# The Generation and Chemistry of Dianions derived from Furancarboxylic Acids

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Methods for the generation of the dianionic species lithium 5-lithiofuran-2-carboxylate (5) and lithium 2-lithio-furan-3-carboxylate (21) from furan-2- and furan-3-carboxylic acids respectively are described. The reactions of (5) and (21) with a range of electrophiles have been examined; in general these are very efficient with aldehydes and ketones but not as satisfactory with alkyl halides and epoxides. The dianions do not couple with allylic or benzylic halides, nor with nitriles or orthoesters. The generation of lithium-5-lithio-3-methylfuran-2-carboxylate (15) from 3-methylfuran-2-carboxylic acid is also described; the chemistry of (15) is very similar to (5) derived from furan-2-carboxylic acid.

THE formation of dianions (1) directly from alkanoic acids and the powerful base lithium di-isopropylamide (LDA) was first reported by Creger [1] who demonstrated the considerable synthetic utility of these species, which has subsequently been exemplified by a number of other workers.[2] More recently,[3] it has been found that αβ-unsaturated carboxylic acids can similarly be converted into dianions, e.g. (2) from crotonic acid. The mode of reaction of such intermediates (i.e. reaction with electrophiles at the α- and/or γ-positions) is heavily dependent on the nature of the counterions. An extension of this type of procedure is the generation of dianions from acetylenic acids, which generally leads to mixtures of substituted ynoic acids and allenic acids, after reaction with electrophiles.[4] The rather different dianion (3)


(1)   (2)   (3)
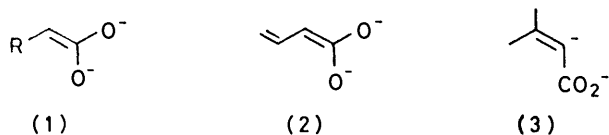
has been obtained from the corresponding α-bromo-acid by metal–halogen exchange.[5]

An interest in the synthesis of naturally occurring furanoterpenes,[6] together with a consideration of the aforementioned work, led us to investigate the possibility of obtaining dianionic species directly from furancarboxylic acids. The synthetic utility of metallated furans has been amply demonstrated in recent years. A variety of such intermediates has been used, the most common being furyl-lithium species, which can be obtained by various means such as direct metallation of furans, at the α-position if available, using n-butyl-lithium [7] or LDA,[8] or by metal–halogen exchange [9,10] (allowing the preparation of β-lithio-furans) or mercury–lithium exchange.[11] Some use has also been made of furyl Grignard reagents [12] and furyl mercury intermediates.[13] We have now established that dianionic species can indeed be formed directly from furancarboxylic acids, and we report herein methods for their generation, together with a survey of their reactivity with a representative range of electrophiles.[14]

Addition of a solution of furan-2-carboxylic acid (4) in tetrahydrofuran (THF) to LDA (2 equivalents) in

THF at −78 °C produced, after 0.5 h, an orange suspension; a sample was withdrawn and immediately quenched with D_2O. A ^1H n.m.r. spectrum of the product showed a virtual absence of resonances at

(4)   (5)   (6)
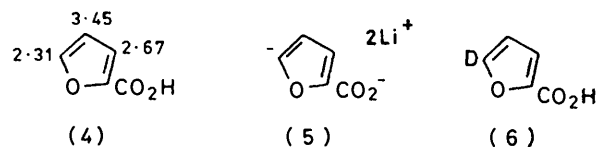
τ 2.31 [see ^1H n.m.r. data associated with formula (4)], indicating the formation of 5-deuteriofuran-2-carboxylic acid (6) and thereby the intermediacy of dianion (5). All other spectral and analytical data exhibited by (6) were consistent with the assigned structure.[10] There was no indication that any other isomers (i.e. [3-^2H]- or [4-^2H]-furan-2-carboxylic acids) had been formed. When a solution of the dianion (5) was slowly warmed and samples were treated with D_2O, it was found that deuterium incorporation slowly decreased until at ca. −10 °C, pure furan-2-carboxylic acid (4) only was isolated. Presumably, the THF solvent acts as the proton source, although this point was not investigated further. In these experiments, the acids (4) and (6) (or mixtures of the two) were always isolated in very high yield and no evidence was found of any decomposition of (5), other than protonation, or the formation of any isomers of (6).

Alkylation of (5) with methyl iodide occurred very rapidly at −78 °C to give 5-methylfuran-2-carboxylic

(7)   (8)   (9)

a; R = Me   a; R = H

b; R = Et   b; R = Me
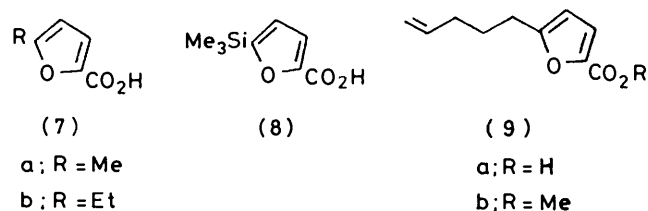
acid (7a) in very high yield. Reaction with trimethyl-silyl chloride was similarly fast and give acid (8), again in very high yield, after aqueous work-up. However, other alkylation reactions were much slower, and only occurred above ca. −30 °C. Thus reaction between (5)

and ethyl iodide at −20 to −10 °C for 3 h gave (7b) in *ca.* 50% isolated yield (69% by ^{1}H n.m.r.) while reaction between (5) and 1-iodopent-4-ene gave (9a) in 55% yield (^{1}H n.m.r.) leading to a 45% isolated yield of the corresponding ester (9b), following esterification (CH_2N_2) and chromatography. These lower yields can be explained, in part at least, by the loss of the dianion (5) by protonation at these higher temperatures (see above). Once again, the material balance of these reactions was very high (>90%). Unfortunately, no coupling of (5) was observed with alkyl tosylates nor with allylic or benzylic halides under a variety of conditions, the starting acid (4) being recovered virtually quantitatively in all cases.

We attempted to modify the reactivity of (5) by the addition of various combinations of copper(I) iodide, hexamethylphosphoramide, and tetramethylethylenediamine, using both catalytic and equivalent amounts of these reagents. However, all such modifications failed to improve the yields of (7b) and (9a) and were similarly ineffective in reactions between (5) and allylic or benzylic halides (*e.g.* geranyl bromide; benzyl bromide); no more than traces (<5%) of the desired products were formed.

In contrast, reactions between (5) and aldehydes or ketones, both enolisable and non-enolisable, were very clean and rapid at −78 °C, and gave the alcohols (10a—d) in 80—85% isolated yields, using benzaldehyde, benzophenone, acetone, and heptanal respectively. After esterification, the alcohol (10c) derived from ace-


(10)

(11)

a ; R^1= Ph, R^2= H

b ; R^1= R^2= Ph

c ; R^1= R^2= Me

d ; R^1= Me[CH$_2$]$_5$, R^2= H
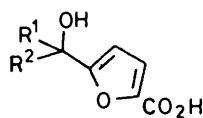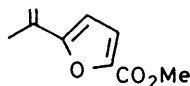
tone could be readily dehydrated to give (11), thus providing an entry to 5-vinylfuran-2-carboxylates. The dianion (5) did not couple to less reactive electrophiles such as nitriles and orthoformates and with epoxides only poor yields (20—30%) of the expected products were isolated (see later).

We have also examined the nature of the dianionic species derived from 3-methylfuran-2-carboxylic acid (12). At the outset, it was not clear whether the 5-position or the 3-methyl group of the acid would be metallated in view of Creger's observation [15] that the dianion (13) can be formed from *o*-toluic acid and particularly in view of some recent work by a Japanese group [16] in which the dianion (14) was obtained from 2,4-dimethylfuran-3-carboxylic acid. In the event, treatment of (12) with two equivalents of LDA at −78 °C produced a pale yellow solution which on treatment
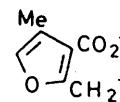
with deuterium oxide gave only the 5-deuterio-derivative (16a) indicating the exclusive formation of the dianion (15). No evidence of metallation at the 3-methyl group was found. Predictably, the behaviour of (15) with electrophiles was found to be closely similar to that of dianion (5), derived from furan-2-carboxylic acid (4).
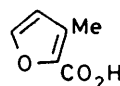

(12)
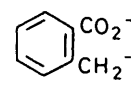
(13)

(14)

Coupling with methyl iodide was very rapid and led to an excellent yield of 3,5-dimethylfuran-2-carboxylic acid (16b) while the reaction between (15) and ethyl iodide (and presumably other alkyl iodides) was much more sluggish and resulted in only a 60% conversion of (15) into 5-ethyl-3-methylfuran-2-carboxylic acid (16c). As in the case of the dianion (5), (15) reacted extremely rapidly and cleanly with carbonyl compounds giving, for example, the alcohols (17a—c) in high yield. The unsaturated furan esters (18) and (19) were also readily

(15)

(16)

(17)
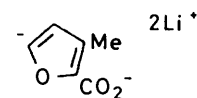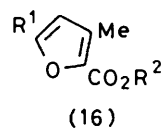
a ; R^1= D, R^2= H

b ; R^1= Me, R^2= H

c ; R^1= Et, R^2= H

d ; R^1= Et, R^2= Me
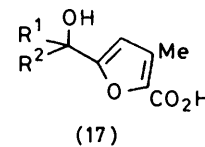
a ; R^1= Ph, R^2= H

b ; R^1= R^2= Me

c ; R^1 R^2 = −[CH$_2$]$_5$
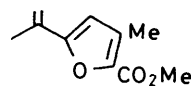
(18)
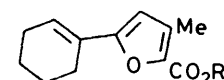
(19)

a ; R = H

b ; R = Me

prepared from (17b) and (17c) respectively, by sequential esterification and acid-catalysed dehydration. Also parallel to (5) was the failure of (15) to couple with allylic halides, nitriles, and orthoformates under the conditions used.

Finally, we have found that furan-3-carboxylic acid (20) also gives rise to only one dianionic species. Addition of a solution of (20) in THF to two equivalents of LDA in THF at −78 °C produced a white precipitate which gradually dissolved during 0.5 h to give a clear,

yellow-green solution. Treatment of a sample of this solution with deuterium oxide gave a homogeneous product which showed a complete absence of resonances at τ 1.91 (furyl 2-H). All other spectral data were consistent with the formation of 2-deuteriofuran-3-carboxylic acid (22a). Furthermore, addition of methyl iodide to the remainder of the dianion solution resulted in the exclusive formation of 2-methylfuran-3-carboxylic

(20) (21) (22)

a ; R = D
b ; R = Me
c ; R = Et
d : R = Me$_3$Si
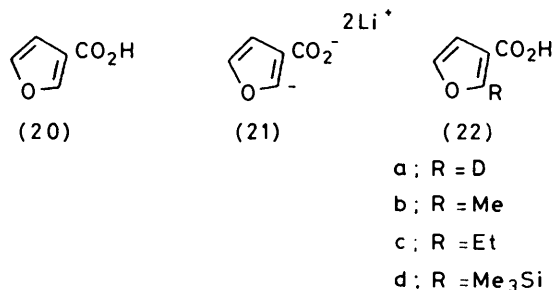
acid (22b) thus establishing the intermediacy of the dianion (21). No evidence of metallation at the 5-position of (20) was found.

We expected that the reactivity of (21) would be somewhat dissimilar to that of (5) and (15), but the only differences observed were in alkylation reactions, with alkyl halides other than methyl iodide, which were slightly less efficient than the corresponding reactions of (5) and (15). Thus, with ethyl iodide, (22c) was formed in 31% isolated yield, the remaining material being recovered furan-3-carboxylic acid (ca. 55%). The reactions of (21) with trimethylsilyl chloride, aldehydes, and ketones were all extremely rapi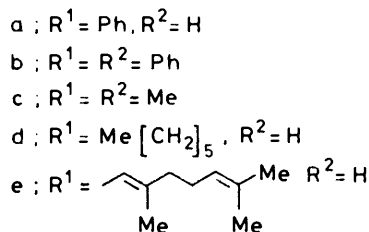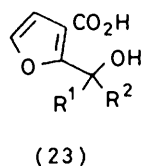d and clean at −78 °C leading to the 2-substituted furan-3-carboxylic acids (22d) and (23a—e) in high yields. The latter products

(23)

a ; R^1 = Ph, R^2 = H
b ; R^1 = R^2 = Ph
c ; R^1 = R^2 = Me
d ; R^1 = Me[CH$_2$]$_5$, R^2 = H
e ; R^1 = [structure] Me R^2 = H

serve as precursors to lactones (24); thus, treatment of (23c) and (23d) with benzenesulphonyl chloride in dry pyridine led to (24a) and (24b) respectively.

As with the dianionic species derived from the furan-2-carboxylic acids, (21) did not couple with allylic or benzylic halides nor with nitriles or orthoformates. Modifications of (21) by the addition of copper(I)

iodide etc., as with (5) (see above), did not result in any improvement, and in all cases furan-3-carboxylic acid was recovered in high yield. The dianion (21) did react slowly with 1,2-epoxyheptane at ca. −20 °C to give,

(24) (25)

a ; R^1 = R^2 = Me
b ; R^1 = Me[CH$_2$]$_5$, R^2 = H
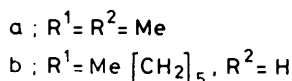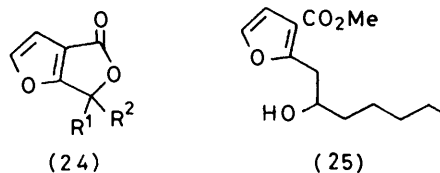
after esterification and chromatography, the 2-(2-hydroxyheptyl) derivative (25) in 32% yield together with recovered methyl furan-3-carboxylate (57%). The low conversion was due to the loss of the dianion (21) by protonation at this temperature, as was observed with the dianion (5).

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are corrected. Infrared spectra were obtained using a Perkin-Elmer 710B spectrometer and ultraviolet spectra determined in ethanol solution using a Pye-Unicam SP800 spectrometer. Molecular weights were determined from mass spectra, obtained using an A.E.I. MS 902 spectrometer. ^{1}H N.m.r. spectra were obtained using a JEOL MH-100 spectrometer, with CDCl$_3$ as solvent, unless otherwise stated, and tetramethylsilane as internal standard. Preparative g.l.c. was carried out using a Pye 105 instrument fitted with a 15 ft × ⅜ in glass column packed with 3% OV225 on Gas Chrome Q at a nitrogen flow rate of ca. 80 ml min^{-1}.

Tetrahydrofuran (THF) was distilled from LiAlH$_4$ immediately prior to use. All organic solutions were dried over anhydrous magnesium sulphate. Light petroleum refers to the fraction of b.p. 40—60 °C.

Generation and Reactions of Lithium 5-Lithiofuran-2-carboxylate (5); *General Procedure.*—n-Butyl-lithium (2.65 ml of a 1.9M-solution in hexane, 5 mmol) was added to di-isopropylamine (0.7 ml, 5 mmol; freshly distilled from solid KOH) with stirring at −10 °C under nitrogen. After 0.25 h, the resulting viscous oil was diluted with THF (10 ml), cooled to −78 °C, and a solution of furan-2-carboxylic acid (0.28 g, 2.5 mmol) in THF (5 ml) was added. The mixture was stirred at −78 °C for 0.5 h, then treated with an electrophile, which was added neat if liquid or, if solid, in THF solution (ca. 1 ml mmol^{-1}). After the reaction period (see below), the reaction mixture was diluted with water and washed with ether (2 × 10 ml). The aqueous portion was acidified with 10% aqueous hydrochloric acid and ether extracted (3 × 15 ml). The combined extracts were washed with saturated brine (30 ml), and then dried and evaporated.

[5-^{2}H]*Furan-2-carboxylic Acid* (6).—Deuterium oxide (0.5 ml, excess) was added to the dianion (5), prepared by the general procedure. The resulting mixture was allowed to reach ambient temperature during 1 h, then worked up as

usual to give the deuterio-acid (6), which crystallised from water as needles (0.26 g), m.p. 129—130 °C, (lit.,[10] 129—130 °C), $\nu_{max.}$ (KBr) 1 681 cm^{-1}, τ 2.67 (d, J 3.5 Hz, 3-H), and 3.45 (d, J 3.5 Hz, 4-H), m/e 113 (100%), 96 (89), and 40 (71). The ^{1}H n.m.r. spectrum indicated >95% deuterium incorporation.

5-Methylfuran-2-carboxylic Acid (7a).—By the general procedure, treatment of the dianion (5) with methyl iodide (0.3 ml) at −78 °C resulted in an apparently instantaneous reaction. The mixture was warmed to room temperature during *ca.* 0.5 h, then worked up as usual to give the acid (7a), which crystallised from water as large needles (0.28 g), m.p. 106.5—107.5 °C (lit.,[17] 108—109 °C), τ −1.90br (CO$_2$H), 2.80 (d, J 3.5 Hz, 3-H), 3.86 (d, J 3.5 Hz, 4-H), and 7.60 (5-CH$_3$), m/e 126 (84%), 109 (29), 81 (33), and 53 (100).

5-Ethylfuran-2-carboxylic Acid (7b).—A solution of dianion (5), prepared as usual, was warmed to −40 °C and ethyl iodide (0.25 ml) was added. The resulting mixture was stirred at −30 °C for 0.25 h, then at −20 to −10 °C for 3 h, then worked up as usual. A ^{1}H n.m.r. spectrum of the product showed that *ca.* 70% ethylation had occurred. Careful crystallisation from water gave the acid (7b) (0.18 g) as prisms, m.p. 89—91 °C (lit.,[7c] 91—92 °C), $\nu_{max.}$ (CHCl$_3$) 1 690 cm^{-1}, τ −1.50br (CO$_2$H), 2.80 (d, J 3.5 Hz, 3-H), 3.86 (d, J 3.5 Hz, 4-H), 7.28 (q, J 7 Hz, CH$_2$CH$_3$), and 8.74 (t, J 7 Hz, CH$_2$CH$_3$), m/e 140 (63%), 125 (100), 95 (29), 41 (21), and 39 (29).

5-Trimethylsilylfuran-2-carboxylic Acid (8).—Trimethylsilyl chloride (0.8 ml) was added to the dianion (5), prepared by the general procedure, at −78 °C, and the resulting mixture was warmed to room temperature during 0.5 h, then diluted with water (3 ml) and acidified with 2M-hydrochloric acid (10 ml). The mixture was vigorously stirred for 0.5 h, then diluted with water (30 ml) and extracted with ether (3 × 15 ml). The combined extracts were washed with brine, dried, and evaporated to leave a residue which was crystallised from light petroleum–ether (2 : 1 v/v) to give the *acid* (8) (0.40 g) as prisms, m.p. 109—111 °C, $\lambda_{max.}$ 258 nm (ε 1 200), $\nu_{max.}$ (KBr) 1 678 cm^{-1}, τ −1.46br (CO$_2$H), 2.90 (d, J 3.5 Hz, 3-H), 3.48 (d, J 3.5 Hz, 4-H), and 9.66 (Me$_3$Si), m/e 184 (21%), 169 (82), 75 (100), and 44 (38) (Found: C, 52.2; H, 6.5. C$_8$H$_{12}$O$_3$Si requires C, 52.1; H, 6.6%).

Methyl 5-(Pent-4-enyl)furan-2-carboxylate (9b).—1-Iodopent-4-ene (0.5 g) in THF (1 ml) was added to a solution of the dianion (5), prepared by the general procedure at −78 °C. The cooling-bath was removed and the solution stirred for 1 h, then worked up in the usual way. A ^{1}H n.m.r. spectrum of the product indicated a *ca.* 55% conversion into acid (9a). The mixture was treated with an excess of ethereal diazomethane and the product was chromatographed over silica gel using light petroleum–ether (19 : 1 v/v) as eluant to give the *ester* (9b) (0.22 g) as an oil, $\nu_{max.}$ (film) 1 700 cm^{-1}, τ 2.73 (d, J 3.5 Hz, furyl 3-H), 3.80 (d, J 3.5 Hz, furyl 4-H), 3.94—4.44 (m, CH=CH$_2$), 4.80—5.15 (m, CH=CH$_2$), 6.08 (CO$_2$Me), 7.29 (t, J 7, CH$_2$C(O)=C], and 7.75—8.32 (m, 4 H) (Found: M^+, 194.093 9. C$_{11}$H$_{14}$O$_3$ requires M, 194.094 3).

5-[Hydroxy(phenyl)methyl]furan-2-carboxylic Acid (10a).—Benzaldehyde (0.25 ml) was added, at −78 °C, to the dianion (5), prepared by the general procedure. After the addition, the cooling-bath was removed and the solution was stirred for a further 0.5 h, then worked up as usual to give the *acid* (10a) which crystallised from light petroleum

as prisms (0.47 g) showing m.p. 120—122 °C (decomp.), $\lambda_{max.}$ 263 (infl.) (ε 11 500) and 258 nm (ε 12 000), $\nu_{max.}$ (KBr) 1 680 cm^{-1}, τ[(CD$_3$)$_2$CO] 2.72—3.04 (m, 5 H), 3.10 (d, J 3.5 Hz, 3-H), 3.86 (d, J 3.5 Hz, 4-H), and 4.32 [CH-(OH)], m/e 218 (41%), 173 (100), 113 (58), 105 (41), 77 (70), 51 (47), and 39 (55) (Found: C, 65.8; H, 4.7. C$_{12}$H$_{10}$O$_4$ requires C, 66.1; H, 4.6%).

5-[Hydroxy(diphenyl)methyl]furan-2-carboxylic Acid (10b).—By the general procedure, reaction between the dianion (5) and benzophenone (0.46 g) at −78 °C followed by warming to room temperature gave, after the usual work-up, the acid (10b) (0.60 g) which crystallised from ether as a powder, m.p. 80—82 °C (decomp.), $\nu_{max.}$ (KBr) 1 683 cm^{-1}, τ[(CD$_3$)$_2$CO] 2.80—3.00 (m, 10 H), 3.08 (d, J 3.5 Hz, 3-H), and 3.98 (d, J 3.5, 4-H). Satisfactory microanalytical data were not obtained for this compound.

5-(1-Hydroxy-1-methylethyl)furan-2-carboxylic Acid (10c).—By the general procedure, reaction between the dianion (5) and acetone (0.18 ml) at −78 °C, followed by warming to room temperature and the usual work-up, gave the *acid* (10c) (0.34 g) as a powder, m.p. 90—92 °C, $\nu_{max.}$ (CHCl$_3$) 1 690 cm^{-1}, τ[(CD$_3$)$_2$CO] 2.98 (d, J 3.5 Hz, 3-H), 3.70 (d, J 3.5 Hz, 4-H), and 8.46 (2 × CH$_3$), m/e 170 (11%), 155 (100), 137 (46), 95 (13), 43 (86), and 39 (23) (Found: C, 56.2; H, 6.0. C$_8$H$_{10}$O$_4$ requires C, 56.5; H, 5.9%).

5-(1-Hydroxyheptyl)furan-2-carboxylic Acid (10d).—By the general procedure, reaction between the dianion (5) and heptanal (0.34 ml) at −78 °C, followed by warming to room temperature and the usual work-up, gave the *acid* (10d) which crystallised from light petroleum as a powder (0.41 g), m.p. 82—84 °C, $\lambda_{max.}$ 258 nm (ε 8 300), $\nu_{max.}$ (CHCl$_3$) 1 690 cm^{-1}, τ 2.82 (d, J 3.5 Hz, furyl 3-H), 2.90br (OH), 3.66 (d, J 3.5 Hz, furyl 4-H), 5.29 (t, J 7, CHOH), 8.00—8.26 (m, CH$_2$CHOH), 8.54—8.88 (m, 8 H), and 9.13br (t, J 7 Hz, CH$_3$), m/e 226 (12%), 181 (26), 141 (100), 123 (56), 113 (16), and 55 (26) (Found: C, 64.1; H, 8.6. C$_{12}$H$_{18}$O$_4$ requires C, 63.7; H, 8.0%).

Methyl 5-Isopropenylfuran-2-carboxylate (11).—5-(1-Hydroxy-1-methylethyl)furan-2-carboxylic acid (10c) (50 mg) was esterified with ethereal diazomethane in the usual way to give the methyl ester (50 mg) as an oil, $\nu_{max.}$ (film) 1 702 cm^{-1}, τ 2.95 (d, J 3.5 Hz, 3-H), 3.66 (d, J 3.5 Hz, 4-H), 6.12 (CO$_2$CH$_3$), and 8.41 (2 × CH$_3$). The ester (45 mg) was heated under reflux for 0.5 h in benzene (5 ml) containing toluene-*p*-sulphonic acid (*ca.* 5 mg). The cooled solution was washed with 1M-aqueous sodium hydroxide (2 ml), water (2 ml), and brine (2 ml), and then dried and evaporated. Purification of the residue by preparative g.l.c. at 200 °C gave the *ester* (11) (20 mg) as an oil, $\nu_{max.}$ (film) 1 695 cm^{-1}, τ 2.85 (d, J 3.5 Hz, 3-H), 3.60 (d, J 3.5 Hz, 4-H), 4.23br (s, =CH), 4.83br (s,.=CH), 6.10 (CO$_2$CH$_3$), and 7.92br (s, CH$_3$C=CH$_2$) (Found: M^+, 166.064 1. C$_9$H$_{10}$O$_3$ requires M, 166.063 0).

Lithium 5-Lithio-3-methylfuran-2-carboxylate (15): *General Procedure and 3-Methyl[5-^{2}H]furan-2-carboxylic Acid* (16a).—n-Butyl-lithium (3.8 ml of a 1.6M-solution in hexane; 6 mmol) was added slowly to di-isopropylamine (0.84 ml, 6 mmol), stirred and cooled to −10 °C under nitrogen. The resulting viscous oil was kept at 0 °C for 0.25 h, then cooled to −78 °C, and diluted with THF (9 ml). A solution of 3-methylfuran-2-carboxylic acid [18] (0.38 g; 3 mmol) in THF (2 ml) was added slowly, to give a clear, pale yellow solution of the dianion (15) which was stirred at −78 °C for 0.25 h and then treated with deuterium

oxide (2 ml). The mixture was warmed to room temperature during 0.5 h, then poured into 2M-hydrochloric acid (20 ml) and extracted with ether (3 × 15 ml). The combined extracts were washed with water and brine, and then dried and evaporated. Crystallisation of the residue from aqueous ethanol gave the *acid* (16a) (0.35 g) as needles, m.p. 134.5—135.5 °C, $\nu_{max.}$ (CHCl$_3$) 1 682 cm^{-1}, τ −0.6br (CO$_2$H), 3.61 (furyl 4-H), and 7.65 (CH$_3$), *m/e* 127 (100%) (Found: C, 56.8; H + D, 5.4. C$_6$H$_5$DO$_3$ requires C, 56.7; H + D, 5.5%).

3,5-*Dimethylfuran-2-carboxylic Acid* (16b).—By the procedure described above, the dianion (15) was prepared and treated at −78 °C with methyl iodide (0.4 ml), then warmed to room temperature and worked up as described above to give the *acid* (16b) (0.38 g) which crystallised from light petroleum as prisms, m.p. 145—145.5 (lit.,[17] 146—147 °C), $\nu_{max.}$ (KBr) 1 693 cm^{-1}, τ 4.01 (furyl 4-H) and 7.73 (2 × CH$_3$).

Methyl 5-Ethyl-3-methylfuran-2-carboxylate (16d).—By the general procedure, reaction betwen the dianion (15) and ethyl iodide (0.35 ml) at −78 °C for 0.25 h, followed by warming to room temperature during 1.5 h, gave a mixture (0.41 g) of starting acid (*ca.* 40%) and 5-ethyl-3-methylfuran-2-carboxylic acid (16c) (*ca.* 60%). The crude mixture was esterified with an excess of ethereal diazomethane and purified by preparative g.l.c. at 190 °C to give the *ester* (16d) (0.21 g) as an oil, $\lambda_{max.}$ 263 nm, $\nu_{max.}$ (film) 1 710 cm^{-1}, τ 4.01 (furyl 4-H), 6.14 (CO$_2$CH$_3$), 7.35 (q, *J* 7 Hz, CH$_2$CH$_3$), 7.71 (furyl 3-CH$_3$), and 8.78 (t, *J* 7 Hz, CH$_2$CH$_3$) (Found: C, 64.0; H, 7.4. C$_9$H$_{12}$O$_3$ requires C, 64.3; H, 7.2%).

5-[*Hydroxy(phenyl)methyl*]-3-*methylfuran-2-carboxylic Acid* (17a).—By the general procedure, reaction between the dianion (15) and benzaldehyde (0.3 ml) at −78 °C, followed by warming to room temperature during 0.5 h and the usual work-up, gave the *acid* (17a) (0.62 g) which crystallised from light petroleum–ether (10 : 1 v/v) as small prisms, m.p. 123—125 °C (decomp.), $\lambda_{max.}$ 262 and 258 (infl.) nm, $\nu_{max.}$ (CHCl$_3$) 1 691 cm^{-1}, τ 2.54—2.68 (m, 5 H), 3.93 (furyl 4-H), 4.18 (CHOH), and 7.74 (3-CH$_3$) (Found: C, 67.0; H, 5.0. C$_{13}$H$_{12}$O$_4$ requires C, 67.2; H, 5.2%).

5-(1-*Hydroxy-1-methylethyl*)-3-*methylfuran-2-carboxylic Acid* (17b) *and Methyl* 5-*Isopropenyl-3-methylfuran-2-carboxylate* (18).—By the general procedure, reaction between the dianion (15) and acetone (0.25 ml) at −78 °C followed by warming to room temperature during 0.5 h, gave the acid (17b) (0.50 g) which resisted attempted crystallisation. The crude acid showed $\lambda_{max.}$ 260 nm, $\nu_{max.}$ (CHCl$_3$) 1 694 cm^{-1}, τ 3.78 (furyl 4-H), 7.67 (3-CH$_3$), and 8.40 (2 × CH$_3$). A sample of the foregoing acid (0.1 g) was esterified with ethereal diazomethane in the usual way to give the ester (0.09 g) as an oil, $\lambda_{max.}$ 260 nm, $\nu_{max.}$ (CHCl$_3$) 1 704 cm^{-1}, τ 3.84 (furyl 4-H), 6.17 (CO$_2$CH$_3$), 7.72 (3-CH$_3$), and 8.46 (2 × CH$_3$). A solution of the ester (0.09 g) in dry benzene (10 ml) containing toluene-*p*-sulphonic acid (*ca.* 10 mg) was refluxed for 0.5 h, then cooled, washed with 1M-aqueous potassium hydroxide (5 ml) and water (5 ml), and then dried and evaporated. Preparative g.l.c. at 200 °C gave the *ester* (18) (0.06 g) as an oil, $\lambda_{max.}$ 282 (infl.), 272, and 266 (infl.) nm, $\nu_{max.}$ (CHCl$_3$) 1 696 cm^{-1}, τ 3.78 (furyl 4-H), 4.32br (s, =CH), 4.91 (q, *J ca.* 1.5 Hz, =CH), 6.17 (CO$_2$CH$_3$), 7.71 (3-CH$_3$), and 8.01 (d, *J ca.* 1.5 Hz, CH$_3$C=CH$_2$) (Found: *M*$^+$, 180.080 0. C$_{10}$H$_{12}$O$_3$ requires *M*, 180.078 6.

Methyl 5-(*Cyclohex-1-enyl*)-3-*methylfuran-2-carboxylate* (19b).—Condensation of the dianion (15) with cyclohexanone

(0.35 ml) at −78 °C followed by warming to room temperature during 0.5 h, and the usual work-up gave a mixture (0.62 g) of the expected product, 5-(1-hydroxycyclohexyl)-3-methylfuran-2-carboxylic acid (17c) and the corresponding dehydrated compound (19a). The mixture was esterified with an excess of ethereal diazomethane and completely dehydrated using toluene-*p*-sulphonic acid in hot benzene as described above. A sample (0.1 g) of the product was purified by preparative g.l.c. at 250 °C to give the *ester* (19b) (0.075 g) as a pale yellow oil, showing $\lambda_{max.}$ 296.5 nm, $\nu_{max.}$ (CHCl$_3$) 1 704 cm^{-1}; τ 3.40—3.54 (m, CH$_2$CH=C), 3.88 (furyl 4-H), 6.16 (CO$_2$CH$_3$), 7.68—7.91 (m, CH$_2$CH=C + CH$_2$C=CH), 7.71 (3-CH$_3$), and 8.20—8.44 (m, 4 H) (Found: *M*$^+$, 220.108 7. C$_{13}$H$_{16}$O$_3$ requires *M*, 220.109 9).

Lithium 2-*Lithiofuran-3-carboxylate* (21); *General Procedure*. [2-^{2}H]-*Furan-3-carboxylic Acid* (22a) *and* 2-*Methylfuran-3-carboxylic Acid* (22b).—Lithium di-isopropylamide (5 mmol), prepared as described in the general procedure for the dianion (5), was treated at −78 °C with a solution of furan-3-carboxylic acid (0.28 g; 2.5 mmol) in THF (5 ml), which resulted in the immediate formation of a white precipitate which slowly dissolved during 0.5 h to give a clear, yellow-green solution of the dianion (21). Reactions with electrophiles were carried out as described below and the reaction mixtures worked up as for dianion (5), unless otherwise stated.

A sample (*ca.* 2 ml) of the solution of the dianion (21) was withdrawn by syringe and immediately added to deuterium oxide (1 ml). The resulting mixture was acidified with 2M-hydrochloric acid and extracted with ether to give [2-^{2}H]furan-3-carboxylic acid (22a) (25 mg) which crystallised from water as prisms, m.p. 123—124 °C, $\nu_{max.}$ (KBr) 1 680 cm^{-1}, τ 2.57 (d, *J ca.* 1.5 Hz, 5-H) and 3.24 (d, *J ca.* 1.5 Hz, 4-H), *m/e* 113 (75%), 96 (100), and 40 (54). The ^{1}H n.m.r. spectrum showed ⩾95% incorporation of deuterium. The remainder of the dianion solution was treated with methyl iodide (0.2 ml) at −78 °C; an apparently instantaneous reaction occurred. The cooling-bath was removed and the mixture stirred for a further 0.5 h, then worked up as usual to give 2-methylfuran-3-carboxylic acid (22b) (0.26 g) which crystallised from light petroleum as fine needles, m.p. 101—102 °C (lit.,[17] 102—103 °C), τ 3.02 (d, *J ca.* 1.5 Hz, 5-H), 3.56 (d, *J ca.* 1.5 Hz, 4-H), and 7.46 (2-CH$_3$), *m/e* 126 (100%), 109 (39), 81 (29), 80 (36), and 53 (27).

2-*Ethylfuran-3-carboxylic Acid* (22c).—Ethyl iodide (0.2 ml) was added to a solution of the dianion (21) prepared by the general procedure, at −78 °C. The solution was warmed to −10 °C and stirred at this temperature for 3 h, then at 0 °C for 2 h, and worked up as usual to give a product, the ^{1}H n.m.r. spectrum of which showed *ca.* 40% conversion to the 2-ethyl derivative. Chromatography over silica gel eluted with chloroform–methanol (49 : 1 v/v) gave 2-*ethylfuran-3-carboxylic acid* (22c) (0.11 g) which crystallised from water as needles, m.p. 84—85 °C, $\nu_{max.}$ (CHCl$_3$) 1 693 cm^{-1}, τ 2.98 (d, *J* 1.5 Hz, 5-H), 3.55 (d, *J* 1.5 Hz, 4-H), 7.08 (q, *J* 7 Hz, CH$_2$CH$_3$), and 8.79 (t, *J* 7 Hz, CH$_2$CH$_3$) (Found: C, 60.2; H, 5.7. C$_7$H$_8$O$_3$ requires C, 60.0; H, 5.8%).

2-*Trimethylsilylfuran-3-carboxylic Acid* (22d).—Trimethylsilyl chloride (0.8 ml) was added to a solution of the dianion (21), prepared by the general procedure, at −78 °C, and the mixture was warmed to room temperature during 0.5 h, and treated with water (3 ml) and 2M-hydrochloric

acid (10 ml). The resulting mixture was vigorously stirred for 0.5 h, then diluted with water (25 ml) and ether extracted (3 × 15 ml). The combined extracts were washed with brine, and then dried and evaporated. Crystallisation of the residue from light petroleum gave the *acid* (22d) (0.41 g) as prisms, m.p. 89—90 °C, $\lambda_{max.}$ 243 nm (ε 3 670), $\nu_{max.}$ (CHCl$_3$) 1 685 cm^{-1}; τ −1.80br (CO$_2$H), 2.68 (d, J 1.5 Hz, 5-H), 3.46 (d, J 1.5, 4-H), and 9.62 (Me_3Si), m/e 184 (22%), 170 (22), 169 (100), 127 (56), 95 (28), 77 (34), and 75 (28) (Found: C, 52.0; H, 6.4. C$_8$H$_{12}$O$_3$Si requires C, 52.1; H, 6.6%).

2-[*Hydroxy(phenyl)methyl*]*furan-3-carboxylic Acid* (23a).—By the general procedure, reaction between the dianion (21) and benzaldehyde (0.25 ml) at −78 °C followed by warming to room temperature during 0.5 h and the usual work-up gave the *acid* (23a) which crystallised from light petroleum–ether (2 : 1 v/v) as prisms (0.44 g), m.p. 115—117 °C, $\lambda_{max.}$ 247 nm (ε 6 550), $\nu_{max.}$ (KBr) 1 675 cm^{-1}, $\tau[(CD_3)_2CO]$ 2.76—2.96 (m, 5 H), 3.02 (d, J 1.5 Hz, 5-H), 3.57 (d, J 1.5 Hz, 4-H), and 3.78 (PhCHOH), m/e 218 (100%), 200 (68), 105 (74), 77 (66), 51 (35), and 39 (36) (Found: C, 66.0; H, 4.8. C$_{12}$H$_{10}$O$_4$ requires C, 66.1; H, 4.6%).

2-[*Hydroxy(diphenyl)methyl*]*furan-3-carboxylic Acid* (23b).—By the general procedure, reaction between the dianion (21) and benzophenone (0.46 g) at −78 °C followed by warming to room temperature gave the *acid* (23b) which crystallised from ether as a powder (0.58 g), m.p. 135—137 °C (decomp.), $\nu_{max.}$ (KBr) 1 680 cm^{-1}, $\tau[(CD_3)_2CO]$ 2.72 (d, J 1.5 Hz, 5-H), 2.80—3.05br (10 H), and 3.30 (d, J 1.5 Hz, 4-H), m/e 294 (14%), 217 (36), 199 (100), 189 (79), 170 (69), 105 (82), and 77 (75) (Found: C, 73.4; H, 4.6. C$_{18}$H$_{14}$O$_4$ requires C, 73.5; H, 4.8%).

2-(1-*Hydroxy-1-methylethyl*)*furan-3-carboxylic Acid* (23c).—By the general procedure, reaction between the dianion (21) and acetone (0.18 ml) at −78 °C followed by warming to room temperature and the usual work-up, gave the *acid* (23c), which crystallised from ether–acetone (2 : 1 v/v) as small prisms (0.32 g), m.p. 125.5—126.5 °C, $\lambda_{max.}$ 246 nm (ε 4 500), $\nu_{max.}$ (CHCl$_3$) 1 680 cm^{-1}, $\tau[(CD_3)_2CO]$ 2.80 (d, J 1.5 Hz, 5-H), 3.50 (d, J 1.5 Hz, 4-H), and 8.48 (2 × CH$_3$), m/e 170 (1%), 155 (39), 137 (100), and 95 (32) (Found: C, 56.6; H, 6.0. C$_8$H$_{10}$O$_4$ requires C, 56.5; H, 5.9%).

2-(1-*Hydroxyheptyl*)*furan-3-carboxylic Acid* (23d).—Reaction between the dianion (21) and heptanal (0.34 ml) by the general procedure at −78 °C followed by warming to room temperature and the usual work-up gave the *acid* (23d), which crystallised from light petroleum as a powder (0.52 g), m.p. 61—63 °C, $\nu_{max.}$ (CHCl$_3$) 1 680 cm^{-1}, τ 1.60br (CO$_2$H), 2.78 (d, J 1.5 Hz, 5-H), 3.36 (d, J 1.5 Hz, 4-H), 4.98 (t, J 7 Hz, CHOH), 7.99—8.28 (m, CH_2CHOH), 8.50—8.90 (m, 8 H), and 9.10br (t, J 7 Hz, CH$_3$), m/e 226 (6%), 141 (85), and 123 (100) (Found: C, 63.9; H, 8.2. C$_{12}$H$_{18}$O$_4$ requires C, 63.7; H, 8.0%).

2-[(E)-1-*Hydroxy-3,7-dimethylocta-2,6-dienyl*]*furan-3-carboxylic Acid* (23e).—By the general procedure, reaction between the dianion (21) and citral (0.43 ml) at −78 °C followed by warming to room temperature during 0.5 h, and the usual work-up, gave the acid (23e) (0.62 g) as an unstable, viscous oil, $\nu_{max.}$ (CHCl$_3$) 1 682 cm^{-1}, τ 2.80 (d, J 1.5 Hz, furyl 5-H), 3.37 (d, J 1.5 Hz, furyl 4-H), 4.23 [d, J 9 Hz, CH(OH), 4.54br [d, J 9 Hz, CH(OH)CH=C], 4.99br [CH=C(CH$_3$)$_2$], 7.76—8.04 (m, 2 × CH$_2$), 8.24 (CH$_3$), 8.36 (CH$_3$), and 8.43 (CH$_3$), m/e 264 (<1%), 246 (2), 152 (8), 151 (6), 136 (50), 135 (100), and 121 (26). Attempts to crystallise the compound or to purify it or its methyl ester by chromatography resulted in rapid decomposition as shown by the loss of the resonances at τ 4.23 and 4.54.

6,6-*Dimethylfuro*[3,4-b]*furan-4(6H)-one* (24a).—Benzenesulphonyl chloride (0.3 ml) was added to an ice-cooled solution of 2-(1-hydroxy-1-methylethyl)furan-3-carboxylic acid (23c) (0.19 g) in dry pyridine (1 ml). The mixture was left at 0 °C overnight then diluted with water (15 ml) and extracted with ether (3 × 15 ml). The combined extracts were washed with saturated aqueous sodium hydrogencarbonate (30 ml) and brine (30 ml) then dried, filtered through a bed of silica gel and evaporated to give the *lactone* (24a) (0.08 g) as a pale yellow, viscous oil, $\nu_{max.}$ (CHCl$_3$) 1 770 cm^{-1}, τ 2.71 (d, J 1.5 Hz, 2-H), 3.65 (d, J 1.5 Hz, 3-H), and 8.35 (2 × CH$_3$), m/e 152 (11%), 137 (40), 109 (22), 95 (100), and 39 (22) (Found: M^+, 152.047 1. C$_8$H$_8$O$_3$ requires M, 152.047 3).

Similarly, 2-(1-hydroxyheptyl)furan-3-carboxylic acid (23d) (22 mg) was converted into the corresponding lactone (24b) (14 mg), a viscous oil, $\nu_{max.}$ (CHCl$_3$) 1 770 cm^{-1}, m/e 208 (4%), 123 (100), 95 (13), 41 (12), and 39 (24).

Methyl 2-(2-Hydroxyheptyl)furan-3-carboxylate (25).—By the general procedure, reaction between the dianion (21) and 1,2-epoxyheptane (0.29 g) at −78 °C for 0.25 h, then −20 to −10 °C for 3 h, followed by the usual work-up gave a product which was esterified with an excess of ethereal diazomethane and chromatographed over silica gel, eluted with light petroleum–ether (20 : 1 v/v), to give the *ester* (25) (0.19 g), $\nu_{max.}$ (CHCl$_3$) 1 702 cm^{-1}, τ 2.93 (m, furyl 5-H), 3.50 (m, furyl 4-H), 5.94—6.24 (m, CHOH), 6.88 (d, J 5 Hz, CH_2CHOH), 8.34—8.82 (m, 8 H), and 9.14br (t, J 7 Hz, CH$_3$) (Found: M^+, 226.120 2. C$_{12}$H$_{18}$O$_4$ requires M, 226.120 5.

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