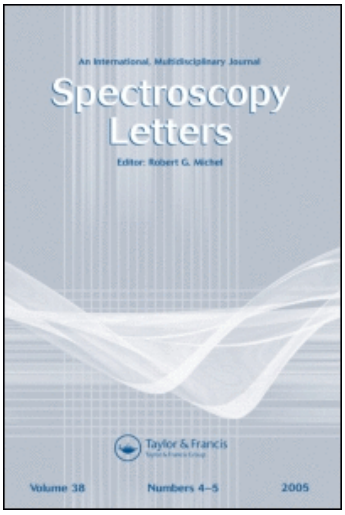

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^{13}C NMR of 4-Substituted *N*-[(Dimethylamino)Methyl]Benzamides

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^{13}C NMR OF 4-SUBSTITUTED N-[(DIMETHYLAMINO)METHYL]BENZAMIDES

KEY WORDS: Carbon-13 NMR spectroscopy; substituent effect correlations; 4-substituted N-[(dimethylamino) methyl]benzamides; local anaesthetics.

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ABSTRACT

^{13}C NMR proton noise and single frequency off-resonance decoupled spectra were obtained for a series of 4-substituted N-[(dimethylamino)methyl]-benzamides. The various carbon resonances have been assigned on the basis of the chemical shift theory, multiplicities observed in partially coupled spectra, signal intensities, additivity rules, and by comparison with structurally related compounds. When the substituent parameters $\mathcal{F}$ of Swain and Lupton were plotted against the $\delta_{C=O}$, a reasonable correlation (r = 0.94) was found.

The $\delta_{C=O}$ of the 4-substituted N-[(dimethylamino)methyl]-benzamides is about 3.0 - 3.8 ppm upfield from the correspondent N,N-dimethylbenzamides and this effect is probably due to a steric

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compression shift between the N,N-dimethylamino group and the carbonyl oxygen.

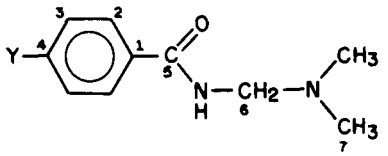
INTRODUCTION

In a recent paper the synthesis of a series of 4-substituted N-[(dimethylamino)methyl]benzamides[1] was reported. These compounds are structurally related to the procainamides, which are widely used as local anaesthetics[2].

This study reports the ^{13}C NMR assignments and conformations of eight 4-substituted N-[(dimethylamino)methyl]benzamides. To investigate the possible relationship between electronic structure and local anaesthetic properties, the ^{13}C chemical shifts of the carbonyl carbon were plotted against the substituent parameter of Swain and Lupton[3]. A table of the anaesthetic effects was not included because the information is not available.

RESULTS AND DISCUSSION

The Carbon-13 NMR chemical shifts of the eight 4-substituted N-[(dimethylamino)methyl]benzamides 1 are presented in Table 1.



1

Structure 1

TABLE 1

Carbon-13 Chemical Shifts of 4-Substituted N-[(dimethylamino)methyl]benzamides.[a]

Y	C-1[b]	C-2	C-3	C-4	C-5	C-6	C-7	Others
H	134.76	127.12	128.52	131.46	168.27	62.73	42.28	
	134.76	127.12	128.52	131.46				
F	130.48	129.56	115.52	164.80	167.24	62.86	42.41	
	130.35	128.70	115.55	167.21				
Cl	132.73	128.46	128.46	137.54	167.09	62.62	42.35	
	132.86	128.52	128.52	137.76				
Br	133.48	128.73	131.77	126.16	167.25	62.87	42.43	
	133.16	128.72	131.72	125.66				
I	134.00	128.71	137.75	98.44	167.41	62.85	42.41	
	133.36	128.72	137.42	97.36				
OMe	126.58	128.85	113.57	162.58	167.58	62.49	42.34	55.27
	127.50	128.16	114.10	162.86				
Me	131.81	127.01	128.97	141.66	167.97	62.46	42.31	21.34
	131.72	127.01	129.18	140.68				
NMe_2	120.99	128.50	110.89	152.31	167.72	62.27	42.28	39.94
	123.16	128.02	113.12	153,96				
NO_2	140.37	128.20	123.53	149.47	166.14	62.94	42.38	
	140.86	128.02	123.62	151.36				

[a] In ppm relative to TMS. The second entries are those calculated using substituent chemical shifts.

[b] The key to the numbering of the carbon atoms is in structure 1.

The range of chemical shift of the carbonyl carbon for the compounds studied is only 2.13 ppm, which indicated that this carbon was rather insensitive to the substitutions. The carbonyl carbon chemical shifts showed a reasonable correlation ($r = 0.94$) with the substituent parameter $\mathcal{F}$ of Swain and Lupton but were not correlated with the substituent parameter σ or σ^+ of Hammett[4-7].

The carbonyl carbon chemical shift of compounds 1 are ca. 3.4 ppm upfield relative to the correspondent 4-substituted N,N-dimethylbenzamides. This shielding effect may be attributed to a steric compression shift between the carbonyl oxygen atom and the N-methyl group[8,9].

The chemical shifts of the aromatic carbons were assigned based on additivity rules, multiplicities observed in SFORD spectra, signal intensities, and by comparison with related compounds[10,11]. In order to confirm the assignments, the chemical shifts of the aromatic carbons were calculated using the substituent increment shifts reported by Ewing[12] and are included in Table 1. The increment of the $-C(O)NHCH_2N(CH_3)_2$ group, which was not found in the literature, was obtained from the non-substituted 1.

The methylene and N-methyl groups of the side chain were easily identified by their intensities and multiplicities in the SFORD spectrum. Since the rotation about the C(O)-NH- bond is known to be restricted at the temperature of the experiment, the single signal observed for the methylene carbon indicated that compounds 1 exist in only one conformation. The conformation of

the amide was found to be anti (amidic proton on the opposite side of the carbonyl) by ^{1}H NMR[13]. This result also agrees with the conformational study of a wide range of monosubstituted amides by LaPlanche and Rogers[14].

Carbon-13 resonances of the $-OCH_3$, CH_3, and $-N(CH_3)_2$, substituents were assigned by comparison with ^{13}C NMR data of anisaldehyde, toluene, and N,N-dimethylaniline[15].

EXPERIMENTAL

The preparations of 4-substituted N-[(dimethylamino)methyl] benzamides 1 are reported elsewhere[1]. The proton noise and single frequency off-resonance decoupled spectra of compound 1 were recorded on a Varian XL-100 operating at 25.2 MHz or on a Varian FT-80A operating at 20 MHz. The compounds were dissolved in deuterated chloroform (concentration 20 % w/v) and tetramethylsilane was used as an internal reference.

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