SYNTHESES AND REACTIONS OF POLYVINYLTHIAZOLES

by

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I hereby recommend that this dissertation prepared under my direction by Curtis Louis Schilling Jr. entitled Syntheses and Reactions of Polyvinylthiazoles be accepted as fulfilling the dissertation requirement of the degree of Doctor of Philosophy

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ABSTRACT

Synthetic approaches to vinyl and isopropenylthiazoles were investigated with the object of preparing polymeric analogs of thiamine. Several new thiazole monomers and precursors were prepared, including 2-(2-hydroxy-2-propyl)thiazole, 2-(2-acetoxy-2-propyl)thiazole, 2-isopropenylthiazole, 4-(1-benzoxyethyl)thiazole, 4-vinylthiazole, 4-isopropenylthiazole, 4-(2-hydroxy-2-propyl)thiazole, 4-(2-benzoxy-2-propyl)-thiazole, 2-methyl-4-(1-benzoxyethyl)thiazole, 2-methyl-4-(2-hydroxy-2-propyl)thiazole, 2-amino-4-(1-benzoxyethyl)thiazole, and 2-amino-4-isopropenylthiazole. Two known thiazole monomers, 2-vinylthiazole and 4-methyl-5-vinylthiazole, were also prepared.

Reactivity ratios and Price-Alfrey Q,e values were determined for 2-vinylthiazole and 4-vinylthiazole from copolymerization experiments with styrene. For styrene (comonomer$_1$) and 2-vinylthiazole (comonomer$_2$), $r_1 = 0.14 \pm 0.07$ and $r_2 = 3.32 \pm 0.48$ by the Mayo-Lewis method, and $r_1 = 0.18$ and $r_2 = 3.45$ by the Fineman-Ross method. The Q,e values for 2-vinylthiazole are $Q = 3.56$ and $e = 0.08$. For styrene (comonomer$_1$) and 4-vinylthiazole (comonomer$_2$), $r_1 = 0.66 \pm 0.11$ and $r_2 = 0.82 \pm 0.13$ by the Mayo-Lewis method and $r_1 = 0.60$ and $r_2 = 0.80$ by the Fineman-Ross method. The Q,e values for 4-vinylthiazole are $Q = 2.82$ and $e = -1.58$.

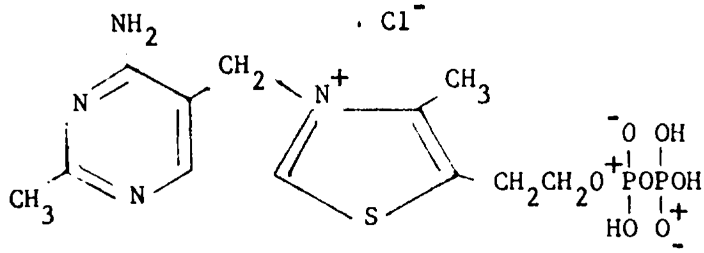
The condensation reaction of thioacetamide with 1-bromo-3-benzoxy-2-butanone and 1-bromo-3-benzoxy-3-methyl-2-butanone, respectively, produced two unusual compounds, $C_{13}H_{15}NO_3S$ and $C_{14}H_{17}NO_3S$,

tentatively assigned the structures of 2-methyl-4-benzoxy-4-(1-hydroxyethyl)-2-thiazoline and 2-methyl-4-benzoxy-4-(2-hydroxy-2-propyl)-2-thiazoline. These compounds may have arisen from intramolecular transesterifications of intermediates which would normally lead to 2-methyl-4-(1-benzoxyethyl)thiazole and 2-methyl-4-(2-benzoxy-2-propyl)-thiazole, respectively.

A copolymer of 4-vinylthiazole and 3-methyl-4-vinylthiazolium iodide and a copolymer of 4-methyl-5-vinylthiazole and 3,4-dimethyl-5-vinylthiazolium iodide were prepared by treatment of poly(4-vinylthiazole) and poly(4-methyl-5-vinylthiazole), respectively, with methyl iodide. The catalytic activity of these copolymers was compared with that of several monomeric thiazolium salts in the formation of furoin from furfural. The yields of furoin using monomeric and polymeric catalysts indicate that the copolymers possess catalytic activity per thiazolium unit equivalent to or higher than that of the monomeric thiazolium salts.

INTRODUCTION

Thiamine pyrophosphate (I) is involved as a coenzyme in a number

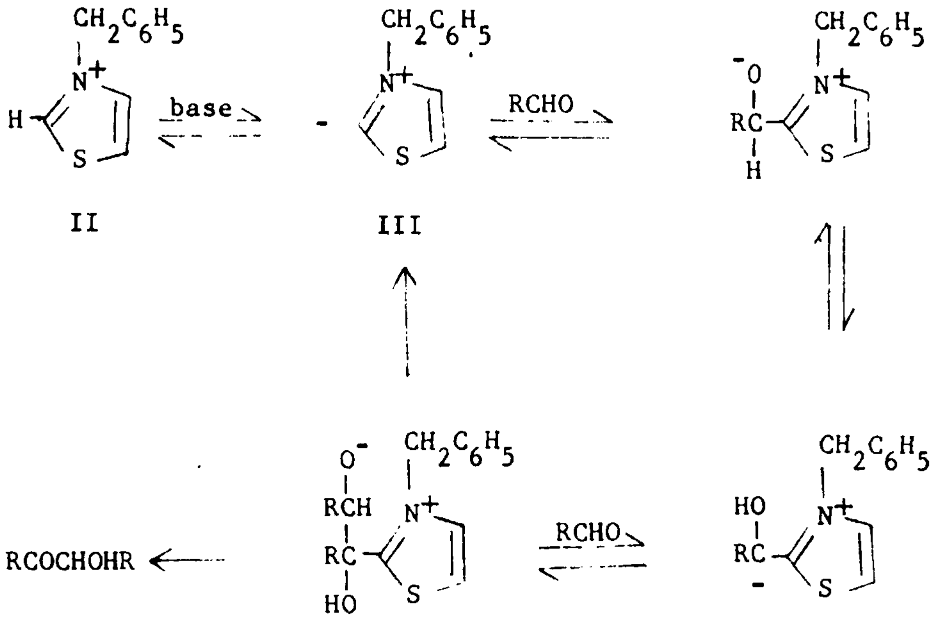


I

of biochemical reactions including oxidative and nonoxidative decarboxylations of α-keto acids and acyloin reactions.[1] The respective equations for these reactions are:

$$RCOCO_2H + \tfrac{1}{2}O_2 \longrightarrow RCO_2H + CO_2,$$
$$RCOCO_2H \longrightarrow RCHO + CO_2, \text{ and}$$
$$RCHO + R'CHO \longrightarrow RCHOHCOR'$$

Early workers demonstrated the catalytic activity of thiamine and even of simple thiazolium salts in the nonenzymatic formation of benzoin and acetoin from the respective aldehydes.[2] Breslow[3-7] was the first to prove that the 2-carbon atom in the thiazolium ring is responsible for the catalytic activity. In brief, Breslow's proof of the mechanism of catalysis is based[6,7] on the discovery that the proton attached to the 2-carbon of compound II exchanges with solvent deuterium at a rate too fast to measure at pH 7. Obviously, the ylid III is readily formed. It is electronically similar to cyanide ion and acts as a specific catalyst for the reaction as shown below. Some of the proposed reactive intermediates have been synthesized and are at least as reactive as the starting thiazolium salt. Considerable evidence[1]

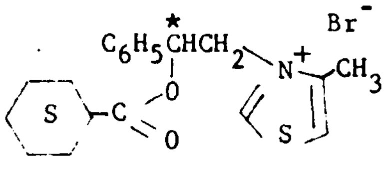


suggests that this mechanism also applies to the enzyme catalyzed reaction.

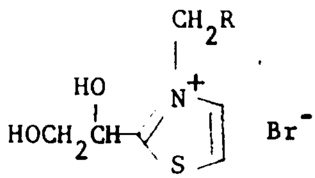
A number of other groups have been active in research related to the catalytic activity of thiazolium salts. Sheehan[8] prepared optically active benzoin from benzaldehyde using a thiazolium salt catalyst (IV) containing an optically active side chain. Lienhard,[9] Bruice,[10] Reed,[11] White and Ingraham,[12-14] and their coworkers have studied various aspects of the preparation, reactions, and kinetics of solvolyses of certain very reactive 2-acylthiazolium salts which are proposed intermediates in the phosphoketolase reaction. Breslow[15] has also published some data on reactions of unisolated 2-acetyl-3,4-dimethylthiazolium iodide.

In an attempt to assess the effect of relative positioning of heteroatoms on the acidity of ring protons, Olofson[16,17] has published two papers dealing with the rates of exchange with deuterium of ring hydrogens of several heterocyclic compounds, including thiazole and thiazolium salts.

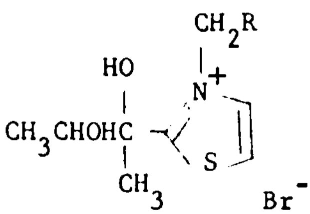
Sykes prepared a number of possibly active thiazolium intermediates for acyloin condensations, including "active glycolaldehyde" (Va),[18] "active acetoin" (Vb),[18] and "active pyruvate" (Vc).[19]



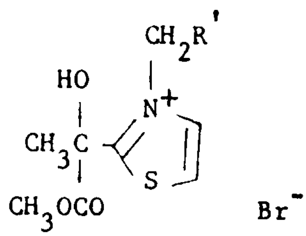
IV



Va



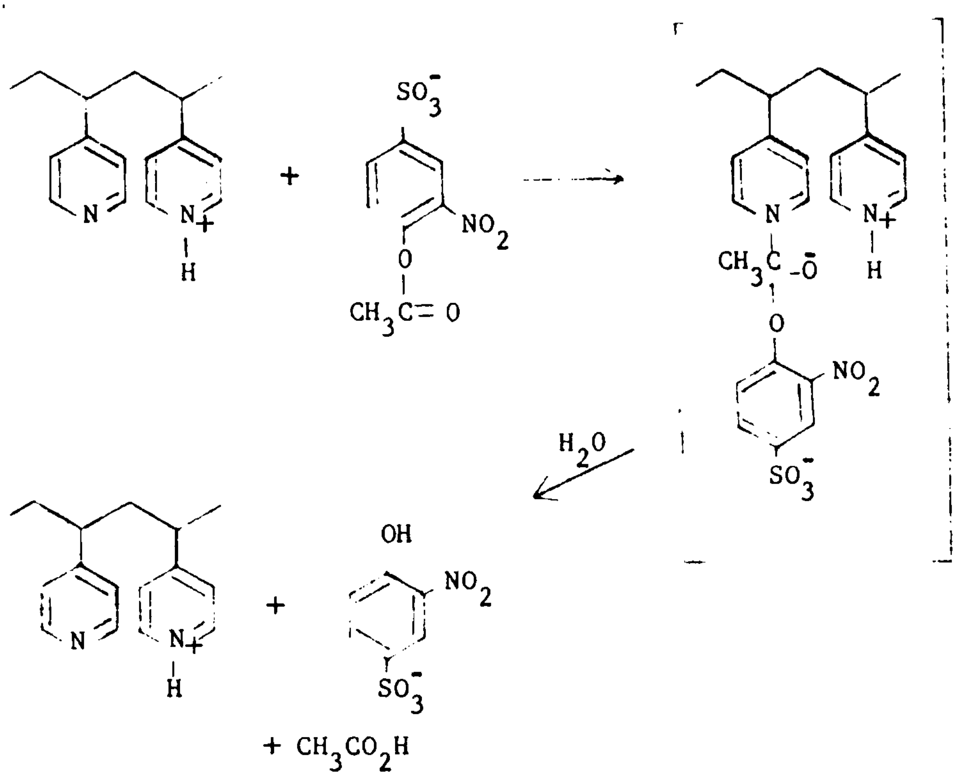
Vb



Vc

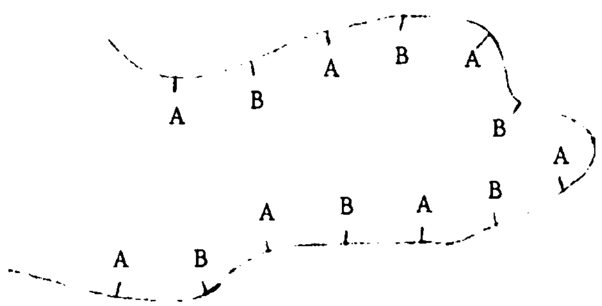
R = p-nitrobenzyl-, R' = benzyl-

Synthesis and examination of the catalytic activity of polymers containing recurring quarternized thiazole units suggested itself for a number of reasons, most of which have to do with the possibility of enhanced reactivity in a polymeric structure.[20] For example, in a solution of a polymer such as poly(4-vinylpyridine), the concentration of the pyridine units in the region of the polymer coil is very high relative to that of a solution of ethylpyridine containing an equivalent amount of pyridine units per liter. The situation has been likened to a microscopic dispersion of oil droplets in an aqueous medium in contrast to a solution of the same amount of droplets in a good solvent. In the latter case the solute is homogeneously distributed throughout the solvent rather than agglomerating in small areas of high local concentration. This phenomenon can lead to rate acceleration by a polymeric species relative to a low molecular weight analog if there is some method of bringing and keeping the substrate in the region of the polymer coil. In special cases this rate acceleration may be achieved by ion-binding, an example being the solvolysis of potassium 3-nitro-4-acetoxybenzenesulfonate catalyzed by partially protonated poly(4-vinylpyridine).[21]



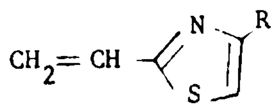
Under conditions where the concentration of free base was the same for the polymer and a model compound, 4-picoline, the pseudo first order rate constant for the polymer was approximately five times that of 4-picoline. Similar behavior in the solvolysis of 4-acetoxy-3-nitrobenzoic acid catalyzed by poly-4(5)vinylimidazole has been reported.[22]

Higher reactivity of polymer molecules may also arise when more than one functional group is required for reaction. Many enzymes possess simple functional groups of extraordinary reactivity, and in part this reactivity results from the close association of two functional groups. Of course, the concept of neighboring functional group anchimeric assistance has been well established for many years. It is well to ask whether there is any reason to believe that a bifunctional copolymer having a structure such as VI should, in principle, have any greater reactivity than the equivalent amount of small A and B molecules in solution. Morawetz[23] in discussing this question has pointed out that rates of reaction of copolymers are extremely sensitive to configuration and the conformational requirements imposed by a polymer chain.



VI

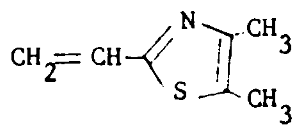
Examination of the literature revealed that a number of vinyl and isopropenylthiazoles, including 2-vinylthiazole (VIIa),[24,25] its 4-methyl,[24-26] 4-phenyl,[24,25] and 4,5-dimethyl[24] derivatives (VIIb, VIIc, and VIII, respectively), 2-isopropenyl-4-methylthiazole (IX),[24-25] 2-acetamido-4-vinylthiazole (X),[27] and 4-methyl-5-vinylthiazole (XI)[29-31] have been prepared.



VIIa, R = H

VIIb, R = CH_3

VII_c, R = C_6H_5



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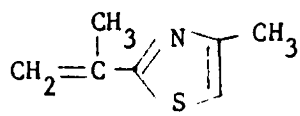
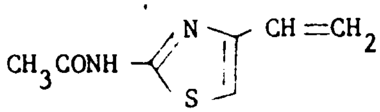
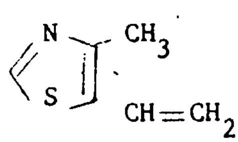


IX



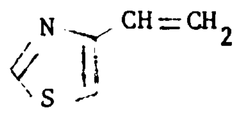
X



XI

2-Amino-4-vinylthiazole has been reported as a nonisolated intermediate in the preparation of X.[27]

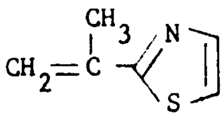
Of the above, only 4-methyl-5-vinylthiazole has the needed carbon bearing only a hydrogen atom at the 2-position. The synthesis of 4-vinylthiazole (XII) was undertaken to provide another example of a monomer capable of providing the necessary active site.



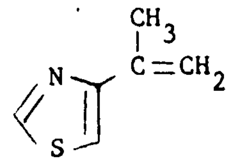
XII

Literature reports[26,32-35] of the polymerization of the known thiazole monomers are confined to the 2- and 5-position derivatives. 4-Methyl-5-vinylthiazole is reported as yielding only viscous oils with benzoyl peroxide as initiator, but hard copolymers with maleic anhydride.[32,33] The 2-vinyl and 2-isopropenylthiazole monomers yield homopolymers[24,26] and copolymers with butadiene and styrene which have been reported in patents.[26,34,35]

There was no quantitative information in the literature concerning reactivity of any of the vinylthiazoles. Accordingly, copolymerizations of the vinylthiazoles with styrene were desirable, leading to monomer reactivity ratios and Q,e values. Since the isopropenyl group, upon polymerization, provides a means of determining the stereochemical structure of polymers through nmr spectroscopy, the synthesis of 2-isopropenylthiazole (XIII) and 4-isopropenylthiazole (XIV) were also undertaken in order to compare the stereochemistry of polymers prepared from them with various initiators.



XIII

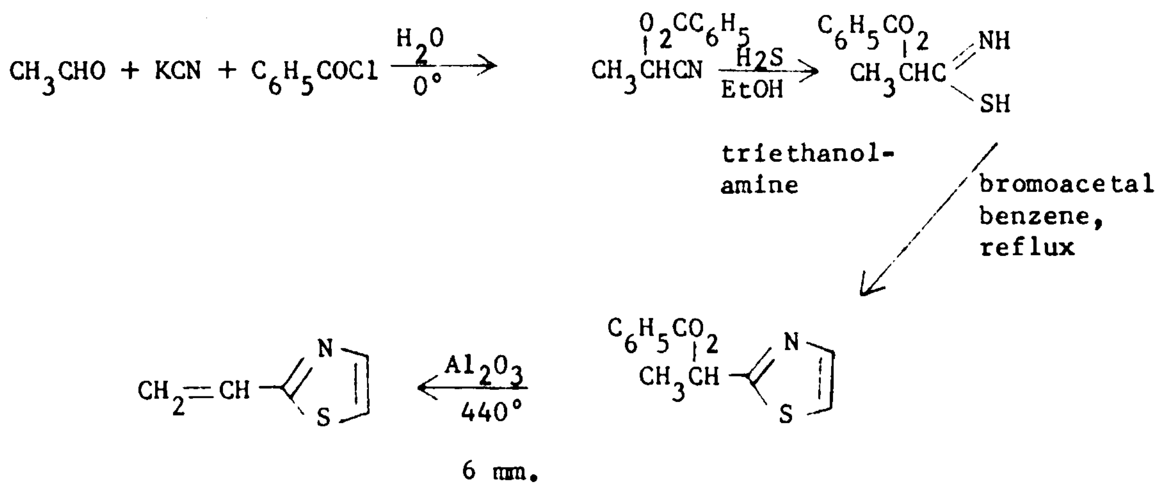


XIV

RESULTS AND DISCUSSION

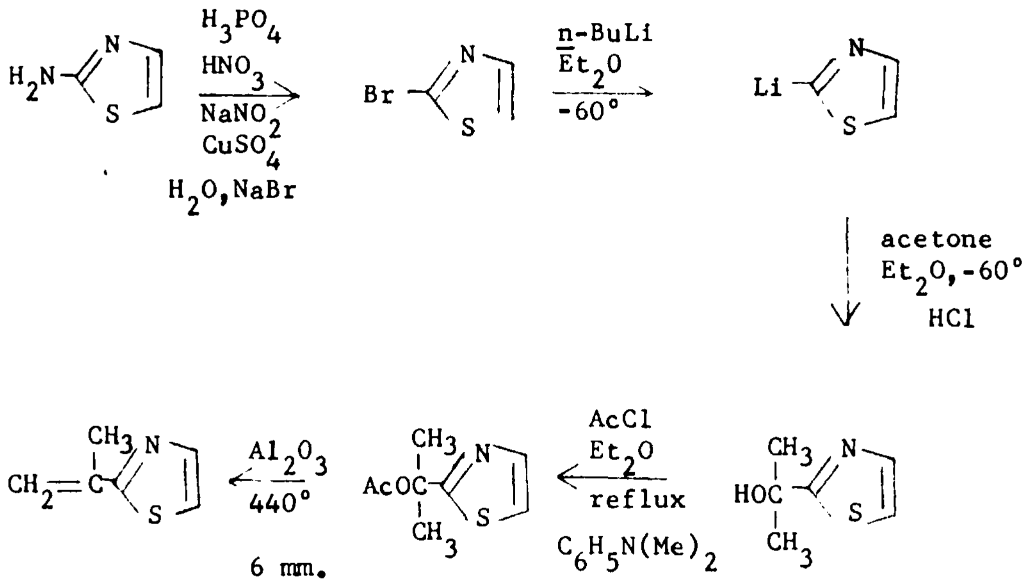
Syntheses and Reactivity of Vinyl and Isopropenylthiazoles

The synthesis of 2-vinylthiazole was repeated according to the procedure of Schoene,[24] with minor variations. The reaction pathway is:



The respective yields for the four steps were 86.1%, 90.6%, 68.0%, and 51.6%, with the overall yield of 2-vinylthiazole based on acetaldehyde being 27.3%.

Attempts to repeat this reaction scheme beginning with acetone instead of acetaldehyde to obtain 2-isopropenylthiazole were less successful. Although the corresponding nitrile ester and thioamide were obtained in low yields, the condensation reaction with bromoacetal did not yield the expected thiazole benzoate. The preparation of the nitrile is reported to proceed with low yield.[36] This reaction series was not fully investigated due to the success of the pathway outlined below, beginning with commercially available 2-aminothiazole.

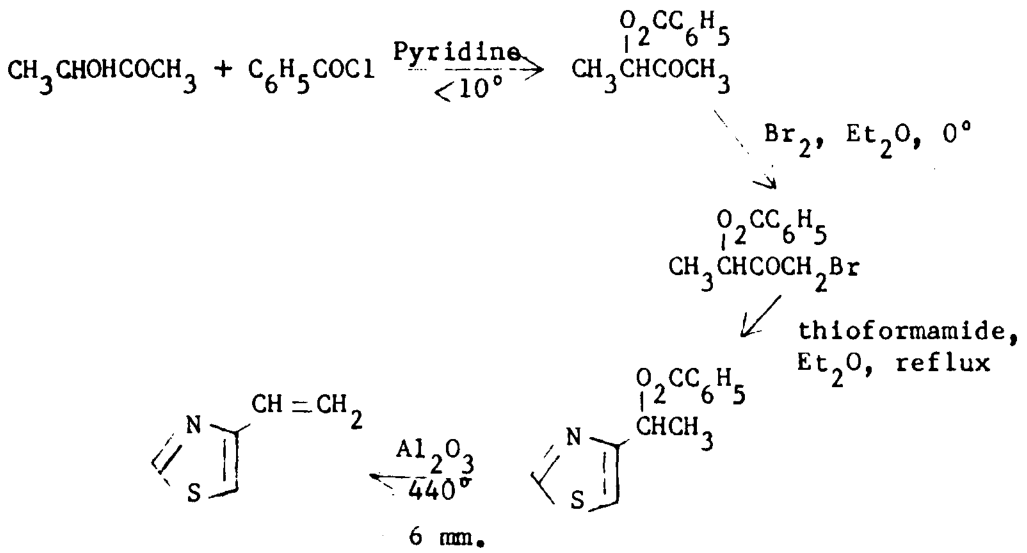


The first step, a Sandmeyer reaction leading to 2-bromothiazole, is that of Ganapathi and Venkataraman.[37] The halogen-lithium exchange of 2-bromothiazole is well known,[38,39] but the reaction with acetone yielded a new carbinol. The esterification procedure reported in Vogel[40] for _t_-butyl acetate yielded the thiazole acetate, 2-(acetoxy-2-propyl)thiazole, which was pyrolyzed to 2-isopropenylthiazole. The yields for the four steps above were 59.1%, 70.0%, 88.3%, and 82.0%, respectively, the overall yield being 30.0% based on the starting amount of 2-aminothiazole.

A route employing 2-lithiothiazole was also attempted for the synthesis of 2-vinylthiazole. The reaction of 2-lithiothiazole with acetaldehyde gave 2-(1-hydroxyethyl)thiazole in low yield.[38] 1,1-Di-(2-thiazolyl)ethanol[41] was also obtained from this reaction and this presumably arose from the reaction of 2-lithiothiazole with traces of acetic acid in the acetaldehyde. Due to these complications this approach was abandoned.

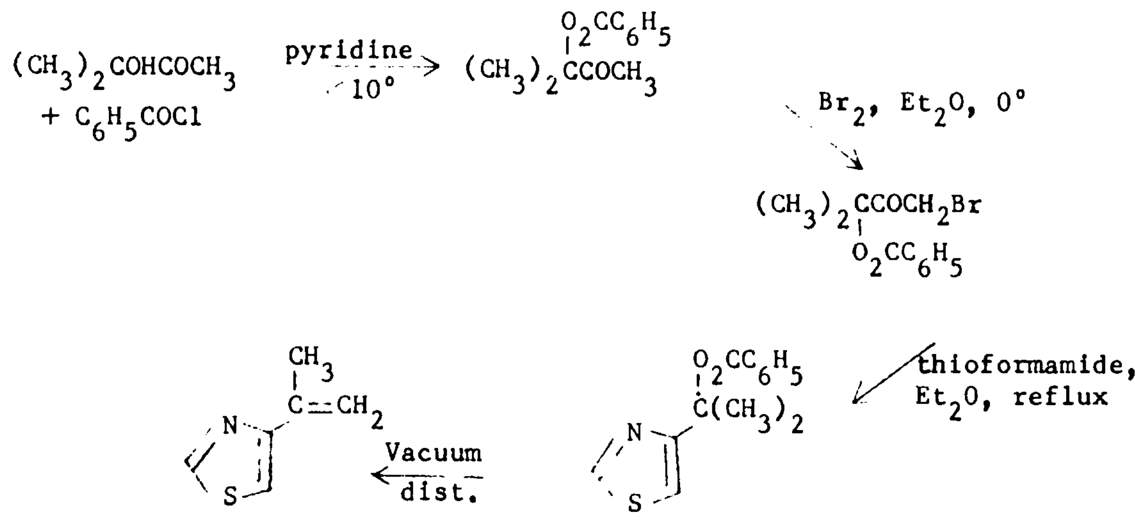
The synthesis of 2-isopropenylthiazole was also attempted by the proposed condensation of 2-acetoxy-2-methylthiopropionamide with bromoacetal and pyrolysis of the resultant 2-(2-acetoxy-2-propyl)thiazole. Although the synthesis of the known 2-acetoxy-2-methylpropionitrile[42] was successful, the addition of hydrogen sulfide, using the conditions of Olin and Johnson,[43] was not. This reaction also was not investigated further due to the accessibility of 2-isopropenylthiazole through the 2-lithiothiazole route.

The 4-vinyl and 4-isopropenylthiazones were both synthesized through a parallel series of reactions beginning with 3-hydroxy-2-butanone and 3-hydroxy-3-methyl-2-butanone, respectively. The pathway for 4-vinylthiazole is as shown.



The first two steps are essentially those of Diels and Stepan.[44,45] Their bromination reactions were carried out by adding a chloroform solution of bromine to a chloroform solution of the benzoate with gentle heating. Higher yields were obtained for this step by adding undiluted bromine to an ethyl ether solution of the benzoate at 0°. Thioformamide was synthesized by the method of Erlenmeyer and Menzi.[46] The condensation product, 4-(1-benzoxyethyl)thiazole, was pyrolyzed under the previously used conditions, yielding 4-vinylthiazole. The yields for these four steps were 72.6%, 70.0%, 82.6%, and 79.3%, respectively, the overall yield based on 3-hydroxy-2-butanone being 33.9%.

In the 4-isopropenylthiazole synthesis, the monomer was usually obtained directly by vacuum distillation of the thiazole benzoate, without isolating the benzoate in a pure state. In one case, the benzoate was isolated

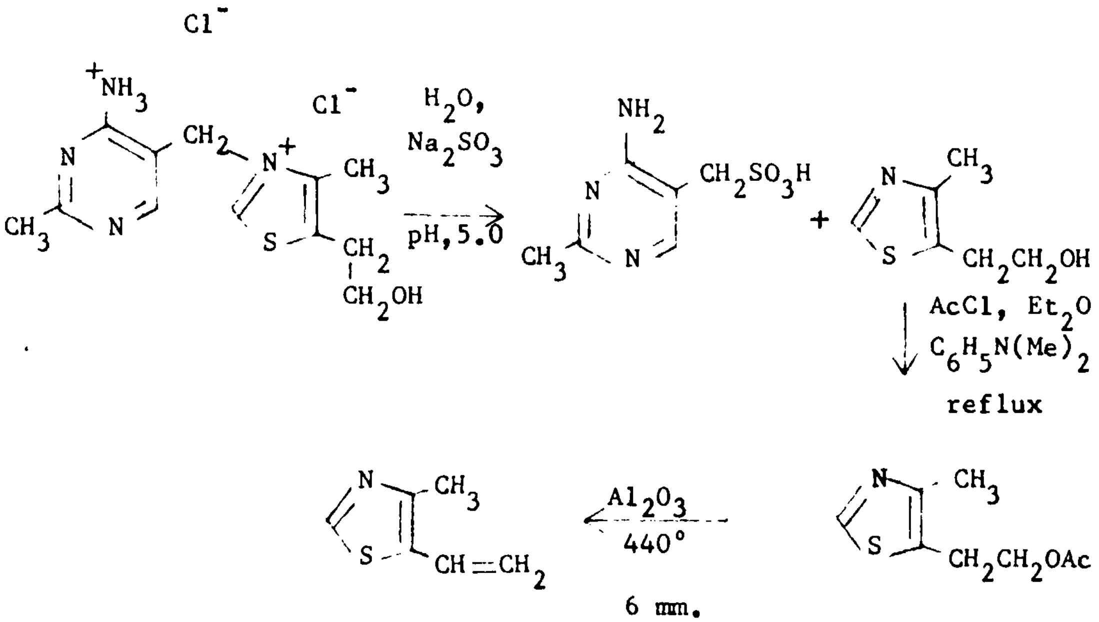


as a crystalline solid, melting at 74.5-75.5°. The yields for the three step procedure, without isolation of the thiazole benzoate, were 73.8%, 85.8%, and 38.3%, respectively, the overall yield based on 3-hydroxy-3-methyl-2-butanone being 24.2%. The yield of 4-isopropenylthiazole was not improved by employing vacuum pyrolysis of the crude thiazole benzoate rather than vacuum distillation. No attempt was made to pyrolyze the pure crystalline 4-(2-benzoxy-2-propyl)thiazole.

The hydrogenation of 4-isopropenylthiazole to 4-isopropylthiazole, which was desired as a monomeric model for the poly(vinylthiazoles), was unsuccessful using platinum oxide as catalyst in acetic acid solution in a low pressure Parr apparatus. This procedure has been successfully used to hydrogenate 2-acetamido-4-vinylthiazole to 2-acetamido-4-ethylthiazole.[27]

The synthesis of 4-methyl-5-vinylthiazole was carried out by the reductive cleavage of thiamine,[47] which gave 4-methyl-5-(2-hydroxyethyl)-thiazole. This was esterified with acetyl chloride in the presence of dimethylaniline.[40] Pyrolysis of the acetate produced the known 4-methyl-5-vinylthiazole.[28-31] The 4-methyl-5-vinylthiazole monomer was chosen for this work rather than the unknown 5-vinylthiazole, due to the facile synthesis of the former by this route.

The monomers were purified by distillation through a spinning-band column, with each showing a single peak in its vapor phase chromatograph. Polymerizations were carried out using benzoyl peroxide or azobisisobutyronitrile as free radical initiators, _n_-butyllithium or phenyl magnesium bromide as anionic initiators, or boron trifluoride etherate as a cationic initiator. All polymerizations were made in



bulk, with the exception of those using phenyl magnesium bromide; these were carried out in toluene solution. The results are summarized in Table I.

As can be seen from Table I, all of the thiazole monomers polymerize under free radical conditions to give solid polymers, although they are of rather low molecular weight (2198-2870, see Experimental). Some preliminary experiments using the listed cationic and anionic initiators indicate some reactivity of the monomers toward ionic polymerization. Most notable is the ease with which 2-isopropenylthiazole is polymerized with phenyl magnesium bromide. One would expect this monomer and 2-vinylthiazole to be particularly susceptible to anionic polymerization, relative to the 4-position monomers because of the possibility of charge delocalization

TABLE I

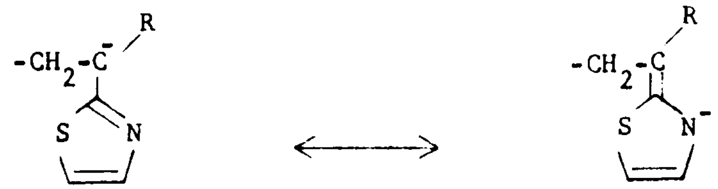
POLYMERIZATIONS OF VINYL AND ISOPROPENYLTHIAZOLES

	Monomer / Grams	Initiator / Amount	Temp. / Time	Yield / Conv.	Soft. Point	η inh / Solvent
1.	2-V-T / 4.47	BPO / 102.3 mg.	80° / 24 hr.	2.24 g. / 50%	80-110°	0.10/benzene 0.21/DMSO
2.	2-V-T / 2.45	ABIN / 15.6 mg.	80° / 5 hr.	1.83 g. / 73%	115-135°	0.95 / DMSO
3.	2-I-T / 5.62	ABIN / 80.0 mg.	90° / 36 hr.	1.80 g. / 32%	150-170°	0.06 / DMSO
4.	4-V-T / 4.30	ABIN / 69.0 mg.	80° / 12 hr.	4.30 g. / 100%	110-130°	0.07/benzene 0.14/DMSO
	Note: 4.00 g. of polymer #4 was insoluble in all solvents, and had softening point 90-100°.					
5.	4-V-T / 2.15	ABIN / 21.4 mg.	80° / 0.8 hr.	1.31 g. / 61%	-	-
	Note: All but traces of polymer #5 were soluble in benzene or chloroform.					
6.	4-V-T / 5.50	BPO / 76.0 mg.	75° / 22.5 hr.	1.60 g. / 29%	135-140°	-
7.	4-I-T / 3.75	BPO / 15.0 mg.	70° / 90 hr.	0.22 g. / 6%	195-210°	-
8.	4-I-T / 2.54	BPO / 43.0 mg.	75° / 87 hr.	0.08 g. / 3%	-	-
9.	4-I-T / 4.10	ABIN / 29.1 mg.	80° / 36 hr.	1.07 g. / 26%	130-170°	0.04/benzene 0.07/DMSO
10.	4-M-5-V-T / 2.22	ABIN / 29.4 mg.	90° / 12 hr.	1.06 g. / 48%	150-180°	0.034 / DMSO
11.	4-V-T / 4.06	BF_3 / 0.03 ml.	25° / 12 hr.	0.12 g. / 3%	80-140°	-
12.	4-I-T / 1.00	BF_3 / 0.03 ml.	25° / 36 hr.	0.11 g. / 11%	130-170°	-

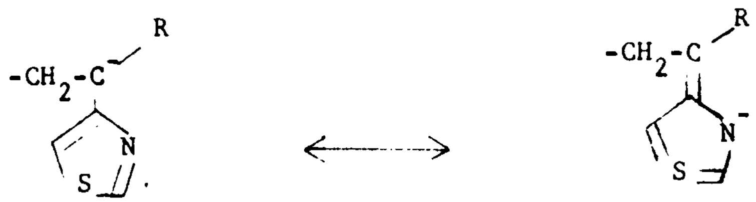
Table I.--Continued.

13.	2-I-T 5.68	BF_3 0.10 ml.	25° 36 hr.	0.49 g. 9%	90- 100°	0.035 DMSO
14.	2-V-T 3.87	n-BuLi 0.10 ml.	25° 24 hr.	0.06 g. 2%	40- 70°	-
15.	4-V-T 2.43	n-BuLi 0.06 ml.	25° 22 hr.	-	220- 240°	-
16.	4-I-T 4.37	n-BuLi 0.02 ml.	25° 87 hr.	0.05 g. 1%	220- 245°	-
17.	2-I-T 5.98	n-BuLi 0.30 ml.	25° 36 hr.	3.06 g. 51%	170- 200°	0.22 DMSO
18.	2-I-T 2.00	n-BuLi 0.50 ml.	0° 5 min.	0.12 g. 6%	-	-
19.	2-I-T 2.07	n-BuLi 0.50 ml.	-20° 10 min.	0.17 g. 8%	-	-
20	2-I-T 2.00	ØMgBr 0.4 ml.	25° 1 hr.	2.00 g. 100%	170- 185°	-
21.	2-I-T 2.00	ØMgBr 0.4 ml.	0° 1 hr.	2.00 g. 100%	175- 190°	-

Note: BPO is benzoyl peroxide, ABIN is azobisisobutyronitrile, DMSO is dimethyl sulfoxide, _n_-BuLi is _n_-butyllithium (1.6M) in hexane, ØMgBr is phenyl magnesium bromide (0.7M) in toluene. #20 and #21 also contained 10 ml. toluene. 2-V-T, 2-I-T, 4-V-T, 4-I-T, and 4-M-5-V-T are 2-vinyl, 2-isopropenyl, 4-vinyl, 4-isopropenyl, and 4-methyl-5-vinylthiazole, respectively.



onto the ring nitrogen. This possibility does not exist in the case of the 4-position monomers unless one considers forms involving expansion of the sulfur octet such as:



The thiazole ring acts as an electron sink when attached to a double bond at the 2-carbon, as shown by the Michael additions which are undergone by 2-isopropenyl-4-methylthiazole.[48]

The nmr and infrared spectra of the monomers and polymers are consistent with polymerization through the vinylic double bond, i.e., 1,2-polyaddition. The nmr spectra of the polymers obtained from 4-isopropenyl and 2-isopropenylthiazole showed well resolved methyl group peaks due to syndiotactic, heterotactic, and isotactic triads in the polymer chains. In the case of the former monomer, these peaks were found at

T 9.9, 9.4, and 9.0, the largest peak being that at T 9.9. The polymer in this case was prepared using azobisisobutyronitrile as a free radical initiator. The polymer formed from 2-isopropenylthiazole using the same free radical initiator showed methyl group peaks at T 9.6, 9.1, and 8.6 with the largest peak being at T 9.6. Poly(2-isopropenylthiazole) prepared anionically using either n-butyllithium or phenyl magnesium bromide as initiator showed methyl group peaks at the same T-values as that prepared with the free radical initiator. The largest peak for the anionically prepared polymers was that at T 9.1, indicating that the triad compositions of the two polymers were different. A similar group of three methyl peaks was observed in the nmr spectrum of poly-α-methylstyrene, with absorptions at T 9.86, 9.65, and 9.18.[49] The author has assigned these, respectively, to syndiotactic, heterotactic, and isotactic triads, on the basis of anisotropic shielding from the phenyl rings. Another group[50] has assigned exactly the opposite triad compositions to the same absorptions, i.e., isotactic, heterotactic, and syndiotactic, respectively, with the authors of each paper stating their assignments to be provisional. 2-Isopropenylthiazole, like α-methylstyrene, is a monomer consisting of an aromatic ring attached to an isopropenyl group, and might therefore be expected to show a similar nmr pattern for the α-methyl groups, in polymerized form. The data, however, do not permit a useful assignment of triad compositions to the various peaks.

As stated, poly(2-isopropenylthiazole), prepared in toluene solution using phenyl magnesium bromide as initiator according to the method of Natta,[51] had the same nmr spectrum as that prepared with n-butyllithium in bulk. Natta and coworkers were able to prepare crystalline poly(2-vinylpyridine) using the former initiator-solvent system. The similarity of 2-vinylpyridine and 2-isopropenylthiazole prompted the use of the Grignard reagent as an initiator with the thiazole monomer. The results indicate that stereoregular polymers were not obtained in the latter case.

The insoluble polymer obtained in polymerization #4 is not easily explained. A polymerization carried out at lower conversion (#5) was soluble in chloroform or benzene, while the majority of the polymer from polymerization #4 was insoluble in all solvents, including hot, concentrated sulfuric acid. It was not cross-linked, however, since it had a softening range of 90-100°. Cross-linked polymers are by definition infusible and insoluble. The infrared spectra of the soluble and insoluble fractions were identical with the exception of a broad peak at 1050 cm^{-1} in the spectrum of the insoluble portion. Further work is required to elucidate this phenomenon.

Copolymerization experiments were conducted with 2-vinylthiazole and styrene and with 4-vinylthiazole and styrene in order to determine the relative reactivities of these monomers. Nine polymerizations were made with each comonomer pair, with seven or eight being selected in each case for the determination of reactivity ratios by both the Fineman-Ross[52] and Mayo-Lewis[53] methods. The copolymerization data are presented in Table II.

Reactivity ratios were determined by the Mayo-Lewis[53] method, using the equation:

TABLE II

COPOLYMERIZATION OF 2-VINYL AND 4-VINYLTHIAZOLE WITH STYRENE

	M_1 g.	M_2 g.	M_1/M_2 mmoles	Time Min.	Yield g.	Conv. %	S-content %
A. 4-Vinylthiazole							
1.	1.04	1.11	10/10	20	0.298	13.9	15.62
2.	0.52	1.71	5/15.4	17	0.275	12.3	21.56
3.	1.56	0.56	15/5	17	0.233	11.0	8.98
4.	0.21	2.00	2/18	13	0.208	9.4	25.03
5.	1.85	0.22	18/2	17	0.231	11.0	3.68
6.	0.83	1.33	8/12	17.5	0.255	11.8	18.47
7.	1.25	0.91	12/8.2	17	0.217	10.0	13.07
8.	1.47	0.69	14.1/6.2	18	0.241	11.2	10.08
9.	0.62	1.55	6/14	16.5	0.256	11.8	20.03
B. 2-Vinylthiazole							
1.	1.04	1.11	10/10	20	0.226	10.5	23.13
2.	1.56	0.56	15/5	20	0.193	9.1	17.13
3.	0.52	1.67	5/15	17.5	0.324	14.8	27.06
4.	1.25	0.88	12/8	22	0.197	9.2	20.73
5.	0.83	1.33	8/12	19	0.280	13.0	24.16
6.	0.67	1.61	6.5/14.5	17	0.292	12.8	25.31
7.	1.40	0.72	13.5/6.5	23	0.223	10.5	18.80
8.	1.79	0.35	17.2/3.2	22	0.215	10.1	12.25
9.	0.16	0.97	1.5/8.7	11	0.132	11.7	25.84

$$r_2 = \frac{M_1'}{M_2'} \left[\frac{m_2}{m_1} \left(1 + \frac{M_1'}{M_2'} r_1\right) - 1 \right]$$

where M_1' and M_2' are substituted for the M_1 and M_2 of the original Mayo-Lewis expression. The M_1' and M_2' values are average values for the millimoles of each comonomer in the feed, determined from the equations:

$$M_1' = \frac{M_1 + (M_1 - m_1)}{2} \quad \text{and} \quad M_2' = \frac{M_2 + (M_2 - m_2)}{2}$$

where M_1 and M_2 represent the initial numbers of millimoles of comonomer (styrene and vinylthiazole, respectively) in the polymerizing mixture and m_1 and m_2 represent the respective number of millimoles of each comonomer in the copolymer.[54] This averaging correction is necessary since conversions were carried to an approximate value of ten percent in each case so that initial feed concentration was not equal to final feed concentration. A plot of r_1 versus r_2 yields a straight line for each copolymerization, with the common intersection being the desired reactivity ratio (r_1,r_2) values.

The equation below was used for the determination of

$$\frac{f - 1}{F} = -r_2 \frac{f}{F^2} + r_1$$

the reactivity ratios by the Fineman-Ross method.[52] In this equation, f represents m_1/m_2, and F represents M_1'/M_2', and m_1, m_2, M_1', and M_2' have the same definitions as above. A plot of $(f-1)/F$ versus f/F^2 yields a single straight line for which the slope is $-r_2$ and the intercept is r_1. The Mayo-Lewis and Fineman-Ross plots, suitably captioned, are shown in Figures 1-4.

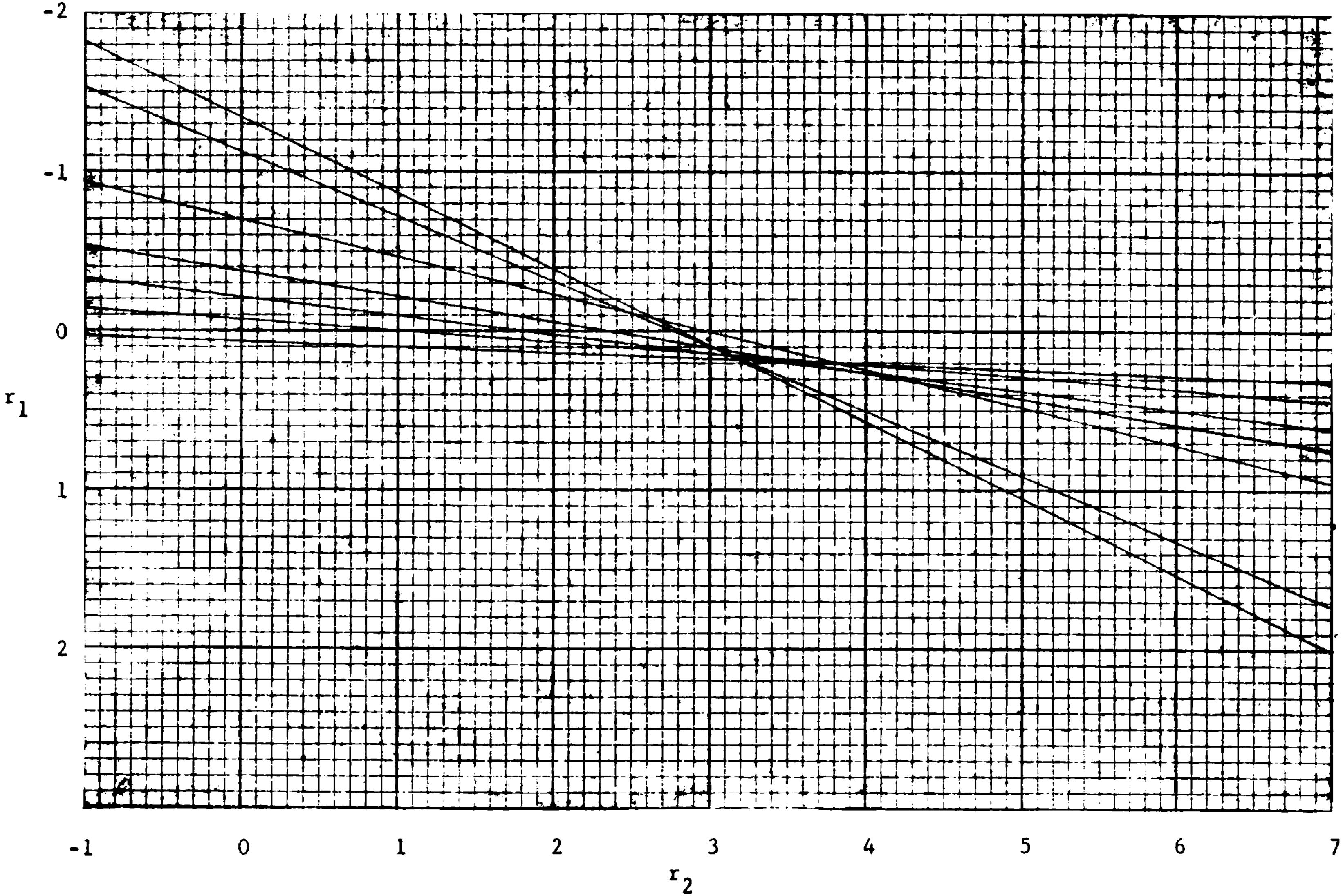


Figure 1.

Mayo-Lewis Plot for Styrene and 2-Vinylthiazole

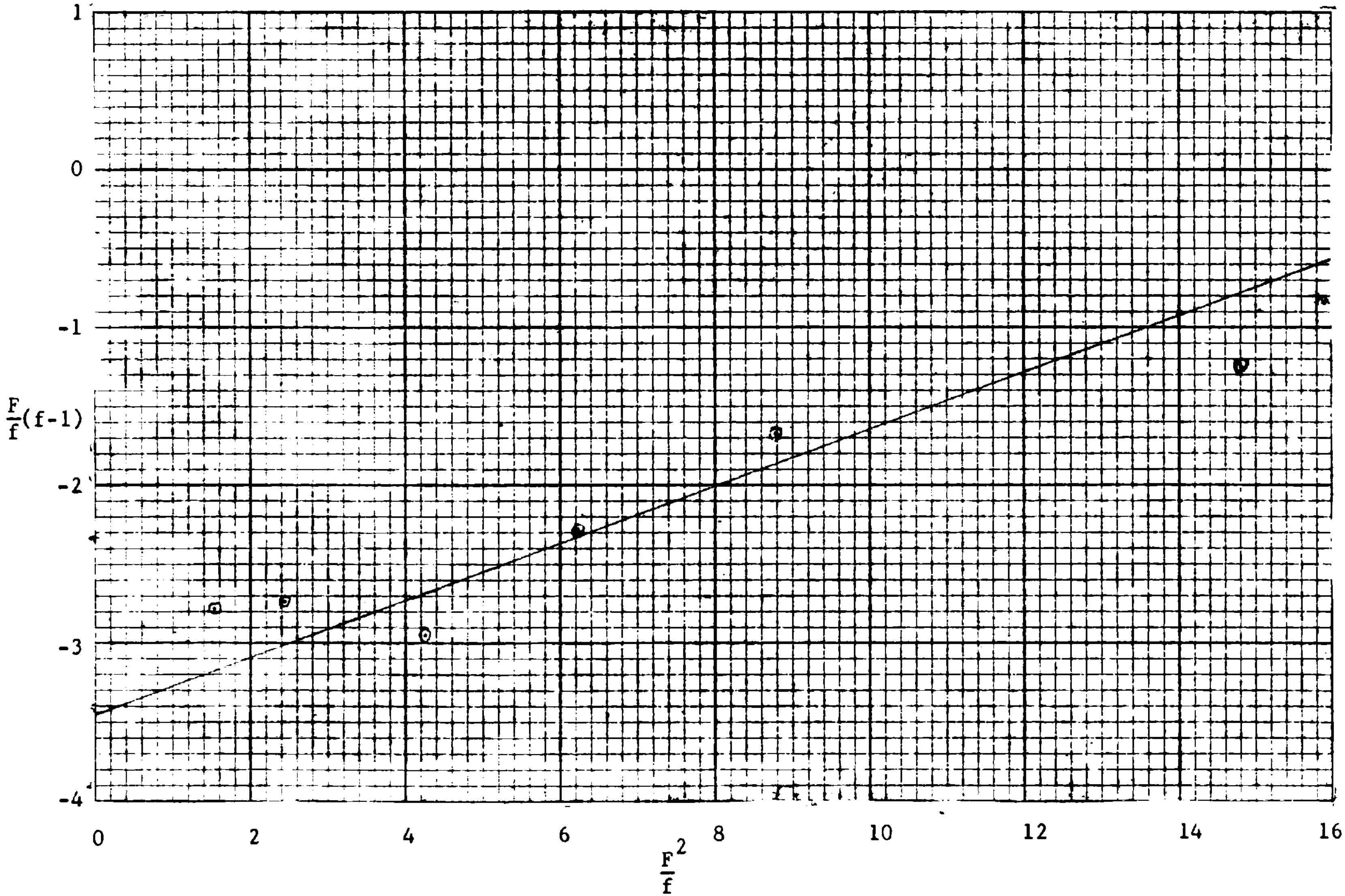


Figure 2.
Fineman-Ross Plot of Styrene and 2-Vinylthiazole

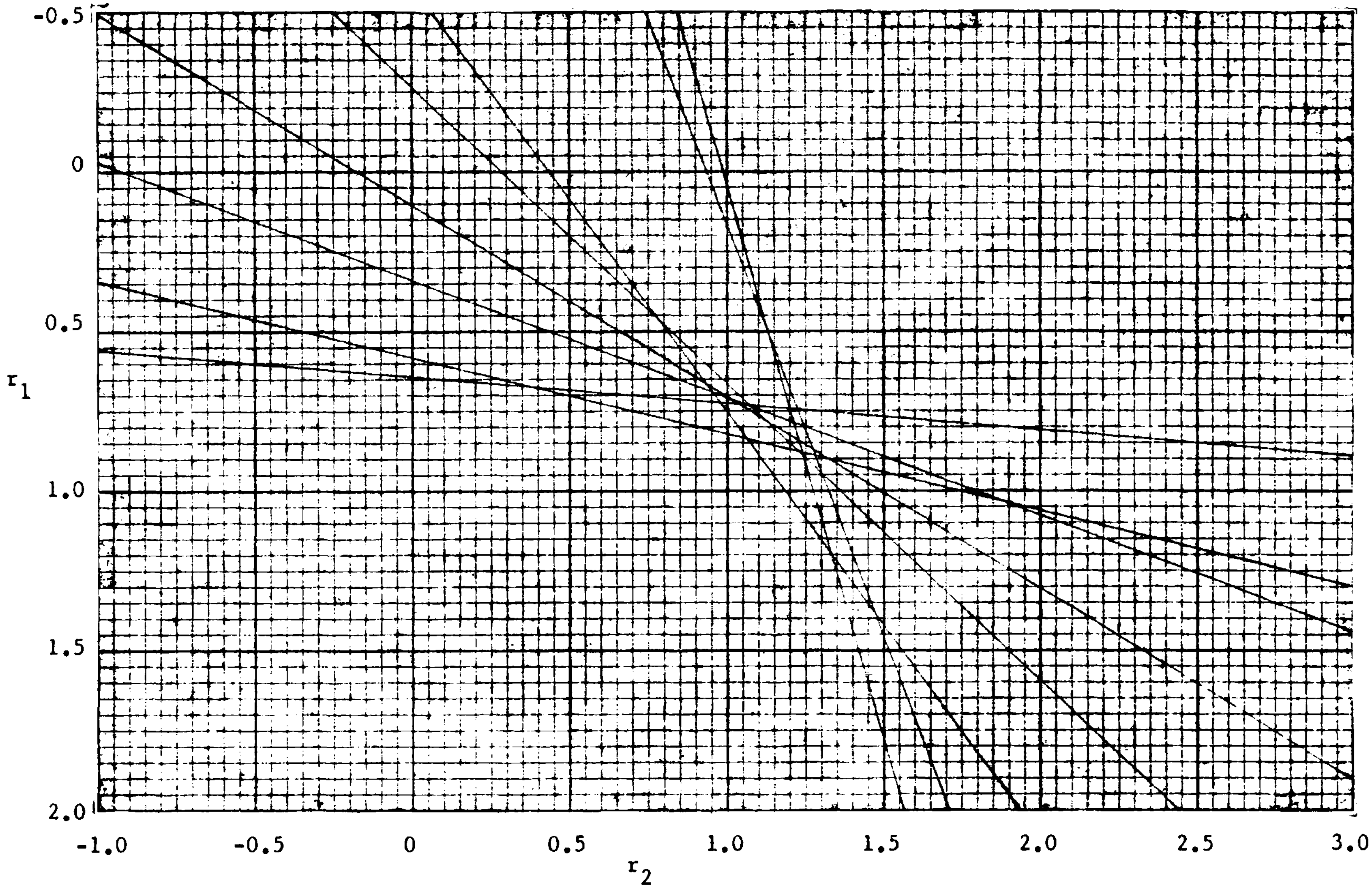


Figure 3.
Mayo-Lewis Plot for Styrene and 4-Vinylthiazole

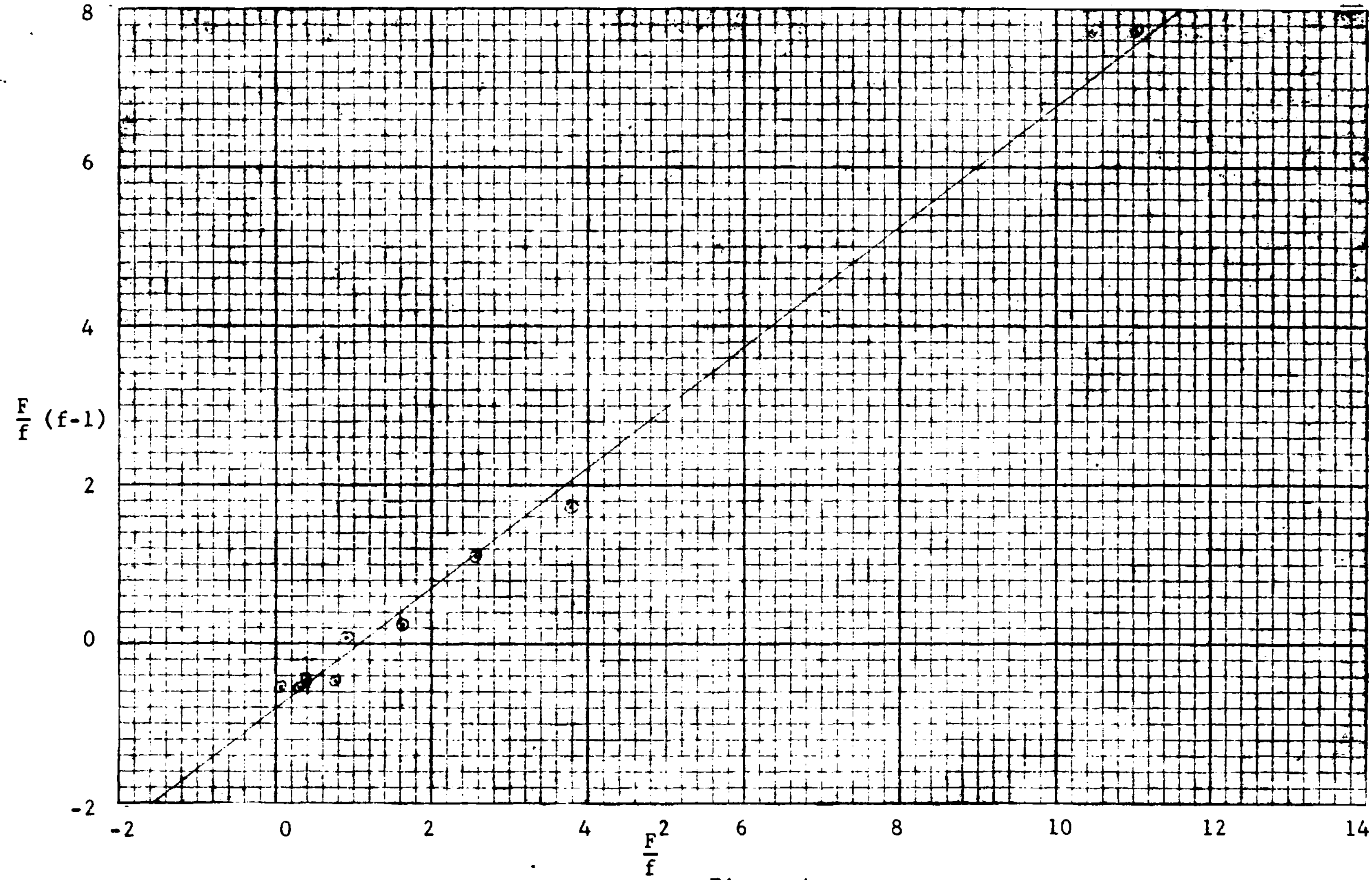


Figure 4.
Fineman-Ross Plot of Styrene and 4-Vinylthiazole

For the system, 2-vinylthiazole (comonomer$_2$) and styrene (comonomer$_1$), the reactivity ratios were determined to be $r_1 = 0.14 \pm 0.07$, and $r_2 = 3.32 \pm 0.48$, by the Mayo-Lewis method. The Fineman-Ross plot values were $r_1 = 0.18$ and $r_2 = 3.45$. The probable errors are values calculated from intersections on the Mayo-Lewis plot. No error values were estimated for the Fineman-Ross plot.

The Price-Alfrey Q,e values[55] were calculated for 2-vinylthiazole using the standard values of $Q_1 = 1.00$ and $e_1 = -0.8$ for styrene. The equations used were:

$$r_1 = (Q_1/Q_2)\exp^{-e_1(e_1-e_2)} \quad \text{and} \quad r_2 = (Q_2/Q_1)\exp^{-e_2(e_2-e_1)}$$

These equations were solved simultaneously using the r_1,r_2 values from the Mayo-Lewis plot, yielding $Q_2 = 3.56$ and $e_2 = 0.08$ for 2-vinylthiazole. In the Price Alfrey scheme, Q represents the resonance stabilization of a monomer, and e is related to the inductive effect of the monomer substituent on the double bond.[56] The Q value for 2-vinylthiazole indicates a high degree of resonance stabilization.

For the 4-vinylthiazole (comonomer$_2$) and styrene (comonomer$_1$) system, $r_1 = 0.66 \pm 0.11$ and $r_2 = 0.82 \pm 0.13$ by the Mayo-Lewis system, and $r_1 = 0.60$ and $r_2 = 0.80$ from the Fineman-Ross plot. The Price-Alfrey Q,e values for 4-vinylthiazole are $Q_2 = 2.82$ and $e_2 = -1.58$, again indicating a high degree of resonance stabilization, but indicating that the 4-thiazolyl group is more strongly electron donating than the 2-thiazolyl group. By way of comparison, the r_1,r_2 and Q_2,e_2 values for the vinylthiazoles and selected other monomers are included in Table III, where comonomer$_1$ is styrene in each case.

TABLE III

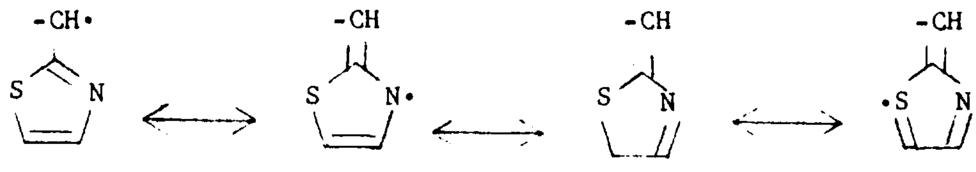
REACTIVITY RATIOS[57]

Monomer$_2$	r_1	r_2	Q_2	e_2
2-vinylthiazole	0.14	3.32	3.56	0.08
4-vinylthiazole	0.66	0.82	2.82	-1.58
2-vinylpyridine	0.55	1.14	1.30	-0.50
4-vinylpyridine	0.55	0.52	0.82	-0.20
4-vinylpyrimidine	0.17	1.20	2.18	0.45
2-vinylthiophene	0.35	3.10	2.86	-0.80
2-vinylquinoline	0.49	2.09	3.79	-0.82

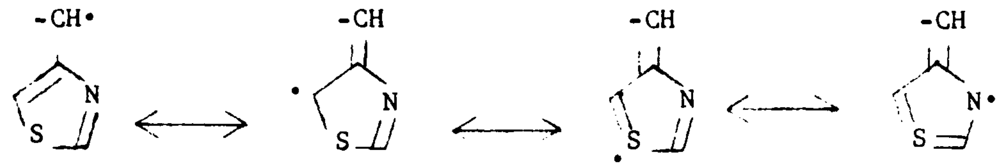
Monomer$_1$, representing r_1, is styrene in each case.

The 2-vinylthiazole is considerably more reactive than styrene toward either the styryl radical or its own radical. This behavior is quite similar to that of 2-vinylthiophene (Table III) and indicates a greater resonance stabilization of the radical in the case of both heterocycles relative to the styryl radical. In contrast, 4-vinylthiazole is considerably less reactive than 2-vinylthiazole, and in fact, the 4-vinylthiazole radical preferentially adds to styrene. The difference in reactivity between the two thiazole monomers may be rationalized in terms of the resonance structures shown below. Three structures may be drawn for 2-vinylthiazole, but only two for 4-vinylthiazole in which the d-orbitals of sulfur are not involved.

2-vinyl

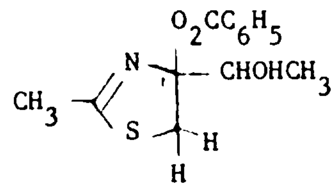


4-vinyl

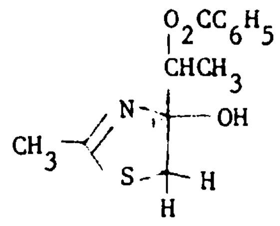


In the interest of preparing thiazole monomers with additional substituents, a number of condensations were carried out using commercially available thioamides.

Thioacetamide and 1-bromo-3-benzoxy-2-butanone condensed smoothly in refluxing benzene to give the expected 2-methyl-4-(1-benzoxyethyl)thiazole in 60% yield. In ethyl ether-benzene, however, the same reactants resulted in only 7% yield of the expected product, and 34% yield of an unexpected product, $C_{13}H_{15}NO_3S$. This compound has been assigned the structure 2-methyl-4-benzoxy-4-(1-hydroxyethyl)-2-thiazoline (XV), with an alternate structure being 2-methyl-4-hydroxy-4-(1-benzoxyethyl)-2-thiazoline (XVI). Any open chain structure is ruled out by the unusual splitting pattern in the nmr spectrum (see Experimental), which may be caused by the presence of two adjacent asymmetric carbons in either possible structure. This compound was recovered unchanged from treatments with refluxing benzene and with acetic anhydride plus acetyl chloride in refluxing benzene.

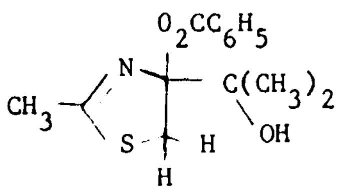


XV

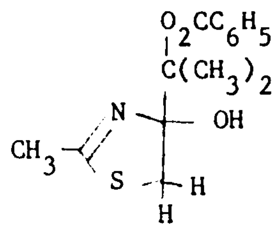


XVI

The condensation reaction between thioacetamide and 1-bromo-3-benzoxy-3-methyl-2-butanone yielded a similar product, $C_{14}H_{17}NO_3S$, assigned the structure 2-methyl-4-benzoxy-4-(2-hydroxy-2-propyl)-2-thiazoline (XVII). Again, an alternative structure, 2-methyl-4-hydroxy-4-(2-benzoxy-2-propyl)-2-thiazoline (XVIII), fits the data equally well, with open chain isomers again being excluded by the nmr splitting pattern. This condensation reaction also yielded 2-methyl-4-(2-hydroxy-2-propyl)thiazole, isolated as a pure compound, and 2-methyl-4-isopropenylthiazole, isolated in mixture with the above carbinol. The expected 2-methyl-4-(2-benzoxy-2-propyl)thiazole was not isolated. The carbinol was also obtained by treatment of $C_{14}H_{17}NO_3S$ with sodium hydroxide in refluxing methanol.

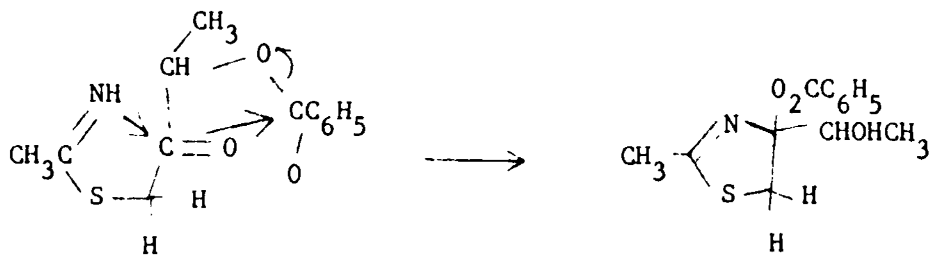


XVII



XVIII

The first thiazoline structure mentioned in each case requires a transesterification, probably intramolecular, with the benzoyl group shifting from the 1-hydroxyethyl hydroxyl group to the hydroxy group formed at the 4-position of the thiazoline ring when the imino nitrogen of the thioamide attacks the 2-keto group of the butanone, as shown below.



Models indicate that the needed groups can be positioned for such a shift, and the fact that $C_{13}H_{15}NO_3S$ can be recovered from refluxing benzene, while it is not obtained when the original reactants are mixed in refluxing benzene, indicates that it could not be the 4-hydroxythiazoline derivative, which is the normal intermediate leading to the expected thiazole product.

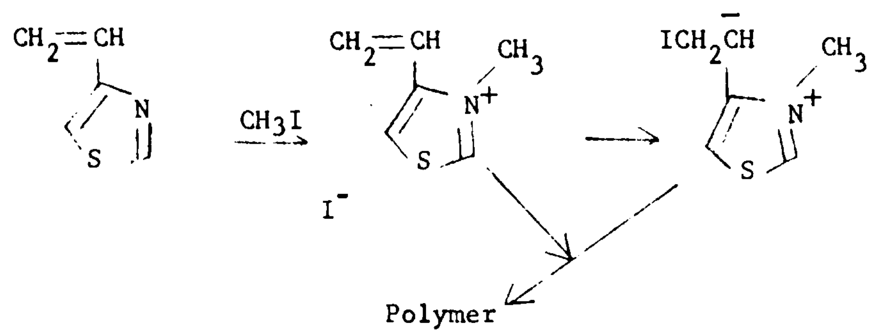
The condensation of thiourea with 1-bromo-3-benzoxy-2-butanone and 1-bromo-3-benzoxy-3-methyl-2-butanone yielded expected products. 2-Amino-4-(1-benzoxyethyl)thiazole was obtained quantitatively, and although 2-amino-4-(2-benzoxy-2-propyl)thiazole was not obtained, 2-amino-4-isopropenylthiazole was, but in low yield.

The final syntheses and polymerizations of the proposed 2-substituted thiazoles were not carried out, but it was felt that the preliminary work should be reported in this dissertation.

Syntheses and Reactivity of Thiazolium Monomers and Polymers

Three of the monomers which were synthesized here, 4-vinyl-, 4-isopropenyl-, and 4-methyl-5-vinylthiazole, have the hydrogen in the 2-position required for catalytic activity in acyloin type condensations.

Attempted quaternization of 4-vinylthiazole with methyl iodide resulted in a quaternized compound, the nmr spectrum of which revealed no vinyl hydrogens. Although this product was not extensively characterized, it is quite likely that polymerization occurs here in the same manner as has recently been demonstrated by Kabanov[58] for the treatment of 4-vinylpyridine with methyl iodide. His proposed mechanism, extended to 4-vinylthiazole, is shown.



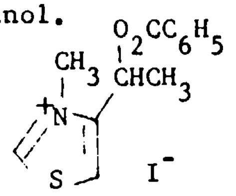
When 4-isopropenylthiazole was treated with methyl iodide, 3-methyl-4-isopropenylthiazolium iodide was obtained in good yield.

Attempts to polymerize this monomer with free radical initiators by the method of Price[59] were unsuccessful. Steric hindrance may pose a serious problem in the polymerization of this monomer, with both the isopropenyl methyl group and the 3-methyl group contributing to the crowding.

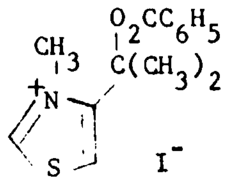
Quaternization of the poly(vinylthiazoles) and poly(isopropenylthiazoles) was more successful. The treatment of poly(4-isopropenylthiazole) with methyl iodide resulted in a copolymer of 4-isopropenylthiazole and 3-methyl-4-isopropenylthiazolium iodide in which 37.5% of the comonomer units were of the latter type, as determined by iodide analyses.

The reaction between poly(4-vinylthiazole) and methyl iodide yielded a copolymer of 4-vinylthiazole and 3-methyl-4-vinylthiazolium iodide in which 42.5% of the total thiazole rings were quaternized. The same reaction, with poly(4-methyl-5-vinylthiazole), produced a copolymer of 4-methyl-5-vinylthiazole and 3,4-dimethyl-5-vinylthiazolium iodide in which 78.0% of the rings were quarternized. Although total quarternization was not realized, the copolymers obtained provide more interesting possibilities for the testing of catalytic activity. This arises from the fact that the nonenzymatic acyloin condensations carried out by Breslow[6,7] and others,[60] required the addition of base to activate the thiazolium salt catalyst. In the vinylthiazole-vinylthiazolium salt copolymers, however, the nonquaternized thiazole rings might be expected to act as basic sites for the removal of a proton from the 2-carbon of the quaternized thiazolium rings, producing the ylid necessary for the acyloin condensation. In short, the local pH around the polymer chain would be higher than that of the macroscopic solution.

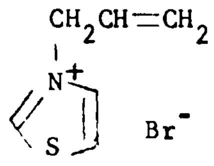
A number of simple thiazolium salts were prepared for comparison of catalytic activity with the polymeric species. These include 3-methyl-4-(1-benzoxyethyl)thiazolium iodide (XIX), 3-methyl-4-(2-benzoxy-2-propyl)thiazolium iodide (XX), 3-allylthiazolium bromide (XXI), 3-benzyl-4-methyl-thiazolium bromide[7] (XXII), 3-methyl-4-isopropenylthiazolium iodide (XXIII), and 3,4-dimethylthiazolium iodide[7] (XXIV). Commercially available thiamine was also used after recrystallization from methanol.



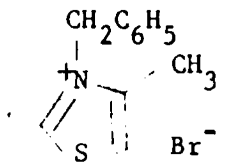
IXX



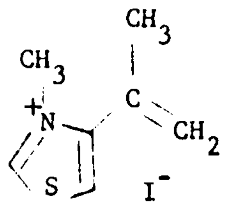
XX



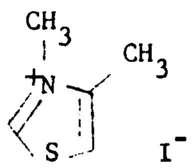
XXI



XXII



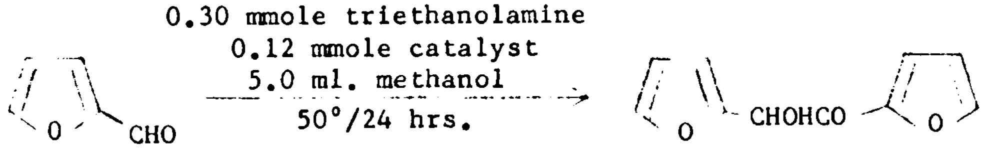
XXIII



XXIV

The system selected for the comparison of the catalytic activity of the simple and polymeric thiazolium salts was a furoin test, slightly modified from that of Breslow.[7] The conditions employed are shown below.

1.0 ml.
(1.2 g.)



Methanol was selected as solvent because the polymers were insoluble in water. Triethanolamine was selected as the base because its water solubility did not complicate the isolation of the product.

The acetoin test, employed by Mizuhara,[2] Breslow,[6,7] and Sykes[60] suffers from the disadvantage that the yields of acetoin based on catalysts are rarely above ten percent and turnover numbers could not be demonstrated. In Breslow's[7] furoin test, a yield of 263% was obtained, based on 3-benzyl-4-methylthiazolium bromide as catalyst, indicating that each active site must have reacted an average of 2.63 times during the test.

The results of the furoin test used in this work are summarized in Table IV. The yield is listed as the average of three runs, plus or minus the average deviation from the mean.

For purposes of comparison, the published data of Sykes[60] and Breslow[6,7] for the acetoin test are shown in Table V. The reaction studied was:

$$CH_3\overset{\overset{O}{\|}}{C}CO_2H + CH_3CHO \longrightarrow CH_3\overset{\overset{OH}{|}}{C}H\underset{\underset{O}{\|}}{C}CH_3 + CO_2$$

The test conditions are 1.0 ml. 0.1 molar aqueous pyruvic acid, 0.3 ml. 1.0 molar aqueous acetaldehyde, and 0.5 ml. 0.1 molar aqueous solution of catalyst, which were mixed in a Thunberg tube and brought to pH 8.4 with dilute sodium hydroxide. The tubes were evacuated and incubated at 34° for 40 hours. Acetoin was determined spectrophotometrically.

Control experiments showed that neither monomeric or polymeric thiazolium salts produce furoin in the absence of triethanolamine, and

TABLE IV

FUROIN TESTS

	Catalyst	Yield mg.	% furfural	% cat.	Turn. No.
1.	Copolymer of 4-vinylthiazole and 3-methyl-4-vinylthiazolium iodide	395 ± 38.4	32.9	1,720	17.2
2.	3-Methyl-4-(1-benzoxyethyl)thiazolium iodide	508 ± 25.4	42.3	2,310	22.1
3.	Copolymer of 4-methyl-5-vinylthiazole and 3,4-dimethyl-5-vinylthiazolium iodide	860 ± 3.7	71.7	3,660	36.6
4.	3-Allylthiazolium bromide	447 ± 51.3	37.3	1,950	19.5
5.	3-Benzyl-4-methylthiazolium bromide	297 ± 28.2	23.9	1,290	12.9
6.	3-Methyl-4-isopropenylthiazolium iodide	308 ± 6.2	25.7	1,340	13.4
7.	Thiamine chloride hydrochloride	18.2 ± 5.0	1.52	79.1	0.791

#1-7 contained 0.12 mmole catalyst (0.02 molar in thiazolium units), 0.30 mmole triethanolamine (0.05 molar), 5.0 ml. methanol, and 1.0 ml. (1.2 g., 1.04 molar) furfural. #1 and #3 respectively contained 0.14 mmole (0.023 molar) and 0.033 mmole (0.0055 molar) nonquaternized thiazole units.

8.	3-Benzyl-4-methylthiazolium bromide	60.3 ± 19.3	5.01	257	2.57

#8 was identical with #1-7 except that 0.12 mmoles of the total triethanolamine was added as its hydrochloride.

9.	Thiamine chloride hydrochloride	68.8 ± 6.4	5.73	293	2.93

#9 was identical to #7 except that 0.12 mmole sodium methoxide was added.

Table IV.--Continued

Catalyst	Yield mg.	% furfural	% cat.	Turn. No.
10. 3-Benzyl-4-methyl-thiazolium bromide	230 ± 27.8	19.2	980	9.80
#10 was identical to #5 except that 0.12 mmole sodium chloride was added.				
11. Copolymer of 4-vinyl-thiazole and 3-methyl-4-vinylthiazolium iodide	0	-	-	-
12. Copolymer of 4-methyl-5-vinylthiazole and 3,4-dimethyl-5-vinyl-thiazolium iodide	0	-	-	-
#11 and #12 contained 0.06 mmole (0.01 molar) thiazolium units, no triethanolamine, 5.0 ml. methanol, and 1.0 ml. furfural.				
13. 3,4-Dimethylthiazolium iodide	0	-	-	-
#13 contained 0.06 mmole (0.01 molar) catalyst, 0.07 mmole (0.012 molar) 4-methylthiazole, 5.0 ml. methanol, and 1.0 ml. furfural, as a monomeric model for #11.				
14. None	0	-	-	-
#14 contained 0.30 mmole triethanolamine, 5.0 ml. methanol, and 1.0 ml. furfural.				
15. 3-Benzyl-4-methyl-thiazolium bromide	0	-	-	-
#15 contained 0.12 mmole catalyst, no triethanolamine, 5.0 ml. methanol, and 1.0 ml. furfural.				

Note: The indicated pH readings for #1-9 and #11-13 were taken with a Beckman Model G pH meter. The values have only relative, rather than absolute significance, since these are methanol solutions. The values are #1-6, 7.25-7.33, #7 and #8, 6.71 and 6.81, #9, 7.44, #11, 4.21, #12, 4.11, and #13, 4.00.

TABLE V

ACETOIN TESTS

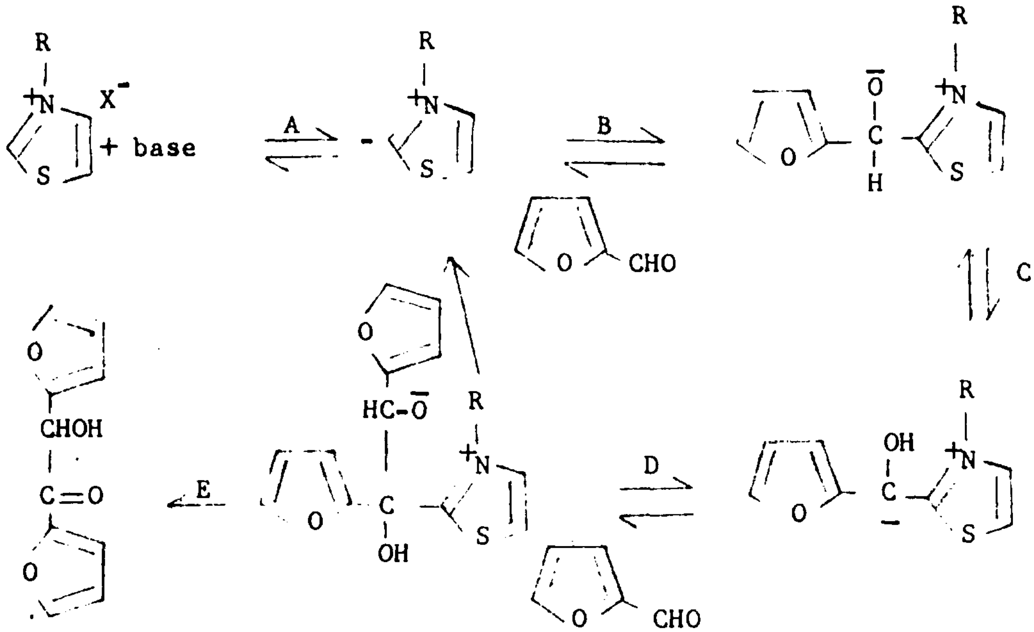
Catalyst	Micrograms acetoin (Mean)
Breslow[7]	
Thiamine chloride hydrochloride	300
Oxythiamine chloride	15
N-Methylthiamine chloride hydrochloride	200
N-Benzyl-4-methylthiazolium chloride	100
N-Benzyl-4-methylthiazolium bromide	90
N-Allyl-4-methylthiazolium bromide	50
N-Ethyl-4-methylthiazolium bromide	15
N-Propyl-4-methylthiazolium bromide	20
4-Amino-5-hydroxymethyl-2-methylpyrimidine	15
No catalyst	15
Breslow[6]	
Thiamine	375
2-(1-Hydroxyethyl)-3-benzyl-4-methylthiazolium bromide	239
3-Benzyl-4-methylthiazolium bromide	79
2-(1-Hydroxyethyl)-3,4-dimethylthiazolium bromide	34
3,4-Dimethylthiazolium iodide	17
No catalyst	15

Table V.--Continued

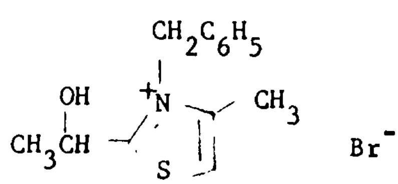
Catalyst	Acetoin formed (gammas)	% thiamine activity on molar basis
Sykes[60]		
Thiamine chloride hydrochloride	1775	-
3-Benzyl-4-methyl-thiazolium chloride	710	40
3-Benzyl-2,4-dimethyl-thiazolium bromide	0	0
3-Allyl-4-methyl-thiazolium bromide	345	19
3-Allyl-2,4-dimethyl-thiazolium bromide	0	0
3-Phenyl-4-methyl-thiazolium iodide	135	8
3-Phenyl-2,4-dimethyl-thiazolium iodide	0	0

that furoin is not produced when the catalyst is omitted from the test solution. Also, furoin was not destroyed under the test conditions, and was recovered in 86.2-95.6% yield when subjected to test conditions.

The rate determining step in the reaction sequence shown is not known. In the case of the acetoin condensation,



3-benzyl-2-(1-hydroxyethyl)-4-methylthiazolium bromide (XXV) was shown by Breslow[6] to be more reactive than 3-benzyl-4-methylthiazolium bromide.



XXV

Since it still was not as effective as thiamine chloride hydrochloride, steps C, D, and E may be important in determining the rate of product formation.

The most striking difference between the furoin test employed in this work and the acetoin test performed in aqueous solution is the lack of activity of thiamine chloride hydrochloride in the former test. In test #7, thiamine chloride hydrochloride was used without modifying the test conditions. Thus the low activity was expected since low pH conditions existed. In test #9, an equivalent amount of sodium methoxide was added to neutralize the bound molecule of hydrogen chloride, raising the pH to that of tests #1-6. This modification did not increase the furoin production beyond that produced in the presence of the other catalysts. Test #8, carried out at the same pH as test #7 shows the depressant effect of added hydrochloric acid on a simple thiazolium salt. Since the addition of sodium methoxide produced sodium chloride, test #10 was performed. Comparison of the results shown by tests #5 and #10 suggests that added electrolyte only slightly decreases furoin production in the presence of 3-benzyl-4-methylthiazolium bromide, and that it should not be responsible for the low activity of thiamine in test #9.

Possibly, steric effects play a larger role than in the case of the acetoin condensation. Steps B, C, and D would all be more sensitive to the size of the group attached to the thiazolium nitrogen when furfural is used rather than acetaldehyde. Further work on model compounds will be necessary to clarify this point.

The most effective catalyst is the copolymer of 4-methyl-5-vinylthiazole and 3,4-dimethyl-5-vinylthiazolium iodide. The higher reactivity of this copolymer points out another striking difference between the furoin test and the acetoin test. Under acetoin test conditions, simple N-alkyl thiazolium compounds have extremely low catalytic effect, presumably because the inductive effect of the alkyl group is in the wrong direction.[6] In the case of this copolymer, a type of polymeric catalysis may exist. Apparently, since no furoin is formed in the absence of triethanolamine, nonquaternized thiazole units in the copolymer are not sufficiently basic to form the ylid. Neighboring thiazole units may assist in later steps of the mechanism, such as C, and possibly E.

Degassing carried out in these furoin tests minimized oxidation of thiamine to either thiochrome or the open chain disulfide in basic solution. Yields of furoin from even the simpler thiazolium salts were increased approximately five fold through the degassing steps.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Polymer softening temperatures were recorded as the range in which the polymers became plastic and turned to a clear melt between the cover glasses of the Fisher-Johns apparatus. Nmr spectra were taken with a Varian A-60 spectrometer using tetramethylsilane as internal or external standard. Nmr spectra are presented in tau (T) units, with peak description and integration in parentheses, followed by assignment. The solvent used is also presented in parentheses preceding the T values. Infrared spectra were taken with a Perkin-Elmer Infracord and were calibrated with a polystyrene reference. Microanalyses and molecular weight determinations were performed by Micro-Tech Laboratories of Skokie, Illinois. Viscosities were determined at 30° using Cannon-Fenske viscometers.

2-Benzoxypropionitrile[43]

Approximately 600 g. cracked ice, 67.0 g. (1.52 moles) of acetaldehyde, 100 g. (1.54 moles) of potassium cyanide, and 214 g. (1.52 moles) of benzoyl chloride were combined and shaken, according to the Olin and Johnson modification[43] of the method of Francis and Davis.[61] The oily lower layer was collected by extracting the mixture 3 times with a total of 1 l. of ethyl ether. The ethereal solution was washed once with 125 ml. of 10% sodium hydroxide solution and dried over sodium sulfate. The ether was removed under aspirator vacuum and the remaining oil vacuum distilled. The product boiling at 100-104° (1.0 mm.) (lit.[43] b.p., 142° (12 mm.)) was redistilled yielding 229 g. (86.1% of clear colorless oil. The nmr spectrum (CCl_4) showed peaks at T 8.24 (doublet, 3H), assigned to the methyl group; T 4.19 (quartet, 1H), assigned to the methine proton; and T 2.23 and 1.62 (2 multiplets, 3H and 2H, respectively), assigned to the meta, para protons and the ortho protons of the phenyl ring, respectively.

2-Benzoxythiopropionamide[43]

Hydrogen sulfide gas was bubbled for 20 hrs. through a solution of 129 g. (0.737 mole) of 2-benzoxypropionitrile in 400 ml. of ethanol containing 10 ml. of triethanolamine. Removal of solvent under vacuum yielded a crystalline solid which was washed with 100 ml. cold ethanol and dried in a vacuum oven at 60° (6 mm.). The yield of product, m.p. 100-102° (lit.[43] m.p., 104°), was 140 g. (90.2%). The nmr spectrum ($CDCl_3$) showed peaks at T 8.24 (doublet, 3H), assigned to the methyl group; T 4.17 (quartet, 1H), assigned to the methine proton; and T 2.70-1.60 (mainly 2 broad multiplets, 7H), assigned to the phenyl ring protons and the protons of the thioamide group.

2-(1-Benzoxyethyl)thiazole[24]

2-Benzoxythiopropionamide (140 g., 0.670 mole), bromoacetaldehyde diethyl acetal (137 g., 0.695 mole), 400 ml. of benzene, and five drops of piperidine were heated at reflux for 28 hrs. After cooling, 500 ml. of water was added; the aqueous layer was separated, made alkaline with 10% sodium hydroxide solution, and extracted 3 times with 100 ml. portions of benzene. The benzene solutions were combined, solvent was removed, and the residual black oil was vacuum distilled, yielding 106 g. (68.0%) of product, boiling at 127-147° (0.8 mm.) (lit.[24] b.p., 137-142° (2.0 mm.)). The nmr spectrum (CCl_4) showed peaks at T 8.16 (doublet, 3H), assigned to the methyl group; T 3.53 (quartet, 1H), assigned to the methine proton; and T 2.75-1.65 (mainly 3 multiplets, 7H), assigned to the aromatic protons of the phenyl and thiazole rings.

2-Vinylthiazole[24]

2-(1-Benzoxyethyl)thiazole (40.0 g., 0.172 mole) was pyrolyzed at 440° (6.0 mm.) through a 37.5 cm. column of 4-6 mesh activated alumina in a 20 mm. inner diameter heavy-walled glass tube held in vertical position in a combustion tube furnace. The receiver, containing a small amount of hydroquinone, was cooled with a Dry Ice-acetone bath. The pyrolyzate was taken up in 100 ml. of ethyl ether, shaken with 50 ml. of 10% sodium hydroxide solution, and dried with potassium carbonate. Removal of solvent and vacuum distillation of the residual clear reddish brown oil yielded 9.80 g. (51.9%) or clear colorless liquid, boiling at 50° (10 mm.) (lit.[24] b.p., 46-47° (1.0 mm.)). An analytical sample, purified by distillation on a spinning band column, boiled at 52.5° (10 mm.), $n_D^{25.5}$ 1.5628 (lit.,[24] n_D^{30} 1.5435). The nmr spectrum (CCl_4) had peaks at T 4.7-3.8 (multiplet, 2H), assigned to the 2 beta protons of the vinyl group; T 3.3-2.8 (multiplet, 2H), assigned to the alpha proton of the vinyl group and to H_5 of the thiazole ring; and T 2.30 (doublet, 1H), assigned to H_4 of the thiazole ring.

Anal. Calcd. for C_5H_5NS: C, 54.05; H, 4.50; S, 28.83.
Found: C, 54.31; H, 4.57; S, 28.57.

2-Bromothiazole[37]

The method of Ganapathi and Venkataraman[37] was employed to prepare 2-bromothiazole, except that the product was extracted with ethyl ether rather than steam distilled. The 2-thiazole diazonium salt was prepared using 1200 ml. of 85% phosphoric acid, 300 g. (3.00 moles) of 2-aminothiazole, 600 ml. of conc. nitric acid, and a solution of 240 g. (3.48 moles) of sodium nitrite in 600 ml. of water; it was decomposed by being poured into a solution prepared from 900 g. (3.60 moles) of cupric sulfate pentahydrate, 371 g. (3.60 moles of sodium bromide, and 3.5 l. of water. The resultant mixture was made slightly basic by the cautious addition (with external cooling) of 2.2 l. of 50% sodium hydroxide solution. An aqua blue solid was removed by suction filtration and triturated several times with a total of 5 l. of ethyl ether. The aqueous solution was extracted 3 times with a total of 3.5 l. of ethyl ether. The ether layers were combined and dried over sodium sulfate. The solvent was removed in vacuo, and the residual oil vacuum distilled, yielding 291 g. (59.1%) of product boiling at 73° (15 mm.), n_D^{25} 1.5905 (lit.[39] b.p., 64-65° (15-20 mm.), N_D^{25} 1.5912). The nmr spectrum (CCl_4) showed 2 doublets, T 2.50 and 2.26, 1H each, assigned to H_5 and H_4, respectively on the thiazole ring.

2-(2-Hydroxy-2-propyl)thiazole

An ethereal solution of n-butyllithium prepared from 17.0 g. (2.43 moles) of lithium wire, 137 g. (1.00 mole) of 1-bromobutane, and 800 ml. of ethyl ether by the method of Gilman[62] was cooled to -70° with a Dry Ice-acetone bath, and a solution of 164 g. (1.00 mole) of 2-bromothiazole in 400 ml. of ethyl ether was added, the temperature being maintained below -60°. After completion of addition, the deep red solution was cooled to -70°, and a solution of 58.0 g. (1.00 mole) of acetone in 200 ml. of ethyl ether was added at a rate which again permitted the temperature to remain below -60°. The mixture was stirred at -70° for 0.5 hr.; the bath was removed and the mixture allowed to warm to -10° with stirring before being poured into 2 l. of cracked ice and water containing 200 ml. of conc. hydrochloric acid. The layers were separated when the ice had melted; the aqueous layer was made basic with 30% ammonium hydroxide solution, and extracted 10 times with a total of 2 l. of ethyl ether. The original ether layer was shaken with a portion of the basic aqueous layer, and all ether solutions were combined for drying over potassium carbonate. Removal of solvent and vacuum distillation yielded a clear colorless oil, b.p. 95-98° (10 mm.), which solidified on standing. An analytical sample, twice recrystallized from 30-60° petroleum ether, had m.p. 38-42°. The yield of 2-(2-hydroxy-2-propyl)thiazole was 100 g. (70.0%) after one recrystallization from 30-60° petroleum ether and vacuum drying at 32° (10 mm.) for 2 hrs. The nmr spectrum (CCl_4) of the carbinol showed peaks at τ 8.44 (singlet, 6H), assigned to the geminal methyl groups; τ 5.15 (broad singlet, 1H), assigned to the hydroxyl proton; τ 2.97 (doublet, 1H), assigned to H_5 on the thiazole ring; and τ 2.55 (doublet, 1H), assigned to H_4 on the thiazole ring.

Anal. Calcd. for C_6H_9NOS: C, 50.35; H, 6.30; S, 22.38.

Found: C, 50.23; H, 6.41; S, 22.27.

2-(2-Acetoxy-2-propyl)thiazole

The acetate was prepared from 100 g. (0.700 mole) of 2-(2-hydroxy-2-propyl)thiazole, 90.0 g. (0.744 mole) of N,N-dimethylaniline, 63.5 g. (0.814 mole) of acetyl chloride, and 300 ml. of ethyl ether, according to the procedure of Vogel[40] for the preparation of t-butyl acetate. The acetyl chloride was added to the solution of the other reactants at a rate permitting gentle reflux, with heat being applied by steam bath to maintain reflux for 1 hr. after completion of addition. With violent stirring, 300 ml. of water was added slowly through the addition funnel. The ether layer was separated and combined with the 500 ml. of ether solution obtained from extraction of the aqueous layer with 4 125 ml. portions of ethyl ether, the total ether solution being dried over potassium carbonate. Solvent was removed in vacuo and vacuum distillation yielded one fraction, b.p. 45-50° (0.2-0.4 mm.) of clear colorless oil, 114 g. (88.3%). The nmr spectrum (CCl_4) showed peaks at τ 8.27 (singlet, 6H), assigned to the geminal methyl groups; τ 8.13 (singlet, 3H), assigned to the acetyl methyl group; τ 2.94 (doublet, 1H), assigned to H_5 on the thiazole ring. The index of refraction, n_D^{27}, of an analytical sample was 1.4969.

Anal. Calcd. for $C_8H_{11}NO_2S$: C, 51.89; H, 5.95; S, 17.30.

Found: C, 51.88; H, 5.92; S, 17.51.

2-Isopropenylthiazole

Using the pyrolysis apparatus described above, 58.4 g. (0.316 mole) of 2-(2-acetoxy-2-propyl)thiazole was pyrolyzed under the same conditions. The same method of isolation used for 2-vinylthiazole yielded 32.4 g. (82.0%) of product, b.p. 54-60° (4-10 mm.). Redistillation on the spinning band column produced an analytical sample, b.p. 62.5° (9.5) mm.), n_D^{27} 1.5532, as a clear colorless oil which rapidly turned yellow on standing. The nmr spectrum (CCl_4) showed peaks at T 7.78 (singlet with fine splitting, 3H), assigned to the methyl group; T 4.73 and 4.18 (2 singlets with fine splitting, 1H each), assigned to the <u>beta</u> protons of the isopropenyl group; T 2.82 (doublet, 1H), assigned to H_5 on the thiazole ring; and T 2.28 (doublet, 1H), assigned to H_4 on the thiazole ring.

<u>Anal</u>. Calcd. for C_6H_7NS: C, 57.60; H, 5.60; S, 25.60.

Found: C, 57.33; H, 5.78; S, 25.33.

<u>2-(1-Hydroxyethyl)thiazole</u>[63]

A solution of <u>n</u>-butyllithium, prepared according to the method of Gilman,[62] from 85.0 g. (0.620 mole) of 1-bromobutane, 9.30 g. (1.33 moles) of lithium wire, and 300 ml. of ethyl ether, was cooled to -78° and a solution of 2-bromothiazole (82.0 g., 0.500 mole) in 80 ml. of ethyl ether was added in 1.5 hrs., the temperature being maintained below -70°. Acetaldehyde (22.0 g., 0.500 mole) was added as a solution in 50 ml. of ethyl ether at below -70° in 1 hr. The reaction mixture was allowed to warm to -10°, and was poured into 1 l. of cracked ice and water containing 100 ml. conc. hydrochloric acid. The ether layer was separated and the aqueous layer made basic with 30% ammonium hydroxide solution before being extracted 5 times with 200 ml. portions of ethyl ether. The original ether layer was shaken with the basic aqueous solution and combined with the ether extraction, the total being dried over potassium carbonate. Removal of solvent left a white solid and a red oil. The solid was collected and identified as 1,1-di-(2-thiazolyl)ethanol by its nmr spectrum ($CDCl_3$) which showed peaks at τ 7.90 (singlet, 3H), assigned to the methyl group; τ 4.90 (broad singlet, 1H), assigned to the hydroxyl proton; τ 2.67 (doublet, 2H), assigned to the 2 H_5 protons of the thiazole rings; and τ 2.24 (doublet, 2H), assigned to the 2 H_4 protons of the thiazole rings. The carbinol had m.p. 150-152.5° (lit.[41] m.p., 142°); the yield was 3.1 g. (5.9% yield based on the starting amount of 2-bromothiazole). Vacuum distillation of the red oil yielded 5.0 g. (7.7%) of 2-(1-hydroxyethyl)thiazole, b.p. 88-90° (3.5 mm.) (lit.[38] b.p., 112-115° (13-15 mm.)). The nmr spectrum (CCl_4) showed peaks at τ 8.40 (doublet, 3H), assigned to the methyl group; τ 4.82 (quartet, 1H), assigned to the methine proton; τ 3.79 (broad singlet, 1H), assigned to the hydroxyl proton; and τ 2.71 and 2.36 (2 doublets, 1H each), assigned to H_5 and H_4 on the thiazole ring, respectively.

The same reaction, run at -60° with commercially available n-butyllithium in hexane, and the other reactants in ethyl ether led to yields of 1.8% thiazole and 4.7% 2-(1-hydroxyethyl)thiazole, both identified by nmr spectra.

2-Acetoxy-2-methylpropionitrile[42]

This compound was prepared by the method of Burns et al,[42] by adding acetone cyanohydrin (85.0 g., 1.00 mole) to acetic anhydride (102 g., 1.00 mole) containing 1.5 ml. of acetyl chloride. The temperature rose to 92.5° initially, followed by heating at reflux for one hour.

The acetic acid produced was removed by distillation at atmospheric pressure and the residual oil vacuum distilled, yielding a forerun below 70° (9.0 mm.) and a fraction 71-79° (9.0 mm.) (lit.[42] b.p., 72-73° (8.0 mm.)). The latter fraction was 119 g. (93.8% yield). The nmr spectrum (CCl_4) showed peaks at τ 8.29 (singlet, 6H), assigned to the geminal methyl groups; and τ 7.94 (singlet, 3H), assigned to the methyl group of the acetate function.

The addition of hydrogen sulfide across the nitrile triple bond to produce the thioamide was attempted. Only starting materials were recovered when 2-acetoxy-2-methylpropionitrile was treated with hydrogen sulfide in ethanol solution in the presence of triethanolamine[43] at room temperature, at 55-58°, and at 60-62°.

<u>3-Benzoxy-2-butanone</u>[44]

This compound was prepared by the method of Diels and Stepan.[44] The procedure, expanded to include the purification of 3-hydroxy-2-butanone, is repeated here. To 400 ml. of ethyl ether, there was added 100 g. of an 85% aqueous solution of 3-hydroxy-2-butanone (acetoin), followed by drying over sodium sulfate. The ether was removed in vacuo and the acetoin vacuum distilled, yielding a fraction b.p. 48-65° (15-30 mm.), n_D^{25} 1.4157 (lit.[64] b.p., 144-145° (760 mm.), n_D^{15} 1.4194). The purified acetoin (75.5 g., 0.857 mole) was dissolved in 300 ml. of pyridine and the solution cooled to 0° with an ice-salt bath. Benzoyl chloride (120 g., 0.851 mole) was added at a rate permitting the temperature to remain below 10°, with stirring being continued for 0.5 hr. after completion of addition. The reaction mixture was poured into 2

l. of 5:1 water:sulfuric acid which had been cooled to 3°. The lighter oil layer was collected by extracting the mixture 4 times with a total of 1 l. of ethyl ether. The ethereal solution was shaken in order with 100 ml. of saturated sodium carbonate aqueous solution and 100 ml. of water, and was dried over sodium sulfate. Solvent removal in vacuo and vacuum distillation yielded 119 g. (72.0%) of product, b.p. 108-118° (1.5 mm.) (lit.[44] b.p., 140-141° (8 mm.)). The nmr spectrum (CCl_4) showed peaks at τ 8.77 (doublet, 3H), assigned to the C_4 methyl group; τ 8.10 (singlet, 3H), assigned to the C_1 methyl group; τ 4.94 (quartet, 1H), assigned to the methine proton; and τ 2.73 and 2.12 (2 multiplets, 3H and 2H, respectively), assigned to the meta, para protons and the ortho protons of the phenyl ring, respectively.

1-Bromo-3-benzoxy-2-butanone[45]

This compound was also prepared by Diels and Stepan;[45] their procedure, with minor variations is repeated here. Two portions of 3-benzoxy-2-butanone (37.8 g., (0.197 mole) and 45.3 g. (0.226 mole)), each dissolved in an equivalent weight of chloroform, were cooled in ice water baths. Equimolar amounts of bromine (32.0 g., (0.200 mole) and 38.4 g. (0.240 mole)), each again dissolved in an equivalent weight of chloroform, were added over 10-15 min. periods. When the bromine color had almost disappeared, aspirator vacuum was applied to remove hydrogen bromide. The two reactions were combined and solvent removed, leaving a crystalline solid which was recrystallized from methanol. The methanol solution yielded two crops of product, totalling 67.1 g. (56.3%), m.p. 70-72° (lit.[45] m.p., 72-73°). The nmr spectrum (CCl_4)

showed peaks at T 8.42 (doublet, 3H), assigned to the C_4 methyl group; T 5.95 (singlet, 2H), assigned to the C_1 methylene group; T 4.47 (quartet, 1H), assigned to the methine proton; and T 2.50 and 1.90 (2 multiplets, 3H and 2H, respectively), assigned to the meta, para protons and the ortho protons of the phenyl ring, respectively.

Higher yields were obtained by the addition of undiluted bromine to an ethyl ether solution of the benzoate. 3-Benzoxy-2-butanone (113 g., 0.589 mole) was dissolved in 133 g. of ethyl ether and the solution cooled to 0° with an external ice water bath. Bromine (104 g., 0.650 mole) was added over a 15 min. period. Hydrogen bromide and solvent were removed under aspirator vacuum, leaving the solid product, 111 g. (70.0%), after washing with ether and vacuum drying. The product was identical in every respect to that prepared in chloroform solution.

Thioformamide[46]

The procedure of Erlenmeyer and Menzi[46] was used with the exception that the supernatant ethyl ether layer was exchanged periodically with fresh anhydrous ethyl ether. Practical grade formamide (200 g., 4.44 moles) was cooled on an ice water bath, and 100 g. (0.450 mole) of phosphorus pentasulfide was added over a 2 hr. period with stirring. Stirring was continued throughout the reaction, with 200 ml. of ethyl ether being added 1 hr. after completion of addition of phosphorus pentasulfide. The ether layer was removed by pipette and replaced with fresh ether at 20, 32.5, and 43 hrs., the last ether layer being decanted at 58 hrs. The flask containing the ether solution was stored in a refrigerator between ether exchanges. The ether solution was concentrated under reduced pressure to 200 ml. volume. Two hundred ml. of water was added, and the mixture suction filtered (to remove a sulfur precipitate) onto enough ammonium sulfate to saturate the aqueous phase. The aqueous solution was extracted 7 times with a total of 1 l. of ethyl ether and the ether solution dried over sodium sulfate in a refrigerator. After removing the sodium sulfate by filtration, the ether solution was placed in an ice water bath and treated with 38 g. of phosphorus pentoxide. The ether solution was decanted from the P_2O_5 residue, replaced in the ice water bath, and retreated with 40 g. of P_2O_5, followed by filtration and concentration under reduced pressure to 100 ml. volume. The concentrated solution was placed in a freezer as was 400 ml. of 30-60° petroleum ether for 2 hrs. The thioformamide was precipitated by pouring the ethyl ether solution into the petroleum ether, collected by suction filtration, dried under pump vacuum in a dessicator, weighed, and redissolved in 400 ml. of ethyl ether for storage in a refrigerator, all as rapidly as possible. The main crop was 38.5 g.; a second crop of 9.4 g. was collected from the mother liquor on storage in a freezer and was added to the main ether solution. The total yield of 47.9 g. represents 34.9% of theory based on P_2S_5, and is an improvement over the 24.5% attained by Erlenmeyer and Menzi.[46] For the synthesis of 4-methylthiazole (see page 74 of this section), the original concentrated ethyl ether solution of thioformamide obtained from extraction of the formamide-phosphorus pentasulfide mixture mixture can be used as a source of thioformamide without the somewhat tedious isolation of the solid thioformamide.

4-(1-Benzoxyethyl)thiazole

A cold solution of thioformamide (7.5 g., 0.12 mole) in 175 ml. of ethyl ether was combined with a solution of 1-bromo-3-benzoxy-2-butanone (20 g., 0.074 mole) in 125 ml. of ethyl ether and 50 ml. of benzene and the mixture heated at reflux for 6 hrs. The organic layer was decanted and 200 ml. of water added to the solid residue, which dissolved as the aqueous mixture was made basic with 10% sodium hydroxide solution. The oil which separated was collected by extraction 3 times with 100 ml. portions of ethyl ether. The original organic layer was shaken with the basic aqueous layer and combined with the ether extraction, followed by drying over sodium sulfate. Removal of solvent and vacuum distillation yielded 14.2 g. (82.6%) of product, b.p. 130-132° (0.4 mm.), n_D^{27} 1.5677, a clear orange oil. The nmr spectrum (CCl_4) showed peaks at T 8.25 (doublet, 3H), assigned to the methyl group; T 3.59 (quartet, 1H), assigned to the methine proton; T 2.70-240 (multiplet, 4H), assigned to the meta, para protons of the phenyl ring and H_5 on the thiazole ring; T 2.00-1.70 (multiplet, 2H), assigned to the ortho protons of the phenyl ring; and T 1.19 (doublet, 1H), assigned to H_2 on the thiazole ring.

Anal. Calcd. for $C_{12}H_{11}NO_2S$: C, 61.80; H, 4.72; S, 13.73.

Found: C, 61.95; H, 4.85; S, 13.55.

4-Vinylthiazole

Using the pyrolysis apparatus described above (see page 44, this section), 75.1 g. (0.322 mole) of 4-(1-benzoxyethyl)thiazole was pyrolyzed under the same conditions. The method of isolation used before yielded 28.3 g. (79.7%) of product, b.p. 58-59° (10 mm.), stored over hydroquinone in a refrigerator. Redistillation through a spinning band column yielded pure product, b.p. 58.5° (10 mm.), $n_D^{26.5}$ 1.5729. The nmr spectrum (CCl_4) showed peaks at T 4.71, 4.53, 3.99, and 3.70 (4 doublets, 2H), assigned to the <u>beta</u> protons of the vinyl group; T 3.40-2.93 (4 singlets, 1H), assigned to the <u>alpha</u> proton of the vinyl group; T 2.81 (doublet, 1H), assigned to H_5 on the thiazole ring; and T 1.16 (doublet, 1H), assigned to H_2 on the thiazole ring.

<u>Anal</u>. Calcd. for C_5H_5NS: C, 54.05; H, 4.50; S, 28.83.

Found: C, 53.70; H, 4.24; S, 28.78.

<u>3-Benzoxy-3-methyl-2-butanone</u>[65]

3-Hydroxy-3-methyl-2-butanone (100 g., 0.980 mole) was treated with 138 g. (0.979 mole) of benzoyl chloride in 400 ml. of pyridine according to the procedure used above for 3-benzoxy-2-butanone.[44] The identical isolation procedure yielded 149 g. (73.8%) of product, b.p. 88-90° (0.3 mm.) (lit.[65] b.p., 140-142° (10 mm.)). The nmr spectrum (CCl_4) showed peaks at T 8.42 (singlet, 6H), assigned to the geminal methyl groups; T 7.90 (singlet, 3H), assigned to the C_1 methyl group; and T 2.57 and 1.98 (2 multiplets, 3H and 2H, respectively), assigned to the <u>meta</u>, <u>para</u> protons and the <u>ortho</u> protons of the phenyl ring, respectively.

<u>1-Bromo-3-benzoxy-3-methyl-2-butanone</u>

3-Benzoxy-3-methyl-2-butanone (29.1 g., 0.141 mole) was brominated by the same method and under the same conditions employed above for 3-benzoxy-2-butanone.[45] Removal of solvent and hydrogen bromide left a clear tan lachrymatory oil. This was vacuum distilled twice, at 124-148° (0.5 mm.) and at 114-117° (0.2 mm.), yielding 20.0 g. (50.0%) of clear colorless viscous oil, which turned to clear tan on standing. The nmr spectrum (CCl_4) showed peaks at T 8.33 (singlet, 6H), assigned to the geminal methyl groups; T 5.90 (singlet, 2H), assigned to the C_1 methylene group, and T 2.55 and 2.00 (2 multiplets, 3H and 2H, respectively), assigned to the meta, para protons and the ortho protons of the phenyl ring, respectively. There were minor impurity peaks at T 7.90 and 8.45 due to starting material, and T 8.20 (unknown). This compound was not isolated in an analytically pure state, but was generally used as prepared after one vacuum distillation.

The same compound was also prepared by the addition of undiluted bromine to an ethyl ether solution of the benzoate. 3-Benzoxy-3-methyl-2-butanone (190 g., 0.922 mole) was dissolved in 140 g. of ethyl ether and the solution cooled to 0° with an external ice water bath. Bromine (176 g., 1.10 moles) was added over a 20 min. period, with hydrogen bromide and solvent being removed by aspirator vacuum 10 min. after completion of addition. The residual oil was vacuum distilled, yielding 244 g. (85.8%) of product, b.p. 114-125° (0.1-0.2 mm.). The product was identical in every respect to that prepared in chloroform solution.

4-Isopropenylthiazole

A solution of 111 g. (0.389 mole) of 1-bromo-3-benzoxy-3-methyl-2-butanone in 150 ml. of ethyl ether was combined with a solution of 28.9 g. (0.474 mole) of thioformamide in 425 ml. of ethyl ether. The mixture was heated at reflux without stirring for 13 hrs., filtered, and the solid residue combined with 250 ml. of water. The aqueous mixture was made basic with 10% sodium hydroxide solution and extracted 4 times with a total of 500 ml. of ethyl ether. The original ether layer was shaken with the basic aqueous layer, combined with the extract, and dried over sodium sulfate. Removal of solvent and vacuum distillation yielded 18.7 g. (38.4%) of clear colorless oil, b.p. 66-80° (6.0 mm.). This material was redistilled through a spinning band column, yielding pure product, b.p. 68.5° (6.3 mm.), $n_D^{26.5}$ 1.5612. The nmr spectrum (CCl_4) showed peaks at T 7.94 (singlet, 3H), assigned to the methyl group; T 4.88 and 4.07 (2 singlets with fine splitting, 1H each), assigned to the <u>beta</u> protons of the isopropenyl group; T 2.97 (doublet, 1H), assigned to H_5 on the thiazole ring; and T 1.38 (doublet, 1H), assigned to H_2 on the thiazole ring.

<u>Anal.</u> Calcd. for C_6H_7NS: C, 57.60; H, 5.60; S, 25.60.

Found: C, 57.37; H, 5.70; S, 25.48.

A higher boiling fraction, b.p. 80-81° (6.3 mm.), was isolated in good purity from the spinning band distillation of 4-isopropenylthiazole. This compound, a clear colorless oil, n_D^{26} 1.5783, showed nmr peaks (CCl_4) at T 8.20 (singlet, 6H), assigned to the geminal methyl groups; T 7.40 (broad singlet, 1H), assigned to the hydroxyl proton; T 2.82 (doublet, 1H), assigned to H_5 on the thiazole ring; and T 1.22 (doublet, 1H), assigned to H_2 on the thiazole ring. It is presumably the carbinol, 4-(2-hydroxy-2-propyl)thiazole, arising from the hydrolysis of 4-(2-benzoxy-2-propyl)thiazole, the nonisolated intermediate in the synthesis of 4-isopropenylthiazole.

The reduction of 4-isopropenylthiazole to 4-isopropylthiazole in the presence of platinum oxide in acetic acid solution in a Parr low pressure hydrogenation apparatus was unsuccessful. There was no hydrogen uptake over a 72 hr. period.

4-(2-Benzoxy-2-propyl)thiazole

Thioformamide (40 g., 0.66 mole) was condensed with 1-bromo-3-benzoxy-3-methyl-2-butanone (160 g., 0.56 mole) in 900 ml. of refluxing ethyl ether for 6 hrs. with stirring. After filtration, the solid residue was dissolved in 400 ml. distilled water. Basification of the aqueous solution with 10% sodium hydroxide solution caused the precipitation of a white crystalline solid, crude m.p. 66-72°. The aqueous solution was extracted 3 times with 125 ml. portions of ethyl ether which was combined with the original reaction solvent after the latter had been shaken with the basic aqueous solution. The combined ether layers were dried over sodium sulfate. Solvent removal and vacuum distillation yielded 14.6 g. (20.9%) of 4-isopropenylthiazole, b.p. 53° (3.5 mm.). The crystalline solid was recrystallized from ethyl ether yielding 49.5 g. (35.9%) of 4-(2-benzoxy-2-propyl)thiazole. The nmr spectrum (CCl_4) showed peaks at T 8.04 (singlet, 6H), assigned to the geminal methyl groups; T 2.77 (doublet, 1H), assigned to H_5 on the thiazole ring; T 2.63 and 2.00 (2 multiplets, 3H and 2H, respectively), assigned to the *meta*, *para* protons and the *ortho* protons on the phenyl ring, respectively; and T 1.40 (doublet, 1H), assigned to H_2 on the thiazole ring.

Anal. Calcd. for $C_{13}H_{13}NO_2S$: C, 63.16; H, 5.26; S, 12.96.

Found: C, 63.40; H, 5.37; S, 12.95.

4-Methyl-5-(2-hydroxyethyl)thiazole[47]

Thiamine chloride hydrochloride was cleaved by sodium sulfite according to the method of Williams.[47] The vitamin (126 g., 0.374 mole) was added to a solution of 240 g. of sodium sulfite in 1600 ml. of distilled water. The pH was decreased to approximately 5.0 (pHydrion paper used for pH determination) by bubbling sulfur dioxide into the solution, and the solution was allowed to stand overnight with stirring. The white precipitate was filtered and the aqueous solution made basic (with cooling) with 50% sodium hydroxide solution. The basic solution was saturated with sodium chloride and extracted 5 times with 700 ml. portions of chloroform. Solvent removal and vacuum distillation yielded 43.7 g. (82.0%) of 4-methyl-5-(2-hydroxyethyl)thiazole, b.p. 88° (0.3 mm.), n_D^{26} 1.5475 (lit.[66] b.p., 93-95° (2.0 mm.), n_D^{20} 1.5475[67]). The nmr spectrum showed peaks at T 7.54 (singlet, 3H), assigned to the methyl group; T 6.95 (triplet, 2H), assigned to the methylene group on C_5 of the thiazole ring; T 6.13 (triplet, 2H), assigned to the methylene group next to the hydroxyl group; T 4.50 (broad singlet, 1H), assigned to the hydroxyl group; T 4.50 (broad singlet, 1H), assigned to the hydroxyl proton; and T 1.35 (singlet, 1H), assigned to H_2 on the thiazole ring.

4-Methyl-5-(2-acetoxyethyl)thiazole[68]

4-Methyl-5-(2-hydroxyethyl)thiazole (25.0 g., 0.175 mole) was combined with 23.0 g. (0.190 mole) of N,N-dimethylaniline in 80 ml. of ethyl ether. Acetyl chloride (14.0 g., 0.179 mole) was added at a rate permitting gentle reflux, according to the method of Vogel.[40] Heat was applied with a steam bath to maintain reflux for 1 hr. after completion of addition and the mixture was allowed to stand overnight. The ether layer was separated and combined with two 160 ml. portions of ethyl ether used to extract the aqueous layer, and the combined ether solution was dried over potassium carbonate. Solvent removal and vacuum distillation yielded 20.0 g. (62.5%) of 4-methyl-5-(2-acetoxyethyl)thiazole, b.p. 85-89° (0.5 mm.) (lit.[68] b.p., 117-118° (6.0 mm.)). The nmr spectrum (CCl_4) showed peaks at T 8.01 (singlet, 3H), assigned to acetate methyl group; T 7.63 (singlet, 3H), assigned to 4-methyl group; T 6.95 (triplet, 2H), assigned to the methylene group on C_5 of the thiazole ring; T 5.83 (triplet, 2H), assigned to the methylene group next to the acetate group; and T 1.51 (singlet, 1H); assigned to H_2 on the thiazole ring.

<u>4-Methyl-5-vinylthiazole</u>[28-31]

4-Methyl-5-(2-acetoxyethyl)thiazole (20.0 g., 0.108 mole) was pyrolyzed under previously described conditions and worked up as before to yield 8.0 g. of product (59%), b.p. 45-47° (4.0 mm.), n_D^{26} 1.5644 (lit.[28] b.p., 76-78° (21 mm.)). The nmr spectrum (CCl_4) showed peaks at T 7.59 (singlet, 3H), assigned to the methyl group; T 4.71 (asymmetric triplet, 2H), assigned to the <u>beta</u> protons of the vinyl group; T 3.18 (asymmetric quartet, 1H), assigned to the <u>alpha</u> proton of the vinyl group; and T 1.43 (singlet, 1H), assigned to H_2 on the thiazole ring.

Polymerizations of Vinyl and Isopropenylthiazoles

The monomers were purified prior to use by distillation through a spinning band column. The purified monomers each showed a single peak on the vapor phase chromatograph (2 m. column of 20% QF-1 on 60-80 firebrick, at 125°). Polymerizations were run in bulk in 15 ml., 1-necked flasks, fitted with micro-magnetic stirrers and stopcock adapters. The polymerization equipment was dried in a 110° oven, and allowed to cool in a glove box under nitrogen. Monomer samples were degassed through 3 freeze-thaw cycles, prior to addition of initiators in the ionic polymerizations, and after the addition of initiator in the free radical polymerizations. All additions and transfers were made under a nitrogen atmosphere. The polymers were precipitated by pouring into 66-75° ligroine and were reprecipitated from benzene or chloroform solutions into ligroine, followed by vacuum drying at 60°. Insoluble products were separated and dried under the same conditions. Inherent viscosities were taken on 0.5% solutions in benzene or dimethyl sulfoxide at 30°. A summary of the polymerizations is presented in Table I. Molecular weights were determined for polymers #1, #3, and #4 from Table I. These were 2198, 2870, and 2019, respectively. The analytical data are presented for those polymers prepared, using azobisisobutyronitrile as a free radical initiator.

Anal. Calcd. for $(C_5H_5NS)_n$: C, 54.05; H, 4.50; S, 28.83.

Found for poly(2-vinylthiazole):

C, 54.08; H, 4.82; S, 28.36.

Found for poly(4-vinylthiazole):

C, 54.07; H, 4.84; S, 28.36.

Calcd. for $(C_6H_7NS)_n$: C, 57.60; H, 5.60; S, 25.60.

Found for poly(2-isopropenylthiazole):

C, 57.14; H, 5.87; S, 23.52.

Found for poly(4-isopropenylthiazole):

C, 57.42; H, 6.05; S, 25.40.

Copolymerizations of 2-Vinyl- and 4-Vinylthiazole with Styrene

The thiazole monomers were purified as above. Commercial styrene was stirred with 10% aqueous potassium hydroxide, washed with water until the wash liquid was neutral, dried over sodium sulfate, and vacuum distilled prior to use from calcium hydride at 34° (6.0 mm.). In general, a combined total of 20 mmoles of comonomers was used for each copolymerization. The copolymerizations were carried out in 15 ml. flasks, cleaned and fitted as above, with all weighings, transfers, and additions being made under a nitrogen atmosphere. Azobisisobutyronitrile (10 mg. per copolymerization) was used as the initiator at a copolymerization temperature of 80° (oil bath). Copolymers were precipitated at low conversions by pouring into 66-75° ligroine and were purified for sulfur analyses by lyophilization from benzene. The copolymerization data are presented in Table II.

2-Methyl-4-(1-benzoxyethyl)thiazole

1-Bromo-3-benzoxy-2-butanone (97.4 g., 0.359 mole) was condensed with thioacetamide (30.0 g., 0.400 mole) in 400 ml. of benzene, the mixture being heated under reflux for 5 hrs. The reaction mixture was cooled with an ice water bath and 250 ml. of water was added. The phases were separated and the aqueous phase made basic with 10% sodium hydroxide solution and extracted 3 times with 100 ml. portions of benzene. The original organic layer was shaken with the basic aqueous layer and combined with the benzene extract, followed by drying over sodium sulfate. Benzene was removed under reduced pressure on an 80° water bath and the residual oil vacuum distilled, yielding a forerun below 107° (0.7 mm.) and a fraction, mainly at 137° (0.7 mm.) of orange oil. Redistillation of the latter fraction at 114° (0.1 mm.) yielded analytically pure product, 57.6 g. (64.9%), $n_D^{25.5}$ 1.5613. The nmr spectrum (CCl_4) showed peaks at T 8.30 (doublet, 3H), assigned to the methyl group of the benzoxyethyl side chain; T 7.35 (singlet, 3H), assigned to the 2-methyl group; T 3.80 (quartet, 1H), assigned to the methine proton; T 2.92 (singlet, 1H), assigned to H_5 on the thiazole ring; and T 2.60 and 1.93 (2 multiplets, 3H and 2H, respectively), assigned to the _meta_, _para_ protons and the _ortho_ protons of the phenyl ring, respectively.

Anal. Calcd. for $C_{13}H_{13}NO_2S$: C, 63.16; H, 5.26; S, 12.96.
Found: C, 63.20; H, 5.10; S, 13.20.

2-Methyl-4-benzoxy-4-(1-hydroxyethyl)-2-thiazoline

1-Bromo-3-benzoxy-2-butanone (75.5 g., 0.279 mole) and thioacetamide (21.0 g., 0.280 mole) were condensed in 375 ml. of ethyl ether and 125 ml. of benzene, the mixture being heated at reflux for 4 hrs. The method of isolation of product used above, i.e., addition of water, separation and basification, followed by ether extraction, of the aqueous phase, yielded a crystalline solid from the ether solution, 25.1 g., m.p. 114-115°, after recrystallization from ethyl ether. Removal of solvent after separation of the solid product, followed by vacuum distillation of the residual oil yielded 5.0 g. of 2-methyl-4-(1-benzoxyethyl)thiazole, identified by nmr. Removal of solvents from the original organic layer led to recovery of 7.0 g. of 1-bromo-3-benzoxy-2-butanone, identified by mixed m.p. The yield of the 114-115° melting product was 34.1%, that of 2-methyl-4-(1-benzoxyethyl)thiazole was 7.3%, and the recovered bromide ester amounted to 9.3%. The 114-115° melting solid has been assigned the structure of 2-methyl-4-benzoxy-4-(1-hydroxyethyl)-2-thiazoline, based on chemical evidence, nmr spectra, and elemental analyses. The nmr spectrum ($CDCl_3$) showed peaks at T 8.65 (triplet, 3H), assigned to the methyl group of the hydroxyethyl side chain; T 7.79 (doublet, 3H), assigned to the 2-methyl group; T 6.53 (AB quartet, 2H), assigned to the C_5 methylene group of the thiazoline ring; T 4.79 (quartet, 1H), assigned to the methine proton; T 4.00 (broad singlet, 1H), assigned to the hydroxyl proton; and T 2.60 and 1.93 (2 multiplets, 3H and 2H, respectively), assigned to the _meta_, _para_ protons and the _ortho_ protons of the phenyl ring, respectively.

Anal. Calcd. for $C_{13}H_{15}NO_3S$: C, 58.87; H, 5.66; S, 12.08.
Found: C, 58.97; H, 5.75; S, 11.97.

The compound $C_{13}H_{15}NO_3S$ (7.0 g.) was treated with 3 ml. of acetic anhydride and 2 ml. of acetyl chloride in 25 ml. of benzene at reflux for 20 min. Hydrolysis, basification, and ether extraction, followed by concentration of the ether solution yielded 2.0 g. of unchanged starting material. In refluxing benzene for 42 hrs., the same starting material (18.5 g.) was recovered in 37.9% yield (7.0 g.).

2-Amino-4-(1-benzoxyethyl)thiazole

1-Bromo-3-benzoxy-2-butanone (14.0 g., 0.0517 mole) and thiourea (5.3 g., 0.070 mole) were condensed in 125 ml. of benzene heated under reflux for 5 hrs., during which time 0.9 ml. of water was collected in a Dean-Stark trap. The mixture was cooled on an ice water bath; the benzene layer was separated and the residual solid was dissolved in 200 ml. of water. The resultant aqueous solution was made basic with 10% sodium hydroxide solution, causing the precipitation of a white solid which was collected by suction filtration and washed with water. The crude yield after vacuum drying was quantitative. An analytical sample, recrystallized 3 times from 100% ethanol had m.p. 164.5-166.0°. The nmr spectrum (D_6-dimethyl sulfoxide) showed peaks at T 8.37 (doublet, 3H), assigned to the methyl group; T 6.37 (singlet, 2H), assigned to the amino group; T 3.96 (quartet, 1H), assigned to the methine proton; T 3.34 (singlet, 1H), assigned to H_5 on the thiazole ring; and T 2.33 and 1.88 (2 multiplets, 3H and 2H, respectively), assigned to the meta, para protons and the ortho protons of the phenyl ring, respectively.

Anal. Calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.06; H, 4.84; S, 12.90.

Found: C, 57.96; H, 4.97; S, 12.81.

2-Amino-4-isopropenylthiazole

A mixture of 1-bromo-3-benzoxy-3-methyl-2-butanone (84.5 g., 0.297 mole) and thiourea (25.0 g., 0.329 mole) in 500 ml. of benzene was heated at reflux for 5.5 hrs., after which time a large yellow mass formed, preventing further stirring. The organic layer was removed by filtration and 200 ml. of water was added to the solid residue. An insoluble yellow gum was separated from the aqueous phase and set aside. The aqueous phase was made basic with 10% sodium hydroxide solution and extracted 3 times with 50 ml. portions of benzene. Drying of the benzene extract over sodium sulfate, followed by solvent removal yielded 10 g. of gummy brown solid. This was subjected to vacuum sublimation at 25° (0.05 mm.), yielding 1.5 g. (3.6%) of 2-amino-4-isopropenylthiazole, m.p. 78-80° (capillary). Removal of solvent from the original organic layer led to the recovery of small amounts of starting materials. The nmr spectrum ($CDCl_3$) of the 2-amino-4-isopropenylthiazole showed peaks at T 7.97 (singlet with fine splitting, 3H), assigned to the methyl group; T 4.90 and 4.30 (2 singlets with fine splitting, 1H each), assigned to the vinylic protons; T 4.12 (broad singlet, 2H), assigned to the amino group; and T 3.63 (singlet, 1H), assigned to H_5 on the thiazole ring.

Anal. Calcd. for $C_6H_8N_2S$: C, 51.43; H, 5.71; S, 22.86.

Found: C, 51.70; H, 5.54; S, 22.98.

The gummy yellow solid was extracted with ethyl acetate, yielding a hard tan powder which was insoluble in water and the common organic solvents, but soluble in dilute hydrochloric acid. This substance was not characterized further.

2-Methyl-4-benzoxy-4-(2-hydroxy-2-propyl)-2-thiazoline and 2-Methyl-4-(2-hydroxy-2-propyl)thiazole

1-Bromo-3-benzoxy-3-methyl-2-butanone (100 g., 0.351 mole) was condensed with thioacetamide (26.3 g., 0.346 mole) in 600 ml. of benzene, heated at reflux for 16 hrs. The mixture was allowed to cool and a tan solid was collected by filtration. The solid was dissolved in

2 l. of water and the aqueous solution made basic with 10% sodium hydroxide solution. A tan solid separated on top of the basic solution and was collected by extracting 5 times with 300 ml. portions of ethyl ether. The ether solution was dried over sodium sulfate and the solvent removed, yielding 34.8 g. of tan solid and 10 ml. of black oil. Another 10 ml. of oil was obtained from the original benzene layer after shaking with 10% sodium hydroxide solution and solvent removal. The combined oils were vacuum distilled, yielding 10 ml. of clear yellow oil, b.p. 42-48° (0.25 mm.), and a crystalline solid which was scraped from the column and recrystallized from ethyl ether. The solid, m.p. 56.0-56.5°, was identified as 2-methyl-4-(2-hydroxy-2-propyl)thiazole. The nmr spectrum ($CDCl_3$) showed peaks at T 8.49 (singlet, 6H), assigned to the geminal methyl groups; T 7.34 (singlet, 3H), assigned to the 2-methyl group; T 6.45 (singlet, 1H), assigned to the hydroxyl proton; and T 3.10 (singlet, 1H), assigned to H_5 on the thiazole ring.

Anal. Calcd. for $C_7H_{11}NOS$: C, 53.50; H, 7.01; S, 20.38.

Found: C, 53.57; H, 7.31; S, 20.29.

The nmr spectrum of the 42-48° (0.25 mm.) oil showed it to be a mixture of 1 part 2-methyl-4-(2-hydroxy-2-propyl)thiazole and 3 parts 2-methyl-4-isopropenylthiazole. In addition to those peaks listed above for 2-methyl-4-(2-hydroxy-2-propyl)thiazole, the nmr spectrum (CCl_4) of the oil showed peaks at T 7.95 (singlet with fine splitting, 3H), assigned to the methyl group of the 4-isopropenyl group; T 7.42 (singlet, 3H), assigned to the 2-methyl group; T 4.89 and 4.05 (2 singlets with fine splitting, 1H each), assigned to the vinylic protons of the

4-isopropenyl group; and T 3.12 (singlet, 1H), assigned to H_5 on the thiazole ring. The olefin was not isolated in a pure state.

The tan solid (34.8 g., 36.1% yield) was recrystallized from 150 ml. of ethyl ether. The recrystallized product had m.p. 114-115°. The nmr spectrum ($CDCl_3$) showed peaks at T 8.23 (doublet, 6H), assigned to the geminal methyl groups; T 7.69 (singlet, 3H), assigned to the 2-methyl group; T 6.40 (AB quartet, 2H), assigned to the C_5 methylene group of the thiazoline ring; T 5.58 (broad singlet, 1H), assigned to the hydroxyl proton; and T 2.55 and 2.05 (2 multiplets, 3H and 2H, respectively), assigned to the <u>meta</u>, <u>para</u> protons and the <u>ortho</u> protons of the phenyl ring, respectively. This nmr and the elemental analyses are consistent with the proposed structure of 2-methyl-4-benzoxy-4-(2-hydroxy-2-propyl)-2- thiazoline.

<u>Anal</u>. Calcd. for $C_{14}H_{17}NO_3S$: C, 60.21; H, 6.09; S, 11.47.

Found: C, 60.25; H, 6.14; S, 11.74.

The compound $C_{14}H_{17}NO_3S$ (6.0 g., 0.022 mole) was treated with sodium hydroxide pellets (1.0 g., 0.025 mole) for 3 hrs. in 50 ml. of absolute methanol at reflux. The reaction mixture was poured into 200 ml. of distilled water, and the aqueous solution was extracted 4 times with 50 ml. portions of ethyl ether. The ether solution was dried over sodium sulfate and the solvent removed, leaving 5.0 ml. of pale orange oil. The oil was extracted with carbon tetrachloride, which was allowed to evaporate from the extraction solution, leaving a tan solid which yielded 1.33 g. (39.3%) of 2-methyl-4-(2-hydroxy-2-propyl)thiazole, identical in melting point and nmr spectrum with that obtained above from the condensation reaction.

Furoin Test

All thiazolium salts were recrystallized and vacuum dried just prior to use with the exception of the copolymers which were washed with ether and vacuum dried. Triethanolamine was vacuum distilled at 135° (0.05 mm.) and was used as a 0.2 molar solution in absolute methanol. Furfural was vacuum distilled prior to use at 54° (6.0 mm.) and had n_D^{23} 1.5247 (lit.,[69] n_D^{20} 1.5261, b.p., 161.7° (760 mm.)). Reagent grade absolute methanol was used without further purification.

Test reagents were combined in 15 ml. flasks fitted with stopcock adapters, and were degassed twice under vacuum at -78° before being placed in a water bath at 50.0 ± 0.05° for 24 hrs. Furoin was isolated by pouring each test into 30 ml. of ice water, collected the precipitated furoin by suction filtration, extracting the aqueous solution 3 times with 125 ml. portions of ethyl ether, evaporating the ether and subjecting the total solid product to vacuum sublimation at 95° (0.05 mm.) in a sublimation apparatus.

In general, tests were determined in triplicate, each test containing 0.12 mmole of catalyst, 0.30 mmole of triethanolamine, 5.0 ml. of methanol, and 1.0 ml. (1.2 g., 12 mmoles) of furfural. Thiamine chloride hydrochloride was also tested using 0.12 mmole of catalyst, 0.30 mmole of triethanolamine, 0.12 mmole of sodium methoxide, 5.0 ml. of methanol, and 1.0 ml. of furfural; and 3-benzyl-4-methylthiazolium bromide was tested using 0.12 mmole of catalyst, 0.18 mmole of triethanolamine, 0.12 mmole of triethanolamine hydrochloride, 5.0 ml. of methanol, and 1.0 ml. of furfural. The copolymers were tested in the absence of added triethanolamine using 25 mg. of copolymer in each one with 5.0 ml. of methanol and 1.0 ml. of furfural. 3,4-Dimethylthiazolium iodide was tested in the presence of 4-methylthiazole as added base as a control for the 4-vinyl copolymer. The latter 3 tests, namely, the copolymers and the control, were run for 72 hrs. rather than 24. The furoin test data are summarized in Table IV.

Copolymer of 4-Vinylthiazole and 3-Methyl-4-vinylthiazolium Iodide

Poly(4-vinylthiazole) (0.62 g., 0.0056 mole) was treated with 9.0 g. (0.063 mole) of methyl iodide in 20 ml. of chloroform at reflux for 5 hrs. The product which precipitated was vacuum dried, ground with mortar and pestle under ethyl ether, and redried prior to submission for iodide analyses. The degree of quaternization was calculated to be 42.5%.

Anal. Found: I, 31.39, 31.67%.

Copolymer of 4-Methyl-5-vinylthiazole and 3,4-Dimethyl-5-vinylthiazolium Iodide

Poly(4-methyl-5-vinylthiazole) (0.68 g., 0.0054 mole) was dissolved in 10 ml. of chloroform and methyl iodide (7.0 g., 0.050 mole) was added. The mixture was heated at reflux for 12 hrs. and the solid product collected, ground, washed with chloroform and ethyl ether, and vacuum dried before submission for iodide analyses. The degree of quaternization was calculated to be 78.0%.

Anal. Found: I, 42.18, 41.94%.

3-Methyl-4-(1-benzoxyethyl)thiazolium Iodide

4-(1-Benzoxyethyl)thiazole (17 g., 0.072 mole) was treated with 18 g. (0.13 mole) of methyl iodide at room temperature for 9 days and at

50° for 2 days. The white crystalline product was collected and vacuum dried (12 g., 43%). An analytical sample, recrystallized 3 times from methanol-ethyl ether, had m.p. 148-150°. The nmr spectrum (D_2O) showed peaks at T 8.19 (doublet, 3H), assigned to the methyl group of the benzoxyethyl side chain; T 5.78 (singlet, 3H), assigned to the 3-methyl group; T 3.75 (quartet, 1H), assigned to the methine proton; T 2.46 and 2.01 (2 multiplets, 3H and 2H, respectively), assigned to the meta, para protons and the ortho protons of the phenyl ring, respectively; and T 1.66 (singlet, 1H), assigned to H_5 on the thiazolium ring. The proton at H_2 on the thiazolium ring was not observed due to exchange with deuterium.

Anal. Calcd. for $C_{13}H_{14}INO_2S$: C, 41.60; H, 3.75; S, 8.53; I, 33.87.
Found: C, 41.98; H, 4.04; S, 8.35; I, 33.14.

3-Methyl-4-isopropenylthiazolium Iodide

4-Isopropenylthiazole (15.6 g., 0.125 mole) and 43.0 g. (0.303 mole) of methyl iodide were heated at reflux for 48 hrs. The addition of 50 ml. of ethyl ether precipitated the crude product (30.0 g., 90.0%, after washing with ethyl ether and vacuum drying). An analytical sample, recrystallized 3 times from methanol-ethyl ether, had m.p. 117-118°. The nmr spectrum (D_2O) showed peaks at T 7.83 (singlet with fine splitting, 3H), assigned to the isopropenyl methyl group; T 5.80 (singlet, 3H), assigned to the 3-methyl group; T 4.47 and 4.18 (2 singlets with fine splitting, 1H each), assigned to the vinylic protons; and T 1.93 and 0.05 (2 doublets, 1H each), assigned to H_5 and H_2 on the thiazolium ring, respectively.

Anal. Calcd. for $C_7H_{10}INS$: C, 31.46; H, 3.75; S, 11.98; I, 47.57.
Found: C, 31.74; H, 3.93; S, 11.97; I, 47.70.

The free radical polymerization of this thiazolium salt was attempted with azobisisobutyronitrile as initiator in aqueous solution, according to the method of Price.[59] The attempts were made at 80°, after degassing through 3 freeze-thaw cycles, for 21 to 72 hrs.; no polymer was obtained from any attempt.

3-Methyl-4-(2-benzoxy-2-propyl)thiazolium Iodide

4-(2-benzoxy-2-propyl)thiazole (6.0 g., 0.024 mole) was treated with 14.2 g. (0.100 mole) of methyl iodide in 3.0 ml. of ethyl ether at reflux for 4 hrs. The crystalline precipitate, 0.60 g. (6.4% after recrystallization from methanol-ethyl ether), had m.p. 179-181°. The nmr spectrum (D_2O-D_6-dimethyl sulfoxide) showed peaks at T 7.80 (singlet, 6H), assigned to the geminal methyl groups; T 5.58 (singlet, 3H), assigned to the 3-methyl group; T 2.07 and 1.65 (2 multiplets, 3H and 2H, respectively), assigned to the meta, para protons and the ortho protons of the phenyl ring, respectively; and T 1.37 (singlet, 1H), assigned to H_5 on the thiazolium ring. The proton at H_2 on the thiazolium ring was not observed due to exchange with deuterium.

Anal. Calcd. for $C_{14}H_{16}INO_2S$: C, 43.19; H, 4.11; S, 8.22; I, 32.65.
Found: C, 43.45; H, 4.23; S, 8.25; I, 32.69.

Thiazole[37]

2-Aminothiazole (150 g., 1.50 moles) was diazotized by the method of Ganapathi and Venkataraman,[37] using 600 ml. of 85% phosphoric acid, 300 ml. of conc. nitric acid, and a solution of 120 g. (1.75

moles) of sodium nitrite in 300 ml. of distilled water. The diazonium salt solution was poured cautiously into 500 ml. of 50% hypophosphorous acid, and the resultant solution diluted to 11 l. with water prior to cooling and basification with 1.3 l. of 50% sodium hydroxide solution. The aqueous solution was divided into 3 portions and extracted several times with a total of 5 l. of ethyl ether. After evaporation to 4 l. in volume, the aqueous solution was re-extracted with 1.5 l. of ethyl ether. The ether solutions were combined, dried over sodium sulfate, and solvent removed under reduced pressure. The residual oil was distilled at atmospheric pressure, yielding 35.2 g. (27.6%) of thiazole, b.p. 113-114° (lit.[41] b.p., 117°). The nmr spectrum (CCl_4) agreed with that published for thiazole.[70]

<u>2-Amino-4-methylthiazole</u>[71]

Thiourea (106 g., 1.39 moles) was condensed with chloroacetone (139 g., 1.51 moles) in 500 ml. of benzene heated at reflux for 7.5 hrs. The chloroacetone was added over a 30 min. period when the benzene had begun to reflux. The reaction mixture was poured into 800 ml. of distilled water after 24.5 ml. of water was collected in a Dean-Stark trap. The benzene layer was extracted with 100 ml. of 10% hydrochloric acid and discarded, and the acid extract combined with the aqueous layer. The aqueous layer was made basic with 10% sodium hydroxide solution, precipitating a brown oil which was collected by extraction 4 times with a total of 1 l. of ethyl ether. The ether solution was dried over sodium sulfate, followed by solvent removal and vacuum distillation.

The product (142 g., 89.9%) had b.p. 97-101° (2.5 mm.) and m.p. 39-42° (lit.[71] b.p. 117-120° (8 mm.), m.p., 44-45°).

<u>4-Methylthiazole</u>[72]

2-Amino-4-methylthiazole (142 g., 1.25 moles) was diazotized by the method of Ganapathi and Venkataraman,[37] using 500 ml. of 85% phosphoric acid, 250 ml. of conc. nitric acid, and a solution of 100 g. (1.45 moles) of sodium nitrite in 200 ml. of distilled water. The diazonium salt solution was poured into 400 ml. of 50% hypophosphorous acid. After standing overnight, the mixture was made basic with 30% ammonium hydroxide solution, with external cooling. Extraction with ethyl ether, drying the ether solution over sodium sulfate, followed by solvent removal and vacuum distillation, yielded 1.8 g. (1.5%) of 4-methylthiazole.

This compound was also synthesized by the condensation of crude thioformamide with chloroacetone.[72] The thioformamide was used as a solution in 100 ml. of ethyl ether obtained by extracting a reaction mixture of 200 g. formamide and 100 g. phosphorus pentasulfide 5 times with 200 ml. portions of ethyl ether over a 24 hr. period, and concentrating the 1 l. ether solution to 100 ml. under reduced pressure. After removing some sulfur by filtration, chloroacetone (47 g., 0.51 mole) was added to the thioformamide solution over a 10 min. period. The temperature rose to 40° and subsided, followed by heating the reaction at reflux for 12 hrs. The ether was removed by distillation through a Dean-Stark trap and the remaining liquid made basic with 10% sodium hydroxide solution. The aqueous solution was extracted 3 times with 150 ml. portions of ethyl ether, the ether solution dried over sodium sulfate, solvent removed, and the residual oil vacuum distilled, yielding 33.1 g. (65.5%) of 4-methylthiazole, b.p. 35-36° (10 mm.) (lit.[72] b.p., 70° (90 mm.)). The nmr spectrum (CCl_4) showed peaks at T 7.57 (singlet with fine splitting, 3H), assigned to the methyl group; T 3.16 (multiplet, 1H), assigned to H_5 on the thiazole ring; and T 1.36 (doublet, 1H), assigned to H_2 on the thiazole ring.

<u>3-Benzyl-4-methylthiazolium Bromide</u>[7]

4-Methylthiazole (1.8 g., 0.018 mole) was quaternized with benzyl bromide (4.0 g., 0.023 mole) in 75 ml. of ethyl ether heated at reflux for 30 min. The product, after recrystallization from methanol-ethyl ether, had m.p. 183.5-184.5° (lit.[7] m.p., 183.5-184°). The nmr spectrum (D_2O) showed peaks at T 7.45 (singlet with fine splitting, 3H), assigned to the 4-methyl group; T 4.30 (singlet, 2H), assigned to the methylene group; T 2.45 (broad singlet, 5H), assigned to the phenyl ring; and T 2.09 (singlet with fine splitting, 1H), assigned to H_5 on the thiazolium ring. The proton at H_2 on the thiazolium ring was not observed due to exchange with deuterium.

<u>3-Allylthiazolium Bromide</u>

Thiazole (4.5 g., 0.053 mole) was quaternized with allyl bromide (10 g., 0.083 mole) in 13 ml. of ethyl ether heated at reflux for 1 hr. The product, recrystallized from methanol-ethyl ether, had m.p. 143.5-145°. The nmr spectrum (D_2O) showed peaks at T 4.89 (2 singlets with fine splitting, 1H each), assigned to the protons on C_3 of the allyl group; T 4.62 (2 multiplets, 1H total), assigned to the proton on C_2 of the allyl group; T 4.38 (singlet with fine splitting, 2H), assigned to the methylene group; and T 1.46 (AB quartet, 2H), assigned to H_4 and H_5 on the thiazolium ring. The proton at H_2 on the thiazolium ring was not observed due to exchange with deuterium.

<u>Anal.</u> Calcd. for C_6H_8BrNS: C, 34.95; H, 3.88; S, 15.53; Br, 38.83.
Found: C, 34.84; H, 4.15; S, 15.51; Br, 38.78.

<u>3,4-Dimethylthiazolium Iodide</u>[7]

4-Methylthiazole (5.1 g., 0.051 mole) was quaternized with methyl iodide (12.5 g., 0.0880 mole) at room temperature for 6 hrs. The white crystalline product was collected by suction filtration, washed with ethyl ether, and vacuum dried. The m.p. was 119.5-120.5° (lit.[7] m.p., 119-120°). The nmr spectrum (D_2O) showed peaks at T 7.26 (singlet with fine splitting, 3H), assigned to the 4-methyl group; T 5.06 (singlet, 3H), assigned to the 3-methyl group; and T 1.84 (singlet with fine splitting, 1H), assigned to H_5 on the thiazolium ring. The proton at H_2 on the thiazolium ring was not observed due to exchange with deuterium.

<u>Copolymer of 4-Isopropenylthiazole and 3-Methyl-4-isopropenylthiazolium Iodide</u>

Poly(4-isopropenylthiazole) (0.65 g., 0.0052 mole) was treated with methyl iodide (4.0 g., 0.028 mole) in 5.0 ml. of benzene for 9 days at room temperature. The product which precipitated was ground under ethyl ether, filtered, and vacuum dried before submission for iodide analyses. The degree of quaternization was calculated to be 37.4%.

<u>Anal.</u> Found: I, 26.58, 26.70%.

Quaternization of 4-Vinylthiazole

4-Vinylthiazole (5.7 g., 0.0051 mole) was treated with methyl iodide (20 g., 0.14 mole) at reflux for 24 hrs. Ethyl ether (30 ml.) was added, precipitating the product, which was filtered, ground under ethyl ether, and vacuum dried. The product had m.p. 225-228°, while a portion of it which was recrystallized from methanol had m.p. 230-232°, and another portion, recrystallized from water by dilution with acetone, had m.p. 234-237°. The nmr spectrum (D_2O) of the product showed peaks at T 7.78 (broad band, 2H), assigned to the methylene groups; T 6.95 (broad band, 1H), assigned to the methine protons; T 5.61 and 5.80 (2 singlets, 3H total), assigned to the 3-methyl groups; T 2.07 (multiplet, 1H), assigned to H_5 on the thiazolium rings; and T -0.03 (multiplet, 1H), assigned to H_2 on the thiazolium rings. This spectrum is consistent with the structure of poly(3-methyl-4-vinylthiazolium iodide). The peak at T -0.03 disappeared on standing overnight, while that at T 2.07 became a singlet, indicating exchange with deuterium at H_2 of the thiazolium ring. Treatment of the product with alcoholic silver nitrate produced a copious white precipitate.

Quaternization of 2-Vinylthiazole

A freshly distilled sample of 2-vinylthiazole was treated with excess methyl iodide at room temperature for 12 hrs. The nmr spectrum of the product, after washing with ethyl ether and drying, was consistent with the structure of poly(3-methyl-2-vinylthiazolium iodide). The nmr spectrum (D_2O) showed peaks at T 8.38 (triplet, 2H), assigned to the methylene groups; T 6.78 (pentet, 1H), assigned to the methine protons; T 5.75 (asymmetric doublet, 3H), assigned to the 3-methyl groups; and T 1.80 (AB quartet, 2H), assigned to H_4 and H_5 on the thiazolium rings. The product, an orange crystalline solid, had m.p. 135-145°. The silver nitrate test was positive.

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