Highly Fluorinated Heterocycles. Part V.[1] The Preparation and Some Reactions of Tetrafluorothiophen and Some Polyfluorothiophens

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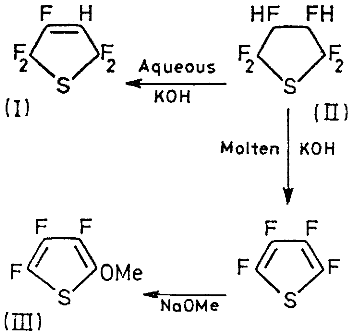
Tetrafluorothiophen has been prepared by dehydrofluorination of 3*H*/4*H*-hexafluorothiolan by molten alkali. It did not react with bromine nor did it polymerise rapidly, unlike tetrafluorofuran. It reacted with sodium methoxide with displacement of the 2-fluorine, as was proved by an independent synthesis of the other possible isomer, 2,3,5-trifluoro-4-methoxythiophen. 2,5-Difluorothiophen and 2,5-difluoro-3-methoxythiophen have also been prepared. The methoxythiophens all polymerised rapidly. In the ^{19}F n.m.r. spectra of the polyfluorothiophens, the α-fluorines resonate to high field of the β; also, the 2—5 F–F couplings are large (26—31 Hz).

We recently published the first full report[2] of a simple, fully fluorinated, five-membered heterocycle, tetrafluorofuran, and of some other polyfluorofurans. This paper presents an account of a second fully fluorinated five-membered heterocycle, tetrafluorothiophen, and of some other polyfluorothiophens; some of the work has been outlined in a communication.[3] There is a patent[4] which briefly describes a different preparation of tetrafluorothiophen but gives no chemical and few physical properties. Our method of preparation is summarised in the scheme. The starting material, 3*H*/4*H*-hexafluorothiolan (II), was prepared[1] by fluorination of thiophen over potassium tetrafluorocobaltate. Dehydrofluorination with aqueous potassium hydroxide gave[1] only the thiolen (I), but with molten potassium hydroxide at *ca.* 250° a low yield (5—10%) tetrafluorothiophen was obtained. It is probable that the main mode of dehydrofluorination, even in the molten hydroxide, is to the thiolen (I); this would certainly be expected on the basis of previous work[5] on polyfluoroalicyclics. This thiolen (I) must then be destroyed by the molten alkali. The minor mode of dehydrofluorination of the thiolan (II) would involve an α-fluorine; the 2-thiolen thus produced could then further dehydrofluorinate only to tetrafluorothiophen. The unfavourable elimination of the α-fluorine would be expected to occur more at high



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[1] Part IV, preceding paper.

[2] J. Burdon, G. E. Chivers, and J. C. Tatlow, *J. Chem. Soc.* (*C*), 1970, 2146.

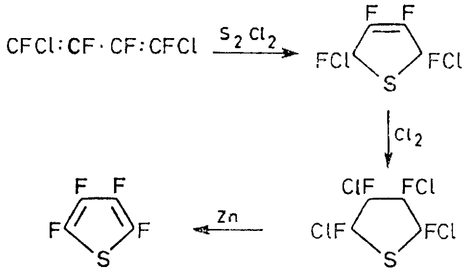
[3] J. Burdon, J. G. Campbell, I. W. Parsons, and J. C. Tatlow, *Chem. Comm.*, 1969, 27.

[4] U.S.P. 2,932,651/1960 (*Chem. Abs.*, 1960, **54**, 18,549i).

[5] R. P. Smith and J. C. Tatlow, *J. Chem. Soc.*, 1957, 2505; G. Fuller and J. C. Tatlow, *ibid.*, 1961, 3198; R. J. Heitzman, C. R. Patrick, R. Stephens, and J. C. Tatlow, *ibid.*, 1963, 281.

temperatures than at low for the usual energetic reasons, and this would explain why no tetrafluorothiophen is detected in the aqueous reaction and why the yield of the thiophen rises as the molten-alkali reaction temperature is raised from 160 to 275°.

Ilgenfritz and Ruh [4] used a very different method for the preparation of tetrafluorothiophen:



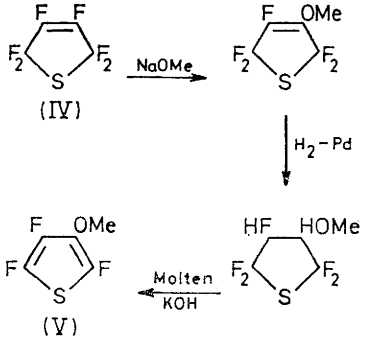
Since our method gives such low yields, this sequence may offer advantages, although no yields are given in the patent.

Tetrafluorothiophen is a liquid which reacts only slowly with bromine and fails to polymerise spontaneously when kept for several months at 0°. This contrasts with the behaviour of the other known five-membered fluorinated heterocycle, tetrafluorofuran [2], which reacts very rapidly with bromine, and polymerises spontaneously in a few hours at 0°. If the bromine reactions are electrophilic, the order of reactivity of tetrafluorofuran and -thiophen parallels the known relative susceptibilities of furan and thiophen towards electrophiles.

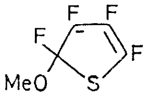
We were able to carry out a nucleophilic reaction of tetrafluorothiophen with sodium methoxide; this could not be achieved with tetrafluorofuran.[2] The reaction was slower than that of hexafluorobenzene, behaviour consistent with the well known greater electron density on the thiophen ring as compared to the benzene. Hence, on the slender evidence we have, the reactivities of tetrafluorothiophen and tetrafluorofuran reflect those of thiophen and furan, that is, the hetero-atoms still have profound effects on the reactivities even in the presence of four fluorine substituents.

The tetrafluorothiophen–sodium methoxide reaction product was a single compound which we have shown to be 2,3,4-trifluoro-5-methoxythiophen (III) by synthesising the other possible isomer, the 4-methoxy-compound (V), as shown; the two methoxy-thiophens [(III) and (V)] had different n.m.r. spectra.

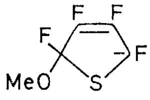
The starting material, hexafluoro-3-thiolen (IV), is a known [4,6] compound and was available to us as a minor product from the fluorination of thiophen over potassium tetrafluorocobaltate.[1] The yield (*ca.* 70%) of the methoxy-thiophen (V) in the dehydrofluorination step was very much better than the yield (5—10%) of tetrafluorothiophen in the analogous step.



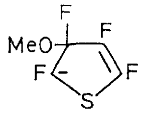
The rationalisation we offer for the position of nucleophilic attack on tetrafluorothiophen is the trite one that a Wheland-type intermediate [(VI) ⟷ (VII)] is more stable than (VIII) because of the greater charge delocalisation. The sulphur must then exert no less a



(VI)



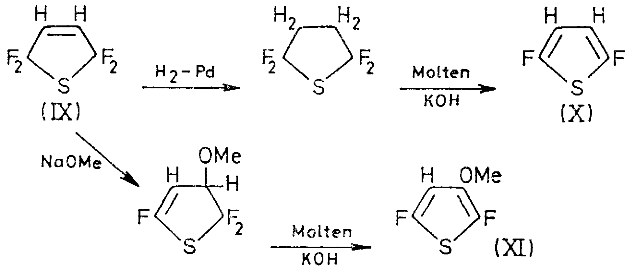
(VII)



(VIII)

stabilising influence on (VII) than on (VIII); a similar explanation has been given [7] for the position of nucleophilic attack on 4,5,6,7-tetrafluorobenzo[*b*]thiophen.

As is described below, polyfluorothiophens have two unusual features about their ^{19}F n.m.r. spectra. In order to confirm this, two more thiophens [(X) and (XI)] were prepared as indicated. The starting thiolen (IX) was a major product in the fluorination [1] of thiophen over potassium tetrafluorocobaltate.



All the methoxy-thiophens [(III), (V), and (XI)] polymerised rapidly and spontaneously at room temperature to very viscous materials. We have not investigated this phenomenon and we cannot explain it; we are not sure that it is related to the ease of polymerisation of polyfluorofurans.[2]

An attempt was also made to convert the thiolen (IX) into 2,3,4-trifluorothiophen by heating it with aluminium fluoride and with sodium fluoride. We had hoped that the double bond of (IX) would rearrange to give the isomeric 2-thiolen which would then lose hydrogen fluoride and yield 2,3,4-trifluorothiophen; instead, no reaction occurred with either reagent.

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[6] U.S.P. 3,069,431/1962 (*Chem. Abs.*, 1963, **58**, 10,173h).

[7] G. M. Brooke and Md. A. Quaseem, *Tetrahedron Letters*, 1967, 2507; M. D. Castle, R. G. Plevey, and J. C. Tatlow, *J. Chem. Soc.* (*C*), 1968, 1225.

[8] E. J. Corey, G. Slomp, S. Dev, S. Tobinaga, and E. R. Glazier, *J. Amer. Chem. Soc.*, 1958, **80**, 1204; S. Gronowitz and R. A. Hoffman, *Arkiv Kemi*, 1958, **13**, 279; 1960, **15**, 45.

It was possible to rationalise the n.m.r. spectra of the five polyfluorothiophens described in this paper only if the α-fluorines were taken as resonating to high field of the β and if the 2—5 F–F coupling constants were large (26—31 Hz). The first feature is contrary both to that expected [8] on simple electronegativity grounds and also to that which occurs [2] in polyfluorofurans. Also, the α-protons in thiophen itself resonate to low field of the β, although the chemical shift between them (0·13 p.p.m.) is less than in furan (1·05 p.p.m.).[8] We can offer no simple explanation for the chemical shifts in polyfluorothiophens. The large coupling constants parallel $J_{2,5}$ in polyfluorofurans, where they are *ca.* 20 Hz.[2] Finally, some of the J_{HF} and J_{FF} *ortho* values are surprisingly small; we have no explanation for this.

EXPERIMENTAL

Preparation of Tetrafluorothiophen.—3*H*/4*H*-Hexafluorothiolan [1] (II) (7·7 g) was volatilised in a stream of nitrogen and bubbled through molten potassium hydroxide (*ca.* 150 g) at 250°; the apparatus has been described before. The crude product (0·6 g) was collected in a liquid-air cooled trap; g.l.c. showed largely (*ca.* 95%) one component. The reaction was carried out at several temperatures between 160 and 275°; the product always consisted almost entirely of the one component but the yield was highest at the highest temperature. In this way 123 g of 3*H*/4*H*-hexafluorothiolan were converted into 7 g of product; it was tetrafluorothiophen (the crude product was satisfactory for preparative experiments; a portion was further purified by g.l.c.), b.p. 60° (cited,[4] 68°); $\nu_{\mathrm{max.}}$ 1670 and 1450 cm^{-1}; strong end absorption in the u.v. (ε, 5800 at 220 nm); M^+ *m/e* 156 (base peak) ($C_4F_4S^+$).

Reaction of Sodium Methoxide with Tetrafluorothiophen.—The thiophen (0·9 g) was heated under reflux with 2·15M-sodium methoxide in methanol (2·7 cm^3) until g.l.c. indicated that the reaction was complete (45 h). The reaction mixture was poured into water and the product (*ca.* 1 g) was isolated by carbon tetrachloride extraction. (The n.m.r. spectra were run on this crude product.) Separation of a sample (only two components were present; the product and a small amount of carbon tetrachloride) by g.l.c. on a 100 mm^3 scale (silicone gum on Celite stationary phase) gave 2,3,4-*trifluoro*-5-*methoxythiophen* (III), M^+ *m/e* 167·986 ($C_5H_3F_3OS^+$ requires 167·987). The crude product polymerised only slowly to a brown resin when set aside, but very quickly when warmed or when distillation was attempted.

Reaction of Sodium Methoxide with Hexafluoro-3-thiolen (IV).—3·27M-Sodium methoxide in methanol (16·2 cm^3) was added dropwise, to a cooled (0°) and stirred solution of hexafluoro-3-thiolen (IV) (10·2 g) in ether (150 cm^3). The mixture was kept for 1 h after the completion of the addition and was then poured into water (200 cm^3); the ether layer was separated, dried ($MgSO_4$), and distilled to give *pentafluoro*-3-*methoxy*-3-*thiolen* (9·9 g), b.p. 119° (Found: C, 29·4; H, 1·6; S, 15·4. $C_5H_3F_5OS$ requires C, 29·1; H, 1·5; S, 15·6%). The ^{19}F n.m.r. spectrum showed three complex multiplets, intensity ratios 2 : 2 : 1, at 78·5, 79·3, and 161·6; the ^1H spectrum showed a doublet (*J* 3·5 Hz) at τ 5·86.

Hydrogenation of Pentafluoro-3-methoxy-3-thiolen.—The thiolen (8·3 g) in ethanol (20 cm^3) was hydrogenated (80 atm. pressure) in an autoclave with 10% palladium on charcoal catalyst (1 g) for 7 days at room temp.; g.l.c. then indicated *ca.* 90% reaction. Distillation gave 3H,4H/3-*methoxypentafluorothiolan* (4·4 g), b.p. 145° (Found: C, 29·1; H, 2·9. $C_5H_5F_5OS$ requires C, 28·8; H, 2·4%); ^{19}F n.m.r. spectroscopy showed two AB patterns at *ca.* 70 and 88·5 (J_{AB} 201 Hz) and *ca.* 70 and 104·5 (J_{AB} 210 Hz), and a signal (intensity equal to ½ of each AB pattern) at 208·0. The ^1H spectrum showed three signals, intensity ratios 1 : 1 : 3, at τ 5·12, 5·87, and 6·38. Further couplings were visible on all (^{19}F and ^1H) signals (except OMe), but these were too complex for analysis.

Preparation of 2,3,5-*Trifluoro*-4-*methoxythiophen* (V).—3*H*,4*H*/3-Methoxypentafluorothiolan (4·0 g) was passed through molten potassium hydroxide at 200—210° as described in the first experiment. A sample (100 mm^3) of the crude product (2·2 g) was separated by g.l.c. (silicone gum on Celite stationary phase) to give 2,3,5-trifluoro-4-methoxythiophen (V), M^+ *m/e* 167·983. The pure compound polymerised to a brown resin after *ca.* 10 min at room temp.; the crude product (the n.m.r. spectra were run on this) lasted for several hours.

Hydrogenation of 3H,4H-*Tetrafluoro*-3-*thiolen* (IX).—The thiolen (IX) (8·0 g) was hydrogenated in ethanol (250 cm^3) as before, but for 4 days. Water (200 cm^3) was added and the mixture was distilled through a 30-cm column packed with glass helices. The early distillate was collected in water; a lower layer formed which was separated and distilled to give 2,2,5,5-*tetrafluorothiolan* (5·3 g), b.p. 92—93° (Found: C, 30·0; H, 2·4. $C_4H_4F_4S$ requires C, 30·0; H, 2·5%).

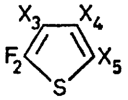
Preparation of 2,5-*Difluorothiophen* (X).—2,2,5,5-Tetrafluorothiolan (5·3 g) was passed through molten potassium hydroxide at 250° as before; the product was passed again and the final crude product (3·7 g) was separated by g.l.c. [4·8 m × 35 mm tube, packed with tricresyl phosphate on Celite (1 : 3), temp. 80°, N_2 flow-rate 20 dm^3/h] into 2,5-*difluorothiophen* (X) (1·4 g), b.p. 68° (Found: C, 40·0; H, 1·5. $C_4H_2F_2S$ requires C, 40·0; H, 1·7%) and a mixture (1·3 g) of this thiophen and starting material.

Reaction of 3H,4H-*Tetrafluoro*-3-*thiolen* (IX) *with Sodium Methoxide.*—3·27M-Sodium methoxide in methanol (18·5 cm^3) was added dropwise to a stirred solution of the thiolen (8·9 g) in dimethylformamide (200 cm^3). After 12 h, the reaction mixture was poured into water and the product was isolated by ether extraction and was then distilled; it was 2,5,5-*trifluoro*-4-*methoxy*-2-*thiolen* (5·0 g), b.p. 130° (Found: C, 35·0; H, 3·0. $C_5H_5F_3OS$ requires C, 35·3; H, 3·0%). ^{19}F N.m.r. spectroscopy showed an AB pattern at 66·5 and 86·9 (J_{AB} 208 Hz) and a signal of half the AB intensity at 107·1; the ^1H spectrum showed three signals, in intensity ratio 1 : 1 : 3, at τ 4·97, 6·39, and 6·50. Again, all the signals (except the OMe) were split into complex multiplets.

Preparation of 2,5-*Difluoro*-3-*methoxythiophen* (XI).—2,5,5-Trifluoro-4-methoxy-2-thiolen (4·9 g) was passed through molten potassium hydroxide at 220—230° as before. The product (4·3 g) was separated by g.l.c. on a 100 mm^3 scale (silicone gum on Celite stationary phase) to give 2,5-*difluoro*-3-*methoxythiophen* (XI), M^+ *m/e* 149·994 ($C_5H_4F_2OS^+$ requires 149·995). The pure compound rapidly polymerised at room temp. to a brown resin.

N.m.r. Spectra.—The ^{19}F and ^1H spectra were measured

N.m.r. spectra of polyfluorothiophens



				Chemical Shifts[a]				Coupling constants (Hz)					
Compound	X_3	X_4	X_5	F_2	X_3	X_4	X_5	F_2X_3	F_2X_4	F_2X_5	X_3X_4	X_3X_5	X_4X_5
Tetrafluorothiophen[b]	F	F	F	164·9	155·6	155·6	164·9	7[c]	17[c]	31[c]	7[c]	17[c]	7[c]
2,5-Difluoothiophen (X)	H	H	F	136·9	4·20	4·20	136·9	3·5	3·5	*d*	*d*	3·5	3·5
2,5-Difluoro-3-methoxythiophen (XI)	OMe	H	F	165·2	6·15	4·05	137·7	2·0	3·8	26·5	0	0	3·8
2,3,5-Trifluoro-4-methoxythiophen (V)	F	OMe	F	166·8	153·1	6·05	164·9	5·4	0	30·6	*e*	15·4	2·1
2,3,4-Trifluoro-5-methoxythiophen (III)	F	F	OMe	164·0	156·1	154·6	6·24	5·4	17·8	0	10·0	0	0·6

[a] Numbers >100, ^{19}F shifts (upfield from internal $CFCl_3$); <100, ^1H shifts (τ scale). [b] This showed an AA′XX′ spectrum. [c] Approximate values (±2 Hz) because some of the lines were incompletely resolved. [d] Not calculable because the outer lines of the AA′XX′ spectrum were not visible; each half of the spectrum was a 1 : 2 : 1 triplet. [e] The lines were broadened, consistent with a coupling of *ca.* 0·2 Hz.

on a Perkin-Elmer R10 instrument at 56·4 and 60 MHz, respectively. The ^{19}F shifts in this paper are in p.p.m. upfield from $CFCl_3$ as internal standard.

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