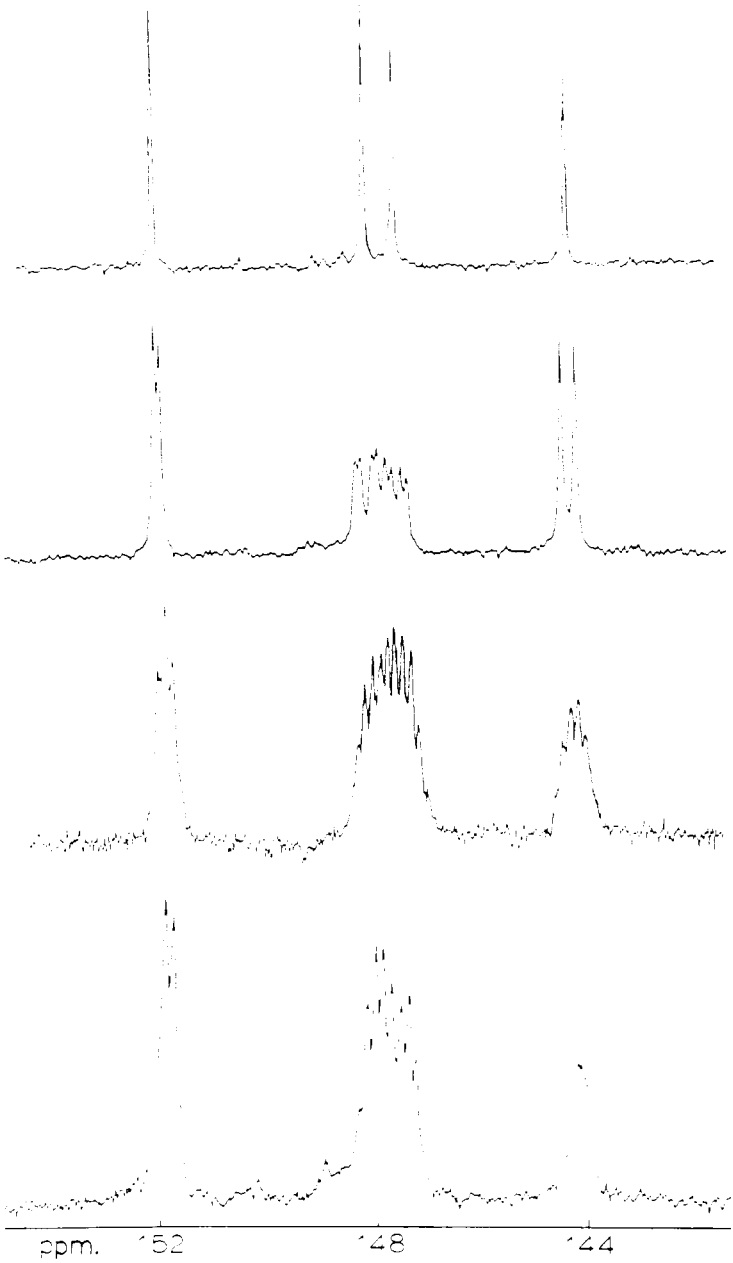


FIG. 1. Absorptions of the oxygenated, aromatic carbon atoms of glaucine in $CDCl_3$.

a) Noise decoupled, $\nu_H = 99{,}538{,}477$ Hz.

b) CW decoupled, $\nu_H = 99{,}538{,}511$ Hz.

c) Gated noise irradiation, $\nu_H 99{,}538{,}477$ Hz.

d) CW decoupled, $\nu_H = 99{,}538{,}803$ Hz. ($\nu_{TMS} = 99{,}538{,}124$ Hz).

gated irradiated spectrum. Of these, that at 111.6 ppm arises from C(11) which is shown by selective irradiation to be coupled ($J=159.9$ Hz) to the proton absorbing at $\delta=8.11$ ppm which had previously been assigned at H(11) (7). The other two absorptions have very similar shifts ($\delta=110.4$, 110.9 ppm); that at 110.9 ppm is also found in thaliporphine (**2**) and predicentrine (**3**) and is therefore assigned to C(8).

We now turn to the assignment of the nine substituted aromatic carbon atoms. These may be divided into two groups on the basis of their chemical shifts. Four absorb in the range 144–153 ppm and are the oxygenated carbon atoms; the remaining five are more shielded, absorbing in the region 124–130 ppm. Of the first group, one has the longest relaxation time of all carbon atoms in the molecule and is therefore assigned as C(1), which is more than 2.5 Å away from the nearest proton. In the spectrum (Figure 1b) in which the methoxyl protons are selectively decoupled, the C(1) absorption is a doublet with a characteristic meta coupling constant (6.7 Hz); ortho constants are normally 2.5–3.5 Hz [$J_{C(2),\ H(3)}=2.6$; $J_{C(9),\ H(8)}=2.5$; $J_{C(10),\ H(11)}=3.2$ Hz]. In the same spectrum, the absorption at 151.8 ppm exhibits no *meta* splitting and is therefore assigned to C(2). The remaining two absorptions in this group both show meta and ortho couplings as expected for C(9) and C(10). Selective decoupling at a frequency corresponding to $\delta=6.7$ ppm [H(3) and H(8)] in the proton spectrum removes the meta splitting (Figure 1d) from the multiplet at 147.4 ppm and the ortho coupling from that at 148.0 ppm. The latter also exhibits a nuclear Overhauser enhancement under

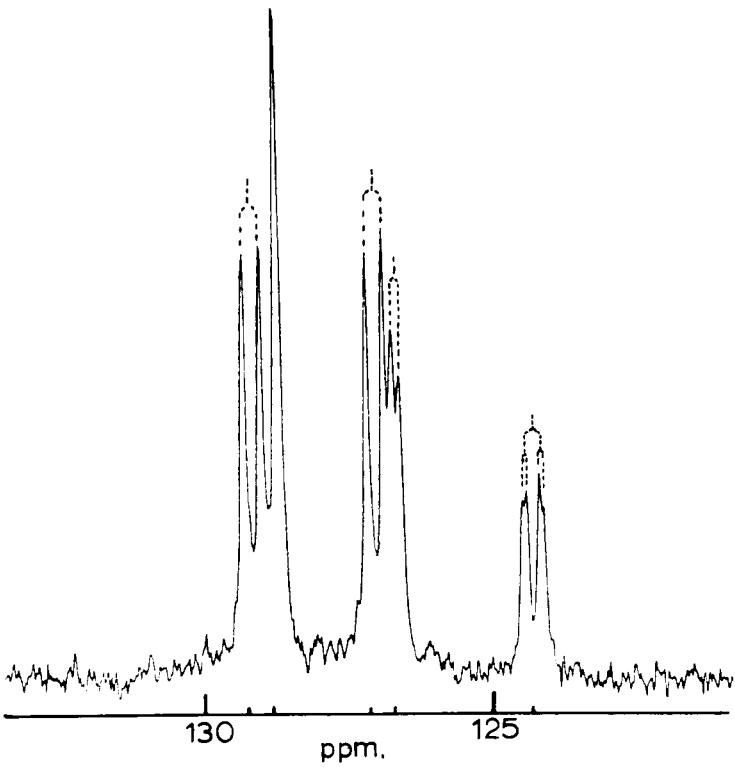


FIG. 2. Absorptions of the carbon substituted aromatic carbon atoms of glaucine in $CDCl_3$. CW decoupled at 99,538,407 Hz. ($\nu_{TMS}=99,538,124$ Hz).

these conditions and must accordingly be assigned to C(9). The coupling constants of the methoxyl protons to the methoxyl-bearing carbon atom are in the range 3.7–4.1 Hz.

Of the group of five absorptions (124–130 ppm), that at 126.8 ppm corresponds to a nucleus with a long relaxation time and is therefore assigned to C(1a) since the nearest proton to it is 2.5 Å distant. The nuclei C(3a) and C(7a) are each within approximately 2.2 Å of three protons and will therefore be the most efficiently relaxed nuclei of the group. They therefore correspond to the absorptions at 128.8 and 129.3 ppm. The former absorption is assigned to C(3a) since selective decoupling of the benzylic methylene protons yields a spectrum (Figure 2) in which this absorption is a singlet, in contrast to that at 129.3 ppm which appears as a doublet with a typical meta splitting ($J=7.3$ Hz). The two remaining absorptions (127.2 and 124.4) are associated with nuclei having intermediate relaxation times as expected for C(1b) and C(11a) which are within 2.2 Å of only one proton. The distinction between the two cannot be readily made by selective irradiation experiments. However, the assignment of the absorption at 124.4 ppm to C(11a) is supported by the somewhat longer relaxation time associated with this absorption. Calculations based on standard bond lengths and angles indicate that C(1b) should be relaxed approximately 10% more rapidly than C(11a). In any event, these assignments are unequivocally confirmed by comparisons of chemical shifts of aporphines with different aromatic substitution patterns. Thus in nuciferine (**11**) the C(1b) absorption remains virtually unchanged at 127.5 ppm in contrast to the C(11a) absorption which is shifted to 131.6 ppm (table 2).

THALIPORPHINE (**2**), PREDICENTRINE (**3**), BOLDINE (**4**) AND ISOBOLDINE (**5**).—In this series of compounds, as well as other 1,2,9,10-tetrasubstituted aporphines discussed below, assignment of the five non-oxygenated, fully substituted aromatic carbon atoms is greatly assisted by the characteristic splittings in spectra in which the benzylic methylene groups were selectively irradiated (figure 2). Thus C(1a) and C(11a) exhibit small but characteristic splittings (3 and 1.5 Hz, respectively). The C(11a) absorption also shows a meta splitting as, of course, do those of C(1b) and C(7a). Finally, the absorption of C(3a) is a singlet.

Thaliporphine (**2**) differs from glaucine in having a hydroxyl rather than a methoxyl at position 1. Consequently only the chemical shifts of the ring A carbon atoms differ from those of glaucine; of these, C(1b) and C(3), which are meta to the hydroxyl group, are scarcely affected (tables 1 and 2). The assignments of the C(1) and C(2) absorptions follow from the fact that the former is split by H(3) but not by an *C*-methyl group. The remaining assignments of the ring A absorptions are based on the multiplicities referred to in the previous paragraph. Similar arguments lead to the assignment of the ring A resonances of predicentrine (**3**), in which the 1- and 2-substituents are reversed. In this system, the carbon atoms ortho and para to C(2) (*i.e.* 1, 3 and 1b) are shifted significantly to lower fields relative to glaucine. A small shift of the C(11) resonance to a higher field is also observed, no doubt due to the proximity of the 1-O-methyl group to C(11) in glaucine.

Boldine (**4**) and predicentrine (**3**) differ in the sense that the former possesses a 9-hydroxyl rather than a 9-methoxyl group. Of the two resonances in boldine arising from the unsubstituted carbon atoms in ring D, one ($\delta=114.2$ ppm) is strongly shifted from the values found in glaucine and is therefore assigned to

C(8), which is ortho to the free hydroxyl group. The resonances of C(7a) and C(11a) are assigned on account of their characteristic multiplicities in the spectrum observed with decoupling of the benzylic methylene protons (*cf.* figure 2). Distinction between the resonances of the two oxygen-bearing carbon atoms of ring D is made, in spite of their near equivalence, on the basis of their spin lattice relaxation times. These effects are best expressed as ratios (R) of the T_1's in glaucine to those in boldine (table 1). This reveals a dramatic shortening of the relaxation times of C(2) and C(9) in boldine due to the proximities of the hydroxyl protons to the carbon atoms in question. It is interesting that there is an analogous, though smaller, shortening of the relaxation times of C(1) and C(10) relative to that observed for the more remote quaternary carbon atoms. This observation indicates that the hydroxyl protons are involved in intra molecular hydrogen bonding to the adjacent methoxyl groups, even in such a good acceptor solvent as dimethyl sulfoxide-d_6. Analogous results have been observed for 1-hydroxyfluorenone (8).

With the exception for that of C(11), the shifts of the aromatic carbon atoms of isoboldine (**5**) are predicted to within 0.8 ppm by using thaliporphine (**2**) and boldine (**4**) as models for rings A and D, respectively. The absorption of C(11) can be uniquely assigned in the fully coupled spectra of this group of compounds because, unlike the absorptions of C(3) and C(8), it is not broadened by weak coupling to adjacent methylene groups. Its anomalous shift is, as noted above, due to the proximity of the 1-O-methyl group in boldine.

NANTENINE (**6**), DOMESTICINE (**7**), AND DICENTRINE (**8**).—The replacement of the 9- and 10-O-methyl groups of glaucine and thaliporphine by the methylenedioxy bridge affords nantenine (**6**) and domesticine (**7**), respectively, and results in a nearly symmetric shift to lower fields of all six aromatic resonances of the ring D carbon atoms. This effect provides the basis for their assignment in the latter pair of compounds. The assignments of C(9) and C(10) are, however, ambiguous because of the near isochronicity of their resonances in both molecules.

Comparison of the cmr spectra of glaucine and dicentrine (**8**) reveals no such symmetric change in the chemical shifts of the ring A carbon atoms. Evidently, the introduction of the methylene bridge substantially reduces the steric distortion of the biphenyl residue. The assignment of the ring D carbons is made on the basis of the observed shifts in glaucine, the agreement being excellent for the 8,9,10- and 11-positions but slightly worse for C(7a) and C(11a) due, presumably, to the difference in strain at the C/D ring junctions in the two systems. The assignment of the ring A resonances is based on the shifts observed in oliveridine (**9**) (see below) with only the 1*b* position being significantly affected by the presence of the 7-hydroxyl group in **9**.

OLIVERIDINE (**9**) AND OLIVERINE (**10**).—The presence of the 7-hydroxyl group affects the chemical shifts not only of C(7) itself, but also of some of the neighboring atoms. Thus, C(6a) exhibits a β-shift of +2 ppm, and the N–CH_3 carbon exhibits a δ-shift of −4 ppm.

The spectrum of oliveridine (**9**) has four resonances at fields lower than 140 ppm. That at 159.1 is attributed to C(9) because its chemical shift is similar to that of the analogous carbon atom in anisole (9). The absorption at 146.5, which is a singlet in the undecoupled spectrum, is assigned to C(2). The remaining two signals in this region must arise from C(1) and C(7a), the latter evidently suffering a substantial β-shift from the 7-hydroxyl group. Both absorptions

exhibit meta-splittings, but they could readily be distinguished from each other by their spin lattice relaxation times, C(7a) (141.3 ppm) being much more efficiently relaxed than C(1) (141.6 ppm).

The signals at 121.4 (two meta splittings) and 122.5 ppm (one meta splitting) are assigned to C(11a) and C(1b), respectively, from their multiplicities in the undecoupled spectrum. The remaining two signals in this region are at 116.3 and 126.9 ppm. The latter is assigned to C(3a) rather than C(1a) from a comparison of the undecoupled spectrum with that obtained with selective decoupling of the benzylic methylene protons.

The absorptions of the four unsubstituted aromatic carbons are, of course, characterized by large splittings in the undecoupled spectrum. That at 127.8 ppm is assigned, on the basis of chemical shift, to C(11), the only unsubstituted carbon atom which does not experience the shielding effect of an ortho oxygen substituent. The resonance at 106.3 ppm, which exhibits no meta splitting, is assigned to C(3). Finally, the distinction between the resonances at 109.0 and 112.5 ppm was achieved by single frequency, off-resonance decoupling experiments. It has been shown (10) that, when the residual splitting due to the directly attached proton is reduced to the same order as the coupling of that proton with those ortho to it, the observed ^{13}C multiplet becomes considerably more complex due to virtual coupling. In the present context, this effect is expected for the C(10) resonance, and indeed the resonance at 112.5 ppm exhibits virtual coupling at low decoupling power. The spectrum of oliverine (**10**) is virtually identical with that of oliveridine except for β,γ and δ shifts in the direction associated with the replacement of the 7-hydroxyl proton by a methyl group.

NUCIFERINE (**11**), *N*-METHYLASIMILOBINE (**12**), OLIVEROLINE (**13**), PACHYPODANTHINE (**14**), AND GUATTERINE (**15**).—This group of aporphines is characterized by the possession of an unsubstituted ring D. In the spectra of nuciferine (**11**) and *N*-methylasimilobine (**12**), the four resonances of the unsubstituted carbon atoms of ring D absorb within a very narrow range (127.2–127.8), so that no assignment was attempted. The C(8) resonances in oliveroline (**13**), pachypodanthine (**14**), and guatterine (**15**) exhibit a significant positive γ-shielding effect from the 7-oxygen substituent and, thus, could be assigned.

The ring A carbon atoms of guatterine are assigned on account of the effect of the 3-methoxyl group on those centers which are *ortho* and *para* to it (9).

ISOCORYDINE METHIODIDE (**16**), CORYDINE METHIODIDE (**17**), APOMORPHINE DIMETHYL ETHER (**18**), AND ISOCORYDINE (**19**).—This group is characterized by oxygen substitution at C(10) and C(11) and includes the only two methiodide salts examined in the present study. The quaternary salts have two diastereotopic N-methyl groups which differ in chemical shift by 10 ppm. These compounds also exhibit positive β-shifts of about 6 ppm for C(5) and C(6a) and negative γ-shifts of the same magnitude for C(1b), C(4) and C(7). These effects have been discussed more thoroughly by Marsaioli and her coworkers (6b).

Of the four resonances of the oxygen-bearing carbon atoms of isocorydine methiodide (**16**), that at 150.2 ppm, which exhibits no meta splitting, is necessarily assigned to C(2). In the spectrum obtained with selective decoupling of the aromatic protons, the signal at 143.7 is a sharp singlet; whereas, the other absorptions in this region exhibit splittings due to coupling with O-methyl groups. It therefore arises from C(11). The remaining signals, 144.0 and 148.4 ppm, are assigned to C(1) and C(10), respectively, on the grounds that the latter is associated with a much shorter relaxation time than the former.

Selective irradiation of the protons of the benzylic methylene groups affords a spectrum in which two resonances, 124.5 and 124.6, appear as singlets. The latter has a much lower intensity (longer T_1) in the noise decoupled spectrum and is therefore assigned to C(1a) whereas the former must be associated with C(3a). The absorption at 118.3 arises from an overlap of the C(8) and C(11a) resonances. The latter assignment is based on the observation that, in the undecoupled spectrum, the absorption exhibits a meta splitting and an additional splitting due to a four bond coupling to the hydroxylic proton. The remaining two absorptions in this region both exhibit a meta splitting, but that at 121.2 ppm in unequivocally identified as arising from C(1b) since it is shown by a selective irradiation at $\delta\sim3.8$ ppm to be broadened by weak coupling with H(6a).

Of the signals associated with the unsubstituted aromatic carbon atoms, that at 118.3 ppm is assigned to C(8) which is meta and para to CH_3O and OH, respectively. The remaining signals (111.2 and 111.6 ppm) arise from C(9) and C(3) but have not been individually assigned.

Almost identical arguments have been developed for the assignments for rings A and D in corydine methiodide (**17**). In this system, however, the resonances of C(9) and C(3) are well resolved and have been separately assigned. This was possible because the absorption (112.1 ppm) due to C(3) was significantly broader (benzylic coupling) than that of C(9) (110.6 ppm) in the spectrum obtained with selective irradiation of the aromatic protons.

Assignment of the resonances of the ring D carbon atoms of apomorphine dimethyl ether (**18**) is reasonably straightforward. The two absorptions, 147.0 and 152.5 ppm, are clearly due to the oxygen-bearing carbon atoms; the former is assigned to C(11) because it is associated with a much longer relaxation time. The resonance at 111.4 ppm is due to the unsubstituted position C(9), the only such position adjacent to a methoxyl group. That at 123.3 ppm is assigned to C(8), since it could be shown by a comparison of the undecoupled spectrum with that obtained with specific irradiation of the benzylic methylene protons that it involves coupling to these protons, but not to meta aromatic protons. Of the signals for the three unsubstituted carbon atoms of ring A, that at 126.5 ppm is readily assigned to C(2), since it does not exhibit a meta splitting. Differentiation of the other two signals, 126.2 and 127.9 ppm, is based on the observation that the latter is additionally split by the benzylic protons and must therefore belong to C(3).

The resonance at 127.8 ppm is assigned to C(11a). Although the associated relaxation time could not be precisely determined because of the proximity of the signal to one of the absorptions of the unsubstituted carbon atoms, it was clearly longer than that of the other non-oxygen-bearing, fully substituted, carbon atoms. The resonances at 131.5 and 129.8 ppm are due to C(3a) and C(7a), since their relaxation times are in the same ratio (15:1) to those of the unsubstituted aromatic carbon atoms as found for glaucine (table 1); the more shielded of the two has been ascribed to C(7a). The remaining fully substituted carbon atoms C(1a) and C(1b) are responsible for the signals at 132.6 and 134.9 ppm, for which the associated T_1's relative to the unsubstituted carbon atoms are 17 and 26, respectively. The latter value is as expected for C(1b), but the former is considerably shorter than predicted for either position. We believe that the relaxation of C(1a) may have an appreciable contribution from the protons of the 11-methoxyl group.

In the undecoupled spectrum of isocorydine (**19**), the resonance of C(2) is readily assigned on the basis of chemical shift and the absence of meta splitting,

while that of C(11) is recognized due to the absence of splitting by O-methyl protons. The distinction between the other two oxygenated centers C(1) and C(10) is based solely on chemical shift, the former having a value close to that found in glaucine and the latter being somewhat more shielded, as expected (see below), since it is ortho to a hydroxyl rather than to a methoxyl group.

Of the signals of the unsubstituted carbon atoms, that at lowest field (118.6 ppm) is assigned to C(8) since it is the only one which is not ortho to a methoxyl group. The resonance at 110.7 ppm was shown to arise from C(9) by the same argument, based on virtual coupling, as discussed above for oliveridine. The assignment of the signal at 125.4 ppm to C(1a) is based on the absence of long range coupling, and that at 119.8 ppm is given to C(11a) because of its unique shift. The remaining three fully substituted atoms absorb within a very narrow range (128.8–129.8 ppm), and their individual assignments have not been attempted.

THALIPORPHINE ACETATE (**20**) AND BOLDINE DIACETATE (**21**).—The assignment of the spectra of these two derivatives follows closely arguments developed for the parent alkaloids. The additional signals introduced by the *O*-acetyl groups do not interfere with the remainder of the spectra.

RELATION OF STRUCTURE TO CHEMICAL SHIFTS.—Consideration of the data in table 2 permits some general correlation of structure to be made. Such correlations are clearly very useful in the determination of the structures of aporphines, and some may have even wider application in alkaloid chemistry. The more important of the correlations are now presented.

(i) *Methylation of Phenolic Hydroxyl Groups:*—Certain groups of aporphines differ only in the degree and orientation of methylation of phenolic hydroxyl groups. Conversion of phenolic hydroxyl to methoxyl is associated with characteristic changes in chemical shifts of the aromatic carbon nuclei of the ring involved. In deuteriochloroform, the chemical shift of the ipso carbon is deshielded by 3.0–3.7 ppm. An unsubstituted ortho carbon atom is shielded by 3 ppm; whereas, if it bears a methoxyl group, it is deshielded by approximately 2 ppm. Para carbon atoms are usually deshielded by about 1 ppm. Meta carbon atoms are slightly shielded (1.5 ppm) if unsubstituted or somewhat deshielded if bonded to carbon. Some of these effects change quite dramatically when the sterically hindered 1- or 11- hydroxyl groups are involved. In these situations, methylation results in large (5–7 ppm) downfield shifts of the ring junction carbon atoms which are ortho or para to the hydroxyl group in question. The downfield shift of the ortho methoxyl-bearing carbon atom is also increased. When the oxygen atom is in a sterically crowded environment, electron release from the oxygen to the ortho and para positions is presumably sterically inhibited by methylation. These various trends are summarized in figure 3.

(ii) *O-Acetylation:*—Conversion of aporphines to *O*-acetyl derivatives is accompanied by increased oxidative stability and good solubility in deuteriochloroform. This transformation is also associated with characteristic changes in chemical shifts. In this case, the ipso carbon is strongly shielded (-5 to -6 ppm), and the ortho and para nuclei are strongly deshielded (4–9 ppm) in relation to the original phenol. These trends are summarized in figure 4.

(iii) *The Methylenedioxy Group:*—As well as giving rise to a characteristic absorption at $\delta = 100$ ppm, the methylenedioxy group is associated with changes in the aromatic absorptions relative to the corresponding dimethoxy compound. The changes for the 9,10-group are symmetrical and primarily affect the two ipso

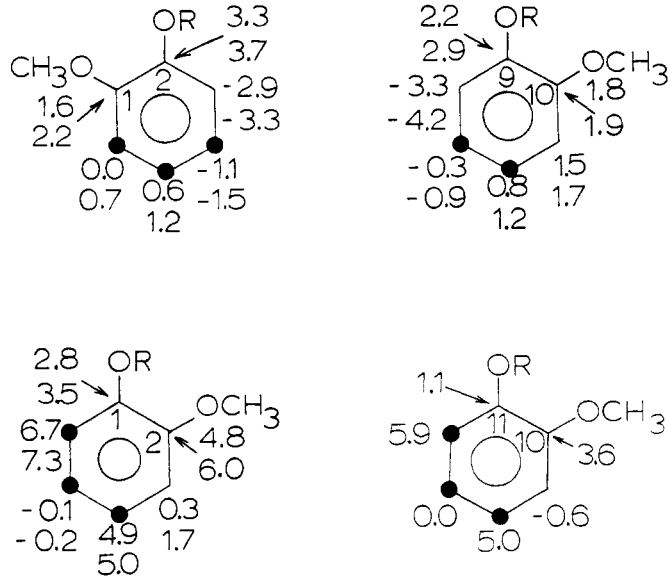


FIG. 3. Shifts ($\delta_{OCH_3}-\delta_{OH}$) associated with methylation of phenolic hydroxyl groups in aporphines.

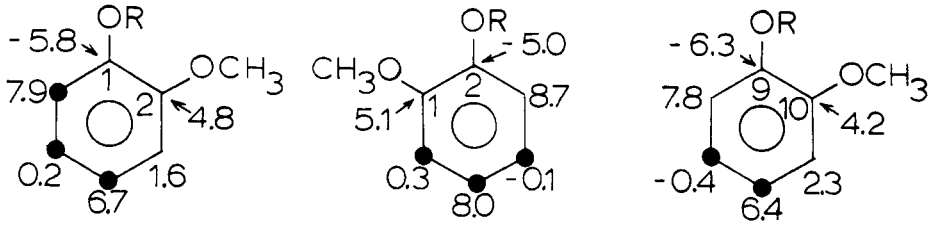


FIG. 4. Shifts ($\delta_{OAc}-\delta_{OH}$) associated with acetylation (R=H→$COCH_3$) of phenolic hydroxyl groups in aporphine.

carbon atoms and their ortho neighbors. The values for the 9,10- and 1,2-methylenedioxy groups are shown in figure 5. The shifts for the former system are almost identical with those observed for the 2,3-methylenedioxy group in protoberberines (11). In contrast, the shifts for the 1,2-group are unsymmetrical, again reflecting the crowded condition of the 1-position.

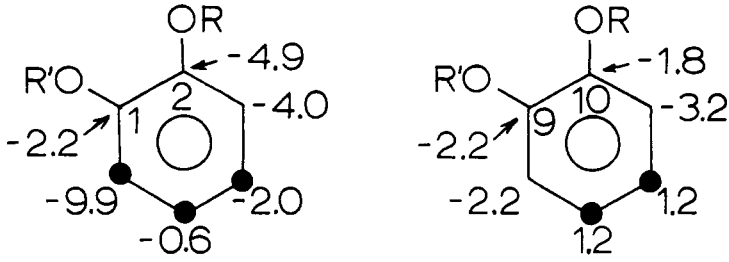


FIG. 5. Shift differences between vicinal dimethoxy aporphines and the corresponding methylenedioxy derivatives.

(v) *7-Oxyaporphines:*—The 7-hydroxy alkaloids are characterized by the low field (approx. 70 ppm) position of the 7-carbon atom which now appears as a doublet in the coupled spectrum. Methylation of the hydroxyl group causes a further shift of about 12 ppm to lower field.

(vi) *Methoxyl Groups:*—The majority of the resonances of the methoxyl groups absorb in a very narrow range near 56 ppm. The sterically crowded methoxyl groups at C(1) and C(11), however, are deshielded by about 4 ppm. The aliphatic methoxyl group at C(7) absorbs at 55 ppm.

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