Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

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To cite this Article Hirai, Kentaro , Sugimoto, Hirohiko and Ishiba, Teruyuki(1983) 'Synthetic Application of 1,3-Dithiolium and 1,3-Oxathiolium Cations', Journal of Sulfur Chemistry, 3: 1, 1 — 28
To link to this Article: DOI: 10.1080/01961778308082439
URL: http://dx.doi.org/10.1080/01961778308082439

Sulfur Reports
Volume 3(1), March 1983, pp. 1–32
0196-1772/83/0301–0001/$12.00/0

Printed in the United States of America

SYNTHETIC APPLICATION OF 1,3-DITHIOLIUM AND 1,3-OXATHIOLIUM CATIONS

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1,3-Dithiolium and 1,3-oxathiolium salts are positively charged 6π electronically conjugated cations containing two hetero atoms in a five-membered ring. They exhibit a high reactivity toward nucleophiles. This study has shown that 1,3-dithiolium cations form an interesting class of compounds because of their non-benzenoid aromaticity and that 1,3-oxathiolium cations are highly versatile synthetic intermediates which can provide a number of novel heterocyclic compounds and their precursors depending on the nature of the nucleophiles and the reaction conditions.

1. INTRODUCTION

1,3-Dithiolium **1** and 1,3-oxathiolium **2** cations are positively charged 6π electronic species consisting of a five-membered ring with two hetero atoms. As these compounds satisfy the Hückel 4n + 2 rule they are expected to possess aromaticity. For example, the 1,3-dithiolium cation is electronically equivalent to one of the representative non-benzenoid aromatic cations,

1 2 3

the tropylium cation **3**. Replacement of the two double bonds in **3** with two sulfur atoms gives the iso-electronic **1**. Not only can the positive charge be localized on the C-2 carbon (the carbon atoms of the 5-membered rings of cations **1** and **2**, 1,3-dithiole and 1,3-oxathiole, are numbered as C-2, C-4, and C-5) which is bonded to two hetero atoms, but it can also reside on the C-4 and C-5 carbons by making use of valence shell expansion of the sulfur atom. The substituent effect of the aromatic groups attached to C-2, C-4, and C-5 on the delocalization of the positive charge or the effect of the replacement of one hetero atom (S vs O) can be evaluated from spectroscopic data of the corresponding substituted cations.

Generally, positively charged heterocyclic conjugated cations which satisfy the 4n + 2 rule have characteristic features, that is, they can be isolated with or without introduction of an appropriate substituent and show high reactivity toward nucleophiles. Taking advantage of this reactivity we can synthesize a large number of compounds which otherwise are difficult to prepare or can convert these cations into other novel heterocyclic systems.

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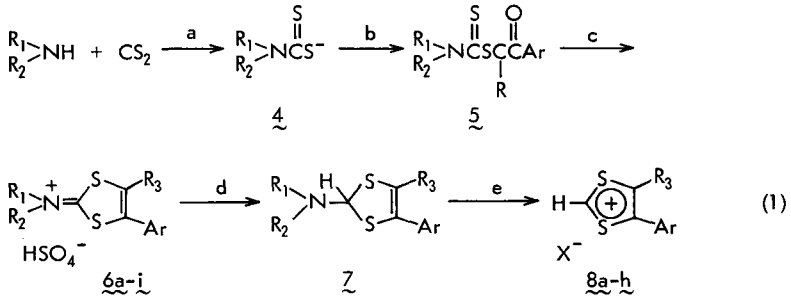
We established a method of synthesizing 1,3-dithiolium and 1,3-oxathiolium cations and studied their electronic structures as well as their chemical behavior toward a variety of nucleophiles. The results led to the conclusion that these cations are highly versatile intermediates for the syntheses of novel heterocyclic compound. We have applied this methodology to the synthesis of biologically active heterocyclic compounds.

The syntheses, physicochemical properties, and chemical reactivities of 1,2- and 1,3-dithiolium cations known up to 1978 have been reviewed by Lozach and Stavaux.[1a] There are two other reviews on this subject by Campaigne and Hamilton in 1970[1b] and by Prinzbach and Futterer in 1966.[1c] However, a systematic review of 1,3-oxathiolium cations has not yet appeared. Thus, we review here the physicochemical properties and synthetic applications of 2-unsubstituted and 2-substituted 1,3-dithiolium or 1,3-oxathiolium cations as well as the aromaticity of the 1,3-dithiolium cation.

2. 4-ARYL-1,3-DITHIOLIUM CATIONS

2.1. *Synthesis*

The 4-aryl-1,3-dithiolium cations **8** can be synthesized by the following route (Figure 1). The dithiocarbamate salt **4**, which is readily prepared by treating a secondary amine with carbon disulfide, reacts with a substituted phenacyl bromide in refluxing EtOH to give the dithiocarbamate ester **5** which can be cyclized in the presence of concentrated sulfuric acid to the 4-substituted 2-(*N*,*N*-dialkylamino)-1,3-dithiolium cation **6**. Subsequent reduction of **6** with $NaBH_4$ affords the 1,3-dithiole derivatives **7**. Elimination of the amine moiety in the presence of acid produces the 1,3-dithiolium cation **8**. Generally, the overall yield of **8** on the basis of secondary amines is very high (about 80%).[2] Data for 1,3-dithiolium and 1,3-oxathiolium cations are summarized in Table I, and the NMR data are listed in Table II.



[a] a Base. b ArCOCH(R3)Br, EtOH, ↑↓. c conc. H_2SO_4, rt. d $NaBH_4$, EtOH, rt. e 2HX, $-R_1R_2NH_2X$

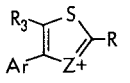
FIGURE 1 Synthetic routes to 1,3-dithiolium cations.

2.2. *Reaction of 2-Unsubstituted 4-Aryl-1,3-dithiolium Cations with Nucleophiles*[3]

Reaction of a nucleophile with **8** generally gives the C-2 adduct, however, a pseudo base, which is the reaction product of **8** with hydroxide anion, is usually an equilibrium mixture of

TABLE I

1,3-Dithiolium and 1,3-Oxathiolium Cations and Their NMR Data

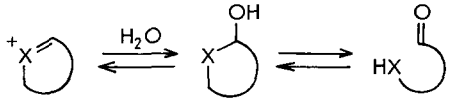


(Ar = p-Y-C_6H_4, R = p-Y'-C_6H_4)

Compd	Z	R_3	Ar	R	X	δ(R_3 = H)
8a-g	S	H	Ar	H	ClO_4	[a]
8h	S	Ph	Ph	H	ClO_4	
6a-g	S	H	Ar	pip[b]	HSO_4	[a]
6h	S	Ph	Ph	pip	HSO_4	
6i	S	H	Ph	mor[c]	HSO_4	
21d-i	S	H	Ph	Ar	ClO_4	[a]
21j	S	H	Ph	*n*-Pr	ClO_4	8.78[e]
21k	S	Ph	Ph	Ph	ClO_4	8.70
58a-g	O	H	Ar	pip[b]	HSO_4	[a]
58h	O	H	Ph	dma[d]	HSO_4	7.33[f]
58i	O	H	Ph	mor[c]	HSO_4	7.43
58j	O	Ph	Ph	mor	HSO_4	
60a	O	H	Ph	Ph	ClO_4	8.12[e]
60b	O	H	Ph	*p*-MeO-C_6H_4	ClO_4	7.86
60c	O	H	Ph	*p*-Cl-C_6H_4	ClO_4	8.10
117a	O	CH_2CO_2Et	Ph	pip[b]	ClO_4	
117b	O	CH_2CO_2Et	*p*-Cl-C_6H_4	pip	ClO_4	
117c	O	CH_2CO_2Et	*p*-MeO-C_6H_4	pip	ClO_4	
117d	O	$CH(Me)CO_2Et$	Ph	pip	ClO_4	
117e	O	$CH(Me)CO_2Et$	*p*-Cl-C_6H_4	pip	ClO_4	

[a]See Table II.
[b]pip: 1-piperidino.
[c]mor: 4-morpholino.
[d]dma: *N,N*-dimethylamino.
[e]CF_3CO_2D.
[f]D_2O.

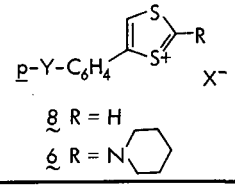
the adduct and the ring-opened product.[4] This equilibrium of the pseudo base can be used to evaluate the stability of the cation toward water (see §2.4).



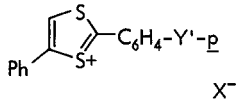
(2)

TABLE II

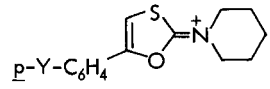
Chemical Shifts of Vinyl Protons of Dithio and Oxathiolium Cations



8 R = H
6 R = N



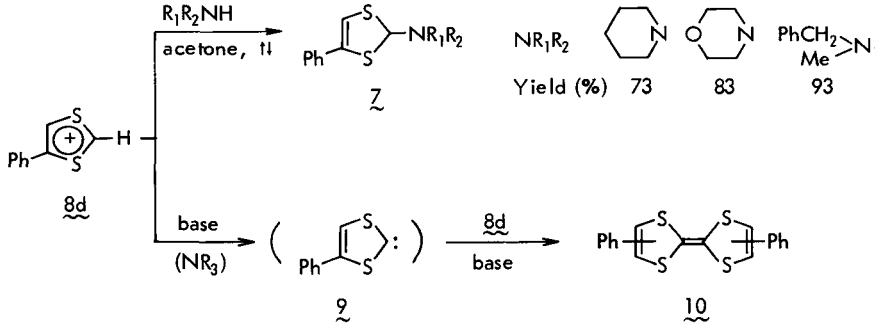
21



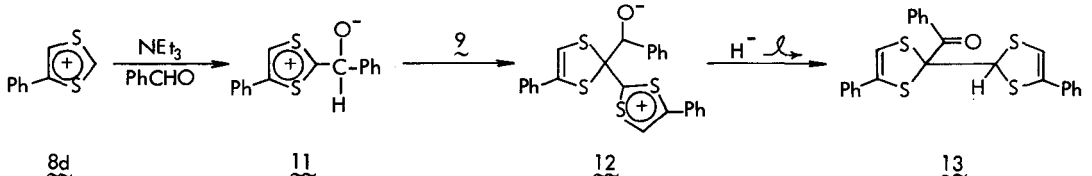
58

Compd	Solv.	(Y / Y')	a NO_2	b Br	c Cl	d H	e Me	f OMe	g OH	h NH_2	i NMe_2
8	CD_3CN		9.39	9.20	9.20	9.20	9.16	9.05	9.02		
6	CF_3CO_2D		7.72	7.37	7.37	7.32	7.25	7.25	7.18		
21	CF_3CO_2D					8.78	8.65	8.52	8.50	8.80	8.95
58	D_2O		7.75	7.43	7.43	7.37	7.24	7.15	7.10		

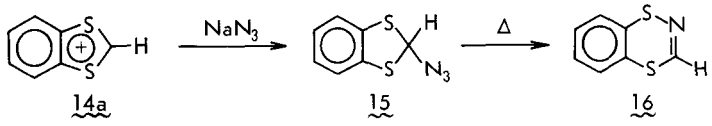
2.2-1. Nitrogen nucleophiles The 2-unsubstituted 4-phenyl-1,3-dithiolium cation reacts with secondary amines giving **7** in high yield. As these products **7** are subject to acid cleavage to the 1,3-dithiolium cation **8** and the starting amine **7** can be used as a blocking group for amines. 2-Unsubstituted 1,3-dithiolium cations undergo proton abstraction upon treatment with a tertiary amine to produce the corresponding carbene intermediate **9**. Attack of the dithiolium cation **8d** on **9** gives the tetrathiafulvalene (TTF, **10**).[3,5] Recently, the charge transfer complex between TTF and tetracyanoquinodimethane (TCNQ) has been investigated from the standpoint of organic metals.[6] Accordingly, 1,3-dithiolium cations are suitable starting materials for TTF and our synthetic method is often applied to prepare 1,3-dithiolium cations.[7]



When a carbene formation reaction is carried out in the presence of benzaldehyde, unlike a thiazolium salt, the benzoin condensation does not occur and **13** is produced instead.[8] The dithiolium carbene **9** is nucleophilic enough to react with benzaldehyde, but the adduct **11** is not an active aldehyde. Another molecule of the carbene **9** reacts with **11** as a nucleophile and

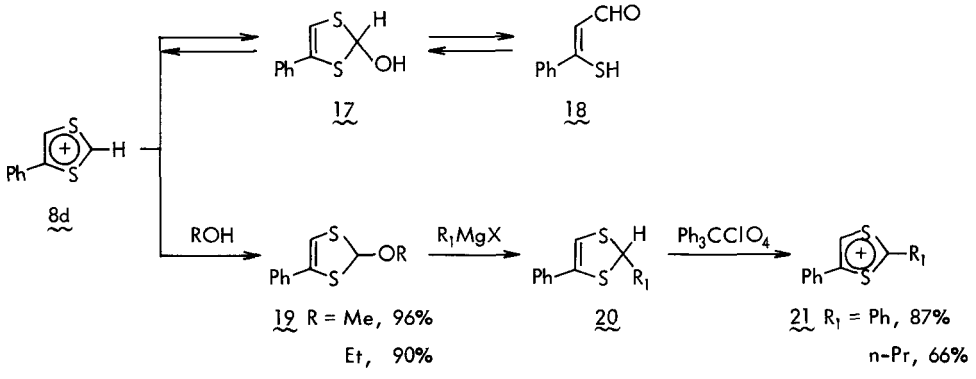


subsequent hydride migration gives the final product **13**. An example of the opening of the dithiole ring has been reported by Nakayama *et al.*[9] The initial adduct **15**, which was obtained from the reaction of the 1,3-benzodithiolium cation with azide anion, undergoes thermal decomposition leading to the new heterocyclic compound, 1,4,2-benzodithiazine **16**. The diazo transfer ability of **15** has been studied, but is not yet completely understood.[10]



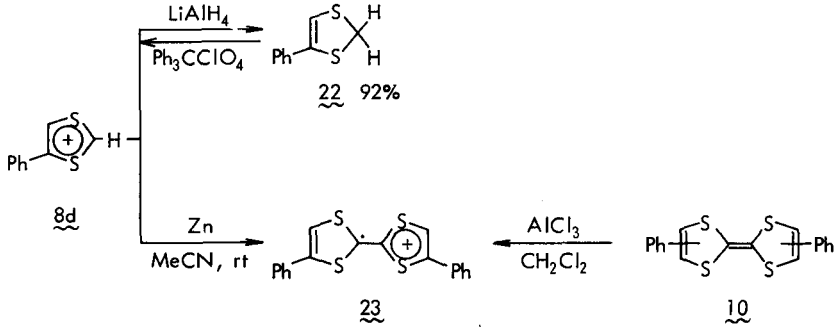
14a 15 16

2.2-2. Oxygen nucleophiles The 4-phenyl-1,3-dithiolium cation as well as the 1,3-benzodithiolium cation react with water and alcohol to give the C-2 adducts **17** and **19**, respectively. The pseudo base **17** is in equilibrium with the ring-opened product **18**. The pK_R+ values of some of the 1,3-dithiolium cations are discussed in §2.4. The 2-alkoxy-1,3-dithiole derivatives **19** are versatile intermediates for preparing 2-substituted 1,3-dithiolium cations. Thus, Grignard reaction of **19** followed by hydride abstraction with trityl perchlorate affords the cation **21**. This method is useful for preparing 2-substituted 1,3-dithiolium cations.



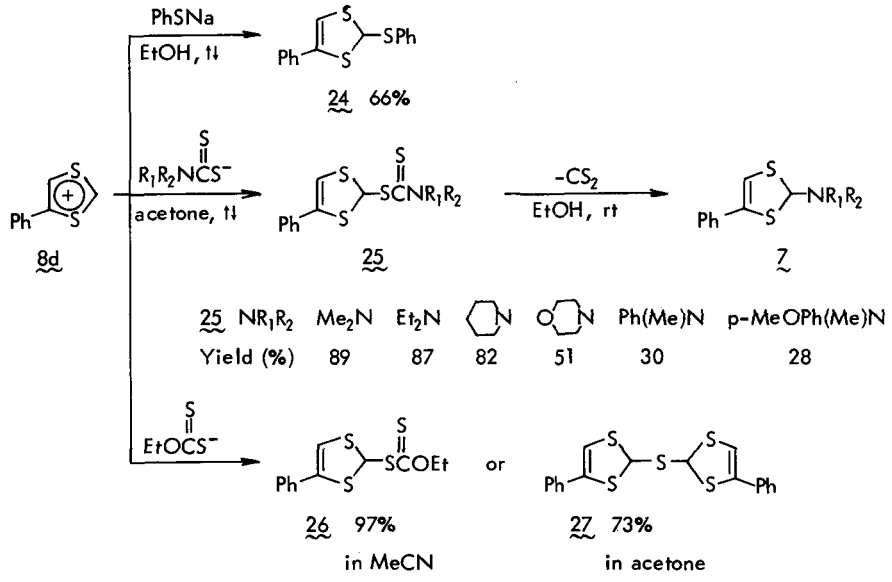
17 18 8d 19 R = Me, 96% Et, 90% 20 21 R1 = Ph, 87% n-Pr, 66%

2.2-3. Reduction Reduction of **8d** with $LiAlH_4$ gives the dithiole compound **22** in high yield, which regenerates the starting cation on treatment with a hydride abstraction reagent. One-electron reduction also takes place readily to give the cation radical **23**. Formation of the stable radical species was demonstrated by the triplet ESR spectrum which showed two equivalent protons (a_H = 1.26G, g_e = 2.0077). The structure of **23** was further confirmed by generation of this radical by an alternate method. Oxidation of TTF **10** with $AlCl_3$ in CH_2Cl_2 gave rise to the same ESR signals. Wudl *et al.*[11] have also prepared the stable cation radical by oxidizing unsubstituted TTF with chlorine and their ESR data are similar to those of **23**.

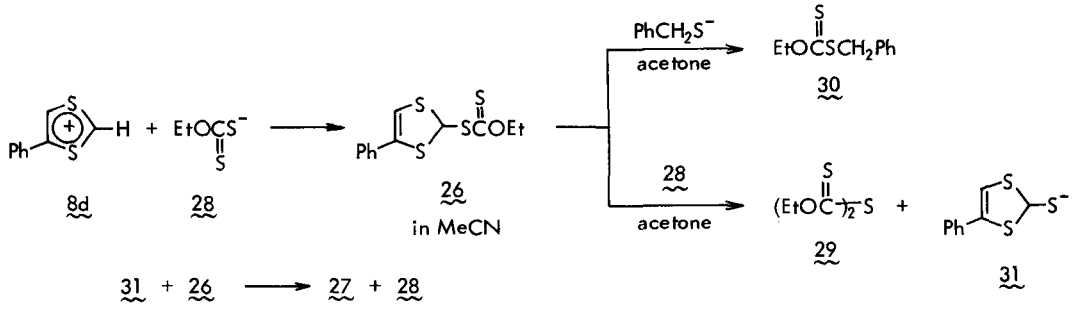


22 92% 8d 23 10

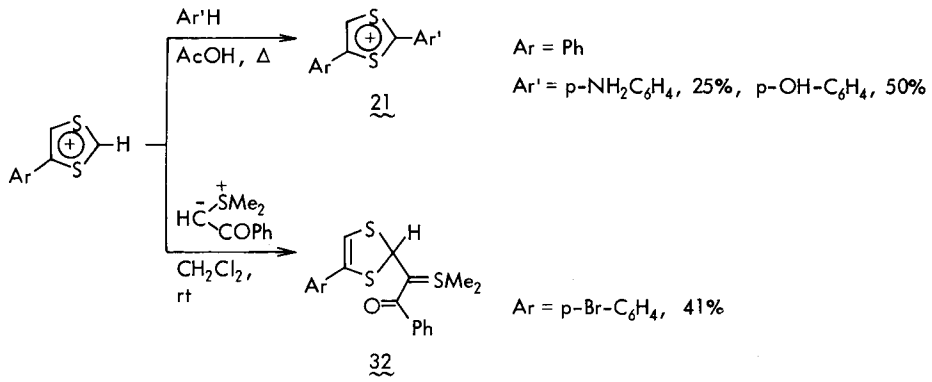
2.2-4. Sulfur nucleophiles Benzenethiolate anion reacts with **8d** in refluxing EtOH, leading to **24**. Addition of dithiocarbamate to C-2 of **8d** occurs readily to give **25**. The reactivity of dithiocarbamates with R_1 = aryl is slightly lower than that of aliphatic dithiocarbamates. The dithiocarbamates **25** exhibits antifungal activity. These compounds are stable as solids, but unstable in solutions. They decompose into aminodithioles **7** with release of carbon disulfide in polar solvents such as EtOH, even at room temperature. The decomposition mechanism is explained in §2.4.



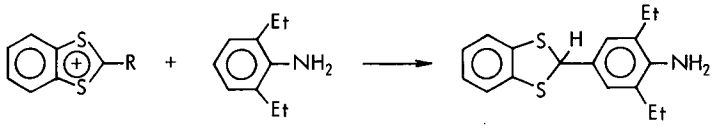
An interesting solvent effect was observed in the reaction of xanthate anion with **8d**. The reaction product in MeCN was the normal C-2 adduct **26**, but the sulfide **27** in acetone. The sulfide **27** could be formed by the following pathway. The extent of the solvation of xanthate in acetone is less than in MeCN, leading to high reactivity of **28** in acetone. Therefore, in acetone the nucleophile **28** further attacks the C-2 adduct **26** at the thiocarbonyl carbon atom giving **29** and another nucleophilic intermediate, **31**. When **26** is treated with phenylmeth-



anethiolate, **29** and **30** can be isolated. The mercaptodithiole anion, unlike the oxygen analog **17**, does not undergo ring opening, but reacts with **26** at the C-2 of the dithiole ring, giving **27** and regenerating **28**. This indicates that excess **28** is not needed for the reaction of **8d** with **28** to occur. In fact, reaction of isolated **26** with a catalytic amount of **28** proceeded smoothly in refluxing acetone, giving **27** in 73% yield. Sulfhydrolysis of sulfide **27** in the presence of $HClO_4$ regenerates the 1,3-dithiolium cation **8d**.

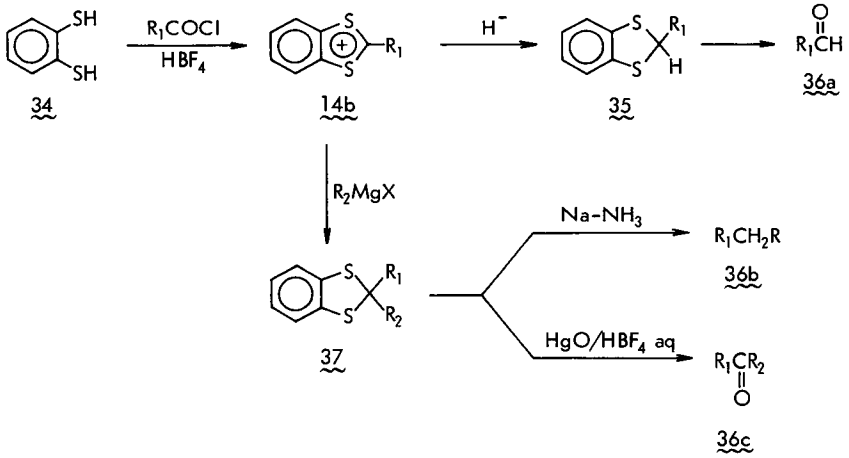


2.2-5. Carbon nucleophiles When the reaction of **8d** with substituted benzene derivatives bearing an electron-donating group was carried out in refluxing glacial acetic acid, both nucleophilic substitution of **8d** and electrophilic substitution of the benzene ring took place in a one-pot reaction to give **21**. Nakayama *et al.*[12] have performed the same type of reaction in MeCN where the product was **33**, that is electrophilic substitution on the benzene ring took place.



The ylide carbanion reacts with **8d** giving another ylide, **32**, which sharply contrasts with the reactivity of the 1,3-oxathiolium cation (see §3.2-1). Buza and Gradowska[13] have reported the reaction of the 4,5-diphenyl-1,3-dithiolium cation with furan where an addition reaction with the cation occurred, the product being of the same type as **33**, namely, 2,5-bis-(4,5-diphenyl-1,3-dithiole-2-yl)-furan.

An interesting synthetic application of the reaction of nucleophiles toward 1,3-dithiolium cations has been developed by Degani *et al.*[14] Benzene-1,2-dithiol **34** reacts with a number of



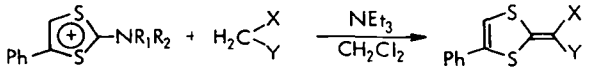
activated carboxylic acids in the presence of acid, giving the 2-substituted 1,3-benzodithiolium salt **14b**. Reduction of **14b** affords **35** which on treatment with chloramine T in EtOH yields the aldehyde **36a**. As a result of these conversions the aldehyde can be conveniently prepared from the corresponding acid. Grignard reaction of **14b** gives the 2,2-disubstituted 1,3-benzodithiol **37** which on treatment with sodium in ammonia or HgO in aqueous HBF_4 produces the methylene compound **36b** or the ketone **36c**, respectively. Thus, 1,3-dithiolium cations can be regarded as potential reagents for functional group transformation.

2.2-6. Phosphorus nucleophiles Phosphines and phosphites react with 2-unsubstituted 1,3-dithiolium cations in MeCN at room temperature to give phosphonium salts and dialkylphosphinyl-1,3-dithioles, respectively, in high yield.[15]

2.3. *Reactions of Nucleophiles with 2-(N,N-dialkylamino)-4-phenyl-1,3-dithiolium Cations*[16–18]

When a good leaving group is attached to C-2 of a 1,3-dithiolium cation, the cation shows a wide variety of reactivities towards nucleophiles, namely C-2 addition, ring opening of the dithiole ring, and reclosure of the ring-opened intermediate leading to a novel heterocyclic compound. We investigated the behavior of the cation **6d** which has a 2-(*N*,*N*-dialkylamino) group as a leaving group.

2.3-1. Reaction with active methylene compounds Reaction of **6d** with active methylene compounds in the presence of NEt_3 in CH_2Cl_2 at room temperature affords 1,4-dithiafulvene derivatives **38** in good yield (**6d** with *N*,*N*-dialkylamino = 1-piperidino). The five-membered ring is preserved in this addition-elimination reaction. The behavior of the corresponding 1,3-oxathiolium cation toward the same nucleophiles is quite different from that of **6d**. Some 1,4-dithiafulvene derivatives have been isolated as a mixture of stereoisomers and their interconversion is discussed in §2.4.



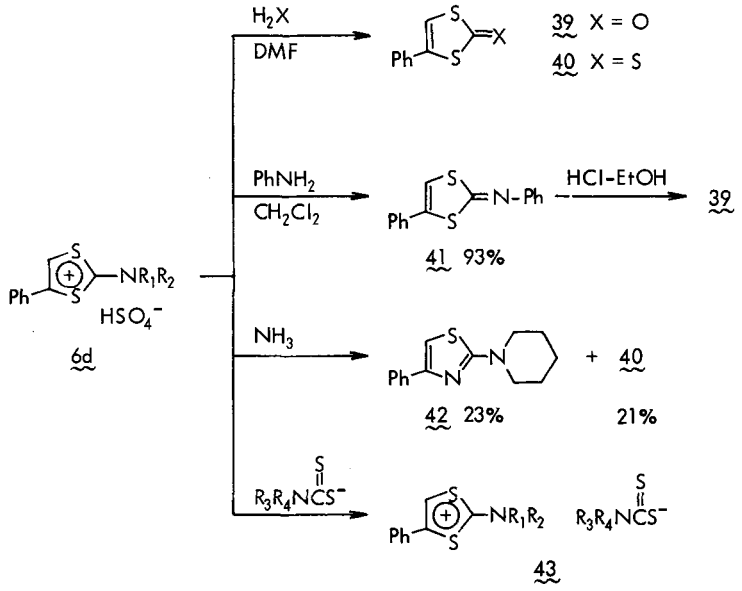
6d HSO_4^- **38**

38	X	CN	Ac	CN	H	Me	PhCO
	Y	CN	CO_2Et	CO_2Et	NO_2	NO_2	Ac
Yield (%)		56	67	92	91	71	61

2.3-2. Nitrogen, oxygen, and sulfur nucleophiles Hydrolysis and sulfhydrolysis of **6d** in DMF under neutral conditions afforded 2-oxo-, **39** (68%) and 2-thioxo- **40** (96%) dithiole derivatives, respectively. Aniline reacts with **6d** to produce **41** in high yield. The structure of **41** was ascertained by hydrolysis of **41** in the presence of acid to give **39**. Ammonolysis of **6d** gives a mixture of thiazole derivatives **42** and thiazole-2-thione **40** in 23% and 21% yield, respectively. Campaigne *et al.*[1b] described the isolation of **40** alone by a similar reaction in NH_3-EtOH.

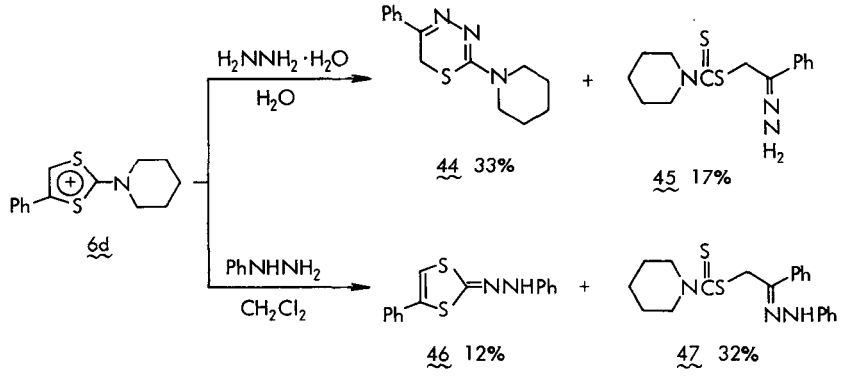
A yellow-colored product was obtained in the reaction of **6d** with a dithiocarbamate salt.

This product was poorly soluble in many organic solvents. Physicochemical data indicated **43**

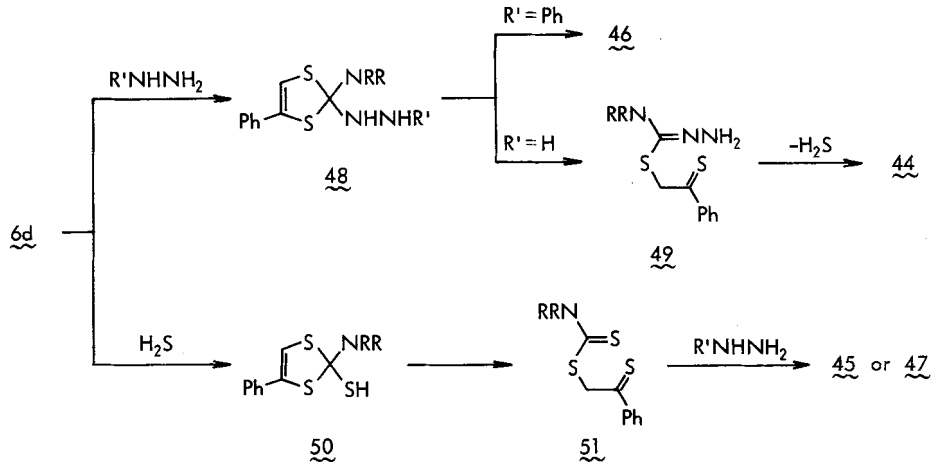


to be a charge-transfer complex between the 1,3-dithiolium cation and the dithiocarbamate anion. Saturated solutions of **43** in EtOH and acetone exhibit UV maxima at 380 and 386 nm, respectively. Dithiocarbamates form charge transfer complexes with the pyridinium cation.[19]

2.3-3. Hydrazine derivatives as nucleophiles When cation **6d** is allowed to react with hydrazine hydrate in H_2O, thiadiazine **44** along with the ring-opened product **45** is obtained. Phenylhydrazine reacts with **6d** in CH_2Cl_2 giving the cyclic products **46** and **47**. Hydrogen sulfide is evolved in both reactions. The by-products **45** and **47** could be formed by the initial



reaction of **6d** with H_2S leading to **50**, followed by ring opening and subsequent hydrazone formation. Generally, reactions of hydrazines with **6d** are rather complex and accompanied by evolution of H_2S. The yields are not high in comparison with those with 1,3-oxathiolium cations (see §3.2-2).



2.4. *Aromaticity of 1,3-Dithiolium Cations*

We have calculated the molecular diagram of the 1,3-dithiolium cation using the simple Hückel molecular orbital method.[20] It shows that the C-4—C-5 bond has the highest double-bond character and that the C-2 carbon has the lowest electron density. This is in accord with the chemical reactivity characterized by the exclusive attack of nucleophiles at C-2. Nakayama and Hoshino[21] have concluded that the positive charge is delocalized over the five-membered ring by calculating the correlation between electron density and substituent effect using ^{7}H and ^{13}C NMR spectroscopic data. The same molecular diagram was obtained by Hartmann *et al.*[22a,b] and Fabian[22c] using the SCF-LCI method.

The substituent effects of C-4 and C-2 aryl groups upon the chemical shift of the C-5 proton are shown in Table II. An aryl substituent containing an electron-donating group attached to C-4 shifts the C-5 proton signal to higher field. This effect is observed in cations **6**, **8**, **21**, and **58**. The higher-field shift of the C-5 proton of the 2-(*N*,*N*-dialkylamino)-1,3-dithiolium cations **6** compared to the corresponding 2-unsubstituted cations **8** can be attributed to the contribution of the iminium structure in **6** to the resonance hybrid. 2-Aryl substituted 1,3-dithiolium cations **21** also delocalize the positive charge to an extent which is intermediate between the delocalizations in **8** and **6** judging from the chemical shift of the C-5 proton. A good linear correlation between σ_p and the chemical shifts of the C-5 protons was obtained for the cations **21**, leading to $\tau = -1.05\ \sigma_p + 1.02$.

The consequences of the C-4[20] and C-2[23] aryl substituent effects for pK_R+ of the cation **8** and **21**, respectively, are shown in Table III. Different dependencies on the substituent

8 21

constant were observed, that is, $pK_R+ = -1.0\ \sigma^+ + 3.33$ for the cations **21** and $pK_R+ = -1.67\ \sigma_p + 2.10$ for the cations **8**. Electron-donating groups stabilize both types of cations. The substituent effect of the C-2 aryl group can be explained by σ^+ because

TABLE III

pK_R+ Values for Cations 8 and 21

Compd	Y or Y′	a NO_2	b Br	d H	e CH_3	f OMe	j OPh
8[a]	0.84	1.73	2.10	2.43	2.59		
21[b]				3.32	3.67	4.11	3.79

[a]10% MeOH.
[b]50% EtOH.

this group is attached directly to the positively charged C-2 carbon. However, conjugation of the C-2 positive charge to the para position of a phenyl group attached to C-4 is not possible by 2pπ resonance alone, and hence valence-shell expansion of the sulfur atom is necessary for the delocalization of the positive charge to the C-4 atom. Therefore the substituent constant σ_p which allows for an inductive effect in addition to conjugation effect can account for the effects of para substituents at the phenyl group attached to C-4.

The UV data (the longest-wavelength absorptions) are shown in Table IV. The UV spectrum of a cation in alcohol or water is that of the equilibrium mixture of Eq. (2) and not of the cation itself. The spectra of the cations **8** in alcohol containing a small amount of $HClO_4$ are actually those of the C-2 adducts **19**.[24] A marked substituent effect of C-2 can be observed in the UV data. Less conjugation of the π electrons of **6** as compared to **8** was observed due to the contribution of the iminium structure to the electron distribution in the former cation. On the other hand, the π electron conjugation is enhanced for cation **21** owing to the direct substitution of the aryl group at C-2. A good linear relationship between

TABLE IV

The Longest-Wavelength Absorptions of 1,3-Dithiolium and 1,3-Oxathiolium Cations, nm (log ε)

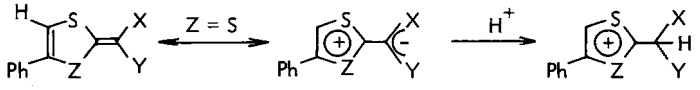
Cation	Solvent	a NO_2	b Br	c Cl	d H	e Me	f OMe	g OH	h NH_2	i NMe_2	X
8	50% H_2SO_4	323 (3.93)	345 (3.61)	344 (3.60)	338 (3.51)	3.57 (3.53)	377 (3.48)	376 (3.50)			ClO_4
6	EtOH	320 (4.31)	322[a] (4.17)	322 (3.83)	322 (4.11)	326 (4.08)	333 (4.00)	336 (3.70)			HSO_4
21	MeCN				390 (4.19)	402 (4.36)	432 (4.49)	428 (4.44)	499 (4.78)	536 (4.82)	ClO_4
58	EtOH	325 (4.13)	284 (4.38)	283 (4.34)	278[b] (4.30)	280 (4.33)	295 (4.31)	283 (4.34)			HSO_4

[a]X = BF_4.
[b]H_2O solvent.

the longest-wavelength absorption and σ_p was obtained for cation **21** (R_1 = Ph) ν ($cm^{-1} \times 10^{-3}$) = 8.8 σ_p + 26.1.

Comparison of 1,3-dithiolium and 1,3-oxathiolium cations (**6** vs **58**) indicates the difference between the hetero atoms oxygen and sulfur. The π electrons are more delocalized in the 1,3-dithiolium cation than in the oxathiolium cation. These data clearly show that the contribution of the iminium structure is important for the stabilization of the 1,3-oxathiolium cations **58**. The UV data suggest that delocalization of the positive charge is necessary for cation stabilization, and introduction of a group which stabilizes the positive charge density at C-2 contributes a great deal to the stability of the cation even if the 6π conjugation of the five-membered ring is decreased.

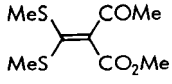
The aromatic stability of 1,3-dithiolium cations is also reflected in the isomerizations of the 1,4-diheterofulvenes **38** and **61**.[25] The NMR data for the vinyl protons of both heterofulvenes in two different solvents are summarized in Table V. Only one isomer, **61**, could



38 Z = S
61 Z = O

52 **53**

be obtained starting with 1,3-oxathiolium cations while the product **38** shows two kinds of vinyl proton signals which shift to lower field in acidic medium. This indicates the existence of the protonated species **53** in equilibrium with **38**. The rotational barrier of **38** is lowered by the contribution of a polar structure such as **52** and this can be evaluated by inspection of the temperature-dependent NMR signals of the vinyl protons of **38** in DMSO. Thus, the rotational barrier obtained, $\Delta H^{\neq}$ = 10 kcal/mole, is substantially lower than that of a normal C=C double bond. A possible contribution of the triplet mechanism to the isomerization can be neglected in the case of **38**.[26] Sandström and Wennerbeck[27] have reported $\Delta H^{\neq}$ = 15 kcal/mole for the compound **54**. A more efficient delocalization of the positive charge of



54

the polarized structure **52** over the five-membered ring in **38** than over the two hetero atoms in **54** decreases the rotational barrier more for **38**. The chemical shifts of the vinyl protons

TABLE V

NMR Data of Vinyl H of 1,4-Heterofulvenes

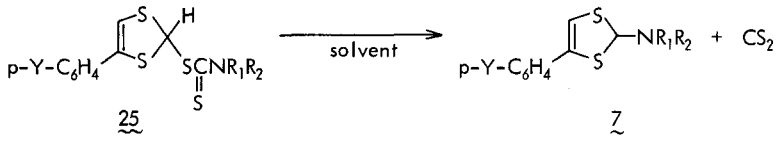
Compd[a]	δ(DMSO)	δ(CF_3CO_2D)
38	7.95, 7.88	8.08
61	7.65	7.73

[a] X = $COCH_3$, Y = CO_2Et

of **38** move to higher field with an increase in temperature. This can be interpreted as a decrease in the anisotropic effect of the C-4 aryl group due to its increased free rotation.

With regard to delocalization of positive charge densities, Timm *et al.*[28] concluded from ^{13}C NMR measurements of 1,3-dithiolium cation derivatives in acidic media that only the two adjacent hetero atoms play a significant role for the delocalization of the C-2 positive charge of the 1,3-dithiolium cation and that the effect of the 6π conjugation is relatively small.

Another example of the effect of the aromatic stability of 1,3-dithiolium cations on their reactivity could be observed in the decomposition of **25** into **7** and CS_2 in a polar solvent.[29]



25 7

The adduct **25** is unstable in EtOH even at room temperature and decomposes quantitatively to the aminodithiole **7**. The decomposition is accelerated in a solvent having strong ionizing power (EtOH > MeCN). In order to elucidate the mechanism of the decomposition of **25** in solution we studied its kinetics spectroscopically. The first-order plot which was obtained from UV data deviated upward from linearity with the progress of the decomposition showing that a product-catalyzed decomposition route exists. The plot $dx/dt/(a - x)$ vs x^2 where a and x are concentration of **25** (T = 0) and **7** (T = t), respectively, had a good linear relationship, indicating the existence of a second-order catalytic term with respect to **7**. The results are shown in Table VI and the activation parameters are listed in Table VII.

Three mechanisms can be considered to explain the first-order decomposition mechanism of **25**. The first is a cyclic four-membered ring transition state mechanism which is observed in the decomposition of dithiocarbamate acyl esters. The electron-withdrawing group attached to the acyl carbon accelerates the conversion while the reverse is the case with the substituent effect of **25**. Accordingly, this path can be ruled out. The second is the heterolysis

TABLE VI

Rate Constants for the Decomposition of 25[a]

Run	Y	Solv	Temp °C	$k_0 \times 10^4$ s^{-1}	$k_2 \times 10^{-5}$ M^{-2} s^{-1}
1	H	EtOH	25.4	1.43	1.19
2	H	EtOH	32.0	3.13	4.62
3	H	EtOH	38.6	5.03	5.69
4	H	MeCN	38.0	0.539	0.819
5	H	MeCN	44.5	1.15	2.08
6	H	MeCN	49.0	1.93	6.04
7	OMe	MeCN	44.5	1.45	4.78
8	Br	MeCN	44.5	0.865	0.829

[a]R_1R_2N = 4-morpholino

TABLE VII

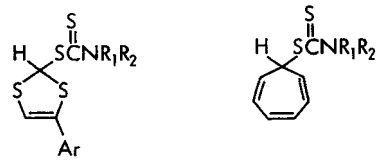
Activation Parameters

Solv.	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (eu)
EtOH	16.5	−21.5
MeCN	22.0	−6.11

[a] R_1R_2N = 4-morpholino.

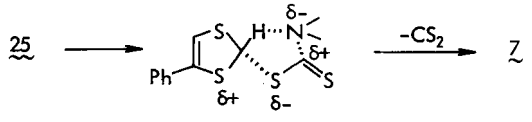
of **25** into cation **8** and a dithiocarbamate anion. The latter anion could further decompose into $R_1R_2N^-$ and CS_2. Recombination of the 1,3-dithiolium cation **8** and the amine anion could give the product **7**. The dithiocarbamate salt is stable under the decomposition conditions and no crossover products have been found in the decomposition of **25**. The third and the most probable mechanism is the simultaneous two-bond heterolysis mechanism, in which C—S and C—N bonds are cleaved at the same time. The decomposition of aralkyl thiocarbamate esters[30] and of *t*-butyl arylperacetate[31] proceed via this mechanism and the solvent and substituent effects are the same as those of **25**.

The decomposition of dithiocarbamate esters ($R—S_2CNR_1R_2$) having an R group which is more stable as a carbonium ion is not necessarily faster than that of corresponding esters with R groups which are less stable as carbonium ion. While cation **3** is more stable than cation **8** the corresponding dithiocarbamate ester **55**,[32] however, is essentially stable under the decomposition conditions of **25**. This apparent contradiction can best be interpreted by



25 **55**

invoking the acidic nature of the C-2 protons of 1,3-dithiolium cations. Since the C-2 hydrogen at the developing positively charged carbon of **25** has an acidic nature, whereas the allylic hydrogen of **55** does not, an intramolecular acid-base interaction of the C-2 proton with the amine moiety is possible leading to the elimination of CS_2. This interaction could be the driving force for the decomposition of **25**.

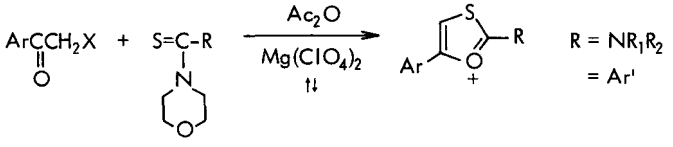


These discussions lead to the conclusion that 1,3-dithiolium cations have more 6π electronic conjugation than the corresponding 1,3-oxathiolium cations due to the electronic properties of the sulfur atom.

3. 2-SUBSTITUTED 5-ARYL-1,3-OXATHIOLIUM CATIONS

3.1. Synthesis

The same synthetic scheme as that for obtaining the 1,3-dithiolium cations was employed (Figure 2). The thiolcarbamates **56**, which were readily prepared by treating secondary amines with carbonyl sulfide instead of carbon disulfide, were esterified with substituted α-bromo ketones giving **57**. The cyclization of **57** was performed in concentrated sulfuric acid to obtain the 2-(*N,N*-dialkylamino)-1,3-oxathiolium cation derivatives **58**.[33] Reduction of **58** with $NaBH_4$ similar to that of **6** to **7** was unsuccessful. Therefore no 2-unsubstituted 1,3-oxathiolium cations could be synthesized by this method. 2-Aryl-1,3-oxathiolium cations **60** can also be prepared by this procedure starting from potassium thiobenzoate.[34] Recently, Ueno and Okawara[35] reported the ring closure of dithiocarbamate esters **5** with dimethyl sulfate leading to **58**. Hartmann[36] also synthesized 1,3-oxathiolium cations **58** and **60** by condensation of thioamide derivatives with α-halo ketones in the presence of magnesium perchlorate.



*3.2. Reactions of 2-(*N,N*-dialkylamino)-1,3-oxathiolium Cations with Nucleophiles*

The cations **58** generally have higher reactivity toward nucleophiles than the corresponding 1,3-dithiolium cations. The general reaction course consists of the addition of the nucleophile at the C-2 carbon, ring opening giving an intermediate, and subsequent ring closure of this intermediate leading to a novel heterocyclic compound. These reactivities of the cations **58**

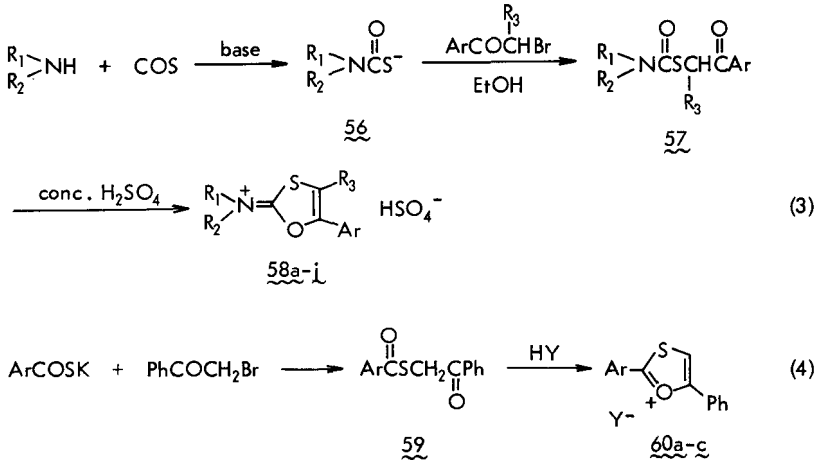
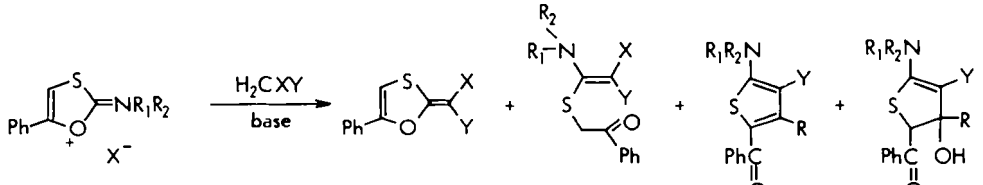


FIGURE 2 Synthetic routes to 1,3-oxathiolium cations.

depend upon the nature of the solvent, the pH, and the reaction temperature. Thus, 1,3-oxathiolium cations proved to be versatile intermediates for obtaining a number of heterocyclic compounds because of the wide variety of reactivities.

3.2-1. Reaction with active methylene compounds The results of the nucleophilic reactions of **58** (**58d**, *N,N*-dialkylamino = 1-piperidino) with active methylene compounds are summarized in Table VIII.[37,38] When the nucleophilic reaction was carried out in CH_2Cl_2 in the presence of an equimolar amount of NEt_3 using **58d**, the dihydrothiophene **67** and the thiophene **63** were obtained. The former product underwent spontaneous dehydration to the thiophene **63**. The thiophene derivatives **63** were preferentially formed from **58d'** in the presence of excess of the sodium salt of the carbanion. As a result, the reaction products of the carbanion reaction are **61–63**.



58d X = HSO_4
58d' X = BF_4

61 62 63 67

The ketene S,N-acetal intermediates **62** can be converted to the thiophene derivatives **63** in the presence of base. Therefore, thiophene derivatives can be readily prepared by the

TABLE VIII

Reaction of 58 with Active Methylene Compounds[a]

	X	Y	R	Yield (%) 61	62	63
a	$COCH_3$	$COCH_3$	Me			42(73)[b]
b	$COCH_3$	COPh	Me			36(82)
c	dimedone			59(49)		
d	1,3-indandione			46		
e	PhCO	Ph	Ph			4(41)
f	$COCH_3$	CO_2Et	CH_3	22		(68)
g	CO_2Et	CN	OH		84(25)	(50)
h	CN	CN	NH_2			86
i	CN	$CONH_2$	(NH_2)		25	
j	PhCO	COOEt	Ph		17	(60)
k	PhCO	CN	Ph			(69)

[a] NR_1R_2 = 1-piperidino, NEt_3/CH_2Cl_2 system (**58d** was used).
[b] The yields for NaH/THF using **58d'** are given in parentheses.

reaction of 1,3-oxathiolium cations with active methylene compound under appropriate conditions. The benzoyl group in **63** can easily be removed by Gassman's method (*t*-BuOK-H_2O-DMSO).[39] This simplifies the structural identification of **63** and also constitutes an extension of its synthetic applications. The difference in the reaction course, which depends upon the nature of the carbanion, can be observed in the reactions of ethyl acetoacetate and ethyl cyanoacetate. With NEt_3 as a base the reaction does not give thiophene derivatives, but favors the formation of the 1,4-heterofulvenes **61** or the ring-opened intermediates **62**. The thiophenes **63** were obtained using the sodium salts of the active methylene compounds.

The courses of the reactions are shown in Figure 3. The carbanion attacks the C-2 carbon of the highest positive charge density giving the unstable adduct **64**. When the cation is the *N,N*-dialkylamino derivative and the nucleophile possesses an α-hydrogen, the C-2 adduct

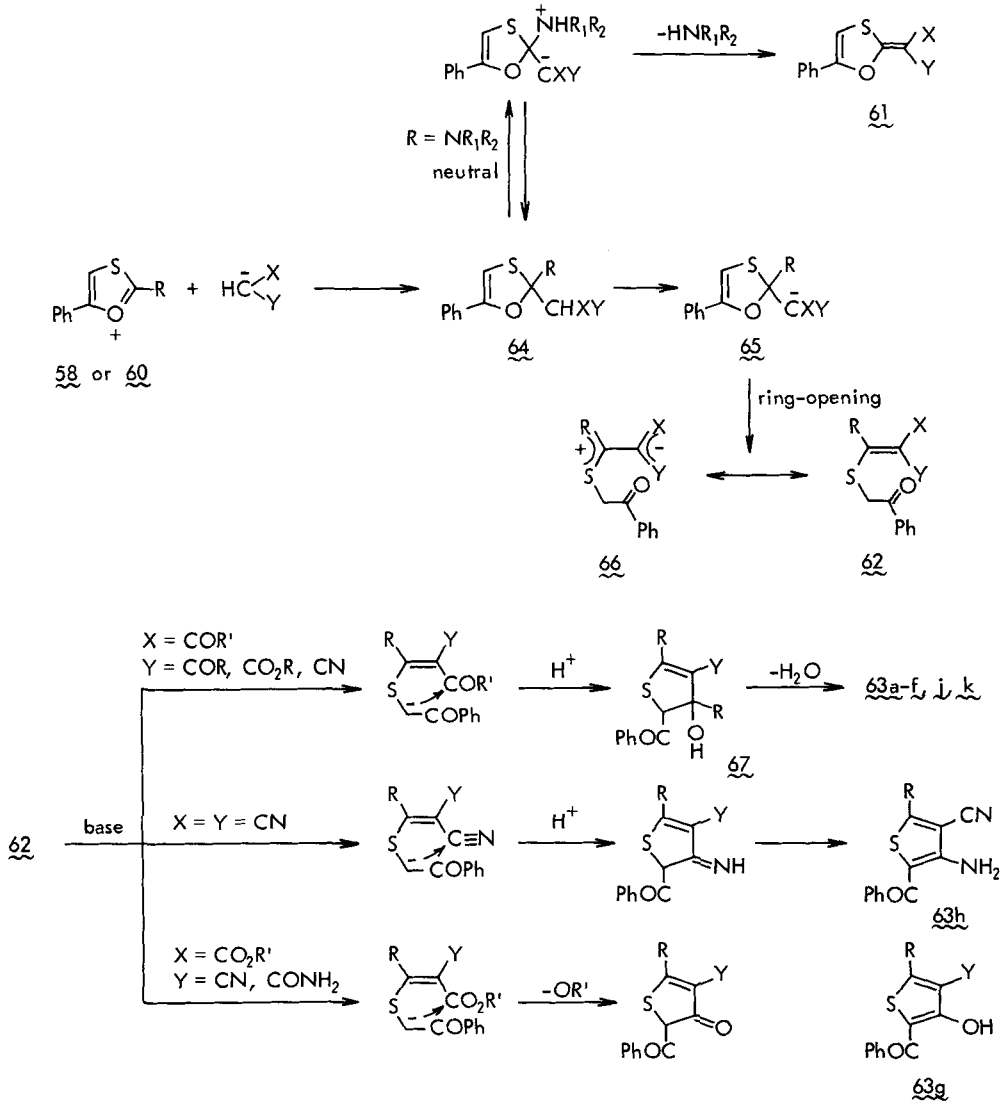
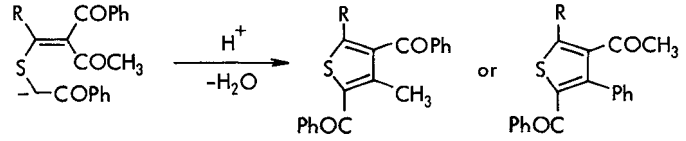


FIGURE 3 Reactions of 1,3-oxathiolium cations with active methylene compounds.

64 has two possibilities for further reaction. Under neutral conditions, intramolecular deprotonation of **64** by the *N,N*-dialkylamino group giving a zwitterion followed by elimination of a dialkylamine produces the 1,4-oxathiafulvene derivative **61**. On the other hand, under basic conditions, species **65**, formed by intermolecular deprotonation, is unstable in the presence of carbanion and ring opening at the C^2—O bond occurs giving the ketene S,N-acetal derivative **62**. When X = COR′ and Y = COR, CO_2R or CN, aldol-type condensation occurs with **62** in the presence of base and in some cases the ketol compound **67** can be isolated by careful work-up. Dehydration of **67** takes place easily to produce the thiophenes **63a-f,j,k**. When X and Y equal CN, Thorpe-Ziegler condensation occurs giving the thiophene **63h**. When X = CO_2R' and Y = CN or $CONH_2$, Claisen- or Dieckmann-type condensation of **62** produces the 3-hydroxythiophene **63g**. With benzoylacetone, there are two paths of Aldol condensation to the intermediate anion **68** or **69** leading to **63b** or **109c**. The anion of **68** attacks the more electrophilic acyl carbon starting an aldol condensation (see §3.3 for the reactivity of **69**). The aminobenzoylthiophene **63h** can be utilized for the preparation of heterocycle-condensed 1,4-diazepines (see §3.4).



68 R = NR_1R_2
69 R = Ph

63b
R = NR_1R_2

109c
R = Ph

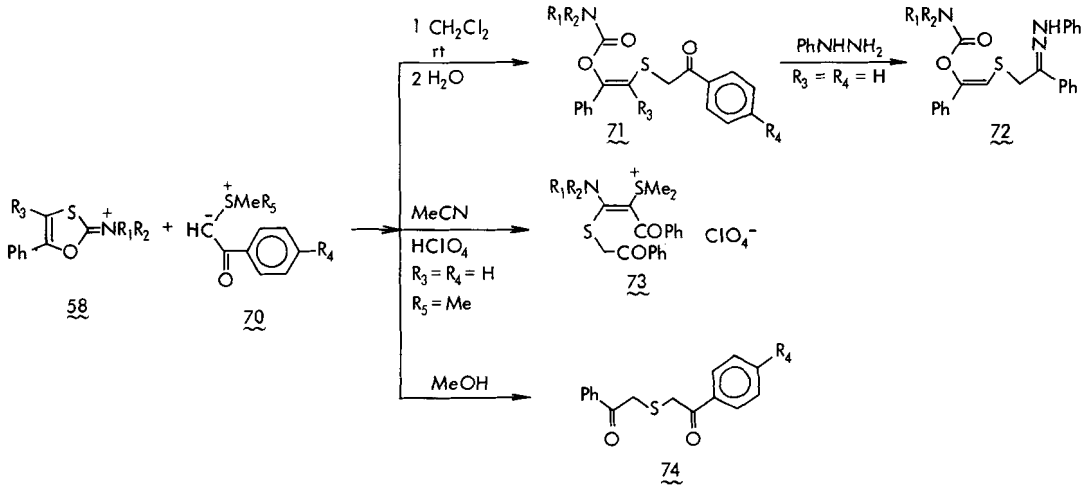
Ylide carbanions react with 1,3-oxathiolium cations.[40] However, this reaction is rather different from that of 1,3-dithiolium cations. The results are summarized in Table IX. The product obtained by the reaction of **58d** with ylide **70a** in CH_2Cl_2 at room temperature followed by quenching with H_2O possesses two carbonyl groups and has no sulfonium group. It gives the monohydrazone **72**. When the same reaction was carried out in MeCN followed

TABLE IX

Reactions of Cations 58 with Ylides 70

58	R_1	R_2	R_3	70	R_4	R_5	Solv.	Prod	Yield (%)
58d	1-piperidino		H	**70a**	H	Me	CH_2Cl_2	**71a**	65
58d				**70b**	H	Ph	CH_2Cl_2	**71a**	62
58d				**70c**	NO_2	Me	CH_2Cl_2	**71b**	58
58j	4-morpholino		Ph	**70c**			CH_2Cl_2	**71c**	71
58i	4-morpholino		H	**70c**			CH_2Cl_2	**71d**	60
58d				**70a**			MeCN	**73**	19
58j				**70d**	Cl	Me	MeOH	**74**	32

by addition of $HClO_4$, the ring-opened hygroscopic sulfonium salt **73** was isolated. On treatment of this salt with diluted aqueous $NaHCO_3$ solution, the above CH_2Cl_2 solvent product was obtained. This result shows that **73** is an intermediate for the final product. We have assigned the structure of the products as carbonate ester derivatives **71** on the basis of spectroscopic data (IR, MS, H and ^{13}C NMR).



A possible reaction route is shown in Figure 4. Although the initial adduct between 1,3-dithiolium cation and ylide carbanion can be isolated, in the case of 1,3-oxathiolium cations ring opening is favored in the presence of base (excess ylide) giving the unstable intermediate salt **73**. Intramolecular attack of the sulfur group and elimination of the sulfonium moiety yields thiirenium cations **77**.[41] Nucleophilic attack of H_2O on **77** produces the carbamate

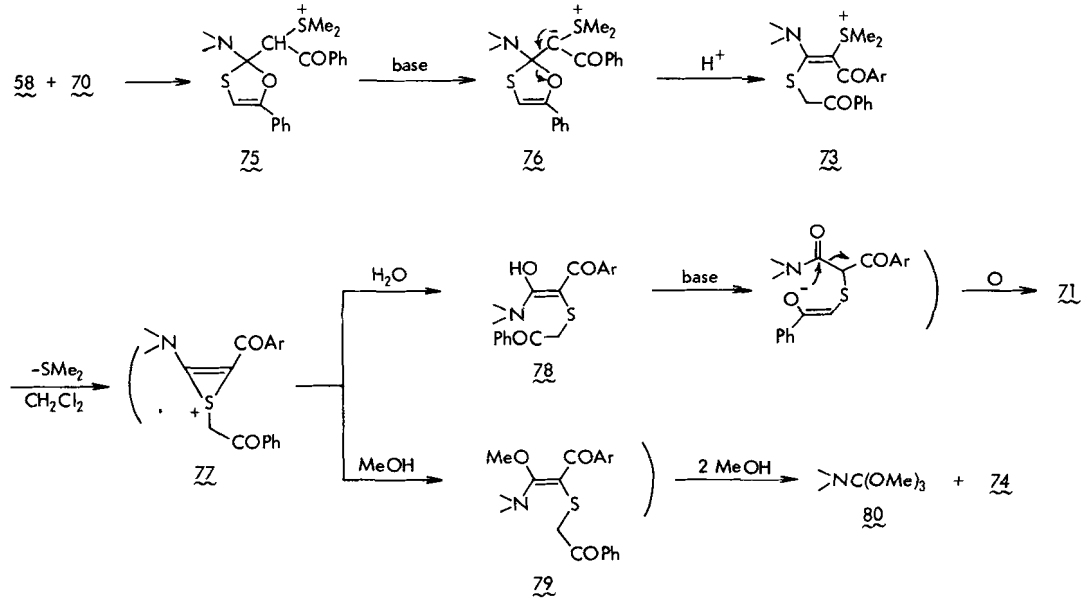
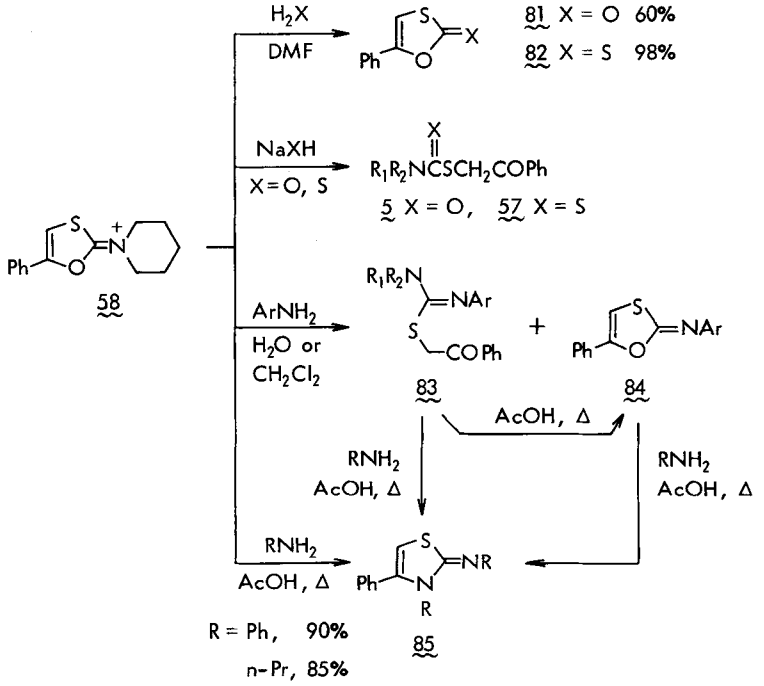


FIGURE 4 Reactions of 1,3-oxathiolium cations with ylide carbanions.

esters **78**. Base-catalyzed rearrangement of the carbamoyl group from carbon to oxygen, which is similar to the corresponding carbon-oxygen ester[42] and sulfur-oxygen carbamoyl[43] rearrangement, gives the final products **71**. The solvent effect (MeCN vs CH_2Cl_2) of the ylide reaction is fundamentally the same as that for the reaction of **8d** with xanthate in which multi-step reactions take place in non-polar solvents. When MeOH was used as a solvent, the reaction of MeOH with **77** gave **79** which further reacted with MeOH to yield **74** together with **80** (not isolated).

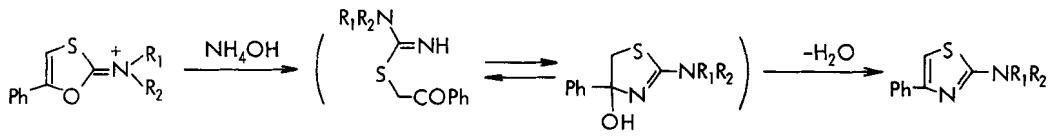
The difference in the reactivity of the carbanion of an active methylene compound and an ylide carbanion can be ascribed to the nature of the ring-opened intermediates **62** and **73**. The presence of the electron-withdrawing sulfonium group in **73** exerts an important effect upon the behavior of the ring-opened intermediate.

3.2-2. Reaction of **58** *with oxygen, sulfur, and nitrogen nucleophiles* Reaction of **58** with H_2X (X = O or S) under neutral conditions in DMF affords the cyclic products **81** or **82**, respectively. Under basic conditions the same reaction yields the ring-opened compounds **5** or **57**. The product distribution depends on the pH of the solvent.



	Ar	Yield 83	Yield 84
H_2O	Ph	32	27
	p-MePh	57	30
CH_2Cl_2	Ph	100	0
	p-MePh	96	0

The reactions of aromatic amines with the cations **58** showed another type of solvent dependence.[44,45] In water, a mixture of **83** and **84** was obtained, however in CH_2Cl_2, **83** was obtained exclusively. The intermediate **83** can be converted into the oxathiole derivative **84** by refluxing in AcOH. When an aliphatic or aromatic amine was allowed to react with **58** in refluxing AcOH, the iminothiazoline **85** was obtained. Further refluxing of **83** or **84** in the presence of an aromatic amine gave **85** in good yield. The entire sequence of the reaction of **58** with amine can be summarized as the conversion of the intermediates **83**→**84**→**85**. Compound **85** has been synthesized from thiourea in several steps,[46] but it can be prepared by a one-pot reaction using the cation reaction.



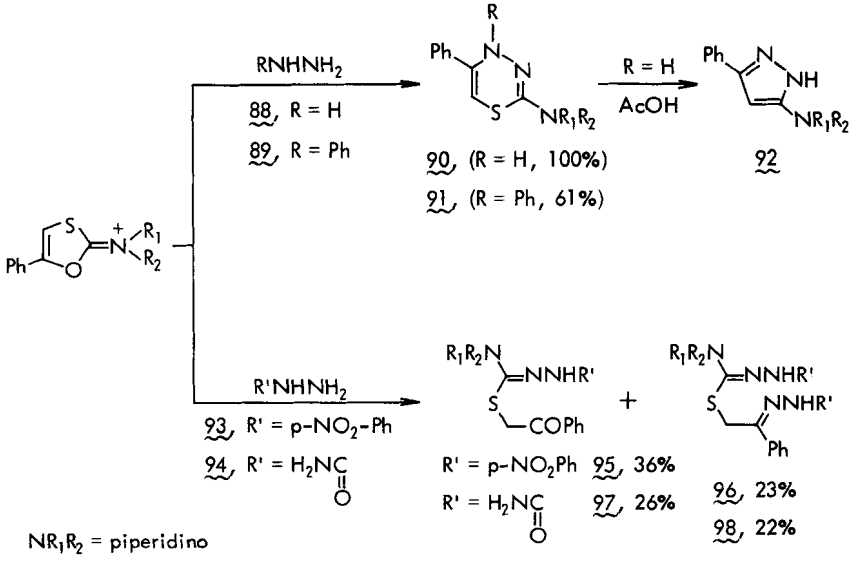
58 86 87 42

R_1R_2N	N◯	Me_2N	N◯O
Yield of 42	85%	89%	91%

A temperature dependence of the product distribution was found for the reaction of **58** with aqueous ammonia. Reaction of NH_3 with **58** in ice water gave the intermediate **86** or **87** in 85% yield (R_1R_2N = 1-piperidino), which in turn was converted to thiazole **42** by heating in AcOEt for 30 min. In order to synthesize the thiazole directly the ammonolysis can be conducted in H_2O at room temperature.

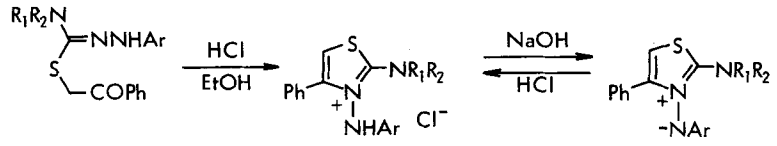
A number of thiazole derivatives can readily be obtained in high yield by this method. Hartmann *et al.*[47] have prepared thiazole or thiophene derivatives by the reaction of 2-aryl-1,3-oxathiolium cation with nitrogen (ammonia) or carbon (active methylene compound) nucleophiles, respectively. A 1,3-oxathiolium cation is a better starting material than the corresponding 1,3-dithiolium cation for synthesizing thiazole derivatives.

The cations **6** and **58** exhibited a different behavior in their reactions with hydrazines. Hydrazine **88** reacted with **58** in H_2O giving the thiadiazine derivative **90** quantitatively which subsequently underwent thermal desulfurization in refluxing AcOH to give the pyrazole derivative **92**. Phenyl hydrazine **89** in CH_2Cl_2 reacted with **58** in a different manner



NR_1R_2 = piperidino

than with cation **6** to preferentially afford the thiadiazine **91**. The aryl hydrazine **93** reacted with **58** in CH_2Cl_2 or MeCN giving the ring-opened products **95** or the dihydrazone **96**, respectively.[48] Treatment of **95** with HCl-EtOH gave the *N*-aminothiazolium salt **99**, which was a precursor for the *N*-imino compound **100**. This was suggested by the spectroscopic

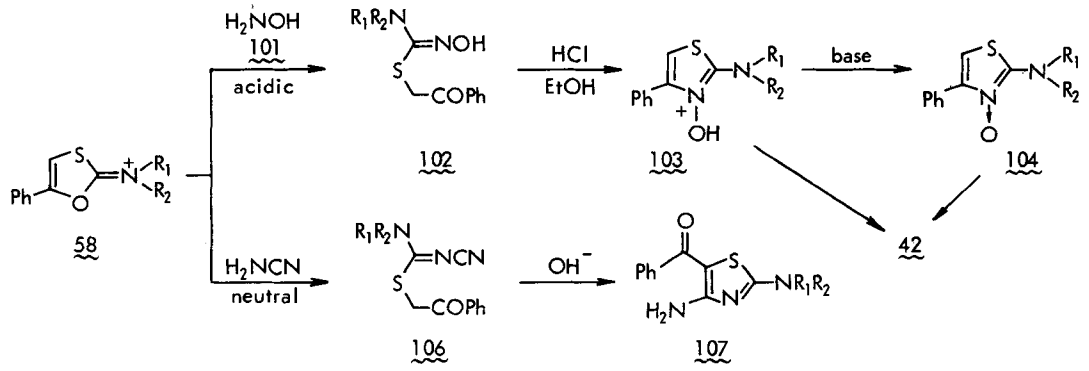


95 99 (350 nm) 100 (480 nm)

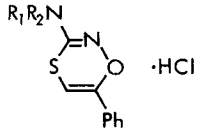
change **99** underwent in alkaline solution and the regeneration of **99** by acidifying the solution. The chemical properties of *N*-imines remain unexplored.[49]

The semicarbazide **94** reacted with **58** in H_2O giving a mixture of the ring-opened product **97** and the dihydrazone **98**. It is likely that the reaction of **58** with amines in a more polar solvent would give complex reaction products (CH_2Cl_2 vs H_2O or CH_2Cl_2 vs MeCN).

A striking pH effect of the solvent was revealed in the reaction of **58** with hydroxylamine **101**.[50] With excess **101** reaction in H_2O gave a complex mixture and partial decomposition. The hydrochloride of **101** in H_2O simply gave the hydrolyzed product **81** upon reaction with **58**. Reaction of **58** with six equivalents of **101** hydrochloride and four equivalents of NaOH



in ice water afforded the ring-opened product **102**. Treatment of **102** with HCl-EtOH at room temperature gave the thiazole *N*-oxide hydrochloride **103** in 81% yield based on **58**. The possibility of **103** possessing the isomeric six-membered ring structure **105** can be ruled

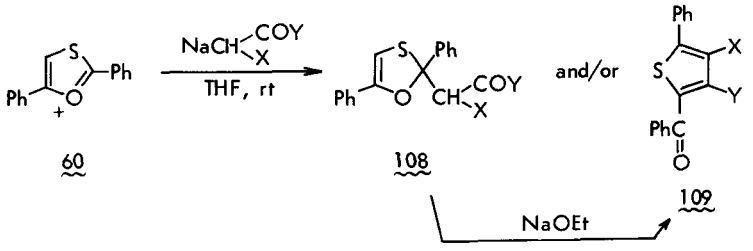


105

out by chemical transformation of **103**. Neutralization of **103** afforded the *N*-oxide **104** and reduction of **103** with Zn or PCl_3 in $CHCl_3$ gave the known compound **42**. Another example of the dependence on solvent pH is the reaction of cyanamide with **58**. Under neutral conditions the ring-opened intermediate **106** was obtained in low yield. However, with base (aqueous NaOH) the aminobenzoylthiazole **107** was produced in high yield. The intermediate **106** can be converted to **107** in the presence of base. The compounds **107** as well as **63h** are starting materials for the synthesis of heterocycle-condensed 1,4-diazepines.

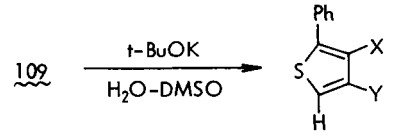
3.3. 2,5-Diaryl-1,3-oxathiolium Cations

Cation **60** reacts with active methylene compound in the presence of base,[34] but the product distribution is somewhat different from that in the case of the 2-(*N,N*-dialkylamino)-1,3-oxathiolium cations **58**. The products of the reaction of **60** with active methylene compounds are a mixture of the C-2 adducts **108** and the thiophene derivatives **109**. No diheterofulvene or ring-opened intermediate, corresponding to **61** or **62**, respectively, was obtained. Base treatment of **108** afforded the thiophene **109** almost quantitatively. The structural identification was based on the spectra of **109** and their debenzoylated derivatives **110**, which were



60 108 109

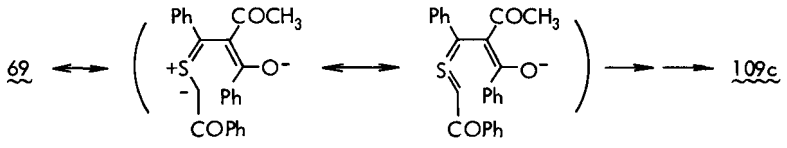
	X	Y	108 (%)	109 (%)	108 + 109
a	Ph	Ph	40		94
b	COMe	Me		91	
c	COMe	Ph	17	21	100



109 110

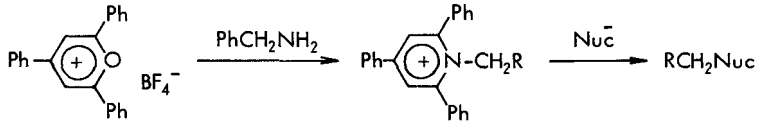
obtained by Gassman's method. In summary, there are two definitive differences in the reactivities of the 2-(*N,N*-dialkylamino cations **58** and the 2-aryl cations **60**: the first is a different product distribution and the second is that with benzoylacetone, a different dehydration course for the intermediate **69** gives **109c**. Formal dehydration between the carbonyl of the benzoyl group and the methyl group in **69** took place leading to **109c**. The difference in the reactivity of the initial adduct **64** leading to the ring-opened intermediate or thiophene is due to the electronic nature of the C-2 substituent. There is no intramolecular deprotonation of the initial adduct **108** because of the lack of a basic moiety (the C-2 substituent is a phenyl group instead of an *N,N*-dialkylamino group). Therefore, the reactivity of the C-2 adduct **108** is decreased compared to **64** with an *N,N*-dialkylamino substituent at the C-2 carbon. The ring-opened intermediate is a resonance hybrid of the neutral structure **62** and the polar structure **66**. The push-pull effect of the *N,N*-dialkylamino group diminishes the intramolecular aldol reactivity in comparison to **69** with R = Ph. Accordingly, the difference in the reactivity of the intermediates is responsible for the different product distribution starting from cations **58** and **60** respectively.

The difference in their propensity for aldol condensation of the ring-opened intermediates **68** and **69** can be explained by the contribution of the ylide structure **111** to **69** (with a phenyl group at C-2) which is reasonable if the possibility of valence shell expansion at the sulfur atom is utilized. Intramolecular cyclization of this ylide can afford the product **109c**.[51] Thus the reactivities of 1,3-oxathiolium cations are affected by the substituents on both the cation and the nucleophiles.



111

With regard to reactions of nucleophiles with heterocyclic cations the synthetic applications of an oxygen-containing positively charged cation, the pyrylium cation **112**, have recently been investigated extensively by Katritzky *et al.*[52] Reaction of the nucleophile RCH_2NH_2 with the substituted pyrylium cation **112** gives the pyridinium cation **113**. Subsequent reaction with nucleophiles affords **114**. A wide variety of **114** are obtained by this facile conversion of the amino group.



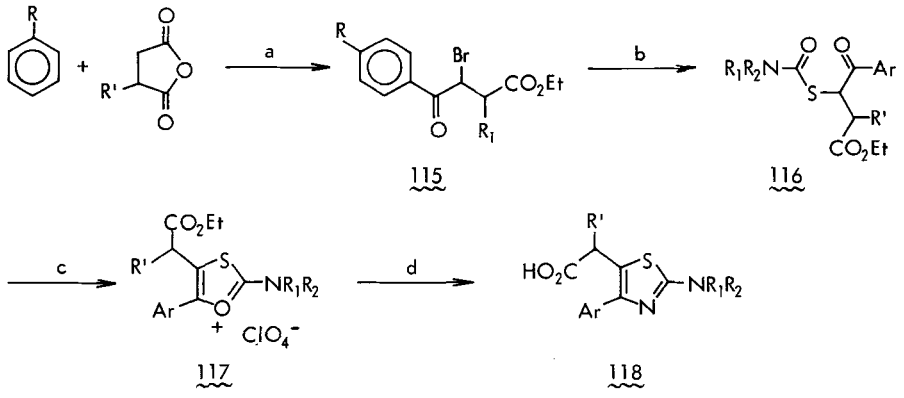
112 113 114

3.4. Synthetic Applications of the 1,3-Oxathiolium Cation Reaction

The reactivity of 1,3-oxathiolium cations toward nucleophiles revealed their versatility for synthesizing a wide variety of heterocyclic compounds. This strategy was applied to prepare pharmacologically active compounds.

3.4-1. Synthesis of thiazol-5-ylalkanoic acids[53] Some aryl- and heteroarylalkanoic acids possess antiinflammatory activity. We tried to synthesize 2-(*N,N*-dialkylamino)-thiazol-5-ylalkanoic acids **118** by the route shown in Figure 5. Friedel-Crafts acylation of a substituted benzene with a substituted succinic anhydride followed by esterification and bromination gave the α-bromo ketone **115**. Thiolcarbamate salts reacted with **115** in refluxing EtOH to give the esters **116**. Ring closure of **116** was carried out in acetic anhydride with added aqueous $HClO_4$ with ice cooling and gave the 1,3-oxathiolium cations **117**. Nucleophilic reaction of aqueous ammonia with the cations **117** readily produced thiazole derivatives. Upon ester hydrolysis, the target molecules **118** were obtained. These alkanoic acids were evaluated as antiinflammatory agents for carragenin-induced abscess in the rat. The activity of **118d** was about twenty times larger than that of phenylbutazone.

3.4-2. Synthesis of hetero[e][1,4]diazepines[54] The 1,4-benzodiazepine **119**[55] (Diazepam) and its ring-opened derivatives **120**[56] are widely used as minor tranquilizers, muscle relaxants,



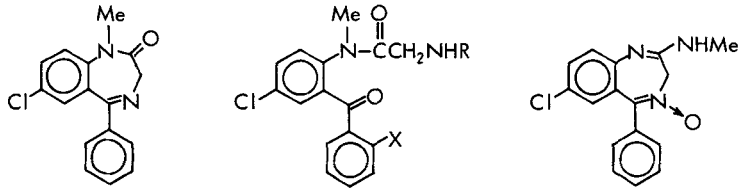
115 116 117 118

[a] a 1) $AlCl_3$, 2) EtOH/H^+, 3) Br_2. b $R_1R_2NC(O)SNa$/EtOH, rt. c $HClO_4/Ac_2O$, 0°. d 1) NH_4OH, 2) H_2O/H^+, rt.

118	NR_1R_2	R'	Ar
a		H	Ph
b	"	H	p-Cl-Ph
c	"	H	p-MeO-Ph
d		H	p-Cl-Ph
e	"	Me	Ph

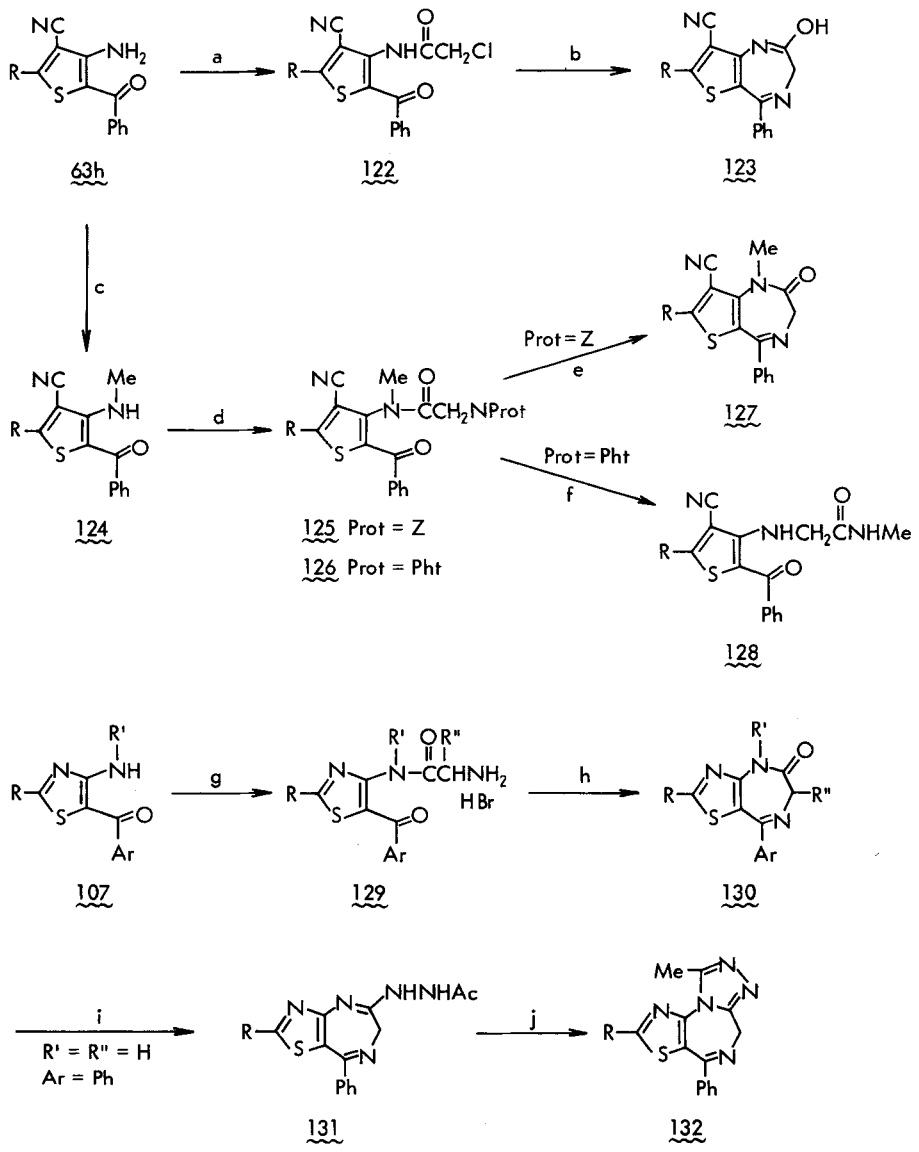
FIGURE 5 Synthesis of thiazol-5-ylalkanoic acids.

and anticonvulsants. Many reports of molecular modifications of the parent compound have appeared since the initial discovery of chlordiazepoxide **121**. We utilized compounds **63h**



119 Diazepam 120 R = amino acid residue X = H or halogen 121

and **107**, which were obtained by the reaction of 2-(*N*,*N*-dialkylamino)-1,3-oxathiolium cations with malononitrile and cyanamide, respectively, to prepare the target compounds. All that is needed is condensation of the glycine unit to amino ketone compounds in order to synthesize hetero[e][1,4]diazepines. The synthetic route is shown in Figure 6. Chloroacetylation of **63h** followed by halogen exchange with KI and ammonolysis afforded 3*H*-thieno[3,2-e][1,4]diazepine **123**. This diazepine **123** exists in the lactim form according to its IR spectrum (3450 cm^{-1}). The *N*-methylthienodiazepine **127** can be obtained by the reaction of the *N*-methylthiophene **124** with Z-Gly-Cl followed by deprotection and cyclization in the presence of base. With Pht-Gly-Cl, condensation took place readily; however, deprotection of **126** by refluxing with hydrazine hydrate in EtOH did not give the expected



[a] a, $ClCOCH_2Cl$/acetone. b, 1) KI/acetone, 2) NH_3/MeOH. c, NaH, MeI/DMF. d, Protected-amino acid chloride/DMF-C_6H_6. e, HBr/AcOH. f, $H_2NNH_2 \cdot H_2O$/EtOH ↓↑. g, 1) Z-amino acid/HMPA-$SOCl_2$, 2) HBr/AcOH. h, DABCO/MeCN, Δ. i, 1) P_2S_5/Py-CH_2Cl_2, 2) $AcNHNH_2/CHCl_3$. j, AcOH ↑↓.

FIGURE 6 Synthesis of hetero[e][1,4]diazepines.

product, but instead the Smiles-rearranged product **128.** This is in accord with the known example of *N*-methyl-4′-nitro-2-pthalimidoacetanilide, which is reported to rearrange on hydrazinolysis to *N*-methyl-2-[(4-nitrophenyl)amino]-acetamide.[57] This rearrangement is facilitated by the electron-withdrawing group on the aromatic ring. The rearrangement of **126** appears to be the first example in which a nitrogen-nitrogen Smiles rearrangement occurs on a thiophene ring.

A reaction sequence similar to that used for obtaining **127** was employed for the synthesis of the thiazolodiazepine **130.** However, the chloroacetylaminothiazole or phthalylglycylaminothiazole derivatives which correspond to **122** or **126,** respectively, regenerated the starting aminobenzoylthiazole **107** upon treatment with ammonia or hydrazine hydrate, respectively. Successful synthesis of **130** was achieved by coupling **107** with a Z-amino acid in HMPA-$SOCl_2$[58] followed by deprotection of **129** and cyclization in the presence of DABCO. The tricyclic derivative **132** can be obtained by activation of the carbonyl group of **130** with P_4S_{10} followed by substitution with acetohydrazide. Subsequent cyclization in refluxing AcOH afforded the triazolo[3,4-c]thiazolo[4,5-e][1,4]diazepines **132.** Some of these hetero[e][1,4]diazepines had central nervous system activities.

IV. CONCLUDING REMARKS

We have thus far investigated the structural and chemical properties of 1,3-dithiolium and 2-substituted 1,3-oxathiolium cations. In order to understand the properties of 1,3-dithiolium cations and 1,3-dithiole derivatives the acidic character of the C-2 proton as well as the aromatic delocalization of the positive charge must be taken into consideration. The oxygen-containing 1,3-oxathiolium cations have revealed a wide variety of reactivities toward nucleophiles. The nature of the reactivity and the product distribution depends upon the substitution of the cation (especially that at C-2) and the nucleophiles, the solvent, the pH, and the temperature. We conclude that 1,3-oxathiolium cations are versatile intermediates since they provide access to a number of novel heterocyclic compounds under appropriate conditions.

Our study of synthetic applications of 1,3-dithiolium and 1,3-oxathiolium cations is continuing.

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