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C-13 NMR SPECTRA OF MORPHINE ALKALOIDS, CODEINE, THEBAINE, AND SINOMENINE, AND RELATED COMPOUNDS

Yoshihiro Terui,* Kazuo Tori, Shin Maeda and Yoshiro K. Sawa

Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka, 553 Japan

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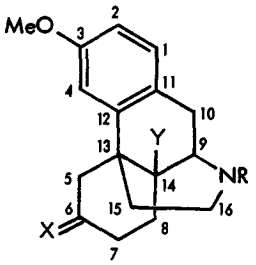
This paper reports full assignments of ^{13}C NMR signals of some morphine alkaloids,[1] codeine (3a), thebain (4a), and sinomenine (2), and their related molecules. The present results will be useful in view of the recent explosive development of ^{13}C NMR spectroscopy in organic chemistry[2] and biosynthetic studies[3] using the ^{13}C-labelling method which generally requires complete signal assignment of each carbon in molecules under study.

Prior to the ^{13}C signal assignments of natural products, 2, 3a, and 4a, we examined the natural-abundance ^{13}C FT NMR spectra of 3-methoxymorphinane (1a) and several derivatives[4] (1b-1h) to obtain reference data. Signal assignments for these molecules were made by ^{1}H noise-decoupling (PND) and single-frequency off-resonance decoupling (SFORD) techniques,[2] using known substituent effects on ^{13}C chemical shifts (δ_C)[2] and comparing δ_C values from compound to compound; the results are shown in the TABLE. It should be noted that considerable upfield chemical shifts of C-10 in all compounds, except NH derivatives 1a and 1e, were observed; this is due to a strong steric γ-effect of the NMe group.[2] As expected from an examination of molecular models, steric γ-effects[2] were observed for C-8, and for C-5, C-7, C-15 on introduction of an OH group into C-6α (from 1b to 1c) and C-14 (from 1f to 1g).

Using these reference δ_C data, we easily assigned ^{13}C signals of 2. The δ_C values for the carbons in aromatic ring A were obtained from the substituent additivity rule for a benzene ring;[2] the carbons in rings B and D were expected to have δ_C values similar to those of the corresponding carbons of 1h; the remaining carbon signals in ring C were readily distinguished. In a similar manner, we assigned ^{13}C signals of codeine (3a) and its derivatives[1] 3b-3f, though the influence of the ether-linkage between C-4 and C-5



(1a· X = H_2, Y = R = H)[4a]

(1b X = H_2, Y = H, R = Me)[4b]

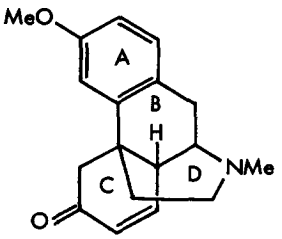
(1c· X =  , Y = H, R = Me)[4c]

(1d· X =  , Y = H, R = Me)[4c]

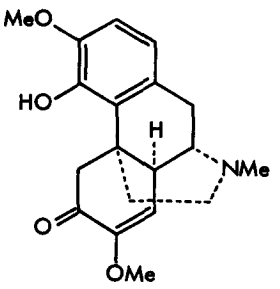
(1e X = O, Y = R = H)[4a]

(1f X = O, Y = H, R = Me)[4c]

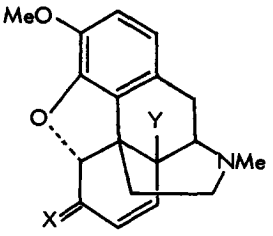
(1g X = O, Y = OH, R = Me)[4d]



(1h)[4c]



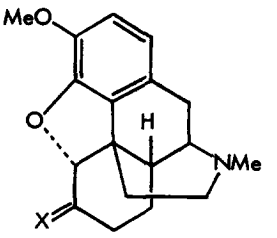
(2)



(3a X =  , Y = H)

(3b X = O, Y = H)

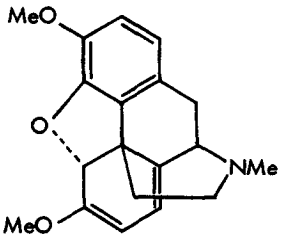
(3c X = O, Y = OH)



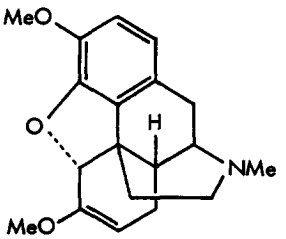
(3d X = H_2)

(3e X = )

(3f X = O)



(4a)



(4b)

TABLE. ^{13}C Chemical Shift Data on Morphine Alkaloids Examined, δ_C in $CDCl_3$[a]

Carbon No.	1a	1b	1c	1d	1e	1f	1g	1h	2	3a	3b	3c	3d	3e	3f	4a	4b
1	128.3	128.2	129.0	128.5	128.4	128.4	128.2	128.3	117.9	119.3	119.7	119.5	118.5	118.7	119.5	119.1	118.3
2	111.0[b]	110.9[b]	111.7	110.7[b]	111.4[b]	111.2[b]	110.0[b]	110.9[b]	109.1	112.8	114.7	115.1	113.2	113.4	115.3	112.9	113.6
3	158.0	158.0	157.7	158.2	158.1	158.0	158.2	158.0	145.2[b]	142.0	142.3	142.5	143.5	141.3	142.7	142.7	142.9
4	110.6[b]	110.6[b]	111.7	111.2[b]	112.2[b]	112.2[b]	112.5[b]	112.0[b]	144.8[b]	146.2	144.6	144.2	144.1	146.4	145.4	144.6	145.0
5	37.1	36.6	41.3	45.6	51.9	51.5	45.0	49.5	49.1	91.3	88.0	87.0	89.6	90.5	91.2	89.0	88.5
6	22.2	22.3	67.6	66.4	192.9	192.8	191.8	197.2	193.4	66.4	194.1	194.2	29.4	66.9	207.0	152.3	152.1
7	26.8[c]	26.8[c]	33.2	35.8	41.3	41.9[c]	37.4[c]	130.9	152.3	133.2	132.2	134.3	21.7	26.8	40.1	95.8	98.0
8	26.7[c]	26.6[c]	21.2	25.5	27.1	26.7	31.7	149.4	115.3	128.1	149.1	147.5	25.1	19.3	25.6	111.3	23.6
9	51.3	57.9	57.7	57.4	50.2	57.0	62.1	56.1	56.6	58.7	58.9	64.1	59.9	59.6	59.2	60.7	58.9
10	33.8	23.4	23.4	23.3	33.4	23.1	23.8	23.8	24.4	20.4	20.4	22.5	20.2	20.1	20.1	29.5	20.3
11	130.1	129.7	129.0	128.8	128.4	128.2	127.0	128.2	130.3	127.0	126.1	125.0	127.2	126.8	126.4	127.6	127.0
12	141.7	141.5	141.5	141.0	138.6	138.6	140.3	138.8	122.7	130.9	129.0	130.3	130.3	130.1	127.4	133.1	129.1
13	38.4	37.2	35.6	37.6	41.9	40.9	45.0	39.9	40.5	43.0	43.1	46.6	42.5	42.1	46.8	46.0	42.5
14	46.2	45.4	45.2	44.1	44.4	43.9	69.0	45.6	45.7	40.7	41.4	67.7	43.4	39.7	42.5	132.3	39.9
15	42.9	42.1	42.8	41.7	42.5	40.9[c]	36.8[c]	39.9	35.8	35.8	33.9	29.5	35.7	37.1	35.5	37.0	35.8
16	39.2	47.2	46.8	46.6	38.0	46.0	46.4	46.4	47.1	46.4	46.7	45.1	47.7	46.6	46.8	46.0	46.4
NMe	--	42.7	42.6	42.6	--	42.7	42.7	42.7	42.5	43.0	42.9	42.5	43.0	42.7	42.7	42.3	43.0
3-OMe	55.2	54.9	55.0	55.2	55.1	55.0	55.1	55.0	55.8	56.2	56.7	56.8	56.5	56.4	57.0	56.2	56.4
OMe	--	--	--	--	--	--	--	--	54.6	--	--	--	--	--	--	54.7	54.2

[a] ^{13}C FT NMR spectra were measured with a Varian NV-14 FT NMR spectrometer at 15.09 MHz in 8-mm tubes at ordinary probe temperature (30°). Samples were dissolved in $CDCl_3$ containing TMS as an internal reference (δ_C 0); concentrations were about 1 mmole/cm^3. PND FT NMR measurement conditions were almost the same for all compounds except for the number of transients for a few samples of small quantities; spectral width. 3319 Hz, pulse width 10 μsec (flipping angles of about 15°), aquisition time. 0.6 sec, number of data points 4077, and number of transients: 3000.

[b,c] These assignments may be interchanged in each column.

signal with a change from 1f to 3f as well as that from 1h to 2. Further, ^{13}C signals of thebaine (4a) followed by those of dihydrothebaine[1] (4b) were assigned on the bases of data on codeine derivatives, SFORD experiments, and/or non-decoupling spectral analyses.

Difficult problems in this assignment work were the differentiation between the C-2 and C-4 signals in morphinanes 1 and those between the C-3 and C-4 signals, and the C-11 and C-12 signals in morphine derivatives 2-4. In fact, the small chemical shifts between C-2 and C-4 in 1, particularly in 1a and 1b, made completely unambiguous assignments difficult. On some of morphine analogues, ^{1}H non-decoupling experiments enabled the carbon signals described above to be distinguished from indirect ^{13}C, ^{1}H spin-coupling features. However, non-decoupled spectra could not always be used effectively.

In this study, the relative signal intensities of the quaternary carbons were found to be useful for assigning the signals of 3 and 4 as a conventional method. The relative intensities were usually observed in the order of C-11 > C-12 $\simeq$ C-3 > C-4 in PND spectra measured under almost the same experimental conditions. The relative signal intensity ratios obtained for these respective carbons of the morphines examined were found to be about 3 2 2 1. Recently, Wehrli[5] assigned these carbon signals in 3a by means of spin-lattice relaxation time (T_1) measurement, taking into consideration the contribution of neighboring protons to a dipolar relaxation mechanism of these carbons. The relative ratios of $1/T_1$ reported for 3a was calculated to be about 5 2 2 1 for C-11 C-12 C-3 C-4, respectively, being in fairly good agreement with the above ratio.

Further studies of the ^{13}C NMR spectra of other morphine and morphinane derivatives are in progress.

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