94. *Heterocyclic Polyfluoro-compounds. Part V.*[1] *High-resolution Nuclear Magnetic Resonance Spectra of Pentafluoropyridine and its Derivatives.*

By J. Lee and K. G. Orrell.

The nuclear magnetic resonance spectra of pentafluoropyridine and a number of its derivatives have been obtained at 60 Mc./sec. and at ambient temperatures. Chemical shifts and coupling constants have been derived, and some empirical correlations are presented.

Whereas a considerable amount of nuclear magnetic resonance spectral data has been accumulated for pyridine [2] and its derivatives,[3] there is no previous record of corresponding work for pentafluoropyridine and derived polyfluoropyridines. Unquestionably, this contrast is to be associated with the comparative unavailability of the latter compounds. The spectral parameters (internal chemical shifts and spin coupling constants) of pyridine were first derived [2] from a 40 Mc./sec. spectrum. Analysis was complicated by small internal chemical shifts (particularly β–γ) in comparison with coupling constants (particulary *ortho*); the use of deuterated derivatives was required to perform the analysis. Similar complications exist in substituted pyridines,[3-5] even at higher radiofrequencies such as 60 or 100 Mc./sec., or under double-irradiation conditions. In contrast, internal chemical shifts in perfluoro-analogues are large compared with coupling constants, and thus spectral analysis is comparatively straightforward. The only remaining complication is the existence of magnetic inequivalence,[6] in pentafluoropyridine and in 4-substituted 2,3,5,6-tetrafluoropyridines, at the 2,6 and at the 3,5 ring sites.

Experimental and Results

With the exception of the three perfluoro(methylpyridines), the preparation of the materials used in the present investigation has been described; [1]* the synthesis of the exceptions will be described in a later Paper in this series.[7]* Liquids were studied as such; solids were examined in appropriate solvents (as detailed below). Trifluoroacetic acid was used as external reference (except where used as solvent, in which case it also acted as internal reference); no correction was applied for differences in bulk diamagnetic susceptibility, it being assumed that such a correction would not be very significant, and in any case reasonably constant for the series of compounds studied.† Both ^1H and ^{19}F spectra were obtained at ambient temperature and 60 Mc./sec., using an Associated Electrical Industries Ltd. model R.S. 2 spectrometer. Calibration was accomplished by a multiple audio-sideband technique.

Pentafluoropyridine.—In the ^{19}F spectrum (Fig. 1) the absorption consists of three distinct band systems centred at 11·77, 57·5, and 86·0 p.p.m. to high field of trifluoroacetic acid; integrated intensities indicate assignment to 2, 1, and 2 fluorine nuclei per molecule, respectively. The lowest-intensity system is clearly to be associated with ring position 4. The low-field absorption is assigned to the 2,6-positions on the grounds of (a) an expectation that proximity to the electronegative nitrogen atom would reduce shielding, and (b) a broadness of component bands to be expected from proximity to a nitrogen quadrupolar nucleus. Fine structure due to spin–spin interaction is quite symmetrical for the highest and intermediate field systems; an

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* Grateful acknowledgment is made to the authors of these Papers for the provision of samples.

† From subsequent susceptibility measurements, the correction appears less than 0·3 p.p.m. This may be compared with the pair acetic acid–pyridine, where the susceptibility correction is 0·15 p.p.m. On the basis of a known interaction shift between chloroform and aromatic systems (Zimmermann and Foster, *J. Phys. Chem.*, 1957, **61**, 282) the adoption of $CFCl_3$ as a reference solvent in the present study seems inadvisable.

[1] Part IV, Banks, Burgess, Cheng, and Haszeldine, preceding Paper.

[2] Schneider, Bernstein, and Pople, *Canad. J. Chem.*, 1957, **35**, 1487.

[3] Brugel, *Z. Elektrochem.*, 1962, **2**, 159.

[4] Kowalewski and Kowalewski, *J. Chem. Phys.*, 1962, **36**, 266; **37**, 2603.

[5] Lee and Orrell, unpublished results.

[6] McConnell, McLean, and Reilly, *J. Chem. Phys.*, 1955, **23**, 1152.

[7] Banks, Burgess, Haszeldine, and Young, unpublished results.

apparent asymmetry in the low-field absorption is ascribed to an unidentified impurity, as is also a weak band at 44·3 p.p.m. (relative to $CF_3\cdot CO_2H$).

Since the spin–spin splitting is small in comparison with the internal chemical shifts, analysis was made on the basis of an AA′XX′P spin-$\frac{1}{2}$ system. The construction of the nuclear spin Hamiltonian matrix, the determination of eigenvalues and eigenvectors, and the subsequent expression of transition energies and intensities in terms of chemical shifts and coupling constants follows the normal pattern.[8] The spectrum can easily be derived from the predictions for an AA′XX′ (or, as it was formerly designated, as A_2X_2) system.[9,10] The following modifications are necessary: (a) each band in the A(X) absorption is split into two by an amount $J_{AP}(J_{PX})$; (b) a first-order P spectrum, *i.e.*, a triplet of triplets with spacings J_{AP}, J_{PX}, is added. The predictions for the A(X) absorption may be summarised as follows: a symmetrical system of four bands of equal intensity; two symmetrical systems each of eight bands, with the central four having greater intensity than the others; the total intensity in each eight-membered system is half of that in the four-membered system. In the present analysis, the 2,6-fluorines are arbitrarily designated X, X′. The 4-absorption (P) is clearly a triplet of triplets, as expected. The 3,5- or A-system appears much simpler than expectation. This is attributed to two factors,

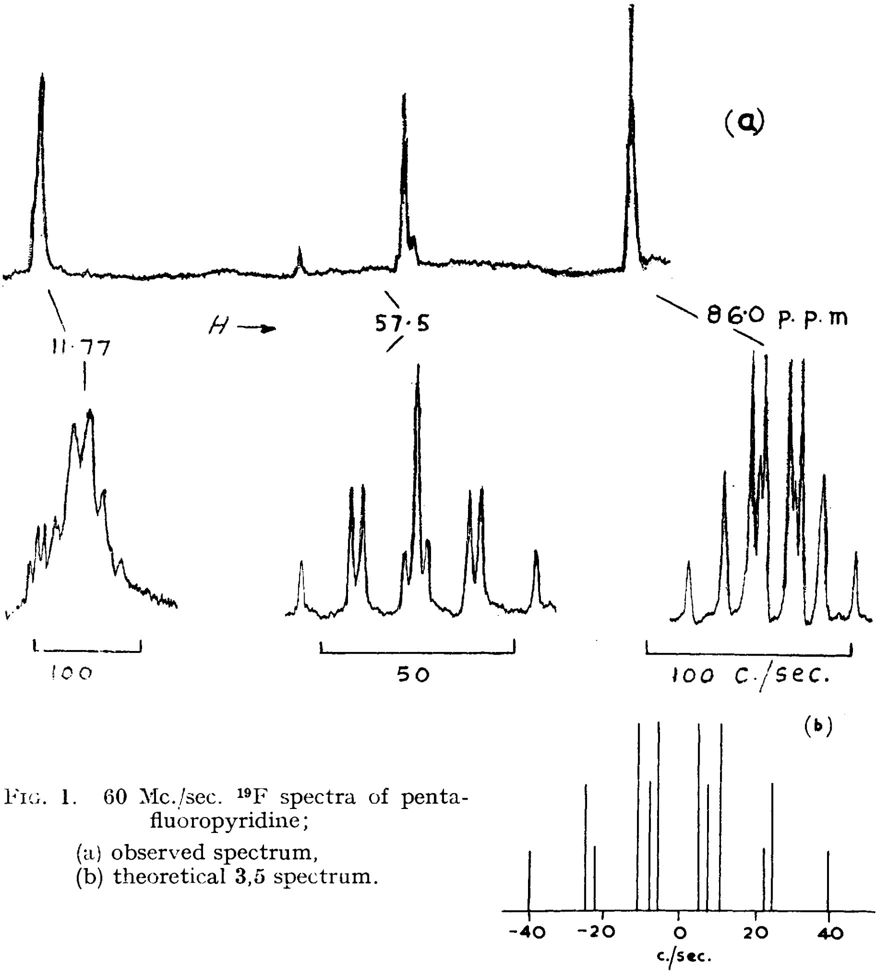

FIG. 1. 60 Mc./sec. ^{19}F spectra of pentafluoropyridine;
(a) observed spectrum,
(b) theoretical 3,5 spectrum.

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[8] Pople, Schneider, and Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, 1959, ch. 6.

[9] McConnell, McLean, and Reilly, *J. Chem. Phys.*, 1956, **24**, 479.

[10] Pople, Schneider, and Bernstein, *Canad. J. Chem.*, 1957, **35**, 1060.

(a) a near zero value for either $J_{AA'}$ or $J_{XX'}$, thus coalescing the two eight-band systems into one, (b) a near equality of $|J_{AP}|$ and the " non-zero " $|J_{AA'}|$ or $|J_{XX'}|$, and therefore yielding essentially (i) the four-band system comprising the four most, and equally, intense bands of the absorption, plus (ii) a six-band remainder of somewhat broader members. For a reason which will emerge later, $J_{AA'}$ rather than $J_{XX'}$ was taken as near zero. A coupling-constant analysis was made on the basis of the A and P absorptions; the broader 2,6- or X-absorption, partially obscured by impurity bands, was used only in confirmation. The results of the analysis are as follows: $|J_{35}| < 1{\cdot}0$; $|J_{26}| = 15{\cdot}6$; $|J_{24}| = 13{\cdot}9$; $|J_{34}| = 17{\cdot}0$; $|J_{23} + J_{25}| = 5{\cdot}7$; $|J_{23} - J_{25}| = 45{\cdot}2$ c./sec. Experimental facilities, involving homonuclear double resonance or a supplementary electric field,[11] were not available for determination of relative or absolute signs. However, from the last two results, one derives $J_{23}, J_{25} = \pm 25{\cdot}5, \pm 19{\cdot}8$ c./sec. The implication here is that, although there is ambiguity in the association of the numerical values with the two constants, there is the clear indication that J_{23} and J_{25} are of opposite sign. The calculated spectrum is included in Fig. 1.

2,3,5,6-*Tetrafluoropyridine*.—The ^{1}H and ^{19}F spectra are shown in Fig. 2. The former is virtually a 1 : 4 : 6 : 4 : 1 quintet, whereas the latter comprises two equally intense absorption regions at 15·61 and 64·1 p.p.m. to high field of trifluoroacetic acid. The lower-field system is broad and structureless, and, for the same reasons as in pentafluoropyridine, was assigned to the 2,6-fluorines. The higher-field absorption has a complex, but symmetrical, fine structure. Again the analysis was made on the basis of an AA′XX′P spin system, this time the P nucleus being ^{1}H, but as before the 2,6-fluorines were designated X, X′. Unlike pentafluoropyridine, the two eight-band systems of the A absorption are distinct; the four-band system comprises the four central and most intense bands, and the remainder is essentially eight close doublets, one member from each eight-band system. The pattern in the ^{1}H spectrum arises from a near equality of $|J_{34}|$ and $|J_{24}|$. The results of the spectral analysis are as follows: $|J_{35} + J_{26}|$, $|J_{35} - J_{26}| = 14{\cdot}6,\ 11{\cdot}9$; $|J_{34}| = 7{\cdot}9$; $|J_{24}| = 7{\cdot}0$; $|J_{23} + J_{25}| = 9{\cdot}4$; $|J_{23} - J_{25}| = 51{\cdot}2$ c./sec. On further manipulation, these results give: $|J_{35}|, |J_{26}| = 13{\cdot}3,\ 1{\cdot}4$; $J_{23}, J_{25} = \pm 30{\cdot}3, \mp 20{\cdot}9$ c./sec. As in the previous analysis, the coupling constants J_{23} and J_{25} take opposite signs. For a reason which will emerge later, $|J_{35}|$ was taken as 1·4 and $|J_{26}|$ as

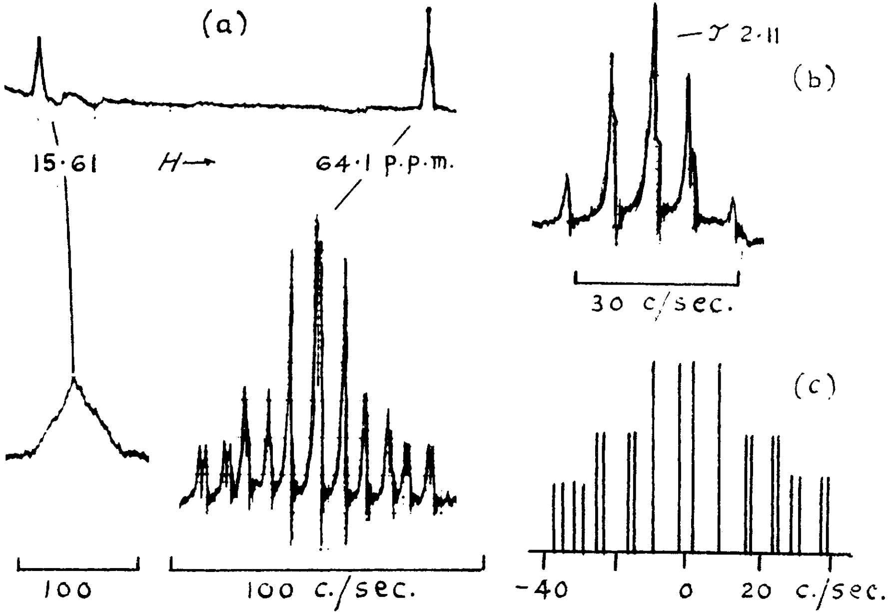

FIG. 2. 60 Mc./sec. spectra of 2,3,5,6-tetrafluoropyridine; (a) observed ^{19}F spectrum, (b) observed ^{1}H spectrum, (c) theoretical 3,5-F spectrum.

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[11] Buckingham and Pople, *Trans. Faraday Soc.*, 1963, **59**, 2421.

13·3 c./sec. rather than the reverse. The calculated A spectrum is included for comparison in Fig. 2.

Perfluoromonomethylpyridines.—(a) *Perfluoro-*(2-*methylpyridine*). The ^{19}F spectrum (Fig. 3) consists of five systems with chemical shifts as shown. The lowest-field system was assigned, on the basis of its intensity, to the side-chain. The absorption at a chemical shift of 5·7 p.p.m. was associated with the ring position 6, because of the comparative broadness of component bands and because of the low-field nature of the system. The three remaining systems were associated with the chemically distinct 3, 4, and 5 fluorines. The five systems were sufficiently separated to permit a first-order analysis; this is in marked contrast to the hydrogen analogue α-picoline,[3] where higher-order perturbations are clearly evident. The coupling constants are present in Table 2. Decision was reached regarding assignment of the three high-field systems on the basis of (a) the axiomatic assumption of highest ring–side-chain coupling from the 3-position, (b) a comparison of chemical shifts with those in pentafluoropyridine. The systems,

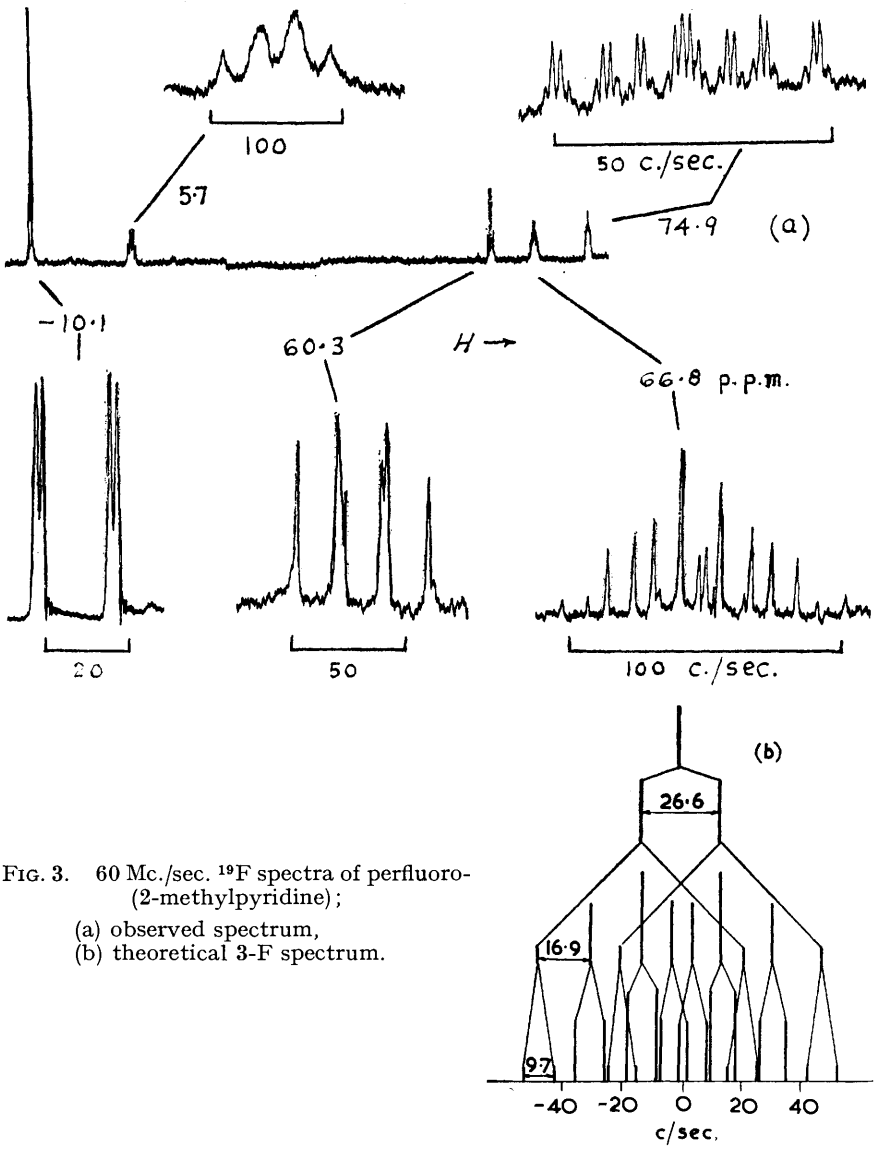

FIG. 3. 60 Mc./sec. ^{19}F spectra of perfluoro-(2-methylpyridine);
(a) observed spectrum,
(b) theoretical 3-F spectrum.

in order of increasing applied field, were then associated with ring positions 4, 3, and 5; the full chemical shift assignment is presented in Table 1 which is a compilation of chemical shifts for all the compounds of the present investigation. The complex fine structure of the band at 66·8 p.p.m. to high field of trifluoroacetic acid was analysed as an overlapping doublet of quintets of doublets; the first-order splitting diagram is included in Fig. 3; the quintet splitting is due to near equality of J_{34} and $J_{3,\mathrm{CF_3}}$.

(b) *Perfluoro-*(3-*methylpyridine*). The complete spectrum of this compound, together with enlargements showing the fine structures, is shown in Fig. 4; chemical shifts are shown in the Figure and in Table 1. Of the five distinct absorption systems, that at lowest field was assigned, on the grounds of its intensity, to the side-group. The low-field absorption systems at −10·86 and 1·38 p.p.m. are associated with the ring positions 2 and 6; unfortunately, fine structure in these systems is obliterated by ^{14}N quadrupolar broadening, as a consequence of which the coupling constant J_{26} became indeterminate. On the basis of CF_3 being a strong electron-attracting group, the absorption at −10·86 p.p.m. is assigned to 2-F, this supposedly having a lower electron density than 6-F. Analysis of the spectrum proceeded on a first-order basis.

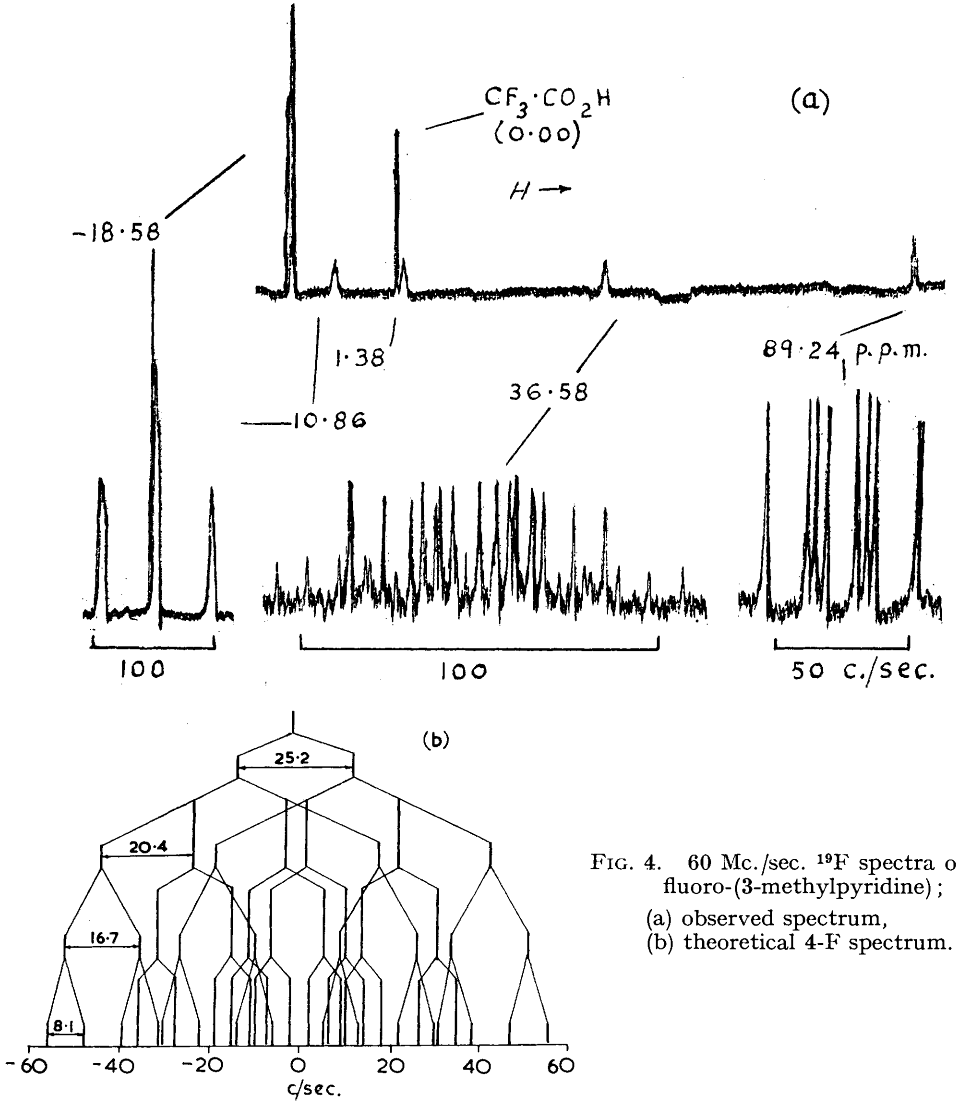

FIG. 4. 60 Mc./sec. ^{19}F spectra of perfluoro-(3-methylpyridine);

(a) observed spectrum,

(b) theoretical 4-F spectrum.

The triplet nature of the CF_3 absorption is attributed to an approximate equality of couplings to the ring positions 2 and 4. The complex structure in the band at 36·58 p.p.m. was analysed as an overlapping doublet of quartets of doublets of doublets; the first-order splitting diagram is shown in Fig. 4. On the expectation of a larger coupling from the side-chain to 4-F rather than 5-F, the system just described was assigned to the 4-position, leaving the absorption at highest field to be associated with 5-F; the fine structure here is simply a doublet of doublets of doublets.

(c) *Perfluoro-(4-methylpyridine).* The ^{19}F spectrum (Fig. 5) consists of three well-separated systems at −17·99, 11·88, and 65·6 p.p.m. to high field of trifluoroacetic acid. The spectrum has been analysed on the basis of an $AA'XX'P_3$ spin system. The lowest-field region is associated with the side-chain (P_3) fluorines and consists of a 1 : 2 : 1 triplet of spacing 20·9 c./sec. This is ascribed to a coupling to the 3,5 ring fluorines, remarkably large for a coupling through four chemical bonds. The highest-field absorption, associated with the 3,5-(A) fluorines is complicated by the large coupling to the side-chain, but the pattern is essentially that of an AA′XX′ system, with each band split into a 1 : 3 : 3 : 1 quartet with spacing J_{AP}. The calculated A spectrum (with and without AP splitting) is included in Fig. 5. The absorption at 11·88 p.p.m., ascribed to the 2,6-(X) fluorines, exhibited the usual broadening.

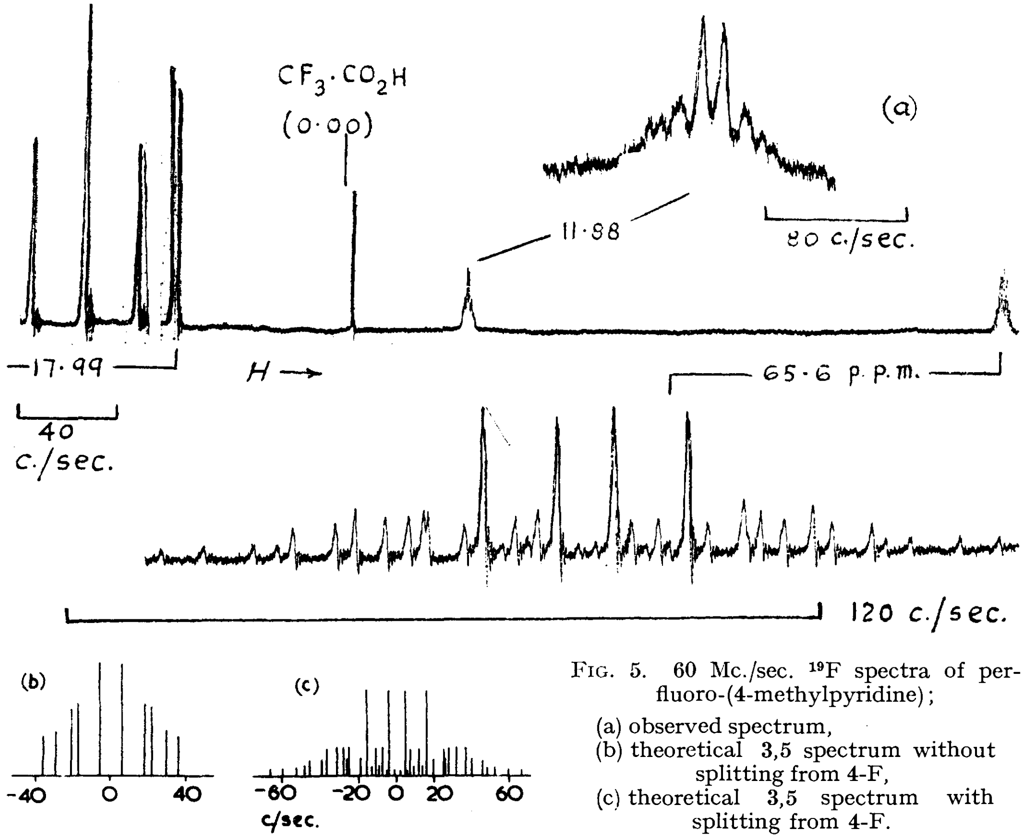

FIG. 5. 60 Mc./sec. ^{19}F spectra of perfluoro-(4-methylpyridine);
(a) observed spectrum,
(b) theoretical 3,5 spectrum without splitting from 4-F,
(c) theoretical 3,5 spectrum with splitting from 4-F.

Other 4-*Substituted* 2,3,5,6-*Tetrafluoropyridines.*—In addition to pentafluoropyridine and perfluoro-(4-methylpyridine), seven other 4-substituted 2,3,5,6-tetrafluoropyridines were examined. In all cases, the 2,3,5,6-fluorines could be treated as an AA′XX′ system or subsystem. When magnetic nuclei (of spin $\frac{1}{2}$) were present in the substituent group, these nuclei were either not fluorine or had a very different chemical shift from the ring nuclei. As a consequence of this, the spectra were " modified " AA′XX′ in type, *i.e.*, with the same kind of modifications mentioned previously on passing from AA′XX′ to AA′XX′P, but with the added complication that the additional sub-system may be more than a single nucleus. The extracted parameters for the various compounds studied are listed in Tables 1 and 2. In all cases, it was assumed that the 2,6-absorption occurred at lower field than that associated with the 3,5 ring positions; this was always confirmed by a quadrupolar broadening of the former, due to incompletely collapsed coupling to the ^{14}N nucleus. It was also assumed that $J_{26} > J_{35}$; the basis of this assumption will be presented later. Detailed description of spectra will not be given, but some of the salient features are summarised below.

TABLE 1.

^{19}F chemical shifts (in p.p.m.) to high field of $CF_3{\cdot}CO_2H$.[a]

	Compound	Ring position				
		2	3	4	5	6
1.	Pentafluoropyridine	11·77	86·0	57·5	86·0	11·77
2.	2,3,5,6-Tetrafluoropyridine	15·61	64·1	—	64·1	15·61
3.	Perfluoro-(2-methylpyridine)	—	66·8	60·3	74·9	5·7
4.	Perfluoro-(3-methylpyridine)	−10·86	—	36·6	89·2	1·38
5.	Perfluoro-(4-methylpyridine)	11·88	65·6	—	65·6	11·88
6.	4-Hydrazino-2,3,5,6-tetrafluoropyridine[b]	19·0	86·1	—	86·1	19·0
7.	4-Dimethylamino-2,3,5,6-tetrafluoropyridine	18·42	80·7	—	80·7	18·42
8.	2,3,5,6-Tetrafluoro-4-methoxypyridine	16·0	84·2	—	84·2	16·0
9.	2,3,5,6-Tetrafluoro-4-hydroxypyridine[c]	17·0	86·1	—	86·1	17·0
10.	2,3,5,6-Tetrafluoro-4-propenylpyridine[g]	15·76	65·1	—	65·1	15·76
11.	,, ,, ,, [h]	7·03	69·7	—	69·7	7·03
12.	2,3,5,6-Tetrafluoropyridine-4-carboxylic acid[d]	13·06	63·3	—	63·3	13·06
13.	4-Amino-2,3,5,6-tetrafluoropyridine[e]	22·8	90·0	—	90·0	22·8
14.	3,5,6-Trifluoro-2,4-dimethoxypyridine	—	91·6	—	84·6	17·9
15.	3,5-Difluoro-2,4,6-trimethoxypyridine	—	90·5	—	90·5	—
16.	3,5,6-Trifluoro-2,4-dihydroxypyridine[c]	—	95·4	—	87·4	18·4
17.	3,5,6-Trifluoro-2,4-dipropenylpyridine[i]	—	48·6	—	61·5	11·55
18.	,, ,, ,, [j]	—	53·1	—	62·2	11·75
19.	,, ,, ,, [k]	—	52·2	—	66·7	12·40
20.	2,4-Bisdimethylamino-3,5,6-trifluoropyridine[f]	—	67·5	—	86·8	15·2
				CF$_3$ side chain		
3.	Perfluoro-(2-methylpyridine)			−10·1		
4.	Perfluoro-(3-methylpyridine)			−18·58		
5.	Perfluoro-(4-methylpyridine)			−17·99		

a, External except where used as solvent; *b*, 20% w/v in dimethylformamide; *c*, 20% w/v in water; *d*, 20% w/v in $CF_3{\cdot}CO_2H$; *e*, in $CF_3{\cdot}CO_2H$; *f*, in carbon tetrachloride; *g*, more abundant isomer; *h*, less abundant isomer; *i*, most abundant isomer; *j*, isomer of intermediate abundance; *k*, least abundant isomer.

TABLE 2.

Moduli of spin–spin coupling constants (c./sec.).

Compound no.*	Ring fluorine–fluorine										Others †
	$\|J_{23}\|$	$\|J_{24}\|$	$\|J_{25}\|$	$\|J_{26}\|$	$\|J_{34}\|$	$\|J_{35}\|$	$\|J_{36}\|$	$\|J_{45}\|$	$\|J_{46}\|$	$\|J_{56}\|$	
1	19·8	13·9	25·4	15·6	16·9	1	25·4	16·9	13·9	19·8	
2	21·0	—	30·4	13·3	—	1·4	30·4	—	—	21·0	$\|J_{24}\| = 7{\cdot}0$ $\|J_{34}\| = 7{\cdot}8$
3	—	—	—	—	16·8	9·7	26·6	16·2	18·2	22·7	$\|J_{23}\| = 17{\cdot}0$ $\|J_{25}\| = 1{\cdot}6$
4	—	8·1	24·3	?	—	—	—	16·7	25·2	20·3	$\|J_{23}\| = \|J_{34}\| = 20{\cdot}4$ $\|J_{36}\| = 1{\cdot}1$
5	19·9	—	31·9	15·5	—	9·6	31·9	—	—	19·9	$\|J_{34}\| = 20{\cdot}9$
7	22·1	—	22·1	15·5	—	9·6	22·1	—	—	22·1	$\|J_{34}\| = 3{\cdot}4$
8	20·0	—	22·6	15·5	—	4·7	22·6	—	—	20·0	$\|J_{34}\| = 2{\cdot}7$
9	20·6	—	22·2	15·5	—	7·9	22·2	—	—	20·6	
10	20·9	—	29·5	14·4	—	1	29·5	—	—	20·9	
12	19·2	—	31·2	13·4	—	4·1	31·2	—	—	19·2	
14	—	—	—	—	—	1	25·5	—	—	22·4	$\|J_{34}\| = \|J_{45}\| = 2{\cdot}2$
15	—	—	—	—	—	?	—	—	—	—	$\|J_{34}\| = \|J_{45}\| = 2{\cdot}2$
16	—	—	—	—	—	2·5	24·4	—	—	24·4	
17	—	—	—	—	—	1	30·2	—	—	27·8	
18	—	—	—	—	—	1	29·9	—	—	27·2	
19	—	—	—	—	—	1	30·8	—	—	28·1	
20	—	—	—	—	—	1	25·6	—	—	25·6	$\|J_{34}\| = \|J_{45}\| = 2{\cdot}7$ $\|J_{23}\| = 2{\cdot}4$

* See Table 1 for key to compounds. † When distinguished from zero.

(a) 4-*Hydrazino*-2,3,5,6-*tetrafluoropyridine* (20% w/v *in dimethylformamide*). The ^{19}F spectrum was identified as AA′XX′, no coupling being observed between the ring and the side-chain ^{1}H (or ^{14}N) nuclei. Spectral intensity was inadequate for extraction of ring coupling constants.

(b) 4-*Dimethylamino*-2,3,5,6-*tetrafluoropyridine*. The ^{19}F spectrum was analysed on the basis of an AA′XX′P_6 spin system, P_6 symbolising the six equivalent hydrogen nuclei in the methyl groups. In the A (3,5) absorption, the pattern was essentially that expected in an AA′XX′ system in which each band is split into a septet by interaction with the P_6 group.

(c) 2,3,5,6-*Tetrafluoro*-4-*methoxypyridine*. The ^{19}F spectrum was treated as the AA′XX′ part of an AA′XX′P_3 total absorption, the three equivalent hydrogens of the side-chain comprising the remainder of the spin system. Each band of the A (3,5) spectrum, as expected from AA′XX′, was further split into a 1 : 3 : 3 : 1 quartet.

(d) 2,3,5,6-*Tetrafluoro*-4-*hydroxypyridine* (20% w/v *in water*). The ^{19}F spectrum in this case was a straightforward AA′XX′ pattern with no apparent coupling to the ^{1}H of OH. The ^{1}H spectrum comprised a single band, to be associated mainly with the solvent. The apparent absence of ring–side-chain coupling is undoubtedly to be associated with short residence of the side-chain hydrogen on any single molecule. Exchange could either be intermolecular (probably involving the water solvent) or intramolecular between oxygen and nitrogen attachment; in other words, there may be hydroxypyridine (pyridinol)–pyridone tautomeric interconversion. The ring fluorines in both tautomers would constitute AA′XX′ systems, so that in the situation of rapid interconversion the spectrum would comprise a single AA′XX′ pattern. Evidence against the presence of an appreciable proportion of pyridone is a similarity in the ring chemical shifts and coupling constants between this compound and 2,3,5,6-tetrafluoro-4-methoxypyridine. Other spectroscopic evidence [1] supports this postulate.

(e) 2,3,5,6-*Tetrafluoro*-4-*propenylpyridine*. The ^{19}F spectrum comprised two AA′XX′ systems with intensity ratio of *ca.* 4 : 1. This is ssociated with two geometrical isomers in the liquid (tetrafluoropyridyl *cis* or *trans* to methyl). In each case the A (3,5) bands were broader than normal, and this was assumed to be due to unresolved splitting from coupling to side-chain hydrogens. Because of inadequate spectral intensity, coupling constants were not obtained for the isomer of lower abundance.

(f) 2,3,5,6-*Tetrafluoropyridine*-4-*carboxylic acid* (20% w/v *in trifluoroacetic acid*). The ring fluorines in this compound did not exhibit any apparent coupling to the hydrogen of the substituent, presumably for reasons of rapid chemical exchange of the carboxylic hydrogen; the ^{19}F spectrum was representative of an AA′XX′ system. The presence of short-lived zwitterions could not be eliminated on the basis of the observed pattern.

(g) 4-*Amino*-2,3,5,6-*tetrafluoropyridine* (*in trifluoroacetic acid*). The ^{19}F spectrum *† was characteristic of an AA′XX′ system; the ^{1}H spectrum * comprised a single coalesced solvent–solute band. These features are similar to those found in the 4-hydroxy-analogue. In each case (i) solute–solvent exchange is indicated, (ii) the existence of rapid tautomeric interconversion is conceivable and not eliminated by the type of spectrum. A comparison of chemical shifts for the 4-amino- and 4-dimethylamino-compounds seems to indicate a predominance of aromatic tautomer.

2,4-*Di and* 2,4,6-*Tri-substituted Fluoropyridines*.—In 2,4-disubstituted 3,5,6-trifluoropyridines and 2,4,6-trisubstituted 3,5-difluoropyridines, there is no coupling corresponding to $J_{XX'}$ (J_{26}) of pentafluoropyridine and 4-substituted 2,3,5,6-tetrafluoropyridines. There is, however, an analogue of $J_{AA'}$ (J_{35}) in the di- and tri-substituted compounds, and spectral analysis yields in each case a value for the latter parameter of less than 3 c./sec. This provides firm evidence for the association of $J_{AA'}$ in AA′XX′ and AA′XX′P_n systems with the numerically smallest of the two values to be assigned to $J_{AA'}$ and $J_{XX'}$. Further evidence on the same lines is provided by perfluoro-(2-methylpyridine).

For each of the five di- or tri-substituted fluoropyridines, the analysis of the ^{19}F spectra was based on first-order perturbation. The results of analyses are presented in Tables 1 and 2. For the same reasons as previously presented for pentafluoropyridine and its 4-substituted

* During a period of unavailability of the R.S.2 spectrometer, the ^{1}H spectrum was obtained on a Perkin-Elmer 60 Mc./sec. spectrometer and the ^{19}F spectrum was recorded on a Varian V4300B spectrometer, operating at 40 Mc./sec. For the use of the latter, we are very grateful to Dr. J. K. Becconsall of Imperial Chemical Industries Limited, Blackley.

† Resolution on the Varian spectrometer at the time of use was insufficient for the extraction of adequate values of fluorine–fluorine coupling constants.

derivatives, spectral assignment for the 6-fluorine in 2,4 derivatives was never in question. However, the problem of assigning the appropriate absorption systems to the 3- and 5-positions was less clear-cut. It was based upon the following arguments. The effect of a 4-substituent alone on the 3- and 5-fluorines was evident from a study of 4-substituted derivatives, as previously described. It was then supposed that a further 2-substituent of the same type would give an enhancement of the effect (on the chemical shift) at the 3- rather than at the 5-position, which perhaps ought to show little change. This argument, in its entirety, appeared to operate only for propenyl and dimethylamino-derivatives; with the others, the key feature was the relative invariance of the 5-fluorine shift on introducing the 2-substituent.

(a) 3,5,6-*Trifluoro*-2,4-*dimethoxypyridine.* This compound exhibits two rather unusual features. (i) The ^{19}F spectrum indicates that, whereas the 4-methoxyl group couples quite strongly ($|J| = 2{\cdot}7$ c./sec.) to the 3- and 5-ring fluorines, the 2-methoxyl group shows no detectable coupling to the ring. (ii) In the ^1H spectrum, the 2-methoxyl group absorbs at higher field (τ 6·07) than the 4-methoxyl group (τ 5·77). This is unexpected since the 2-substituent is located closer to the electronegative nitrogen, and one might therefore expect a lower electron-density in this substituent than in that at the 4-position; indeed, this prediction is verified in 2,4-lutidine.[12]

(b) 3,5-*Difluoro*-2,4,6-*trimethoxypyridine.* The two curious features encountered in 3,5,6-trifluoro-2,4-dimethoxypyridine, as described above, are also found in the trimethoxy-compound. The τ values in the ^1H spectrum are: 2,6-methoxyl, τ 6·05; 4-methoxyl, τ 5·84. The ring fluorine shift helped to confirm the 3- and 5-fluorine chemical-shift assignments of 3,5,6-trifluoro-2,4-dimethoxypyridine.

(c) 3,5,6-*Trifluoro*-2,4-*dihydroxypyridine* (20% w/v *in water*). No coupling to the hydrogens of the OH groups has been detected, presumably owing to hydrogen exchange processes. Because of a similarity in chemical shifts and coupling constants between this compound and 3,5,6-trifluoro-2,4-dimethoxypyridine, one is led to believe that pyridone forms are in zero or low abundance, cf. 2,3,5,6-tetrafluoro-4-hydroxypyridine.

(d) 3,5,6-*Trifluoro*-2,4-*dipropenylpyridine.* Four geometrical isomers are possible here. The ^{19}F spectrum clearly indicates the presence of three such isomers in the abundance ratios 13 : 4 : 3, but it was not possible from this evidence to allocate a particular structural formula to particular absorption systems.

(e) 2,4-*Bis*(*dimethylamino*)-3,5,6-*trifluoropyridine* (*in carbon tetrachloride*). The ^{19}F spectrum * comprises three absorption regions. The lowest-field system, associated with the 6-fluorine, is essentially a 1 : 2 : 1 triplet, indicating near equality of coupling to the 3- and 5-positions. Each of the other two systems is a doublet of rather broad bands; the broadness here is ascribed to unresolved multiplet structure. The ^1H spectrum * consists of a triplet ($|J| = 2{\cdot}7$ c./sec.) centred at τ 7·00, and a doublet ($|J| = 2{\cdot}4$ c./sec.) centred at τ 7·08. The coupling is ascribed to *ortho*-fluorine nuclei and thus the lower-field system is associated with the 4-substituent. As in 3,5,6-trifluoro-2,4-dimethoxypyridine, the substituent more remote from the ring nitrogen absorbs at lower field, but in the present case the difference is much less pronounced. In contrast to 3,5,6-trifluoro-2,4-dimethoxypyridine, both side-chains show *ortho*-coupling. The chemical-shift assignment (Table 1) is further supported by the fact that the doublet bands of the intermediate-field system in the ^{19}F spectrum are somewhat broader than those in the high-field system; presumably this is due to the fact that the 3-fluorine is coupling (significantly) to twelve side-chain hydrogens in contrast to six for the 5-fluorine.

DISCUSSION

Chemical Shifts.—In pyridine and its substituted derivatives [2,3] the chemical shifts, in order of increasing field, are 2-H < 4-H < 3-H, with the greater internal shift between the first pair of ring positions. The same situation obtains in corresponding fluorpyridines (Table 1), but, as is normal with ^{19}F in comparison with ^1H, the internal chemical shifts are many times larger. In pyridine, the chemical shift has been directly correlated [13,14] with

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* See footnote on previous page.

[12] Elvidge and Jackman, *J.*, 1961, 859.

[13] Dailey, Gawer, and Neikam, *Discuss. Faraday Soc.*, 1962, **34**, 18.

[14] Gil and Murrell, *Trans. Faraday Soc.*, 1964, **60**, 248.

π-electron density at the carbon atom to which the particular hydrogen is bonded. Corresponding electron-density data for pentafluoropyridine are not available for a similar correlation to be made, although qualitative indications of electron distribution on the basis of a $-$I effect from the nitrogen atom would indicate the same order of electron densities as in pyridine and thus suggest a direct relationship to chemical shifts. However inclusion of electronic effects from the fluorine atoms [15] may produce a modification of π-electron densities. The mesomeric effect will increase the density on all the carbon atoms, but particularly the 3,5-positions which have each two *ortho*- and one *para*-fluorine; the comparative effects on the 2,6- and 4-carbons are less easy to predict, the former having each one *ortho*- and one *para*-fluorine and the latter two *ortho*-fluorines. On the other hand, a negative inductive effect from the fluorines will diminish electron densities, particularly at *ortho*-sites, thus opposing the *ortho*-mesomeric effect; 2,6-carbons, having only one *ortho*-fluorine, may be affected by the inductive effect less than the other positions, these having each two *ortho*-fluorines. If one makes the simplifying assumption that an *ortho*-inductive exactly compensates an *ortho*-mesomeric effect, the predicted electronic effects from the fluorine atoms would increase the π-electron densities of the 2,3,5,6-carbons and leave the 4-carbon essentially unaffected. On this basis, the electron-density order could possibly become 4-C $<$ 2-C $<$ 3-C; indeed, chemical evidence [1] based upon the sites for nucleophilic substitution tends to favour this order. Unfortunately, this could preclude a direct relationship of electron density to nuclear shielding.

Table 1 shows a clear dependence of ring chemical shift upon the nature and position of substituents. In the case of the two propenyl derivatives, there is an appreciable effect from the geometrical isomerism. This latter effect, resulting from an apparently small structural modification, indicates a hazard in making correlations of chemical shifts with electronegativities and other substituent characteristics, especially when the chemical-shift variations are of the same order of magnitude as those changes resulting from geometrical isomerisation.

Despite this reservation, empirical correlations have been sought, particularly for chemical shifts of fluorine nuclei *meta* to the 4-substituent in 4-substituted 2,3,5,6-tetrafluoropyridines. In such compounds, the *para* ring atom is nitrogen so that *para* correlations were out of the question; there was no obvious correlation of group characteristics to *ortho*-shifts, but perhaps this is not surprising since this position will experience a combination of electronic and steric effects from the substituent. An approximate first-order relationship between the *meta*-shift and the Hammett σ_m-constant [16] was found; this is reminiscent of similar relationships for substituted monofluorobenzenes.[17] In the present case, the correlation is with the chemical shift relative to the 2-fluorine in 2,3,5,6-tetrafluoropyridine; Table 3 lists these shifts, δ_m, alongside corresponding σ_m-values, and the same data is presented graphically in Fig. 6. With the three exceptions of the less-abundant

TABLE 3.

Correlation of *meta* chemical shifts of 4-substituted 2,3,5,6-tetrafluoropyridines with Hammett σ_m-constants.

4-Substituent	δ_m [a]	σ_m	4-Substituent	δ_m	σ_m
$CH{:}CH{\cdot}CH_3$ [b]	-8·58	0·141 [d]	OCH_3	0·39	0·115
F	-3·84	0·337	OH	1·39	0·100
CF_3	-3·73	0·415	$N(CH_3)_2$	2·81	-0·211
CO_2H	-2·55	0·355	$NH{\cdot}NH_2$	3·39	-0·020
H	0·00	0·000	NH_2	7·19	-0·161
$CH{:}CH{\cdot}CH_3$ [c]	0·15	0·141 [d]			

a, 2,6-F chemical shift in p.p.m. to high field of 2,3,5,6-tetrafluoropyridine; *b*, more abundant isomer; *c*, less abundant isomer; *d*, value for $CH{:}CHPh$.

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[15] Banks, Cheng, and Haszeldine, unpublished results.

[16] Hammett, " Physical Organic Chemistry," McGraw-Hill, New York, 1940, p. 186.

[17] Gutowsky, McCall, McGarvey, and Meyer, *J. Amer. Chem. Soc.*, 1952, **74**, 4809.

geometrical isomer of 2,3,5,6-tetrafluoro-4-propenylpyridine (omitted from the Figure), 2,3,5,6-tetrafluoropyridine, and 4-dimethylamino-2,3,5,6-tetrafluoropyridine, the points are quite close to the straight line, $\delta_m = -19\sigma_m + 3{\cdot}2$, which is also shown in Fig. 6.

It is of interest to compare the chemical shifts in 4-substituted 2,3,5,6-tetrafluoropyridines with those in pentafluorophenyl derivatives,[18] the substituent being the same in the two cases. While there is no simple linear correlation, Table 4 clearly shows a similarity of trends in *ortho*-shifts; this is not so, however, with the *meta*-shifts.

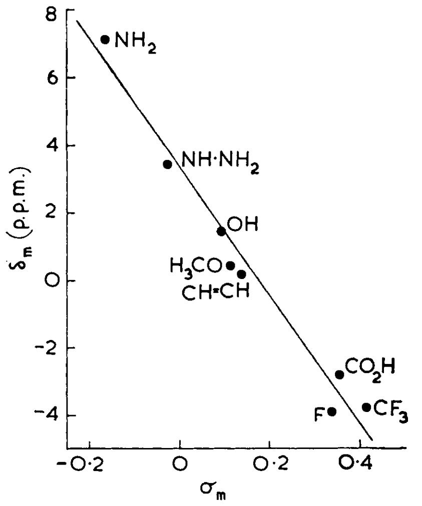

FIG. 6. Plot of δ_m against Hammett σ_m-values for 4-substituted 2,3,5,6-tetrafluoropyridines.

The three perfluoro(methylpyridines) form a series of compounds in which the non-fluorine substituent is the same but the position is variable. The CF_3 chemical shifts, in order of increasing field, are 3-CF_3 < 4-CF_3 < 2-CF_3, which is exactly the reverse of the order for ring fluorines in these positions. The reason for the reversal is not clear; it may have some association with the possibility of a participation of a ring fluorine in the π-electron system, and the absence of a corresponding effect for a fluorine atom of a CF_3 substituent; alternatively or additionally, the CF_3 group may be affected by negative hyperconjugation. The effects of the variably-positioned common group on the ring shifts may be summarised as follows. In all three cases, the substituent displaces the *ortho*-fluorines to low field by

TABLE 4.

Chemical shifts of 4-substituted 2,3,5,6-tetrafluoropyridines and monosubstituted pentafluorobenzenes.[e]

	Pyridine deriv.		Benzene deriv.[18]	
Substituent	δ_0 [a]	δ_m [b]	δ_0 [c]	δ_m [d]
CO_2H	−0·8	−2·55	−0·4	−1·9
H	0·0	0·00	0·0	0·0
$CH{:}CH{\cdot}CH_3$	1·0	0·15	0·7	0·2
	5·6	−0·90	4·8	0·7
OCH_3	20·1	0·39	19·7	1·7
F	21·9	−3·84	25·4	1·2
$NH{\cdot}NH_2$	22·0	3·39	17·8	0·1
OH	22·0	1·39	24·9	2·0

a, 3,5-F chemical shift in p.p.m. to high field of corresponding system in 2,3,5,6-tetrafluoropyridine; *b*, 2,6-F chemical shift in p.p.m. to high field of corresponding system in 2,3,5,6-tetrafluoropyridine; *c*, 2,6-F chemical shift in p.p.m. to high field of corresponding system in pentafluorobenzene; *d*, 3,5-F chemical shift in p.p.m. to high field of corresponding system in pentafluorobenzene; *e*, non-fluorine substituent site designated as 1.

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[18] Mowthorpe, unpublished results.

an almost constant amount of 20 p.p.m. relative to pentafluoropyridine; the *meta*-shifts are much smaller ($<3{\cdot}5$ p.p.m.) and in fact to high field; *para*-fluorine absorptions are displaced to low field by 6—10 p.p.m. Thus, the order of displacement magnitudes is *ortho* > *para* > *meta*; this is also the order of ring–side-chain coupling constants (Table 2). The results indicated here are in harmony with similar conclusions [19] for substituted benzotrifluorides.

F–F *Coupling Constants.*—The moduli of fluorine–fluorine coupling constants for the compounds of the present investigation are collected in Table 2. With certain exceptions, there has been no relative (or absolute) sign determination; the exceptions are $J_{23}(J_{56})$ and $J_{25}(J_{36})$ in AA'XX' systems (and sub-systems), where, in all cases, the coupling constants have been shown as having opposite signs. Furthermore, on the basis of individual spectral analyses of AA'XX' systems (and of larger systems containing AA'XX'), there is ambiguity in the assignments of (a) $J_{AA'}$ and $J_{XX'}$, and of (b) J_{AX} and $J_{AX'}$. For the compounds of this investigation, falling in this category, the two parameters of (a) are of considerably different magnitude, the one being quite near zero in several cases and the other being of the order of 15 c./sec.; by comparison with corresponding couplings determined in systems of lower nuclear spin symmetry, there can be little doubt that the coupling constant of larger magnitude is $J_{XX'}$, *i.e.*, J_{26}. The other ambiguity, under (b) above, is by no means so obvious to resolve. As will be seen from Table 2 under $|J_{23}|$ ($|J_{56}|$) and $|J_{25}|$ ($|J_{36}|$), the magnitudes are quite comparable. In the 2-, 3-, and 2,4-substituted fluoropyridines, these two parameters are unambiguously assigned (assuming unambiguity of chemical-shift assignments). With the two exceptions, 3,5,6-trifluoro-2,4-dihydroxypyridine and 2,4-bisdimethylamino-3,5,6-trifluoropyridine, where J_{36} and J_{56} have virtually equal magnitude, the *para*-coupling constant is a little larger in magnitude than the *ortho*-constant. In the present investigation, it has been supposed that this same inequality is true in the symmetrical systems. Noticeably, *meta*-coupling constants are generally smaller in magnitude than either *ortho*- or *para*-constants.

It will be apparent that certain of the coupling constants are sensitive to ring substitution; this rather contrasts with non-fluorinated pyridines (where the Fermi contact contribution [20] to coupling may be expected to predominate). The ranges of coupling-constant moduli, together with mean values are shown in Table 5. The coupling constants which show the smallest variation, both proportionate and absolute, are (J_{34},J_{45}), J_{26}, and (J_{23},J_{56}); the range of the last couplings appears rather large in Table 5 because of an anomalously large value of J_{56} in 3,5,6-trifluoro-2,4-dipropenylpyridine. The coupling constants which show the greatest variation are particularly those *meta*-interactions across the non-fluorine-substituted carbon. Of the latter couplings, the present investigation has been most concerned with J_{35}, which varies in magnitude from 0 to 10 c./sec. according to the 4-substituent. As yet, it has not been possible to relate the coupling to substituent characteristics such as electronegativities or σ-constants.

TABLE 5.

Range of magnitudes of coupling constants.

Coupling constant	Range of magnitudes (c./sec.)	Mean value (c./sec.)
J_{23},J_{56}	19·8 to 27·8	21
J_{24},J_{46}	8·1 to 25·2	15
J_{25},J_{36}	22·1 to 31·9	26
J_{26}	13·3 to 15·6	14·8
J_{34},J_{45}	16·2 to 16·9	16·7
J_{35}	0 to 9·7	5

The coupling constant, J_{26}, across the heteroatom has an average modulus of 14·8 c./sec. In comparison with non-fluorinated pyridines, where the corresponding coupling is hardly ever detected and always less than 1 c./sec., this seems surprisingly large.

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[19] Richards and Schaefer, *Trans. Faraday Soc.*, 1958, **54**, 1447.

[20] Ramsey, *Phys. Rev.*, 1953, **91**, 303.

^{14}N *Quadrupolar Broadening of* 2,6-*Ring Absorption*.—The ^{14}N quadrupolar broadening found in the absorption due to 2,6-fluorines, varied considerably in the compounds studied. In 2,3,5,6-tetrafluoropyridine, the broadening was so pronounced as almost to mask all signs of multiplet structure, whereas, in contrast, the broadening was only just noticeable in the spectrum of 2,3,5,6-tetrafluoropyridine-4-carboxylic acid. The variation might be associated with a corresponding variation of coupling constants J_{12},J_{16} (but no correlations could be made here), and the existence of isomeric interconversion, where appropriate.

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