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Proximity Effects in Pyridines. Proton Chemical Shifts in Substituted Methyl Pyridinecarboxylates

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Abstract—Ring and ester proton chemical shifts in six series of substituted methyl pyridinecarboxylates have been measured. Results for ring protons *ortho* and *para* to the substituent can generally be accounted for by additive substituent, ester and nitrogen effects. Shifts for protons *meta* to the substituent, when compared with analogous shifts in monosubstituted benzenes, provide evidence of substituent–nitrogen interactions. In particular, a special effect is noted for series where both the proton and substituent are adjacent to the nitrogen. The origin of this effect is discussed. The ester proton results lead to essentially the same conclusions. Although this probe is much less sensitive to substituent effects, the same special effect is evident for the methyl 6-X-picolinate series.

ALKALINE hydrolysis studies[1] of extensive series of substituted methyl pyridinecarboxylates (**1** to **6**) revealed some anomalous transmissions of substituent effects, especially for series **4** where the ring nitrogen was *ortho* to both the substituent and ester function (the probe for this series of measurements). Solvolysis of the 6-substituted 2-(2-pyridyl)-2-chloropropanes (**7**) also showed this abnormal behaviour.[2] It was of interest, therefore, to see if this substituent–nitrogen interaction was evident in ^{1}H NMR measurements. The series of pyridine esters available allowed measurements to be made on a good range of substituents in a variety of orientations under identical conditions. We report here on ring and ester proton chemical shifts in these series with comment on the anomalies observed in this and previous work.

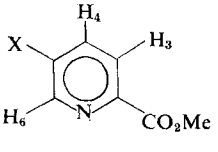
Since a substituent's effect on a magnetic property need not exactly parallel its effect on chemical reactivity,[3] we have in general preferred to compare shifts directly with a reference series rather than with reactivity results as expressed by Hammett sigma values. The reference chosen for the ring protons was a series of monosubstituted benzenes where extensive accurate data were available.[4] This leaves the possibility open that any deviations observed in such correlations could be due to substituent–carbonyl as well as substituent–nitrogen interactions. Some data on substituted benzoic acids in DMSO are available[5] and any effects of substituent–carbonyl interactions will be considered by reference to these results. The analysis of substituent effects on the ester protons requires a comparison with the appropriate methyl benzoates. There have been a number of systematic studies of substituent effects on chemical shifts of aromatic sidechain methyl groups including methyl,[6,7] methoxy[6] and acetyl,[6,7] but only a few isolated measurements[8–10] have been reported for methyl benzoates.

EXPERIMENTAL

Chemicals

Most of the substituted methyl pyridinecarboxylates were prepared by published methods[11] with some minor modifications. Diesters were prepared from the corresponding dicarboxylic acids by treatment with methanol–sulphuric acid. 2-Fluoro-4-, 5- and 6-pyridinecarboxylic acids were prepared by oxidation of the corresponding 2-fluoropicolines[12] and these were subsequently esterified with diazomethane.

Methyl 5-fluoronicotinate. Isoamylnitrite (12·5 g) was added, dropwise, with stirring to a solution of 5-aminonicotinic acid (5·0 g) and aqueous 40% hydrofluoroboric acid (10 ml) in acetone at 0 °C. The mixture was stirred for 1 h after the addition was complete and the brown slurry was filtered, washed well with ether and dried over P_2O_5. A suspension of this diazonium fluoroborate (m.p. 58 °C with decomp.) in cyclohexane was heated at 60 °C for 10 min. The cyclohexane was decanted and the residue was dried at 100 °C. The crude 5-fluoronicotinic acid was esterified with methanol–sulphuric acid in the normal way and gave methyl 5-fluoronicotinate, m.p. 46 to 47 °C (Lit.[13] 48 °C) after recrystallisation from light petroleum (b.p. 40 to 60 °C).



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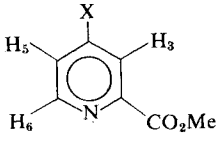

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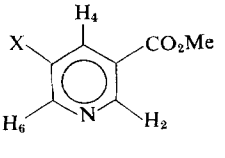

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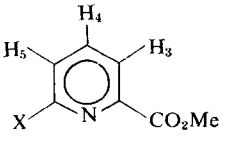

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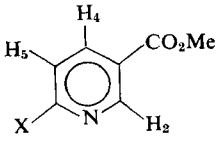

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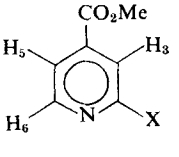

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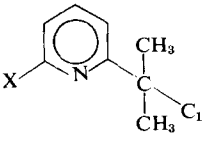

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TABLE 1. RING PROTON CHEMICAL SHIFTS (δ) IN METHYL PYRIDINECARBOXYLATES MEASURED AT 5 MOL % IN DEUTEROCHLOROFORM

Series	Substituent Proton	NMe_2	OMe	Me	H	F	Br	CO_2Me	NO_2
	H3	7·97	8·11	8·04	8·14		(8·01)[a]	8·20	8·36
(1)	H4	6·92	7·27	7·63	7·86		(8·01)[a]	8·44	8·62
	H6	8·17	8·40	8·67	8·76		(8·81)[a]	9·30	9·52
	H3	7·39	7·66	7·97	8·14		8·31	8·64	8·81
(2)	H5	6·59	6·97	7·30	7·49		7·67	8·04	8·25
	H6	8·32	8·54	8·61	8.76		8·58	8·91	9·10
	H2	8·55	8·14	9·02	9·22	9·04	9·13	9·36	9·48
(3)	H4	7·63	7·75	8·09	8·23	7·98	8·41	8·85	9·02
	H6	8·26	8·47	8·60	8·77	8·64	8·84	9·36	9·58
	H3	7·34	7·69	7·93	8·14		8·08	8·31	8·50
(4)[b]	H4	7·51	7·66	7·71	7·86		7·71	8·04	8·25
	H5	6·62	6·91	7·33	7·49		7·64	8·31	8·42
	H2	8·79	8·82	9·01	9·22	8·87	8·95	9·30	9·20
(5)	H4	7·98	8·13	8·16	8·28	7·40	8·12	8·44	8·65
	H5	6·44	6·75	7·22	7·38	7·00	7·58	8·20	8·32
	H3	7·08	7·29	7·69	7·83	7·48	8·03	8·64	8·75
(6)	H5	7·03	7·38	7·63	7·83	7·73	7·79	8·04	8·25
	H6	8·25	8·26	8·63	8·78	8·36	8·51	8·91	8·82

[a] Approximate values, see Experimental.
[b] Cl: $H_3 = 8·05$, $H_4 = 7·83$, $H_5 = 7·53$.

Measurements

For solubility reasons, spectra were recorded in $CDCl_3$ as 5 mol percent solutions, on a Varian A-60D spectrometer. Chemical shifts are quoted in ppm relative to TMS. In series **6**, measurements were also made in CCl_4 solution and the two sets of results correlate about a line of unit slope (i.e. $\rho = 1·0$). It was therefore judged acceptable to compare the $CDCl_3$ results with those for monosubstituted benzenes which were available from CCl_4 solution measurements. All spectra were calibrated by the usual audio sideband technique and the measured line frequencies used were the average of 6 to 8 determinations.

The LAOCOON program,[14] modified to fit a PDP15 computer, was used in the spectral analysis of the ring protons. RMS deviations between calculated and experimental line frequencies were ~0·03 to 0·1 Hz. With one exception, all spectra except series **4** were ABX systems and were handled readily. Methyl 5-bromopicolinate (**1**, X = Br) could not be fully analysed due to the apparent magnetic equivalence of H_3 and H_4. Thus, chemical shifts based on a first order spectrum are recorded for this compound. Some of the tightly coupled ABC spectra of series **4** were more difficult to analyse. In general, however, good trial parameters were obtained from assuming additive substituent effects on various protons in the other ester series.

RESULTS AND DISCUSSION

Ring protons

Tables 1 and 2 list the various ring proton chemical shifts and coupling constants for the six methyl pyridinecarboxylate series, obtained from dilute $CDCl_3$ solutions.

Protons para *to* X(**3**-H_2, **4**-H_3, **6**-H_5). *Para* proton shifts in substituted benzenes and 2-substituted pyridines are mainly determined by the π-density at the attached carbon atom,[15] i.e. resonance effects of the substituents are important and they correlate well with σ_p.[16]

In the pyridine esters, *para* proton chemical shifts (range $\approx$ 1·4 ppm) correlate well with those in the corresponding monosubstituted benzenes about a line with slope $\approx$ 1·0. This sort of correlation can also be obtained from the available data[17] for H_5 in 2-X-pyridines. Figure 1 is typical of these correlations. *Para* proton shifts therefore seem to be produced by inde-

TABLE 2. RING PROTON COUPLING CONSTANTS (Hz) IN METHYL PYRIDINECARBOXYLATES[a]

J_{24}	J_{25}	J_{34}	J_{35}	J_{36}	J_{45}	J_{46}	J_{56}
1·72(**3a**)	0·40(**3a**)	9·09(**1a**)	2·75(**2a**)	0·48(**1a**)	8·91(**4a**)	3·23(**1a**)	5·88(**2a**)
1·68(**3b**)	0·32(**3b**)	9·01(**1b**)	2·62(**2b**)	0·54(**1b**)	8·41(**4b**)	3·00(**1b**)	5·65(**2b**)
1·39(**3c**)	0·40(**3c**)	8·18(**1c**)	1·71(**2c**)	0·61(**1c**)	8·09(**4c**)	2·35(**1c**)	4·95(**2c**)
2·14(**3d**)	0·30(**3d**)	8·08(**1d**)	1·11(**2d**)	0·94(**1d**)	7·58(**4d**)	1·79(**1d**)	4·76(**2d**)
1·59(**3h**)	0·45(**3h**)	8·19(**1f**)	1·94(**2e**)	1·04(**1e**)	8·20(**4i**)	2·12(**1e**)	5·29(**2e**)
1·88(**3e**)	0·30(**3e**)	8·67(**1g**)	1·57(**2f**)	0·91(**1f**)	7·99(**4e**)	2·14(**1f**)	4·95(**2f**)
2·23(**3f**)	0·36(**3g**)	7·47(**4a**)	2·18(**2g**)	0·70(**1g**)	8·10(**4f**)	2·48(**1g**)	5·41(**2g**)
1·82(**3g**)	0·74(**5a**)	7·54(**4b**)	0·66(**4a**)	0·45(**2a**)	8·51(**4g**)	3·15(**3a**)	5·33(**6a**)
2·40(**5a**)	0·76(**5b**)	7·98(**4c**)	0·74(**4b**)	0·40(**2b**)	9·31(**5a**)	2·98(**3b**)	5·35(**6b**)
2·47(**5b**)	0·42(**5c**)	8·08(**4d**)	1·02(**4c**)	0·70(**2c**)	8·98(**5b**)	2·89(**3c**)	5·17(**6c**)
2·17(**5c**)	0·91(**5d**)	7·83(**4i**)	1·11(**4d**)	0·94(**2d**)	8·31(**5c**)	1·77(**3d**)	5·15(**6d**)
2·14(**5d**)	0·72(**5h**)	7·70(**4e**)	0·88(**4i**)	0·47(**2e**)	8·13(**5d**)	2·99(**3h**)	5·27(**6h**)
2·49(**5h**)	0·68(**5e**)	8·10(**4f**)	1·13(**4e**)	0·85(**2f**)	8·76(**5h**)	2·36(**3e**)	5·11(**6e**)
2·50(**5e**)	0·43(**5f**)	8·01(**4g**)	0·87(**4g**)	0·61(**2g**)	8·47(**5e**)	2·23(**3f**)	4·95(**6f**)
2·23(**5f**)	0·74(**5g**)		1·36(**6a**)	0·86(**6a**)	8·19(**5f**)	2·65(**3g**)	5·00(**6g**)
2·19(**5g**)			1·38(**6b**)	0·79(**6b**)	8·58(**5g**)		
			0·96(**6c**)	0·61(**6c**)			
			1·85(**6d**)	1·01(**6d**)			
			1·29(**6h**)	0·76(**6h**)			
			1·42(**6e**)	0·77(**6e**)			
			1·57(**6f**)	0·85(**6f**)			
			1·38(**6g**)	0·81(**6g**)			

[a] Substituents: a = NMe_2, b = OMe, c = Me, d = H, e = Br, f = CO_2Me, g = NO_2, h = F, i = Cl.

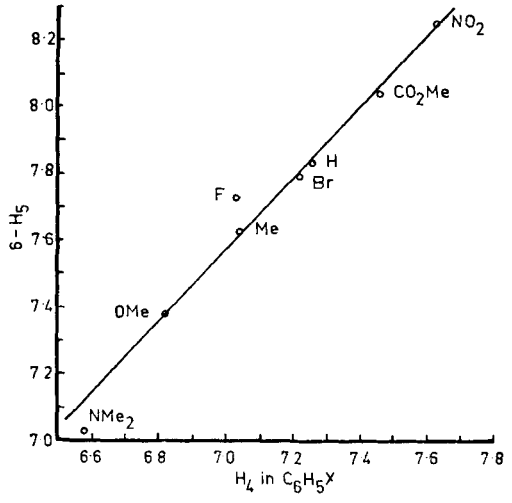


FIG. 1. *para* Ring proton chemical shifts (δ).

pendent and additive effects of the substituent and ring nitrogen.

Protons ortho *to* *X*(**1**-$H_{4,6}$, **2**-$H_{3,5}$, **3**-$H_{4,6}$, **4**-H_5, **5**-H_5, **6**-H_3). *Ortho* proton shifts are the largest in monosubstituted benzenes. As with *para* shifts, substituent resonance effects are important and correlations with σ_p have been observed,[18] though with significant deviations for some substituents. The inductive effect and second order effects play a more important role in determining δ_0 because of the small separation of substituent and proton.

In the pyridine esters (range $\approx$ 1·8 ppm) correlations with appropriate benzene results are generally good though deviations to low field are observed for strong donor substituents in **2**-H_3, **2**-H_5 (Fig. 2), **1**-H_4 (but not **1**-H_6) and **5**-H_5. These deviations arise when the donor substituent is *para* to the nitrogen or ester and are explicable in terms of through conjugation. Thus, similar deviations are evident in the corresponding plots

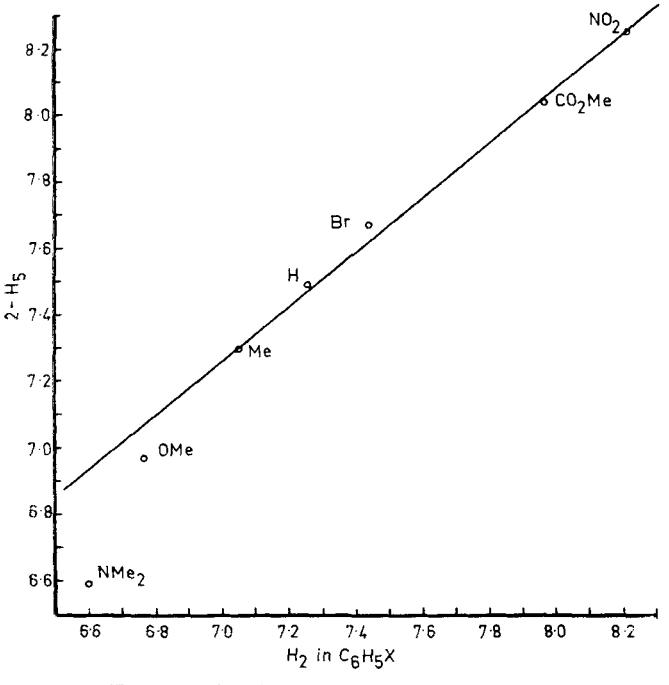


FIG. 2. *ortho* Ring proton chemical shifts (δ).

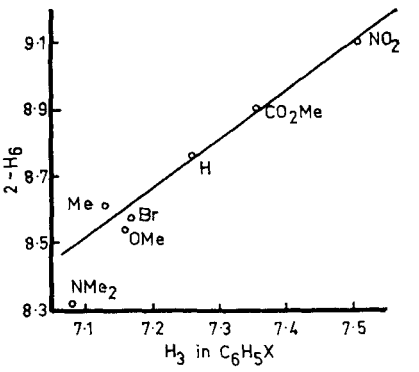


FIG 3. *meta* Ring proton chemical shifts (δ) in 2-H_6.

for H_3 in 4-substituted pyridines[19] and H_3 in 4-substituted benzoic acids.[5]

The slopes of the correlation lines (obtained by omitting the deviant points mentioned above) fall into two categories. For those series where the substituent is adjacent to the nitrogen, $\rho = 1{\cdot}0$, while for β or γ substituents (irrespective of the orientation of the proton relative to the nitrogen) $\rho \approx 0{\cdot}8$ (Fig. 2).

To summarise, *ortho* proton shifts tend to give more evidence of non-additivity of substituent and nitrogen effects than do *para* shifts, but deviations are not large.

Protons meta *to* *X*(**1**-H_3, **2**-H_6, **4**-H_4, **5**-$H_{2,4}$, **6**-H_6). *Meta* proton chemical shifts in monosubstituted benzenes occur over a relatively small range and appear to be determined as much by secondary effects as by charge densities. For example, there is no correlation with σ_m or σ_I parameters.[6]

Interestingly, the *meta* shifts in the pyridine esters (range $\approx$ 0·8 ppm) are more indicative of substituent–nitrogen interactions than either of the two previous classes. They can be separated into three groups: (A) **4**-H_4, **5**-H_4 and **2**-H_6 (Fig. 3) correlate with the corresponding *meta* shifts in monosubstituted benzenes,[4] as do H_4 in 2-X-pyridines[17] and H_2 in 4-X-pyridines,[19] all with $\rho \approx 1{\cdot}5$. An additional small downfield shift is noted for X = NMe_2 when *para* to the nitrogen. (B) **1**-H_3 also correlates, but here $\rho = 0{\cdot}8$. (C) **6**-H_6 (Fig. 4) and **5**-H_2, together with H_6 in 2-X-pyridines[17] do not show any significant correlation.

The protons in group A, while *meta* to the substituent are, however, *ortho* or *para* to the nitrogen. The substituents are also *ortho* or *para* to the nitrogen, i.e. in position for maximum interaction. Thus, the transmission of the substituent effect to the *meta* proton is

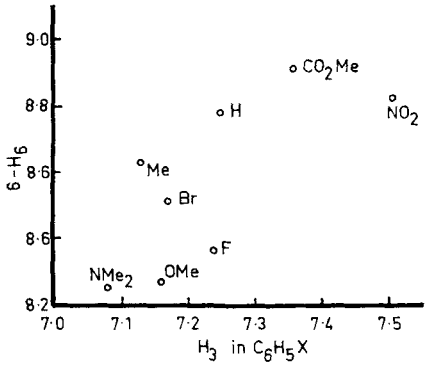


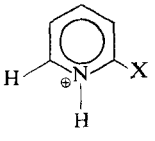
FIG. 4. *meta* Ring proton chemical shifts (δ) in 6-H_6.

enhanced by the indirect involvement of the nitrogen. Since *meta* shifts are small, the effect of these interactions is more evident here than in *ortho* or *para* shifts.

In B, the substituent, nitrogen and proton are *meta* to each other and, with no possibility of the relay of resonance effects, the transmission of substituent effects is attenuated by the nitrogen relative to the situation in monosubstituted benzenes.

Group C results show the same type of substituent effects that were found in reactivity studies[1,2] for the apparently special case where the substituent and probe are separated by the nitrogen. Substituent effects are therefore transmitted across a ring nitrogen by a different mechanism to that operating across a ring carbon atom. This conclusion was reached from the previous study of ring proton shifts in 2-X-pyridines,[17] but our explanation of the cause is different. Smith and Roark decided that the chemical shift of H_6 was correlated by σ_m, i.e. the lone pair of electrons on the nitrogen facilitated transmission of the field effect of the 2-substituent to H_6. However, in the σ_m plot, the points for methyl and cyano deviated from the correlation. The point for pyridine itself[20] was not included, but would in fact be the furthest point from the correlation line.

An alternative interpretation of the results for group C is possible, which gives a better correlation of the data. This is that the nitrogen effectively *insulates* the α-proton from the field (or inductive) effect of the substituent, and that resonance between the substituent and adjacent nitrogen is the important factor that determines the chemical shift. Accordingly, plots of chemical shift against the resonance parameter, σ_R° (Fig. 5) give a significant improvement over σ_m plots for all series in this group, irrespective of the position of the ester group. An even greater dependence of chemical shift on substituent resonance effects is evident when the data[17] on 2-X-pyridinium salts (**8**) are considered. In



(8)

this case, the $\sigma_R^\oplus$ parameter (required for situations of strong resonance interaction between donor substituents and electron deficient 'site') is required to provide a reasonable correlation.

It is not clear exactly how the nitrogen in this particular orientation so efficiently relays the substituent resonance effect as the explanation must be applicable to both NMR and reactivity studies. Field effects associated with the lone pair dipole have been shown[21] to be important in determining the chemical shift of the α-protons

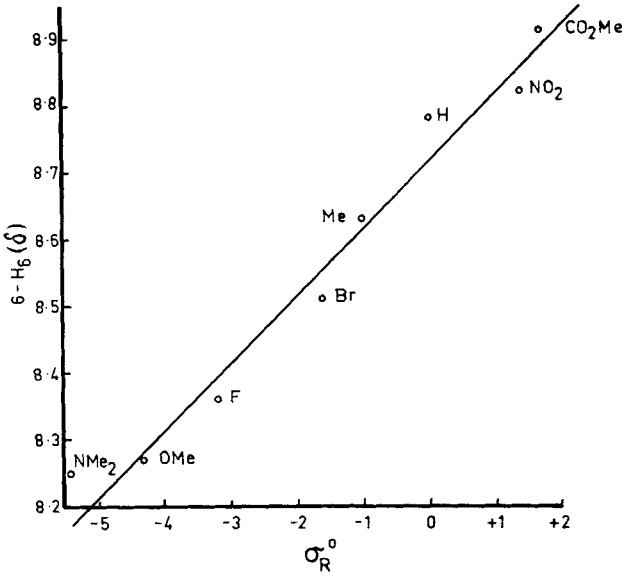


FIG. 5.

in pyridine. Resonance between the adjacent substituent and the nitrogen would markedly alter the polar character of this 'part' of the molecule and it seems reasonable that the probe responds to the field effect of the resultant interaction. Such a mechanism would apply to both NMR and reactivity.

Ester protons

The ester proton shifts are listed in Table 3.

Inspection of the methyl benzoate results reveals that the chemical shifts are essentially governed by the same inductive and resonance factors that determine the pK_a of the corresponding acids. Statistical correlation with the reactivity parameters σ_m (SD/RMS = 0·22) and σ_p (0·23) is only fair, but this was foreseen in the introduction.

Though the range of shifts is small, comparison of the pyridine ester results with the corresponding benzoate shifts reveals that in all series except **4**, a good correlation about a line of slope 1·0 exists, although there is a clear upfield deviation for the strongest donor substituent, NMe_2, when it is *ortho* or *para* to the ring nitrogen (series **2**, **5** and **6**).

The other series, **4**, in which both the substituent and the ester probe are adjacent to the nitrogen, is analogous to **6**-H_6 of the ring proton series and the same anomalous results are observed (Fig. 6). It is clear that here too there is more substituent resonance effect involved in determining the chemical shift than expected from the formal *meta* orientation of substituent and probe.

TABLE 3. METHYL ESTER PROTON CHEMICAL SHIFTS (δ) IN DEUTEROCHLOROFORM (5 MOL %)

Substituent/Series:	*p*-Benzoate	*m*-Benzoate	(1)	(2)	(3)	(4)	(5)	(6)
NMe_2	3·84	3·89	3·95	3·97	3·93	3·93	3·85	3·91
OMe	3·88	3·91	3·98	4·02	3·95	3·96	3·91	3·96
CH_3	3·89	3·90	4·00	4·02	3·94	4·00	3·94	3·95
H	3·91	3·91	4·02	4·02	3·96	4·02	3·96	3·96
F	3·91	3·92			3·98	4·00	3·96	3·98
Cl	3·91	3·92				4·01		
Br	3·91	3·92	4·02	4·04	3·96	4·00	3·96	3·97
CO_2Me	3·94	3·95	4·04	4·05	4·00	4·03	3·99	4·01
NO_2	4·00	4·00	4·08	4·11	4·05	4·07	4·04	4·06

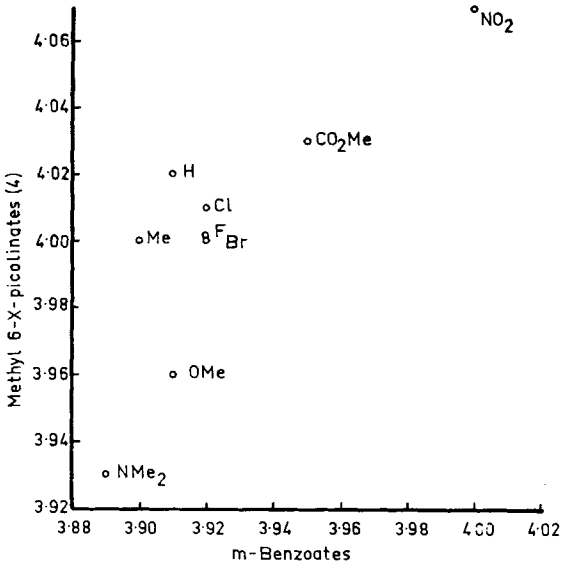


FIG. 6. *meta* Ester proton chemical shifts (δ).

A clear idea of the uniqueness of series **4** can be gained by applying the dual parameter Hammett Eqn.[22] (1) to the data

$$\delta - \delta_0 = \rho_I\sigma_I + \rho_R\sigma_R \qquad (1)$$

and comparing $\lambda(= \rho_R/\rho_I)$ values, i.e. the relative susceptibilities to inductive and resonance effects of the substituents, for some of the series. The correlations are not particularly good (SD/RMS = 0·23 to 0·34), but from values of λ = 0·85 (*m*-benzoates), 0·90 (**6**), 0·91 (**3**), 0·84 (**2**) and 4·00 (**4**), it is evident that series **4** stands alone in the '*meta*' series with respect to the importance of substituent resonance effects.

Thus, there is now a growing body of reactivity and spectral† evidence for a special transmission of substituent effects across the ring nitrogen in 2-substituted pyridines.

† We also have IR data on these esters, in which the same anomalies are apparent.

The details are not entirely clear and further investigations of these effects in related heterocycles will doubtless prove of interest.

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