Substituent Effects in Heterocyclic Systems by Carbon-13 Nuclear Magnetic Resonance. Isoxazoles

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The carbon-13 nmr spectra of a series of 3-aryl-5-phenylisoxazoles (I) and 3-phenyl-5-arylisoxazoles (II) have been recorded and the signals assigned. Carbon-13 data for series I show little effect of substituent on the chemical shift of the isoxazole ring carbons. However, a plot of the carbon-13 chemical shift of carbon-5 in the isoxazole system I *versus* the chemical shift of carbon-3 in the 3-(4'-aryl)-1-phenylpropenones gives a straight line (r = .989) with a slope of 0.35. In series II, the chemical shifts of both carbon-4 and -5 are relatively sensitive to substituent effects. Fair correlations between Hammett sigma values and the chemical shifts of these two carbons are found; dual substituent parameter treatment improves the correlations. The results obtained from correlations with carbon-4 in series II are similar to those obtained from β-carbons of a number of styrene systems. The data show that carbon-4 in series II is approximately 20% less sensitive to substituent effects than the previously reported data for carbon-3 of 2-arylfurans. Transmission of substituent effects in the isoxazole system compare well with those of the benzothiazole system.

Carbon-13 nmr has been successfully used to examine the transmission of substituent effects in a variety of aromatic (1) and heteroaromatic (2) carbon frameworks including heterocyclic systems (3) in which transmission to distal carbons could occur by different pathways. Our interest in substituent effects in heterocyclic (2b,3) and cross-conjugated systems (4) led us to examine the carbon-13 nmr spectra of series of 3-aryl-5-phenylisoxazoles (I) and 3-phenyl-5-arylisoxazoles (II). The isoxazole systems were chosen for study to evaluate the transmission of substituent effects from a substituted phenyl group to various carbons in the heterocyclic ring system. We have previously shown (3) in other heterocyclic systems that the transmission of electronic effects by the same network of σ and π bonds is significantly altered by reversing the location of the substituent relative to the carbon atom examined by carbon-13 nmr. Specifically, we were interested in comparing electronic effects caused at carbon-5 by a substituted phenyl group at carbon-3 and the reverse arrangement in the two isoxazole series I and II.
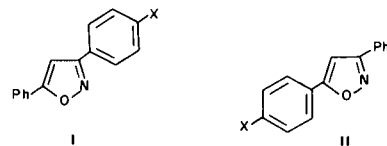
Results and Discussion.

The carbon-13 nmr chemical shifts for the carbons of

Table I

Carbon-13 NMR Chemical Shifts Assignments for Series I

Compound Number	X	3	4	5	6	7	8	9	10	11	12	13	X-Shift
1	CH₃O	161.8	98.0	168.9	126.6	125.2	128.8	129.9	120.6	127.7	114.2	163.3	55.1
2	EtO	161.8	98.0	168.9	126.7	125.2	128.8	129.9	120.5	127.7	114.6	159.6	14.4, 63.1
3	AcNH	161.8	98.1	169.1	126.7	125.2	128.9	130.0	122.7	126.8	118.9	140.8	24.0, 168.1
4	CH₃	162.1	98.2	169.2	126.7	125.5	128.9	130.0	125.5	126.2	129.3	139.6	20.9
5	H	162.2	98.3	169.3	126.5	125.2	128.9	130.0	128.2	126.2	128.7	129.8	
6	F	161.3	98.3	169.4	126.5	125.5	128.9	130.2	124.6	128.6	115.9	157.8	
7	Cl	161.2	98.3	169.5	127.1	125.2	128.9	130.2	126.4	128.0	128.9	134.6	
8	Br	161.3	98.3	169.5	127.4	125.2	128.9	130.2	126.4	128.2	131.8	123.3	
9	CF₃	161.2	98.6	169.9	126.3	125.3	129.0	130.3	132.5	127.1	125.7	(a)	(a)
10	CN	161.0	98.6	169.9	126.3	125.3	128.9	130.3	132.5	127.0	132.7	112.5	118.0
11	NO₂	160.8	98.8	170.1	126.2	125.3	129.0	130.4	134.4	127.6	124.0	148.1	

(a) Not determined.

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the two series of isoxazoles examined were determined in DMSO-d_6 solution and the results are listed in Table I and II. The chemical shift assignments were made according to techniques we have previously employed (5). The synthetic approach is a standard one which we have used previously (5). Physical data on the isoxazoles studied are recorded in Table 5.

Examination of the data arising from the 3-aryl-5-phenylisoxazoles (I) reveals that substituents in this case have little effect on the carbons of the isoxazole ring. The chemical shift data show that carbon-3 is shielded by electron withdrawers, whereas carbons-4 and -5 are deshielded. The range in chemical shift from strong electron donor to strong electron withdrawer is small, about 1 ppm for all the isoxazole ring carbons. This result is not unanticipated since the point of attachment of the substituted phenyl is similar to that of the 3-(4'-aryl)-1-phenyl-propenones which showed, by carbon-13 nmr, limited substituent effects (6). A plot of the carbon-13 chemical shift of carbon-5 in the isoxazole system I versus the chemical shift of carbon-3 in

the 3-(4'-phenyl)-1-phenylpropenones (6) gave a straight line (r = .989) with a slope of 0.35 indicating that the substituent effect is greater in the chalcone system.

The effect of substituents in the 5-aryl series (II) was more pronounced. In this series, chemical shifts for carbons-3 and -4 are deshielded by electron withdrawers whereas, the chemical shift of carbon-5 is shielded. In comparison to series I, the point of attachment to the heterocyclic ring, carbon-5, in series II is approximately twice as sensitive to substituent effects. A reasonable correlation is obtained between the chemical shift of C-5 and Hammett sigma values (See Table 3). The quality of the correlation and the magnitude of the rho value are comparable to those obtained for carbon-3 in the 3-(4-aryl-1-phenylpropenones (6) and with those obtained for carbon-2 in 2-arylfurans and pyrroles (2a). Chemical shift data from carbon-4 in II give a reasonable correlation with Hammett sigma values. The magnitude of the rho value is about 20% smaller than for the similar 3-carbons in the analogous furan and pyrrole systems (2a). The data show

Table II

Carbon-13 NMR Chemical Shifts Assignments for Series II
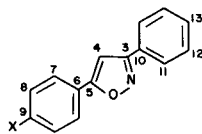
Compound Number	X	3	4	5	6	7	8	9	10	11	12	13	X-Shift
12	(CH₃)₂N	161.9	94.9	170.3	114.0	126.4	111.6	151.1	128.6	126.2	128.6	129.6	39.6
13	CH₃O	162.0	96.8	169.3	119.3	126.9	114.4	160.5	128.4	126.2	128.7	129.7	55.2
14	EtO	162.0	96.7	169.3	119.2	126.9	114.8	159.8	128.4	126.1	128.7	129.7	14.4, 63.2
15	AcNH	162.1	97.2	169.3	121.2	126.1	118.9	140.9	128.4	126.2	128.7	129.8	24.0, 168.2
16	CH₃	162.1	97.6	169.4	123.9	125.1	129.4	140.0	128.3	126.2	128.7	129.8	20.9
17	F	162.2	98.2	168.3	123.2	127.7	116.0	157.7	128.2	126.2	128.7	129.8	
18	Cl	162.3	98.9	168.1	125.3	127.0	129.0	134.8	128.1	126.3	128.8	130.0	
19	Br	162.3	98.9	168.2	125.7	127.1	131.9	123.5	128.1	126.2	128.7	129.9	
20	CF₃	162.4	100.3	167.7	128.5	126.0*	(a)	(a)	127.9	126.3*	128.8	130.1	(a)
21	CN	162.4	100.6	167.4	130.2	125.9	132.8	112.4	127.8	126.2	128.7	130.0	117.9
22	NO₂	162.5	101.3	167.1	131.9	126.4	124.2	147.8	127.8	126.3	128.8	130.1	

(a) Not determined.

Table III

Correlations of Carbon-13 Data with Substituent Constants (a)

Series Number	Substituent Constant	C Atom Observed	ϱ	i	r	f	SE	n
I	σ	4	0.658	--0.092	0.950	0.31	0.08	11
I	σ⁺	4	0.437	0.026	0.981	0.19	0.05	11
I	σ	5	1.12	−0.030	0.982	0.18	0.08	11
I	σ⁺	5	0.723	0.168	0.985	0.16	0.07	11
II	σ	4	4.02	−0.33	0.986	0.17	0.31	12
II	σ⁺	4	2.49	0.40	0.985	0.17	0.31	12
II	σ	5	−2.09	−0.47	0.961	0.23	0.27	12
II	σ⁺	5	−1.26	−0.84	0.929	0.31	0.36	12

(a) All ¹³C nmr data was treated as the difference from 3,5-diphenylisoxazole.

that the formal introduction of a nitrogen into the furan ring decreases the effect of substituents, a surprising result if one considers electron demand of the sp^2 hybridized nitrogen atom.

Evaluation of the results shown in Table III shows only fair correlations are obtained for carbons-4 and -5 in series I and II. The f-test results are generally high. Interestingly, if the results for carbon-4 in series II are graphed vs. σ^+, one obtains a bifunctional plot with the break occurring at $\sigma^+ = 0$. Treatment of the data as two lines gave better correlations than treating the data as one set (7). The slope is greater, by a factor of almost two for the line representing electron withdrawers than the one for electron donors. A similar bifunctional result has been noted for a number of styrene systems (8) and explained in terms of differing resonance contributions from various canonical forms. A

bifunctional plot of carbon-13 data versus σ^+ has also been observed for certain diaryl carbocations (9). The carbocation results differ from the ones reported here in that electron donors give a line with a larger slope than the one for the withdrawers with the break in the other direction. The results for the diaryl carbocations were interpreted in terms of varying degrees of coplanarity of the two aryl rings.

While comparisons to the analogous furan and pyrrole systems seem appropriate, see above, it also is possible to compare series II with previously reported styrene systems (8,10). The isoxazole systems under study contain an analogous carbon network to the chalcones, a system for which proton and carbon-13 nmr results have been reported (4,6). For series II, the results of the single parameter approach compare well with those of the 4-sub-

Table IV

Dual Substituent Parameter Treatment Results

Series Number	C Atom Observed	σR type	ϱI	ϱR	f	r	SE	N
I	4	BA (a)	0.466	0.716	0.25	0.972	0.06	10
I	5	BA	1.05	1.02	0.14	0.992	0.06	10
II	4	BA	3.43	4.34	0.10	0.996	0.18	11
II	5	BA	−3.13	−1.47	0.11	0.995	0.13	11

(a) Correlation with σR° gives a slightly better correction (f = .25, r = 0.976).

Table V

Physical Data for 3,5-Diarylisoxazoles

Compound Number	Mp °C	(lit. mp)	Analysis Formula	Calcd.		Found	
				C	H	C	H
1	115-117	(115-117) (13)	$C_{16}H_{13}NO_2$				
2	130-131		$C_{17}H_{15}NO_2$	75.94	5.70	76.97	5.71
3	200-202	(200-202) (5)	$C_{17}H_{14}N_2O$				
4	128-130	(130-131) (12)	$C_{16}H_{13}NO$				
5	140-141	(140-141) (13)	$C_{15}H_{11}NO$				
6	165-166	(169-170) (14)	$C_{15}H_{10}FNO$				
7	174-176	(174-175) (13)	$C_{15}H_{10}ClNO$				
8	178-179	(178-179) (14)	$C_{15}H_{10}BrNO$				
9	184-185		$C_{16}H_{10}F_3NO$	66.43	3.49	66.43	3.51
10	178-180		$C_{16}H_{10}N_2O$	78.03	4.10	77.78	4.22
11	220-221	(225) (16)	$C_{15}H_{10}N_2O_3$				
12	169-170	(179) (17)	$C_{17}H_{16}N_2O$				
13	125-126	(128-129) (12)	$C_{16}H_{13}NO_2$				
14	105-106		$C_{17}H_{15}NO_2$	76.94	5.70	76.61	5.81
15	185-186	(185-186) (13)	$C_{17}H_{14}N_2O$				
16	136-137	(138-139) (13)	$C_{16}H_{13}NO$				
17	165-166	(165-166) (5)	$C_{15}H_{10}FNO$				
18	176-177	(178-179) (12)	$C_{15}H_{10}ClNO$				
19	179-180	(180) (18)	$C_{15}H_{10}BrNO$				
20	185-186		$C_{16}H_{10}F_3NO$	66.43	3.49	66.38	3.52
21	194-196		$C_{16}H_{10}N_2O$	78.03	4.10	77.77	4.24
22	220-222	(222-224) (13)	$C_{15}H_{10}N_2O_3$				

stituted chalcones (6). However, the results for the 4'-substituted chalcones (6) do not compare as well with those from series I. The chalcones seem to be a good model system for series II but not for series I.

Dual substituent parameter (DSP) treatment of the data for carbons-4 and -5 in series I and II is shown in Table IV. The σ_R^{BA} values were found to give the best correlations. For all carbons analyzed, except carbon-4 series I, improvement in both correlation coefficient and f-test is noted in comparison to the single parameter approach. The relative magnitude of the effects observed at carbon-4 series I is small; nevertheless, the results are included for comparison. The results for carbon-4 series II are similar to the results obtained for substituted styrenes (8). As before, the results for series II compared well with the similar DSP treatment (11) of the 4-substituted chalcone data (6). The results for carbons-4 and -5 showed the same relative dependence on inductive and resonance effects as determined for carbons-2 and -3 of the 4-substituted chalcone (11). Similar to the single parameter results, the chalcone model for series I appears less accurate. Comparison of the results from carbon-5 series I with data for carbon-3 of 4'-substituted chalcones shows the continued similar dependence of inductive and resonance effects. However, the data for carbon-4 series I and that of carbon-2 4'-substituted chalcones show an intrinsic difference. The data for carbon-4 series I show a dependence on resonance effects while the analogous chalcone data show no appreciable resonance contribution to the DSP correlation.

Although the effects of substituents on the chemical shifts for carbon-5 in I and carbon-3 in II are small, comparison of transmission through this heterocyclic ring system can be estimated. The chemical shift of carbon-5 series I is roughly 3 times as sensitive to substituent effects as the chemical shifts of carbon-3 series II. The relative sensitivity of carbon-4 for series I vs II is approximately 1/6. A difference in sensitivity of the proton chemical shift for the 4 proton in series I and II has been noted earlier although no estimate of the magnitude of the effects was made (12). The magnitude of the ratio of the rho values for substituent effects in the isoxazoles is larger than that measured in the thiophene system and approximately the same as that measured in the benzothiazole systems (3). Work is in progress on the isoxazoles to evaluate the effect of changing electron density by quaternarization to further study transmission of electron effects in heterocyclic systems.

EXPERIMENTAL

Melting points were determined with a Thomas Hoover Uni-Melt apparatus in open capillary tubes and are uncorrected. Microanalyses

were performed by Atlantic Microlabs, Atlanta, Georgia. ^{13}C nmr spectra were obtained, at 50°, with a JEOL FX-60Q Fourier transform spectrometer operating at 15.04 MHz. Data were accumulated on a Texas Instrument 980B computer using 8192 data points over a 4 KHz spectra width to yield a data point resolution of 0.06 ppm. Noise-decoupled spectra were obtained by irradiation with a pulse width corresponding to 45° and 5-s pulse repetition time. The ^{13}C nmr samples were prepared by weight as 0.2M solutions in commercial grade DMSO-d_6. Spectra of less soluble isoxazoles were obtained from saturated solutions. The signals were referenced to tetramethylsilane by giving the most intense DMSO-d_6 signal the value of 39.6 ppm.

The various 3,5-diarylisoxazoles were prepared by a standard procedure (5). Table 4 contains melting point values and literature citations for previously reported compounds and analytical results for new ones.

REFERENCES AND NOTES

(1a) G. L. Nelson, G. C. Levy and J. D. Cargioli, *J. Am. Chem. Soc.*, **92**, 3089 (1972); (b) Y. Nakai, T. Takabayashi and F. Yamada, *Org. Magn. Reson.*, **13**, 94 (1980); and (c) R. E. Bilbo and D. W. Boykin, *J. Chem. Res. (S)*, 332 (1980).

(2a) G. Dana, O. Convert, J.-P. Girault and E. Mulliez, *Can. J. Chem.*, **54**, 1827 (1976); (b) A. D. Harsch, S. Johnson and D. W. Boykin, *J. Chem. Soc., Chem. Commun.*, 119 (1977); (c) C. N. Robinson and C. C. Irving, Jr., *J Heterocyclic Chem.*, **16**, 921 (1979).

(3a) A. Perjéssy, M. Janda and D. W. Boykin, *J. Org. Chem.*, **45**, 1366 (1980); (b) S. N. Sawhney and D. W. Boykin, *ibid.*, **44**, 1136 (1979).

(4) N. L. Silver and D. W. Boykin, *ibid.*, **35**, 759 (1970).

(5) A. L. Baumstark, D. R. Chrisope, R. A. Keel and D. W. Boykin, *J. Heterocyclic Chem.*, **17**, 1719 (1980).

(6a) E. Solaniova, S. Toma and S. Gronowitz, *Org. Magn. Reson.*, **8**, 439 (1976); (b) E. Solaniova and S. Toma, *ibid.*, **14**, 138 (1980).

(7) The line representing the electron donors gives: $\varrho = 1.98$, i = −0.0095, r = 0.999, f = 0.04, S.E. 0.06, n = 7; while the line for the withdrawers gives: $\varrho = 3.43$, i = 0.078, r = .992, f = 0.08, S.E. 0.15, n = 6.

(8) H. O. Krabbenhoft, *J. Org. Chem.*, **43**, 1830 (1978).

(9) D. G. Farnum, R. E. Botto, W. T. Chambers and B. Lam, *J. Am. Chem. Soc.*, **100**, 3847 (1978).

(10a) J. Bromilow, R. T. C. Brownlee, D. T. Craik, M. Sadek and R. W. Taft, *J. Org. Chem.*, **45**, 2429 (1980); (b) G. K. Hamer, I. R. Peat and W. F. Reynolds, *Can. J. Chem.*, **51**, 897 (1973); (c) T. B. Posner and C. D. Hall, *J. Chem. Soc., Perkin Trans. II*, 729 (1976).

(11) DSP treatment of chalcone data (6) with σ_R^{BA} gave: for 4'-substituted C-2 $\varrho_I = -1.12$, $\varrho_R = -0.08$, f = 0.31, r = 0.962, SE = 0.15, n = 8; C-3 $\varrho_I = 2.78$, $\varrho_P = 2.54$, f = 0.09, r = 0.997, SE = 0.10, n = 8; for 4-substituted C-2 $\varrho_I = 4.47$, ϱ_R 5.98, f = 0.12, r = 0.994, SE = 0.31, n = 10; C-3 $\varrho_I = -3.95$, $\varrho_R = -1.75$, f = 0.06, r = 0.998, SE = 0.08, n = 10.

(12) A. Battaglia, A. Dondoni and F. Taddei, *J. Heterocyclic Chem.*, **7**, 721 (1970).

(13) U. Türek and H. Behringer, *Chem. Ber.*, **98**, 3020 (1965).

(14) C. F. Beam, R. S. Foote and C. R. Hauser, *J. Heterocyclic Chem.*, **9**, 183 (1972).

(15) A. H. Blatt, *J. Am. Chem. Soc.*, **53**, 1133 (1931).

(16) P. Ykman, G. Mathys, G. L'Abbé, G. Smets, *J. Org. Chem.*, **37**, 3213 (1972).

(17) K. S. R. Rao, M. Krishna, N. V. Subba Rao, *Indian J. Chem.*, 66 (1968).

(18) P. Grunanger, *Gazz. Chim. Ital.*, **84**, 359 (1954).