Reactions of Thiols with 2,5-Dihydro-2,5-dimethoxyfuran.
A New Synthesis of 2-Furyl Thioethers

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Aliphatic and aromatic thiols readily undergo an acid-catalyzed reaction with 2,5-dihydro-2,5-dimethoxy-furan (1) to form the corresponding 2-furyl thioethers in moderate yields. Their *slow* reaction with maleic anhydride is promoted by mildly acidic catalysts and leads to 3-substituted thioethers of phthalic anhydride. Under mildly basic conditions a slow, light-catalyzed, free-radical addition of thiols to 1 is effected. One of the adducts (from propanethiol) has been converted by pyrolysis into 3-propylthiofuran.

The chemistry of 2,5-dialkoxy-2,5-dihydrofurans, which has evolved since the original investigations of Clauson-Kaas, has been reviewed by Elming.[1] Reactions of these interesting compounds with thiols to give furyl thioethers have not yet been recorded.

A few simple 2-furyl thioethers have recently been reported[2,3] by a route involving metalation of furan, followed by sulfurization and reaction with an alkyl halide. Other methods[4,5] involve reactions of 5-bromo-2-furoic acid or ester with a mercaptide, followed by decarboxylation.

An early attempt to effect a simple free-radical addition of methyl mercaptoacetate to the readily available[6] 2,5-dihydro-2,5-dimethoxyfuran (1) to give 2 (R = $CH_2CO_2CH_3$) led to a mixture of products, the major component of which proved to be methyl 2-furylthioacetate (3, R = $CH_2CO_2CH_3$). It later became evident that this product had arisen from a combination of circumstances: (1) the free-radical reaction (A) of these substrates is unusually slow, and (2) the ionic reaction (B) occurs more readily, especially in the presence of acidic substances which apparently were present as impurities in the ester. Nevertheless, it was possible, by proper choice of conditions, to obtain either product 2 or 3.
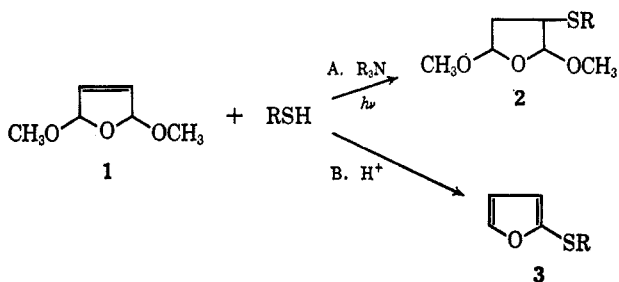
The structure of product 3 was established by its nmr spectrum (one α and two β hydrogens) and that of its Diels–Alder adduct with maleic anhydride (two vinyl hydrogens). This excluded the possibility of the 3 isomer which could have arisen by elimination of methanol from 2. It was also found that such an elimination does not occur under the mild conditions of reaction B.

This new synthesis of 2-furyl thioethers has certain advantages over the earlier methods, in that (1) it is a simple one-step synthesis from easily available materials and (2) it can serve as a source of aryl 2-furyl thioethers (Table I). This paper is concerned primarily with the ionic reaction B, although the free-radical addition was also studied briefly.

Ionic Reaction.—The acid-catalyzed reaction of thiols with 1 was usually carried out at ambient temperatures with acetonitrile as solvent and *p*-toluenesulfonic acid as catalyst (method A). Under these conditions, reactions were essentially complete in 0.5–4 hr. When the reaction was unnecessarily prolonged, considerably lower yields resulted.[7] Less polar solvents (benzene) and/or weaker acids can be used, but the reaction is slower, and yields are not significantly better than those from a carefully monitored reaction (by vpc) with the stronger acid. Use of maleic acid in refluxing acetonitrile (method B) would be preferable, if one is unable to follow the progress of the reaction.

Near the end of this investigation, it was found that omitting the catalyst and passing air into the refluxing acetonitrile solution was quite effective in promoting the formation of 3, and showed promise of higher yields. The air, presumably, generates catalytic amounts of maleic acid *in situ* from the dialdehyde which is formed from 1 by hydrolysis.

Mercapto acids were found to yield predominantly the methyl esters of the expected products. This can be circumvented with benzene as the solvent to remove the methanol as it is formed in the reaction. As an alternative, 2,5-diacetoxy-2,5-dihydrofuran can be substituted for 1 in method A.

Dodecanethiol reacted normally in method A, but use of a weaker catalyst, acetic acid, and a small excess of thiol in refluxing acetonitrile gave as the predominant product 2,5-bis(dodecylthio)-2,5-dihydrofuran (4) in 26–29% yield. A 2:1 molar ratio of 1-dodecanethiol to 1, however, produced a gross mixture of products from which were isolated small amounts of 4 and the dimercaptal 5 (R = $C_{12}H_{25}$). 1-Propanethiol failed to react with 1 under the same conditions; longer heating with additional acetic acid produced a mixture consisting largely of 3 (R = C_3H_7) and 5 (R = C_3H_7). Since 4 was found to decompose to a mixture of 3 and the thiol at 275°, failure to find the

(1) N. Elming, *Advan. Org. Chem.*, **2**, 67 (1960).

(2) Y. L. Gol'dfarb, Y. L. Ganyushevskii, and M. A. Vinogradova, *Dokl. Akad. Nauk SSSR*, **151**, 539 (1963).

(3) E. Niwa, H. Aoki, H. Tanaka, K. Munakata, and M. Namiki, *Chem. Ber.*, **99**, 3215 (1966).

(4) R. Adams and A. Ferretti, *J. Amer. Chem. Soc.*, **81**, 4927 (1959).

(5) D. G. Manly and E. D. Amstutz, *J. Org. Chem.*, **21**, 516 (1956).

(6) D. M. Burness, *Org. Syn.*, **40**, 29 (1960).

(7) Both reactant 1 and products (3) are gradually decomposed under these conditions, particularly in the absence of a thiol. The latter apparently moderates the acidity of the medium, presumably by formation of a hydrosulfonium ion, RSH_2^+. A check of yields *vs.* time (by vpc analysis of the reaction mixture) in a reaction with 1-propanethiol indicated yields of 54% (0.5 hr), 40% (4 hr), and 25% (22 hr). Neither maleic nor oxalic acid caused significant decomposition of the thioethers (3) in refluxing acetonitrile.

TABLE I
2-FURYL THIOETHERS (3)

R	Method	Yield,[a] %	Bp (mm) or mp, °C	n^{25}D	Formula[s]	Calcd, % C	H	S	Found, % C	H	S
CH3	A	27	67 (75)[b]	1.5191	C5H6OS	52.6	5.3	28.0	52.7	5.6	27.8
(sulfoxide)	NaIO4	69	49–50 (0.06)		C5H6O2S	46.1	4.6	24.6	45.8	4.8	24.4
CH3(CH2)2	B	35–40	70 (15)	1.5028	C7H10OS	59.1	7.1	22.5	58.9	7.2	22.5
CH3(CH2)2	C	47									
CH3(CH2)5	B	66	61–63 (0.1)	1.4919	C10H16OS	65.2	8.8	17.4	64.8	8.5	17.2
CH3(CH2)11	B[c]	35	110–115 (0.01)	1.4835	C16H28OS	71.6	10.5	11.9	70.8	10.6	12.0
–CH2CH2–	A	17	64 (0.12)	1.5805	C10H10O2S2	53.1	4.5	28.3	53.2	4.7	27.9
–(CH2)4–	B	38	114–117 (0.015)	1.5621	C12H14O2S2	56.6	5.6	25.2	56.7	5.8	25.1
HOCH2CH2	B	45	59–64 (0.08)	1.5379	C6H8O2S	50.0	5.6	22.2	49.6	5.6	21.9
Cl2CHCH2	A	45	48–52 (0.4)	1.5455	C6H6Cl2OS	36.5	3.1	16.3	36.7	3.3	16.3
C6H5CH2	B[d]	60	67–71 (0.07)[e]	1.5845	C11H10OS	69.5	5.3	16.8	69.3	5.1	17.1
(sulfone)	H2O2	58	89–90		C11H10O3S	59.5	4.5	14.4	59.8	4.8	14.2
C6H5	f	59	55–57 (0.25)[g]	1.5964	C10H8OS	68.2	4.6	18.2	68.3	4.8	18.5
p-ClC6H4	A	50	86–88 (0.1)	1.6048	C10H7ClOS	57.0	3.4	15.2	56.8	3.5	15.4
CH3OCOCH2	B	62	60–63 (0.07)	1.5140	C7H8O3S	48.8	4.7	18.6	48.7	4.7	18.0
CH3OCOCH2	A[h]	44									
(sulfone)	H2O2	21	49.5–51		C7H8O5S	41.2	4.0	15.7	41.2	4.1	15.7
HOCOCH2	i	24–32	48–49		C6H6O3S	45.5	3.8	20.2	45.2	3.5	20.0
CH3OCOCH(CH3) }	A[j]	35	52 (0.25)	1.5054	C8H10O3S	51.6	5.4	17.2	51.4	5.6	16.9
HOCOCH(CH3) }		7	64–65		C7H8O3S	48.7	4.7	18.6	49.0	5.0	18.4
HOCO(CH2)2	A[k]	9[l]	51.5–52.5		C7H8O3S	48.7	4.7	18.6	49.0	4.8	18.3
HOCOCH2 / HOCOCH	A	28[l]	136–138		C6H8O5S	44.4	3.7	14.8	44.3	3.8	14.4
o-HOCOC6H4	m	10[l,n]	170–171		C11H8O3S	60.0	3.7	14.5	60.0	3.4	14.5
CH3CO	A	49	70–73 (5.5)[o]	1.5260	C6H6O2S	50.7	4.3	22.5	50.9	4.2	22.5
o-C6H4—N=C— (S)	A	0[p]									
C6H5N—N=N—N=C—	A	4.5 of 6[q]	105–107		C11H8N4OS	52.2	4.4	11.6	51.5	4.4	11.3
CH3C=CH—CH=CSC6H13 (—O—)	A[r]	43	55–58 (1.1)	1.4928	C11H18OS	66.6	9.2	16.1	66.4	9.5	16.4

[a] Yields are for purified products. [b] Lit.[3] bp 42–43° (9 mm). Sulfoxide by method of N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962). [c] This reaction with acetic acid as catalyst yielded 4 instead (see Experimental Section). [d] This was also prepared in 66% yield from 2,5-diacetoxy-2,5-dihydrofuran under conditions of method A. [e] Lit.[3] bp 106–109° (7 mm). Sulfones by method of H. S. Schultz, H. B. Freyermuth and S. R. Buc, *ibid.*, **28**, 1140 (1963). [f] The reaction was run in glacial acetic acid, 3.5 hr at 90°. [g] Lit.[4] bp 97–98° (2.5 mm). m^{25}D 1.5976. [h] From reaction with mercaptoacetic acid under conditions of method A. [i] See Experimental Section. [j] Mixture from reaction with α-mercaptopropionic acid. See Experimental Section. [k] Distillation in an oil-jacketed pot still at 8 μ (100–160° pot temp) was required to obtain a crystallizable product (90–120° ligroin). [l] Low yield due in part to ester formation. [m] Reaction in benzene solution. See 2-(furylthio)acetic acid. [n] Large recrystallization losses. [o] Lit.[3] bp 70–71° (10 mm). [p] No reaction even after 6-hr reflux period. [q] Structure confirmed by nmr. [r] Using the 2-methyl derivative of 1. [s] Respective registry no. are 13129-38-9, 16003-05-7, 16003-06-8, 19003-07-9, 16003-08-0, 16003-09-1, 16003-10-4, 16003-11-5, 16003-12-6, 13129-40-3, 16031-72-4, 16003-14-8, 16003-15-9, 16003-16-0, 16003-17-1, 16003-18-2, 16003-19-3, 16003-20-6, 16003-21-7, 16003-22-8, 16003-23-9, 13129-41-4, 16031-73-5, and 16003-25-1.

bis compound in the case of 1-propanethiol may have been due to a similar decomposition during distillation.
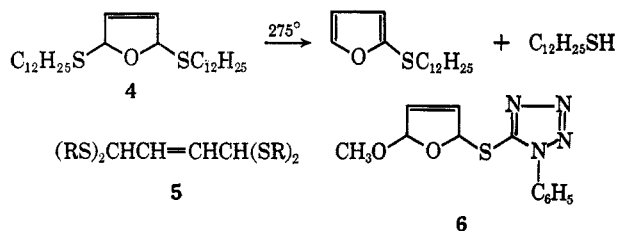

Heterocyclic thiols failed to give the expected products. 2-Mercaptobenzothiazole showed no sign of reaction after a 6-hr reflux period (p-TS acid), and 1-phenyl-1H-tetrazole-5-thiol after 22 hr at 25° produced a gross mixture from which 6 (4.5% yield) was the only isolable product. Thiourea and aminoalkane-thiols also failed to react.

The variety of products isolated in these specific cases help to explain why yields are moderate, at best, in this new synthesis of furyl thioethers.

Since 1 is readily hydrolyzed to maleic and fumaric dialdehydes,[1] it seemed possible that maleic dialdehyde is a transient intermediate in the formation of 2-furyl thioethers from 1. This possibility is supported by the results of an experiment in which fumaric dialdehyde (which apparently is isomerized under the reaction conditions) reacted readily with 1-propanethiol to produce a good yield of 3 under conditions which are ineffective with 1 (brief reaction in refluxing acetonitrile with acetic acid as catalyst).

Mechanisms.—Two alternate routes are proposed to account for the formation of 3 and the various other products isolated in these acid-catalyzed reactions. One route depends primarily on the direct formation of a carbonium ion from 1, followed by the steps outlined in Scheme I. The dimercaptal (5) could arise from ring cleavage of an oxonium ion arising from the carbonium ion or from direct protonation of the ring oxygen in 1. A similar mechanism could account for the acid-catalyzed conversion of 1 into 1,1,4,4-tetra-methoxy-2-butene in methanol.[8]

(8) M. Janda, *Collect. Czech. Chem. Commun.*, **28**, 2524 (1963).
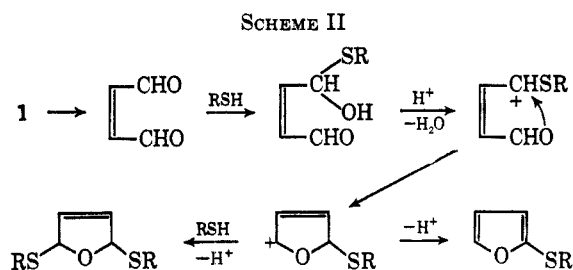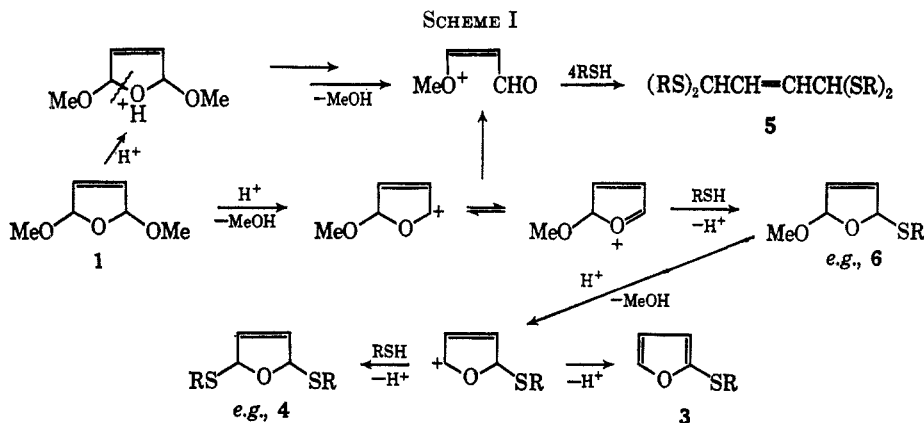
SCHEME I

SCHEME II

A second route depending on the intermediacy of maleic dialdehyde (only traces of water would be necessary) is also possible, as experiment has shown (Scheme II).

2-Methoxyfuran, which can be prepared from 1 under acid catalysis,[9] failed to yield any 3 under the conditions of method A; accordingly, 2-methoxyfuran is not an intermediate in the reaction.

Free Radical Addition.—The ionic reaction can be suppressed by the presence of a small amount of base (triethylamine) in the reaction mixture. The ensuing free-radical addition of aliphatic mercaptans to 1 proceeded very slowly and gave only fair yields (30–40%) of adducts (2) by ultraviolet irradiation. (Table II). Benzenethiol failed to react appreciably during a 10-day period.

Properties and Reactions of Furyl Thioethers.— The 2-furyl thioethers are reasonably stable at room temperature, but are best kept cold and protected from light. They are apparently more stable than the corresponding oxygen analogs.[10] A tendency to discolor is partially inhibited by an antioxidant, such as hydroquinone. The benzyl, 2-hydroxyethyl, and dodecyl derivatives are particularly stable. 2-(Furylthio)acetic acid, a crystalline solid, gradually decomposed at 25° to a thick, red syrup, whereas 2-(furylthio)succinic acid was stable under these conditions. As already mentioned,[7] the 2-furyl thioethers are readily decomposed by strong acids. They can be oxidized easily to the sulfoxides and sulfones. Unlike their oxygen analogs, 2-furyl thioethers do not readily undergo the Diels–Alder reaction with maleic anhydride (Table III), and yields are low, even in the presence of small amounts of maleic or oxalic acids which have a mild catalytic effect (oxalic > maleic). The catalyst evidently serves to promote dehydration of the adduct (7) to the more stable phthalic anhy-

(9) G. F. D'Alelio, C. J. Williams, Jr., and C. L. Wilson, *J. Org. Chem.*, **25**, 1028 (1960).
(10) R. J. Petfield and E. D. Amstutz, *ibid.*, **19**, 1944 (1954).

dride derivative (8) under the reaction conditions (50° in benzene). Maleic anhydride adducts of 2-alkoxyfurans are even more readily aromatized.[9]
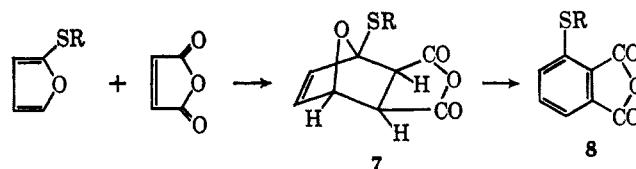
An adduct (7), indicated by nmr to have the *exo* configuration shown, was isolated in only one instance: with methyl (2-furylthio)acetate in ether at 25°. 2-Propylthiofuran, under the same conditions, gave no adduct and only a trace of 8 (R = C₃H₇).

One of the tetrahydro-3-furyl thioethers (2, R = C₃H₇) on acid-catalyzed pyrolysis yielded 3-propylthiofuran. A considerable amount of the 2 isomer was also produced in this reaction. Similar rearrangements have been observed previously in acid-catalyzed reactions of thienyl and pyrrolyl thioethers.[11] 3-Propylthiofuran reacted readily with maleic anhydride to give an *exo* adduct (9) which was not readily aromatized in 50° benzene.[12]

Experimental Section[13]

The purity of Eastman Practical Grade 2,5-dihydro-2,5-dimethoxyfuran (1) was adequate for the ionic reactions; however, it was distilled, to remove inhibitor, for the free-radical addition reactions. Eastman thioacetic acid, mercaptoacetic

(11) S. Gronowitz and P. Moses, *Acta Chem. Scand.*, **16**, 155 (1962).
(12) The nmr spectrum of this product in CDCl₃ appeared inconsistent with structure **9**, inasmuch as the H₄ and H₅ protons appeared as a sharp

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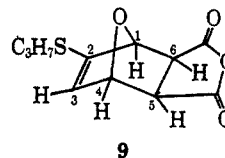
singlet at τ 6.69. In C₆D₆, however, they have unequal chemical shifts appearing as an AB quartet centered at τ 7.41 (δ_AB = 11.2 Hz, J_AB = 6.5 Hz). In neither case was there evidence for J₁₅ or J₄₆ coupling, thus indicating an *exo* configuration. On the other hand, long-range coupling across the oxygen bridge, J₁₄ [previously noted by J. Gagnaire and E. Payo-Subiza, *Bull. Soc. Chim. France*, 2627 (1963)] was seen in C₆D₆ (H₁, H₄ at τ 5.00 and 4.72) and in CDCl₃ (H₁, H₄ at τ 5.46 and 6.03). The doublet for H₃ (J₃₄ = 0.8 Hz) appeared at τ 5.02 in C₆D₆ and 4.78 in CDCl₃. Confirmation of the typical Diels–Alder type of structure arose from its thermal reversibility, as indicated by mass spectral data.

(13) All melting points were taken with a Thomas–Hoover melting point apparatus and are uncorrected. The nmr spectra were obtained with a Varian A-60 spectrometer and tetramethylsilane as an internal standard (τ 10.0). Vpc analyses were carried out with an F & M Model 720 chromatograph and a 6-ft silicone column.

TABLE II
TETRAHYDRO-2,5-DIMETHOXY-3-FURYL THIOETHERS (2)

R	Method	Reaction time, days	Yield, %	Bp, °C (mm)	$n^{25}D$	Formula[a]	Calcd, %			Found, %		
							C	H	S	C	H	S
CH₃CH₂CH₂	A	21	29	60–69 (0.36)	1.4678	$C_9H_{18}O_3S$	52.4	8.8	15.5	52.8	8.9	15.9
CH₃CH₂CH₂	C	8.3	40.6									
CH₃(CH₂)₅	A	8	36	66 (0.004)	1.4663	$C_{12}H_{24}O_3S$	58.1	9.7	12.9	58.4	9.9	12.9
CH₃OCOCH₂	B	1.3	40	98–100 (0.03)	1.4782	$C_9H_{16}O_5S$	45.8	6.8	13.5	45.4	6.5	13.4
CH₃OCOCH₂	C	3	44									
C₆H₅	A	10	No reaction									

[a] Respective registry no. are 16003-26-2, 16003-34-2, and 16003-27-3.

TABLE III
REACTION OF FURYL THIOETHERS WITH MALEIC ANHYDRIDE

No.	R	Temp, °C	Solvent	Time, days	Catalyst	Structure no.[a] of product	Yield, %	Mp, °C	Formula	Calcd, %			Found, %		
										C	H	S	C	H	S
3	CH₂CO₂CH₃	25	Ether	12	...	7[b]	17–28	79–80	$C_{11}H_{10}O_6S$	49.0	3.7	11.8	48.7	3.9	11.7
	CH₂CO₂CH₃	50	Bz	7	Oxalic acid	8[c]	20	113.5 114.5	$C_{11}H_8O_5S$	52.4	3.2	12.7	52.4	3.6	12.9
3	CH₃	80	Bz	4	h	8[d]	28	188.5–189.5	$C_9H_6O_5S$	55.7	3.1	16.5	55.4	3.4	16.4
3	C₃H₇	25	Ether	24	h	8[e]	Trace								
3	C₃H₇	50	Bz	7	Maleic acid	8[e]	39	147–148	$C_{11}H_{10}O_5S$	59.5	4.5	14.4	59.4	4.9	14.5
3	C₃H₇	50	Bz	1.3	Oxalic acid	8[e]	45 (crude)								
3	C₆H₅CH₂	50	Bz	7	Oxalic acid	8[f]	35	170–171	$C_{15}H_{10}O_5S$	66.7	3.7	11.9	66.5	3.4	12.2
3	COCH₃	65	Bz	5	Oxalic acid	...	No reaction								
	C₃H₇ (3 isomer)	25	Ether	1.7	...	9[g,i]	87[j]	90–91	$C_{11}H_{12}O_4S$	55.0	5.0	13.3	55.1	5.0	13.4

[a] Respective registry no. are as follow: [b] 16065-63-7, [c] 1600-35-3, [d] 15533-50-3, [e] 16003-29-5, [f] 16003-30-8, [g] 16003-31-9. [h] A small amount of maleic acid impurity may have catalyzed this reaction. [i] The nmr spectrum of this product is given in the text. [j] Mixture of 2- and 3-propylthiofuran used; only the latter reacted. Yield is based on the 65% of 3 isomer in the mixture.

acid, and 1-dodecanethiol were distilled before use; the other thiols and solvents (Eastman Grade) were not purified further. 2,2-Dichloroethanethiol (Aldrich Chemical Co.) and 2-mercaptopropionic acid (K & K Laboratories) were used as received.

2-Furyl Thioethers (Table I). Method A.—To a solution of 0.4 mol of 1 and 0.4–0.5 mol of the thiol in 200 ml of acetonitrile was added 0.1 g of p-toluenesulfonic acid monohydrate, and the solution was stirred at 25° until reaction was essentially complete (0.5–4 hr).[14] Except for the products from mercapto acids, the reaction mixture was diluted with an equal volume of water, neutralized (NaHCO₃), extracted with ether, dried (MgSO₄), and distilled through a spinning-band column, where possible. The reaction mixtures from mercapto acids were stripped of solvent, the residues were extracted with alkali, and the acids were precipitated by hydrochloric acid, and recrystallized.

Method B.—The solution of 1 and the thiol in acetonitrile containing 0.15 g of maleic acid was heated under reflux in a nitrogen atmosphere until reaction was complete (4–6 hr).[14]

Method C.—Although not extensively investigated, this procedure shows promise of higher yields (Table I) by minimizing acid-catalyzed decomposition of the product. A solution of the thiol and 1 was heated at reflux and air was bubbled slowly through the mixture for a 0.5-hr period. Refluxing was continued until no further reaction was apparent[14] (5 hr for 1-propanethiol).

(2-Furylthio)acetic Acid.—A solution of 30.9 g of mercaptoacetic acid and 0.12 g of maleic acid in 350 ml of benzene was heated to the boiling point, and 43.7 g of 1 in 30 ml of benzene was added, dropwise, over a 2-hr period. The benzene–methanol azeotrope was removed during this time through a 6-in. Vigreaux column, and the reaction was continued for an additional 9 hr, yields 27–32%.

This compound was also prepared in 24% yield from 2,5-diacetoxy-2,5-dihydrofuran (which avoids ester formation) in acetonitrile at 25–35° for 20 hr, without a catalyst.

α-(2-Furylthio)propionic Acid and Methyl Ester.—The reaction of 2-mercaptopropionic acid using method A was complete in 1 hr, and vpc indicated a predominance of the expected acid. After 2.5 days at 25°, this had largely been converted into its methyl ester. Distillation produced the pure ester and a small yield of crude acid (bp 97–100° at 0.035–0.05 mm) which was recrystallized from ligroin (bp 90–120°).

2,5-Didodecylthio-2,5-dihydrofuran (4).—A mixture of 23.4 g (0.18 mol) of 1 and 45 g (0.22 mol) of 1-dodecanethiol in 100 ml of acetonitrile containing 2 ml of glacial acetic acid was heated at reflux for 6 hr. After 2.5 days at 25°, the oily solid which had separated was recrystallized from ligroin (bp 100–115°) to give 15 g of colorless plates, mp 54–55°, which is 29% of the theoretical amount (based on the mercaptan) of 4. The identity was confirmed by nmr.

Anal. Calcd for $C_{28}H_{54}OS_2$: C, 71.5; H, 11.6; S, 13.1. Found: C, 71.7; H, 11.6; S, 13.1.

This compound was shown by differential thermal analysis and vpc to break down at 275 ± 10° to give 2-dodecylthiofuran and 1-dodecanethiol.

Use of a 1:2 ratio of 1 to thiol under the same conditions produced a less tractable mixture from which small amounts of 4 and 1,1,4,4-tetra(dodecylthio)-2-butene, mp 68.5–69.5°, were isolated. The structure of the latter was confirmed by nmr.

Anal. Calcd for $C_{52}H_{104}S_4$: C, 72.8; H, 12.2; S, 14.9. Found: C, 72.9; H, 12.1; S, 14.8.

1,1,4,4-Tetra(propylthio)-2-butene.—An attempt to prepare 2,5-dihydro-2,5-dipropylthiofuran with a 1:2 ratio of 1 to 1-propanethiol, under the conditions of the preceding experiment, produced no reaction until an additional 2 ml of acetic acid was added and refluxing continued for another 7 hr. The resulting product was a mixture of 2-propylthiofuran (32% yield, based on 1) and a fraction consisting largely of 1,1,4,4-tetra(propylthio)-2-butene (45% yield, based on 1-propanethiol). The latter distilled at a pot temperature of 131–135° (9–7 μ) in an oil-jacketed pot still, $n^{25}D$ 1.5413–1.5428.

Anal. Calcd for $C_{16}H_{32}S_4$: C, 54.5; H, 9.2; S, 36.4. Found: C, 54.5; H, 8.9; S, 36.9.

Although the analysis is satisfactory, nmr and mass spectral data indicate the presence of impurities, including some 1,1,2,4,4-pentakis(propylthio)butane.

2-Propylthiofuran from Fumaric Dialdehyde.—A solution of 2 g of fumaric dialdehyde[15] and 2.07 g of propanethiol in 9.5 g of acetonitrile failed to produce the thioether during 3.5 hr at 25°. The reaction was completed, however, by the addition of 0.015 ml of acetic acid and heating the mixture under reflux for 1.25 hr. The yield of 2-propylthiofuran in the reaction mixture was 52% (estimated by vpc).

Tetrahydro-2,5-dimethoxy-3-furyl Thioethers (Table II).—Three variations in procedure were used. Purity of the products isolated, as determined by vpc, ranged from about 95 to 98%. Attachment of the sulfur to the 3 position of the furan ring was confirmed by nmr.

Method A.—A solution of 0.2 mol each of 1 and the thiol in 175 ml of benzene containing 0.15 ml of triethylamine and 2 ml of acetone as sensitizer was irradiated under a nitrogen atmosphere with a G.E. sunlamp. The solution temperature was held at 10–20° by external cooling of the Pyrex glass flask. The reaction

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(14) As determined by vpc analysis.

(15) K. Alder, H. Betzing, and K. Heimbach, *Ann.*, **638**, 187 (1960).

was continued until there was no further increase in product.[14] The products were isolated by distillation through a 6-in. Vigreaux column.

Method B.—The procedure of method A was varied by use of a Vycor flask, omission of the acetone, and use of a 360-W G.E. UA-3 ultraviolet lamp for irradiation. The ester was distilled in a stirred boiling point still.[16]

Method C.—The reaction is the same as in method B, but run neat.

3-Propylthiofuran.—Dibutyl phthalate (25 ml) containing 0.05 g of 2-naphthalenesulfonic acid monohydrate was placed in a flask equipped with a thermometer, dropping funnel, and a short Vigreaux still head, attached to a receiver under slightly reduced pressure (300–400 mm). The flask was heated and stirred magnetically, while 38 g of tetrahydro-2,5-dimethoxy-3-propyl-thiofuran was added, dropwise, during a 1.5-hr period. No significant reaction was observed until a reaction temperature of 285–295° was reached. The distillate was dissolved in benzene, washed with water, and distilled through a 6-in. packed column to give 14.7 g of pale yellow oil: bp 80–82° (28 mm); n^{25}D 1.4993. The nmr spectrum indicated an approximate 65:35 mixture of 3- and 2-propylthiofuran.

Anal. Calcd for $C_7H_{10}OS$: C, 59.1; H, 7.1; S, 22.5. Found: C, 59.1; H, 6.9; S, 22.6.

(16) E. S. Perry, "Technique of Organic Chemistry," Vol. IV, Interscience Publishers, Inc., New York, N. Y., 1951, p 511.

Reactions of Furyl Thioethers with Maleic Anhydride (Adducts 7 and 9).—A solution of equimolar amounts of the furyl thioether and maleic anhydride in ether was used (see Table III for conditions). The products crystallized in analytically pure form.

Phthalic Anhydrides (8).—A solution of 0.10 mol of the thioether and 0.11 mol of maleic anhydride in 150 ml of benzene containing 0.1 g oxalic acid was used (see Table III for conditions). Disappearance of the thioether was followed by vpc. The products were isolated by filtration and recrystallized from toluene–ligroin (bp 100–115°); 3-methylthiophthalic anhydride was recrystallized from 2-butanone.

Registry No.—4, 16031-74-6; 1,1,4,4-tetra(dodecyl-thio)-2-butene, 16003-32-0; 1,1,4,4-tetra(propylthio)-2-butene, 16003-33-1; 3-propylthiofuran, 16031-75-7.

Mechanism of the Prins Reaction.
## Kinetics and Product Composition in Acetic Acid

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The Prins reaction of formaldehyde with anethole in acetic acid, to give *trans*-4-anisyl-5-methyl-1,3-dioxane and the equilibrium mixture of *erythro*- and *threo*-1-anisyl-5-methyl-1,3-diacetoxypropanes obeys the kinetic law, $-d[anethole]/dt = [anethole]\{k_1[CH_2O]/(K + [CH_2O])\}$. It is postulated that formaldehyde and anethole are in rapid equilibrium with a molecular complex (dissociation constant $K = 1.8$), which is converted in a rate-determining step (rate constant $k_1 = 24.3 \times 10^{-4}$ sec^{-1}) into an intramolecularly stabilized carbonium ion. Throughout a range of formaldehyde concentrations in which the order in formaldehyde of the rate-determining process decreases from first to zero order, the product ratio shows that the dioxane-forming process remains strictly one order in formaldehyde greater than the diacetate-forming process. The stabilized carbonium ion is therefore presumed to react stereospecifically with formaldehyde to yield the dioxane product and to open to a second carbonium ion which reacts with acetic acid and/or acetate ion to produce finally the two diacetate products.

The Prins reaction of anethole (1) with formaldehyde in refluxing acetic acid yields *trans*-4-anisyl-5-methyl-1,3-dioxane and a mixture of the *erythro* and *threo* forms of 1-anisyl-2-methyl-1,3-diacetoxypropane.[2,3]
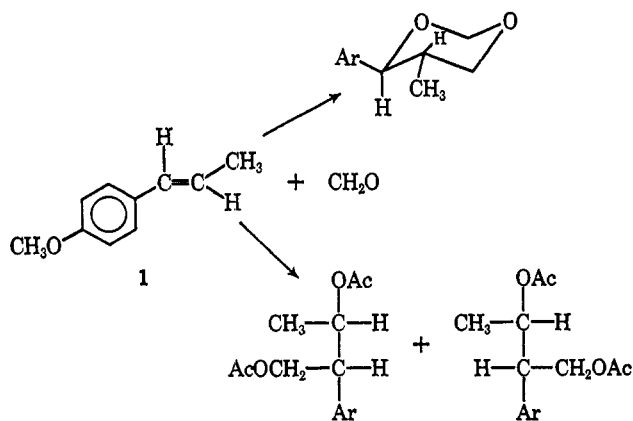
The dioxane is thus formed in a highly stereoselective process, whereas the diacetates are not.[4] This information was used by Smissman, Schnettler, and Portoghese[3] to formulate structures for some possible intermediate species in the reaction. The present paper reports studies of the kinetics and ratios of products formed in the Prins reaction in acetic acid at 125° and a mechanism consistent with the experiments.

Results

Kinetics.—The disappearance of anethole, followed spectrophotometrically at 259 mμ, is first order in anethole under conditions of excess formaldehyde (at least 40-fold in all cases) to at least 95% reaction. The first-order rate constants so obtained are given for

(1) To whom inquiries concerning this paper should be addressed.
(2) P. S. Portoghese and E. E. Smissman, *J. Org. Chem.*, **27**, 719 (1962).
(3) E. E. Smissman, R. A. Schnettler, and P. S. Portoghese, *ibid.*, **30**, 797 (1965).

(4) Of course, this observation applies only to acetic acid solvent, under the experimental conditions used. It is unsurprising that less clear-cut stereochemical results are obtained, for example,[5] in nucleophilic solvents such as dioxane which are likely to promote interconversion of reactants, intermediates, and products. Attempts[5] to extrapolate conclusions from studies in such systems to those in acetic acid are unwise.
(5) L. J. Dolby, C. Wilkins, and T. G. Frey, *ibid.*, **31**, 1110 (1966).