The Generation and Synthetic Utility of Dianions derived from Benzofurancarboxylic Acids

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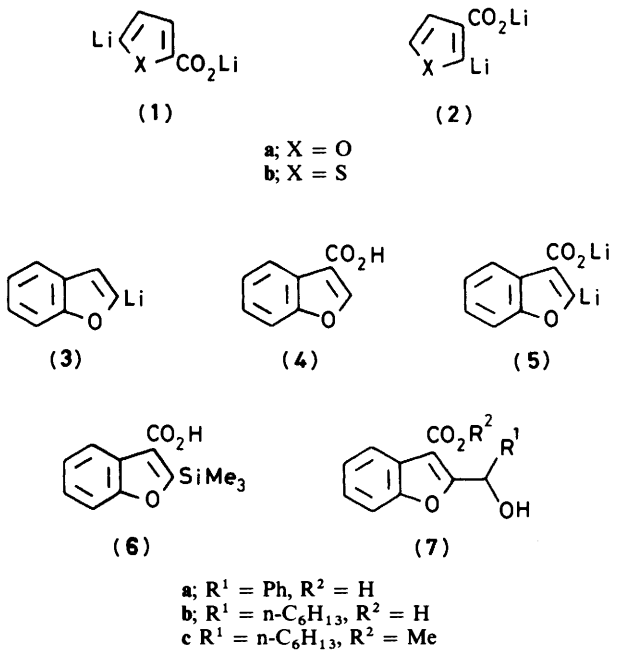
The dianionic species, lithium 2-lithiobenzofuran-3-carboxylate (**5**) and lithium 3-lithiobenzofuran-2-carboxylate (**11b**) can be readily generated from the parent acids by reaction with lithium di-isopropylamide in tetrahydrofuran at low temperatures. While compound (**5**) is a useful synthetic intermediate, which reacts efficiently with a number of electrophiles, (**11b**) instead undergoes rapid opening of the furan ring to give (2-hydroxyphenyl)propynoic acid (**10a**). By contrast, 5- and 7-methoxybenzofuran-2-carboxylic acids (**13a**) and (**13c**) give rise to the dianions (**14a**) and (**14c**) which are sufficiently stable at $\leqslant -90$ °C to be trapped by aldehydes. The dianion (**14b**) derived from 6-methoxybenzofuran-2-carboxylic acid (**13b**), however, suffers rapid ring opening before it can be trapped, even at very low temperatures. A plausible explanation of these observations is given. Metallation of 3-methylbenzofuran-2-carboxylic acid (**18**) affords the dianion (**20**), which cannot undergo ring opening and which is a valuable intermediate for the synthesis of a range of 3-substituted benzofuran-2-carboxylic acids.

A recent comprehensive review[1] of anionic species derived from aromatic heterocycles serves to emphasise the value of such intermediates in organic synthesis. We have recently shown that the useful dianionic intermediates (**1**) and (**2**) can be readily derived from the corresponding furan-[2] and thiophene-carboxylic acids.[3] Only a very limited number of reports have appeared in the literature concerning the generation and synthetic utility of similar dianions derived from other heterocyclic carboxylic acids.[1,3] In view of the wide occurrence of the benzofuran nucleus in natural products and useful pharmaceuticals *etc.*,[4] we have examined the possibilities of generating dianions related to (**1**) and (**2**) from benzofurancarboxylic acids in the hope of defining some new and useful intermediates for the elaboration of diversely substituted benzofurans. Herein, we report the successful outcome of these studies.

In common with many other aromatic heterocycles,[1] benzofuran itself undergoes direct metallation (*i.e.* hydrogen–metal exchange) at the carbon α to the heteroatom when treated with n-butyl-lithium[2,4,5] or lithium di-isopropylamide (LDA)[6] to give 2-lithiobenzofuran (**3**). This useful intermediate can also be obtained from 2-bromobenzofuran by halogen–metal exchange using n-butyl-lithium.[7] In view of our observations that the 3-carboxylate group directs metallation exclusively into the 2-position in both 3-furan- and 3-thiophene-carboxylic acids, leading to (**2a**)[2] and (**2b**)[3] respectively, it was expected that benzofuran-3-carboxylate acid (**4**)[8] could give rise to the dianion (**5**). In the event, treatment of compound (**4**) with LDA (2.1 equiv.) in tetrahydrofuran (THF) at −78 °C for 0.5 h resulted in the formation of an orange solution which was instantly decolourised on addition of chlorotrimethylsilane. Subsequent work-up, using aqueous acid to hydrolyse the silyl ester group, then gave the 2-trimethylsilyl derivative (**6**) in virtually quantitative yield. The material was pure according to ^{1}H n.m.r. spectroscopy, indicating that metallation had not occurred at any other site in compound (**4**). Subsequent crystallisation gave analytically pure silyl acid (**6**) in 79% yield. Similar reactions with both benzaldehyde and n-heptanal were slower but nevertheless lead to the expected derivatives (**7a**) and (**7b**) in *ca.* 75% isolated yields. However, treatment of the dianion (**5**) with iodoethane failed to give more than traces of the 2-ethyl derivative under various conditions; in all cases, the starting material (**4**) was recovered in high yield. This result was not unexpected in view of our previous observations that similar alkylations of the dianions (**1**) and (**2**) also failed or gave only low yields.[2,3]



(**1**) (**2**)

a; X = O
b; X = S

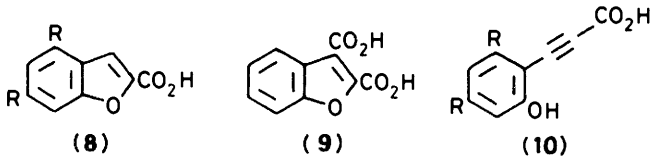
(**3**) (**4**) (**5**)

(**6**) (**7**)

a; R^1 = Ph, R^2 = H
b; R^1 = n-C_6H_{13}, R^2 = H
c R^1 = n-C_6H_{13}, R^2 = Me

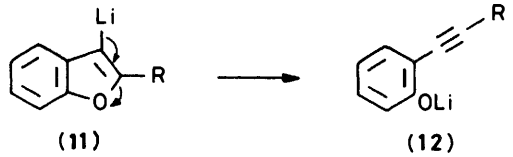
On warming solutions of the dianion (**5**) in THF, the reactive intermediate is slowly protonated. For example, when a solution of compound (**5**), generated at −78 °C, was warmed to 0 °C during 0.5 h and then treated with chlorotrimethylsilane followed by the usual work-up, only a 35% conversion into the 2-silyl derivative (**6**) had occurred according to ^{1}H n.m.r. analysis; the remainder of the product was the starting acid (**4**). This property is also displayed by the dianions (**1**) and (**2**).[2,3] We assume that in all cases the THF solvent is acting as the proton source, although this has not been proven.

We next examined the synthetic potential of the isomeric dianion (**11b**) derived from benzofuran-2-carboxylic acid (**8a**).[9] Dean *et al.*[6] have reported that treatment of compound (**8a**) with two equivalents of LDA at −70 °C followed by the addition of carbon dioxide gives a good yield of the diacid (**9**) accompanied by a little of the acetylenic acid (**10a**), and furthermore that a similar reaction sequence starting with the 4,6-dimethyl derivative (**8b**) leads almost entirely to the acetylenic acid (**10b**). These results clearly indicate that the



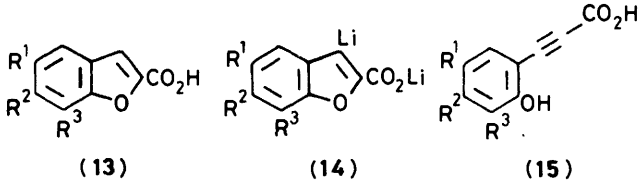
(8) (9) (10)

a; R = H
b; R = Me



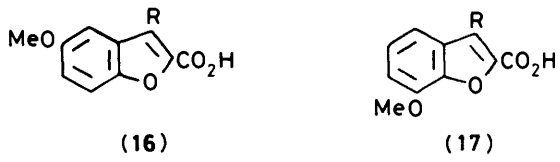
(11) (12)

a; R = H
b; R = CO_2Li



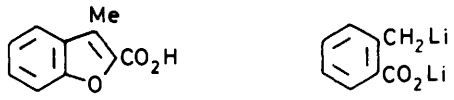
(13) (14) (15)

a; R^1 = OMe, R^2 = R^3 = H
b; R^2 = OMe, R^1 = R^3 = H
c; R^3 = OMe. R^1 = R^2 = H



(16) (17)

a; R = Me
b; R = CH(OH)Ph
c; R = CH(OH)(n-C_6H_{13})



(18) (19)

(20) (21)

a; R = Me
b; R = $SiMe_3$
c; R = CH(OH)Ph
d; R = CMe(OH)Ph
e; R = CH(OH)(n-C_6H_{13})
f; R = $CH_2CH(OH)Et$
g; R = Et

dianion (**11b**) can indeed be formed, but that such intermediates are rather unstable with respect to ring opening of the furan ring [*i.e.* (**11**)→(**12**)]. There are many examples in the literature of similar ring openings of heterocyclic anions when a heteroatom is positioned β to the site of metallation. For example, 3-lithiobenzofuran (**11a**) rapidly isomerises to 2-hydroxyphenylacetylene (**12a**) at room temperature,[7] although at lower temperatures the anion (**11a**) is sufficiently stable to be used in the synthesis of 3-substituted benzofurans.[10]

We were not able to extend the synthetic utility of the dianion (**11b**) derived from the acid (**8a**). In our hands, all attemps to trap the dianion (**11b**) before ring opening occurred failed to give more than traces of the corresponding 3-substituted benzofuran-2-carboxylic acids, even when the reactions were conducted at lower temperatures (≤ −90 °C); in all cases the acetylenic acid (**10a**) was formed in high yield. Indeed treatment of benzofuran-2-carboxylic acid with LDA (2.1 equiv.) at −78 °C followed by warming to room temperature is a very effective method for the preparation of (2-hydroxyphenyl)-propynoic acids [*e.g.* (**10**)]. Thus, similar treatment of the methoxy-substituted benzofurancarboxylic acids (**13a**—**c**) provided the acetylenic acids (**15a**—**c**) in 85—90% isolated yields. Attempts to trap the intermediate dianions (**14a**—**c**) at −78 °C were not successful; even with very reactive electrophiles such as iodomethane or benzaldehyde, only traces of products in which the furan ring remained intact [*i.e.* (**16**) and (**17**)] were present in the crude reaction products, as shown by ^{1}H n.m.r. analysis. However, metallation of 5-methoxybenzofuran-2-carboxylic acid (**13a**) at ≤ −90 °C followed by addition of iodomethane gave an essentially quantitative yield of the 3-methyl derivative (**16a**) and the acetylenic acid (**15a**) in the ratio 73:27; subsequent crystallisation gave the pure derivative (**16a**) in 58% yield. Inspection of the ^{1}H n.m.r. spectra of both the crude and purified products showed the absence of any isomers of compound (**16a**) and hence that metallation had occurred only at the 3 position in (**13a**). When the intermediate dianion (**14a**) was treated with either benzaldehyde or n-heptanal at ≤ −90 °C, virtually quantitative yields of the 3-substituted derivatives, (**16b**) and (**16c**), respectively, were obtained accompanied by only traces of the ring-opened product (**15a**) (as shown by ^{1}H n.m.r. and t.l.c. analyses of the crude reaction products). Subsequent crystallisation provided analytically pure products in *ca.* 80% yields. Similarly, metallation and trapping of 7-methoxybenzofuran-2-carboxylic acid (**13c**) with both iodomethane and n-heptanal at ≤ −90 °C gave the 3-substituted derivatives (**17a**) and (**17c**), respectively, although in both cases the ring-opened product (**15c**) was also formed to an extent of *ca.* 20%, indicating that the dianion (**14c**) is slightly less stable with respect to ring opening than (**14a**). The extra stability of the dianions (**14a**) and (**14c**), relative to the corresponding unsubstituted dianion (**11b**), can be attributed to the resonance effect of the methoxy substituents which, because they are positioned *para* and *ortho* to the furan oxygen, cause the latter to be a poorer leaving group in the ring-opening reaction. In line with this is our finding that the dianion (**14b**) derived from the 6-methoxy isomer (**13b**) could not be trapped even at ≤ −90 °C; in such experiments only the acetylenic acid (**15b**) was isolated. In the dianion (**14b**), the methoxy substituent is *meta* to the furan oxygen and thus would not be expected to exert a significant stabilising effect.

Although we had achieved some success in the synthesis of 3-substituted benzofuran-2-carboxylic acids using these dianionic intermediates, the method is clearly not generally applicable. In an attempt to circumvent the problem of ring opening, we reasoned that it should be possible to form a dianionic species from the readily available[11] 3-methylbenzofuran-2-carboxylic acid (**18**), particularly in view of the observation that the dianion (**19**) can be generated from *o*-toluic acid.[12] Such a dianion should be stable with respect to ring opening. We were pleased to find that dianion (**20**) could indeed be obtained from (**18**) by reaction with LDA (2.1 equiv.) in THF. Although our initial experiments were conducted at −78 °C, we subsequently found that compound (**20**) could equally well be generated at the more convenient temperature of −10 °C, without any

detrimental effects upon the subsequent reactions. Condensations with aldehydes and ketones as well as with iodomethane and chlorotrimethylsilane were all very clean, leading to the 3-substituted derivatives (**21a—e**) in isolated yields of >75%. Examination of the crude products from such reactions, by both ^{1}H n.m.r. spectroscopy and t.l.c., showed the virtual absence of the starting material (**18**) and in no instance did we detect products arising from metallation of any other site in (**18**). The dianion (**20**) also reacted cleanly with both 1,2-epoxybutane and iodoethane to give the products (**21f**) and (**21g**) respectively in excellent yields. This contrasts with the reactivity of the vinyl dianions (**1**), (**2**),[2,3] and (**5**) which do not react efficiently with epoxides or iodoalkanes (except iodomethane). Thus, the dianion (**20**) appears to be more nucleophilic and less basic than the related vinyl dianions, all of which abstract a proton from the solvent THF at temperatures above −30 °C. Presumably this reflects the lower degree of s character in the dianion (**20**) relative to the dianions (**1**), (**2**), and (**5**).

Experimental

For general details, see ref. 2. In this work, unless otherwise stated, all ^{1}H n.m.r. spectra were obtained using a Perkin-Elmer R32a 90 MHz spectrometer, with $(CD_3)_2CO$ as solvent, and all i.r. spectra were determined using KBr discs. All reactions were carried out under nitrogen. Ether refers to diethyl ether.

2-Trimethylsilylbenzofuran-3-carboxylic Acid (**6**).—A solution of benzofuran-3-carboxylic acid[8] (0.162 g, 1 mmol) in tetrahydrofuran (1 ml) was added to a stirred solution of lithium di-isopropylamide [from di-isopropylamine (0.3 ml, 2.15 mmol) and n-butyl-lithium (1.3 ml of a 1.6M-solution in hexane; 2.1 mmol)] in tetrahydrofuran at −78 °C. The resulting yellow-orange solution of the dianion (**5**) was stirred for 0.25 h at −78 °C, then chlorotrimethylsilane (0.25 ml, 2 mmol) was added. The solution was instantly decolourised. The mixture was diluted with 2M-hydrochloric acid (20 ml) and extracted with ether. The dried extracts were evaporated and the residue crystallised from water–methanol (3:1) to give the *2-silyl acid* (**6**) (0.185 g, 79%), m.p. 197—198 °C, $\nu_{max.}$(CHCl$_3$) 1 685 cm^{-1}; δ 0.50 (9 H, Me_3Si), 7.55—7.96 (3 H, m), and 8.38 (1 H, dd, *J* 7 and 4 Hz), *m/z* 234 (M^+, 27%), 219 (100), 177 (58), 159 (19), 145 (12), 137 (18), and 115 (15) (Found: C, 61.6; H, 6.0. $C_{12}H_{14}O_3Si$ requires C, 61.5; H, 6.0%).

In another experiment, samples of the dianion solution were withdrawn as the temperature was allowed to rise slowly during 1.5 h and immediately quenched with an excess of chlorotrimethylsilane. Analysis of the products by ^{1}H n.m.r. spectroscopy using integration of the Me_3Si resonance of the 2-silyl acid (**6**) and the 2-H resonance at δ 8.67 of benzofuran-3-carboxylic acid gave the following results [temperature, % (**6**): % benzofuran-3-carboxylic acid]: −60 °C, 90:10; −40 °C, 80:20; −30 °C, 60:40; −10 °C, 55:45; 0 °C, 35:65; +15 °C, 30:70.

2-Hydroxy(phenyl)methylbenzofuran-3-carboxylic Acid (**7a**).—Benzaldehyde (0.11 g, 1 mmol) in tetrahydrofuran (1 ml) was added to a solution of the dianion (**5**) (1 mmol) at −78 °C, and the resulting mixture slowly warmed to room temperature during 1 h, then worked up in the usual way. Crystallisation of the product from water–methanol (1:1) then gave the *hydroxy acid* (**7a**) as a powder (0.2 g, 75%), m.p. 178—179 °C, $\nu_{max.}$(Nujol) 3 360 and 1 685 cm^{-1}; δ 7.00 (1 H, C*H*OH), 7.38—7.98 (8 H, m), and 8.29 (1 H, dd, *J* 7 and 4 Hz); *m/z* 268 (47%) 251 (53), 250 (40), 221 (43), 145 (68), 105 (100), 89 (46), and 77 (97) (Found: C, 71.7; H, 4.6. $C_{16}H_{12}O_4$ requires C, 71.6; H, 4.5%).

Methyl 2-(1-Hydroxyheptyl)benzofuran-3-carboxylate (**7c**).—n-Heptanal (0.14 ml) in tetrahydrofuran (1 ml) was added to a solution of the dianion (**5**) (1 mmol) at −78 °C. The mixture was allowed to reach room temperature during 1 h, then worked up in the usual way. ^{1}H N.m.r. analysis [$(CD_3)_2CO$] of the product (0.24 g) showed *ca.* 80% conversion into the desired 2-substituted acid (by considering the integration of the benzofuran-3-carboxylic acid 2-H at δ 8.77 *versus* the triplet at δ 5.68 due to C*H*OH in the desired product). The mixture was esterified with ethereal diazomethane and the esters were separated by chromatography over silica gel, eluting with dichloromethane to give the *2-hydroxyheptyl ester* (**7c**) as an oil (0.19 g, 66%), $\nu_{max.}$(CCl$_4$) 3 440 and 1 698 cm^{-1}; δ(CCl$_4$) 0.88 (3 H, br t, *J ca.* 7 Hz, CH_2CH_3), 1.18—1.50 (8 H, m), 1.75—2.00 (2 H, m, $CHOHCH_2$), 3.97 (CO_2CH_3), 5.03 (1 H, t, *J* 7 Hz, C*H*OH), 7.18—7.52 (3 H, m), and 7.88 (1 H, dd, *J* 7 and 4 Hz); *m/z* 290 (M^+, 2%), 205 (54), 187 (11), 173 (100), and 145 (40) (Found: M^+, 290.1506. $C_{17}H_{22}O_4$ requires *M*, 290.1518).

3-(2-Hydroxyphenyl)propynoic Acid (**10a**).—A solution of benzofuran-2-carboxylic acid[9] (0.32 g, 2 mmol) in tetrahydrofuran (2 ml) was added dropwise *via* a syringe to a stirred solution of lithium di-isopropylamide (4.2 mmol) in tetrahydrofuran (10 ml), maintained at −78 °C. After 10 min, the cooling bath was removed and the mixture stirred for a further 0.5 h, then diluted with 2M-hydrochloric acid (30 ml) and extracted with ether (3 × 20 ml). The combined extracts were dried and evaporated to leave a residue which on crystallisation from ethyl acetate–light petroleum afforded the *acetylenic acid* (**10a**) (0.3 g, 92%), m.p. 128—130 °C (decomp.) [lit.,[13] m.p. 117—118 °C (decomp.); lit.,[14] m.p. 143 °C (decomp.)], $\nu_{max.}$ 2 230 and 1 675 cm^{-1}; δ 6.85—7.25 (2 H, m) and 7.37—7.75 (2 H, m); *m/z* 162 (M^+, 65%) 145 (22), 116 (100), 90 (95), 89 (97), and 63 (49) (Found: C, 66.9; H, 4.0. $C_9H_6O_3$ requires C, 66.7; H, 3.7%).

Using the same procedure, the following acids were also prepared in similar yields.

3-(2-Hydroxy-5-methoxyphenyl)propynoic acid (**15a**) was obtained from 5-methoxybenzofuran-2-carboxylic acid (**13a**)[9] and showed m.p. 135—137 °C (decomp.) (EtOAc–light petroleum), $\nu_{max.}$ 2 230 and 1 667 cm^{-1}; δ 3.65 (3 H, OCH_3) and 6.68—6.82 (3 H, m); *m/z* 192 (M^+, 56%), 146 (100), and 77 (48) (Found: C, 62.8; H, 4.4. $C_{10}H_8O_4$ requires C, 62.5; H, 4.2%).

3-(2-Hydroxy-4-methoxyphenyl)propynoic acid (**15b**) was prepared from 6-methoxybenzofuran-2-carboxylic acid (**13b**),[9] and showed m.p. 161—163 °C (decomp.) ($CHCl_3$–n-hexane); $\nu_{max.}$ 2 230 and 1 670 cm^{-1}; δ 3.69 (3 H, OCH_3), 6.30 (1 H, dd, *J* 7 and 2 Hz, 5-H), 6.38 (1 H, d, *J* 2 Hz, 3-H), and 7.28 (1 H, d, *J* 7 Hz, 6-H); *m/z* 192 (M^+, 90%) and 146 (100) (Found: C, 62.3; H, 4.3%).

3-(2-Hydroxy-3-methoxyphenyl)propynoic acid (**15c**) was prepared from 7-methoxybenzofuran-2-carboxylic acid (**13c**)[9] and showed m.p. 132—133 °C (decomp.) (EtOAc–light petroleum), $\nu_{max.}$ 2 220 and 1 675 cm^{-1}; δ 3.87 (3 H, OCH_3) and 6.63—7.08 (3 H, m); *m/z* 192 (M^+, 17%), 146 (100), 105 (53), and 77 (85) (Found: C, 62.7; H, 4.3%).

Formation and Trapping of Dianions (**14a**) *and* (**14c**) *derived from 5- and 7-Methoxybenzofuran-2-carboxylic Acids. General Procedure.*—A stirred solution of lithium di-isopropylamide (4.2 mmol) in tetrahydrofuran (10 ml) was cooled to < −90 °C (cyclohexene–liquid N_2 bath) and a solution of the acid (0.38 g, 2 mmol) in tetrahydrofuran (*ca.* 2 ml) added dropwise *via* a syringe. After 0.25 h, the electrophile (2 mmol) in tetrahydrofuran (1 ml) was added; after 5 min, the cooling bath was removed and the mixture warmed to room temperature, then worked up as described above.

5-Methoxy-3-methylbenzofuran-2-carboxylic acid (**16a**). The reaction between 5-methoxybenzofuran-2-carboxylic acid (**13a**) and iodomethane provided a mixture of the desired 3-methyl derivative (**16a**) and the acetylenic acid (**15a**) (73:27 by ^{1}H

n.m.r. integration) in essentially quantitative yield. Crystallisation of the crude product from ethyl acetate–light petroleum provided the 3-*methyl derivative* (**16a**) (0.23 g, 58%), m.p. 208—209 °C (lit.,[15] m.p. 208 °C; lit.,[16] m.p. 210 °C); $\nu_{max.}$ 1 670 cm^{-1}; δ 2.57 (3 H, 3-CH_3), 3.89 (3 H, OCH_3), 7.13 (1 H, dd, *J* 8 and 2 Hz, 6-H), 7.24 (1 H, d, *J* 2 Hz, 4-H), and 7.52 (1 H, d, *J* 8 Hz, 7-H); *m/z* 206 (M^+, 100%), 191 (55), and 146 (20) (Found: C, 64.0; H, 4.9. $C_{11}H_{10}O_4$ requires C, 64.1; H, 4.9%).

3-(α-*Hydroxybenzyl*)-5-*methoxybenzofuran*-2-*carboxylic acid* (**16b**). The reaction between the acid (**13a**) and benzaldehyde gave a product which contained only traces (^1H n.m.r. and i.r. analysis) of the acetylenic acid (**15a**). Crystallisation from ethyl acetate–light petroleum gave the pure 3-*hydroxybenzyl derivative* (**16b**) (0.45 g, 76%), m.p. 144—145 °C, $\nu_{max.}$ 3 270 and 1 675 cm^{-1}, δ 3.79 (3 H, OCH_3), 6.92 (1 H, C*H*OH), 7.11 (1 H, dd, *J* 8 and 2 Hz, 6-H), and 7.29—7.77 (7 H, m); *m/z* 298 (M^+, 45%), 280 (100), 252 (28), 175 (34), and 105 (33) (Found: C, 68.4; H, 4.9. $C_{17}H_{14}O_5$ requires C, 68.5; H, 4.7%).

3-(1-*Hydroxyheptyl*)-5-*methoxybenzofuran*-2-*carboxylic acid* (**16c**). The reaction between the acid (**13a**) and n-heptanal gave a product which contained only traces of the acetylenic acid (**15a**). Crystallisation from ethyl acetate–light petroleum gave the *hydroxyheptyl derivative* (**16c**) (0.49 g, 80%), m.p. 85—87 °C, $\nu_{max.}$ 2 380 and 1 670 cm^{-1}; δ 0.84 (3 H, br t, *J ca.* 7 Hz, CH_2CH_3), 1.17—1.46 (8 H, m), 1.59—1.90 (2 H, m, 2-CH_2), 3.85 (3 H, OCH_3), 5.65 (1 H, t, *J* 7 Hz, C*H*OH), 7.12 (1 H, d, *J* 8 and 2 Hz, 6-H), 7.50 (1 H, d, *J* 8 Hz, 7-H), and 7.56 (1 H, d, *J* 2 Hz, 4-H); *m/z* 306 (M^+, 18%), 288 (39), 221 (92), and 203 (100) (Found: C, 66.7; H, 7.3. $C_{17}H_{22}O_5$ requires C, 66.7; H, 7.2%).

7-*Methoxy*-3-*methylbenzofuran*-2-*carboxylic acid* (**17a**). Using the general procedure, the reaction between 7-methoxybenzofuran-2-carboxylic acid (**13c**) and iodomethane gave an essentially quantitative yield of the desired 3-methyl derivative (80%) and the acetylenic acid (**15c**) (20%). Crystallisation from ethyl acetate–light petroleum afforded the pure 3-*methyl derivative* (**17a**) (0.25 g, 61%), m.p. 213—215 °C (lit.,[16] m.p. 216 °C; lit.,[17] m.p. 211—213 °C), $\nu_{max.}$ 1 675 cm^{-1}; δ 2.55 (3 H, 3-CH_3), 3.86 (3 H, OCH_3), and 6.62—7.02 (3 H, m); *m/z* 206 (M^+, 100%) and 191 (36) (Found: C, 63.8; H, 4.9. $C_{11}H_{10}O_4$ requires C, 64.1; H, 4.9%).

3-(1-*Hydroxyheptyl*)-7-*methoxybenzofuran*-2-*carboxylic acid* (**17c**). The reaction between the acid (**13c**) and n-heptanal gave a mixture of the desired product (**17c**) (78%) and the acetylenic acid (**15c**) (22%). Crystallisation from ethyl acetate–light petroleum gave the *hydroxyheptyl derivative* (**17c**) (0.355 g, 58%), m.p. 129—131 °C, $\nu_{max.}$ 3 400 and 1 680 cm^{-1}; δ 0.86 (3 H, br t, *J ca.* 7 Hz, CH_2CH_3), 1.22—1.48 (8 H, m), 1.81—2.02 (2 H, m, 2-CH_2), 4.04 (3 H, OCH_3), 5.55 (1 H, t, *J* 7 Hz, C*H*OH), 7.03 (1 H, dd, *J* 8 and 1 Hz, 6-H), 7.27 (1 H, t, *J* 8 Hz, 5-H), and 7.55 (1 H, dd, *J* 8 and 1 Hz, 4-H); *m/z* 306 (M^+, 27%), 288 (17), 221 (98), and 203 (100) (Found: C, 66.4; H, 7.4. $C_{17}H_{22}O_5$ requires C, 66.7; H, 7.2%).

Generation and Reactions of the Dianion (**20**) *from* 3-*Methylbenzofuran*-2-*carboxylic Acid* (**18**). *General Procedure.*—A stirred solution of lithium di-isopropylamide (4.2 mmol) in tetrahydrofuran (10 ml) was maintained at −10 °C while a solution of 3-methylbenzofuran-2-carboxylic acid (0.352 g, 2 mmol) in tetrahydrofuran (3 ml) was added dropwise *via* a syringe. The resulting deep-orange solution was stirred for 0.5 h at −10 °C, then treated with the electrophile (2 ml). The solution was allowed to slowly warm to room temperature during 1 h. In cases where very reactive electrophiles such as iodomethane were used, the dianion solution was decolourised virtually immediately and was therefore worked up straight away.

The reaction mixtures were worked up by dilution with water (30 ml) followed by washing with ether (2 × 20 ml), acidification (dilute hydrochloric acid or solid citric acid) and extraction with ether (3 × 30 ml). The combined organic extracts were washed with brine, then dried and evaporated and the residue crystallised from an appropriate solvent.

In larger scale reactions, most of the tetrahydrofuran was evaporated prior to the addition of water.

3-*Ethylbenzofuran*-2-*carboxylic acid* (**21a**). The reaction between 3-methylbenzofuran-2-carboxylic acid (0.352 g, 2 mmol) and iodomethane (0.2 ml, freshly distilled from P_2O_5) using the general procedure, followed by crystallisation of the crude product from ethyl acetate–light petroleum gave the 3-*ethyl derivative* (**21a**) (0.3 g, 79%), m.p. 170—171 °C, $\nu_{max.}$ 1 675 cm^{-1}; δ 1.32 (3 H, t, *J* 7 Hz, CH_2CH_3), 3.13 (2 H, q, *J* 7 Hz, CH_2CH_3), 7.21—7.55 (3 H, m), and 7.72 (1 H, d, *J* 7 Hz, 7-H), *m/z* 190 (M^+, 88%), 175 (100), 145 (58), 115 (44), and 91 (46) (Found: C, 69.5; H, 5.3. $C_{11}H_{10}O_3$ requires C, 69.5; H, 5.3%).

3-*Trimethylsilylmethylbenzofuran*-2-*carboxylic acid* (**21b**). A solution of the dianion, derived from 3-methylbenzofuran-2-carboxylic acid (0.352 g, 2 mmol) in the usual way was treated, at −10 °C, with chlorotrimethylsilane (0.64 ml, 5 mmol). After 0.25 h, the cold solution was diluted with 2M-hydrochloric acid (50 ml) and extracted with ether. The combined extracts were washed with water and brine, then dried and evaporated. Crystallisation of the residue from benzene gave the *silyl derivative* (**21b**) (0.37 g, 75%), m.p. 190—191 °C, $\nu_{max.}$ 1 670 cm^{-1}; δ 0.99 (9 H, (Me_3Si), 2.76 (2 H, CH_2), 7.40—7.70 (3 H, m), and 7.83 (1 H, d, *J* 7 Hz, 7-H); *m/z* 248 (M^+, 40%), 233 (80), 189 (43), 158 (71), 130 (74), 114 (58), 102 (63), and 73 (100) (Found: C, 62.6; H, 6.6. $C_{13}H_{16}O_3Si$ requires C, 62.9; H, 6.5%).

3-(2-*Hydroxy*-2-*phenylethyl*)*benzofuran*-2-*carboxylic acid* (**21c**). Using the general procedure, the reaction between 3-methylbenzofuran-2-carboxylic acid (0.352 g, 2 mmol) and freshly distilled benzaldehyde (0.22 ml) gave the *hydroxy acid* (**21c**) (0.51 g, 90%), m.p. 149—151 °C (EtOAc–light petroleum), $\nu_{max.}$ 3 430 and 1 688 cm^{-1}; δ * 3.53 (2 H, m, 1′-CH_2), 5.18 (1 H, app. t, *J* 6 Hz, 2′-H), 7.24—7.70 (8 H, m), and 7.77 (1 H, d, *J* 7 Hz, 7-H); *m/z* 264 ($M^+ - H_2O$, 18%), 176 (100), 156 (61), 131 (98), 102 (85), and 77 (82) (Found: C, 72.5; H, 5.2. $C_{17}H_{14}O_4$ requires C, 72.3; H, 5.0%).

3-(2-*Hydroxy*-2-*phenylpropyl*)*benzofuran*-2-*carboxylic acid* (**21d**). Condensation of 3-methylbenzofuran-2-carboxylic acid (0.352 g, 2 mmol) with acetophenone (0.25 ml) under the usual conditions afforded the *hydroxy acid* (**21d**) (0.45 g, 76%), m.p. 147.5—148.5 °C (C_6H_6); $\nu_{max.}$ 1 670 cm^{-1}; δ 1.62 (3 H, CH_3), 3.46 (1 H, d, *J* 14 Hz, CH_aH_b), 3.75 (1 H, d, *J* 14 Hz, CH_aH_b), and 7.20—7.90 (9 H, m); *m/z* 296 (M^+, <1%), 278 ($M^+ - H_2O$, 8), 176 (90), 121 (100), and 43 (84) (Found: C, 73.2; H, 5.6. $C_{18}H_{16}O_4$ requires C, 73.0; H, 5.4%).

3-(2-*Hydroxyoctyl*)*benzofuran*-2-*carboxylic acid* (**21e**). By the general procedure, the reaction between 3-methylbenzofuran-2-carboxylic acid (0.352 g, 2 mmol) and freshly distilled n-heptanal (0.3 ml) gave the *hydroxy acid* (**21e**) (0.45 g, 76%), m.p. 113—115 °C (C_6H_6); $\lambda_{max.}$ 3 410 and 1 675 cm^{-1}; δ * 0.89 (3 H, t, *J ca.* 7 Hz, 8′-CH_3), 1.16—1.48 (8 H, m, 4′—7′-CH_2), 1.56 (2 H, m, 3′-CH_2), 3.32 (1 H, d, *J* 6 Hz, 1′-CH_aH_b), 3.30 (1 H, d, *J* 2 Hz, 1′-CH_aH_b), 4.02 (1 H, m, 2′-H), 7.32—7.45 (3 H, m, 4-, 5-, and 6-H), and 7.63 (1 H, d, *J* 7 Hz, 7-H); *m/z* 272 ($M^+ - H_2O$, 5%), 246 (26), 176 (83), 161 (100), and 131 (59) (Found: C, 70.8; H, 7.8. $C_{17}H_{22}O_4$ requires 3, 70.4; H, 7.6%).

3-(3-*Hydroxypentyl*)*benzofuran*-2-*carboxylic acid* (**21f**). By the general procedure, the reaction between 3-methylbenzofuran-2-carboxylic acid (0.352 g, 2 mmol) and 1,2-epoxybutane (0.2 ml) gave the *hydroxy acid* (**21f**) (0.46 g, 92%), m.p. 131—133 °C (EtOAc–light petroleum), $\nu_{max.}$ 3 350 and 1 680 cm^{-1}; δ * 0.93 (3 H, t, *J* 7 Hz, 5′-CH_3), 1.49 (2 H, m, 4′-CH_3), 1.87 (2 H, m,

* Primed numbers refer to the side chain.

2'-CH_2), 3.32 (2 H, t, *J* 8 Hz, 1'-CH_2), 3.60 (1 H, m, 3'-H), 6.50—7.00 (2 H, br, 2 × OH), 7.32—7.71 (3 H, m, 4-, 5-, and 6-H), and 7.90 (1 H, d, *J* 7 Hz, 7-H); *m/z* 248 (M^+, 12%), 230 (24), 176 (92), 175 (57), 131 (58), 61 (55), and 43 (100) (Found: C, 67.4; H, 6.7. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.5%).

3-*Propylbenzofuran-2-carboxylic acid* (**21g**). Using the general procedure, the reaction between 3-methylbenzofuran-2-carboxylic acid (0.352 g, 2 mmol) and iodoethane (0.2 ml; freshly distilled from P_2O_5) gave the 3-*propyl derivative* (**21g**) (0.3 g, 74%), m.p. 175—177 °C, $\nu_{max.}$ 1 670 cm^{-1}; δ * 0.99 (3 H, t, *J* 7 Hz, CH_3), 1.77 (2 H, m, 2'-CH_2), 3.16 (2 H, t, *J* 7 Hz, 1'-CH_2), 7.20—7.60 (3 H, m), and 7.82 (1 H, d, *J* 7 Hz, 7-H); *m/z* 204 (M^+, 100%), 189 (43), 175 (90), 131 (59), and 91 (39) (Found: C, 71.6; H, 6.1. $C_{12}H_{12}O_3$ requires C, 70.6; H, 5.9%).

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References

1 H. W. Gschwend and H. R. Rodriguez, *Org. React.*, 1979, **26**, 1. For other reviews, see H. Gilman and J. W. Morton, Jr., *ibid.*, 1954, **8**, 258; J. M. Mallan and R. L. Bebb, *Chem. Rev.*, 1969, **69**, 693; E. B. Pedersen, *J. Chem. Soc., Perkin Trans. 2*, 1977, 473.
2 D. W. Knight and A. P. Nott, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1125.
3 D. W. Knight and A. P. Nott, *J. Chem. Soc., Perkin Trans. 1*, 1983, 791; see also N. P. Gould and T.-J. Lee, *J. Org. Chem.*, 1980, **45**, 4528.
4 A. Mustafa, 'Benzofurans,' The Chemistry of Heterocyclic Compounds, John Wiley and Sons, 1974, vol. 29; R. C. Enderfield and V. B. Meyer, Heterocyclic Compounds, ed. R. C. Enderfield, John Wiley and Sons, 1951, vol. 2, p. 1.
5 V. Ramanathan and R. Levine, *J. Org. Chem.*, 1962, **27**, 1216.
6 A. M. B. S. R. C. S. Costa, F. M. Dean, M. A. Jones, D. A. Smith, and R. S. Varma, *J. Chem. Soc., Chem Commun.*, 1980, 1224.
7 T. Reichstein and J. Baud, *Helv. Chim. Acta.*, 1937, **20**, 892; H. Gilman and D. S. Melstrom, *J. Am. Chem. Soc.*, 1948, **70**, 1655; M. Cugnon De Serricourt and M. Robba, *Bull. Soc. Chim. Fr.*, 1977, 142.
8 V. Titoff, H. Muller, and T. Reichstein, *Helv. Chim. Acta.*, 1937, **20**, 883.
9 S. Tanaka, *J. Am. Chem. Soc.*, 1951, **73**, 872.
10 See, for example, D. S. Noyce and R. W. Nichols, *J. Org. Chem.*, 1972, **37**, 4311.
11 W. R. Beohme, *Org. Synth.*, Coll. Vol. IV, 1963, 590.
12 P. L. Creger, *J. Am. Chem. Soc.*, 1970, **92**, 1396, 1397; see also M. Tada and T. Takahashi, *Chem. Lett.*, 1978, 275; M. Tada, Y. Sugimoto, and T. Takahashi, *ibid.*, 1979, 1441.
13 V. A. Zagorevskii and V. I. Savel'ev, *Zh. Org. Khim.*, 1967, **3**, 1707 (*Chem. Abstr.*, 1968, **68**, 12640a).
14 P. Babin, P. Bourgeois, and J. Dunogies, *C.R. Acad. Sci.*, 1976, **C283**, 149.
15 V. J. Dalvi and S. Sethna, *J. Indian. Chem. Soc.*, 1949, **26**, 469.
16 W. B. Whally, *J. Chem. Soc.*, 1953, 3479.
17 B. Sila, *Rocz. Chem.*, 1968, **42**, 553 (*Chem Abstr.*, 1968, **69**, 43707c).

* Primed numbers refer to the side chain.

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