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THE NMR SPECTRA OF 4,5,6,7-TETRAFLUOROBENZO[b]-THIOPHEN AND SOME OF ITS DERIVATIVES

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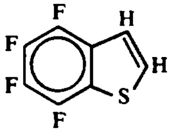
Abstract—The ^1H and ^{19}F spectra of the 5,6,7-, 4,6,7- and 4,5,7-trifluoro- and the 4,5,6,7-tetrafluorobenzo[b]thiophens and of the corresponding 2-carboxylic acids have been analysed. A large *para* FF coupling has been shown to be present in these compounds but additionally a long-range coupling between H_3 and F_7 has been revealed in the 2-carboxylic acids. In the thiophens a long-range H_2–F_7 coupling is present in addition to the long-range H_3–F_7 coupling. The origin of these couplings, together with that of the H_2–F_5 coupling in the 5,6,7-trifluorobenzo[b]thiophen, are discussed.

Using the parameters, established from the analysis of the spectra of these compounds, nucleophilic substitution of the 4,5,6,7-tetrafluorobenzo[b]thiophen has been confirmed to occur in the 6-position.

INTRODUCTION

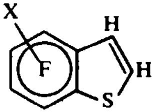
WHILE the ^1H and ^{19}F spectra usually permit unambiguous assignment of the position of substituents in fluoroaromatics, we have recently discussed the difficulties in assigning the position of substitution in 1,2,3,4-tetrafluorodibenzofuran.[1] The difficulty in this instance was due to a *para* FF coupling being of the same order of magnitude as that of the *ortho* FF couplings. We now present a discussion of some similar difficulties associated with the analysis of the spectra of 4,5,6,7,-tetrafluorobenzo[b]thiophen (I) in which there was again a large *para* FF coupling but in addition long-range ^1H–^{19}F coupling was found between H_3, and in some cases H_2, of the heterocyclic ring and F_4 or F_7 of the benzene ring. It was this latter ambiguity which presented the greatest difficulty since, by analogy to related systems, both modes of coupling receive equal support. The problem was resolved by the investigation of the spectra of compounds prepared by unambiguous synthesis.



I

RESULTS

The chemical shifts and coupling constants of the 5,6,7- and the 4,6,7- and the 4,5,7-trifluoro- and 4,5,6,7-tetrafluorobenzo[b]thiophens and the thiophen-2-carboxylic acids (II and III) are shown in Tables 1 and 2. Consideration of the spectra of these compounds permitted the assignments shown and the basis for making these assignments is discussed below. Nucleophilic substitution was shown, by



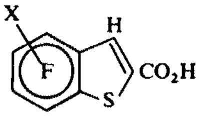
II

TABLE 1. NMR PARAMETERS OF THE POLYFLUOROBENZO[b]THIOPHENS

Substituent at position				Chemical shifts†						Coupling constants (Hz)									
4	5	6	7	H_2	H_3	4	5	6	7	23	25	27	37	45	46	47	56	57	67
F	F	F	F	2·57 τ	2·61 τ	145·18	160·18	160·19	141·66	0·0	0·0	0·95	2·8	20·6	1·25	16·2	19·1	0·33	19·1
H	F	F	F	2·58 τ	2·82 τ	2·70 τ	137·15	164·29	136·3	5·55	0·75	0·7	3·4	8·8	6·05	1·7	18·9	4·7	19·4
F	H	F	F	2·68 τ	2·68 τ	120·37	3·12 τ	140·00	145·3	0·0	0·0	1·9	1·9	8·7	1·55	18·2	10·2	5·75	20·0
F	F	H	F	2·58 τ	2·61 τ	148·78	140·36	3·13 τ	117·40	0·0	0·0	1·45	2·75	19·15	5·45	18·85	10·3	1·45	8·85
F	F	—OMe	F	2·64 τ	2·67 τ	146·47	155·52	5·93 τ^a	136·06	0·0	0·0	0·0	4·35	19·0	0·0	14·65	0·75^b	3·2	1·8^b
F	F	—OH	F	2·74 τ	2·74 τ	146·92	160·86	4·52 τ^c	142·73	0·0	0·0	2·1	2·1	19·2	0·0	16·3	0·0	4·8	0·0
F	F	—NHNH$_2$	F	2·61 τ	2·61 τ	147·87	155·69	5·6 τ^d	136·20	0·0	0·0	2·2	2·2	19·8	0·0	16·9	0·0	4·55	0·0

† Chemical shifts given as ϕ^* values, unless shown. ^{a} —OMe resonance, ^{b} J_{OMe-F}, ^{c} —OH resonance, ^{d} —NHNH$_2$ resonance.

TABLE 2. NMR PARAMETERS OF THE POLYFLUOROBENZO[b]THIOPHEN-2-CARBOXYLIC ACIDS

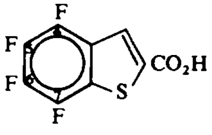


III

Substituent at position				Chemical shifts†						Coupling constants (Hz)						
4	5	6	7	2-CO_2H	H_3	4	5	6	7	37	45	46	47	56	57	67
F	F	F	F	−0·45 τ	2·04 τ	142·77	159·80	156·83	141·68	3·29	18·8	−0·4	16·1^{1}	18·39	0·70	18·68
H	F	F	F	−0·72 τ	1·96 τ	2·35 τ	136·97	161·23	137·35	3·28	10·0	6·55	1·55	19·2	4·62	19·15
F	H	F	F	0·98 τ	2·15 τ	117·38	2·78 τ	136·13	145·75	3·35	9·22	3·23	18·82	10·81	5·58	19·71
F	F	H	F	1·55 τ	1·89 τ	147·01	139·5	2·61 τ	117·0	3·47	19·1	6·2	19·0	10·7	1·99	9·4

† Shifts given in ϕ^* values unless indicated.

complete analysis of the spectra, to occur in the 6-position; this was confirmed chemically since dehydrazination of the hydrazino derivative afforded a trifluoro compound which was identical to the 4,5,7-trifluorobenzo[b]thiophen. The NMR parameters of the 6-methoxy-, 6-hydroxy- and 6-hydrazino-4,5,7-trifluorobenzo[b]-thiophens are included in Table 1. The conclusion that nucleophilic substitution occurred in the 6-position was in agreement with the recent observations of Brooke and Quasem,[2] who based their evidence upon the magnitude of the ^1H–^{19}F couplings found in the ethyl-trifluorobenzene obtained on opening the heterocyclic ring system.



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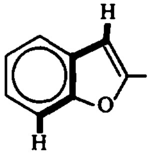

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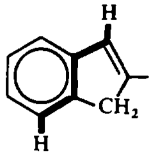

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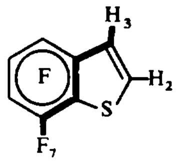
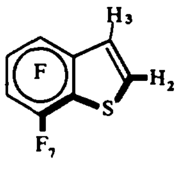
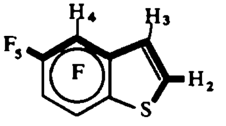


VII



VIII



IX

DISCUSSION

Inspection of the ^1H and ^{19}F spectrum of the 4,5,6,7-tetrafluorobenzo[b]thiophen-2-carboxylic acid (IV) showed that the olefinic proton coupled (3·3 Hz) to one of the aromatic fluorine atoms. This coupling could arise by interaction of the olefinic proton with the *ortho*-fluorine atom F_4; such coupling is well recognized in fluoroaromatics, e.g. 2·3 Hz for the methyl-*ortho*-fluorine coupling in pentafluorotoluene,[3] and 1·0 Hz for the CH–*ortho*-fluorine coupling in fluorinated benzaldehydes and fluorinated benzylidene rhodanines,[4] the latter having the $>CH{=}CHC_6F_5$ grouping. However, in both benzofuran and indene, long-range coupling was found to occur over five bonds between H_3 and H_7 (V and VI);[5] similar coupling could occur in the benzo[b]thiophen although this was not investigated by these authors. We have examined benzo[b]thiophen in the present work and, because of the near coincidence of the shifts of the two olefinic protons, it was not possible to determine whether the H_3–H_7 coupling was definitely present. However, from the sharpness of the olefinic proton resonance, half-band width 0·5 Hz, it would suggest that the coupling, if present, is very small, but the possibility of H_3–H_7 coupling cannot be neglected in the fluorinated benzo[b]thiophen derivatives.

In the 4,5,6,7-tetrafluorobenzo[b]thiophen it was not possible to assign which of the resonance signals at 141·66 or 145·18 ϕ^*, or in the case of the 2-carboxylic acid which of the signals at 141·68 or 142·77 ϕ^*, should in each instance be assigned to F_4. Although one of the signals in each of these two compounds has the same chemical shift, it is difficult to predict whether the introduction of a carboxylic group in position 2 would have the greatest effect upon the shielding of F_4 or F_7. In order to facilitate the clarification of this point the compounds will be considered individually.

Trifluorobenzo[b]*thiophen-2-carboxylic acids.* Of the four possible isomeric compounds only three have been obtained in the present work; the inability to obtain the 4,5,6-trifluoro derivative is discussed elsewhere.[6] In each of the three isomers the resonance signal of the olefinic proton H_3, which has a chemical shift in the fairly narrow range of 1·89–2·15 τ, is a doublet with J_{HF} = 3·2–3·3 Hz. Since this coupling is present in the 5,6,7-trifluorobenzo[b]thiophen-2-carboxylic acid in which there is no fluorine in position 4, (Figs 1 and 2) and, furthermore, apart from other small couplings which are readily assigned to either *meta* FF couplings or in one instance to the *para* HF coupling the only fluorine signal which reveals a coupling of 3·3 Hz is the latter signal with the small *para* HF coupling, namely that of F_7. It is thus

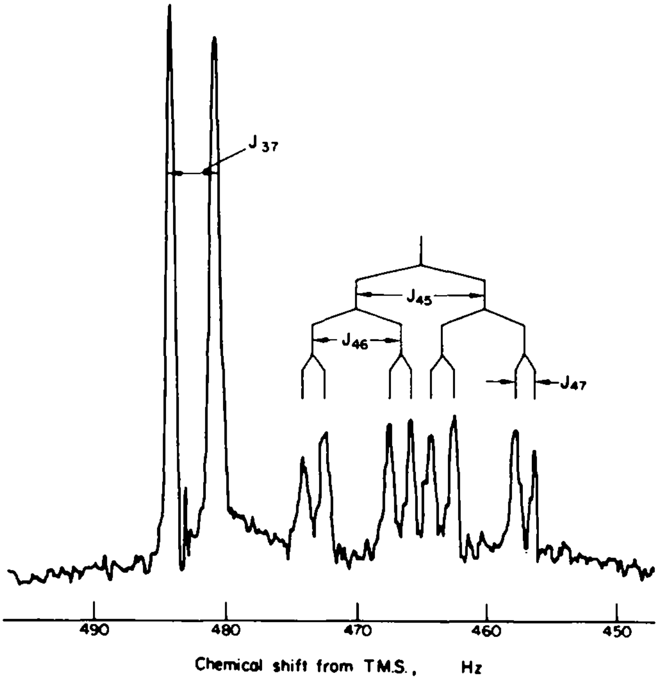


FIG. 1 ^1H Spectrum of 5,6,7-trifluorobenzo[b]thiophen-2-carboxylic acid showing coupling of 3H to 7F.

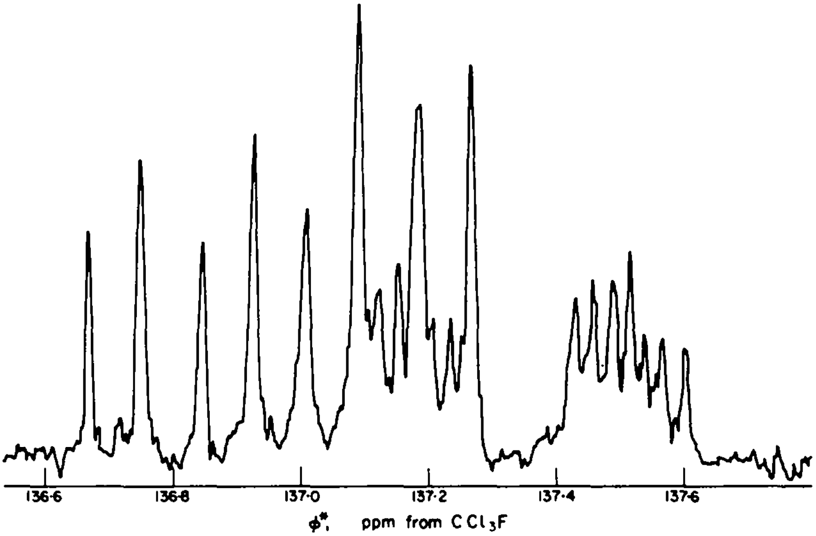


FIG. 2 ^{19}F Resonance signal of 5 and 7F of the 5,6,7-trifluorobenzo[b]thiophen-2-carboxylic acid. The multiplicity of the signal of 7F, the high field component being separated from the signal of 5F, arises from the *para* 4H–7F, the *meta* 5F–7F and the long-range 3H–7F couplings.

evident that these compounds are characterized by the presence of a long-range H_3F_7 coupling similar to that found in benzo[b]furan.[5]

4,5,6,7-*Tetrafluorobenzo*[b]*thiophen-2-carboxylic acid.* Using the criterion of the H_3F_7 coupling it is possible to assign the low field signal of this compound at 141·68 ϕ^*, which shows this coupling to 3·2 Hz, to F_7. The next signal to higher field is assigned to F_4 despite the fact that analysis of this signal shows the presence of two large FF couplings of 18·8 and 16·0 Hz; the latter arises from the *para* F_4F_7, coupling while the former is the *ortho* F_4F_5 coupling. The large *para* FF couplings are found in both the 4,5,7 and 4,6,7-trifluoro derivatives and in each of these cases the F_4F_7 coupling is 19·0 Hz, while the corresponding 5,6,7-trifluoro derivative, in which there can be no *para* FF coupling, shows no abnormally large coupling constants except for those from F_5F_6 and F_6F_7 which are the normal *ortho* FF couplings of 19·2–19·3 Hz. Consequently this is another example of a heteroaromatic system in which there are abnormally large *para* FF couplings. The presence of such couplings, especially being the same order of magnitude as the *ortho* FF couplings could lead to errors in structural assignment being made unless a complete refined analysis had been performed and in the majority of cases would require an unambiguous synthesis of a derivative to be made.[1] For example, in the case of the 4,6,7-trifluorobenzo[b]-thiophen-2-carboxylic acid, the single large coupling in each of the signals of F_4 and F_6 and the two large couplings in the signal of F_7 would at first imply that there is an F_4–F_7–F_6 arrangement round the aromatic ring (the subscript numbers are used here to identify the fluorine atoms and the numbers refer to the correct assignments given in Table 2). The other coupling constants for this arrangement, with the exception of the *para* H_5F_6, would not be unreasonable. The choice therefore could be between an abnormally large FF or HF coupling.

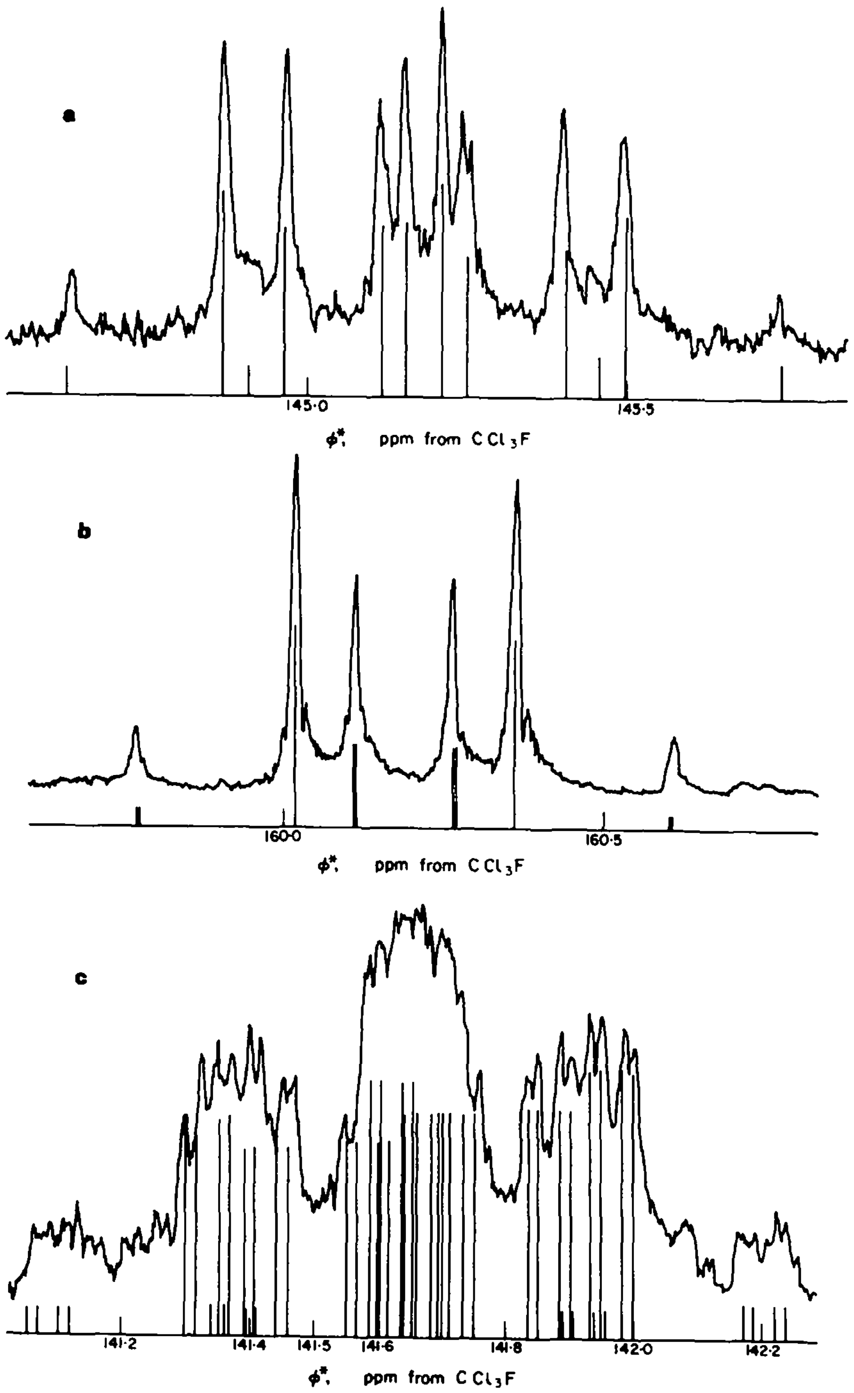


FIG. 3 The ^{19}F resonance signals of 4,5,6,7-tetrafluorobenzo[b]thiophen (a) the 4F signal, (b) the 5 and 6F signals, (c) the 7F signal. Only that of 7F shows the long-range coupling to 2H and 3H. The calculated spectra, for the parameters given in Table 1, are shown under each of the signals.

4,5,6,7-Tetrafluorobenzo[b]*thiophen.* In the thiophens the two protons of the heterocyclic ring usually have nearly coincident chemical shifts and while the 3-hydrogen shows the H_3F_7 coupling of the same order of magnitude as observed in the carboxylic acids, the 2-hydrogen also shows coupling and the splitting from this coupling is also revealed in the signal of F_7 (see later discussion). The resonance signals of F_5 and F_6 are also nearly coincident and the six-spin system was treated as an AB_2CX_2 case, and the experimental and calculated ^{19}F spectra are shown in Fig. 3. It will be observed from Table 1 that the *para* F_4F_7 coupling in this compound is again fairly large, namely 16·2 Hz.

4,5,7- and *4,6,7-Trifluorobenzo*[b]*thiophens.* In both these compounds the H_3F_7 coupling is in the range of 2·2–2·75 Hz. However, the magnitude of the H_2F_7 coupling has also increased considerably (Table 1) and in the 4,6,7-trifluoro isomer is of the same magnitude as that of the H_3F_7 coupling. Because of the coincidence of the shifts of H_2 and H_3 the resonance signal of these two protons appears as essentially a simple doublet (Fig. 4), and the similarity of the H_3F_7 coupling is seen by the triplet appearance in the high field signal of F_7, while the signals from F_4 and F_6 show no small coupling other than that arising from the *meta* F_4F_6 coupling (Fig. 5).

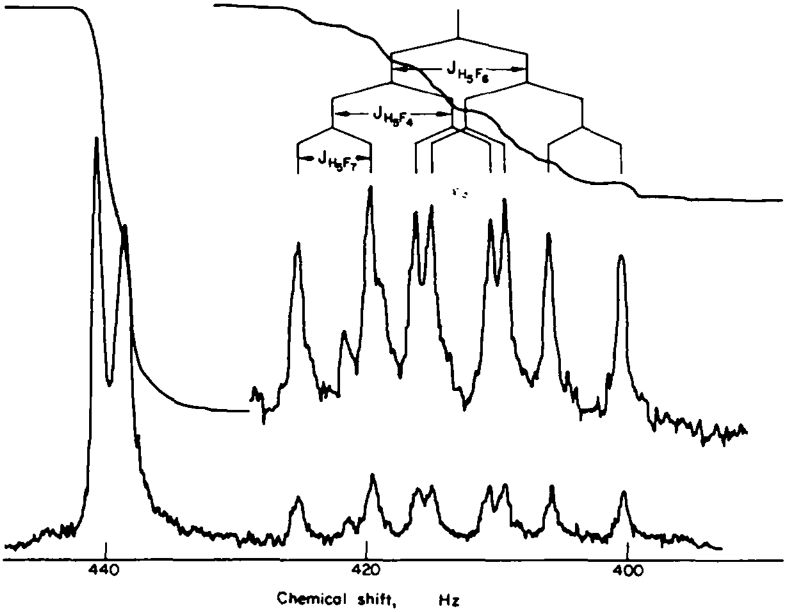


FIG. 4 ^1H Spectrum of 4,6,7-trifluorobenzo[b]thiophen showing the coupling of 2 and 3H to 7F.

In this isomer both F_4 and F_6 resonate at a lower field than F_7 due to the deshielding influence of the hydrogen in position 5. Both the 4,5,7- and 4,6,7-trifluoro isomers show a rather larger *para* F_4F_7 coupling (18·2–18·8 Hz) than was found in the tetrafluoro compound.

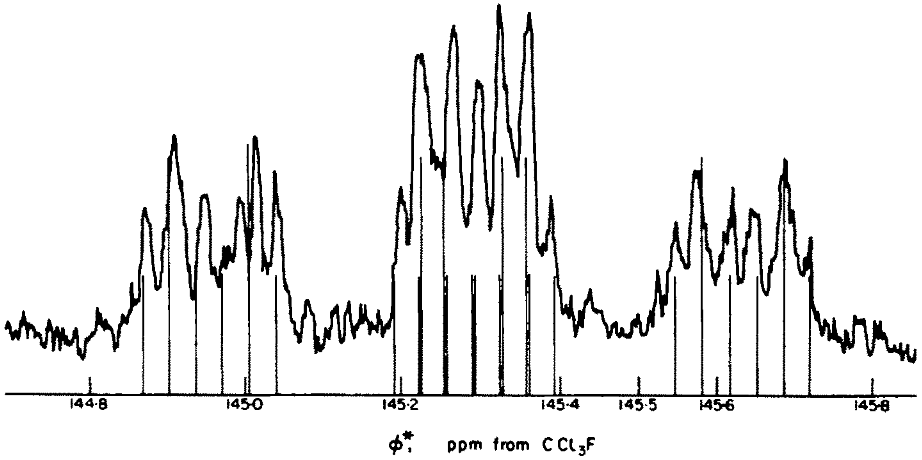


FIG. 5 The ^{19}F resonance signal of 7F of the 4,6,7-trifluorobenzo[b]thiophen showing the near equality of the coupling of 7F to 2H and 3H. The calculated signal of 7F is also shown.

5,6,7-*Trifluorobenzo*[b]*thiophen*. This isomer warrants separate consideration for there are a number of interesting features. Firstly the chemical shifts of H_2 and H_3 are no longer coincident. The two heterocyclic protons at C_2 and C_3 of benzo[b]-thiophen have a coincident chemical shift of 2·94 τ, while in the 4,5,6,7-tetrafluorobenzo[b]thiophen the two proton shifts are also nearly coincident for H_2 is at 2·57 τ

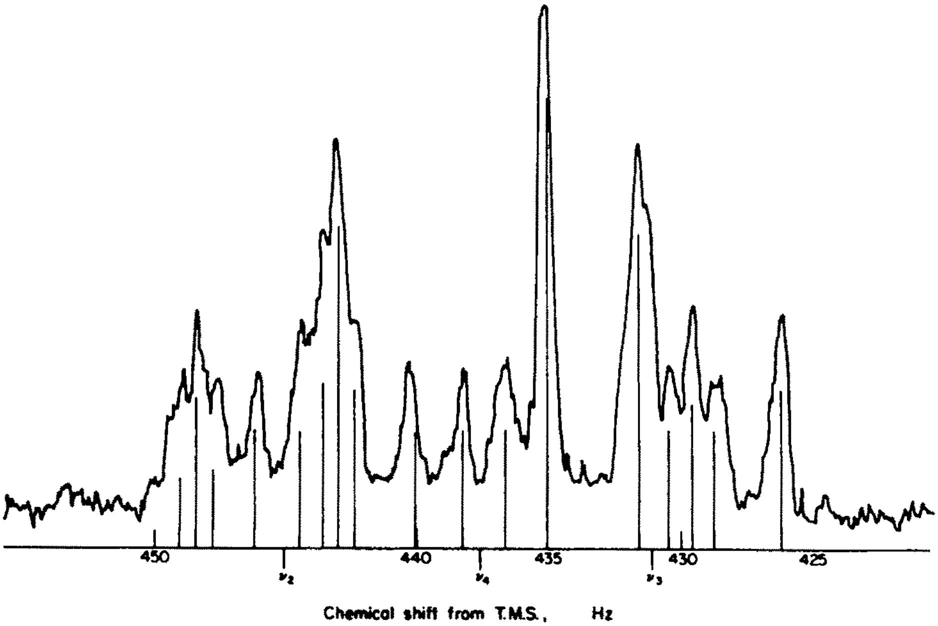


FIG. 6 ^1H spectrum of 5,6,7-trifluorobenzo[b]thiophen showing the coupling of 2H to both 5F and 7F and the coupling of 3H to 7F. The calculated spectrum is shown below that of the experimental spectrum.

and H_3 is at 2·61 τ. It would appear that the sulphur atom of the heterocyclic ring has little shielding effect upon the protons H_2 and H_3 and the chemical shift is predominantly determined by the nature of the substituents on C_4 and C_7. Thus with fluorine atoms at C_4 and C_7 there is a deshielding of the protons H_2 and H_3, and consequently in 5,6,7-trifluorobenzo[b]thiophen H_2 is still deshielded by the fluorine at C_7 while H_3 has a chemical shift nearer to that of the purely hydrocarbon analogue because of the hydrogen on C_4. The spectrum of H_2 and H_3 constitutes as AB part of an ABMX spectrum (Fig. 6), in which the high field component is split by the H_3F_7 coupling and the low field component shows fine structure in part due to the H_2F_7 coupling of 0·7 Hz and to an additional small coupling (0·75 Hz) which is assigned to the H_2F_5 coupling; this latter assignment is based upon the doublet appearance of each of the resonance lines of the signal of F_5. The F_5 and F_7 signals, which have similar chemical shifts, are readily assigned as that of F_5 shows a typical *ortho* HF coupling of 8·8 Hz while that of F_7 shows a typically small *para* HF coupling of 1·7 Hz.

The 6-substituted-4,5,7-*trifluorobenzo*[b]*thiophens*. The 6-methoxy, 6-hydroxy and 6-hydrazino derivatives were prepared by direct nucleophilic substitution of the 4,5,6,7-tetrafluorobenzo[b]thiophen.[6] Prior to the completion of this work on the trifluorobenzo[b]thiophens and the 2-carboxylic acids the position of substitution was uncertain for the reasons already stated. The position of substitution has been confirmed chemically since dehydrazination of the hydrazino derivative afforded the 4,5,7-trifluorobenzo[b]thiophen.[6]

The use of substituent shielding parameters is sometimes helpful in ascertaining the position of the substituent in aromatic ring systems. Using the shielding parameters for the methoxy group of −4·4 (*ortho*), +2·0 (*meta*) and 1·7 (*para*) ppm, the calculated shifts for the ring fluorine atoms in the 4-, 5-, 6- and 7-methoxy-trifluorobenzo derivatives are shown below:

	4-Methoxy	*5-Methoxy*	*6-Methoxy*	*7-Methoxy*
4F	—	140·8	147·2	146·9
5F	155·8	—	155·8	162·2
6F	162·2	155·8	—	155·8
7F	143·4	143·7	137·7	—

Comparison of these figures with those given for the methoxy trifluorobenzo[b]-thiophen in Table 1 shows that there is a good correspondence with the shifts expected for the 6-methoxy compound. It should be emphasized that these figures are dependent upon having the correct chemical shift assignment for F_4 and F_7. If the shifts of these two atoms are reversed then the revised figures would have been consistent with substitution in position 5.

However, in the case of the trifluorobenzo[b]thiophens and the 2-carboxylic acids the calculated shielding constants for the fluorine atoms *meta* to the hydrogen atom are fairly constant being in the range +3·1 to 4·4 ppm. The *ortho* shielding parameters are, however, more variant and are in the range −19·8 to −25·4 ppm. It is clear that an uncertainty of ±3 ppm in the calculated shifts, the results would not be sufficiently reliable to ascertain whether the hydrogen were on C_5 or C_6. The discrepancies found between the calculated and experimentally determined chemical shifts found in the trifluorobenzo[b]thiophens, and also experienced in the study of the 1,2,4-trifluorodibenzofurans,[1] are almost certainly due to changes in the electron density of the hetero-atom as we would expect this change to be reflected on the chemical shifts of the 5- and 6-fluorine atoms since these are *para* to the C—S and C—C bonds respectively. This work therefore affords an excellent example of the caution which must be exercised in using shielding parameters in a too dogmatic manner.

The para F_4F_7 *couplings.* It is now clear that in both the fluorinated naphthalenes and in the benzo-heterocyclic systems the large *para* FF coupling is to be expected. In the 1,2,3,4-tetrafluorodibenzofuran the para F_1F_4 coupling was 15·3 Hz, while in both the 4,5,6,7-tetrafluorobenzo[b]thiophen and the 2-carboxylic acid the *para* F_4F_7 couling is 16 ± 1 Hz. Introduction of a hydrogen atom into the ring causes this coupling to increase, 19·4 Hz in 1,2,4-trifluorodibenzofuran and 18·5 ± 0·5 Hz in the 4,5,7- and 4,6,7-trifluorobenzo[b]thiophens and the 2-carboxylic acids, while the introduction of a methoxy group causes the coupling to decrease, 14·65 Hz in the 6-methoxy 4,5,7-trifluorobenzo[b]thiophen. We have insufficient data at present to be able to explain either the magnitude, or the variability, of this *para* FF coupling, but, from recent studies[7] on the basic strength of fluoroaromatics, the π-orbital overlap of the fluorine atoms with the π-aromatic electron system enhances the electron density of the carbocyclic system, and the extent of orbital overlap from each fluorine atom is dependent upon the nature of the other ring substituents. Consequently with a hydrogen substituent we can consider that the p_π–p_π interaction between the remaining three fluorine atoms will increase, while in the methoxy derivative the p_π–p_π overlap from the oxygen lone-pair into the ring π-electron system correspondingly reduces the p_π–p_π overlap from the fluorine atoms. The magnitude of the *para* FF coupling can be considered to arise because there are two conjugated paths by which electronic interaction could occur, firstly through the normal bond system of the benzo-ring and secondly through the heterocyclic ring system. These suggestions must of necessity be tentative but it is hoped that further examples will become available, which will permit this problem to be elucidated.

The H_2 *and* H_3–F *couplings.* By analogue with the long-range coupling found in indene and in benzo[b]furan[5] the H_3F_7 coupling can be explained by the suitable *trans* arrangement of H_3 and F_7 (VII) for coupling over five bonds. The H_2F_7 coupling was a little more surprising, but again involves coupling over five bonds, and examination of (VIII) shows that there is a *trans* configuration of the C_7—C with the S—C_2 bonds and the coupling probably involves electronic interaction of F_7 (which we have postulated above to undergo p_π–p_π overlap) with H_2 along the *trans* C_7—C—S—C_2 path. The presence of the H_2F_5 coupling in 5,6,7-trifluorobenzol[b] thiophen was even more unexpected, and we must tentatively suggest that the C_5—C_4—C—C_3—C_2 forms essentially a "*trans*" arrangement (IX) and again because of the p_π–p_π overlap from F_5 there is a small coupling between H_2 and F_5 over 6-bonds.

EXPERIMENTAL

The preparation of all the compounds considered has been discussed elsewhere.[6] The ^1H and ^{19}F spectra of the 4,5,6,7-tetrafluoro- and the trifluorobenzo[b]thiophen-2-carboxylic acids were recorded in acetone-d_6 soln while the tetra- and trifluorobenzo[b]thiophens were recorded in CCl_4 soln using

TMS and Cl_3FC as internal standards for the measurement of the ^1H and ^{19}F chemical shifts respectively. A Perkin–Elmer R.10 spectrometer operating at 60 and 56·4 MHz for the ^1H and ^{19}F resonances respectively was used. The spectra were analysed to obtain the refined NMR parameters using LAOCOON II program[8] which had been modified for use on the University KDF 9 computer.

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