Carbon-13 Magnetic Resonance Spectra of the Tropane Alkaloids: Cocaine and Atropine

Virgil I. Stenberg, N. K. Narain and S. P. Singh*

Department of Chemistry, The University of North Dakota, Grand Forks, North Dakota 58202

Received November 5, 1976

Complete Carbon-13 magnetic resonance spectral assignments of cocaine and atropine were made. ^{13}C Nmr spectra of atropine provides an interesting example of long range coupling on chemical shifts.

J. Heterocyclic Chem., 14, 225 (1977).

As part of our continuing interest in the tropane alkaloids (1), their photoproducts (2) and related compounds, we now wish to report the carbon-13 magnetic resonance (cmr) spectra and signal assignments of cocaine **1** and atropine **2.** Earlier the cmr spectra of various classes of alkaloids (3) have been reported including some results on the tropane alkaloids (4). Though the cmr of cocaine provides no surprises, atropine exhibits an unusual ring dissymmetry attributable to long range influence of the asymmetric carbon on the tropic acid portion of the molecule.

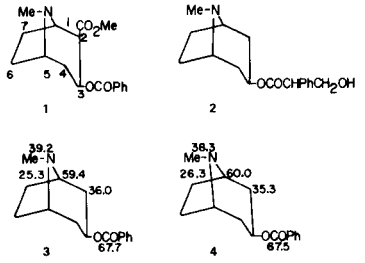


Table I lists the cmr chemical shifts of cocaine and atropine together with the signal assignments. Included in the Table are the atropine signal assignments of Wenkert, *et al* (4). A noise resonance decoupled spectrum of cocaine revealed signals for all the eleven nonaromatic and four signals for aromatic carbons. For cocaine many of the assignments could readily be made on the basis of the earlier assigned chemical shifts of benzoyl pseudotropine **3** (4) in conjunction with the multiplicity data of a gated decoupled spectrum. The signals for C_2 and the carbomethoxy methyl group are near one another but could readily be assigned by their multiplicity. The carbon at C_2 then appears as a doublet and the methyl group as a quartet. The two carbonyl signals can be assigned on the basis that carbonyl carbons of acetates are more deshielded and occur at lower field than that of benzoates, for example, the signals for carbonyl carbons of methyl acetate, acetone and acetic anhydride occur at 170.7, 204.1 and 167.3 ppm, respectively, whereas the corresponding carbons of methyl benzoate, phenyl methyl ketone and benzoic anhydride are at 167.0, 196.9 and 162.8 ppm, respectively (5).

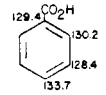
Table I

Comparative ^{13}C Nmr Chemical Shifts of Cocaine and Atropine (a)

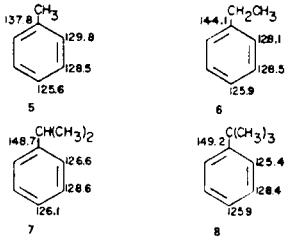
Carbon atom	Cocaine	Atropine
C_1	62.13	59.94 (59.3)(4)
C_2	50.78	36.50 (35.7)(4)
C_3	67.50	68.48 (67.6)(4)
C_4	35.94	36.31
C_5	65.37	59.86
C_6	25.80	25.21
C_7	25.81	25.63 (24.8)(4)
CO_2CH_3	51.51	
NCH_3	41.38	40.41 (39.7)(4)
Aromatic	133.60 (*p*)	128.36 (*p*)
	131.00 (*o*)	129.58 (*m*)
	129.10 (*m*)	128.97 (*o*)
	130.50 (C_2')	136.90 (C_1')
CO_2CH_3	171.63	
COPh	167.11	
$COCHPhCH_2OH$		173.16
$COCHPhCH_2OH$		55.11
$COCHPhCH_2OH$		64.45

(a) The shifts are reported in parts per million with respect to tetramethylsilane.

The four signals between 129.1 and 133.6 ppm are in the range for aromatic carbons linked to an acid or ester group (5). The values for cocaine compare favorably to those of benzoic acid.



For the preliminary carbon-to-signal assignment of atropine, the cocaine, atropine (C_1, C_2, C_3, C_7 and NCH_3) (4) and benzoyl tropine **4** (4) assignments were helpful. For the tropic acid portion, the signal centered at 64.45 ppm is best assigned to the carbon bearing the hydroxyl group because of comparable values of similar carbons in *n*-propanol (64.00), 1,3-dihydroxybutane (66.00) and 3-chloro-1,2-dihydroxypropanediol (63.50) (7). Thus, the methine carbon of tropic acid causes the signal at 55.11 ppm. These assignments agree with those given for the tropic ester of scopolamine (4). The chemical shifts of the aromatic carbon were assigned by analogy with those of toluene and its derivatives, **5-8** (5,6). For this series, increasing substitution at the methyl carbon of toluene



changes the chemical shift of the *ortho* carbon to progressively higher fields (5). Furthermore the *meta* carbon shielding in the substituted benzenes are relatively insensitive to substitution effects. On this basis the assignment is made assuming the order of chemical shifts is $m > o > p$. This is further confirmed by comparative spin-lattice relaxation times, T_1, for *ortho* (1.77 seconds), *meta* (1.52 seconds) and *para* (1.23 seconds) which agrees with the general trend of $o > m > p$ (5,8).

The unique feature of the atropine cmr is that the chemical shifts of C_1, C_2 and C_7 differ from those of C_5, C_4 and C_6, respectively. The differences are 0.07 ppm for the C_1-C_5 pair, 0.19 for C_2-C_4 and 0.42 for C_6 and C_7. Though these differences are not large compared to close range steric interactions which are ordinarily in the range of 2-4 ppm, they are significant compared to the resolving power of the spectrometer and give evidence of the long range influence of the tropic acid asymmetry upon the bicyclic portion of the molecule. Interestingly the asymmetry influence is greatest on the C_6-C_7 pair of carbons. Studies based on atropine models using Dreiding stereomodels indicate that the observed long range effect in cmr can be explained if the hydroxyl function is hydrogen bonded to the ester carbonyl group. Indeed, only the hydrogen bonded hydroxyl stretching frequency at 3587 cm^{-1} could be observed in the chloroform infrared spectrum of atropine regardless of dilution.

EXPERIMENTAL

The ^{13}C nmr (cmr) spectra were recorded on a Bruker HFX-90 spectrometer equipped with a Fourier transform system. The samples were spun in a 10 mm tube using deuteriochloroform as internal lock and tetramethylsilane as a reference at ambient temperature. The spectra were obtained at 5000 MHz sweep width. The cmr solution contained the 100 mg. sample in 1 ml. of deuteriochloroform. Cocaine hydrochloride was supplied by Merck and Co., Inc., St. Louis, Missouri. Free cocaine was obtained by neutralizing the hydrochloride solution with 10% ammonium hydroxide followed by extraction with ether and recrystallization with ethanol to yield white crystals, m.p. 96-98°; ^1H nmr (deuteriochloroform): δ 8.2 (m, 2H of C_6H_5), 7.6 (m, 3H of C_6H_5), 5.5 (m, 1H, C*H*OCOPh), 3.71 (OCH_3), 3.55 (1H, C_1H), 3.25 (1H, C_5H), 3.03 (1H, C_2H), 2.21 (NCH_3) and 1.75-2.00 (m, ring CH_2 protons). Atropine, m.p. 116-118°, was obtained from Aldrich Chemical Company, Milwaukee, Wisconsin; ^1H nmr (deuteriochloroform): δ 7.35 (s, 5H, aromatic), 5.05 (t, J = 5 Hz, 1H, C_3H), 4.08 (m, 1H, COC*H*PhCH_2OH), 3.77 (m, 2H, CH_2OH), 3.01 (br s, 1H, C_5H), 3.00 (br s, 1H, C_1H), 2.2 (s, 3H, NCH_3), 1.3-2.15 (br s, 9H, C_4-, C_6-, C_7-CH_2, OH). The spin lattice relaxation times (T_1) were measured at 180°-90° pulse sequence on a JEOL FX-60.

Acknowledgment.

This investigation was supported by a research grant 1 RO1 GM21590-01 from the National Institutes of Health, United States Public Health Service and in part by a Public Health Service Research Career Development Award (No. K4-GM-9888) from the National Institute of General Medical Sciences. We are also grateful to Drs. Neil Woolsey and Thomas Ballintine for their assistance in obtaining the C-13 proton magnetic resonance spectra.

REFERENCES AND NOTES

(1) V. I. Stenberg, S. P. Singh, N. K. Narain and S. S. Parmar, *J. Chem. Soc., Chem. Commun.*, 262 (1976).

(2) V. I. Stenberg, N. K. Narain, S. P. Singh and S. S. Parmar, *J. Heterocyclic Chem.*, **13**, 363 (1976).

(3) F. L. Carroll, C. G. Moreland, G. A. Brine and J. A. Kepler, *J. Org. Chem.*, **41**, 996 (1976); C. G. Moreland, A. Philip and F. I. Carroll, *ibid.*, **39**, 2413 (1974); E. Wenkert, C. J. Chang, A. O. Clouse and D. W. Cochran, *J. Chem. Soc., Chem. Commun.*, 961 (1970).

(4) E. Wenkert, J. S. Bindra, C. J. Chang, D. W. Cochran and F. M. Schell, *Accounts Chem. Res.*, 7, 46 (1974), and references cited therein.

(5) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York, N.Y., 1972, pp. 110-121, 81, 31, 83, 187.

(6) J. B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York, N.Y., 1972, p. 97.

(7) L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra," John Wiley and Sons, New York, N.Y., 1972, p. 39, 91, 32.

(8) G. C. Levy, "Topics in Carbon-13 NMR Spectroscopy," John Wiley and Sons, New York, N.Y., 1974, p. 55, 116.