Phytochemistry, 1979, Vol. 18, pp. 165–169. © Pergamon Press Ltd. Printed in England. 0031-9422/79/0101-0165$02.00/0

^{13}C NMR ANALYSIS OF APORPHINE ALKALOIDS

ANITA J. MARSAIOLI, FRANCISCO DE A. M. REIS, ADERBAL F. MAGALHÃES and EDMUNDO A. RÚVEDA
Instituto de Química, Universidade Estadual de Campinas, C.P. 1170, 13100 Campinas, São Paulo, Brasil
and
ALFREDO M. KUCK*
Facultad de Farmacia y Bioquímica, Junin 956, Universidad de Buenos Aires, Argentina

(*Received* 10 *May* 1978)

Key Word Index—^{13}C NMR spectra; aporphine alkaloids; glaucine methiodide; xantoplanine iodide; laurifoline chloride; dicentrine methiodide; isocorydine methochloride; corydine methochloride; *O,O'*-dimethylmagnoflorine iodide; magnoflorine iodide; ocoteine; boldine; ocoteine methiodide; boldine methiodide.

Abstract—The ^{13}C NMR spectra of some tertiary and quaternary aporphine alkaloids are recorded and the signals assigned. The substituent shielding effects together with the effects of *N*- and *O*-methylation, and the twisting of the biphenyl system, are analysed and utilized in the spectral interpretation.

INTRODUCTION

The presence of a twisted biphenyl system and the steric effects produced by substituents in the skeleton of aporphines, make them very attractive for spectral analysis. Evidence obtained by UV, ORD, PMR and MS studies [1, 2] were useful for distinguishing between the 1,2,9,10 and 1,2,10,11 oxygenated patterns [3], but the nature (MeO— or HO—) of a particular substituent at a determined position remained difficult to assign. Consequently, and in view of the striking sensitivity of carbon shifts to steric effects, it was decided to carry out an analysis of some representative members of this large group of isoquinoline alkaloids [4], as continuation of our project on ^{13}C NMR spectral analysis of natural products [5].

RESULTS AND DISCUSSION

The assignment of glaucine methiodide **2a** was based on the reported data for glaucine **1** [6] and on the effects of *N*-methylation on the neighbouring carbon shifts. The quaternization of the *N*-atom of **1** causes deshielding of C-5 and C-6a and shielding of C-1b, C-3a, C-7 and C-7a by magnitudes similar to those previously observed in the 1-benzyltetrahydroisoquinoline alkaloid series [5].

Comparison of **2a** with the monophenolic and diphenolic alkaloids xantoplanine iodide **2b** and laurifoline chloride **2c**, respectively, shows that the replacement of the OMe (δ = 56 ppm) on C-9 of **2a** by an OH group as in **2b**, produces the normal effects on the carbons *ortho* to the phenolic function, while the *para* position (C-11a) is essentially unaffected. In **2c**, however, the replacement of the sterically hindered OMe (δ = 60.4 ppm) on C-1 of **2a** by an OH group, induces stronger shielding effects on C-1a, C-2 and C-3a, *ortho* and *para* respectively to the oxygenated function, as previously described for other crowded systems [7]. The carbon signals of *O*-ethylxantoplanine iodide **2d** and *O,O'*-diethyllaurifoline iodide **2e** are similar to the ones observed in **2a**, the CH_2 of the *O*-ethyl group on C-1 of **2e**, being sterically hindered, resonates at lower field than the CH_2 of the *O*-ethyl group on C-9 of **2d** and **2e**.

It is known that the replacement of two OMe groups of an aromatic system by a methylenedioxy moiety induces shielding of the oxycarbons and their neighbours by 1–2 and 3–4 ppm, respectively, and deshielding of the remaining ones by 1–2 ppm [6]. Comparison of the ring A carbon shifts of **2a** with those of dicentrine methiodide **2f**, shows stronger shielding effects on C-2 and C-1a, while C-1b and C-3a are also shielded. These apparently anomalous observations are consequences of the fact that the interactions of the methoxyl oxygens with the aryl carbons are more easily altered than the corresponding ones of the planar and rigid methylenedioxy group in highly substituted systems. These data establish that the reported effects of changing two OMe by a —OCH_2O— moiety on the benzene carbon shifts, are valid only for systems free of severe steric interactions.† In the aporphine series, for example, comparison of the reported shifts of ring D of **1**, carrying two OMe groups without steric interactions, with similar sites of nantenine **3**, shows the normal effects [6]. The remaining carbon shifts of **2f**, are practically unaffected by comparison with **2a**. The shifts of compounds **2a–2f** are listed in Table 1.

The shifts of the highly strained 1,2,10,11-tetrasubstituted quaternary aporphines, isocorydine methochloride **5a**, *O,O'*-dimethylmagnoflorine iodide **5b**, corydine methochloride **5c** and magnoflorine iodide **5d**, are listed in Table 2. The assignments are based on the δ values recorded for isocorydine **4** [6], on the effects of *N*-quaternization and *O*-methylation of sterically hindered OH groups and on comparison of the signals of the 4 compounds with each other.

* Present address: Pfizer S.A.C.I., Buenos Aires, Argentina.

† In agreement with these observations, the transformation of (−)-*O*-methylcapaurine into 1-methoxy-2,3-methylenedioxytetrahydroprotoberberine and 1,2-methylenedioxy-3-methoxytetrahydroprotoberberine shows shielding of all ring A carbon shifts (Kametani, T., Fukumoto, K., Ihara, M., Ujiie, A. and Koizumi, H. (1975) *J. Org. Chem.* **40**, 3280).

Table 1. *§ ^{13}C NMR data of aporphine alkaloids and their derivatives

	2a	2b	2c	2d†	2e†	2f
1	145.6	145.9	142.2	145.6	144.5	143.1
1a	127.7	127.6	118.2‡	127.7	128.0	116.7
1b	118.6	118.4	118.3‡	118.5	118.6	117.9
2	153.9	153.6	148.0	153.9	153.9	148.5
3	110.2	109.8	108.0	110.1	110.0	106.4
3a	124.1‡	124.4	119.8	123.9	124.0‡	121.8‡
4	24.3	24.0	23.5	24.2	24.2	24.0
5	61.4	61.5	61.5	61.3	61.4	61.8
6a	70.3	69.9	69.7	70.4	70.3	69.8
7	29.5	28.9	28.6	29.6	29.5	28.7
7a	124.0‡	123.9	123.7	123.9	123.8‡	123.3
8	111.4	114.5	114.3	112.3	112.3	111.6
9	148.8	145.9	145.4	148.4	148.1	148.8
10	148.2	146.5	146.2	148.2	148.1	148.2
11	111.4	111.4	112.1	111.6	111.8	110.2
11a	123.0	122.0	122.5	122.8	123.1	122.0‡
$-N^+Me_2$	44.0; 54.8	43.6; 54.3	42.6; 53.4	43.8; 54.7	43.5; 54.7	43.6; 54.3
—OMe (C-1)	60.5	60.1		60.4		
—OMe (C-2)	55.7	55.8	55.7	55.9	55.9	
—OMe (C-9)	56.1					55.9
—OMe (C-10)	56.1	55.8	55.7	55.9	55.9	55.9
$-OCH_2O-$						101.3
—OEt (C-1)					15.7; 69.0	
—OEt (C-9)				14.8; 64.5	14.5; 64.5	

* Spectra were obtained at 25.2 MHz in Fourier transform mode in $CDCl_3$ solutions with some MeOH for better dissolution of the compounds. The δ values are in ppm downfield from TMS.

† In $CDCl_3$ solution.

‡ Signals may be reversed.

§ Although the fully coupled spectra showed complex fine structures preventing unambiguous assignments, some of the carbon shifts listed in this and in Tables 2 and 3, were confirmed by ^{13}C-^1H long-range couplings.

Table 2.* ^{13}C NMR data for aporphine alkaloids and their derivatives

	5a†	5b‡	5c‡	5d§
1	143.0	146.9‖	143.6	140.2
1a	126.0	124.5	119.2¶	118.9
1b	118.3	121.0	119.2¶	117.7
2	152.9	153.0	150.9	148.8
3	110.6	111.0	110.6	109.6
3a	125.2	122.9	119.6¶	120.3‖
4	23.8	23.4	23.9	23.4
5	60.3	60.8	61.0	61.5
6a	69.1	69.3	69.8	69.7
7	30.6	30.4	30.7	30.3
7a	124.3	125.2	124.7‖	123.8
8	119.6	122.6	125.3	120.8
9	111.5	112.3	111.8	110.9
10	149.7	152.4	152.5	147.6
11	143.5	147.1‖	143.6	140.2
11a	120.2	123.8	124.6‖	119.2‖
$-N^+Me_2$	42.9; 53.5	43.1; 53.9	44.0; 54.8	43.4; 54.2
—OMe (C-1)	62.1	60.7		
—OMe (C-2)	55.8	55.9	56.1	55.8
—OMe (C-10)		55.9	56.1	55.8
—OMe (C-11)	55.8	60.7	62.2	

* Spectra were obtained at 25.2 MHz in Fourier transform mode. The δ values are in ppm downfield from TMS.

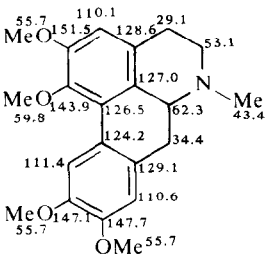
† In $CDCl_3$ solution with some MeOH.

‡ In $CDCl_3$ solution.

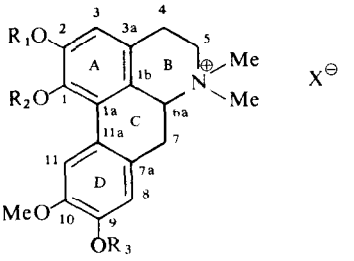
§ In $CDCl_3$ solution with some TFA.

‖ Signals may be reversed.

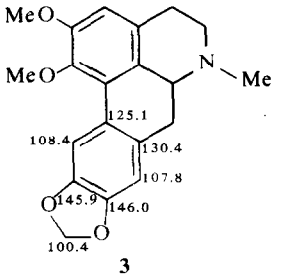
¶ Signals may be reversed.



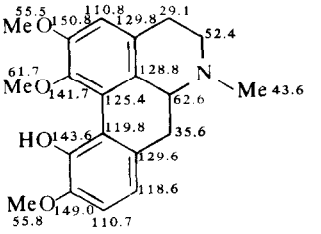
1



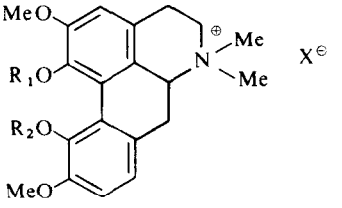
2a $R_1 = R_2 = R_3 = Me$; X = I
2b $R_1 = R_2 = Me$; $R_3 = H$; X = I
2c $R_1 = Me$; $R_2 = R_3 = H$; X = Cl
2d $R_1 = R_2 = Me$; $R_3 = Et$; X = I
2e $R_1 = Me$; $R_2 = R_3 = Et$; X = I
2f $R_1 = R_2 = —CH_2—$; $R_3 = Me$; X = I



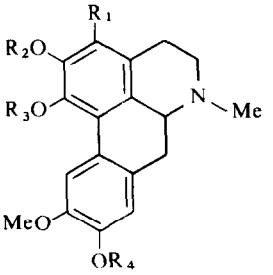
3



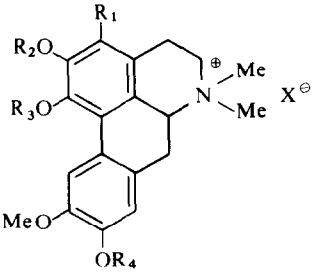
4



5a $R_1 = Me$; $R_2 = H$; X = Cl
5b $R_1 = R_2 = Me$; X = I
5c $R_1 = H$; $R_2 = Me$; X = Cl
5d $R_1 = R_2 = H$; X = I



6a $R_1 = R_2 = R_4 = H$; $R_3 = Me$
6b $R_1 = OMe$; $R_2 = R_3 = —CH_2—$; $R_4 = Me$



7a $R_1 = R_2 = R_4 = H$; $R_3 = Me$; X = I
7b $R_1 = OMe$; $R_2 = R_3 = —CH_2—$; $R_4 = Me$; X = I

Table 3* ^{13}C NMR data for aporphine alkaloids and their derivatives

	6a	6b	7a†	7b†
1	141.9	143.2	143.9	144.7
1a	126.6	110.4	127.1	110.7
1b	125.8	127.4	117.1	118.7
2	147.9	134.8	151.1	135.3
3	113.2	139.1	113.6	138.6
3a	129.7‡	119.1	124.1‡	114.3
4	28.8	23.6	23.4	19.3
5	53.3	53.2	61.4	61.5
6a	62.5	62.3	69.7	69.5
7	34.1	34.1	28.7	28.6
7a	130.1‡	127.4	123.8‡	122.6
8	114.1	111.1	114.5	111.6
9	144.9	147.5	145.8	148.0
10	145.4	147.5	146.6	148.0
11	110.1	110.0	110.9	109.5
11a	123.5	123.5	121.8	121.9
$-N^+Me_2$			43.2; 53.7	43.6; 54.4
—OMe (C-1)	60.2		59.6	
—OMe (C-3)		59.3		59.4
—OMe (C-9)		56.0		56.0
—OMe (C-10)	56.1	55.8	55.5	55.9
$-OCH_2O-$		100.4		101.1

* Spectra were obtained at 25.2 MHz in Fourier transform mode in $CDCl_3$ solutions. The δ values are in ppm downfield from TMS.

† Some MeOH was added for better dissolution.

‡ Signals may be reversed.

The *N*-methylation of **4** produces the expected changes on the neighbour carbons, as observed above for the transformation of **1** into **2a**, allowing the complete shifts assignment of isocorydine methochloride, **5a**.

Comparison of **5a** with **5b** shows that methylation of the phenolic OH (**5a** → **5b**) affects not only C-11, C-11a, C-10 and C-8, producing the expected deshielding effects, but also C-1 and C-3a, inducing deshielding and shielding effects, respectively. In corydine methochloride **5c**, the OH on C-1 induces shielding of C-1, C-1a, C-2 and C-3a, and further C-11 and C-8 shows signals at higher and lower fields respectively, than comparable sites of the tetramethoxy alkaloid **5b**, while the remaining aromatic carbons are much less affected.

The analysis of the OMe shifts in this group of alkaloids shows some interesting results. The δ value of the OMe group on C-1 of **5a** is similar to that observed for the OMe group on C-11 of **5c**, both having *ortho* substituents, an OMe group and ring D or ring A, respectively. The mentioned OMe groups are deshielded in comparison with the *O*-methyl shifts on C-1 and/or on C-11 of the more crowded system of **5b**. This is unexpected since it has been observed that methoxyl carbon resonates at progressively lower field as the bulk of the *ortho* substituents increases [8]. In **5b**, however, the steric interactions of the OMe groups on C-1 and C-11 could induce an increase of the angle of twist of the biphenyl system and these OMe groups show signals at higher field than the corresponding ones of **5a** and **5c**, and at δ values similar to the ones observed above for the OMe on C-1 of glaucine **1**, and related alkaloids. Further support for these observations are the shielding shown by C-3a and C-8 of **5b** in comparison with C-3a and C-8 of **5a** and **5c** respectively, indicating a better conjugation of the O atoms to the corresponding aromatic rings.

The shifts of magnoflorine iodide **5d**, although recorded in $CDCl_3$ with some TFA, because of its low solubility, are essentially the expected ones from the above analysis on **5a**, **5b** and **5c**.

The tertiary aporphine alkaloids boldine **6a** and ocoteine **6b** were also analysed. Boldine shows the expected shifts based on those reported for glaucine **1** [6]. The replacement of both OMe groups by a methylenedioxy moiety, in addition to the introduction of a third oxygenated function on C-3, as in ocoteine **6b**, produces dramatic changes on the chemical shifts of ring A carbon atoms of **1**. The high field signal shown by C-1a could be explained by the sum of the strong effect produced by a $-OCH_2O-$ in an aporphine system (as in **2f**) and by the shielding effect of a OMe group on *para* and *ortho* positions, as also observed on C-2 and C-3a. On C-4 however, a γ effect produced by the OMe group on C-3, can be invoked to explain its chemical shift, while the remaining carbon signals are virtually unaffected. The transformation of **6a** and **6b** into their corresponding methosalts **7a** and **7b** respectively, produces the expected changes confirming the above assignments. The shifts of compounds **6a–7b** are listed in Table 3.

According to the results presented in this communication, ^{13}C NMR spectroscopy seems to be more sensitive than the routine physical methods, to the position and nature of a given substituent in the aporphine skeleton, providing valuable information for the rapid identification of a known alkaloid or for proposing the structure of a new one.

Acknowledgements—We thank FINEP and CNPq (Grant No. 222220314/77) for financial support.

REFERENCES

1. Jackson, A. H. and Martin, J. A. (1966) *J. Chem. Soc.* (C) 2181 and refs. cited therein.
2. Albónico, S. M., Comin, J., Kuck, A. M., Sanchez, E., Scopes,

P. M., Swan, R. J. and Vernengo, M. J. (1966) *J. Chem. Soc.* (*C*) 1340.
3. For a recent review see: Guinaudeau, H., Leboeuf, M. and Cave, A. (1975) *Lloydia* **38**, 275.
4. Kuck, A. M., Albónico, S. M., Deulofeu, V. and Escalante, M. G. (1967) *Phytochemistry* **6**, 1541; Barallc, F., Busch, A., Vernengo, M. J. and Kuck, A. M. (1972) *Lloydia* **35**, 300.
5. Marsaioli, A. J., Rúveda, E. A. and Reis, F. A. M. (1978) *Phytochemistry* **17**, 1655.
6. Wenkert, E., Buckwalter, B. L., Burfitt, I. R., Gasić, M. J., Gottlieb, H. E., Hagaman, E. W., Schell, F. M. and Wovkulich, P. M. (1976) *Topics in Carbon-13 NMR Spectroscopy* (Levy, G. C., ed.) Vol. 2. Wiley-Interscience, New York.
7. Wenkert, E. and Gottlieb, H. E. (1977) *Phytochemistry* **16**, 1811.
8. Dhami, K. S. and Stothers, J. B. (1966) *Can. J. Chem.* **44**, 2855.