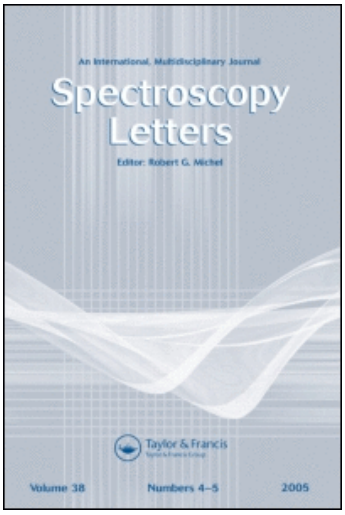

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Carbon-13 Nuclear Magnetic Resonance of the Isoquino-Llne Alkaloid, Noscapine and other Related Compounds

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CARBON-13 NUCLEAR MAGNETIC RESONANCE OF THE ISOQUINOLINE ALKALOID, NOSCAPINE AND OTHER RELATED COMPOUNDS

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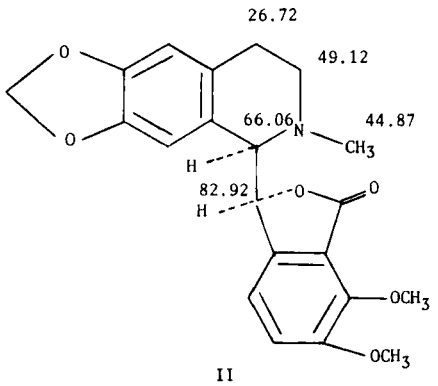
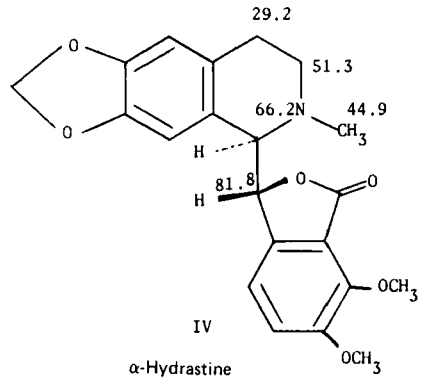
ABSTRACT - The natural abundance, noise decoupled and off-resonance C-13 magnetic resonance spectra of noscapine [(-)-α-narcotine], (-)-β-hydrastine, their protonated and quaternized forms were recorded. Their carbon chemical shifts were compared to other related compounds and model compounds. The relative stereochemistry at C-1 and C-1' of noscapine was established to be the same as that of (-)-β-hydrastine. $\Delta\delta^{13}C$ for their protonated and quaternized forms was determined. The highfield and lowfield shifts for C-3 and C-4 were similar and comparable to other related compounds. The results have confirmed the similar relative stereochemistry of both compounds at C-1 and C-1'. Therefore, the data are diagnostic of the relative stereochemistry of these systems and C-13 magnetic resonance protonation and quaternization chemical shifts may thus be used to confirm the relative configuration of phthalideisoquinolines as well as other related compounds.

INTRODUCTION - Natural abundance carbon-13 nuclear magnetic resonance spectroscopy has proved to be a successful technique in the study of natural products, e.g., alkaloids (Crain et al, 1970; Moreland et al, 1974). Also carbon chemical shifts were used for the study of stereochemical and conformational problems, particularly the use of substituent-induced chemical shift additivity relationships (Jones and Hassan, 1972; Jones et al, 1976). Hughes et al, 1975 have reported the carbon chemical shifts of some phthalideisoquinolines as well as the use of chemical shifts of C-3 and C-4 as diagnostic of the relative stereochemistry of these compounds at C-1 and C-1′. But despite the medicinal importance of noscapine [(-)-α-narcotine] (I) as antitussive agent, there was no mention of any carbon chemical shift assignments (Shamma and Hindenlang, 1979). Also it should be pointed out that it has been proved chemically that (-)-α-narcotine (I) has the same substitution (except for the C-8 methoxyl substituent) and stereochemistry at C-1 and C -1′ as the naturally occuring (-)-β-hydrastine (II)(Battersby and Spencer 1965). This finding has been substantiated by PMR studies (Shamma and Georgiev, 1974; 1976). The purpose of the present paper is to assign the carbon chemical shifts of noscapine and to establish its relative stereochemistry at C-1 and C-1′ as compared to that of (-)-β-hydrastine(II). Also to assign the carbon chemical shifts for their hydrochlorides and methiodides and to determine the protonation and quaternization-induced chemical shifts at C-3, C-4, C-10 and C-1′ and using these data to confirm the relative stereochemistry at C-1 and C-1′ for noscapine and (-)-β-hydrastine (II). The additivity parameters so obtained could be applied to other related structures.



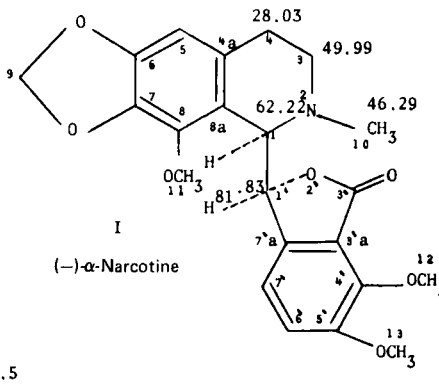
II

(−)-β-Hydrastine



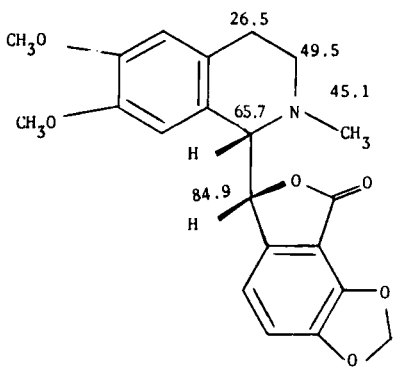
IV

α-Hydrastine



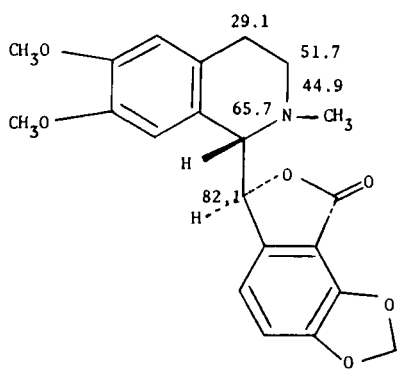
I

(−)-α-Narcotine



III

Corlumine



V

Adlumine

RESULTS AND DISCUSSIONS

The observed carbon-13 chemical shifts of the free bases, their hydrochlorides, trifluoroacetate and their methiodides are presented in Table 1. The choice of solvents shown in Table 1 was dictated by the solubility of the various species. In general solvent effects on carbon chemical shifts are considered sufficiently small (~ 0.5 ppm) to be insignificant unless conformational changes occur in different solvents (Jones and Hassan, 1972). The earlier PMR studies indicate that no conformational changes occur in the systems presently being described (Shamma and Georgiev, 1974 and 1976). The observed carbon-13 chemical shifts for (-)-β-hydrastine (II)(Table 1) are in good agreement with that reported earlier (Hughes et al, 1976). Assignment of the carbon-13 resonances to the appropriate carbon position in the compounds studied was based on the additivity rules, the off-resonance spectra and comparison with the previously reported phthalideisoquinolines whenever possible.

It is evident from Table 1 that the carbon-13 chemical shifts for noscapine (I), (-)-β-hydrastine (II) and Corlumine (III) are very similar, particularly for C-3, C-4 and C-1′. C-3 and C-4 are shielded compared to that of α-hydrastine (IV) and adlumine (V). However, the opposite is true for C-1′ as it is deshielded in II and III than in IV and V. But this is not the case in I as its C-1′ carbon-13 chemical shift is equal to that of IV, 81.83 and 81.80 ppm respectively. So C-1′ can not be of value in determining the relative stereochemistry of these systems. It should also be noted that the carbon-13 chemical shift of C-4 in I is slightly higher, occurring at 28.03 ppm compared to that of II occuring at 26.70 ppm. Also the magnitude of the highfield shift at C-4 going from α-hydrastine (IV) to (-)-β-hydrastine (II) $\Delta\delta^{13}C$ =+2.48 is

Carbon No. / Compound No.	Chemical Shift δ (ppm) From TMS																						
	1	3	4	4a	5	6	7	8	8a	9	10	11	12	13	14	1'	3'	3'a	4'	5'	6'	7'	7'a
I Base[a]	62.22	49.99	28.03	132.09	117.65	140.45	141.14	152.18	121.18	100.73	46.29	59.36	60.84	56.78	-	81.83	168.06	117.11	148.37	147.67	102.29	118.19	134.03
HCl[a]	58.33	45.37	21.54	126.45	118.94	139.07	139.95	152.57	106.81	101.11	39.91	58.04	62.13	56.92	-	78.74	166.50	117.00	150.29	147.14	102.47	119.43	133.66
TFA[b]	58.42	45.09	21.43	126.52	119.00	138.73	140.02	152.88	106.67	101.22	39.98	61.70	62.17	56.89	-	78.91	166.50	117.30	150.42	147.65	102.65	119.59	133.68
MeI[a]	68.81	52 13	24.19	126.4	120.17	137.44	139.90	152.82	107.73	101.27	54.08	59.00	62.17	57.01	54.08	75.33	166.32	117.13	150.50	147.20	102 33	119.24	133.51
II Base[a]	66.06	49 12	26.72	124.81	108.40	146.70	145.80	107.70	130.30	100.80	44.87	-	62.15	56.78	-	82.92	167.60	119.60	147.90	152.50	118.70	117.70	140.70
HCl[c]	65.04	46.65	21.39	125.88	106.26	146.29	144.34	107.60	116.53	100.05	40.10	-	61.33	55.87	-	78.12	167.86	113.97	146.17	152.18	120.41	118.12	136.84
TFA[b]	66.93	46.06	21.31	124.88	107.14	149.04	146.45	108.85	117.71	101.60	40.16	-	62.27	56.74	-	79.28	166.53	113.94	148.45	153.59	121.35	119.94	137.58
MeI[a]	72 51	53.25	24.01	124.04	108.08	148.77	145.80	108.38	115.43	105.51	51.50	-	62.17	56.70	51.50	75.33	166.09	117.65	148.18	153.29	119.77	117.56	137.44
III[a]	65.70	49.50	26.50	123.40	111.30	148.20	147.20	110.70	129.50	103.30	45.10	-	55.90	55.90	-	84.90	167.20	110.30	144.50	149.10	113.10	115.50	140.80
IV[a]	66.20	51.30	29.20	125.30	108.20	146.30	145.80	107.40	130.00	100.70	44.90	-	62.20	56.70	-	81.80	168.00	119.30	147.60	152.30	118.40	118.10	141.10
V[a]	65.70	51.70	29.10	123.90	111.00	147.40	146.90	110.00	128.40	103.10	44.90	-	55.60	55.90	-	82.10	167.70	109.70	144.10	148.80	112.80	116.10	140.90

a, $CDCl_3$; b, TFA + $CDCl_3$; c, D_2O.

Table 2 : Stereochemical, N-Protonation and N-Quaternization Additivity Shifts.

Carbon No. / Compound No.	$\Delta\delta C^{13}$					
	C-2	C-3	C-4	C-7 N-Me	C-10 N-Me	C-1'
IV - II	-	+ 2.18	+ 2.48	-	-	- 1.12
V - III	-	+ 2.20	+ 2.60	-	-	- 2.80
IV - I	-	+ 1.31	+ 1.17	-	-	- 0.03
I - I HCl or TFA	-	+ 4.62	+ 6.49	-	+ 6.38	+ 3.09
I - I MeI	-	- 2.14	+ 3.84	-	- 7.79	+ 6.50
II - II HCl or TFA	-	+ 2.47	+ 5.33	-	+ 4.77	+ 3.64
II - II MeI	-	- 4.13	+ 2.71	-	- 6.63	+ 7.59
N-Methylpipe- HCl	+ 1.00	+ 2.10	+ 2.40	+ 2.30	-	-
ridine. MeI	- 7.10	+ 5.20	+ 2.80	- 6.20	-	-
N-Methyl-4- HCl	+ 3.37	+ 2.50	+ 3.14	+ 2.94	-	-
piperidone MeI	- 5.18	+ 4.97	+ 4.57	- 6.69	-	-

The plus and minus signs mean the upfield and downfield shifts.

larger than that of (-)-α-narcotine (I) $\Delta\delta^{13}C$ = +1.17 (Table 2). This is also true for C-3 which is + 2.18 and + 1.31 respectively (Table 2). These shift differences in the carbon-13 chemical shifts of (-)-α-narcotine (I) and (-)-β-hydrastine (II) might be anticipated from the additional C-8 methoxyl substituent in the former.

The effects of protonation (hydrochlorides and trifluoroacetates) and methiodation in (-)-α-narcotine (I) and (-)-β-hydrastine (II) calculated as $\Delta\delta^{13}C$ by difference from the corresponding free bases are presented in Table 2. Also protonation and methiodation additivity shifts for N-methylpiperidine (Crain et al, 1971) and N-methyl-4-piperidone (Jones and Hassan, 1972) are included for comparison. From Table 2 it is clear that protonation causes highfield shifts for C-3, C-4, C-10 and C-1' of (-)-α-narcotine (I) and (-)-β-hydrastine (II). The magnitudes of the high field shifts are generally greater in case of (-)-α-narcotine (I) as it reaches +6.49 ppm for C-4 and +6.38 ppm for C-10. Although the high field shift parameters for C-3, C-4 and C-10 follow the same pattern reported for N-methylpipridine and N-methyl-4-piperidone at C-2, C-3, C-4 and C-7, their magnitudes are larger. Also the N-methyl substituent in (-)-α-narcotine (I) and (-)-β-hydrastine (II) suffered a high field shift of +6.38 ppm and +4.77 ppm respectively. It should be noted that C-1' of both compounds has suffered a high shift of +3.09 and +3.64 for 1 and II respectively. This finding renders C-1', $\Delta\delta^{13}C$ value diagnostic of the relative stereochemistry in these systems (Cf-free bases).

Quanternization of I and II has caused a downfield shift of $\Delta\delta^{13}C$ -2.14 ppm and -4.13 ppm for C-3; -7.79 ppm and -6.63 ppm for C-10 respectively. These data are comparable to C-2 and C-7 of N-methylpiperidine and N-methyl-4-piperidone. On the other hand C-4 and C-1' of I and I have suffered high field shifts of $\Delta\delta^{13}C$ + 3.84 ppm, + 2.71

ppm and + 6.50 ppm, + 7.59 ppm respectively. This finding renders C-1', $\Delta\delta^{13}C$ diagnostic for the relative stereochemistry at C-1 and C-1' in these compounds.

The highfield shifts in case of protonation and quaternization may be due to polarizations of carbon-hydrogen bond of the isoquinoline skeleton to produce C^{-}-H^{+} structure and that the electron on the hydrogen atom could be transmitted through the carbon skeleton onto the positively charged nitrogen atom. Therefore the highfield C-13 chemical shift is attributable to the increase in the total charge densities on the carbons (Morishima et al, 1972).

In conclusion the similarity of the pattern of carbon-13 chemical shifts of (-)-α-narcotic (I) and (-)- -hydrastine (II) is indicative of similar relative stereochemistry at C-1 and C-1'. Also the additivity parameters $\Delta\delta^{13}C$ of protonation and quaternization summarized in Table 2, in addition to the considerations outlined in the discussion section, should provide a useful basis for the analysis of structure and relative stereochemistry of phthalideisoquinolines and other related compounds.

EXPERIMENTAL

Materials:

Noscapine was obtained from E. Merk AG, Damstadt, West Germany. (-)-β-Hydrastine (II) was obtained from Fluka AG, CH-9470 Buchs, Switzerland.

Noscapine hydrochloride: 1 g. of noscapine was dissolved in the least amount of ethanol and treated with ethanolic hydrochloric acid. Then evaporated to dryness using a mixture of benzene , ethanol 1:1 and left in a drying desiccator overnight. Attempts to crystallise the product were unsuccessful, so it was used as such.

(-)-β-hydrastine (II): 1g. of hydrastine was treated as above to give crystalline powder and used as such.

Noscapine methiodide: 1 g. of noscapine was dissolved in the least amount of chloroform and treated with methyliodide 5 ml. The reaction mixture was refluxed for 6 hours. Then it was cooled and treated with dry ether. The separated solid was recrystallised from ethanol-ether to give yellowish-white crystalline solid, m.p. 156°C with decomposition.

(-)-β-hydrastine methiodide: 1 g. of (-)-β-hydrastine (II) was treated as above to give a white crystalline solid, m.p. 200-201°C with decomposition.

Methods

Proton noise decoupled and off-resonance natural abundance carbon -13 nuclear magnetic resonance spectra were measured on a Jeol FX 100 Varian FT-80 and Varian XL-200 fourier transform NMR spectrometers operating at 23.5 MHz. Samples were prepared in 10 mm o.d. tubes as approximately 10% solutions in deuterochloroform, trifluoroacetic acid and deuterium oxide with 2% TMS or DSS as reference. The deuterium of the solvent provided the lock signal. Spectra were recorded with 8 K data points; the probe temperature was 23°C. For an average spectral width of 5000 Hz; a 4 μs pulse corresponding to a tilt angle of 30° was employed with a 2s interval (acquisition time plus 1s pulse delay) between pulses.

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REFERENCES

Battersby, A.R., and Spencer, H. 1965. The Absolute Stereochemistry of Narcotine and Narcotoline, J. Chem. Soc., : 1087.

Crain, W.O., Wildman, W.C. and Roberts, J.D., 1971. Nuclear Magnetic Resonance Spectroscopy. Carbon-13 Spectra of Nicotine, Quinine and Some Amaryllidaceae Alkaloids, J. Am. Chem. Soc. Vol. 93, : 990-994.

Hughes, D.W., Holland, H.L., and MacLean, D.B., 1976. ^{13}C magnetic resonance spectra of some isoquinoline alkaloids and related model compounds, Can. J. Chem. Vol. 54, : 2252-2260.

Jones, A.J., Beeman, C.P., Hasan, M.U., Casy, A.F., and Hassan, M.M.A., 1976. Morpholines: Stereochemistry and Preferred Steric Course of Quaternization, Can. J. Chem., Vol. 54, : 126-135.

Jones, A.J., Hassan, M.M.A., 1972. Carbon-13 Magnetic Resonance - Chemical Shift Additivity Relationships in N-Methyl-4-piperidone, J. Org. Chem., Vol. 37, : 2332-2338.

Moreland, C.G., Philip, A., and Carroll, F.F., 1974. Carbon-13 Nuclear Magnetic Resonance Spectra of Cinchona Alkaloids, J. Org. Chem., Vol. 39, : 2413-2416.

Morishima, I., Koshikawa, K., Okada, K., Yonezawa, T., and Goto, K., 1972. The Conformational Dependence of the Inductive Effect in the σ-electron System as Studied by Carbon-13 Nuclear Magnetic Resonance. J. Am. Chem. Soc. Vol. 95, : 166-171.

Shamma, M., and St. Georgiev, V., 1974. A Short Route to the Phthalideisoquinolines. Conformational Analysis., Tetrahedron Lett., : 2339.

Shamma, M., and St. Georgiev, V., 1976. A Short Route to the Phthalideisoquinolines and the 13-Hydroxylated Protoberberines. Tetrahedron, Vol. 32, : 211-215.

Shamma, M., and Hindenlang, D.M., 1979. Carbon-13 NMR Shift Assignments of Amines and Alkaloids. New York, Plenum Press, p.p. 160-163.

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