Preparation of Substituted Furan- and Thiophen-2-carbaldehydes and -2-[^{2}H]carbaldehydes, and of 2-Furyl Ketones

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A series of heterocyclic 2-carbaldehydes and 2-[^{2}H]carbaldehydes have been prepared, most of them by Vilsmeier formylation of mono- and di-substituted furans and thiophens. Isopropylation of methyl furan-2-carboxylate was used to obtain the 4- and 5-monoisopropyl- and 4,5-di-isopropyl-furan-2-carboxylic acids. With different aryl 2-furyl ketones bromine may attack either the benzenoid ring or the heterocyclic ring preferentially.

To extend our study [1] of heterocyclic systems containing a C=O group at position 2 we required a series of 2-carbaldehydes, 2-[^{2}H]carbaldehydes, and 2-ketones containing a variety of substituents in the heterocyclic ring. Scheme 1 shows the products, other than those containing deuterium, described here and the final stages of the preparations. Improved routes to some of the starting materials are portrayed in Scheme 2 (the rest of the starting materials were obtained by the published methods cited in Scheme 1), and the preparations of the deuteriated compounds are shown in Scheme 3. In view of the detailed nature of the Schemes comment is restricted to points of interest arising from the work.

The Vilsmeier reaction [2] led cleanly to one aldehyde from each of the 2-mono- and 2,3- and 3,4-di-substituted furans and thiophens (Scheme 1). The 3-monosubstituted compounds gave mixtures of the 2-aldehydes and isomers (presumably the 5-aldehydes) in ratios of about 7 : 1. Rigorous purification of the 2-aldehydes,

[1] D. J. Chadwick, J. Chambers, G. D. Meakins, and R. L. Snowden, (*a*) *J.C.S. Perkin I*, 1973, 1766; (*b*) *J.C.S. Chem. Comm.*, 1972, 742; *J.C.S. Perkin II*, 1972, 1959.

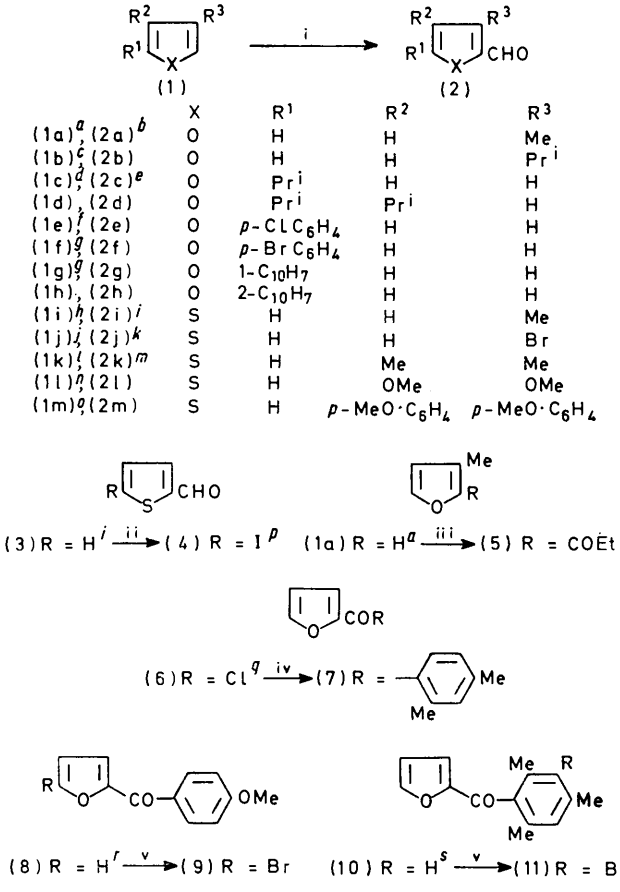
[2] A. Vilsmeier and A. Haack, *Ber.*, 1927, **60**, 119.

by gas–liquid or preparative layer chromatography or *via* crystalline derivatives, was essential since they were required for spectrometric comparison with other heterocyclic aldehydes.[1b] [Earlier work on the formylation of 3-methylthiophen[3] (1i) using the Vilsmeier method, and of 3-methylfuran[4] (1a) using the Gattermann reaction did not reveal the presence of minor

SCHEME 1

2-Oxo-furans and -thiophens

References are given to known compounds; the rest are new



	X	R^1	R^2	R^3
(1a)[a] (2a)[b]	O	H	H	Me
(1b)[c] (2b)	O	H	H	Pr^i
(1c)[d] (2c)[e]	O	Pr^i	H	H
(1d), (2d)	O	Pr^i	Pr^i	H
(1e)[f] (2e)	O	*p*-ClC_6H_4	H	H
(1f)[g] (2f)	O	*p*-BrC_6H_4	H	H
(1g)[g] (2g)	O	1-$C_{10}H_7$	H	H
(1h), (2h)	O	2-$C_{10}H_7$	H	H
(1i)[h] (2i)[i]	S	H	H	Me
(1j)[i] (2j)[k]	S	H	H	Br
(1k)[l] (2k)[m]	S	H	Me	Me
(1l)[n] (2l)	S	H	OMe	OMe
(1m)[o] (2m)	S	H	*p*-$MeO\cdot C_6H_4$	*p*-$MeO\cdot C_6H_4$

Reagents: i, $POCl_3$–$Me_2N\cdot CHO$; ii, $Tl(O\cdot CO\cdot CF_3)_3$, then KI; iii, $(Et\cdot CO)_2O$–BF_3; iv, *m*-xylene–$AlCl_3$; v, Br_2–$Cl[CH_2]_2Cl$

[a] Ref. 13. [b] Ref. 4. [c] Ref. 9. [d] Ref. 8. [e] Ref. 5. [f] D. C. Ayres and J. R. Smith, *J. Chem. Soc.*, 1968, 2737. [g] A. W. Johnson, *J. Chem. Soc.*, 1946, 895. [h] Commercially available. [i] Ref. 3. [j] S. Gronowitz and T. Raznikiewicz, *Org. Synth.*, 1964, **44**, 9. [k] Ref. 6. [l] Ref. 18. [m] B. F. Crowe and F. F. Nord, *J. Org. Chem.*, 1950, **15**, 1177. [n] Ref. 17. [o] Ref. 19. [p] Ref. 7. [q] Ref. 14. [r] Ref. 15. [s] Ref. 16.

products. The previous routes to 5-isopropylfuran-2-carbaldehyde[5] (2c), 3-bromothiophen-2-carbaldehyde[6] (2j), and 5-iodothiophen-2-carbaldehyde[7] (4) are less convenient than the present ones.]

Bromination of 2-furyl 4-methoxyphenyl ketone (8) led, as expected, to substitution in the furan (here, more reactive) ring. The reverse behaviour of the mesityl ketone (10) may be attributed to steric inhibition of coplanarity between the carbonyl group and the di-*o*-substituted benzene ring and hence to reduced mesomeric deactivation of the latter.

4-Isopropylfuran-2-carbaldehyde (17) is produced in low yield by the anomalous isopropylation of 2-furaldehyde (16).[8,9] Repetition of the reaction using a later procedure[10] gave a complex mixture from which material (12% yield) consisting largely of the 4-isopropyl aldehyde was obtained. Purification was difficult and it is doubtful whether the literature descriptions refer to pure samples. Isopropylation of methyl furan-2-carboxylate (12) by the published method[8] gave more of the 4,5-di-isopropylfuran ester (15) than of the 5-isopropylfuran ester (13) reported as the main product. Under carefully controlled conditions (see Experimental section) the reaction can be stopped after one alkyl group has been introduced; this gives a mixture from which the 5- and the 4-monoisopropylfuran esters [(13) and (14); ratio *ca.* 4 : 1] were obtained. A reaction in which more isopropyl chloride was present led satisfactorily to the di-isopropylfuran ester (15). The different Friedel–Crafts reactions in Scheme 2 thus afford two routes to 4-isopropylfuran-2-carboxylic acid (18), used here for preparing 3-isopropylfuran (1b), but the yield is low in both.

Vilsmeier reactions using deuterio-*NN*-dimethylformamide led efficiently to the new furan-2-[^{2}H]aldehyde (19) and the corresponding thiophen-aldehyde (20), previously obtained by a longer route.[11] The more economical preparation of the furan-aldehyde from furil is an adaption of that used recently for deuteriobenzaldehyde.[12] A general method for selective introduction of the deuterioaldehyde group is illustrated by the conversion of 2,3-dibromothiophen (22) into the bromo-aldehyde (23). Bromination of the latter gave little of the expected 3,5-dibromo-2-aldehyde (24); surprisingly, the main product was tetrabromothiophen (25).

EXPERIMENTAL

For general directions see ref. 1*a* and for details of preparative layer chromatography (p.l.c.) see *J. Chem. Soc.* (*C*), 1971, 1136. Preparative g.l.c. was carried out on a Pye Series 104 Chromatograph with a 2 m column of 20% dodecyl phthalate on Embacel. Petrol refers to light petroleum (b.p. 60—80°).

Vilsmeier Reactions (*Scheme* 1).—The general procedure,

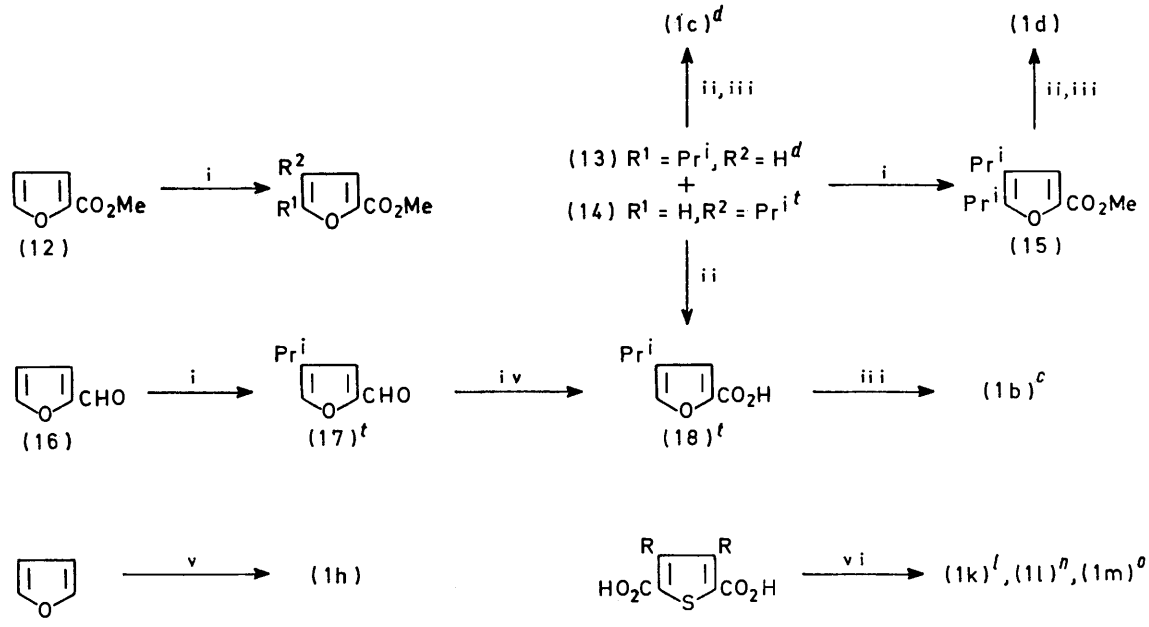
[3] E. Campaigne and W. L. Archer, *J. Amer. Chem. Soc.*, 1953, **75**, 989.
[4] T. Reichstein, H. Zschokke, and A. Goerg, *Helv. Chim. Acta*, 1931, **14**, 1280.
[5] H. Gilman and R. R. Burtner, *J. Amer. Chem. Soc.*, 1935, **57**, 909.
[6] S. Gronowitz and K. Dahlgren, *Arkiv. Kemi*, 1963, **21**, 201.
[7] V. I. Rogovik and Y. L. Goldfarb, *Khim. geterotsikl. Soedinenii*, 1965, 657.
[8] H. Gilman and N. O. Calloway, *J. Amer. Chem. Soc.*, 1933, **55**, 4197.
[9] H. Gilman, N. O. Calloway, and R. R. Burtner, *J. Amer. Chem. Soc.*, 1935, **57**, 906.
[10] N. Elming, *Acta Chem. Scand.*, 1952, **6**, 605.
[11] C. Andrieu, R. Pinel, and Y. Mollier, *Bull. Soc. chim. France*, 1971, 1314.
[12] A. W. Burgstahler, D. E. Walker, J. P. Kuebrich, and R. L. Schowen, *J. Org. Chem.*, 1972, **37**, 1272.

given in detail for the first compound, is followed by a Table showing the results of these reactions. The products' i.r. absorptions will be presented and discussed in later papers.

3-Methylfuran [13] (1a) (4·2 g) was added during 20 min to a stirred mixture of $POCl_3$ (10·7 g) and $Me_2N{\cdot}CHO$ (5·1 g) at 0 °C. After a further 40 min the stirred mixture was heated at 40 °C for 10 min, poured onto ice (60 g), and neutralised with Na_2CO_3 (18 g). Isolation with Et_2O and distillation gave material (3·7 g), b.p. 58—60° at 11 mmHg, shown by g.l.c. (at 75 °C) to contain three components in proportions 30 : 4 : 1. Preparative g.l.c. (at 140 °C) of a portion (1 g) gave 3-methylfuran-2-carbaldehyde [4] (2a) (710 mg) and material (80 mg; $\nu_{max.}$ 1689 cm^{-1}) presumed to be 4-methylfuran-2-carbaldehyde.

5-Iodothiophen-2-carbaldehyde (4).—Thiophen-2-carbaldehyde [3] (3) (4·1 g) in MeCN (50 ml) was stirred with thallium(III) trifluoroacetate (24·4 g) at 20 °C for 26 h. KI (40 g) in H_2O (75 ml) was added, followed, after 15 min, by $Na_2S_2O_5$ (4 g). The mixture was made alkaline with 2N-NaOH and extracted with Et_2O to give a red oil (2·5 g).

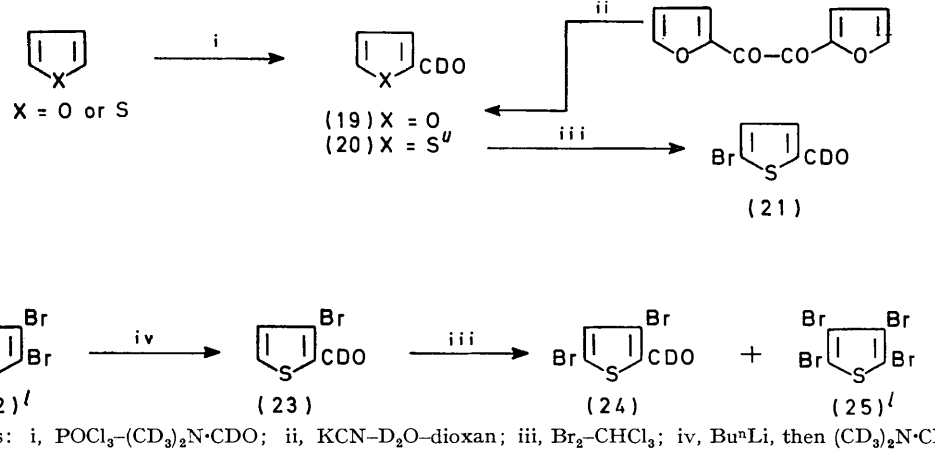
SCHEME 2
Routes to some of the starting materials in Scheme 1



Reagents: i, Pr^iCl–$AlCl_3$; ii, aq. 20% NaOH, then 5N-HCl; iii, Cu–quinoline, heat; iv, Ag_2O–NH_3; v, $(\beta\text{-}C_{10}H_7N_2^+)_2$-$ZnCl_4^{2-}$–NaOH–NaOAc; vi, Cu, 300 °C

Refs. as in Scheme 1, and [t] ref. 10

SCHEME 3
Preparation of deuteriated aldehydes



Reagents: i, $POCl_3$–$(CD_3)_2N{\cdot}CDO$; ii, KCN–D_2O–dioxan; iii, Br_2–$CHCl_3$; iv, Bu^nLi, then $(CD_3)_2N{\cdot}CDO$

Refs. as in Scheme 1, and [u] ref. 11

P.l.c. [4 large plates, 3 × petrol–Me_2CO (49 : 1)] afforded the iodo-aldehyde [7] (1·6 g), m.p. 55·5—56° (from MeOH–H_2O) (lit.,[7] 56°), τ (CCl_4) 0·30 (s, CHO) and 2·67 (s, 3-H and 4-H), τ (Me_2CO) — 0·19 (s, CHO), 2·36 (d, *J* 3·5 Hz, 3-H or 4-H), and 2·46 (d, *J* 3·5 Hz, 4-H or 3-H).

Ethyl 3-Methyl-2-furyl Ketone (5).—BF_3,Et_2O (peroxide free; 0·4 ml) was added to a stirred solution of 3-methylfuran (1a) (1·0 g) in $(EtCO)_2O$ (2·6 g) at 0 °C. After 1 h

[13] D. M. Burness, *Org. Synth.*, Coll. Vol. IV, 1963, 628.

H_2O (400 ml) was added, and the mixture was extracted with $CHCl_3$. The product was chromatographed on SiO_2 (80 g), and the material eluted with petrol–Me_2CO (4 : 1) was purified by p.l.c. [2 large plates, 4 × petrol–Me_2CO (19 : 1)] to give *ethyl 3-methyl-2-furyl ketone* (460 mg) as an oil (Found: C, 69·3; H, 7·4. $C_8H_{10}O_2$ requires C, 69·5; H, 7·3%), τ 2·70 (d, *J* 1·6 Hz, 5-H), 3·70 (d, *J* 1·6 Hz, 4-H), and 7·21 (q, *J* 7·8 Hz, $O{\cdot}CH_2{\cdot}CH_3$), *m/e* 138 (M^+, 63%) and 109 (100).

2,4-*Dimethylphenyl* 2-*Furyl Ketone* (7).—2-Furoyl chloride[14] (6·5 g) in CH_2Cl_2 (20 ml) was added during 30 min to a stirred mixture of $AlCl_3$ (7·3 g), *m*-xylene (5·3 g), and CH_2Cl_2 (20 ml), and the mixture was then boiled under reflux for 12 h. After work-up the product was chromatographed on SiO_2 (150 g). The material eluted with petrol–Me_2CO (4 : 1) was distilled to give the *2-furyl ketone* (5·5 g), b.p. 141—142° at 1·5 mmHg (Found: C, 77·7; H, 5·9. $C_{13}H_{12}O_2$ requires C, 78·0; H, 6·0%), τ 2·36 (4 lines, *J* by p.l.c. [1 large plate, 4 × petrol–Me_2CO (49 : 1)] to give the *2-furyl ketone* (150 mg) as an oil (Found: C, 56·9; H, 4·4; Br, 27·3. $C_{14}H_{13}BrO_2$ requires C, 57·3; H, 4·45; Br, 27·25%), $\lambda_{max.}$ 278 nm (ε 5300), τ 2·38 (1H, 4 lines, *J* 1·7 and 0·8 Hz, furyl 5-H), 3·06 (2H, m, benzenoid 5-H and furyl 3-H), and 3·50 (1H, 4 lines, *J* 3·8 and 1·7 Hz, furyl 4-H), *m/e* 292 (M^+, 64%).

The Methyl Isopropylfuran-2-carboxylates (13)—(15).—(*a*) Methyl furan-2-carboxylate (14) (10·7 g) in CS_2 (200 ml) was added to a stirred slurry of $AlCl_3$ (finely powdered; 20 g) in CS_2 (150 ml) at 20 °C. Pr^iCl (2·4 ml) was added, the mixture was warmed briefly to 35 °C, and the heating bath was then removed. Pr^iCl (13 ml) was added during 2 h, and the stirring was continued for 2 days. Work-up gave an oil (12 ml) which, after two fractional distillations, afforded *methyl 4,5-di-isopropylfuran-2-carboxylate* (15) (9·5 g), b.p. 61—62° at 0·05 mmHg (Found: C, 68·6; H, 8·8. $C_{12}H_{18}O_3$ requires C, 68·55; H, 8·65%), g.l.c.

Results of Vilsmeier reactions

Starting material	Conditions Temp. (°C)	Time	Main product and yield	B.p. or * m.p.	Analysis (%) C	H	Other	Signals (τ) and coupling constants (*J*/Hz) of heterocyclic ring protons
(1a)	40	20 min	3-Methylfuran-2-carbaldehyde (2a) (51%)	60—61° at 12mmHg (lit.,[b] 60° at 12 mmHg				2·55 (4 lines, 1·5 and 0·6, 5-H) 3·64 (m, 4-H)
(1b)	40	20 min	*3-Isopropylfuran-2-carbaldehyde* † (2b) (61%)	(Oil) ‡	Found:	69·8	7·3	2·55 (4 lines, 1·8 and 0·5 5-H)
					$C_8H_{10}O_2$ req:	69·5	7·3	3·53 (m, 4-H)
(1c)	25	30 min	5-Isopropylfuran-2-carbaldehyde (2c) (68%)	85—86° at 10 mmHg (lit. [e] 91° at 11mmHg)				2·98 (d, 3·8, 3-H) 3·86 (d, 3·8, 4-H)
(1d)	25	1 h	*4,5-Di-isopropylfuran-2-carbaldehyde* † (2d) (68%)	108—110° (bath temp.) at 10mmHg	Found:	73·1	8·95	3·01 (s, 3-H)
					$C_{11}H_{16}O$ req:	73·3	8·95	
(1e)	70	1 h	*5-(4-Chlorophenyl)furan-2-carbaldehyde* (2e) (80%)	128·5—129° (after sublimation *in vacuo*)*	Found:	63·8	3·7	Cl, 16·9 2·68 (d, 3·8, 3-H)
					$C_{11}H_7ClO_2$ req:	63·9	3·4	Cl, 17·2 3·06 (d, 3·8, 4-H)
(1f)	70	1 h	*5-(4-Bromophenyl)furan-2-carbaldehyde* (2f) (76%)	151—153° (after sublimation *in vacuo*)*	Found:	53·0	3·0	Br, 31·4 2·60 (d, 3·8, 3-H)
					$C_{11}H_7BrO_2$ req:	52·6	2·8	Br, 31·8 3·06 (d, 3·8, 4-H)
(1g)	70	1 h	*5-(1-Naphthyl)furan-2-carbaldehyde* † (2g) (82%)	(Oil)	Found:	80·9	4·65	2·70 (d, 3·8, 3-H)
					$C_{15}H_{10}O_2$ req:	81·05	4·55	3·13 (d, 3·8, 4-H)
(1h)	70	1 h	*5-(2-Naphthyl)furan-2-carbaldehyde* (2h) (85%)	106—107° (from MeOH)*	Found:	81·0	4·5	2·70 (d, 3·8, 3-H)
					$C_{15}H_{10}O_2$ req:	81·05	4·55	3·13 (d, 3·8, 4-H)
(1i)	100	1 h	3-Methylthiophen-2-carbaldehyde § (2i) (33%)	96—97° at 12 mmHg (lit.,[f] 83—85° at 5 mmHg)				2·48 (d, 4·6, 5-H) 3·15 (d, 4·6, 4-H)
(1j)	100	2 h	3-Bromothiophen-2-carbaldehyde † (2j) (70%)	72—74° at 0·03 mmHg (lit.,[k] 122—123° at 18 mmHg)				2·46 (4 lines, 5·25 and 1·55, 5-H) 3·03 (d, 5·25, 4-H)
(1k)	110	2 h	3,4-Dimethylthiophen-2-carbaldehyde † (2k) (63%)	68—69° (from MeOH)* (lit.,[m] 69—70°)				2·81 (d, 0·8, 5-H)
(1l)	50	1 h	*3,4-Dimethoxythiophen-2-carbaldehyde* † (2l) (69%)	69—69·5° (from MeOH)*	Found:	48·6	4·75	S, 18·7 3·41 (d, 1·2, 5-H)
					$C_7H_8O_3S$ req:	48·8	4·7	S, 18·6
1m)	140	3 h	*3,4-Bis-(4-methoxyphenyl)thiophen-2-carbaldehyde* † (2m) (45%)	(Oil)	Found:	70·3	5·2	2·57 (d, 1·2, 5-H)
					$C_{19}H_{16}O_3S$ req:	70·4	5·0	

† Purified by p.l.c. [5—15 elutions with petrol–Me_2CO mixtures]. ‡ The derived *2,4-dinitrophenylhydrazone* had m.p. 172—174° (from MeOH) (Found: C, 52·6; H, 4·5; N, 17·4. $C_{14}H_{14}N_4O_5$ requires C, 52·8; H, 4·4; N, 17·6%). § The initial mixture of products (ratio by g.l.c., 81:19) was treated with semicarbazide hydrochloride to give the semicarbazone of aldehyde (2i) (m.p. 204·5—205° after five crystallisations from EtOH; lit.,[f] 208—209°) which was hydrolysed with 3N-HCl at 60 °C.

Refs. as in Scheme 1.

1·7 and 0·9 Hz, 5-H), 2·99 (4 lines, *J* 3·6 and 0·9 Hz, furyl 3-H), and 3·49 (4 lines, *J* 4·6 and 1·7 Hz, furyl 4-H).

5-Bromo-2-furyl 4-Methoxyphenyl Ketone (9).—Br_2 (2·4 g) in $Cl[CH_2]_2Cl$ (10 ml) was added during 4 h to a solution of 2-furyl 4-methoxyphenyl ketone[15] (8) (3 g) in $Cl[CH_2]_2Cl$ (25 ml) boiling under reflux. AcOH (0·05 ml) was added; the solution was boiled under reflux for a further 12 h, and worked up to give a red oil (2·5 g). P.l.c. of a portion (305 mg) [1 large plate, 4 × petrol–Me_2CO (49 : 1)] gave the *bromo-ketone* (253 mg), m.p. 73—74° (from MeOH–H_2O) (Found: C, 51·15; H, 3·05; Br, 28·7. $C_{12}H_9BrO_3$ requires C, 51·3; H, 3·2; Br, 28·45%), $\lambda_{max.}$ 309 nm (ε 19,400), τ 2·02 and 3·1 (4H, m, benzenoid), 2·87 (1H, d, *J* 3·5 Hz, furyl 3-H), and 3·50 (1H, d, *J* 3·5 Hz, furyl 4-H), *m/e* 280 (M^+, 78%).

3-Bromo-2,4,6-trimethylphenyl 2-Furyl Ketone (11).—2-Furyl 2,4,6-trimethylphenyl ketone[16] (10) (1·4 g) in $Cl[CH_2]_2Cl$ (20 ml) was treated with Br_2 (1·3 g) in $Cl[CH_2]_2Cl$ (10 ml) as in the foregoing experiment to give impure material (1·1 g). A portion (212 mg) of this was purified by p.l.c. [1 large plate, 4 × petrol–Me_2CO (49 : 1)] to give the *3-furyl ketone* (150 mg) as an oil (Found: C, 56·9; H, 4·4; Br, 27·3. $C_{14}H_{13}BrO_2$ requires C, 57·3; H, 4·45; Br, 27·25%), $\lambda_{max.}$ 278 nm (ε 5300), τ 2·38 (1H, 4 lines, *J* 1·7 and 0·8 Hz, furyl 5-H), 3·06 (2H, m, benzenoid 5-H and furyl 3-H), and 3·50 (1H, 4 lines, *J* 3·8 and 1·7 Hz, furyl 4-H), *m/e* 292 (M^+, 64%).

The Methyl Isopropylfuran-2-carboxylates (13)—(15).—(*a*) Methyl furan-2-carboxylate (14) (10·7 g) in CS_2 (200 ml) was added to a stirred slurry of $AlCl_3$ (finely powdered; 20 g) in CS_2 (150 ml) at 20 °C. Pr^iCl (2·4 ml) was added, the mixture was warmed briefly to 35 °C, and the heating bath was then removed. Pr^iCl (13 ml) was added during 2 h, and the stirring was continued for 2 days. Work-up gave an oil (12 ml) which, after two fractional distillations, afforded *methyl 4,5-di-isopropylfuran-2-carboxylate* (15) (9·5 g), b.p. 61—62° at 0·05 mmHg (Found: C, 68·6; H, 8·8. $C_{12}H_{18}O_3$ requires C, 68·55; H, 8·65%), g.l.c. retention time (t_R) (at 100 °C) 26·8 min, τ 3·06 (s, 3-H), *m/e* 210 (M^+, 15%).

Repitition of the reported preparation of the 5-isopropyl ester (12) gave a mixture containing the starting material (40%) and more of the di-isopropyl ester (15) (35%) than of the mono-isopropyl esters [(13) and (14)] (combined, *ca.* 20%).

(*b*) Methyl furan-2-carboxylate (270 g) in CS_2 (500 ml) was added during 1 h to a vigorously stirred slurry of $AlCl_3$ (finely powdered; 480 g) in CS_2 (1500 ml), and the mixture was warmed to 30 °C. Pr^iCl (30 ml) was added, and the heating bath was removed. Six further portions of Pr^iCl (each 20 ml) were added at intervals of 5 h. Samples (1 ml) were withdrawn at various times and worked up, and the mixtures were analysed by g.l.c. at 100 °C [t_R of esters: (12) 5·5 min, (13) 12·5, (14) 19·7, (15) 26·8]. Work-up of the reaction mixture after a total of 35 h gave an oil (300 g) which was purified by three fractional distillations. The results of the sampling and of the distillations were as follows.

The product after 6 h consisted of esters (12) (90%), (13) (8%), and (14) (2%); after 21 h, (12) (55%), (13) (35%),

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

[15] W. Borsche and H. Leditschke, *Annalen*, 1937, **529**, 108.

[16] R. Fuson and H. Wallingford, *J. Amer. Chem. Soc.*, 1953, **75**, 5950.

and (14) (10%); after 35 h, (12) (20%), (13) (60%), (14) (15%), and (15) (5%).

Fractional distillation (at 20 mmHg) gave fractions (i) (130 g), b.p. 80—114°; (ii) (60 g), 114—115°; (iii) (58 g), 115—116°; (iv) (10 g), 116—118°; (v) (21 g), 118—133°; and (vi) (10 g), 133—136°. Redistillation (at 18 mmHg) of combined fractions (ii) and (iii) gave fractions (vii) (64 g), 111—112°; (viii) (35 g), 112—114°; and (ix) (16 g), 114—130°. Redistillation (at 19 mmHg) of combined fractions (v) and (ix) gave fractions (x) (20 g), 116—120°; and (xi) (7 g), 120—123°. Fractions (vi) [consisting of (15) (98%) and (14) (2%)], (vii) [(13) (98%) and (14) (2%)], and (xi) [(14) (96%) and (13) (4%)] were sufficiently pure for use in further reactions. Preparative g.l.c. (at 170 °C) of small portions of fractions (vii) and (xi) gave pure samples of methyl 5-isopropylfuran-2-carboxylate [8] (13), τ 3·07 (d, *J* 3·4 Hz, 3-H) and 3·98 (4 lines, *J* 3·3 and 0·9 Hz, 4-H), and methyl 4-isopropylfuran-2-carboxylate [10] (14), τ 2·75 (t, *J* 1·0 Hz, 5-H) and 3·04 (m, 3-H).

The Isopropylfurans (1b—d).—Methyl 4,5-di-isopropylfuran-2-carboxylate (15) (4 g) was boiled under reflux for 1·5 h with NaOH (8 g)–H_2O (40 ml). The solution was cooled, washed with Et_2O, acidified with 5N-HCl, and extracted with EtOAc. Crystallisation of the product gave *4,5-di-isopropylfuran-2-carboxylic acid* (3·1 g), m.p. 107—108° (from MeOH–H_2O) (Found: C, 67·2; H, 8·2. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%), τ ($CDCl_3$) 2·80 (s, 3-H). A mixture of this acid (5·2 g), Cu bronze (1·5 g), and quinoline (distilled from anhydrous BaO; 10 ml) was heated at 250 °C in a distillation apparatus fitted with a short Vigreux column. Volatile material was collected during 2·5 h; the temperature of the mixture was then raised, collection of the product being stopped when the temperature of the distilling vapour rose rapidly to above 130 °C. Redistillation gave *2,3-di-isopropylfuran* (1d) (2·74 g), b.p. 122—124° (Found: C, 78·5; H, 10·5. $C_{10}H_{16}O$ requires C, 78·9; H, 10·6%), τ 2·95 (d, *J* 2·1 Hz, 5-H) and 3·95 (m, 4-H), *m/e* 152 (M^+, 56%).

Similarly, the 5-isopropylfuran ester (13) (6 g) gave the 5-isopropylfuran acid (5 g), m.p. 65—66° (lit.,[8] 65—66°), and then 2-isopropylfuran (1c) (2·8 g), b.p. 107—108° (lit.,[8] 106—109°). The 4-isopropyl ester (14) (6 g) gave the 4-isopropylfuran acid (18) (5·2 g), m.p. 76—77° (lit.,[10] 76—77·5°), and then 3-isopropylfuran (1b) (2·9 g), b.p. 111—112° (lit.,[10] 111—113°), τ 2·73 (m, 5-H), 2·88 (m, 3-H), and 3·78 (8 lines, *J* 2·0, 1·0, and 0·5 Hz, 4-H). An alternative route to the 4-isopropylfuran acid (18) is described in the following section.

4-Isopropylfuran-2-carbaldehyde (17).—The procedure of ref. 10 was followed using furan-2-carbaldehyde (96 g). After work-up and distillation in steam for 6 h the volatile material was fractionally distilled under N_2. The fraction (16 g) with b.p. 106—110° at 30 mmHg was shown by g.l.c. to contain the 4-isopropyl aldehyde (85%) and other furan aldehydes (15%). P.l.c. of a sample (1 g) [2 large plates, 10 × petrol–Me_2CO (19 : 1) and then 8 × petrol–Et_2O (19 : 1)] gave 4-isopropylfuran-2-carbaldehyde (650 mg), τ 2·53 (m, 5-H) and 2·86 (4 lines, *J* 1·0 and 0·5 Hz, 3-H). The residue from the steam distillation (8 g) was shown by n.m.r. examination [τ 3·00 (s, 3-H)] to consist mainly (*ca.* 60%) of 4,5-di-isopropylfuran-2-carbaldehyde (2d).

Oxidation of the impure 4-isopropyl aldehyde (15 g) with Tollens reagent [1a] gave 4-isopropylfuran-2-carboxylic acid [10] (10·5 g), m.p. 75—76° (from EtOH–H_2O).

2-(2-Naphthyl)furan (1 g).—$NaNO_2$ (6·9 g) in H_2O (10 ml) was added during 30 min to a stirred solution of 2-naphthylamine (14·3 g) in 1·4N-HCl (175 ml) at 0 °C, and $ZnCl_2$ (13·6 g) in H_2O (50 ml) was then added during 20 min. The precipitate was collected, dried, and stirred for 24 h at 25 °C with a mixture of furan (150 ml), powdered NaOH (1 g), and anhydrous NaOAc (10 g). Steam distillation and isolation with ether gave a red solid (4·2 g). P.l.c. [1 large plate, 3 × petrol–Me_2CO (49 : 1)] of a portion (400 mg) gave *2-(2-naphthyl)furan* (1h) (351 mg), m.p. 70—72° (from MeOH) (Found: C, 86·3; H, 5·35. $C_{14}H_{10}O$ requires C, 86·55; H, 5·2%), τ 2·40 (m, naphthyl H and furyl 5-H), 3·43 (4 lines, *J* 3·2 and 1·8 Hz, furyl 3-H), and 3·67 (4 lines, *J* 3·2 and 1·8 Hz, furyl 4-H), *m/e* 194 (M^+, 85%).

3,4-Disubstituted Thiophens (1k—m).—Intimate mixtures of the appropriate 2,5-dicarboxylic acids (prepared by Hinsberg reactions; [17–20] 2 g) and Cu bronze (1 g) were heated at 300 °C for 1 h. The materials extracted with Et_2O were chromatographed on SiO_2 (75 g). Elution with petrol–Me_2CO mixtures gave the 3,4-disubstituted thiophens, (1k) (1·2 g), b.p. 141—143° (lit.,[18] 144—146°), (1l) (1·25 g), b.p. 109° at 12 mmHg (lit.,[17] 108—115° at 12 mmHg), and (1 m) (1·35 g), m.p. 110—111° (lit.,[19] 117—118°).

Work in Scheme 3.—*The deuterioaldehydes* (19) *and* (20). $POCl_3$ (1 g) was added dropwise to a stirred mixture of $(CD_3)_2N{\cdot}CDO$ (0·43 g) and furan (1 g) at 0 °C. After 4 h at 25 °C work-up gave *furan-2-[²H]carbaldehyde* (19) (0·45 g), b.p. 70° (bath temp.) at 12 mmHg, τ 2·32 (4 lines, *J* 0·8 and 1·8 Hz, 5-H), 2·82 (4 lines, *J* 0·8 and 3·5 Hz, 3-H), and 3·43 (4 lines, *J* 1·8 and 3·5 Hz, 4-H) (no signal at τ 0·29), *m/e* 97 (M^+, 57% and 43 (100). Similarly $POCl_3$ (1 g), $(CD_3)_2N{\cdot}CDO$ (0·35 g), and thiophen (1 g), initially at 0 °C and then at 80 °C for 2 h, gave thiophen-2-[²H]carbaldehyde [11] (20) (0·42 g), b.p. 95° (bath temp.) at 18 mmHg, τ 2·13 (d, *J* 3·8 Hz, 3-H), 2·14 (d, *J* 4·8 Hz, 5-H), and 2·71 (4 lines, *J* 3·8 and 4·8 Hz, 4-H) (no signal at τ 0·08), *m/e* 113 (M^+, 50%) and 111 (100).

Four portions (each 4 g) of KCN were added at 2 min intervals to a stirred suspension of furil (bi-2-furoyl) (38 g) in dioxan (120 ml)–D_2O (50 ml) under N_2 at 25 °C. After a further 10 min the mixture was poured into H_2O (500 ml). Isolation with Et_2O gave furan-2-[²H]carbaldehyde (19) (5·6 g), b.p. 72—74° at 16 mmHg, identical with authentic material.

Br_2 (300 mg) in $CHCl_3$ (3 ml) was added to thiophen-2-[²H]carbaldehyde (20) (210 mg) in $CHCl_3$ (3 ml) and the solution was boiled under reflux for 4 h. Work-up and p.l.c. [1 large plate, 5 × petrol–Me_2CO (49 : 1)] gave *5-bromothiophen-2-[²H]carbaldehyde* (21) (125 mg), τ 2·48 (d, *J* 4·0 Hz, 3-H) and 2·83 (d, *J* 4·0 Hz, 4-H) (no signal at τ 0·32), *m/e* 193 (M^+, 48%) and 191 (M^+, 100).

2,3-Dibromothiophen [18] (22) (1·6 g) in Et_2O (10 ml) was cooled to −75 °C, and added dropwise under N_2 to a stirred solution of Bu^nLi in Et_2O (0·31M; 30 ml) at −75° C. After 15 min $(CD_3)_2N{\cdot}CDO$ (0·4 g) in Et_2O (5 ml) was added. The mixture was allowed to warm to 20 °C, and then boiled under reflux for 1·5 h. Acidification with 2N-HCl, isolation with Et_2O, and p.l.c. [2 large plates, 2 × petrol–Me_2CO

[17] E. W. Fager, *J. Amer. Chem. Soc.*, 1945, **67**, 2217.
[18] 'Chemistry of Carbon Compounds,' Vol. IVA, ed. E. H. Rodd, Elsevier, London, 1957, 211.
[19] O. Dann and G. Hauck, *Arch. Pharm.*, 1960, **293**, 187.
[20] D. J. Chadwick, J. Chambers, G. D. Meakins, and R. L. Snowden, *J.C.S. Perkin I*, 1972, 2079.

(24 : 1)] gave 3-*bromothiophen*-2-[^{2}H]*carbaldehyde* (23) (0·65 g), b.p. 77—79° (bath temp.) at 0·1 mmHg, τ 2·32 (d, *J* 5·2 Hz, 5-H) and 2·90 (d, *J* 5·2 Hz, 4-H) (no signal at τ 0·19), *m/e* 193 (M^+, 46%) and 191 (M^+, 100).

A solution of the foregoing aldehyde (295 mg) and Br_2 (0·3 ml) in $CHCl_3$ (5 ml) was boiled under reflux for 60 h. Work-up and p.l.c. [1 large plate, 2 × petrol–Me_2CO (24 : 1)] gave tetrabromothiophen (25) (higher R_F) (245 mg), m.p. 108—113° (lit.,[8] 117—118°) and 3,5-*dibromothiophen*-2-[^{2}H]*carbaldehyde* (24) (lower R_F) (51 mg), m.p. 56—58°, τ 2·90 (s, 4-H) (no signal at τ 0·23), *m/e* 273 (M^+, 28%), 271 (M^+, 87), and 269 (M^+, 100).

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