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PARTIALLY FLUORINATED HETEROCYCLIC COMPOUNDS PART 28 [1]. THE HYDROLYSIS OF 1,3,4,5,6,7,8-HEPTAFLUORO-2-NAPHTHYLIDENERHODANINE TO FORM RING-FUSED THIOPHENES. A SIGNIFICANT PROPORTION OF A LINEAR NAPHTHO[2, 3-b]THIOPHENE DERIVATIVE ACCOMPANYING AN ANGULAR NAPHTHO[1, 2-b]THIOPHEN DERIVATIVE

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SUMMARY

1,3,4,5,6,7,8-Heptafluoronaphthalene-2-carbaldehyde (7), prepared via a Grignard reaction from 2-bromo-1,3,4,5,6,7,8-heptafluoronaphthalene (9) with N-methylformanilide, reacted with rhodanine to give 1,3,4,5,6,7,8-heptafluoro-2-naphthylidenerhodanine (5). Hydrolysis of (5) with base gave a mixture of 4,5,6,7,8,9-hexafluoronaphtho[2, 3-b]thiophene-2-carboxylic acid (11) and 4,5,6,7,8,9-hexafluoronaphtho[1, 2-b]thiophene-2-carboxylic acid (12) resulting from the intermediate thiolate (6) displacing fluorine at sites 3 and 1 in the naphthalene ring in the ratio of 22:78 respectively, which represents a significantly high proportion of the linearly cyclised product accompanying the angularly cyclised product. Decarboxylation of the mixture of (11) and (12) gave 4,5,6,7,8,9-hexafluoronaphtho[2, 3-b]thiophene (13) and 4,5,6,7,8,9-hexafluoronaphtho[1, 2-b]thiophene (14) respectively, while treatment of the mixture of (11) and (12) with diazomethane gave an inseparable mixture of the methyl 2-carboxylates (15) and (16) respectively.

INTRODUCTION

In the 1960s, two reactions were published for the 'one pot' preparation of partially fluorinated benzo[b]thiophene derivatives via intramolecular

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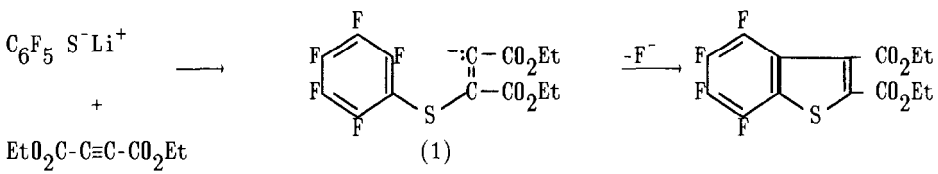
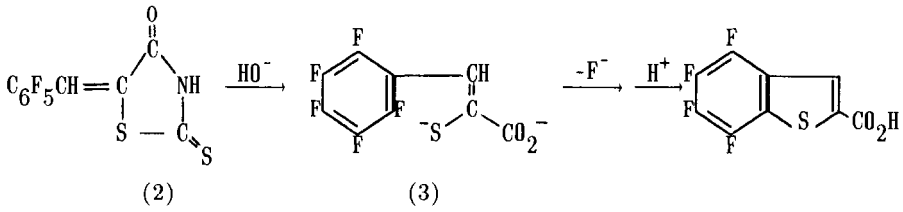
nucleophilic displacement of fluorine. The first process [2] involved cyclisation via an intermediate carbanionic species (1) (Scheme 1). The



Scheme 1.

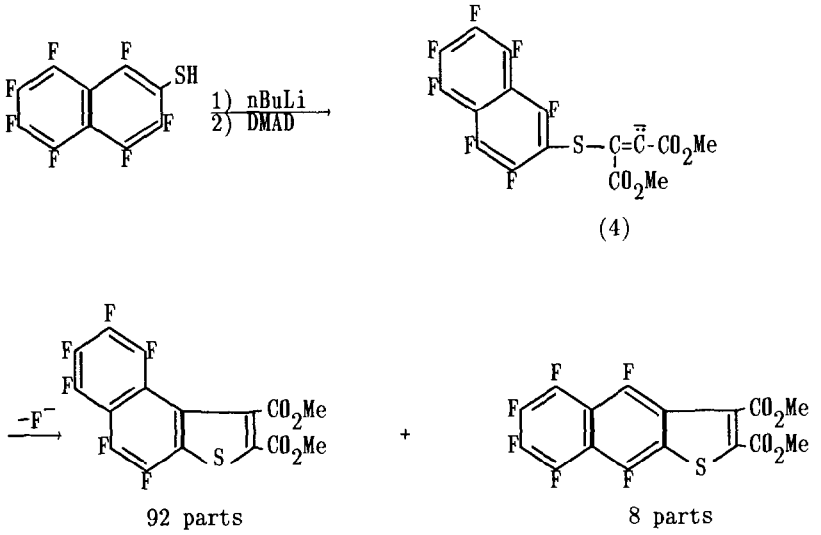
second cyclisation reaction [3] started with the benzylidenerhodanine derivative (2) (Scheme 2) which on ring-opening of the heterocycle with alkali produced an intermediate (3) containing a sulphur nucleophile for ring-closure with the aromatic nucleus.



Scheme 2.

Recently we reported the reaction of lithium 1,3,4,5,6,7,8-heptafluoro-2-naphthalenethiolate with dimethyl acetylenedicarboxylate (DMAD) [4], a reaction of interest since being an intramolecular reaction, it enabled for the first time a comparison to be made between the relative reactivity of fluorine displacement at two sites in the same ring, namely the 1-F and the

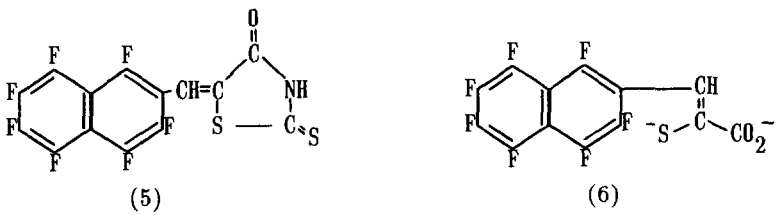
3-F which are both less reactive than the fluorine at the 6-F site. The result of the reaction, shown in Scheme 3, indicated clearly that the fluorine



Scheme 3.

at position 1 in the naphthalene ring was more reactive than the fluorine at position 3.

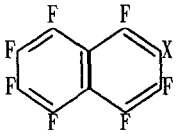
The application of the Birmingham cyclisation reaction using the 2-naphthylrhodanine derivative (5) described in this paper provided another opportunity to explore the relative reactivity of the fluorines at sites 1 and



3 in the intermediate (6), in a situation which is completely different to that prevailing in the intermediate (4).

RESULTS AND DISCUSSION

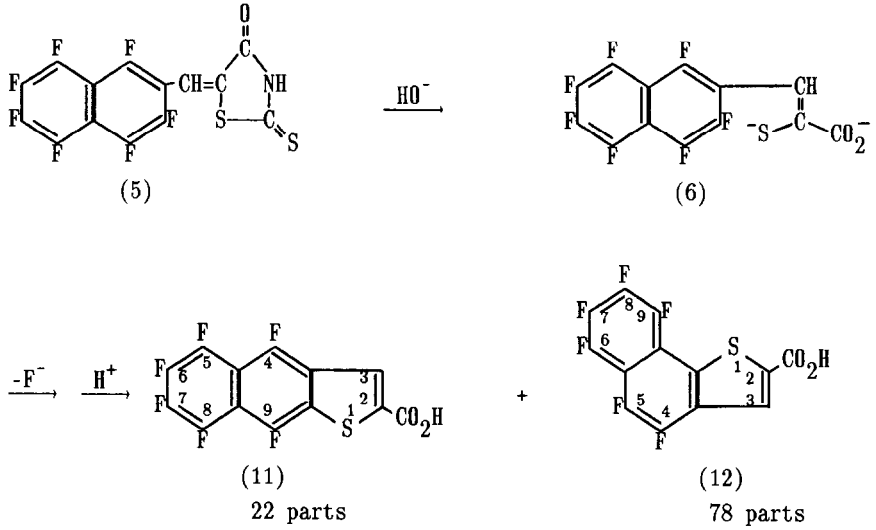
1,3,4,5,6,7,8-Heptafluoronaphthalene-2-carbaldehyde (7), previously



(7) X = CHO
(8) X = CH_2SOCH_3
(9) X = Br
(10) X = $NHNH_2$

isolated in low yield from a reaction of 1,3,4,5,6,7,8-heptafluoro-2-naphthylmethyl methyl sulphoxide (8) with butyl-lithium [1], was prepared by an alternative route involving 1,3,4,5,6,7,8-heptafluoro-2-naphthylmagnesium bromide and N-methylformanilide. The precursor to the Grignard reagent, 2-bromo-1,3,4,5,6,7,8-heptafluoronaphthalene (9) [5] was prepared from 1,3,4,5,6,7,8-heptafluoro-2-naphthylhydrazine (10) [6] and copper (II) bromide.

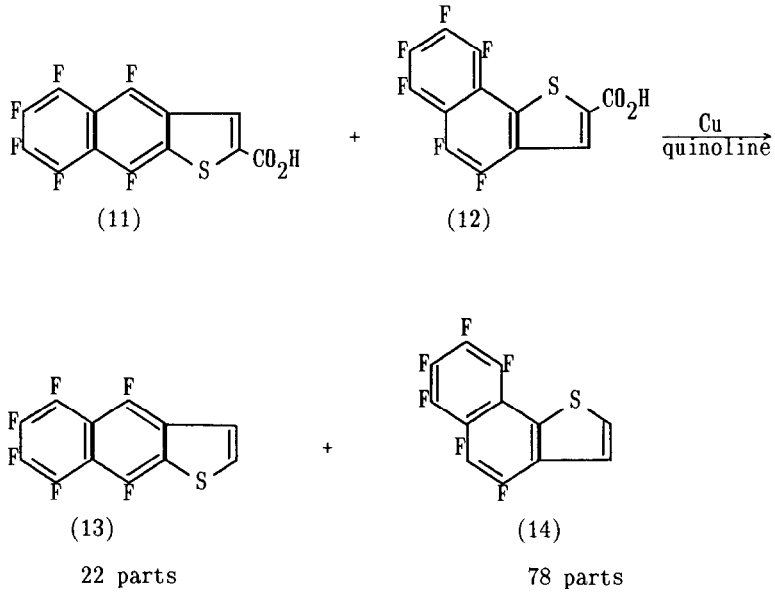
The 2-carbaldehyde (7) formed the naphthylidene derivative (5) with rhodanine under alkaline conditions [3]. Hydrolysis of (5) with aqueous sodium hydroxide and acidification gave a mixture of carboxylic acids (11) ar (12) in the ratio of 22:78 respectively (Scheme 4).



Scheme 4.

The structure of the major isomer (12) was identified by the presence of only one large peri J_{F-F} coupling constant (61 Hz) in the ^{19}F NMR spectrum, whereas the minor isomer had two large peri J_{F-F} coupling constants (60 and 63 Hz) and was therefore (11).

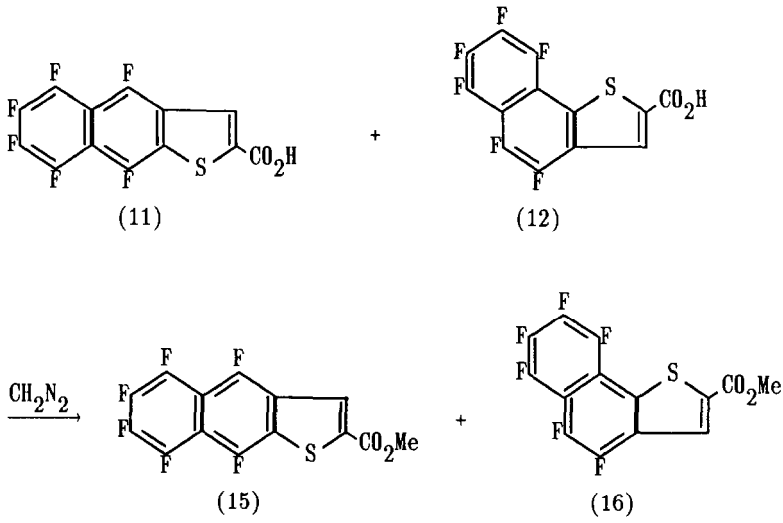
The separation of the crude mixture of carboxylic acids was not attempted as they were considered inseparable by chromatography. Instead, the crude cyclised material was decarboxylated with copper bronze in quinoline to give a mixture (67%) of 4,5,6,7,8,9-hexafluoronaphtho[2,3-b]thiophene (13) and 4,5,6,7,8,9-hexafluoronaphthalene[1,2-b]thiophen (14) in the ratio 22:78 respectively (Scheme 5). The major component (14) was easily separated from



Scheme 5.

the mixture by chromatography of alumina, but the minor component (13) proved to be much more difficult to obtain pure (see EXPERIMENTAL section). The structures of these products were identified by ^{19}F NMR spectroscopy; the major isomer had <u>one</u> large peri J_{F-F} coupling constant (60 Hz) and was therefore (14), while the minor component had <u>two</u> large peri J_{F-F} coupling constants (61.6 and 62.7 Hz) and was therefore (13).

In an attempt to produce more easily separable cyclic materials, the mixture of crude carboxylic acids (11) and (12) was treated with excess diazomethane to give the esters (15) and (16) (100%) in the ratio 23:77 respectively (Scheme 6). However, chromatography failed to separate the two

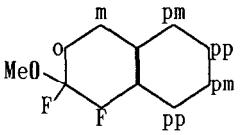


Scheme 6.

components, which were again identified by ^{19}F NMR. Recrystallisation of the mixture effected some enrichment of the major isomer, and correct analytical data were obtained on a 94:6 ratio of (16):(15) respectively.

Electrophilic substitution in naphthalene in kinetically controlled reactions occurs at position 1 in the ring and the orientation is rationalised in terms of the smaller localisation energy at this site of reaction [7]. However, in octafluoronaphthalene the fluorine at position 2 is always the predominant site of substitution, with methyl-lithium giving the least ratio of 2-:1- substitution (91.6 : 8.4) [8]. Kinetics studies have shown that fluorine atoms that are substituents at positions ortho- and meta- to the site of attack in highly fluorinated aromatic systems are significantly activating, whereas para- fluorine is slightly deactivating with respect to hydrogen atoms at the same position [9]. In highly fluorinated naphthalene compounds,

related studies have shown that fluorine atoms remote from the reaction site [see structure (17)] follow a similar reactivity pattern, namely 'pseudo-meta'

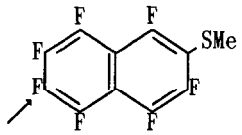


(17)

o, m = ortho-, meta -
pm, pp = 'pseudo-meta','pseudo-para'

is activating whereas 'pseudo-para' is slightly deactivating with respect to hydrogen at the same site [10]. The preferential nucleophilic substitution in octafluoronaphthalene at position 2 follows from the requirement that the activating influences of fluorine substituents at the site of attack be maximised.

The most reactive site in the methyl sulphide (18) is the 'pseudo-para' site 6 [4], and it can be argued that the same site will be the most reactive



(18)

site in the intermediate sulphide (4) in Scheme 3. Consequently the intramolecular cyclisation of (4) has to take place at two less reactive sites 1 and 3 on the naphthalene ring, and there is some evidence that in such a situation meta- activation by a fluorine substituent dominates ortho-activation [11]. Fluorine at sites 1 and 3 in (4) both have only one activating meta- fluorine, so that the preferential substitution at site 1 must be the result of more favourable localisation energy considerations.

In the work described in this paper, the ratio of the cyclisation via replacement of fluorines at F-3 and F-1 (22:78 respectively) by the thiolate in (6) has increased by a factor of 3 2 over replacement of fluorine at the same sites by the carbanion in (4) (8:92 respectively). It should be noted, however, that in the former case, (6), the two fluorines are ortho to a vinylic carbon whereas in (4) they are ortho to a sulphide substituent. Nevertheless, it is clear from this present work where thiolate is the attacking nucleophile, that the intrinsically lower localisation energy usually associated with substitution at site 1 in the naphthalene ring system compared with a site 2 position [of course, it is actually site 3 in (6)] is somewhat less important than in the reaction proceeding via the carbanion (4), so that a significantly higher proportion of linearly fused product (11) is formed in the cyclisation reaction of (6).

It is remarkable that in Friedel-Crafts cyclisations of appropriate naphthalene derivatives substituted at position 2 designed to form an extra six membered carbocycle, only phenanthrene derivatives are mentioned as the product, via angular cyclisation reactions; linear cyclisations giving anthracene derivatives are never even mentioned [12].

EXPERIMENTAL

NMR spectra were obtained with a Bruker AC250 [^{1}H (250 MHz) and ^{19}F (235 MHz)]. Chemical shifts are downfield from internal $SiMe_4$ (δ_F). Mass spectroscopy data were obtained with a VG 7070E instrument. Molecular ions M^+ are quoted for electron ionisation unless chemical ionisation (CI) is stated.

Reaction of 1,3,4,5,6,7,8-heptafluoro-2-naphthylhydrazine(10) with copper (II) bromide

1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazine (10) [6] (27.5g), copper (II) bromide (175 g) and hydrobromic acid (400 ml, 48%) were heated together under reflux for 1 h. The mixture was then distilled in steam, the distillate extracted with ether, and the extracts washed with sodium hydroxide solution (2M) and dried. Evaporation of the solvent gave the crude product (35 g - slightly wet) which was recrystallised first from light petroleum (bp 30-40°C) at -18°C and then from methanol/water to give 2-bromo-1,3,4,5,6,7,8-heptafluoronaphthalene (9) mp 74-74.5°C (lit [8] mp 73-74°C).

Preparation of 1,3,4,5,6,7,8-heptafluoronaphthalene-2-carbaldehyde (7)

Magnesium turnings (0.73 g) in dry ether (50 ml) were activated with 1,2-dibromoethane and treated with 2-bromo-1,3,4,5,6,7,8-heptafluoronaphthalene (9) (10.12 g) in dry ether (20 ml) over 15 min. The mixture was heated under reflux for 1 h, cooled to room temperature and treated with N-methylformanilide (5.01 g) in dry ether (10 ml). After being heated under reflux for 1 h, the solution was cooled to room temperature, acidified with sulphuric acid (2 M) and extracted with ether. The dried ($MgSO_4$) extracts were evaporated, and the crude product (6.15 g, 72%) purified by sublimation at ca. 50°C/0.05 mm Hg followed by crystallisation from light petroleum (bp 40-60°C), was identified as 1,3,4,5,6,7,8-heptafluoronaphthalene-2-carbaldehyde (7) by comparison of its i.r. with that of the authentic compound [1].

Reaction of 1,3,4,5,6,7,8-heptafluoronaphthalene-2-carbaldehyde (7) with rhodanine

A mixture of 1,3,4,5,6,7,8-heptafluoronaphthalene-2-carbaldehyde (7) (2.899 g), rhodanine (1.420 g), ammonium chloride (1.085 g), ammonium

hydroxide solution (1 ml; sg. 0.880) and water (1.5 ml) was heated with shaking to almost boiling using a hair-drier over ca. 4 min. The dark orange coloured product was dissolved in ethyl acetate, the solution dried ($MgSO_4$) and the solvent evaporated. The crude product was further purified by flash chromatography on silica using ethyl acetate as eluant to give 1,3,4,5,6,7,8-heptafluoro-2-naphthylidenerhodanine (nc) (5) (3.26 g, 80%) mp 199-200°C [from ethylacetate/light petroleum (bp 60-80°C)] (Found: C, 42.54; H, 0.49; N, 3.58%; M^+ 397. $C_{14}H_2F_7NOS_2$ requires C, 42.32; H, 0.51; N, 3.53%; M, 397).

Hydrolysis of 1,3,4,5,6,7,8-heptafluoro-2-naphthylidenerhodanine (5) followed by (a) decarboxylation, and (b) methylation with diazomethane

(a) The rhodanine derivative (5) (6.166 g) was hydrolysed in aqueous sodium hydroxide (15% w/w, 19 ml) diluted with water (21 ml), at 100°C for 30 min. The mixture was acidified with sulphuric acid (2 M), extracted with ether and the dried ($MgSO_4$) extracts evaporated to give a mixture of two hexafluoro carboxylic acids (5.244 g) (11) and (12) in the ratio 22:78 respectively, accompanied by some very minor components (as shown by ^{19}F NMR spectroscopy in acetone). In the ^{19}F NMR spectrum the major component (12) had δ_F (acetone) -140.7 (t, 9-F), -142.9 (m, 4-F), -144.9 (dt, peri $J_{5\text{-}F,6\text{-}F}$ 61 Hz, 6-F), -151.2 (dd, peri $J_{5\text{-}F,\ 6\text{-}F}$ 61 Hz, 5-F), and -155.6 and -156.5 ppm (both t, unassigned 7-F/8-F). The minor component (11) had δ_F (acetone) -122.3 (dd, peri $J_{4\text{-}F,\ 5\text{-}F/8\text{-}F,\ 9\text{-}F}$ 63 Hz, unassigned 4-F/9-F), -122.9 (dd, peri $J_{4\text{-}F,\ 5\text{-}F/8\text{-}F,\ 9\text{-}F}$ 60 Hz, unassigned 4-F/9-F), -146.0 (dt, peri $J_{4\text{-}F,\ 5\text{-}F/8\text{-}F,\ 9\text{-}F}$ 63 Hz, unassigned 5-F/8-F), -147.4 (dt, peri $J_{4\text{-}F,\ 5\text{-}F/8\text{-}F,\ 9\text{-}F}$ 60 Hz, unassigned 5-F/8-F), and -155.5 and -157.3 ppm (both t, unassigned 6-F/7-F).

The crude mixture of carboxylic acids (5.244 g), freshly distilled quinoline (50 ml) and powdered copper bronze (4.01 g) were heated under reflux for 1 h, acidified with sulphuric acid (2 M) and organic matter extracted with ether. The ether extracts were dried ($MgSO_4$), the solvent evaporated and the residue sublimed at 100°C/0.05 mm Hg to give a mixture of the naphtho[2,3-b]thiophene (13) and the naphtho[1,2-b]thiophene (14) in the ratio 22:78 respectively, together with some very minor components (as shown by ^{19}F NMR in acetone) (3.019 g, 67%).

Repeated chromatography on alumina (activity 2-3, 70-230 mesh) (6" x 2.5") using light petroleum (bp 40-60°C) as eluant gave as the faster moving component 4,5,6,7,8,9-hexafluonaphtho[1,2-b]thiophene (nc) (14) mp 137.5-138°C [from light petroleum (bp 40-60°C)] (Found: C, 49.36; H, 0.58%; M^+, 292. $C_{12}H_2F_6S$ requires C, 49.32; H, 0.69%; M, 292) δ_F ($CDCl_3$) -141.8 (t, 9-F), -143.5 (nm, 4-F), -145.4 (dt, peri $J_{5\text{-}F,\ 6\text{-}F}$ 60 Hz, 6-F), -152.6 (dd, peri $J_{5\text{-}F,\ 6\text{-}F}$ 60 Hz, 5-F), and two overlapping absorptions at -157.5 (complex m, 7-F/8-F); δ_H ($CDCl_3$) 7.64 (dd, unassigned 2-H/3-H) and 7.79 (d, unassigned 2-H/3-H). Fractions enriched in the slower moving isomer were rechromatographed again on alumina (10" x 2.5") as before and the even more enriched fractions were recrystallised five times from light petroleum (bp 40-60°C) to give a very small amount of 4,5,6,7,8,9-hexafluoronaphtho[2, 3-b]thiophene (nc) (13) mp 118-118.5°C. Correct microanalytical data were obtained on a slightly less pure sample, mp 117.5-117.8°C which contained < 7% impurity (estimated by ^{19}F NMR). (Found: C, 49.62; H, 0.66%; M^+, 292. $C_{12}H_2F_6S$ requires C, 49.32; H, 0.69; M, 292) δ_F ($CDCl_3$) -123.0 (dd, peri $J_{4\text{-}F,5\text{-}F/8\text{-}F,\ 9\text{-}F}$ 61.6 Hz, unassigned 4-F/9-F), -126.1 (dd, peri $J_{4\text{-}F,\ 5\text{-}F/8\text{-}F,\ 9\text{-}F}$ 62.7 Hz, unassigned 4-F/9-F) - 146.7 (dt, peri $J_{4\text{-}F,5\text{-}F/8\text{-}F,9\text{-}F}$ 62.7 Hz, unassigned 5-F/8-F), -147.5 (dt, peri $J_{4\text{-}F,}$

5-F/8-F, 9-F 61.6 Hz, unassigned 5-F/8-F), and -157.0 and -157.8 ppm (both t, unassigned 6-F/7-F).

(b) The rhodanine derivative (5) (3.659 g) in aqueous sodium hydroxide (15% w/w; 11 ml) was placed in an oil bath at 100°C, and after 8 min water (11 ml) was added. After heating for 30 min. overall, the mixture was cooled, acidified with sulphuric acid (2 M), extracted with ether and the extracts treated with excess diazomethane in ether. The excess diazomethane/ether was removed by evaporation, the residue dissolved in fresh ether, and the dried ($MgSO_4$) solution was evaporated to give a mixture of crude esters (3.187 g, 99%), the ^{19}F NMR spectrum of which showed that the naphtho[2,3-b]thiophene and naphtho[1,2-b]thiophene compounds (15) and (16) were present in the ratio of 23:77 respectively. Flash chromatography on silica using $CCl_4/CHCl_3$ (50:50 v/v) failed to effect any separation of the isomers. Recrystallisation (x 4) of the mixture from toluene-light petroleum (bp 100-120°C) followed by recrystallisation from light petroleum (bp 100-120°) gave an isomeric mixture of methyl 4,5,6,7,8,9-hexafluoronaphto[1,2-b]thiophene-2--carboxylate(nc)(16) (94 parts) and methyl 4,5,6,7,8,9-hexafluoronaphtho-[2,3-b]thiophene-2-carboxylate (nc) (15) (6 parts). (Found: C, 48.06; H, 1.03%; M^+, 350 (CI), $C_{14}H_4F_6SO_2$ requires C, 40.01; H, 1.15%; M, 350) δ_F ($CDCl_3$) for the major component (16) -140.0 (t, 9-F), -142.7 (nm, 4-F), -144.4 (dt, peri $J_{5\text{-}F,6\text{-}F}$ 60 Hz, 6-F), -150.8 (dd, peri $J_{5\text{-}F}$, 6-F 60 Hz, 5-F), and -154.8 and -155.9 ppm (both t, unassigned 7-F/8-F); δ_H ($CDCl_3$) for (16) 4.02 (CH_3) and 8.24 (nd, 3-H). δ_F ($CDCl_3$) for the minor component (15) -122.3 (two overlapping absorptions, complex m, peri $J_{4\text{-}F}$, 5-F and peri $J_{8\text{-}F,\ 9\text{-}F}$ both 64 Hz, for unassigned 4-F/9-F), -145.6 (dt, peri J 64 Hz, unassigned 5-F/8-F), -146.9 (dt, peri J 64 Hz, unassigned 5-F/8-F), and -154.6 and -156.6 ppm (both t, unassigned 6-F/7-F).

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