Generation and Synthetic Utility of Dianions Derived from Thiophencarboxylic Acids

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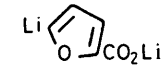
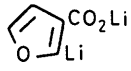
Thiophen-2- and -3-carboxylic acid are rapidly and regioselectively metallated by lithium di-isopropylamide in tetrahydrofuran at −78 °C. The resulting dianionic species [(10) and (4), respectively] react with a range of electrophiles to give the expected thiophencarboxylic acid homologues in good-to-excellent yields.

The metallation of simple heterocycles and the subsequent reactions of the resulting anionic species with electrophiles had long been recognised as an extremely valuable method in heterocyclic synthesis.[1] We have recently found that the dianionic species (1) and (2) can be obtained from the corresponding furancarboxylic acids using lithium di-isopropylamide (LDA) as the metallating agent, and that these intermediates provide a useful entry into a range of homologated furancarboxylic acids.[2] In view of the broadly similar chemistry of furyl-lithium and thienyl-lithium species, we reasoned that it should be possible to form similar dianions from thiophencarboxylic acids and that these could also be useful synthetic intermediates.

In common with other heterocycles containing a single heteroatom, thiophen itself undergoes metallation at an α-position.[1,3] Although many substituents have been used to control the site of metallation in a variety of heterocycles [1] (*e.g.* regioselective metallation at the 2-position of a 3-substituted furan or thiophen), there are few reports of the metallation of heterocyclic acids. Apart from our own work on the furancarboxylic acids,[2] Dean and his co-workers [4] have recently reported the formation and trapping by carbon dioxide of the dianion (3) derived from benzo[*b*]furan-2-carboxylic acid and LDA, while Davies and Davies [5] have briefly reported that sequential treatment of thiophen-3-carboxylic acid with LDA followed by either deuterium oxide or trimethylsilyl chloride leads only to the 2-substituted derivative, implying that dianion (4) can indeed be formed. We have been able to confirm these latter observations and to extend the utility of this intermediate (*vide infra*). In addition, the related dianionic species (5) and (6) have been obtained from 3-methylisothiazole-4-carboxylic acid [6] and oxazole-4-carboxylic acid,[7] respectively, using n-butyl-lithium. Metallated intermediates containing carboxylate groups have also been used in syntheses of 2-deuteriobenzo[*b*]thiophen-3-acetic acid [8] and of 4-substituted 2,3,5,6-tetrafluorobenzoic acids; [9] in both cases, n-butyl-lithium was used. In all of these examples, direct metallation (*i.e.* metal–hydrogen exchange) has been used to generate the dianionic species. An alternative to this is the preparation of dianions such as (7) and (8) from the corresponding 3,4,5-tribromo- and 3,4-dibromothiophen-2-carboxylic acids using metal–halogen exchange with n-butyl-lithium.[10] Probably the main reason why there are few reports in the older literature concerning the metallation of heterocyclic acids with n-butyl-lithium is because of the propensity for attack by this reagent on carboxylate groups to give ketones; [11] hence such metallations either fail or give only low yields of the desired dianions, except where formation of the latter is very rapid. In this respect the use of the more recently developed base LDA, a much weaker nucleophile, offers obvious advantages. Herein we report the results of a study of the generation, stability, and reactivity of dianions derived from thiophen-2- and -3-carboxylic acid.[12]


(1)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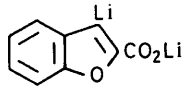
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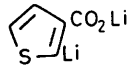
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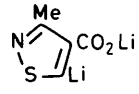
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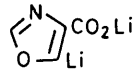
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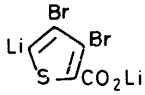
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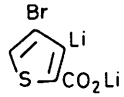
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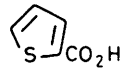
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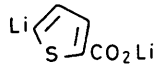
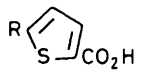
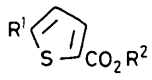

(10)

Treatment of a solution of thiophen-2-carboxylic acid (9) in tetrahydrofuran (THF) at −78 °C with 2.0 equiv. of LDA produced a white suspension. When samples were withdrawn and immediately quenched with deuterium oxide, only 5-deuteriothiophen-2-carboxylic acid was formed (^{1}H n.m.r. analysis), clearly indicating that only dianion (10) had been formed. Using this method of analysis we found that formation of the dianion (10) was essentially complete within 10 min at −78 °C. Hence, the acid (9) shows the usual preference for metallation in an α-position, a reaction characteristic of both thiophens and furans. The dianion (10) was slowly protonated at 0 °C; presumably the solvent THF acted as the proton source. After *ca.* 1 h at room temperature, protonation was complete. This contrasts with the behaviour of the corresponding furan dianion (1) which was protonated at lower



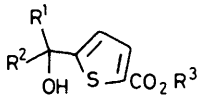
(11)

a; R = Me
b; R = Et
c; R = $SiMe_3$



(12)

a; R^1 = $CH_2CH{=}CH_2$, R^2 = H
b; R^1 = $CH_2CH{=}CH_2$, R^2 = Me
c; R^1 = CH_2Ph, R^2 = H
d; R^1 = CH_2Ph, R^2 = Me



(13)

a; R^1 = $Me[CH_2]_5$, R^2 = R^3 = H
b; R^1 = Ph, R^2 = R^3 = H
c; R^1 = R^2 = Me, R^3 = H
d; R^1 = $Me[CH_2]_5$, R^2 = H, R^3 = Me
e; R^1 = R^2 = R^3 = Me

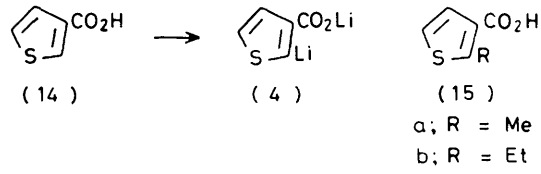
temperatures.[2] No other decomposition products were formed and no other dianions, isomeric with (10) were detected.

Dianion (10) was alkylated rapidly by both methyl and ethyl iodide to give the acids (11a) and (11b), respectively, in high yield. In the case of the furan dianion (1), the reaction with ethyl iodide was slower and less efficient.[2] Dianion (10) also condensed rapidly and cleanly with trimethylsilyl chloride to provide the acid (11c) in 85% isolated yield, and with both alkyl and benzyl bromide to give the acids (12a) and (12c), respectively. However, these latter two reactions were not so efficient, as the crude reaction mixture was found to contain *ca.* 30—40% unchanged starting material (9). It was found to be most expedient to separate the products from starting material (9) by first esterifying the mixture with diazomethane and then chromatographing the mixed esters. In this way the esters (12b) and (12d) were isolated in 40 and 58% yield, respectively. The overall material balances of these reactions were *ca.* 90%. Again, this is in contrast to the reactions of the furan dianion (1) which completely failed to couple with either allyl or benzyl bromide.[2] The conversions into the acids (12a) and (12c) were slightly improved by the addition of 2 equiv. of tetramethylethylene diamine (TMEDA) to the reaction mixture prior to the addition of the electrophile. The yields of the acids (12a) or (12c) were, however, not improved when hexamethylphosphoric triamide (HMPA) was added; when the reactions were run in diethyl ether, toluene, or dimethoxyethane, or in the presence of Cu^{I}I, only starting material (9) was isolated. Similar yields of the acid (12a) were obtained when n-BuLi–TMEDA was used as base in place of LDA.

Condensations between the dianion (10) and aldehydes or ketones were much more sluggish than the corresponding reactions of the furan dianion (1). Nevertheless, good yields of the hydroxy-acids (13a—c) were obtained from n-heptanal, benzaldehyde, and acetone, respectively, the acids (13a) and (13c) being isolated after diazomethylation as their methyl esters (13d) and (13e), respectively.

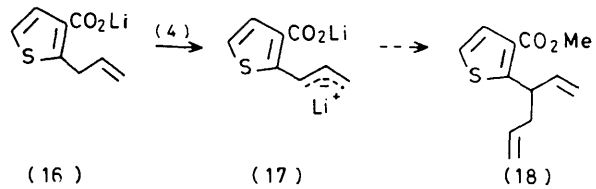
We have also examined the synthetic utility of the dianion (4)[5] derived from thiophen-3-carboxylic acid (14). As in the case of the dianion (10), we found that the dianion (4) was completely formed within *ca.* 10 min using 2.0 equiv. of LDA at −78 °C. Dianion (4) was significantly more stable than its isomer (10) with respect to protonation, which was still not complete after 3 h at room temperature. Throughout all this work we found no evidence of metallation at the 5-position in compound (14).

Dianion (4) was alkylated very cleanly by methyl iodide to give the acid (15a) in 87% yield. However, alkylation with ethyl iodide, and probably its high homologues, could not be

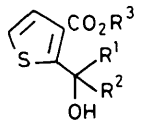


(14) (4) (15)

a; R = Me
b; R = Et



(16) (17) (18)



(19)

a; R^1 = $Me[CH_2]_5$, R^2 = R^3 = H
b; R^1 = Ph, R^2 = R^3 = H
c; R^1 = R^2 = Me, R^3 = H
d; R^1 = Ph, R^2 = H, R^3 = Me
e; R^1 = R^2 = R^3 = Me

effected in high yield under a variety of conditions; in our hands the best isolated yield of compound (15b), as its methyl ester, was 26%. In contrast to the case of the dianion (10), we were unable to detect more than trace amounts of a benzyl derivative of compound (14) when the dianion (4) was treated with benzyl bromide. However, compound (4) did couple with allyl bromide but the product was not the expected 2-allyl derivative (16) but rather the bis-allyl compound (18) which was isolated in 38% yield after esterification and chromatography. Only trace amounts of the methyl ester of compound (16) were detected. Presumably, the ester (18) is formed by way of the dianion (17), derived in turn from compound (16), by reaction with the original dianion (4). Hydrogenation of the olefin (18) gave the expected 2-(1-ethylbutyl) derivative.

Condensation between the dianion (4) and aldehydes or ketones was relatively slow but, as in the case of the dianion (10), good yields of the expected adducts (19a—c) were realised from n-heptanal, benzaldehyde, and acetone, respectively; the latter two products were characterised as their methyl esters (19d) and (19e), respectively.

In general, the thiophen dianions (4) and (10) are more stable and less reactive than the corresponding furan dianions (1) and (2). Whereas the latter are rapidly protonated at *ca.* −30 °C, compounds (4) and (10) appear to be relatively stable at this temperature. Also notable is the marked difference in reactivity with carbonyl compounds; the furan dianions (1) and (2) appeared to react instantly and virtually quantitatively at −78 °C while the thiophens (4) and (10) required much higher temperatures and the condensations generally resulted in only *ca.* 80% conversion into the desired products.

During the later stages of this work Gould and Lee[13] reported that dianions related to compound (10) could be obtained from methylated thiophen-2-carboxylic acids using LDA. Their results are similar to ours except that they found that 3-methylthiophen-2-carboxylic acid underwent metallation at *both* the 5- and the 3-methyl-position. By contrast, we have observed that 3-methylfuran-2-carboxylic acid is only metallated at the 5-position.[2]

Experimental

For general details, see ref. 2. Thiophen-2-carboxylic acid (9) was obtained from Aldrich and was used as received after being

dried *in vacuo*. Thiophen-3-carboxylic acid (14) was prepared from thiophen-3-carbaldehyde (Aldrich) by oxidation using silver oxide.[14]

Preparation of the Dianions (10) *and* (4) *from Thiophen-2- and -3-carboxylic Acid.—General procedure.* A solution of the thiophencarboxylic acid (0.32 g, 2.5 mmol) in THF (2 ml) was added dropwise *via* a syringe to a stirred solution of LDA [5 mmol; prepared from n-butyl-lithium (2.65 ml of a 1.9M solution in hexane) and di-isopropylamine (0.7 ml)] in THF (10 ml) maintained at −78 °C under nitrogen. The progress of the metallation was monitored by withdrawing aliquots into deuterium oxide and analysing the products by ^{1}H n.m.r. spectroscopy. Both dianions were completely formed after *ca.* 10 min at −78 °C. The electrophile was then added, either neat or in THF (1 ml), under the conditions detailed below.

The reaction mixtures were worked up by dilution with water (30 ml) followed by washing with diethyl ether (2 × 15 ml). The aqueous solutions were then acidified with solid citric acid and were extracted with diethyl ether (3 × 15 ml). The combined extracts were washed with brine (20 ml) and were then dried and evaporated to dryness.

5-Methylthiophen-2-carboxylic Acid (11a).—A solution of the dianion (10) (2.5 mmol) was treated with methyl iodide (0.16 ml, 2.5 mmol) at −78 °C. An instantaneous reaction occurred. The cooling bath was removed and the mixture was stirred for 0.5 h and was then worked up to give the acid (11a) which crystallised from water–ethanol (19 : 1) as needles (0.282 g, 80%), m.p. 138—139 °C (lit.,[15] 138—139 °C); $\nu_{max.}$ ($CHCl_3$) 1 678 cm^{-1}; τ 2.38 (d, *J* 4 Hz, 3-H), 3.29 (d, *J* 4 Hz, 4-H), and 7.48 (Me); *m/z* 142 (100%), 141 (20), 125 (68), and 97 (95).

5-Ethylthiophen-2-carboxylic Acid (11b).—A solution of the dianion (10) (2.5 mmol) was treated with ethyl iodide (0.2 ml, 2.5 mmol) at −78 °C. The mixture was kept for 0.25 h at this temperature, the cooling bath was removed, and the mixture was stirred for a further 0.5 h and was then worked up to give the acid (11b) which crystallised from water–ethanol (9 : 1) as a powder (0.324 g, 83%), m.p. 65—66 °C (lit.,[16] 71 °C); $\nu_{max.}$ ($CHCl_3$) 1 685 cm^{-1}; τ 2.36 (d, *J* 4 Hz, 3-H), 3.25 (d, *J* 4 Hz, 4-H), 7.13 (q, *J* 7 Hz, C*H*$_2$Me), and 8.68 (t, *J* Hz, CH$_2$*Me*); *m/z* 156 (41%), 141 (100), and 111 (12).

5-Trimethylsilylthiophen-2-carboxylic Acid (11c).—Trimethylsilyl chloride (0.33 ml, 2.5 mmol) was added to a solution of the dianion (10) (2.5 mmol) at −78 °C. A rapid reaction appeared to occur. The cooling bath was removed and the mixture was stirred for 0.5 h and was then worked up to give the acid (11c) which crystallised from water–ethanol (6 : 1) as needles (0.425 g, 85%), m.p. 133—134 °C (lit.,[17] 134—135 °C); $\nu_{max.}$ ($CHCl_3$) 1 680 cm^{-1}; τ 2.14 (d, *J* 4 Hz, 3-H), 2.82 (d, *J* 4 Hz, 4-H), and 9.71 (Me_3Si); *m/z* 200 (16%), 185 (100), and 75 (25).

Methyl 5-Allylthiophen-2-carboxylate (12b).—TMEDA (0.76 ml, 5 mmol) was added to a solution of the dianion (10) (2.5 mmol) at −78 °C. The mixture was kept for 5 min at this temperature, allyl bromide (0.22 ml, 2.5 mmol) was added, and the cooling bath was removed. After being kept for 1 h the mixture was worked up to give a 1 : 1 mixture (ratio from ^{1}H n.m.r.) (0.35 g) of the starting acid (9) and the desired acid intermediate (12a). The crude mixture was esterified with ethereal diazomethane and the product was chromatographed over silica gel with methylene dichloride as eluant to give the *ester* (12b) as an oil (0.18 g, 40%) with $\nu_{max.}$ (CCl_4) 1 710 cm^{-1}; τ (CCl_4) 2.46 (d, *J* 4 Hz, 3-H), 3.26 (d, *J* 4 Hz, 4-H), 3.83—4.29 (m, C*H*=CH$_2$), 4.74—4.99 (m, CH=C*H*$_2$), 6.19 (CO_2Me), and 6.45 (d, *J* 7 Hz, C*H*$_2$CH=); *m/z* 182 (65%) and 151 (100) (Found: C, 59.7; H, 5.6%; *M*$^+$, 182.0395. $C_9H_{10}O_2S$ requires C, 59.3; H, 5.5%; *M*, 182.0401).

Methyl thiophen-2-carboxylate (0.17 g) was also isolated.

Methyl 5-Benzylthiophen-2-carboxylate (12d).—Benzyl bromide (0.3 ml, 2.5 mmol) was added to a solution of the dianion (10) (2.5 mmol) at −78 °C and the cooling bath was removed. After being kept for 1 h the mixture was worked up as above and the crude acid product (12c) was esterified with ethereal diazomethane. Chromatography of the mixed esters over silica gel with methylene dichloride as eluant gave the *ester* (12d) (0.34 g, 58%) as a viscous oil which resisted attempted crystallisation; $\nu_{max.}$ (CCl_4) 1 716 cm^{-1}; τ (CCl_4) 2.48 (d, *J* 4 Hz, 3-H), 2.80br (Ph), 3.31 (d, *J* 4 Hz, 4-H), 5.90 (CH_2), and 6.20 (CO_2Me); *m/z* 232 (63%), 217 (17), 201 (20), 173 (100), 171 (17), and 129 (26) (Found: *M*$^+$, 232.0566. $C_{13}H_{12}O_2S$ requires *M*, 232.0558).

Methyl thiophen-2-carboxylate (0.11 g) was also isolated.

The conversion could be improved by *ca.* 8% by the addition of TMEDA (5 mmol) to the dianion solution prior to the addition of benzyl bromide.

Methyl 5-(1-Hydroxyheptyl)thiophen-2-carboxylate (13d).—Heptanal (0.34 ml, 2.5 mmol) was added to a solution of the dianion (10) (2.5 mmol) at −78 °C and the cooling bath was removed. After being kept for 1 h the mixture was worked up as above and the crude product was esterified with ethereal diazomethane. Chromatography of the product over silica gel with methylene dichloride as eluant then gave the *ester* (13d) (0.41 g, 64%) as fine *needles*, m.p. 69—71 °C; $\nu_{max.}$ (CCl_4) 3 620 and 1 723 cm^{-1}; τ (CCl_4) 2.94 (d, *J* 4 Hz, 3-H), 3.58 (d, *J* 4 Hz, 4-H), 5.52 [t, *J* 6 Hz, C*H*(OH)], 6.06br (OH), 6.40 (CO_2Me), 8.37 [m, C*H*$_2$CH(OH)], 8.77br (4 × CH$_2$), and 9.17 (t, *J* 6 Hz, CH$_2$*Me*); *m/z* 256 (6%), 171 (100), 143 (74), 139 (86), and 111 (69) (Found: C, 60.9; H, 8.1. $C_{13}H_{20}O_3S$ requires C, 60.9; H, 7.8%).

Methyl thiophen-2-carboxylate (0.07 g) was also isolated.

5-(α-Hydroxybenzyl)thiophen-2-carboxylic Acid (13b).—Benzaldehyde (0.26 ml, 2.5 mmol) was added to a solution of the dianion (10) (2.5 mmol) at −78 °C and the cooling bath was removed. After being kept for 0.5 h the mixture was worked up as above; ^{1}H n.m.r. analysis of the product showed *ca.* 90% conversion into the desired compound. Crystallisation of the crude product from water–methanol (5 : 1) gave the *acid* (13b) (0.44 g, 75%) as needles, m.p. 154—155 °C; $\nu_{max.}$ (Nujol) 3 340 and 1 676 cm^{-1}; τ [$(CD_3)_2CO$] 2.32 (d, *J* 4 Hz, 3-H), 2.36—2.66 (m, Ph), 3.01 (d, *J* 4 Hz, 4-H), and 3.87 [C*H*(OH)]; *m/z* 234 (93%), 217 (62), 189 (48), 155 (85), and 129 (100) (Found: C, 61.4; H, 4.5. $C_{12}H_{10}O_3S$ requires C, 61.5; H, 4.3%).

Methyl 5-(1-Hydroxy-1-methylethyl)thiophen-2-carboxylate (13e).—Acetone (0.19 ml, 2.5 mmol) was added to a solution of the dianion (10) (2.5 mmol) at −78 °C and the cooling bath was removed. After being kept for 1 h the mixture was worked up as above and the product (0.41 g) was esterified with ethereal diazomethane and chromatographed on silica gel (methylene dichloride as eluant) to give the desired *ester* (13e) (0.31 g, 63%) as prisms, m.p. 64—66 °C; $\nu_{max.}$ (CCl_4) 3 600 and 1 720 cm^{-1}; τ 2.70 (d, *J* 4 Hz, 3-H), 3.36 (d, *J* 4 Hz, 4-H), 6.29 (CO_2Me), 6.9br (OH), and 8.40 (2 × Me); *m/z* 200 (8%), 185 (51), 182 (56), and 151 (100) (Found: C, 54.1; H, 6.2. $C_9H_{12}O_3S$ requires C, 54.0; H, 6.0%).

Methyl thiophen-2-carboxylate (0.08 g) was also isolated.

2-*Methylthiophen*-3-*carboxylic Acid* (15a).—Methyl iodide (0.16 ml) was added to a solution of the dianion (4) at −78 °C and the cooling bath was removed. After being kept for 1 h the mixture was worked up as above and the product was crystallised from water–ethanol (9 : 1) to give the *acid* (15a) (0.31 g, 87%), m.p. 114—116 °C (lit.,[18] 115—117 °C); $\nu_{max.}$ ($CHCl_3$) 1 685 cm^{-1}; τ 2.65 (d, *J* 5.5 Hz, 5-H), 3.09 (d, *J* 5.5 Hz, 4-H), and 7.26 (Me); *m/z* 142 (100%), 125 (23), 124 (22), and 97 (79).

Methyl 2-*Ethylthiophen*-3-*carboxylate*.—Ethyl iodide (0.2 ml) was added to a solution of the dianion (4) (2.5 mmol) at −78 °C. The mixture was slowly warmed to 0 °C and was maintained at this temperature overnight. Standard work-up gave a product (0.33 g) which contained *ca.* 30% of the desired intermediate 2-ethyl-acid (15b). After esterification of the acid with ethereal diazomethane, and chromatography of the product over silica gel (methylene dichloride as eluant), the *methyl ester* (0.10 g) was obtained as an oil, $\nu_{max.}$ 1 721 cm^{-1}; τ (CCl_4) 2.77 (d, *J* 5.5 Hz, 5-H), 3.13 (d, *J* 5.5 Hz, 4-H), 6.22 (CO_2Me), 6.83 (q, *J* 7 Hz, CH_2Me), and 8.69 (t, *J* 7 Hz, CH_2Me); *m/z* 170 (71%), 169 (58), 155 (62), 139 (50), and 137 (100) (Found: M^+, 170.0412. $C_8H_{10}O_2S$ requires *M*, 170.0401).

Methyl thiophen-3-carboxylate (0.21 g) was also isolated.

Methyl 2-(1-*Vinylbut*-3-*enyl*)*thiophen*-3-*carboxylate* (18).—Allyl bromide (0.45 ml) was added to a solution of the dianion (4) at −78 °C. The mixture was slowly warmed to 0 °C and was stirred at this temperature for 16 h. The usual work-up gave a mixture (0.39 g) which was esterified with ethereal diazomethane. Chromatography of the resulting mixture of esters over silica gel (methylene dichloride as eluant) then gave the *title ester* (18) (0.21 g, 38%) as an oil, $\nu_{max.}$ (CCl_4) 1 718 and 1 640 cm^{-1}; τ 2.61 (d, *J* 5.5 Hz, 5-H), 2.89 (d, *J* 5.5 Hz, 4-H), 3.95—4.09 (m, CH=CH_2), 4.14—4.31 (m, CH=CH_2), 4.84—5.03 (m, 2 × CH=CH_2), 5.23 [apparent q, *J* 7.25 Hz, CH(CH=CH_2)CH_2] 6.15 (CO_2Me), and 7.47 (apparent t, *J* 7 Hz, CH_2CH=CH_2); *m/z* 222 (5%), 221 (3), 189 (15), and 181 (100) (Found: C, 64.9; H, 6.6%; M^+, 222.0694. $C_{12}H_{14}O_2S$ requires C, 64.9; H, 6.3%; *M*, 222.0714).

Methyl thiophen-3-carboxylate (0.14 g) was also isolated.

Methyl 2-(1-*Ethylbutyl*)*thiophen*-3-*carboxylate*.—A solution of compound (18) (45 mg, 0.2 mmol) in ethyl acetate (5 ml) containing 10% Pd–C (5 mg) was shaken at 15 °C under hydrogen at 1 atm until *ca.* 9 ml (0.4 mmol) of hydrogen had been taken up. The solution was filtered and the filtrate was evaporated to dryness to give the *title ester* (40 mg) as an oil, $\nu_{max.}$ (CCl_4) 1 718 cm^{-1}; τ 2.63 (d, *J* 5.5 Hz, 5-H), 2.88 (d, *J* 5.5 Hz, 4-H), 6.08 (m, $CH[CH_2]_2$), 6.16 (CO_2Me), 8.18—8.88 (m, 3 × CH_2), and 9.16br (t, *J* *ca.* 8 Hz, 2 × Me); *m/z* 226 (12%), 195 (30), 155 (48), 151 (33), 137 (23), 111 (22), and 85 (100) (Found: M^+, 226.0989. $C_{12}H_{18}O_2S$ requires *M*, 226.1027).

2-(1-*Hydroxyheptyl*)*thiophen*-3-*carboxylic Acid* (19a).—Heptanal (0.34 ml) was added to a solution of the dianion (4) (2.5 mmol) at −78 °C. The mixture was allowed to warm slowly to 0 °C and was then maintained at this temperature overnight. Standard work-up gave a solid which was crystallised from hexane–ethyl acetate (9 : 1) to give the *acid* (19a) (0.46 g, 76%) as prisms, m.p. 103—105 °C; $\nu_{max.}$ ($CHCl_3$) 1 681 cm^{-1}; τ 2.71 (d, *J* 5.5 Hz, 5-H), 3.05 (d, *J* 5.5 Hz, 4-H), 4.75 [t, *J* 6 Hz, CH(OH)], 8.16 [m, CH_2CH(OH)], 8.69br (4 × CH_2), and 9.13 (t, *J* 6 Hz, CH_2Me); *m/z* 242 (11%), 224 (9), 157 (100), 139 (98), and 111 (83) (Found: C, 59.4; H, 7.6. $C_{12}H_{18}O_3S$ requires C, 59.5; H, 7.4%).

Methyl 2-(α-*Hydroxybenzyl*)*thiophen*-3-*carboxylate* (19d).—Benzaldehyde (0.26 ml) was added to a solution of the dianion (4) (2.5 mmol) at −78 °C and the resulting mixture was stirred at 0 °C overnight. The usual work-up gave a mixture (0.51 g) which contained *ca.* 80% of the desired intermediate acid (19b), according to ^1H n.m.r. analysis. The mixture was esterified with ethereal diazomethane and the esters were separated by chromatography over silica gel with methylene dichloride as eluant to give the *ester* (19d) (0.42 g, 68%) as a viscous oil which resisted crystallisation; $\nu_{max.}$ (CCl_4) 3 460 and 1 697 cm^{-1}; τ (CCl_4) 2.47—2.78 (total 6 H, m, Ph and 5-H), 2.94 (d, *J* 5.5 Hz, 4-H), 3.62br [sharpened on addition of D_2O, CH(OH)], 5.65br (OH), and 6.17 (CO_2Me); *m/z* 248 (30%), 215 (100), 171 (45), 139 (45), and 111 (60) (Found: C, 62.8; H, 4.7. $C_{13}H_{12}O_3S$ requires C, 62.9; H, 4.8%).

Methyl thiophen-3-carboxylate (0.05 g) was also isolated.

Methyl 2-(1-*Hydroxy*-1-*methylethyl*)*thiophen*-3-*carboxylate* (19e).—Acetone (0.19 ml) was added to a solution of the dianion (4) (2.5 mmol) at −78 °C and the mixture was warmed to 0 °C and stirred at this temperature overnight. The usual work-up afforded a mixture (0.37 g) containing *ca.* 70% (^1H n.m.r. analysis) of the desired intermediate acid (19c). Esterification with ethereal diazomethane followed by chromatography over silica gel with methylene dichloride as eluant gave the *ester* (19e) (0.28 g, 56%) as needles, m.p. 39.5—40.5 °C; $\nu_{max.}$ (CCl_4) 3 430 and 1 702 cm^{-1}; τ 2.46 (d, *J* 5.5 Hz, 5-H), 2.89 (d, *J* 5.5 Hz, 4-H), 3.49 (OH), 6.00 (CO_2Me), and 8.23 (2 × Me); *m/z* 200 (<1%), 185 (64), 153 (100), and 111 (79) (Found: C, 53.8; H, 6.2. $C_9H_{12}O_3S$ requires C, 54.0; H, 6.0%).

Methyl thiophen-3-carboxylate (0.09 g) was also isolated.

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