CARBON-13 NMR SPECTRA OF SOME HASUBANAN ALKALOIDS[1]

MATAO MATSUI and YASUO WATANABE

Daiichi College of Pharmaceutical Sciences, 22-1 Tamagawa-Cho, Minami-Ku, Fukuoka 815, Japan

and

TETSU HINOMOTO

Application Laboratory, Scientific Instrument Division, JEOL Ltd., 1418 Nakagami, Akishima, Tokyo 196, Japan

ABSTRACT.—An attempt was first made to assign the cmr spectra of hasubanan alkaloids, oxostephamiersine (**1**), stephamiersine (**2**), epistephamiersine (**3**), dihydroxostephamiersine (**4**), and dihydrostephamiersine (**5**). Low power ^1H irradiation, including long-range selective proton decoupling (lspd), selective proton decoupling (spd), and gated decoupling with NOE-mode operations were applied for full assignments. As a result, the C-9 and the N-methyl carbons of hasubanan alkaloids exhibited signals at higher field than those reported for morphinan alkaloids. Further, the N-methyl carbons of **1** and **4** having a carbonyl function at C-16 revealed signals at extremely upper field (δ 27.8 and 27.7) than those found to **2**, **3**, and **5** (δ 36.3, 35.9, and 37.7). The characteristic resonances of hasubanan alkaloids may well be applied to the further structure elucidation of these congeners, including the distinction between hasubanan and morphinan alkaloids.

Research on the chemistry of natural products has undergone acceleration by use of ^{13}C nuclear magnetic resonance (cmr) spectroscopy. As a consequence, a large body of data has been acquired over the last decade in the alkaloid field (1). However, no report of a cmr for the hasubanan alkaloid has appeared in the literature. We recently attempted to assign the cmr spectra of five known hasubanan alkaloids, oxostephamiersine (**1**), stephamiersine (**2**), epistephamiersine (**3**), dihydrooxostephamiersine (**4**), and dihydrostephamiersine (**5**), whose steric features had been confirmed by the proton magnetic resonance (pmr) (2). Hence, the present work may well contribute to further elaboration of the structure elucidation of hasubanan alkaloids.

This paper deals with the cmr assignments of the hasubanan alkaloids and the relationship between the structures and ^{13}C resonances.

RESULTS AND DISCUSSION

The signal assignments for each alkaloid were carried out by the following technique; proton noise decoupling (pnd), selective proton decoupling (spd), low power selective proton decoupling (lspd), and gated decoupling with NOE-mode. The δ-values and ^{13}C–^1H coupling constants recorded in $CDCl_3$ for **1–5** are listed in table 1 and table 2.

ASSIGNMENT FOR RESONANCE OF OXOSTEPHAMIERSINE (**1**).—The two carbonyl carbons exhibited multiplets at the downfield (δ 204.6 and 172.3). Low power irradiation of C-7 proton caused an enhancement and a simplification of the most downfield resonance (δ 204.6), but the other signal (δ 172.3) remained unchanged. Therefore, the former was assigned to C-6 and the latter to C-16, respectively. The assignments were further supported by the fact that compounds **2** and **3**, having no carbonyl group at the C-16 showed no signal at this region (δ 172.3).

The six aromatic carbons (C-1, 2, 3, 4, 11, and 12) exhibited signals at the region of δ 111.3–153.4. Irradiation of the C-10 proton with low power caused the C-1 doublet of double quartet (δ 119.7, $^1J=161.1$, $^2J=4.3$, $^3J=1.2$ Hz) to change into a *quasi*-doublet, whereas the C-2 signal (δ 111.3) revealed no appreci-

[1]Part 273 in the series "Studies on the Alkaloids of Menispermaceous Plants". Part 272: J. Kunitomo, M. Oshikata, and M. Akasu, *Yakugaku Zasshi* in press.

TABLE 1. Cmr chemical shifts and ^{13}C–^{1}H coupling constants in oxostephamiersine (1).[a]

No. of carbon	Chemical shift[b]	Direct coupling	$^{1}J_{C-H}$ (Hz)	Long-range coupling	$^{2}\sim J_{C-H}$ (Hz)
1	119.7	d	161.1	dd	4.3, 1.2
2	111.3	d	159.3	m	
3	153.4	s		m	
4	148.4	s		m	
5	42.3	dd	125.7, 141.0	m	
6	204.6	s		m	
7	80.6	d	150.1	qd	4.9, 3.1
8	104.3	s		m	
9	34.6	t	137.3	m	
10	75.4	d	158.7	m	
11	133.7	s		m	
12	129.9	s		m	
13	47.0	s		m	
14	71.9	s		m	
15	44.4	dd	129.4, 142.2	m	
16	172.3	s		m	
3–OMe	55.7	q	144.6		
4–OMe	60.3	q	144.7		
7–OMe	58.0	q	142.8	d	3.7
8–OMe	47.7	q	143.4		
N–Me	27.8	q	139.8		

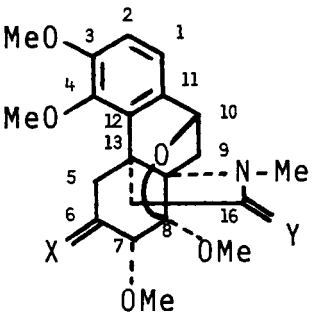
[a]Spectrum was recorded at 25.05 MHz under the following FT measurement condition; spectral width, 5 KHz; data point, 32 K; repetition time, 1.5 sec; flip angle, 45°; number of pulses, 25000; pulse width 5 μsec.
[b]δ ppm in $CDCl_3$ using TMS as an internal standard.

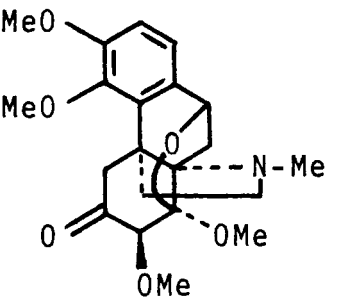
able change. The C–3 and C–4 carrying the methoxy groups exhibited multiplets at δ 153.4 and δ 148.4. On irradiation of the aromatic protons (H–1 and H–2) with low power, these signals, as expected, resulted in collapse of the multiplets into *quasi*-quartets, and the signal intensity of the C–3 caused an Overhauser C_3–H_2 enhancement due to the elimination of $^{3}J(C_3–H_1)$. Similar irradiation of the aromatic protons caused the C–11 signal (δ 133.7) to change from the multiplet

TABLE 2. Comparison of cmr data of some hasubanan alkaloids.[a]

carbon	alkaloid				
	1	2	3	4	5
1	119.7 (d)	119.6 (d)	119.6 (d)	119.9 (d)	119.5 (d)
2	111.3 (d)	110.4 (d)	110.4 (d)	110.4 (d)	109.8 (d)
3	153.4 (s)	153.3 (s)	153.2 (s)	153.7 (s)	153.6 (s)
4	148.4 (s)	148.2 (s)	147.5 (s)	148.4 (s)	148.3 (s)
5	42.3 (dd)	43.5 (dd)	46.3 (dd)	33.6 (dd)	34.9 (dd)
6	204.6 (s)	206.6 (s)	202.9 (s)	71.4 (d)	68.4 (d)
7	80.6 (d)	81.7 (d)	88.3 (d)	75.3 (d)	76.5 (d)
8	104.3 (s)	105.5 (s)	106.9 (s)	102.4 (s)	104.2 (s)
9	34.6 (t)	38.3 (t)	38.3 (t)	34.5 (t)	37.4 (t)
10	75.4 (d)	76.1 (d)	76.7 (d)	74.6 (d)	76.5 (d)
11	133.7 (s)	133.8 (s)	133.6 (s)	133.6 (s)	137.3 (s)
12	129.9 (s)	132.9 (s)	131.8 (s)	132.4 (s)	133.0 (s)
13	47.0 (s)	52.9 (s)	53.2 (s)	43.1 (s)	49.0 (s)
14	71.9 (s)	74.6 (s)	75.3 (s)	71.4 (s)	73.8 (s)
15	44.4 (dd)	29.3 (dd)	28.8 (dd)	45.0 (dd)	28.5 (dd)
16	172.3 (s)	54.1 (t)	54.1 (t)	172.8 (s)	54.2 (t)
3–OMe	55.7 (q)	55.7 (q)	55.7 (q)	55.7 (q)	55.6 (q)
4–OMe	60.3 (q)	60.3 (q)	60.2 (q)	60.4 (q)	60.3 (q)
7–OMe	58.0 (q)	58.6 (q)	59.1 (q)	58.4 (q)	59.1 (q)
8–OMe	47.7 (q)	47.7 (q)	50.8 (q)	47.9 (q)	47.7 (q)
N–Me	27.8 (q)	36.3 (q)	35.9 (q)	27.7 (q)	37.7 (q)

[a]All values are δ ppm, for $CDCl_3$ solution at 25.05 MHz with TMS as an internal standard, and ^{13}C–^{1}H direct coupling constant values (^{1}J) is shown herein.





1: X = O, Y = O

2: X = O, Y = H_2

4: X =  , Y = O

5: X =  , Y = H_2

3

into a double doublet because of the long-range coupling with C–9 and C–10 protons, whereas the C–12 signal (δ 129.9) changed the shape of the multiplet; for the long-range coupling with C–5, C–10, and C–15 protons remained intact. Further, irradiation of C–9 and C–10 protons increased the signal intensity of the C–11 in comparison with that of the C–12.

The eight sp^3 carbons of the skeleton appeared as signals at the region of δ 27.8–104.3. Inspection of the pnd data revealed signal: noise (S/N) ratio at δ 47.0, δ 71.9, and δ 104.3 was lower than those of any others. Hence, these signals were preliminarily assigned to the quaternary carbons, C–8, C–13, and C–14, respectively. Since the substituent effect due to the heteroatoms is predictable to the C–8 and C–14, the downfield resonances (δ 104.3 and 71.9) were alternatively assigned to the C–8 or the C–14, and the upfield one (δ 47.0) was assigned to the C–13. These assignments were confirmed by the following lspd experiments. The C–8 (δ 104.3) and C–14 (δ 71.9) revealed a signal enhancement upon irradiation of C–7 proton, and irradiation of C–9 proton with low power caused the similar change of the C–8 signal. The C–7 revealed a multiplet at δ 80.6 because of the long-range interaction with C–5 methylene and C–7 methoxy protons, and the multiplet changed into a singlet upon irradiation of C–7 proton by spd. Further, on irradiation of the C–10 proton by spd, the C–10 multiplet changed into a singlet.

The methylene carbons (C–5, 9, and 15) exhibited signals at δ 42.3, δ 34.6, and δ 44.4, whose assignments were made as follows. The signal of C–9 (δ 34.6) revealed a population transfer (3) upon irradiation of one of C–9 methylene protons by lspd. On irradiation of C–7 proton with low power, the C–5 signal (δ 42.3) caused the improvement in S/N and simplification in the shape.

The four methoxy carbons exhibited signals at δ 47.7, δ 55.7, δ 58.0, and δ 60.3 as each quartet (^1J = 142.8–144.8 Hz) due to the direct ^{13}C–^1H coupling, and the N-methyl carbon revealed a signal at the most upfield (δ 27.8) as a quartet (^1J = 139.8 Hz). These assignments were clarified by irradiation of each bearing proton. Of these resonances, it was noticeable that only the C–7 methoxy carbon

exhibited a signal at δ 58.0 as a double doublet ($^1J = 142.8$ Hz, $^2J = 3.7$ Hz) by the long-range coupling with C–7 proton. On irradiation of the C–7 proton with low power, a population transfer was observed for the above signal. From this finding, the C–7 methoxy carbon was unambiguously differentiated from the others.

COMPARISON OF THE SPECTRA OF OXOSTEPHAMIERSINE (1) AND STEPHAMIERSINE (2).—The structure of **2** is the same as that of **1**, except that this alkaloid possesses no carbonyl group at the C–16. The signal assignments for **2** were carried out by the foregoing technique, and the observed data are given in table 2.

The spectrum, as expected, differed from that of **1** with respect to the ethanamine-ring and its environment carbons. The C–15 and C–16 resonated at the upper field by −15.1 ppm and −118.2 ppm, but the C–9, C–13, C–14, and N-methyl carbon resonated at the lower field by +3.7 ppm, +5.9 ppm, +2.7 ppm, and +8.5 ppm than those for **1**. The downfield shift (+8.5 ppm) of N-methyl carbon of **2** suggests the steric interaction with the C–16 carbonyl group in **1**.

COMPARISON OF THE SPECTRA OF OXOSTEPHAMIERSINE (1) AND DIHYDROOXOSTEPHAMIERSINE (4).—Hydroxylated compound **4** possesses a β-axial hydroxyl group at the C–6, and the full assignments for each signal are given in table 2.

On changing the C–6 substituent from carbonyl to hydroxyl, the resonances of C-ring carbons, C–5, C–6, C–7, C–8, and C–13 shifted to upfield. Especially, the upfield shifts of C–13 (−3.9 ppm) and C–8 (−1.9 ppm) in their resonances could be ascribed to the γ-effect of the hydroxyl group.

COMPARISON OF THE SPECTRA OF DIHYDROOXOSTEPHAMIERSINE (4) AND DIHYDROSTEPHAMIERSINE (5).—The structure of **5** is the same as that of **4** except the C–16, and the signal assignments are given in table 2.

The resonances of C–9, C–13, C–14, and N-methyl carbon of **5** showed the downfield shift compared to those for **4**, whereas the C–15 and C–16 resonances shifted to upfield. These facts also indicate the effect of the C–16 carbonyl group as described in the spectra of **1** and **2**.

COMPARISON OF THE SPECTRA OF STEPHAMIERSINE (2) AND EPISTEPHAMIERSINE (3).—Naturally occuring alkaloids **2** and **3** are epimers with respect to the C–7 methoxy group, and the C–7 methoxy configuration of **2** is in α-axial, and that of **3** lies in β-equatorial.

A significant difference was observed in the neighborhood of the epimer center at C–7. In the case of the C–6 resonance, **3** exhibited a signal at δ 202.9, while **2** showed this signal at δ 206.6 (see table 2). This shift (3.7 ppm) may be interpreted by the difference of C–7 methoxy configuration, as well as the downfield shift for C–5 (+2.8 ppm), C–7 (+6.6 ppm), C–8 (+1.4 ppm) of **3**.

CHARACTERISTIC RESONANCES OF HASUBANAN ALKALOIDS.—From the foregoing evidence, a characteristic resonance of hasubanan alkaloids possessing the N-methyl group was summarized as follows: the C–9 exhibited about 20 ppm higher field shift in its resonance than those reported for morphinan alkaloids (4). The resonance of N-methyl carbon also revealed a −6 ppm shift. In particular, the N-methyl carbon of hasubanan derivatives having the carbonyl group at C–16 exhibited a −15 ppm shift in its absorption.

The above characteristic shifts may well be applied to further structure elucidation of the congeners, especially the distinction between hasubanan and morphinan alkaloids.

EXPERIMENTAL

MATERIAL.—The naturally occurring **1**, **2**, and **3** were isolated from *Stephania japonica* Miers as previously reported (2). The hydroxylated compounds **4** and **5** were derived from the corresponding natural products on reduction with $NaBH_4$ followed by SiO_2 chromatography

with $CHCl_3$ (2). The compounds were fully identical with an authentic sample in every respects.

CMR MEASUREMENT.—The spectra were obtained by a JEOL JNM-FX 100 spectrometer (25.05 MHz). Samples were measured for 2 W/V % solution in $CDCl_3$ with TMS as an internal standard in a 5 mm sample tube. The FT measurement conditions were as follows: spectral width, 5 KHz; data point, 32 K; repetition time, 1.5 sec; flip angle, 45°; number of pulses, 25000; pulse width, 5 μsec. In the measurement of low power ^1H irradiation, a JEOL low power irradiation unit was used, and the power level was about 0.01 w.

ACKNOWLEDGMENT

We are grateful to Mr. K. Matsushita, JEOL Co., Ltd., for FT-nmr measurement and helpful discussion.

Received 18 October 1979

LITERATURE CITED

1. T. A. Crabb, *Annu. Rep. NMR Spectrosc.*, **8**, 1 (1978); M. Shamma and D. M. Hindenlang, "Carbon-13 NMR Shift Assignments of Amines and Alkaloids", Plenum Press, New York and London, 1979.
2. M. Matsui, Y. Watanabe, T. Ibuka, and K. Tanaka, *Tetrahedron Lett.*, 4263 (1973); *Idem*, *Chem. Pharm. Bull.*, **23**, 1323 (1975).
3. K. G. B. Pachler, R. L. Wessels, *J. Mag., Res.*, **12**, 337 (1973); S. Sorensen, R. S. Hansen, and H. J. Jacobson, *ibid.*, **14**, 243 (1974).
4. F. I. Carroll, C. G. Moreland, G. A. Brine, and J. A. Kepler, *J. Org. Chem.*, **37**, 1881 (1972); F. W. Wehrli, *Chem. Commun.*, 379 (1973); Y. Terui, K. Torii, S. Maeda, and Y. S. Sawa, *Tetrahedron Lett.*, 2853 (1975).