[CONTRIBUTION FROM THE WM. H. CHANDLER CHEMISTRY LABORATORY, LEHIGH UNIVERSITY]

Simple Furan Ethers. II: 2-Alkoxy- and 2-Aryloxy-furans

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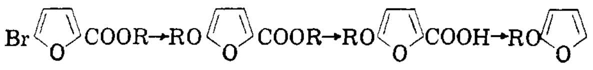
2-Ethoxy-, 2-isopropoxy-, 2-phenoxy-, 2-*n*-octyloxy-, 2-cyclohexyloxy-, and 2-thiophenoxy-furan as well as the corresponding 5-oxy-2-furoic acids have been prepared and characterized. Although the oxyacids are stable enough to permit bromination with N-bromosuccinimide, the 2-furyl ethers could be made only to undergo reactions, other than ring opening, in basic media. The methods were extended to the synthesis of a thiofuryl ether which affords a convenient method of preparation of the unknown furan sulfones.

A previous paper[2] described the first synthesis of a simple alkoxyfuran. The present paper[3] extends this work to the syntheses of other furan ethers, the chemistry of these compounds and their derivatives, and the preparation of a furan sulfone.

Since neither 2-bromo- nor 2-iodo-furan could be made to react with sodium methoxide in the presence of a cupric oxide catalyst at temperatures up to 100°, all of the furan ethers were prepared by the following reaction sequence:



I II III IV

The bromoesters (I) were converted to the oxyesters (II) by reaction with the appropriate sodium alkoxide under anhydrous conditions. Traces of moisture led to saponification which greatly diminished the yield. All but the isopropoxy compound were solids and all could be purified by vacuum- or steam-distillation. Since a few of these esters were very high boiling, they were not purified but were saponified directly to the acid.

A study of the reaction of sodium methoxide with methyl 5-bromo-2-furoate (I, R = Me) at 100° proved that a maximum yield was obtained after 1.5 hours since a shorter reaction time produced incomplete reaction whereas a longer time led to excessive decomposition. No attempt has been made to determine the optimum reaction conditions for the other reactions reported.

Saponification of the oxyesters (II) gave rise to the oxyacids (III) shown in Table II and subsequent decarboxylation produced the 2-furyl ethers (IV) shown in Table III. The phenyl thioether was also prepared by this method and was reacted with hydrogen peroxide to produce phenyl 2-furyl sulfone.

Attempted nitration of 5-methoxy-2-furoic acid (III, R = Me) was unsuccessful and gave a high molecular weight compound of undetermined structure rather than 4-nitro-5-methoxy-2-furoic acid, 5-methoxy-2-nitrofuran, or 5-nitro-2-furoic acid as might be predicted from the results of nitration of 5-bromo-2-furoic acid.[4] Similarly bromination of methyl 5-methoxy-2-furoate (II, R = Me) pro-

TABLE II
ETHERS OF 5-HYDROXY-2-FUROIC ACID

Furoic Acid	M.p., °C.	Neut. Equiv. Calc'd	Neut. Equiv. Found
5-Methoxy[2]	136–141	142	145
5-Ethoxy	140–141	156	155
5-Isopropoxy	118–119	170	174
5-Phenoxy	122–123	204	205
5-*n*-Octyloxy	125–126	240	237
5-Cyclohexyloxy	138–139	210	208
5-Thiophenoxy	139–141	220	217

TABLE I
5-ETHERS OF 2-FUROIC ESTERS ($RO—C_4H_2O—CO_2R$)

R	Yield (%)	T (°)	t (hours)	B.p., °C.	Mm.	M.p., °C.	Analyses Calc'd C	Analyses Calc'd H	Analyses Found C	Analyses Found H
Methyl[2]	42	100[a]	1.5	121–122	15	51–53	53.8	5.16	53.8	5.34
Ethyl	22	100[a]	3.0	149–150	27	40–41	58.6	6.57	58.2[d]	6.64
Isopropyl	37	100[a]	5.0	146–147	20	liquid	62.3	7.60	62.3	7.85
tert-Butyl	0	100[a]	2[b]	—		—	—	—	—	—
Phenyl	20	145	2.0	192–194	0.3[c]	52–53	72.8	4.32	72.8	4.52

[a] In a sealed citrate bottle. [b] Also run for 5 hours with no catalyst, and for 5 hours with 1 g. of cupric oxide and 1 g. of potassium iodide. [c] Also b.p. 240–245° at 13 mm. [d] Because of the close proximity of boiling points this could not be freed of a trace of bromo ester.

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[1] Taken in part from the Ph.D. thesis of Donald G. Manly, Quaker Oats Company Fellow in Organic Chemistry 1954.

[2] Petfield and Amstutz, *J. Org. Chem.*, **19**, 1944 (1954).

[3] Presented in part before the Delaware Valley Regional meeting of the A. C. S. in Philadelphia, Feb. 16, 1956.

[4] Rinkes, *Rec. trav. chim.*, **50**, 981 (1931).

TABLE III
FURAN ETHERS

Furan	Diels Alder Adduct M.p., °C.	B.p. (°C.)	d_4^t	t^b	n_D^t	$Mr_{calc'd}$	Mr_{obs}	Analysis			
								Calc'd		Found	
								C	H	C	H
2-Methoxy-[2]	121–122	110–111	1.0646	25	1.4468	25.44	25.14	61.2	6.17	61.1	6.32
2-Ethoxy-	132–134	125–126	0.9849	23	1.4500	30.06	30.56	64.2	7.14	63.6[a]	7.11
2-Isopropoxy-	134–135	135–136	0.9689	20	1.4419	34.68	34.41	66.6	7.91	66.8	7.99
2-Phenoxy-	132–134	105–106/18 98–99/14	1.1010	23	1.5418	45.03	45.72	75.5	5.00	75.1	5.08
2-*n*-Octyloxy-	137–138	129–130/18	0.9214	28	1.4520	57.91	57.39	73.6	10.2	73.3	10.3
2-Cyclohexyloxy-	138–139	118–119/18	1.0200	28	1.4861	45.33	46.73	72.2	8.43	72.0	8.56
2-Thiophenoxy-	139–140	119–120/8	1.1341	26	1.5977	51.25	52.96	68.2	4.55	67.8	4.46

[a] Quite volatile and explosive during combustion. [b] Densities and refractive indices measured at this temperature.

duced considerable tar along with a small amount of methyl 4-bromo-5-methoxy-2-furoate. However the reaction proceeded smoothly and in somewhat better yield using N-bromosuccinimide as the brominating agent. The methoxy acid reacted with thionyl chloride, with some tar formation, to produce the acid chloride which was quite unstable and which was converted to the amide in aqueous ammonia. This compound was also synthesized by direct ammonolysis of the ester in a much better over-all yield. In contrast to reactions involving acidic conditions, the reduction of methyl 5-methoxy-2-furoate (II, R = Me) with lithium aluminum hydride gave a good yield of 5-methoxy-2-furfuryl alcohol. This alcohol is quite unstable and decomposed rapidly on standing.

The 2-furyl ethers were found to be extremely acid sensitive, as one would predict from a consideration of the ketene acetal structure and the nature of the furan ring itself. Ring opening in methanolic hydrochloric acid produces the dimethyl acetal of methyl β - formylpropionate. Reaction of this product with the 2,4-dinitrophenylhydrazine reagent gave the same product (the 2,4-dinitrophenylhydrazone of ethyl β-formylpropionate) as that obtained directly with the reagent from 2-phenoxyfuran. Attempted bromination of 2-methoxyfuran with N-bromosuccinimide resulted in an unidentified high molecular weight compound whereas 2-methoxythiophene has been reported[5] to give a good yield of 5-methoxy-2-bromothiophene.

That 2-methoxyfuran possesses a greater general reactivity than its thiophene analog[5] was indicated by mercuration which produced only a trimercurated product. However the unoccupied 5-position is the most reactive carbon of the ring toward metallation as evidenced by reaction of 2-phenoxyfuran with phenyllithium which upon carbonation gave 5-phenoxy-2-furoic acid.

All of the 2-furyl ethers are colorless liquids of a sweet ether-like odor which are unstable to air oxidation and, over a period of several weeks, become yellow and viscous on standing, even when stored under nitrogen in a sealed tube at ice temperatures.

EXPERIMENTAL

All alcohols used were refluxed and distilled from sodium. *Furoic acid* was a technical grade (m.p. 129–133°) which was generously supplied by The Quaker Oats Company and was used without further purification.

5-Bromo-2-furoic acid was prepared by the method of Raiford and Huey[6] and was recrystallized from water to a melting point of 187–189° (reported:[7] 185°; 190–191°).

5-Bromo-2-furoyl chloride was prepared by reacting the acid with a 100% excess of thionyl chloride at reflux for two hours. Removal of excess thionyl chloride and subsequent vacuum distillation afforded the product in 76% yield boiling at 108–112°/15 mm. (reported:[7] 89°/8 mm.).

Methyl 2-furoate, isopropyl 2-furoate, and methyl 5-bromo-2-furoate were prepared by esterification of one mole of the appropriate acid using 13 moles of the alcohol and 35 ml. of concentrated sulfuric acid.

Methyl 5-bromo-2-furoate: Methyl furoate (126 g., 1 mole) was placed in a one-liter 3-necked flask equipped with a dropping-funnel, stirrer, and condenser. To this rapidly stirred liquid, 160 g. (51.3 ml.) of bromine was added dropwise while heating on a steam-bath. After stirring an additional ten minutes and cooling, the contents of the flask solidified and were washed thoroughly with cold water and steam-distilled to give 94.1 g. (49.2%) of the product. The residue from steam-distillation on recrystallization from water afforded 34 g. of 5-bromo-2-furoic acid melting at 188–190°.

Isopropyl 5-bromo-2-furoate was prepared in 32.5% yield; b.p. 132–133°/28 mm. by bromination of isopropyl 5-bromo-2-furoate as above.

Phenyl 5-bromo-2-furoate and tert-butyl 5-bromo-2-furoate were prepared by adding 30 g. (0.134 mole) of 5-bromo-2-furoyl chloride carefully to a previously cooled solution of 3.5 g. (0.15 mole) of sodium in 80 g. of the alcohol. After heating at gentle reflux (phenyl, 1 hour; butyl, 3 hours), the mixture was poured into cold water, decanted, extracted twice with boiling water, and vacuum-distilled. *tert*-Butyl 5-bromo-2-furoate was obtained in 38% yield; b.p. 123–128°/16 mm. Phenyl 5-bromo-2-furoate was obtained in 63% yield; b.p. 190–195°/14 mm. and m.p. 50–52°.

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(5) Sicé, *J. Am. Chem. Soc.*, **75**, 3697 (1953).

(6) Raiford and Huey, *J. Org. Chem.*, **6**, 858 (1941).

(7) Dunlop and Peters, *The Furans*, Reinhold Publishing Corporation, p. 115, 1953.

The oxyesters, II, were prepared by adding 0.06 mole of the appropriate ester[8] of 5-bromo-2-furoic acid to a previously prepared solution of 1.61 g. (0.072 mole) of clean sodium in 75–100 g. of the alcohol and heating for the time and at the temperature shown in Table I. The residue, after removing most of the solvent under a vacuum, was poured into 300 ml. of water and extracted with ether. The product was then obtained by vacuum-distillation of the ether solution. The *tert*-butyl compound could not be prepared under the conditions shown and in all cases the starting material was recovered.

The ethers of furoic acid, III, were obtained by refluxing II for three hours in 10% sodium hydroxide followed by acidification at temperatures below 10°. The acids were not recrystallized since decomposition occurs in hot water, but they were obtained in sufficiently pure form simply by washing with large amounts of ice-water and drying *in vacuo* over potassium hydroxide pellets. The over-all yields of the alkoxyfuroic acids obtained without isolation of the intermediate alkoxy ester were *n*-octyloxy-18%, cyclohexyloxy-23%, and thiophenoxy-73%.

The furyl ethers, IV, shown in Table III were obtained by decarboxylation in the presence of copper powder and quinoline. The resulting products were immediately redistilled to yield clear colorless mobile liquids. The phenoxy acid was decarboxylated without using quinoline since both compounds boil at nearly the same temperature and the resulting phenoxyfuran then could be purified only by extraction with dilute hydrochloric acid. The phenoxy, thiophenoxy, octyloxy, and cyclohexyloxy acids were decarboxylated under a vacuum of 8–25 mm. The yields are only approximate because of the small quantities of materials involved and are: methoxy 36%, ethoxy 56%, isopropoxy 52%, *n*-octyloxy 36%, cyclohexyloxy 53%, phenoxy 74%, and thiophenoxy 50%.

Phenyl 2-furyl sulfone. Thiophenoxyfuran (2 g.) was dissolved in 5 ml. of glacial acetic acid and 6 ml. of 30% hydrogen peroxide was added along with enough glacial acetic acid to form a homogeneous solution. After standing at room temperature for five days, the mixture was vacuum-distilled to one half its volume and diluted with four times its volume of water. The resulting oily solid was recrystallized twice by dissolving it in 95% ethanol and adding water to the cloud point. The final product (2.1 g.) was a white crystalline solid; m.p. 68.8–69.2°.

Anal. Calc'd for $C_{10}H_8O_3S$: C, 57.7; H, 3.85. Found: C, 57.8; H, 4.09.

Nitration of 5-methoxy-2-furoic acid. A solution of the acid (10 g.) in acetic anhydride (72 ml.) was prepared and cooled to −10°. The procedure used for nitration was essentially that of Rinkes.[3] A yellow solid was obtained which on recrystallization from petroleum ether (b.p. 90–100°) melted at 154–156°. A calculated empirical formula is $C_{10}H_{10}NO_{10}$ which could arise only from a ring-opened and polymerized product.

Anal. Calc'd for $C_{10}H_{10}NO_{10}$: C, 38.6; H, 3.40; N, 4.62. Found: C, 38.6; H, 3.50; N, 3.94.

5-Methoxy-2-furoyl chloride. 5-Methoxy-2-furoic acid (10 g.) and thionyl chloride (10 ml.) were mixed and a vigorous endothermic reaction took place followed by the evolution of hydrogen chloride for 30 minutes. After heating to 50°, the excess thionyl chloride was removed under a vacuum and the remaining dark red residue was vacuum-distilled to give 5 g. (44%); b.p. 108–110°/18 mm. The distillate solidified (m.p. 75–78°) on cooling and rapidly decomposed when standing in air.

5-Methoxy-2-furoyl amide. I. Addition of 5 g. of the acid halide to 45 ml. of concentrated ammonium hydroxide produced 1.5 g. (35%) of the amide which melted at 124–126° after recrystallization from water. *II.* Methyl 5-methoxy-2-furoate (5 g.) and concentrated ammonium hydroxide (50 ml.) were heated in a sealed tube for 2 hours at 60°. After filtration and recrystallization from water 4 g. (80%) of the product was obtained; m.p. 123–126°. A mixture melting point showed no depression.

Anal. Calc'd for $C_6H_7NO_3$: N, 9.93. Found: N, 10.21.

5-Methoxy-2-furoyl-2,4-dinitrophenylhydrazide was obtained by heating methyl 5-methoxy-2-furoate in methanol with the 2,4-dinitrophenylhydrazine reagent; m.p. 95–97°. *Anal.* Calc'd for $C_{12}H_8N_4O_7$: N, 17.5. Found: N, 17.8.

5-Methoxy-2-furfuryl alcohol. A solution of methyl 5-methoxy-2-furoate (6 g.) in 25 ml. of dry ether was added dropwise to a rapidly stirred solution of lithium aluminum hydride (1.84 g.) in 60 ml. of dry ether. After refluxing 1.5 hours, 4 ml. of water was added cautiously followed by 25 ml. of sodium hydroxide. After extraction of the aqueous layer with ether, the combined ether extracts were vacuum-distilled to give 2.7 g. (55%) of a colorless liquid; b.p. 112–115°/14 mm. and 103–105°/8 mm.

Anal. Calc'd for $C_6H_8O_3$: C, 56.2; H, 6.26. Found: C, 56.5; H, 6.56.

Methyl 5-methoxy-4-bromo-2-furoate. A solution of 5.9 g. of N-bromosuccinimide and 5.2 g. of methyl 5-methoxy-2-furoate in 10 ml. of carbon tetrachloride was refluxed for 30 minutes. Extraction of the residue with ether followed by vacuum-distillation of the combined ether-carbon tetrachloride solutions gave 1.2 g. of a pale yellow oil; b.p. 100–140°/4 mm. This oil solidified on cooling and was crystallized from methanol-water (60:40) to give white needles melting at 63–64°. Direct bromination of methyl 5-methoxy-2-furoate required 2 hours heating time and gave a liquid in poor yield which was distilled and recrystallized to m.p. 63–64°.

Anal. Calc'd for $C_7H_7BrO_4$: C, 35.5; H, 2.98. Found: C, 35.5; H, 3.24.

5-Methoxy-4-bromo-2-furoic acid was obtained as a white powder melting at 188–190° by saponification of the methyl ester.

Neut. Equiv. Calc'd for $C_6H_5BrO_4$: 221. Found: 218.

Ring opening of phenoxyfuran. Refluxing phenoxyfuran in methanol containing one drop of concentrated hydrochloric acid for 30 minutes followed by vacuum-distillation gave an oil; b.p. 120–170°/14 mm. Reaction of this phenyl ester of dimethyl acetal of β-formylpropionic acid with the 2,4-dinitrophenylhydrazine reagent in ethanol gave red needles; m.p. 101–102°. The reaction of phenoxyfuran directly with this reagent gave the same product.

Anal. Calc'd for $C_{12}H_{14}N_4O_6$: C, 46.5; H, 4.52; N, 18.1. Found: C, 46.6; H, 4.67; N, 17.9.

Refluxing in methanolic hydrochloric acid for six hours gave the dimethyl acetal of methyl β-formylpropionate; b.p. 96–97°/18 mm.

Anal. Calc'd for $C_7H_{14}O_3$: C, 57.5; H, 9.60. Found: C, 57.7; H, 9.40.

Bromination of methoxyfuran with N-bromosuccinimide in carbon tetrachloride gave a yellow viscous oil; b.p. 160–170°/20 mm. Analysis of this product gave results which did not appear to fit any simple formula.

Anal. Found: C, 51.5; H, 5.38.

Mercuration of methoxyfuran. A solution of 4.61 g. (0.017 mole) of mercuric chloride and 9.25 g. (0.068 mole) of sodium acetate trihydrate in 102 ml. of water was prepared. This solution was added dropwise (30 drops/min.) over 45 minutes to a rapidly stirred solution of 1.7 g. (0.017 mole) of methoxyfuran in 7 ml. of ethanol. After stirring the solution an additional hour and then allowing it to stand overnight a pale yellow solid separated; m.p. 206–210°. This was presumed to be tris-chloromercurimethoxyfuran.

Anal. Calc'd for $C_5H_3Cl_3Hg_3O_2$: C, 7.37; H, 0.38. Found: C, 7.01; 1.39.

5-Phenoxy-2-furyllithium. A solution of phenyllithium was prepared by adding a solution of 2.36 g. of bromobenzene

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(8) The thiophenoxy ester was prepared from phenyl 5-bromo-2-furoate while the octyloxy and cyclohexyloxy esters were prepared from methyl 5-bromo-2-furoate. These esters were not identified but were saponified directly to the acid.

in 10 ml. of ether to 0.21 g. of lithium in 25 ml. of ether and stirring one half hour after addition was complete. Then 2.0 g. of 2-phenoxyfuran in 10 ml. of ether was added dropwise. After stirring an additional five minutes, the reaction mixture was poured into crushed Dry Ice with stirring. Extraction with water followed by acidification of the aqueous extracts produced a solid melting at 95–105°. Recrystallization from ethanol-water gave 0.6 g. of 5-phenoxy-2-furoic acid; m.p. 121–123°; N.E. 201 (Calc'd 204). The ether extract on distillation gave 1.2 g. of recovered 2-phenoxyfuran. The yield of 5-phenoxy-2-furoic acid based on the amount of phenoxyfuran used was 82%.

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