Preparation of Deuteriated Furan- and Thiophen-2-carbaldehydes and -2-carboxylic Esters

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Methods have been developed for introducing deuterium at some or all of the furan and thiophen ring positions. The compounds prepared include all the mono-, di-, and tri-deuteriofuran-2-carbaldehydes and -2-carboxylic acids, 5-deuteriofuran-2-[^{2}H]carbaldehyde, and the monodeuteriothiophen-2-carbaldehydes. Furyl- and thienyllithium compounds are the key intermediates for replacing hydrogen or halogen atoms by deuterium, and for carrying out selective reactions at the α- or β-positions of the heterocyclic rings.

DURING investigations into the cause of the multiple carbonyl absorptions shown by furan- and thiophen-2-carbaldehydes and certain esters of the corresponding acids,[1a] we required analogues having deuterium at various positions of the heterocyclic nuclei. Apart from 3,4,5-trideuteriofuran- and 5-deuteriothiophen-2-carboxylic acids [1b] there appears to be little information about such compounds in the literature.[2] In order to establish the general trends it seemed desirable to prepare the complete set of deuteriated aldehydes and acids in one of the series; since a range of furan derivatives which appeared to be suitable as starting materials was already available [3a] this system was selected for detailed study. The main object was to obtain specifically labelled products of high isotopic purity, and in evaluating alternative preparations this was regarded as more important than length or overall yield.

The routes finally adopted are reported in the Scheme and require little discussion; however, since validation of the results depends almost entirely on n.m.r. and mass spectral examination of the products, the main features of the spectra are presented (Tables 1 and 2 of the Experimental section). Furyl- and thienyllithium compounds were the key intermediates, not only for introducing deuterium efficiently but also for carrying out selective reactions at the α- or β-positions of

[1] (*a*) D. J. Chadwick, J. Chambers, G. D. Meakins, and R. L. Snowden, *J.C.S. Chem. Comm.*, 1971, 625; 1972, 742; (*b*) *J.C.S. Perkin I*, 1973, 201.

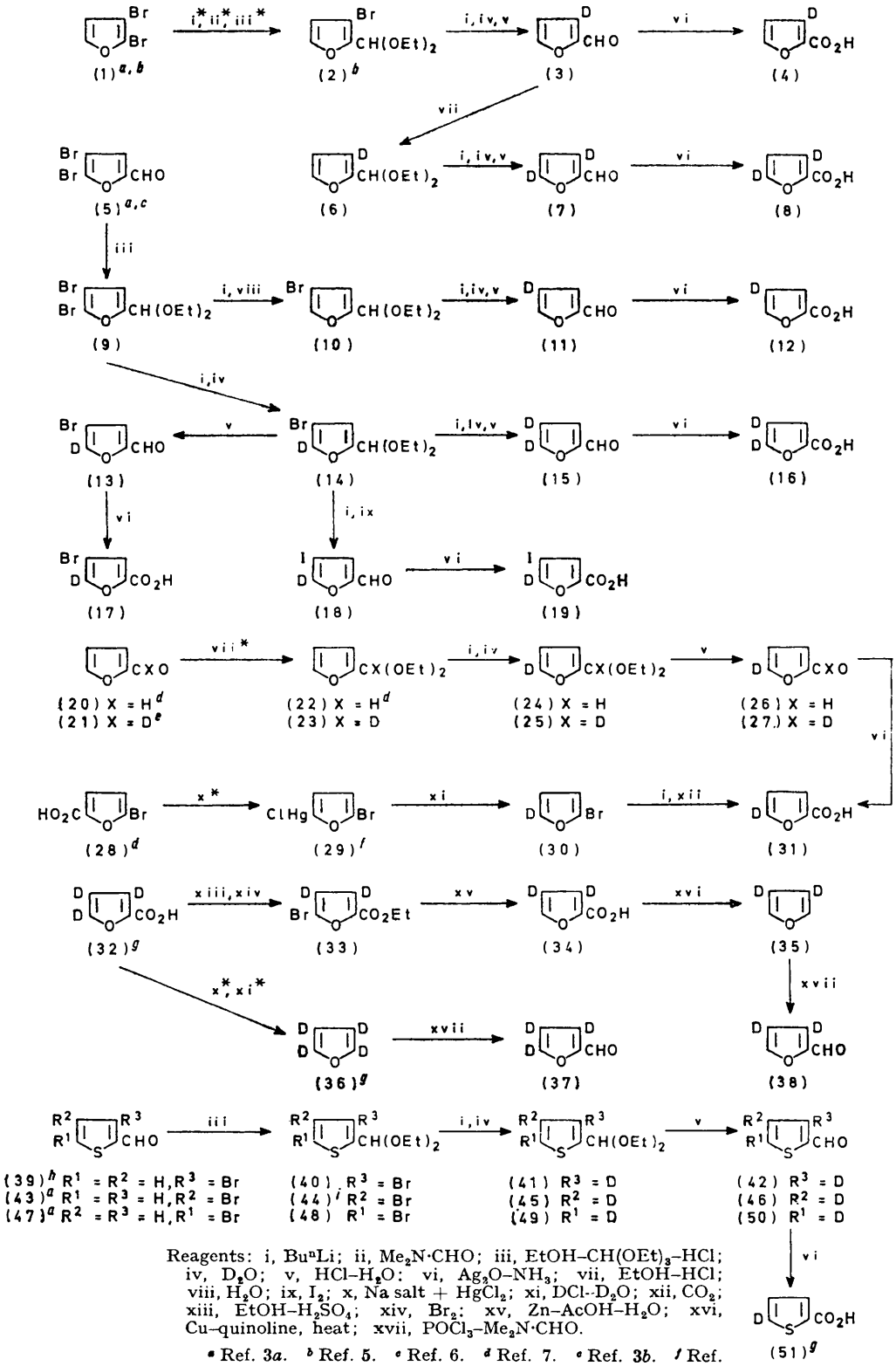
[2] 'Deuterium Labelling in Organic Chemistry,' A. F. Thomas, Meredith Corporation, New York, 1971.

[3] (*a*) D. J. Chadwick, J. Chambers, G. D. Meakins, and R. L. Snowden, *J.C.S. Perkin I*, 1973, 1766; *J.C.S. Perkin II*, 1972, 1959; (*b*) D. J. Chadwick, J. Chambers, H. E. Hargraves, G. D. Meakins, and R. L. Snowden, *J.C.S. Perkin I*, 1973, 2327.

SCHEME

Routes to deuteriated furan- and thiophen-2-carbaldehydes and -2-carboxylic acids

References are given to known compounds; the rest are new. Stages conducted by the published methods (see references to products) are marked with an asterisk.



Reagents: i, Bu^nLi; ii, $Me_2N{\cdot}CHO$; iii, EtOH–$CH(OEt)_3$–HCl; iv, D_2O; v, HCl–H_2O; vi, Ag_2O–NH_3; vii, EtOH–HCl; viii, H_2O; ix, I_2; x, Na salt + $HgCl_2$; xi, DCl–D_2O; xii, CO_2; xiii, EtOH–H_2SO_4; xiv, Br_2; xv, Zn–AcOH–H_2O; xvi, Cu–quinoline, heat; xvii, $POCl_3$–$Me_2N{\cdot}CHO$.

[a] Ref. 3a. [b] Ref. 5. [c] Ref. 6. [d] Ref. 7. [e] Ref. 3b. [f] Ref. 8. [g] Ref. 1b. [h] Ref. 9. [i] Ref. 10.

the heterocycles. The Scheme shows routes to all the mono-, di-, and tri-deuteriofuran-2-carbaldehydes and -2-carboxylic acids, and to the monodeuteriothiophen-2-carbaldehydes. {5-Deuteriofuran-2-[^{2}H]carbaldehyde (27) links the present compounds, deuteriated in the nucleus, with the 'unsubstituted' 2-[^{2}H]carbaldehydes.[3b] 5-Deuteriothiophen-2-carboxylic acid (51) is isotopically purer than the previous material [1b] which contained an appreciable amount of deuterium at the β-positions. Esters of the deuteriated acids are listed in the Experimental section.} Although some of the sequences are long, for example the twelve-stage conversion of furan-2-carboxylic acid into its 3,5-dideuterio-derivative (8), most of the experimental procedures are convenient and efficient.

EXPERIMENTAL

For general directions see ref. 3*a*. When a general procedure is first mentioned the experimental details are recorded, or a reference to a paper containing the details is given; subsequent uses of the same reactions, or sequences of reactions, are described only briefly. The variations in the conditions of the reactions involving butyl-lithium, although small, are important in obtaining the stated yields. The chemical purity of the products was checked by g.l.c. or t.l.c. The structures of the deuteriated compounds were established, and their isotopic purity was assessed, by comparing their n.m.r. spectra (Table 1) and mass spectra (Table 2) with those of the protio-analogues; no product had an isotopic purity lower than 93%, and for the majority the value was greater than 95%.

All the deuteriated esters in Table 1 are new compounds. With the exception of ethyl 5-bromo-3,4-dideuteriofuran-2-carboxylate (33), whose preparation is given in one of the following sections, they were obtained from 2-carboxylic acids by standard methods.[3a] All but three of the corresponding protio-esters have been described recently;[3a,b] since the m.p.s or b.p.s of the protio-esters are close to those observed with the deuterio-analogues the values are not recorded here.[4] [Values are given in Table 2 for the three esters of the bromo-deuterio-acid (17).] The C and (H_2O + D_2O) percentages found by combustion were in satisfactory agreement with the calculated values.[4] The i.r. spectra of the deuteriated compounds will be reported later.

Petrol refers to light petroleum (b.p. 60—80°).

3-Deuterio- and 3,5-Dideuterio-furan-2-carboxylic Acids [(4) *and* (8)].—3-Bromofuran-2-carbaldehyde diethyl acetal [5] (2) (65 g) in Et_2O (80 ml) was added during 30 min to a solution of Bu^{n}Li [prepared under N_2 at −10 °C from Li wire (4·4 g), Bu^{n}Br (dried over molecular sieve; 45 g), and Et_2O (200 ml)] which was stirred vigorously at −70 °C. After a further 40 min D_2O (50 ml) was added, and the temperature of the mixture was allowed to reach 5 °C during 3 h. 2N-HCl (100 ml) was added, and the stirring was continued for 1 h at 5 °C. Work-up gave *3-deuteriofuran-2-carbaldehyde* (3) (12·2 g), b.p. 57—59° at 12 mmHg [Found: C, 61·9; (H_2O + D_2O), 37·7. $C_5H_3DO_2$ requires C, 61·9; (H_2O + D_2O), 38·1%]. Oxidation of this aldehyde (5 g) with Tollens reagent under the conditions described previously [3a] gave the *3-deuterio-acid* (4) (4·2 g), m.p. 128—130° (Found: C, 52·8. $C_5H_3DO_3$ requires C, 53·1%).

A mixture of the aldehyde (3) (5 g), EtOH (80 ml), and EtOH saturated with dry HCl (0·5 ml) was boiled under reflux for 2 h, cooled, neutralised with anhydrous Na_2CO_3, and worked up to give *3-deuteriofuran-2-carbaldehyde diethyl acetal* (6) (2·8 g), b.p. 73—75° at 12 mmHg. This acetal (1·7 g) in Et_2O (5 ml) was treated with Bu^{n}Li [from Li (200 mg) and Bu^{n}Br (2·1 g) in Et_2O (20 ml)] at −50 °C. The temperature of the stirred mixture was allowed to reach 25 °C during 1·5 h, and the mixture was boiled under reflux for 2 h, cooled, stirred with D_2O (10 ml) at 25 °C for 1 h, and then with 2N-HCl (30 ml) for 1 h. Work-up gave *3,5-dideuteriofuran-2-carbaldehyde* (7) (460 mg), b.p. 71—74° (bath temp.) at 12 mmHg, which was oxidised with Tollens reagent to the *3,5-dideuterio-acid* (8) (323 mg), m.p. 127—129°.

4-Deuterio- and 4,5-Dideuterio-furan-2-carboxylic Acids [(12) *and* (16)].—A mixture of 4,5-dibromofuran-2-carbaldehyde [3a,6] (5) (85 g), $HC(OEt)_3$ (dried over molecular sieve; 67 g), EtOH (350 ml), and 2N-HCl (0·6 ml) was boiled under reflux for 2 h. Evaporation, and fractional distillation gave the *dibromo-acetal* (9) (95 g), b.p. 93—95° at 0·2 mmHg (Found: C, 32·6; H, 3·8. $C_9H_{12}Br_2O_2$ requires C, 32·9; H, 3·7%). This acetal (55 g) in Et_2O (50 ml) was added during 30 min to Bu^{n}Li [from Li (2·7 g) and Bu^{n}Br (27·4 g) in Et_2O (100 ml)] at −70 °C. The mixture was allowed to warm to 0 °C during 2 h, and was then stirred with H_2O (50 ml) for 1 h to give *4-bromofuran-2-carbaldehyde diethyl acetal* (10) (36·5 g), b.p. 63—66° at 0·02 mmHg (Found: C, 43·2; H, 5·1. $C_9H_{13}BrO_3$ requires C, 43·4; H, 5·2%). The bromo-acetal (35·2 g) in Et_2O (50 ml) was added during 30 min to Bu^{n}Li [from Li (2·4 g) and Bu^{n}Br (24·7 g) in Et_2O (120 ml)] at −70 °C. After a further 40 min D_2O (25 ml) was added at −70 °C, and the mixture was allowed to warm to 5 °C during 3 h, and then stirred with 2N-HCl (50 ml) at 5 °C for 1 h. Work-up gave *4-deuteriofuran-2-carbaldehyde* (11) (6·1 g), b.p. 66—67° at 16 mmHg [Found: C, 61·9; (H_2O + D_2O), 37·7. $C_5H_3DO_2$ requires C, 61·9; (H_2O + D_2O), 38·1%]. Oxidation of this aldehyde (4·5 g) gave the *4-deuterio-acid* (12) (3·8 g), m.p. 125—127°.

Similarly, but with D_2O used instead of H_2O, the dibromo-acetal (9) (76 g) gave the *4-bromo-5-deuterio-acetal* (14) (42 g) (b.p. 62—64° at 0·02 mmHg), a portion (17·5 g) of which was converted into *4,5-dideuteriofuran-2-carbaldehyde*(15) (2·8 g) (b.p. 66—68° at 16 mmHg), and thence into the *4,5-dideuterio-acid* (16) (2·4 g), m.p. 127—129° [Found: C, 52·7; (H_2O + D_2O), 33·8. $C_5H_2D_2O_3$ requires C, 52·6; (H_2O + D_2O), 33·3%].

4-Bromo-5-deuterio- and 5-Deuterio-4-iodo-furan-2-carboxylic Acids [(17) *and* (19)].—Hydrolysis of the foregoing bromo-deuterio-acetal (14) (7·5 g) with 2N-HCl at 25 °C for 1 h gave 4-bromo-5-deuteriofuran-2-carbaldehyde (13) (4·8 g), m.p. 52—53° [Found: C, 34·0; Br, 45·8; (H_2O + D_2O), 15·3. $C_5H_2BrDO_2$ requires C, 34·1; Br, 45·4; (H_2O + D_2O), 15·9%], a portion (3·6 g) of which was oxidised to the *bromo-deuterio-acid* (17) (3·1 g), m.p. 123—125°.

The bromo-deuterio-acetal (14) (4 g) in Et_2O (10 ml) was

[4] Details are recorded in the D.Phil Theses of J. Chambers and R. L. Snowden, Oxford, 1973.

[5] R. Sornay, J.-M. Meunier, and P. Fournari, *Bull. Soc. chim. France*, 1971, 990.

[6] B. Roques, M.-C. Zaluski, and M. Dutheil, *Bull. Soc. chim. France*, 1971, 238.

treated with Bu^nLi [from Li (270 mg)] in Et_2O (40 ml) at −70 °C, and, after 40 min, I_2 (5·1 g) in Et_2O (60 ml) was added at −70 °C. Standard manipulation including hydrolysis with 2N-HCl (100 ml) gave *5-deuterio-4-iodofuran-2-carbaldehyde* (18) (2·3 g) [m.p. 72—74° (Found: C, 26·8. $C_5H_2DIO_2$ requires C, 26·9%); τ 0·35 (s, CHO) and 2·74 (s, 3-H); *m/e* 223 (M^+, 100%)], a portion (1·4 g) of which was oxidised to the *deuterio-iodo-acid* (19) (1·2 g), m.p. 137—138°.

78° at 12 mmHg, which was converted similarly and in comparable yields into the *5-deuterio-*[^{2}H]*acetal* (25), b.p. 80—81° at 19 mmHg, and the *5-deuterio-*[^{2}H]*aldehyde* (27), b.p. 72—76° (bath temp.) at 14 mmHg.

5-Deuteriofuran-2-carboxylic Acid (31).—5-Bromo-2-chloromercuriofuran [8] (29) (11·6 g) was boiled under reflux with 20% DCl–D_2O (30 ml) for 20 min; work-up gave 2-bromo-5-deuteriofuran (30) (3·5 g), b.p. 100—102°. This compound (2·7 g) in Et_2O (15 ml) was treated with

TABLE 1

N.m.r. signals (τ values). Spectra were recorded at 100 MHz for solutions in $CDCl_3$ (carboxylic acids) or CCl_4 (all other types). For signals other than singlets (s), doublets (d), triplets (t), and multiplets the number of lines is indicated by an italicised number, and where appropriate the descriptions are followed by *J* values or apparent *J* values (in Hz) as described earlier.[11]

Compd.	2-Substituent *	Ring protons
(3)	0·40 (d, 0·8)	2·33 (*4*, 1·8, 0·8; 5-H)
		3·43 (d, 1·8; 4-H)
(4)	−1·86 (s)	2·37 (d, 1·8; 5-H)
		3·46 (d, 1·8; 4-H)
(4) *Me ester*	6·17 (s)	2·51 (d, 1·8; 5-H)
		3·56 (d, 1·8; 4-H)
(4) *Et ester*	8·64 (t, 7·2)	2·51 (d, 1·8; 5-H)
		3·58 (d, 1·8; 4-H)
(4) *But ester*	8·45 (s)	2·52 (d, 1·8; 5-H)
		3·59 (d, 1·8; 4-H)
(7)	0·33 (s)	3·44 (s; 4-H)
(8)	−1·64 (s)	3·48 (s; 4-H)
(8) *Me ester*	6·20 (s)	3·57 (s; 4-H)
(8) *Et ester*	8·65 (t, 7·2)	3·58 (s; 4-H)
(8) *But ester*	8·46 (s)	3·59 (s; 4-H)
(9)	4·63 (d, 0·8)	3·58 (d, 0·8; 3-H)
(10)	4·61 (m)	2·66 (*4*, 0·9, 0·5; 5-H)
		3·59 (*4*, 0·9, 0·5; 3-H)
(11)	0·40 (m)	2·37 (m; 5-H)
		2·86 (m; 3-H)
(12)	−2·03 (s)	2·43 (d, 0·8; 5-H)
		2·73 (d, 0·8; 3-H)
(12) *Me ester*	6·20 (s)	2·50 (d, 0·8; 5-H)
		2·95 (m; 3-H)
(12) *Et ester*	8·65 (t, 7·2)	2·51 (d, 0·8; 5-H)
		2·96 (m; 3-H)
(12) *But ester*	8·48 (s)	2·56 (d, 0·8; 5-H)
		3·05 (d, 0·8; 3-H)
(13)	0·39 (s)	2·83 (s; 3-H)
(15)	0·39 (s)	2·86 (s; 3-H)
(16)	−2·10 (s)	2·65 (s; 3-H)
(16) *Me ester*	6·19 (s)	2·94 (s; 3-H)
(16) *Et ester*	8·65 (t, 7·2)	2·96 (s; 3-H)
(16) *But ester*	8·46 (s)	3·05 (s; 3-H)
(17)	−1·24 (s)	2·70 (s; 3-H)
(17) *Me ester*	6·15 (s)	2·89 (s; 3-H)
(17) *Et ester*	8·64 (t, 7·2)	2·89 (s; 3-H)
(17) *But ester*	8·48 (s)	3·02 (s; 3-H)
(18)	0·35 (s)	2·74 (s; 3-H)
(19)	−1·57 (s)	2·64 (s; 3-H)
(19) *Me ester*	6·17 (s)	2·82 (s; 3-H)
(19) *Et ester*	8·60 (t, 7·2)	2·81 (s; 3-H)
(19) *But ester*	8·47 (s)	2·92 (s; 3-H)
(24)	4·59 (s)	3·77 (m; 3-H and 4-H)
(25)		3·78 (m; 3-H and 4-H)
(26)	0·37 (s)	2·77 (d, 3·8; 3-H)
		3·43 (d, 3·8; 4-H)
(27)		2·82 (d, 3·5; 3-H)
		3·46 (d, 3·5; 4-H)
(30)		3·72 (m; 3-H and 4-H)
(31)	−1·32	2·66 (d, 3·4; 3-H)
		3·45 (d, 3·4; 4-H)
(31) *Me ester*	6·16 (s)	2·90 (d, 3·8; 3-H)
		3·53 (d, 3·8; 4-H)
(31) *Et ester*	8·66 (t, 7·2)	2·93 (d, 3·8; 3-H)
		3·57 (d, 3·8; 4-H)
(31) *But ester*	8·48 (s)	2·99 (d, 3·8; 3-H)
		3·62 (d, 3·8; 4-H)
(32) *Me ester*	6·19 (s)	
(32) *Et ester*	8·67 (t, 7·2)	
(32) *But ester*	8·46 (s)	
(33)	8·65 (t, 7·2)	
(34)	−1·71	2·38 (s; 5-H)
(34) *Me ester*	6·23 (s)	2·53 (s; 5-H)
(34) *Et ester*	8·65 (t, 7·2)	2·52 (s; 5-H)
(34) *But ester*	8·45 (s)	2·54 (s; 5-H)
(35)		2·70 (s; 2-H and 5-H)
(37)	0·39 (s)	
(38)	0·38 (d, 0·7)	2·28 (m; 5-H)
(40)	4·40 (s)	2·83 (d, 5·8; 5-H)
		3·13 (d, 5·8; 4-H)
(41) †	4·38 (s)	2·80 (d, 5·0; 5-H)
		3·02 (d, 5·0; 4-H) ‡
(42)	0·16 (d, 1·2)	2·31 (*4*, 5·0, 1·2; 5-H)
		2·87 (d, 5·0; 4-H) ‡
(44)	4·39 (s)	2·92 (d, 1·5; 5-H)
		3·13 (d, 1·5; 3-H)
(45) †	4·41 (s)	2·85 (d, 2·1; 5-H?) ‡
		3·05 (d, 2·1; 3-H?) ‡
(46)	0·10 (d, 1·1)	2·28 (m; 3-H and 5-H)
(48)	4·43 (s)	3·13 (d, 4·0; 3-H)
		3·29 (d, 4·0; 4-H?)
(49)	4·35 (s)	3·05 (d, 4·0; 3-H?)
		3·15 (d, 4·0; 4-H?)
(50)	0·13 (s)	2·28 (d, 4·0; 3-H)
		2·86 (d, 4·0; 4-H) ‡
(51)	−2·39 (s)	2·13 (d, 3·6; 3-H)
		2·88 (d, 3·6; 4-H) ‡
(51) Me ester	6·30 (s)	2·45 (d, 3·7; 3-H)
		3·12 (d, 3·7; 4-H) ‡
(51) But ester	8·43 (s)	2·42 (d, 4·0; 3-H)
		3·05 (d, 4·0; 4-H) ‡

* CHO, CO_2H, $CH(OEt)_2$, or $CO_2{\cdot}C{-}CH_3$. † Not isolated. ‡ Broadened doublet.

5-Deuteriofuran-2-carbaldehyde (26) *and -2-*[^{2}H]*carbaldehyde* (27).—A mixture prepared by adding furan-2-carbaldehyde diethyl acetal [7] (22) (60 g) during 10 min to Bu^nLi [from Li (8·6 g) and Bu^nBr (86·5 g) in Et_2O (300 ml)] at −10 °C was warmed to 25 °C during 2 h, boiled under reflux for 3 h, cooled to 25 °C, and stirred with D_2O (10 ml) for 12 h. Work-up gave the *5-deuterio-acetal* (24) (40 g), b.p. 79—80° at 20 mmHg [Found: C, 63·0; (H_2O + D_2O), 74·0. $C_9H_{13}DO_3$ requires C, 63·1; (H_2O + D_2O), 74·3%]. Hydrolysis of this acetal (32 g) in Et_2O (250 ml) with 2N-HCl (140 ml) at 25 °C for 2 h gave *5-deuteriofuran-2-carbaldehyde* (26) (17 g), b.p. 57—58° at 15 mmHg [Found: C, 61·9; (H_2O + D_2O), 38·3. $C_5H_3DO_2$ requires C, 61·9; (H_2O + D_2O), 38·1%].

Treatment of furan-2-[^{2}H]carbaldehyde [3b] (21) with dry EtOH containing HCl gave the [^{2}H]acetal (23), b.p. 75—

[7] A. Dunlop and F. Peters, 'The Furans,' Reinhold, New York, 1953.

Bu^nLi [from Li (450 mg) and Bu^nBr (4·5 g) in Et_2O (20 ml)] at −30 °C. After 1·5 h at −30 °C the mixture was warmed to 10 °C, and then poured on to a slurry of solid CO_2–Et_2O. H_2O (150 ml) was added after 30 min, and the mixture was acidified with 5N-HCl. Isolation with Et_2O gave *5-deuteriofuran-2-carboxylic acid* (2 g), m.p. 129—130° [Found: C, 53·0; (H_2O + D_2O), 32·6. $C_5H_3DO_3$ requires C, 53·1; (H_2O + D_2O), 32·7%]. This acid was also obtained (84% yield) by oxidising the 5-deuterio-aldehyde (26).

3,4-*Di- and* 3,4,5-*Tri-deuteriofuran-2-carbaldehydes* [(38) *and* (37)].—Br_2 (25 g) in $Cl[CH_2]_2Cl$ (10 ml) was added during 1 h to a solution of ethyl 3,4,5-trideuteriofuran-2-carboxylate (see Table 1; 20 g) in $Cl[CH_2]_2Cl$ (80 ml) boiling under reflux, and the boiling was continued for a further 4 h. Evaporation and fractional distillation gave

[8] H. Gilman and G. F. Wright, *J. Amer. Chem. Soc.*, 1933, **55**, 3302.

ethyl 5-bromo-3,4-dideuteriofuran-2-carboxylate (33) (24·2 g), b.p. 70—71° at 0·05 mmHg [Found: C, 38·3; (H_2O + D_2O), 28·4; Br, 36·6. $C_7H_5BrD_2O_3$ requires C, 38·0; (H_2O + D_2O), 29·4; Br, 36·2%]. A mixture of this ester (19·2 g), Zn (60 mesh powder; 8·3 g), AcOH (7·2 g), and H_2O (19·2 ml) was stirred at 110° for 3 d. Addition of Et_2O, filtration, acidification with 5N-HCl, and extraction with EtOAc gave the *dideuterio-acid* (34) (9 g), m.p. 129—130° (from MeOH) [Found: C, 52·7; (H_2O + D_2O), 32·9. $C_5H_2D_2O_3$ requires C, 52·6; (H_2O + D_2O), 33·4%]. Decarboxylation of this acid (6 g) by heating with Cu bronze (2 g) and quinoline (20 g) at 250 °C for 3 h gave 3,4-dideuteriofuran (35) (3 g), b.p. 30—32°. Vilsmeier formylation [3b] of this compound (820 mg) and preparative g.l.c. gave the *3,4-dideuterioaldehyde* (38) (625 mg) [Found: C, 61·3; (H_2O + D_2O), 38·6. $C_5H_2D_2O_2$ requires C, 61·3; (H_2O + D_2O), 38·8%].

Formylation [3b] of tetradeuteriofuran [1b] (36) (710 mg) similarly gave *3,4,5-trideuteriofuran-2-carbaldehyde* (37) (615 mg) [Found: C, 60·6; (H_2O + D_2O), 39·0. $C_5HD_3O_2$ requires C, 60·6; (H_2O + D_2O), 39·4%].

3-, 4-, and 5-Deuteriothiophen-2-carbaldehydes [(42), (46), *and* (50)] *and 5-Deuteriothiophen-2-carboxylic Acid* (51).—A mixture of 3-bromothiophen-2-carbaldehyde [9] (39) (1·44 g), $HC(OEt)_3$ (5 g), EtOH (30 ml), and EtOH saturated with dry HCl (1 ml) was boiled under reflux for 9 h, cooled, neutralised with anhydrous Na_2CO_3, and worked up to give the acetal (40) (1·62 g), b.p. 130—133° at 16 mmHg. This acetal (1·49 g) in Et_2O (10 ml) was treated with Bu^nLi [from Li (160 mg) and Bu^nBr (1·6 g) in Et_2O (25 ml)] at −60 °C. After 10 min at −60 °C, D_2O (8 ml) was added and the temperature of the stirred mixture was allowed to reach 25 °C during 1 h. Isolation with Et_2O gave an oil (780 mg) shown by n.m.r. examination to consist of the 3-deuterio-acetal (41) (80%) and the 3-deuterio-aldehyde (42) (20%). A solution of this material in Et_2O (10 ml) was stirred with 5N-HCl at 25 °C for 2 h and gave *3-deuteriothiophen-2-carbaldehyde* (42) (480 mg), b.p. 84—87° (bath temp.) at 12 mmHg.

4-Bromothiophen-2-carbaldehyde [10] (43) (6·8 g) was converted into its acetal (44) (6·3 g), b.p. 107—109° at 0·7 mmHg (lit.,[10] 138—144° at 16 mmHg). This acetal (6·2 g) in Et_2O (25 ml) was treated with Bu^nLi [from Li (2 g) and Bu^nBr (16 g) in Et_2O (60 ml)] at −65 °C for 10 min, and then with D_2O (6 ml) at −65 °C to give a mixture (4·3 g), b.p. 120—125° at 10 mmHg, consisting of the 4-deuterio-acetal (45) (50%) and the 4-deuterio-aldehyde (46) (50%). Hydrolysis followed by p.l.c. [3 large plates, 4 × petrol–Me_2CO (49 : 1)] and distillation afforded *4-deuteriothiophen-2-carbaldehyde* (46) (1·85 g), b.p. 95—100° (bath temp.) at 10 mmHg.

5-Bromothiophen-2-carbaldehyde [3a] (47) (8 g) gave the corresponding acetal (48) (7·5 g) (b.p. 83—85° at 0·07 mmHg), which was dissolved in Et_2O (20 ml) and added during 20 min to Bu^nLi [from Li (3·9 g) and Bu^nBr (38·5 g) in Et_2O (150 ml) at −70 °C. The mixture was allowed to warm to 25 °C and was then stirred with D_2O (5 ml) for 10 min. Work-up gave *5-deuteriothiophen-2-carbaldehyde diethyl acetal* (49) (4·4 g) (b.p. 102—104° at 11 mmHg), which was hydrolysed with 5N-HCl to *5-deuteriothiophen-2-carbaldehyde* (50) (1·2 g), b.p. 116—118° (bath temp.) at 25 mmHg. Oxidation of this aldehyde (1·1 g) gave 5-deuteriothiophen-2-carboxylic acid (51) (880 mg), m.p. 125—126° (lit.,[1b] 125—127°).

TABLE 2

Mass spectra. The *m/e* value of the molecular ion is followed, in parentheses, by its percentage abundance; the base-peak is listed when it is not the molecular ion

Compd.	M^+	Base-peak	Compd.	M^+	Base-peak
(3)	97 (98)	96	(19) Me ester	253 (100)	
(4)	113 (100)		(19) Et ester	267 (88)	222
(4) Me ester	127 (38)	96	(19) But ester	295 (14)	239
(4) Et ester	141 (22)	96	(24)	171 (10)	97
(4) But ester	169 (12)	96	(25)	172 (6)	98
(7)	98 (96)	97	(26)	97 (94)	96
(8)	114 (100)		(27)	98 (92)	96
(8) Me ester	128 (36)	97	(31)	113 (100)	
(8) Et ester	142 (18)	97	(31) Me ester	127 (35)	96
(8) But ester	170 (10)	97	(31) Et ester	141 (17)	96
(11)	97 (23)	59	(31) But ester	169 (12)	96
(12)	113 (100)		(32) Me ester	129 (32)	98
(12) Me ester	127 (38)	96	(32) Et ester	143 (20)	98
(12) Et ester	141 (18)	96	(32) But ester	171 (11)	98
(12) But ester	169 (14)	96	(33)	220 • (35)	175
(13)	175 • (100)		(34)	114 (100)	
(15)	98 (36)	97	(34) Me ester	128 (38)	97
(16)	114 (100)		(34) Et ester	142 (17)	97
(16) Me ester	128 (38)	97	(34) But ester	170 (12)	97
(16) Et ester	142 (19)	97	(37)	99 (100)	
(16) But ester	170 (10)	97	(38)	98 (60)	97
(17)	191 (100)		(42)	113 (87)	112
(17) Me ester †	207 • (46)	176	(46)	113 (84)	112
(17) Et ester ‡	219 • (44)	174	(50)	113 (86)	112
(17) But ester §	247 • (22)	56	(51)	129 (74)	112
(18)	223 (100)		(51) Me ester	143 (37)	112
(19)	239 (100)		(51) But ester	185 (14)	112

• For the ^{79}Br isotope. † M.p. 44—46°. ‡ B.p. 60—62° (bath temp.) at 0·5 mmHg. § B.p. 68—70° (bath temp.) at 0·5 mmHg.

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