Substituent Effects in Heterocyclic Systems.
1H-NMR Study of Methyl 3,5-Diarylisoxazolium Iodides

Alfons L. Baumstark* and Tambra Dunams

Department of Chemistry, Laboratory for MBS, Georgia State University, Atlanta, GA 30303
Received March 24, 1981

Methyl 3-aryl-5-phenylisoxazolium iodides (I) and methyl 3-phenyl-5-arylisoxazolium iodides (II) were synthesized from the corresponding isoxazoles in moderate yields. The 1H-nmr chemical shifts for H-4, series I and II, and the quaternary methyl group series II were found to correlate with σ^+ values. The rho value observed for H-4 series II was 3.3 times that observed in series I. The correlation observed in series I contrasts with the lack of (poor) correlations reported in the corresponding isoxazole and chalcone systems. The rho value observed in the correlation of the quaternary methyl group series II correlates well with an estimate based on methyl pyridinium salt data. The chemical shifts of the quaternary methyl group series I showed little or no variation. Swain-Lupton and DSP treatments did not show improved correlations over the single parameter results. However, interpretation of these treatments reveals that similar processes are occuring in all three cases. The results for H-4 series I showed that the reduction of transmission of the substituent effect in series I compared to that in series II was essentially due to equal reduction of both inductive and resonance effects. The mechanism of transmission seems to differ only in degree and not type.

1H-nmr chemical shifts in aromatic systems have been found to correlate with single parameter substituent constants (1). The 1H chemical shift data are sensitive to the electron distribution in aromatic π-systems. The transmission of substituent effects through an aromatic system to a proton indirectly attached via another group (as measured by changes in 1H chemical shift) has been shown to exhibit excellent linear-free-energy-relationships (1,2). 1H chemical shift data have been successfully employed to study substituent effects in heteroaromatic systems (1,2). Relatively little information is available on substituent effects on 1H-nmr chemical shifts in quaternary heterocyclic systems. Our interest (3) in heterocycles has led to an investigation of substituent effects in the quaternary salts of isoxazoles. We wish to report the synthesis and 1H-nmr study of methyl 3-aryl-5-phenylisoxazolium iodides (I) and methyl 3-phenyl-5-arylisoxazolium iodides (II).
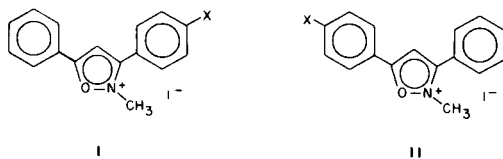
Results and Discussion.

The methyl 3-aryl-5-phenylisoxazolium iodides (I) and the methyl 3-phenyl-5-arylisoxazolium iodides (II) were synthesized from the corresponding isoxazoles (3) in moderate yield. The 1H-nmr spectra for series I and II were taken in DMSO-d_6. The chemical shift results for the isoxazolium ring protons and the quaternary methyl groups are recorded in Table 1.

Examination of the data arising from series I reveals that the substituents have a small effect on the chemical shift of the ring proton, H-4. The range in chemical shift from strong electron donor to strong electron withdrawer is 0.13 ppm, well within the accuracy limitations of the instrumentation. The effects of substituents in series II were more pronounced (a range of 0.4 ppm). A small substituent effect was also observed for the quaternary methyl group of series II. As might be expected from simple resonance

Table 1

1H-NMR Chemical Shift Data for Methyl
3,5-Diarylisoxazolium Iodides (I and II)

Series I

No	x	H-4	CH₃	x
1	CH₃O	8.29	4.48	3.93
2	CH₃	8.33	4.48	2.48
3	F	8.35	4.49	
4	H	8.36	4.49	
5	Cl	8.36	4.48	
6	Br	8.35	4.47	
7	CF₃	8.40	4.49	
8	CN	8.41	4.49	
9	NO₂	8.42	4.49	

Series II

No	x	H-4	CH₃	x
10	CH₃O	8.18	4.43	3.92
11	AcNH	8.18	4.44	2.13
12	CH₃	8.28	4.46	2.46
13	F	8.33	4.48	
14	Cl	8.38	4.49	
15	Br	8.39	4.48	
16	CF₃	8.54	4.54	
17	CN	8.53	4.53	
18	NO₂	8.58	4.54	

Table II

Correlations of ¹H-NMR Data for Series I and II with Substituent Constants (a)

Series	Subst. Const.	Position	p	r	f	SE	n
I	σ	H-4	0.11	0.956	0.29	0.012	9
I	σ^+	H-4	0.081	0.988	0.15	0.006	9
II	σ	H-4	0.38	0.937	0.35	0.50	10
II	σ^+	H-4	0.27	0.994	0.10	0.14	10
II	σ	CH₃	0.10	0.925	0.38	0.015	10
II	σ^+	CH₃	0.073	0.985	0.17	0.007	10

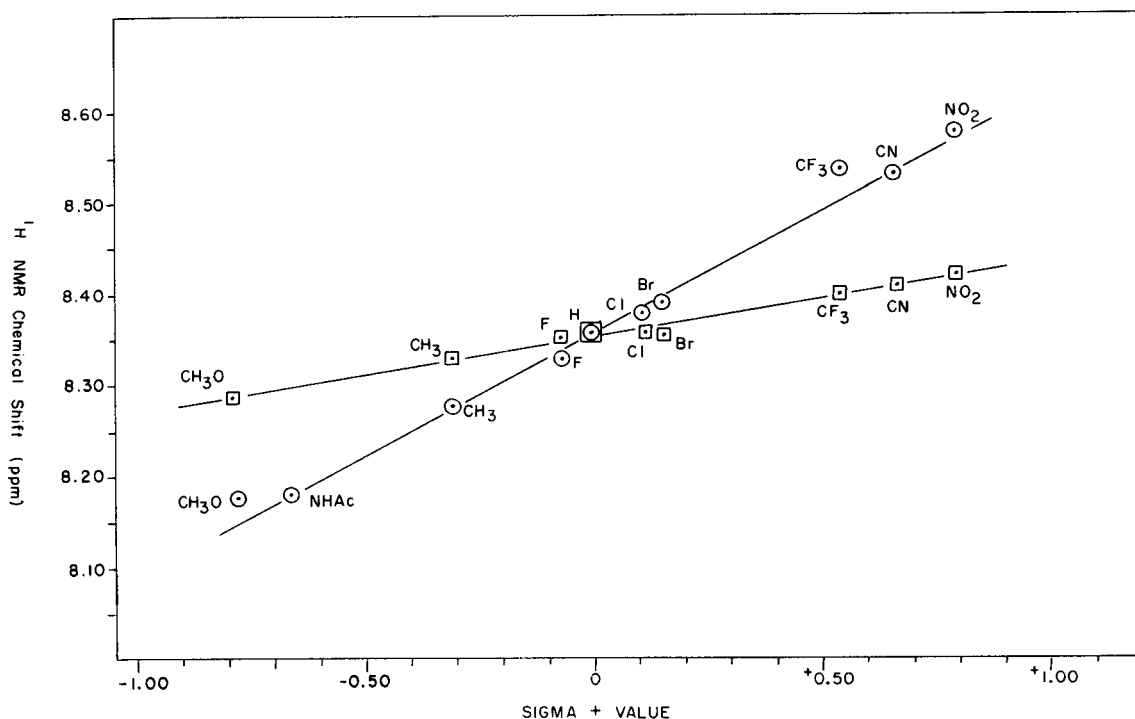(a) Data treated as difference from that of methyl 3,5-diphenylisoxazolium iodide.

Figure 1. Plot of ¹H-nmr chemical shift data for H-4, series I ⊡ and series II ⊙, vs sigma + values.

considerations, electron donating substituents resulted in shielding effects while electron withdrawing substituents resulted in deshielding effects.

Single parameter correlations for the ¹H-nmr data for series I and II are shown in Table II. Reasonable correlations are obtained between the chemical shifts of H-4 series I and II and σ^+ constants (Figure 1). Judging from the rho values, the chemical shift for H-4 is approximately 3.3 times more sensitive to substituent effects in series II than in series I.

In the case of 3,5-diarylisoxazoles, correlations of chemical shift of H-4 with σ are reported for the 5-aryl compounds (4). Substitutions on the 3-aryl group of isoxazoles yield no correlations of chemical shift with substituent constants (4). Reported substituent effects (5) on the

¹H-nmr spectra of chalcones (acyclic model compounds for isoxazoles) are also of interest. The chemical shifts for H-α for 4'-substituted chalcones show a poor correlation (r = 0.947), with σ with a rho value of 0.20 while the chemical shifts for H-α for 4-substituted chalcones show almost no correlation (r = 0.85) with σ values (rho = −0.08) (5). Thus the isoxazolium system differs not only in that the data correlate with σ^+ instead of σ but also in that a correlation for H-4 chemical shift series I is found while none is observed in the isoxazole or chalcone models. Comparison of the rho value for series II with that observed in the corresponding isoxazole (4) must be made with extreme caution since the two sets of data were collected in different solvents. However, it appears that the rho values for the isoxazolium data are larger. Unfortunately, data

Table III

Swain-Lupton and DSP Treatment of the ¹H-NMR Data for Methyl 3,5-Diarylisoxazolium Iodides

a) Swain-Lupton

Series	Position		a (i)	b (ii)	r	f	SE	n
I	H-4		0.050	0.15	0.974	0.25	0.010	9
II	H-4		0.20	0.49	0.953	0.34	0.046	10
II	CH$_3$		0.042 ·	0.14	0.949	0.35	0.013	10

b) DSP

I	H-4	σ^+_R	0.070	0.089	0.990	0.16	0.006	9
II	H-4	σ^+_R	0.27	0.27	0.990	0.16	0.021	10
II	CH$_3$	σ^+_R	0.062	0.079	0.977	0.24	0.009	10

(i) For Swain-Lupton treatment, a = f. For DSP treatment, a = ϱ_I. (ii) For Swain-Lupton treatment, b = r. For DSP treatment, b = ϱ_R.

Table IV

Physical Data for Methyl 3,5-Diarylisoxazolium Iodides

No.	Formula	Mp (a)	% yield		Analysis % Calcd.	% Found
1	C$_{17}$H$_{16}$O$_2$NI·1H$_2$O	172-173	69	C	49.65	49.63
				H	4.41	4.44
2	C$_{17}$H$_{16}$ONI	173-174	41	C	54.13	54.09
				H	4.28	4.29
3	C$_{16}$H$_{13}$ONIF	162-163	24	C	50.42	50.19
				H	3.44	3.48
4	C$_{16}$H$_{14}$ONI	160-161	60	C	52.91	52.81
				H	3.89	3.95
5	C$_{16}$H$_{13}$ONICl	178-179	31	C	48.33	48.35
				H	3.30	3.34
6	C$_{16}$H$_{13}$ONIBr·½H$_2$O	176-177	74	C	42.60	42.57
				H	3.13	3.17
7	C$_{17}$H$_{13}$ON$_1$IF$_3$·1H$_2$O	184-186	39	C	45.45	45.45
				H	3.37	3.37
8	C$_{17}$H$_{18}$ON$_2$I·1H$_2$O	190-191	65	C	50.27	50.61
				H	3.72	3.38
9	C$_{16}$H$_{18}$O$_3$N$_2$I	216-218	36	C	47.08	46.91
				H	3.21	3.25
10	C$_{17}$H$_{16}$O$_2$NI·½H$_2$O	180-181	74	C	50.76	50.98
				H	4.26	4.33
11	C$_{18}$H$_{17}$O$_2$N$_2$I·1H$_2$O	172-173	86	C	49.33	49.30
				H	4.37	4.37
12	C$_{17}$H$_{16}$ONI	172-173	86	C	54.13	53.90
				H	4.28	4.36
13	C$_{16}$H$_{13}$ONIF·1H$_2$O	162-163	24	C	48.14	48.75
				H	3.79	3.72
14	C$_{16}$H$_{13}$ONICl	176-178	29	C	48.33	48.10
				H	3.30	3.36
15	C$_{16}$H$_{13}$ONIBr	178-179	71	C	43.47	43.51
				H	2.96	2.97
16	C$_{17}$H$_{13}$ONIF$_3$	186-187	66	C	47.35	47.14
				H	3.05	3.07
17	C$_{17}$H$_{13}$ON$_2$I·½H$_2$O	195-197	25	C	51.40	51.82
				H	3.55	3.53
18	C$_{16}$H$_{13}$O$_3$N$_2$I·½H$_2$O	161-163	81	C	46.17	45.65
				H	3.15	3.15

(a) All compounds decomposed.

for H-4 for the isoxazoles in DMSO-d_6 are hidden by the aromatic signals.

The ^{1}H-nmr chemical shift of the quaternary methyl group series II was also found to give a reasonable correlation with σ^+ values, although the rho value was small (0.073). The ^{1}H-nmr chemical shifts of the quaternary methyl group of pyridinium salts has also been reported (6) to correlate with a σ^+ constants with a substantially larger rho value. A crude estimate of the rho value for the present case can be made assuming a percentage reduction in the pyridinium rho value similar to that observed (7) for benzoic acids vs Ar-(CH=CH)$_2$CO$_2$H to yield a value of approximately 0.09. Thus the results of series II and the pyridinium salts seem in good agreement. The ^{1}H chemical shift of the methyl group series I showed little or no variation with substituent changes. The lack of sensitivity of the chemical shifts for the quaternary methyl group series I is difficult to understand. A 3-fold reduction in rho value compared to that of series II might be predicted and would be observable with the instrumentation. A possible explanation may involve steric effects of the *ortho* hydrogens of the 3-aryl group on the methyl group. Steric interactions between groups on positions-2 and -3 have been noted (8) in the reaction of 3,5-dimethylisoxazole with carbocations.

Swain-Lupton (9) and DSP treatment (10) of the data did not improve the correlation of the chemical shifts over the single parameter treatment (see Table III). Analysis of these results is useful in determining the relative nature of the processes resulting in the substituent effects. The Swain-Lupton approach resulted in poor correlation but the contribution to the correlation by resonance in all three cases was approximately 75%. All three sets of data showed that Taft σ_R^+ constants gave the best correlations in the DSP treatment. The results for series I are interesting since they show that the reduction of transmission of the substituent effect in series I compared to that in series II is due to essentially equal reduction of both inductive annd resonance effects.

Substituent effects on ^{1}H chemical shifts in neutral heteroaromatic systems have been found to correlate, in general, with sigma values (1,2). However, the proton nmr data for purines were found to correlate with sigma + values (11). The ^{1}H-nmr data on a charged heteroaromatic system (pyridinium salts) were found to correlate with sigma + values. Thus, it seems reasonable that the isoxazolium data would correlate with sigma + values. The isoxazolium data allow a number of interesting observations. The data indicates that transmission of substituent effects in the quaternary system is more effective than in the neutral systems (4). A comparison of the data for series I and II allows assessment of transmission of substituent effects from positions-3 and -5. Substituents on position-3 effect the chemical shift of position-4 by a similar mechanism to that observed for substituents on position-5 only to a lesser degree.

EXPERIMENTAL

The following general procedure (3,12) for the preparation of isoxazole quaternary salts was followed for all compounds reported. 0.50 g (approximately 0.002 mole) of 3,5-diarylisoxazole was combined with 2.7 g (0.021 mole) of dimethyl sulfate in a roundbottom flask. The mixture was heated under reflux for 4 hours with an oil bath at 95-100°. The resulting homogeneous mixture was allowed to cool. 5.0 Ml of 24% hydroiodic acid was added. Yellow powdery crystals immediately formed. For those cases in which the crystals were very water soluble, solid sodium iodide was also added. The crystals were collected and washed with 95% ethanol. After air drying, the crystals were further dried at 90° for one hour. The salts were recrystallized from 95% ethanol to yield analytically pure samples. In most cases, recrystallization from ethanol increased the melting point. Upon melting all of the compounds gave off a purple color indicative of decomposition. No effort was made to maximize the isolated yields. The physical data for the methyl 3,5-diarylisoxazolium iodides are summarized in Table IV.

REFERENCES AND NOTES

(1) See M. T. Tribble and J. G. Traynham, in "Advances in Linear Free Energy Relationships," N. B. Chapman and J. Shorter, eds., Plenum Press, New York, N.Y., 1972, pp 143-201 and references therein.

(2) See P. Tomasik and C. D. Johnson, in "Advances in Heterocyclic Chemistry", A. R. Katritzky and A. J. Boulton, eds., Academic Press, New York, N.Y., Vol. 20, 1976, pp 1-65 and references therein.

(3a) A. L. Baumstark, D. R. Chrisope, R. A. Keel and D. W. Boykin, *J. Heterocyclic Chem.*, 17, 1719 (1980); (b) D. R. Chrisope, R. A. Keel, A. L. Baumstark and D. W. Boykin, *ibid.*, in press.

(4a) A. Battaglia, A. Dondoni and F. Taddei, *J. Heterocyclic Chem.*, 7, 721 (1970); (b) P. Beltrame, C. Veglio and M. Simonetta, *J. Chem. Soc.*, *(B)*, 867 (1967); (c) Also see reference 1, p. 170.

(5) E. Solcaniova and S. Toma, *Org. Magn. Reson.*, 14, 133 (1980).

(6) F. W. Wehrli, W. Giger and W. Simon, *Helv. Chim. Acta*, 54, 229 (1971).

(7) See O. Exner, in "Advances in Linear Energy Relationships", N. B. Chapman and J. Shorter, eds., Plenum Press, New York, N.Y., 1972, pp 1-69.

(8) D. J. Woodman, *J. Org. Chem.*, 33, 2397 (1968).

(9) C. G. Swain and E. C. Lupton, *J. Am. Chem. Soc.*, 90, 4328 (1968).

(10) S. Ehrenson, R. T. C. Brownlee and R. W. Taft, *Prog. Phys. Org. Chem.*, 10, 1 (1973).

(11) W. C. Coburn, M. C. Thorpe, J. A. Montgomery and K. Hewson, *J. Org. Chem.*, 30, 1110 and 1114 (1965).

(12a) See A. H. Blatt, *J. Am. Chem. Soc.*, 71, 1861 (1949); (b) See B. D. Wilson and D. M. Burness, *J. Org. Chem.*, 31, 1565 (1966).