Chemistry and Biological Activity of Thiazolidinones

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Contents

I. Introduction and Scope

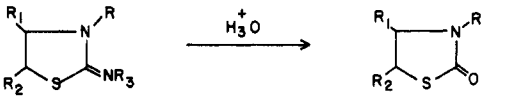
Thiazolidinones are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds. Thiazolidinones, with a carbonyl group at position 2, 4, or 5, have been subject of extensive study in the recent past. Numerous reports have appeared in the literature which highlight their chemistry and use. A comprehensive review[1] has been written on 4-thiazolidinones in 1961. Later on, a review article[2] appeared which deals with the use of thiazolidinone derivatives as stabilizers for polymeric materials. Recently two reviews[3,4] have been presented; one relates to the preparation of rhodanines (2-thiono-4-thiazolidinones) and the other describes their uses as intermediates in organic syntheses.

Diverse biological activities such as bactericidal, pesticidal, fungicidal, insecticidal, anticonvulsant, tuberculostatic, antiinflammatory, antithyroidal, potentiation of pentobarbital-induced sleeping time, etc., have been found to be associated with thiazolidinone derivatives. In recent years, several new methods for the preparation of thiazolidinone derivatives and reactions have been reported in the literature. Thiazolidinones, in the presence of various reagents, undergo different types of reactions to yield other heterocyclic compounds, e.g., thiazole, benzimidazole, thiopyranothiazolone, benzodiazepine, triazoles, benzothiophenes, triazinones, etc. These advances warrant to review the chemistry and biological properties of various 2-, 4-, and 5-thiazolidinones.

II. Preparation of Thiazolidinones

A. 2-Thiazolidinones

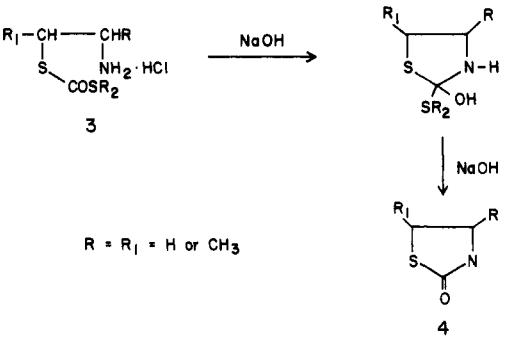
The acid hydrolysis of 2-iminothiazolidines (1) gives the corresponding 2-thiazolidinones (2) in good yields.[5,6]



1 2

R = p-$NO_2C_6H_4SO_2$, p-$CH_3CONHC_6H_4SO_2$
R_1 = H, CH_3
R_2 = H, CH_3 , C_6H_5
R_3 = H, p-$CH_3CONHC_6H_4SO_2$

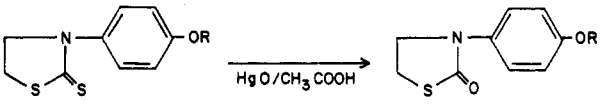
The treatment of 2-aminoethyl benzyl dithiocarbamate hydrochloride (3) with 1 N NaOH solution followed by neutralization with hydrochloric acid resulted in the formation of 2-thiazolidinones[7] (4).



3 4

R = R_1 = H or CH_3

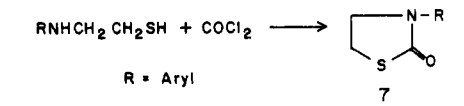
2-Thiothiazolidinones (5), on refluxing with mercuric oxide[8] in acetic acid, give 2-thiazolidinone (6).



5 6

R = CH_3 or C_2H_5

The reaction of *N*-(β-mercaptoethyl)arylamines with phosgene in toluene[9,10] yields 3-aryl-2-thiazolidinones (7).



R = Aryl 7

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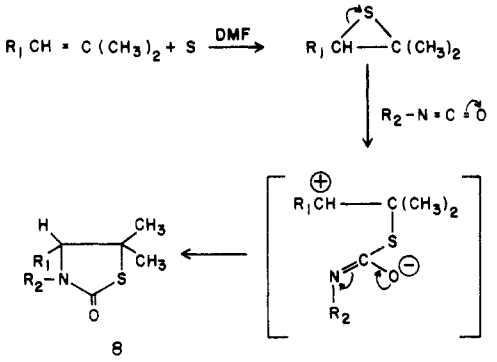
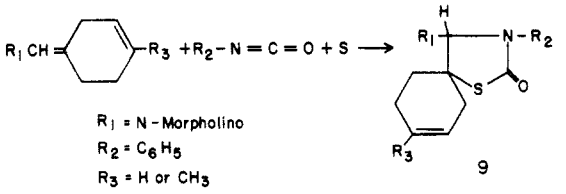
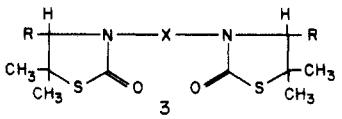
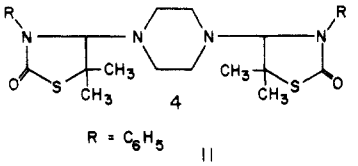
The synthesis of several substituted 2-thiazolidinones (8) is reported by the condensation of α-aminoalkenes,



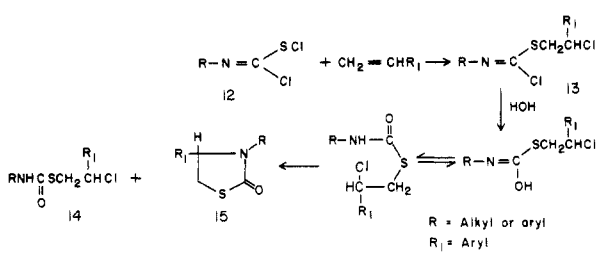




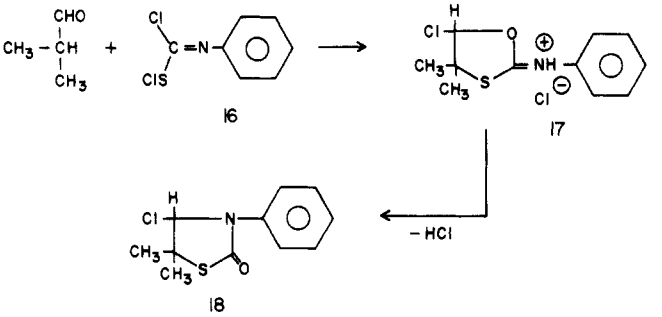


sulfur, and isocyanates.[11] The optimum yield is obtained when sulfur is first condensed with the aminoalkene in a solvent containing carbonyl group, preferably dimethylformamide, and the adduct thus obtained is treated with the appropriate isocyanate. The derivatives of (aminomethylene)cyclohexane or (aminomethylene)cyclohexene, on condensation with sulfur and isocyanates, give their corresponding spiro compounds (9). Under similar conditions, reaction of diisocyanates or diaminodienes yield the corresponding bicyclic derivatives 10 and 11, respectively.

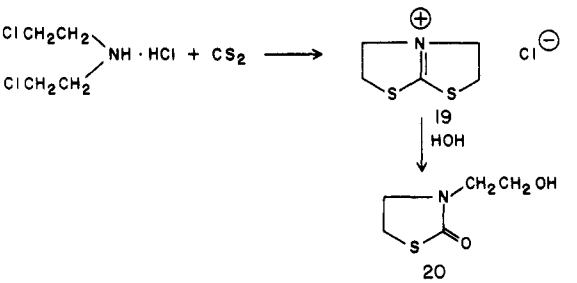
The reaction of *S*-chloroisothiocarbamoyl chloride (12) with olefins at 0–20 °C under anhydrous condition gives *S*-(2-chloro-2-alkyl(aryl))isothiocarbamoyl chlorides (13). The hydrolysis[12] of compound 13 leads to *S*-(2-chloroalkyl) *N*-alkyl- or *N*-arylthiocarbamates (14). However, the hydrolysis of 13 results in the formation of 2-thiazolidinones (15) as a major product and thiocarbamates (14) as a minor product when substituted R′ in olefins is a more strongly electron-attracting moiety such as phenyl group.



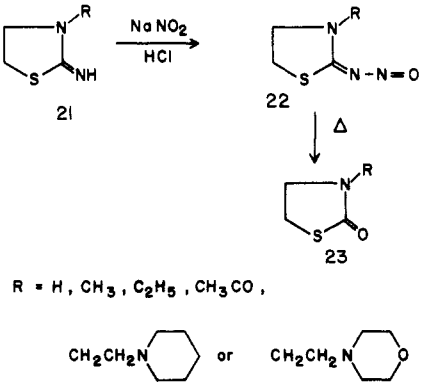
The addition of *N*-alkyl- or *N*-aryl-*S*-chloroisothiocarbamoyl chloride (16) to the ethereal solution of isobutyraldehyde at 25–30 °C leads to the formation of an adduct (17) which is of limited stability at room temperature and in a dry environment.[13] The intermediate 17 rearranges exothermally with the evolution of hydrogen chloride to form 4-chloro-5,5-dimethyl-3-alkyl-(aryl)-2-thiazolidinones (18). The *N*-alkyl-substituted adducts (17) are the least stable and rearrange spontaneously either partly or completely during their preparation.



The aqueous solution of 1,6-dithia-3a-azonia-2,3,4,5-tetrahydropentalene salt (19), obtained by the reaction of bis(2-chloroethyl)amine hydrochloride with carbon disulfide in pyridine, gives *N*-(2′-mercaptoethyl)-2-thiazolidinone (20) either by heating in a sealed tube for few hours or by standing for several days at room temperature.[21]



The reaction of 3-alkyl-2-iminothiazolidines (21) with aqueous $NaNO_2$ at 0 °C in the presence of hydrochloric acid or acetic acid produces 3-alkyl-2-nitrosoiminothiazolidines (22) which on refluxing in *n*-butyl alcohol



give the corresponding 3-alkyl-2-thiazolidinones[15] (23). Brown et al.[16] reexamined the thermal decomposition of 22 and noticed that the 3-methyl-2-(nitrosoimino)-thiazolidine decomposed smoothly in pyridine within 10 min to give 3-methyl-2-thiazolidinone in 87% yield. Decomposition also occurred in *p*-xylene, toluene, *o*-dichlorobenzene, and dimethyl sulfoxide.

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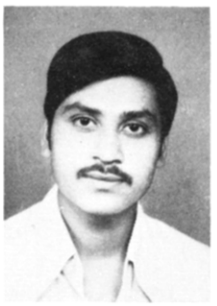
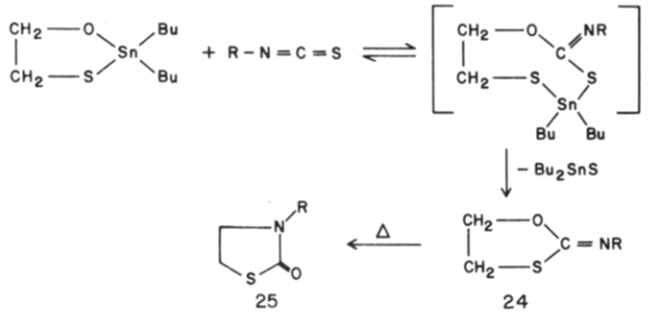
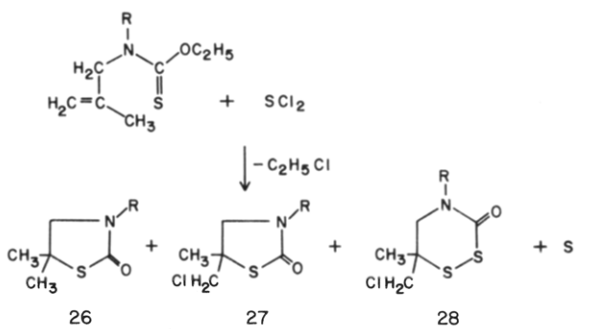


Krishna Raman is a research associate in the Department of Chemistry at the University of North Dakota, Grand Forks. He was born in India in 1951 and obtained his B.Sc. and M.Sc. degrees and Ph.D. (Chemistry) degree under the guidance of Dr. Surendra S. Parmar from Lucknow University at Lucknow, India. He was a postdoctoral research associate with Dr. S. Ranganathan at the Indian Institute of Technology, Kanpur, India, before joining the University of North Dakota. His research interests are in the field of synthetic organic, medicinal, and prostaglandin chemistry.

Cyclic organostannyl sulfides such as 2,2-dibutyl-1,3,2-oxathiastannolane react with phenyl or alkyl isothiocyanate to give 2-iminooxathiolane (**24**) with the



elimination of dibutylstannyl sulfide.[17] At higher reaction temperature, the rearrangement of the product **24** occurs to give 2-thiazolinidinones (**25**).

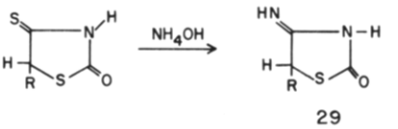


Surendra S. Parmar is Professor of Physiology at the School of Medicine of the University of North Dakota at Grand Forks, ND. He took his B.Sc., M.Sc., and Ph.D. (Chemistry) degrees at Lucknow University, Lucknow, India, and Ph.D. (Biochemistry) degree at McGill University, Montreal, Canada. Prior to his present position he had served as Professor of Pharmacology at the University of North Dakota and Professor of Medical Chemistry and Chemical Pharmacology at Lucknow University. He has also been associated with The Johns Hopkins University, University of Manitoba, University of Michigan, Boston University, The Chicago Medical School, and The University of Pennsylvania. His research interests are in the field of neurochemistry, psychopharmacology, biochemical pharmacology, and medicinal chemistry.

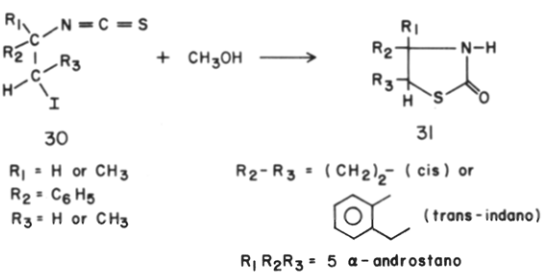
Virgil I. Stenberg is Chester Fritz Professor of Chemistry in the Department of Chemistry at the University of North Dakota, Grand Forks, ND. He was born in 1935 and obtained a B.A. from Concordia College, Moorhead, MN, and a Ph.D. in natural products, organic chemistry, from Iowa State University under the guidance of Dr. Ernest Wenkert. Dr. Stenberg was Visiting Professor at the Imperial College of Science and Technology, London, 1971–1972.

Sulfur dichloride reacts with the unsaturated thiocarbamic acid esters to yield heterocycles of the 2-thiazolidinone (**26** and **27**) and 3-dithiazinone (**28**) type.[18]

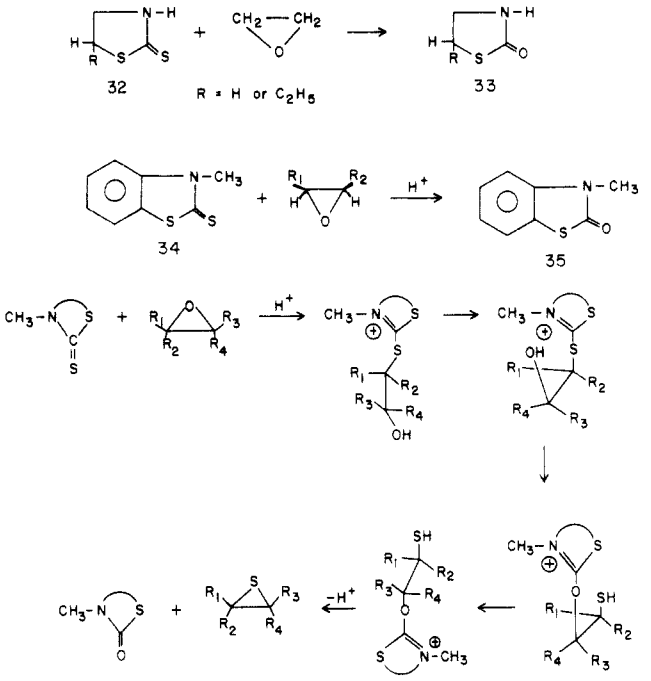
Isorhodanine[19] and 5-substituted isorhodanines,[20] on heating with 25% NH_4OH for 15 min at 80 °C, yield the corresponding 4-imino-2-thiazolidinones (**29**).



A convenient one-step cyclization reaction leading to the synthesis of 2-thiazolidinone derivatives from 2-iodoalkyl isothiocyanates has been recently reported.[21] Refluxing of *vic*-iodo isothiocyanates (**30**) with anhydrous methanol in tetrachloroethylene in the dark gives



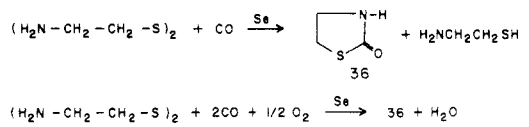
SCHEME I



various substituted 2-thiazolidinones (**31**) in good yields.

Treatment of thiazolidine-2-thiones (**32**) with ethylene 1,2-oxide gives the corresponding 2-thiazolidinones (**33**) via the exchange reaction between the oxygen of epoxide and sulfur atom of thiazolidine-2-thiones.[22] Similarly, 3-methylbenzothiazole-2-thione (**34**) reacts with cyclohexene oxide, styrene oxide, epichlorohydrin, and *cis*-stilbene oxide in presence of trifluoroacetic acid in dichloromethane at 0 °C and gives 3-methylbenzothiazol-2-one (**35**) in all cases.[23] The exchange reaction between oxygen of epoxides and sulfur atoms of **32** and **34** is represented mechanistically as in Scheme I.

2-Thiazolidinone (**36**) is obtained in high yields by the reaction of 2,2′-bifunctional disulfide with carbon monoxide using selenium as a catalyst. In this process



1 mol of disulfide gives 1 mol of 2-thiazolidinone and 1 mol of amino thiol. However, only 2-thiazolidinone is obtained when the above reaction is carried out in the presence of oxygen which reoxidizes the thiol to disulfide.[24]

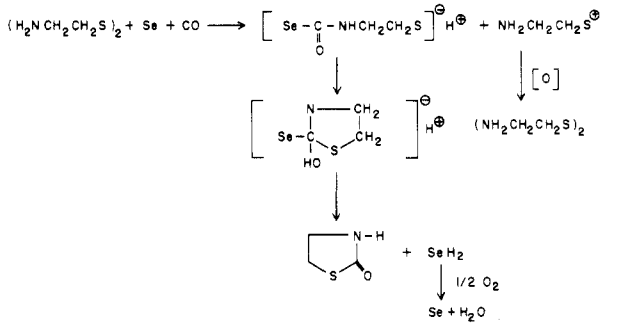
The mechanistic picture of the above reaction may be described as in Scheme II.

Sonoda et al.[25] reported the synthesis of 2-thiazolidinone by the reaction of 2-amino thiol with carbon monoxide using selenium as a catalyst in the presence of triethylamine in DMF. They proposed the mechanism in Scheme III.

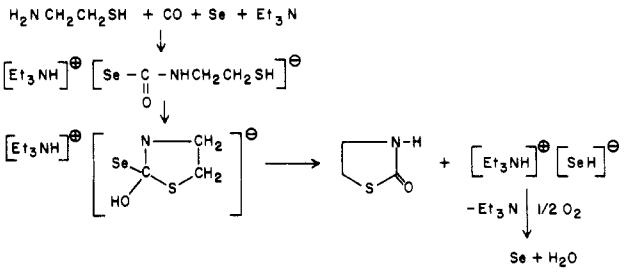
B. 4-Thiazolidinones

The dithiocarbamates, formed by the reaction of primary amine with carbon disulfide in the presence of a base, react with α-haloalkanoic acids in the presence

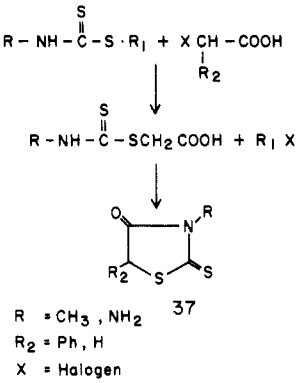
SCHEME II



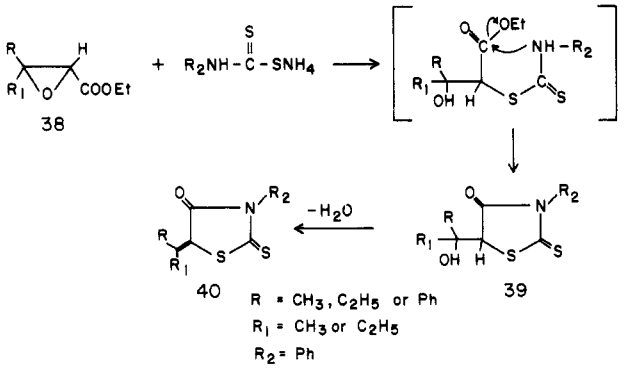
SCHEME III



of $NaHCO_3$ to give substituted 2-thiono-4-thiazolidinones[26,27] (**37**).

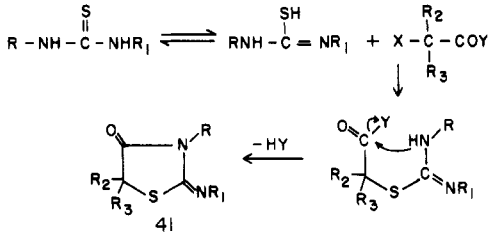


Ammonium dithiocarbamates condense with the glycidic esters **38** to give 2-thiono-3-substituted-5-(hydroxyalkyl)-4-thiazolidinones (**39**) which are readily dehydrated in refluxing acetic acid to 2-thiono-3-substituted-5-alkylidene-4-thiazolidinones[28] (**40**).



Substituted 2-imino-4-thiazolidinones (**41**) are obtained in good yields by the reaction of symmetrical and unsymmetrical thioureas with various substituted and unsubstituted α-haloalkanoic acids, their esters, acid chlorides, amides, or carbamates.[29-95] The reaction proceeds via the intermediate isothiourea which cyclizes in refluxing acetic acid, ethanol, or benzene in the

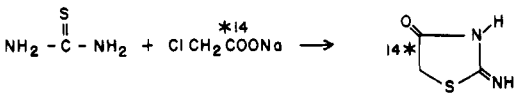
presence of sodium acetate or pyridine.



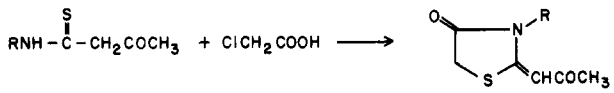
41

R = Alkyl, aryl or heterocyclic
R_1 = Alkyl, aryl or heterocyclic
R_2 = H or alkyl
R_3 = H or alkyl
R_2R_3 = Alkylidene or arylidene

The synthesis of 2-imino-4-thiazolidinones-*4*-^{14}C has been reported by using thioureas and sodium salt of the labeled monochloroacetic acid.[96]



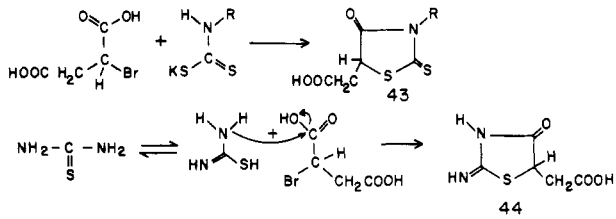
Various N-substituted acetylthioacetamides on treatment with monochloroacetic acid in the presence of sodium acetate in refluxing acetic acid yield 2-acetylmethylene-3-substituted-4-thiazolidinones[97] (**42**).



R = Aryl

42

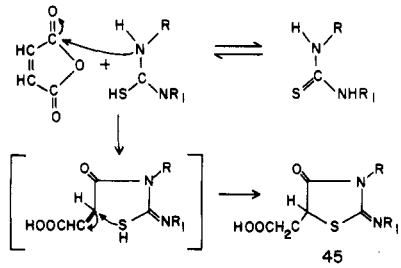
4-Oxo-5-thiazolidineacetic acids can be conveniently prepared from dicarboxylic acids.[98] α-Bromosuccinic acid mixed with dithiocarbaminates on neutralization with $NaHCO_3$ followed by acidification and boiling yields 2-thiono-4-oxo-5-thiazolidineacetic acids (**43**). However, α-bromosuccinic acid on treatment with thioureas in the presence of sodium acetate in methanol yields 2-imino-4-oxo-5-thiazolidineacetic acids (**44**).



43

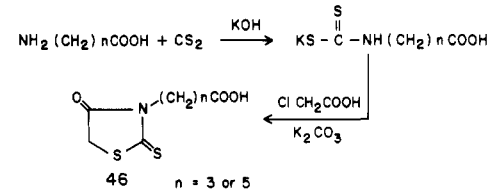
44

2-Imino-4-oxo-5-thiazolidineacetic acids can also be synthesized in good yields by refluxing equimolar amounts of substituted and unsubstituted thioureas and maleic anhydride in acetone (**45**).[99-101]



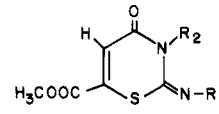
45

3-Carboxyalkyl-2-thiono-4-thiazolidinones have been synthesized from long-chain amino acids,[102,103] $NH_2(CH_2)_nCOOH$. The amino acids react with CS_2 and chloroacetic acid in the presence of bases to give the corresponding *N*-substituted-4-thiazolidinones (**46**) through the intermediate formation of dithionate.



46 n = 3 or 5

Dimethyl acetylenedicarboxylate (DMAD) reacts readily with substituted and unsubstituted thioureas, dithiocarbamates, thiocarbamates, thiosemicarbazides, and thiosemicarbazones to give 4-thiazolidinones.[104,105] Lown et al.[106] have proposed the six-membered structure, 2,3-dihydro-1,3-thiazine-4-one (**47**), for the reaction

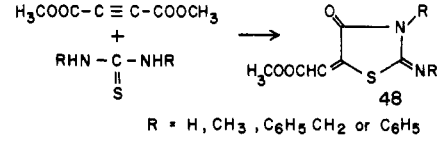


47

R_1 = H, CH_3, $(CH_3)_2CH$, $C_6H_5CH_2$ or C_6H_5

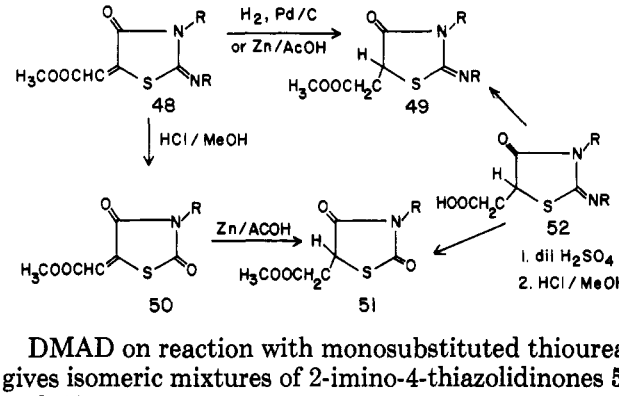
R_2 = H, CH_3, $C_6H_5CH_2$, C_6H_5 or O-CH_3OC_6H_4

products of DMAD and thioureas on the basis of NMR and mass spectra. Structure **47** was supported by Winterfeldt et al.[107] and Kishida et al.[108] but is without any chemical evidence. Products **47** were, however, proved to have the five-membered structure **48** by chemical reactions and spectroscopic data.[104] The structure was confirmed by the characteristic fragmentations in the mass spectra. The principal daughter ions were determined by means of deuterium exchange and high-resolution mass spectroscopy.



48

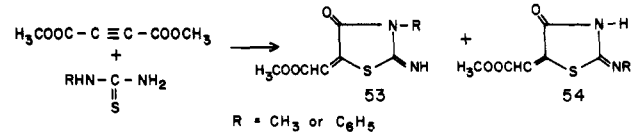
R = H, CH_3, $C_6H_5CH_2$ or C_6H_5



48 49 50 51 52

I. dil H_2SO_4
2. HCl / MeOH

DMAD on reaction with monosubstituted thioureas gives isomeric mixtures of 2-imino-4-thiazolidinones **53** and **54**.

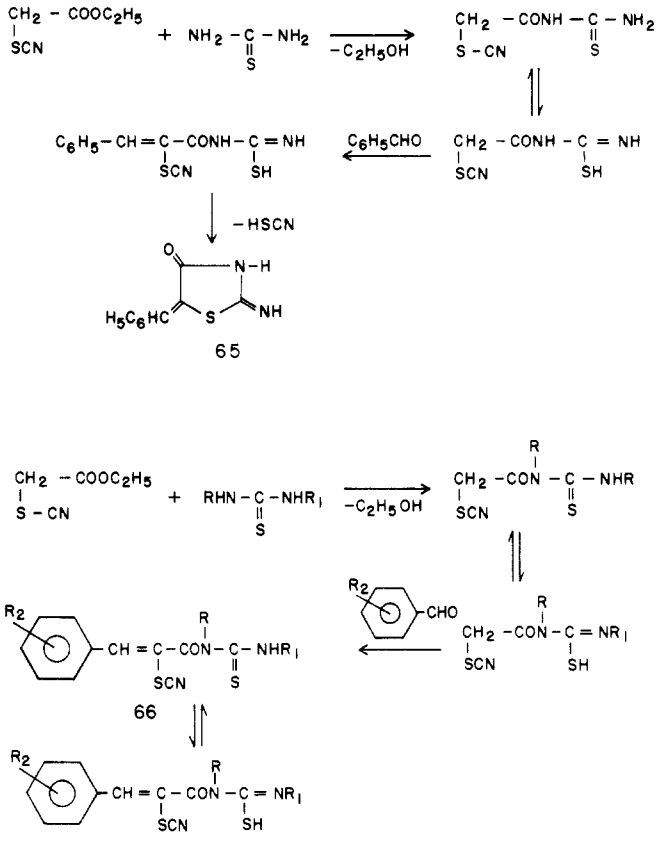


53 54

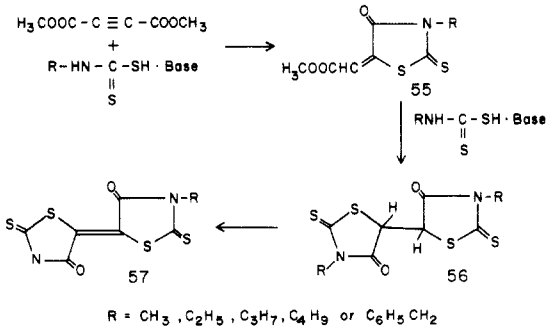
R = CH_3 or C_6H_5

DMAD reacts readily with dithiocarbamates in methanol at room temperature to give 2-thiono-4-thiazolidinones.[104,105] The course of the reaction was, however, found to be markedly influenced by the reaction conditions. When DMAD is added to the methanolic

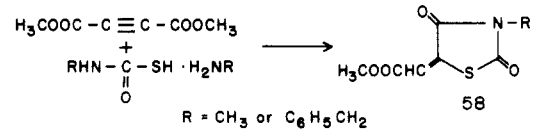
SCHEME IV



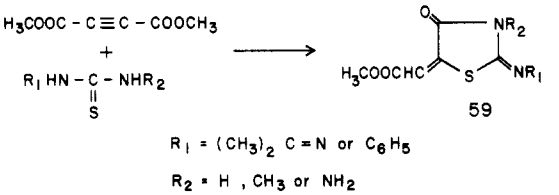
solution of ammonium N-substituted dithiocarbamate, 3,3′-disubstituted-2,2′-dithiono-$\Delta^{5,5'}$-bi-4-thiazolidinones (**57**) are obtained as a result of the reaction of DMAD with 2 equiv of N-substituted dithiocarbamates. On the other hand, when ammonium N-substituted dithiocarbamates are added slowly to the methanolic solution of small excess amounts of DMAD, 3-substituted-5-[(methoxycarbonyl)methylidene]-2-thiono-4-thiazolidinones (**55**) are obtained. The studies suggest that the reaction of DMAD with dithiocarbamates give 4-thiazolidinones (**55**) and that dithiocarbamates react readily with **55** to give 2,2′-dithiono-5,5′-bi-4-thiazolidinones (**56**) which are autoxidized to 2,2′-dithiono-$\Delta^{5,5'}$-bi-4-thiazolidinones (**57**).



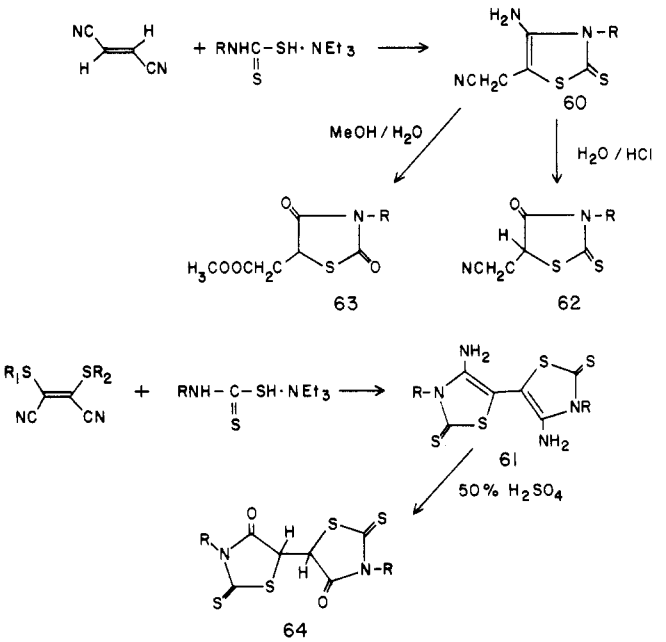
DMAD reacts with methylammonium *N*-methylthiocarbamate in methanol at room temperature to give 3-substituted-5-[(methoxycarbonyl)methylidene]-2,4-thiazolidinediones (**58**).



DMAD also reacts with thiosemicarbazides and thiosemicarbazones to give various 4-thiazolidinones (**59**).



Nagase[109] extended the study of addition reactions of dithiocarbamates to activated double bonds and reported the reactions of dithiocarbamates with fumaronitrile and bis(alkylthio)maleonitrile to give intermediates **60** and **61**, respectively, which on acid treatment

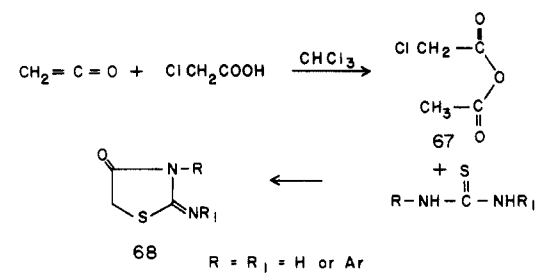


resulted into the formation of 4-thiazolidinones (**62–64**). The double bonds of the nitriles are activated by cyano groups which react readily with nucleophiles.

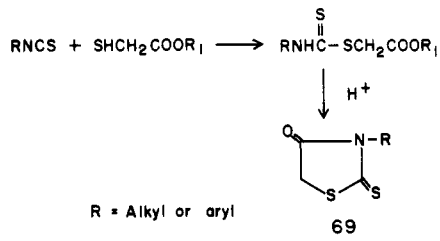
Ethyl thiocyanoacetate has been reported to react with benzaldehyde in the presence of thiourea to afford 5-benzylidene-2-iminothiazolidinone[110] (**65**). A plausible reaction sequence is illustrated in Scheme IV. However, the reaction of ethyl thiocyanoacetate with aromatic aldehydes in the presence of *N,N′*-dialkylthioureas leads to the formation of arylidene-*N,N′*-dialkyl-*N*-thiocarbamoylthiocyanoacetamides (**66**) which are not cyclized further.

We, however, believe that the ring closure might occur with the elimination of hydrogen thiocyanide.

Mixed anhydride (**67**), prepared by passing ketene into chloroacetic acid, reacts with substituted and unsubstituted thioureas in chloroform at 60 °C to give various 2-imino-4-thiazolidinones[111,112] (**68**).

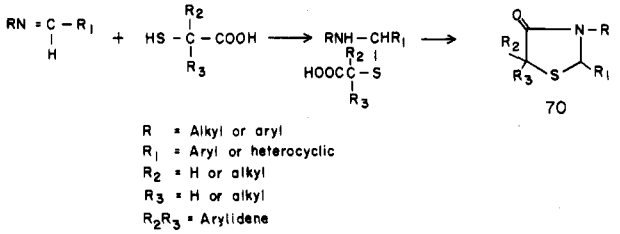


Various 3-substituted-2-thiono-4-thiazolidinones (69) can be conveniently prepared by the reaction of substituted isothiocyanates with α-mercaptoacetic acid or its ester followed by acid cyclization of the resulting (thiocarbamoyl)mercaptoacetic acids and acetates.[113]



69

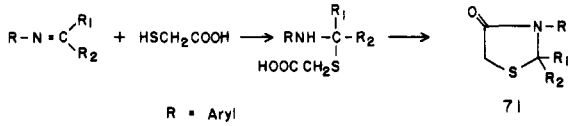
α-Mercaptoalkanoic acids have been extensively used for the synthesis of 4-thiazolidinones. The substituted and unsubstituted α-mercaptoalkanoic acids react conveniently with Schiff bases of aromatic or heterocyclic aldehydes and aliphatic or aromatic amines in different solvents to give a variety of 2-substituted-4-thiazolidinones[114-143] (70).



70

R = Alkyl or aryl
R_1 = Aryl or heterocyclic
R_2 = H or alkyl
R_3 = H or alkyl
R_2R_3 = Arylidene

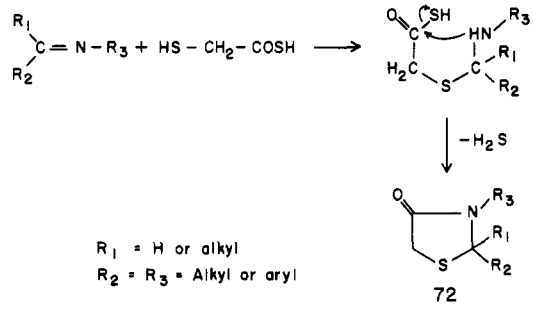
Schiff bases obtained by the condensation of ketones and amines also react with α-mercaptoacetic acid to give 2,2-disubstituted-4-thiazolidinones[144] (71).



71

R = Aryl
R_1 = Alkyl
R_2 = Alkyl

α-Mercaptothiocarboxylic acids can also be used for the synthesis of 4-thiazolidinones (72) by the reaction with different Schiff bases[145] by refluxing in ether.

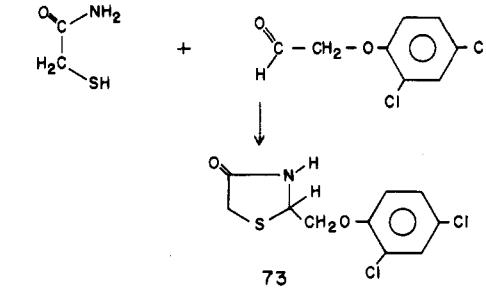


R_1 = H or alkyl
R_2 = R_3 = Alkyl or aryl

72

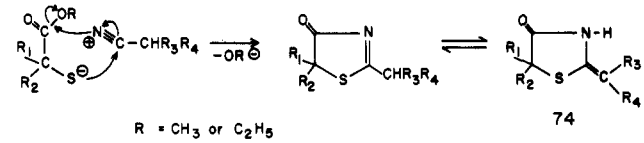
α-Mercaptoacetamide reacts with the carbonyl function of aldehydes in the presence of catalytic amounts of *p*-toluenesulfonic acid or boron trifluoride ethereate in inert solvent to give 2-substituted-4-thiazolidinones[146] (73).

Substituted and unsubstituted α-mercaptoacetic acid esters react smoothly with the compounds containing activated nitrile groups in the presence of an equivalent



73

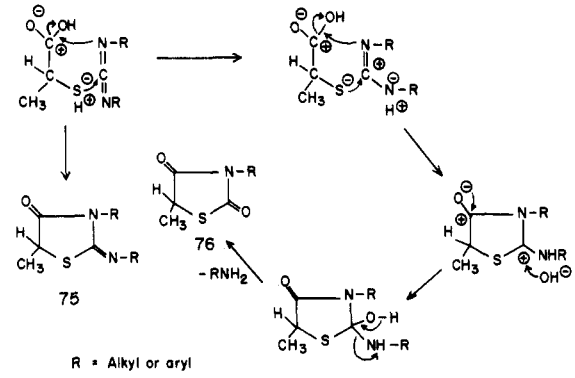
amount of alcoholate to give 4-thiazolidinones[147,148] (74).



74

R = CH_3 or C_2H_5
R_1 = H or C_2H_5
R_2 = H, C_2H_5, Ph or O-$CH_3C_6H_4$
R_3 = H or Ph
R_4 = -COOEt, $-CONH_2$, -CN, Bz, Ph, Pyridyl or indoyl

Monforte et al.[149] have recently synthesized 4-thiazolidinones (75) and 2,4-thiazolidinediones (76) by reacting carbodiimides with α-mercaptopropionic acid.

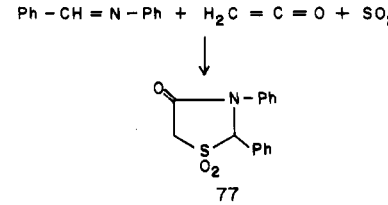


R = Alkyl or aryl

The acid reacts with one of the two carbodiimidic C=N groups to give 3-substituted 2-imino-5-methyl-4-thiazolidinones (75). The related 3-substituted 5-methyl-2,4-thiazolidinediones are also formed except in the reaction with dicyclohexylcarbodiimide.

In contrast to the 4-thiazolidinones (75), the infrared spectra of the 2,4-thiazolidinedione derivatives show a complex carbonyl pattern due to the multiple carbonyl absorptions in the 1765–1675-cm^{-1} range. "Fermi resonance" effects are probably responsible for such a complexity.

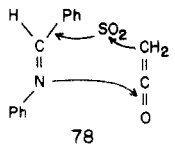
Gomes and Joullié[150] reported the formation of 2,3-diphenyl-4-thiazolidinone 1,1-dioxide (77) by reaction



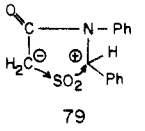
77

with benzylideneaniline with ketene in liquid SO_2 at −70 °C. The cycloaddition may proceed through a concerted mechanism (78) or through the reaction of 1,4-dipole intermediate, formed from ketene and the imine with sulfur dioxide (79).

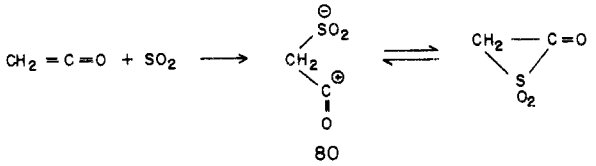
Gomes and Joullié[151] further demonstrated the formation of a reactive intermediate species (80) from



78

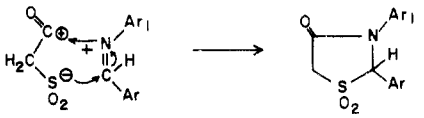


79



80

ketene and sulfur dioxide, though not by isolation but by interception with appropriate reagents and low-temperature NMR study. They have studied 1,3-dipolar additions of the intermediate with benzylideneaniline and its derivatives to give 2,3-disubstituted-4-thiazolidinones (81) and demonstrated the reaction to be sensitive to electronic effects. Electron-withdrawing

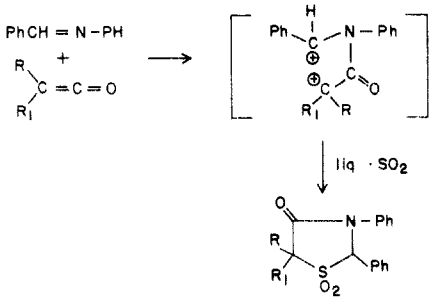


81

groups in the benzylidene ring favored the reaction while the same groups in the aniline ring of the Schiff base hindered the reaction. They have shown that other ketenes such as dimethyl-, ethylbutyl-, and diphenylketenes do not form adducts with sulfur dioxide. The lack of reactivity of diphenylketene toward sulfur dioxide could be explained as the result of steric hindrance or delocalization of the negative charge.

Decazes et al.[152] studied the cycloaddition of disubstituted ketenes and benzylideneaniline in liquid sulfur dioxide and proposed a two-step ionic mechanism involving dipolar species followed by ring closure (Scheme V). In this manner two diastereomeric thiazolidinone 1,1-dioxides (**82** and **83**) can be formed. However, X-ray diffraction and spectral studies have confirmed that the reaction of a ketene with benzylideneaniline in liquid sulfur dioxide as solvent yields only the *trans*-thiazolidinone 1,1-dioxides **82**.

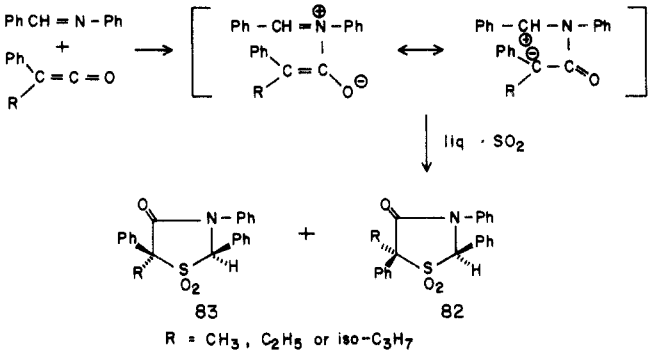
Bellus[153] has demonstrated the facile synthesis of **84** where at least one of the substituents R or R_1 is halogen (Cl or Br) or alkylthio and their simple transformation to derivatives where both R and R_1 are hydrogen atoms or alkyl groups.



R = Cl, Br, SCH_3 or SC_2H_5 84
R_1 = H, Cl, Br, $n-C_4H_9$, C_6H_9 or SC_2H_5
RR_1 = $-S(CH_2)_2S-$

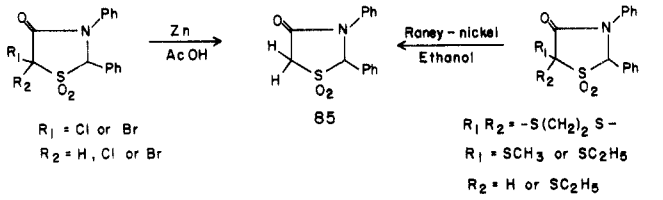
The 5-halogenated and 5-alkylthio derivatives of **84** are conveniently dehalogenated and desulfurized by

SCHEME V



83 82
R = CH_3, C_2H_5 or iso-C_3H_7

SCHEME VI

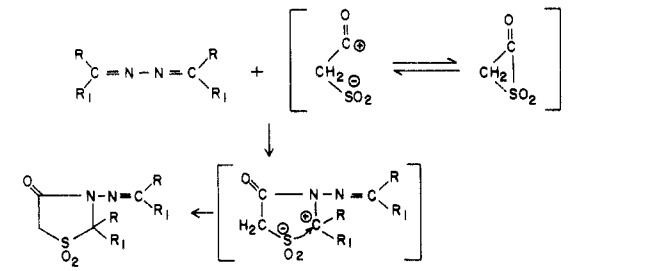


R_1 = Cl or Br
R_2 = H, Cl or Br

85

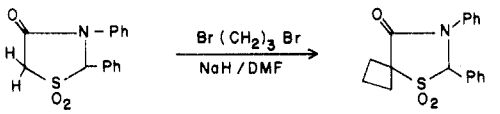
R_1R_2 = $-S(CH_2)_2S-$
R_1 = SCH_3 or SC_2H_5
R_2 = H or SC_2H_5

SCHEME VII



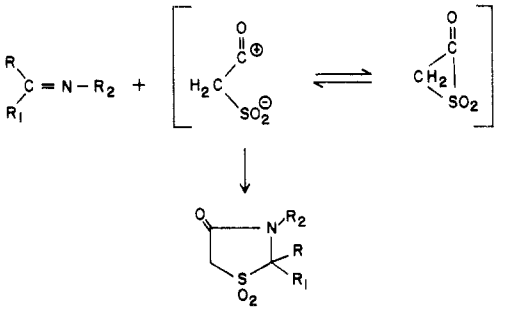
88 R = 2-Furyl, 5-methyl-2-furyl, 2-thienyl, 3,4-dimethoxyphenyl, 3-methoxyphenyl or styryl
R_1 = H or CH_3

treatment with zinc in acetic acid and Raney nickel in ethanol, respectively, to **85**.



85 86

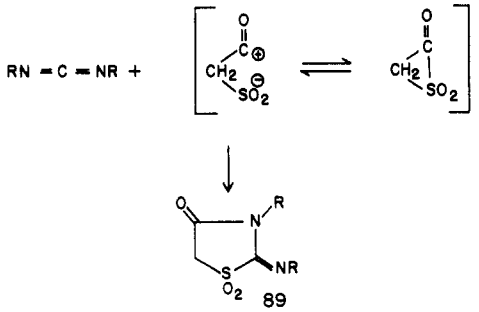
The product **85** is easily dialkylated in the 5-position, leading to the formation of spiro compound **86** using dibromopropane in the presence of NaH in dimethylformamide.



R = Aryl 87
R_1 = H or aryl
R_2 = Alkyl or aryl

Lysenko and Joullié[154] have reported the reaction of ketene–SO_2 adduct with different compounds containing the imino function, thereby illustrating the gener-

SCHEME VIII



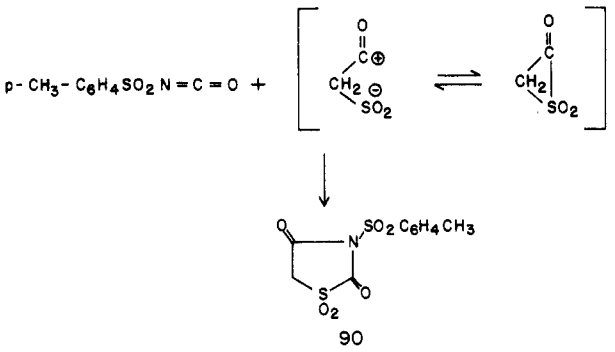
R = Bz, 4-tolxyl, 4-anisyl, 3,5-$Me_2C_6H_3$ or 2,4,5-Me_3C_6H

ality of this reaction (Scheme VI).

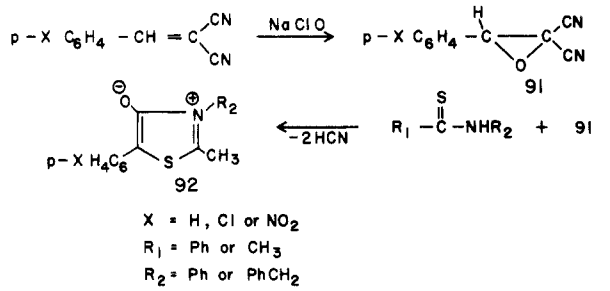
In order to further extend the reactions of the ketene–sulfur dioxide adduct to dipolarophiles, Lysenko and Joullié[154] have reported the reactions of both aldehyde and ketone azines with the adduct at −78 °C in liquid sulfur dioxide (Scheme VII).

Fisher et al.[155] extended the study of the cycloaddition reactions of ketene–sulfur dioxide adduct to the carbodiimides (Scheme VIII).

Bohen and Joullié[156] studied the reaction of isocyanates with ketene–sulfur dioxide adduct. Both aryl and alkyl isocyanates were found to be unreactive. However, the highly active *p*-tolylsulfonyl isocyanate has been shown to undergo cycloaddition with ketene–sulfur dioxide adduct at −10 °C, resulting in the formation of 2,4-thiazolidinedione (**90**).



Baudy and Robert[157] have synthesized mesoionic thiazoles, anhydro-5-hydroxythiazolium hydroxides (**92**), in good yields by the reaction of *gem*-dicyano epoxides (**91**) with thioamides in neutral medium. In most



X = H, Cl or NO_2

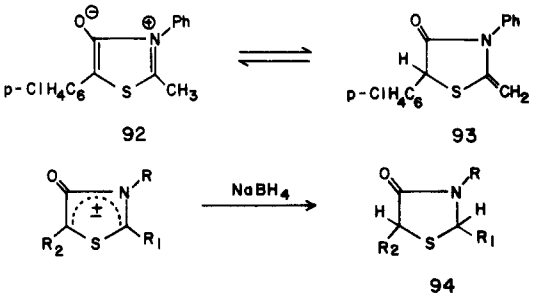
R_1 = Ph or CH_3

R_2 = Ph or $PhCH_2$

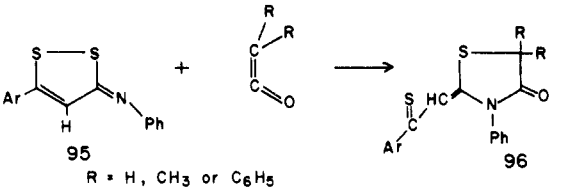
cases the reaction is complete after 2 h at room temperature.

The NMR spectrum of compound **92**, where X = Cl, R_1 = Me, and R_2 = Ph, shows the existence of a tautomeric equilibrium between **92** and 4-thiazolidinone derivative **93**.

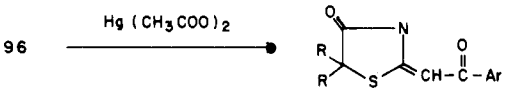
Takayanagi et al.[158] reported the synthesis of 4-thiazolidinones (**94**) by the reduction of 4-thiazones with sodium borohydride.

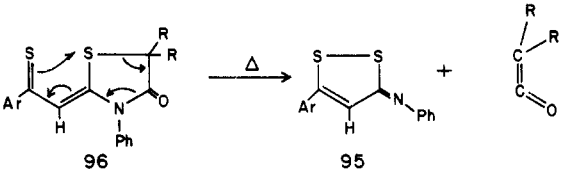


5-Aryl-3-(phenylimino)-1,2-dithioles (**95**) react easily with various ketenes[159] to give 2-(2-aryl-2-thioxoethylidene)-3-phenyl-5,5-disubstituted-4-thiazolidinones (**96**). Sulfur atom in the side chain at position 2 of **96** is readily exchanged by oxygen on treatment with mercuric acetate.



R = H, CH_3 or C_6H_5



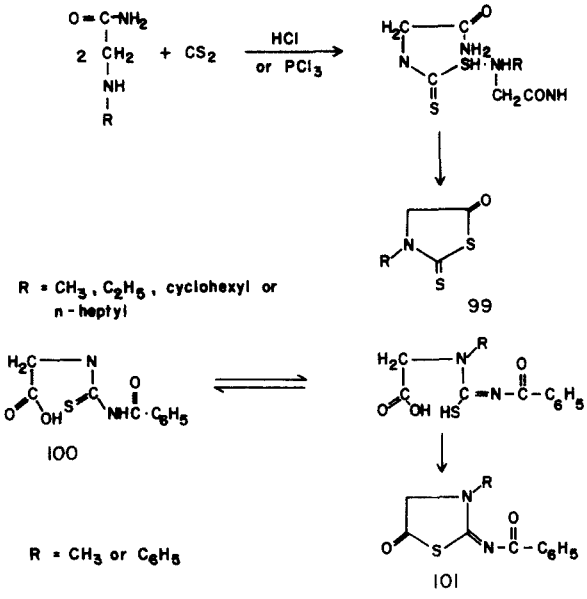


Compounds **96** are fragmented to their starting materials on pyrolysis. However, such compounds loose phenyl isocyanate on oxidation and give 1-aryl-3,4-epithio-4,4-disubstituted-butene-2-thione (**97**) which quickly rearranges to a new product, 3-(disubstituted methylene)-5-aryl-1,2-dithioles (**98**).

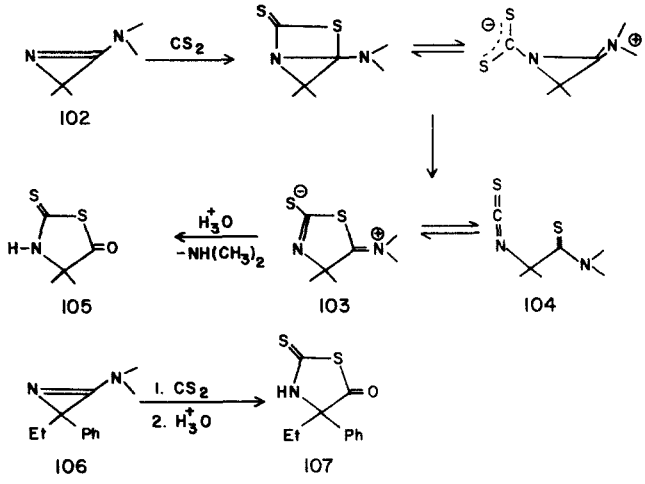
C. 5-Thiazolidinones

N-Methylglycine amide reacts with carbon disulfide in the presence of methanol and gives *N*-methyl-*N*-(carbamoylmethyl)ammonium *N*-methyl-*N*-(carbamoylmethyl)dithiocarbamate. This dithiocarbamate on acidification[160,161] with concentrated hydrochloric acid or phosphorus trichloride gives 2-thio-3-methyl-5-thiazolidinone (**99**).

N-Benzoylthiocarbamoyl N-substituted glycines (**100**) undergo acid-catalyzed[162,163] cyclization to give 3-substituted-5-thiazolidinones (**101**).



3-(Dimethylamino)-2,2-dimethyl-2*H*-azirine (**102**) reacts with carbon disulfide to give crystalline product which have the dipolar structure **103** [4,4-dimethyl-5-(dimethyliminium)-2-thiazoline-2-thiolate]. In solution, nondipolar (charge-free) isomeric form **104** (1-(dimethylthiocarbamoyl)-1-methylethyl isothiocyanate) is almost exclusively populated. The hydrolysis of **103** with 3 N hydrochloric acid results in the formation of 4,4-dimethyl-2-thiono-5-thiazolidinone (**105**) in 84% yield. The structure of **105** is confirmed on the basis of IR, NMR, and mass spectral data analysis.[164]

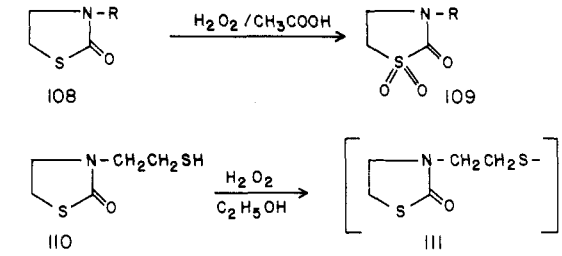


Similarly, Schaumann et al.[165,166] reported the synthesis of 4-ethyl-4-phenyl-2-thiono-5-thiazolidinone (**107**) and **105** starting with 3-(dimethylamino)-2-ethyl-2-phenyl-2*H*-azirine (**106**) and 3-(dimethylamino/diethylamino/morpholino)-2,2-dimethyl-2*H*-azirine (**102**), respectively.

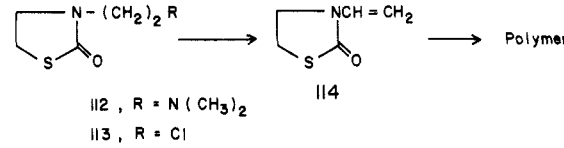
III. Reaction of Thiazolidinones

A. 2-Thiazolidinones

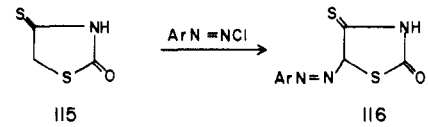
The oxidation of 3-substituted-2-thiazolidinones (**108**) with 30% hydrogen peroxide[167] in the presence of hot acetic acid results in the formation of a new class of cyclic sulfones (**109**). On the other hand, a mixture of ethanolic solution of *N*-(2-mercaptoethyl)-2-thiazolidinone (**110**) and 10% hydrogen peroxide[14] solution on standing overnight at room temperature gives β-(2-thiazolidinon-3-yl)ethyl disulfide (**111**).



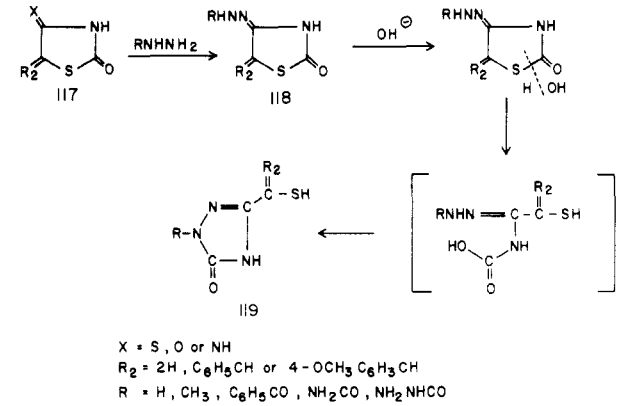
N-Vinyl-2-thiazolidinone (**114**), obtained either by the Cope degradation of *N*-(2-(dimethylamino)ethyl)-2-thiazolidinone (**112**) or by dehydrohalogenation of *N*-(2-chloroethyl)-2-thiazolidinone (**113**), is readily polymerized to a white solid in the presence of a radical catalyst such as α,α′-azobisisobutyronitrile or benzoyl peroxide.[168] This polymer is resistant to acid or alkali hydrolysis, though the 2-thiazolidinone is readily hydrolyzed to 2-aminoethanethiol on treatment with mineral acids.[169]



The reaction of various substituted benzenediazonium chloride with 5-thiono-2-thiazolidinone (**115**) in dioxane at 0 °C gives the corresponding 5-substituted phenylazo-2-thiazolidinones (**116**) in good yield.[170]

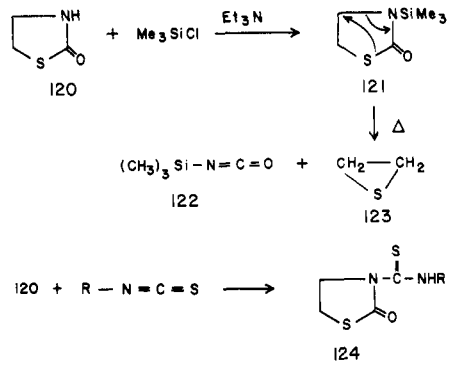


Hydrazine and hydrazide derivatives,[20,171-173] on condensation with 4-thiono-, 4-oxo-, and 4-imino-2-thiazolidinones (**117**) in boiling water or ethanol, yield 4-(substituted-hydrazono)-2-thiazolidinones (**118**) which on recrystallization in alkaline medium undergo rearrangement and give 5-(mercaptomethyl)-2-substituted-1,2,4-triazol-3-ones (**119**).



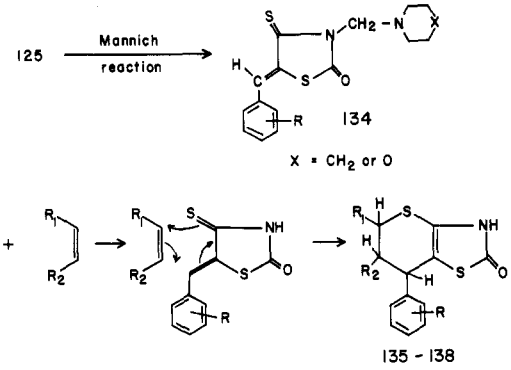
Silylation[174] of 2-thiazolidinone (**120**) is achieved with trimethylsilyl chloride in tetrahydrofuran in the presence of triethylamine. The silylated 2-thiazolidinone **121** undergoes ring opening during thermolysis and gives trimethylsilyl isocyanate (**122**) and ethylene sulfide (**123**).

2-Thiazolidinone (**120**) reacts with alkyl isothiocyanate in the presence of pyridine[175] to give 3-(*N*-alkylthiocarbamoyl)-2-thiazolidinones (**124**).



Treatment of 5-arylidene-4-thiono-2-thiazolidinones (**125**) with diazomethane in ether–chloroform mixture gives both N- and S-methylated derivatives **126** and **127**, respectively (Scheme IX). The S-substituted derivatives **127** and **128** are obtained only when **125** is treated with ethereal diazomethane or ethyl bromoacetate, respectively. On the other hand, 5-arylazo-4-thiono-2-thiazolidinones (**129**) give both N- and S-methylated derivatives, **130** and **131**, respectively, when treated with ethereal diazomethane.[176] 5-Arylidene-4-(arylimino)-2-thiazolidinones (**132**) yield *N*-methyl derivatives (**133**) in the presence of ethereal diazomethane or methyl iodide and potassium ethoxide.[177]

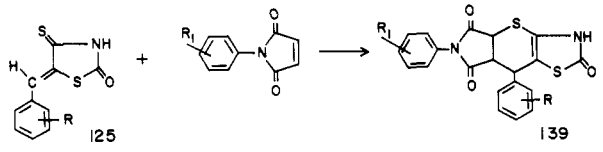
Compound **125** undergoes Mannich reaction[176] and gives N-alkylated derivatives (**134**). Furthermore, the



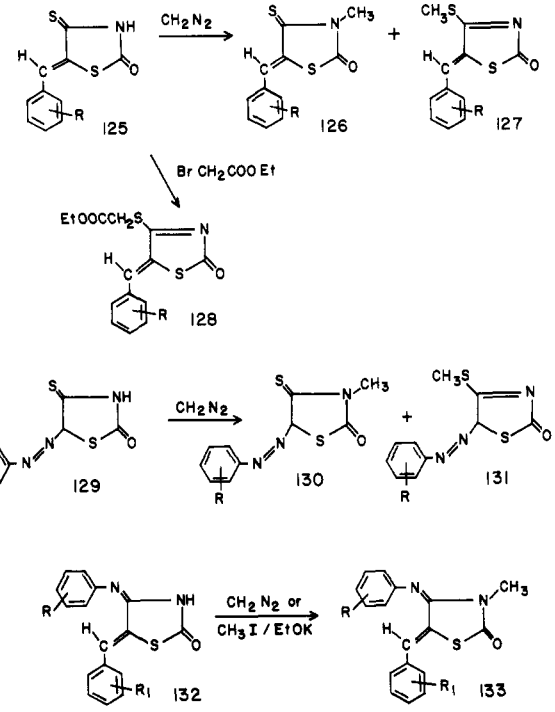
135 - R_1 = H, R_2 = CN
136 - R_1 = H, R_2 = $COOC_2H_5$
137 - R_1 = C_6H_5, R_2 = NO_2
138 - R_1 = C_6H_5, R_2 = COC_6H_5

reaction of **125** with acrylonitrile, ethyl acrylate, ω-nitrostyrene, or β-styryl ethyl ketone at room temperature in benzene or ether solution in the presence of pyridine as a catalyst gives the corresponding tetrahydro-7*H*-thiopyrano[2,3-*d*]thiazol-2-one derivatives **135**, **136**, **137**, and **138**, respectively. The formation of **135–138** takes place via S-β-cyanoethylation, S-β-carboxyethylation, S-β-nitrophenylethylation, or S-β-carbonylphenylethylation followed by Michael addition to the unsaturated center.[176,178]

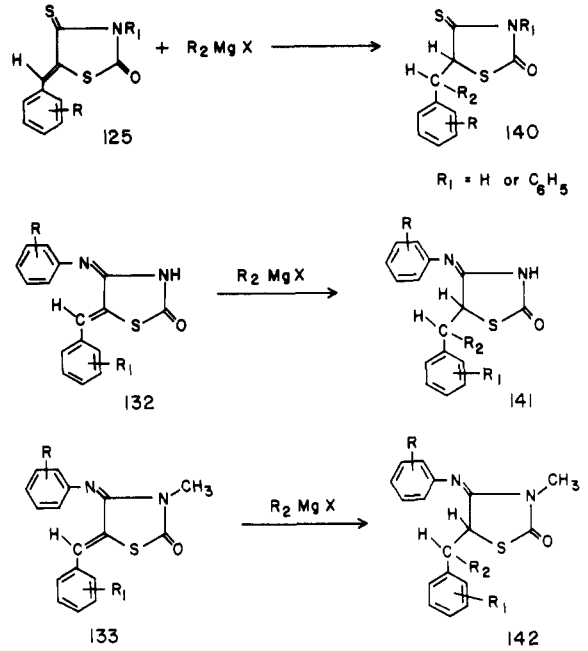
Thiazolidinones (**125**) also react with *N*-arylmaleimides[178] in glacial acetic acid to give corresponding Michael addition products, i.e., 5,6-bis(hydroxycarbonyl)tetrahydro-7*H*-thiopyrano[2,3-*d*]thiazol-2-one *N*-arylimides (**139**).



SCHEME IX

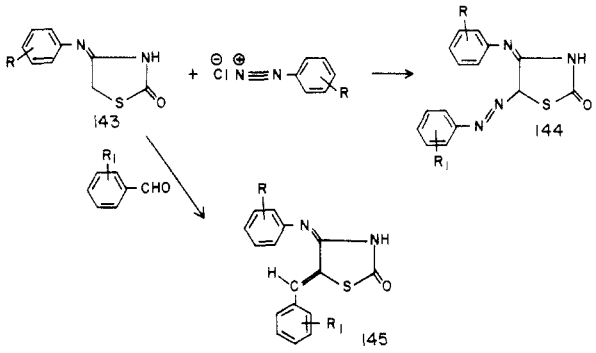


The reaction of Grignard's reagents[177-179] with various substituted-2-thiazolidinones **125**, **132**, and **133** gives 5-substituted-4-thiono-2-thiazolidinones (**140**), 5-substituted-4-(arylimino)-2-thiazolidinones (**141**), and 5-substituted-4-(arylimino)-3-methyl-2-thiazolidinones (**142**), respectively. In this reaction, the carbanion of

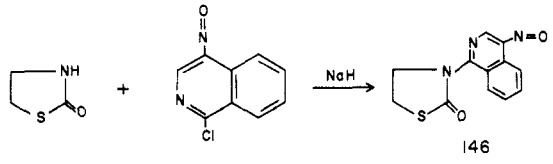


the reagent attacks the exocyclic electrophilic carbon atom of **125**, **132**, and **133**.

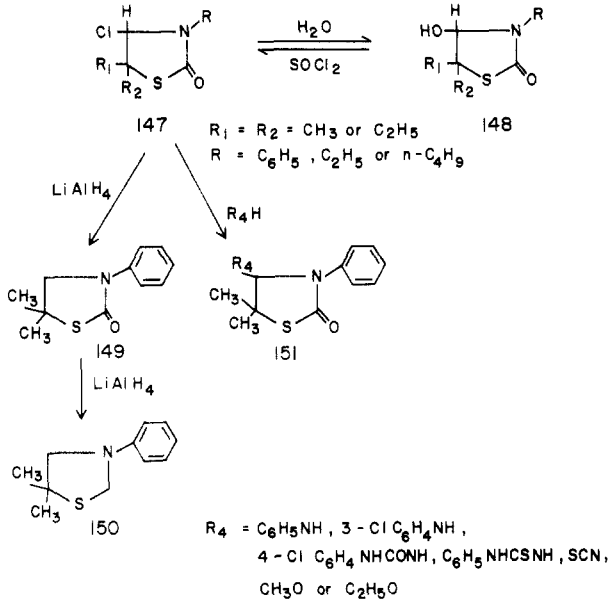
4-(Arylimino)-2-thiazolidinones (**143**) undergo diazocoupling reaction[177] with aryldiazonium chlorides to give 5-(arylazo)-4-arylimino-2-thiazolidinones (**144**). Compounds represented by **143** also condense with the appropriate aromatic aldehydes to give 5-arylidene-4-(arylimino)-2-thiazolidinones (**145**). Similarly, 4-imino-2-thiazolidinone with aromatic aldehydes in the presence of anhydrous sodium acetate and glacial acetic acid gives 5-arylidene-4-imino-2-thiazolidinone.[19]



2-Thiazolidinone reacts with 1-chloro-4-nitroisoquinoline[180] in the presence of NaH in DMF to yield 3-(4-nitroisoquinolin-1-yl)-2-thiazolidinone (**146**).

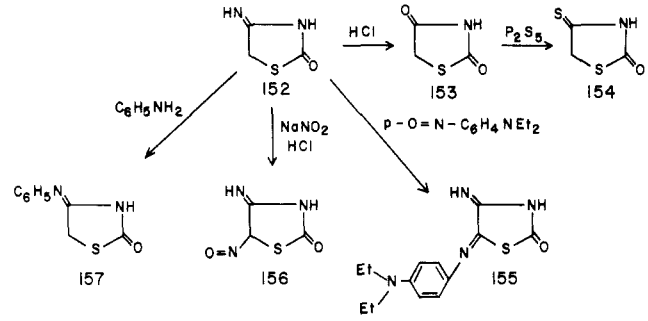


4-Chloro-5,5-dialkyl-2-thiazolidinones (**147**) possessing an exceptionally reactive chlorine atom are very susceptible to nucleophilic attack.[13] These compounds react readily with water, alcohols, amines, etc. The



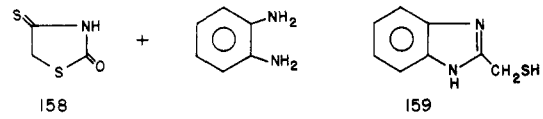
4-hydroxy-5,5-dialkyl-2-thiazolidinone (**148**), obtained by the reaction of **147** with water, is converted back to **147** by reaction with thionyl chloride. In other reactions, *N*-phenyl-4-chloro-5,5-dimethyl-2-thiazolidinone gives dehalogenated derivative **149** in the first step and *N*-phenyl-5,5-dimethylthiazolidine (**150**) in the second step when treated with lithium aluminium hydride. Replacement of chlorine of *N*-phenyl-4-chloro-5,5-dimethyl-2-thiazolidinone by alcohol, aromatic amine, urea, thiourea, and isothiocyanate gives *N*-phenyl-4-substituted-5,5-dimethyl-2-thiazolidinones (**151**).

4-Imino-2-thiazolidinone[19,20] (**152**), on refluxing with concentrated HCl, gives 2,4-thiazolinedione (**153**) which on treatment with phosphorus pentasulfide in boiling dioxane gives 4-thiono-2-thiazolidinone (**154**). The reaction of **152** with *p*-nitroso(diethylamino)benzene in the presence of acetic anhydride on standing for 20 h yields 5-[[(*p*-(diethylamino)phenyl]imino]-4-imino-2-thiazolidinone (**155**). Sodium nitrite reacts with **152** in



the presence of 5% HCl at 0 °C to give 5-nitroso-4-imino-2-thiazolidinone (**156**). Treatment of **152** with aniline in the presence of sodium acetate and glacial acetic acid gives 4-(phenylimino)-2-thiazolidinone (**157**).

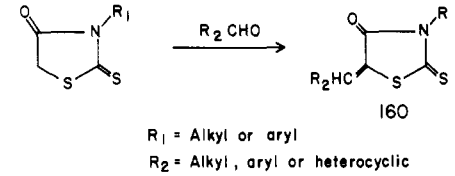
4-Thiono-2-thiazolidinone (**158**), on treatment with *o*-phenylenediamine, recyclizes[181] through an intermediate Schiff base to give benzimidazole (**159**).



B. 4-Thiazolidinones

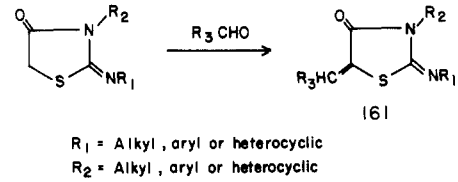
The aldol condensation reaction of the methylene group at the position 5 of 4-thiazolidinones has been widely attempted. The methylene carbon atom possesses nucleophilic activity. The degree of nucleophilic activity and the formation of the anion in the presence of a base depend upon the electron-withdrawing effect of the adjacent carbonyl group and also on the presence of other electron-withdrawing groups present on the position 2. The product of the reaction contains α,β-unsaturated carbonyl group.

Different 2-thiono-4-thiazolidinones have been reported[102,103,182-184] to undergo aldol condensation reactions with a variety of aliphatic, aromatic, and heterocyclic aldehydes to give good yields of 5-unsaturated derivatives (**160**). The 5-unsaturated derivatives are



very useful synthetic reagents which will be discussed elsewhere. The reactions have mostly been carried out in the presence of anhydrous sodium acetate in benzene or acetic acid.

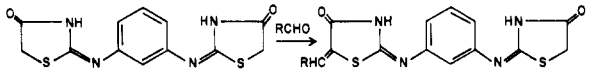
Substituted 2-imino-4-thiazolidinones also undergo aldol condensation with good ease in the presence of anhydrous sodium acetate in acetic acid (**161**). A wide

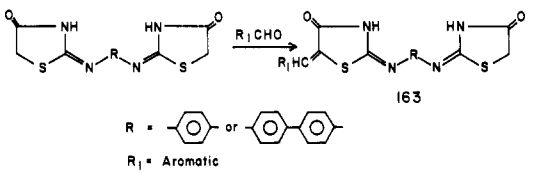


variety of alphatic, aromatic, and heterocyclic aldehydes (ref 36, 49, 54, 59, 64, 67, 68, 73, 74, 182, 185–187) have been reported to react with the 4-thiazolidinones. The

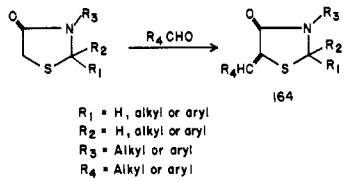
mobility of the hydrogen atoms in the methylene group depends much upon the electronegativity and coplanarity of substitution on the exocyclic nitrogen.

The aldehydes, however, react only on one 4-thiazolidinone moiety of *m*- or *p*-bis(2-imino-4-thiazolidinon-N^2-yl)benzene or *p,p'*-bis(2-imino-4-oxothiazolidin-N^2-yl)biphenyl[60,61,63] to give the corresponding 5-unsaturated products (**162, 163**).

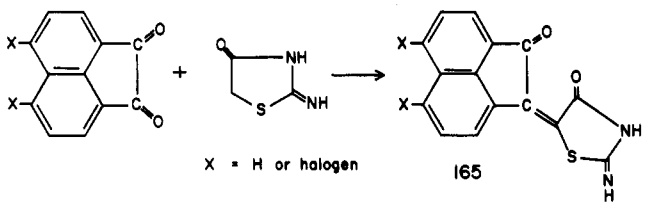




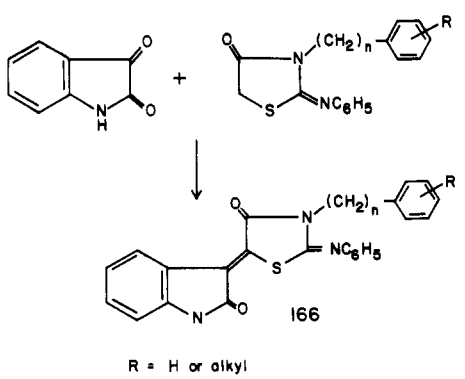
2-Substituted-4-thiazolidinones, prepared by the Schiff bases and mercaptoacetic acids, react with aldehydes in the presence of anhydrous sodium ethoxide in dry benzene to give 5-arylidene or alkylidene derivatives[135,188,189] (**164**) in good yields.



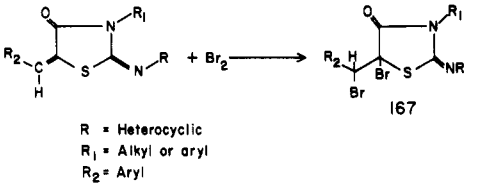
The condensation of aldehydes with the 2-alkyl- or -aryl-4-thiazolidinones in the presence of sodium acetate and acetic acid does not occur, possibly because of the decreased reactivity of the methylene group due to the absence of thioxo or imino groups at position 2. Karishin and Samusenko[190] have reported the condensation where only one carbonyl group of acenaphthenequinone or its halogen derivatives at the 5-position of 2-imino-4-thiazolidinone occurs in hot acetic acid (**165**).

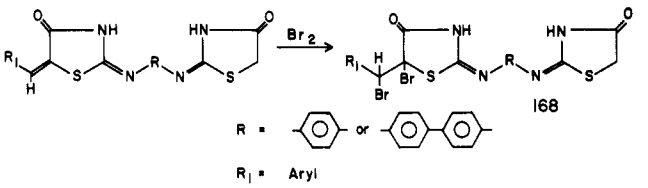


Similarly, isatin also condenses only with one of its carbonyl groups at the 5-position of various 2-imino-4-thiazolidinones, giving thioindigoid dyes of type[191,192] **166**.

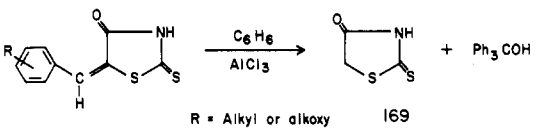


5-Arylidene derivatives, obtained by the aldol condensation, react with bromine in chloroform at the carbon–carbon double bond to give dibromo compounds[60,61,73,74] (**167, 168**).

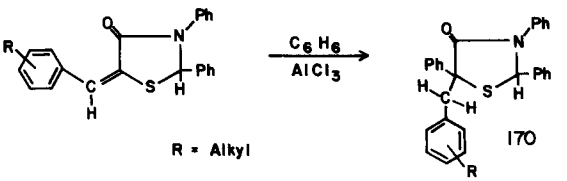




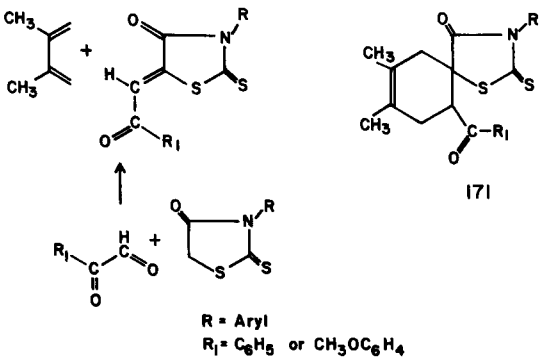
Snider et al.[189] have reported Friedel–Craft reactions with 5-arylidene-4-thiazolidinones using benzene and anhydrous aluminum chloride. The reaction of 5-arylidenerhodanines with benzene and ≥4 mol of aluminum chloride cleaves the arylidene substituent to give rhodanine (**169**) and triphenylcarbinol.



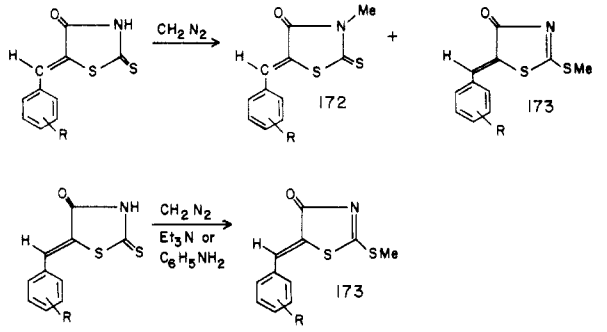
However, 2,3-diphenyl-5-arylidene-4-thiazolidinones under similar conditions add benzene to the unsaturated linkage to give 2,3,5-triphenyl-5-benzyl-4-thiazolidinones (**170**).



2,3-Dimethylbutadiene reacts at the carbon–carbon double bond of 5-(aroylmethylidene)-2-thiono-4-thiazolidinones to give thiazolidinone spirocyclohexenes[193] (**171**).

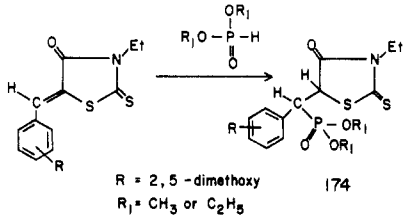


5-Arylidenerhodanines on treatment with gaseous diazomethane give mixtures of *N*-methyl and *S*-methyl derivatives[194] (**172, 173**). Linear correlation exists between the log of the relative yields (*N*-methyl/*S*-methyl) and substituent constants of substitution groups R. Increasing the dielectric constants of the solvents increased the relative yields of *N*-methyl derivatives; in amines like triethylamine and aniline, only

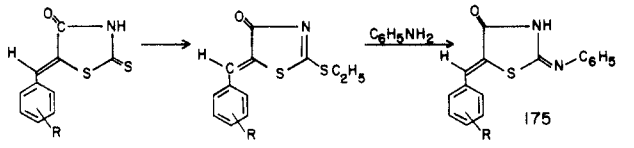


S-methylthiazolone derivatives are formed (**173**).

Lugovkin[196] has reported phosphorylation of 5-arylidenerhodanines (**174**) by substituted phosphorus acids.

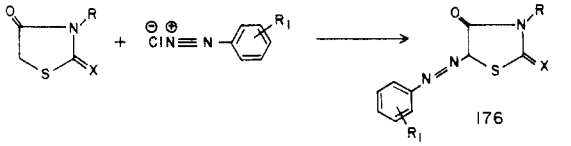


5-Arylidene-2-(alkylthio)-4-thiazolones easily condense with aniline to give 2-imino-4-thiazolidinones[195] (**175**). This reaction can be used as a good method for

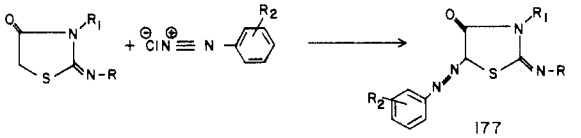


the conversion of rhodanines to 2-imino-4-thiazolidinones.

Diazonium salts undergo coupling reaction with a variety of substituted 4-thiazolidinones at the 5-methylene group in the presence of aqueous ammonium hydroxide to give 5-arylazo-4-thiazolidinones (ref 37, 39, 49, 53, 57, 64, 78, 79, 197–199) (**176**, **177**).

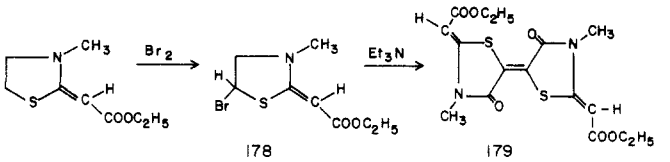


R = Alkyl or aryl
R_1 = Alkyl, alkoxy, halo or heterocyclic
X = S or O

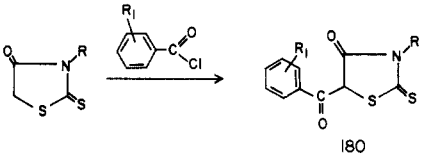


R = Alkyl, aryl or heterocyclic
R_1 = Alkyl, aryl or heterocyclic
R_2 = Alkyl

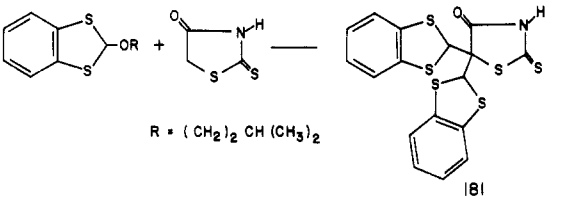
2-(Carbethoxymethylene)-3-methyl-4-thiazolidinone reacts with bromine[147] to give 2-(carbethoxymethylene)-3-methyl-5-bromo-4-thiazolidinone (**178**). The bromo compound on treatment with triethylamine gives **179**.



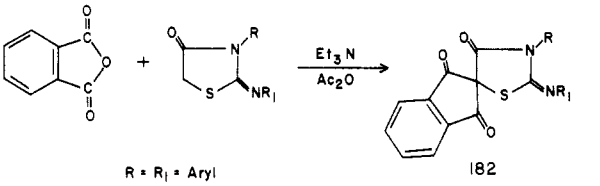
Kvitko et al.[200] have reported the reaction of substituted benzoyl chlorides with various 2-thiono-4-thiazolidinones, giving 5-aroyl-4-thiazolidinones (**180**).



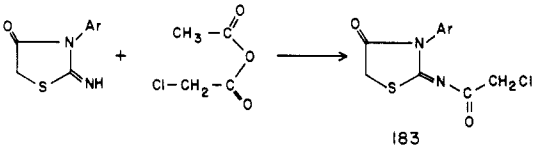
Nakayama[201] has studied the introduction of cyclic dithioacetal functions into activated methylene compounds by treatment with 2-alkoxy-1,3-benzodithioles. 2-(3-Methylbutoxy)-1,3-benzodithiole on treatment with rhodanine in anhydrous acetic acid gives 5-bis(1,3-benzodithiol-2-yl)rhodanine in high yields (**181**).



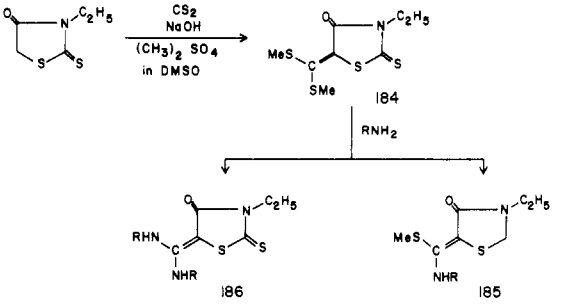
Phthalic anhydride undergoes condensation[202] at the 5-position of various 2-substituted imino-4-thiazolidinones in acetic anhydride and triethylamine to give 2-substituted imino-5-phthalyl-4-thiazolidinones (**182**).



However, mixed anhydride reacts spontaneously with 2-imino-3-aryl-4-thiazolidinones at room temperature to give *N*-chloroacetyl derivatives[111] (**183**).



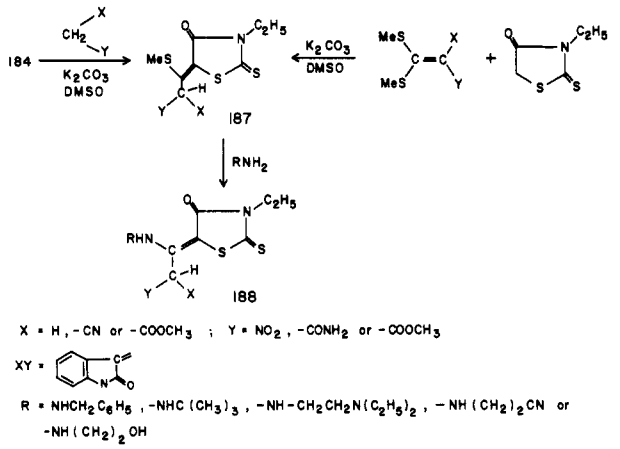
Tominaga et al.[203] have reported the reaction of 3-ethylrhodanine with carbon disulfide in the presence of sodium hydroxide in dimethyl sulfoxide, giving 3-ethyl-5-[bis(methylthio)methylene]-2-thioxo-4-thiazolidinone (**184**). This on treatment with nucleophilic



reagents such as amines or active methylenes yields the corresponding replacement products of one (**185**) or two (**186**) methylthio group in good yields, respectively.

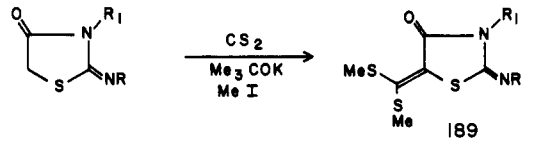
The active ketene thioacetal group of **184** reacts with active methylene compounds in the presence of K_2CO_3 in dimethyl sulfoxide; this results in the corresponding

replacement product (187) of one methylthio group of



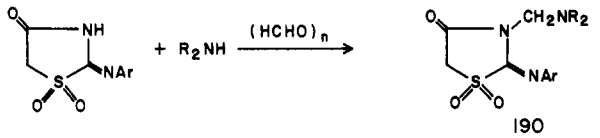
184 in good yields. 3-Ethylrhodanine also reacts with ketene thioacetal in the presence of K_2CO_3 in dimethyl sulfoxide to give 187. The compounds (187) having an active methylthio group react with amines to give the amine derivatives (188).

Fisher et al.[155] synthesized 2-imino-3-substituted-5-[bis(methylthio)methylene]-4-thiazolidinones (189) in

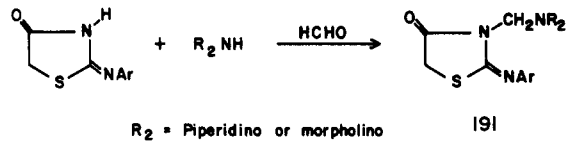


27–43% yields by the reaction of 2-imino-3-substituted-4-thiazolidinones with carbon disulfide, potassium–trimethyl methoxide, and methyl iodide.

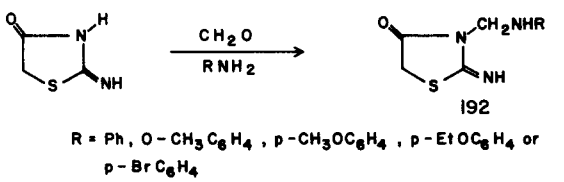
2-(Arylimino)-4-thiazolidinone 1,1-dioxides undergo Mannich reaction in the presence of paraformaldehyde and amine hydrochloride to give 2-(arylimino)-3-(substituted-aminomethyl)-4-thiazolidinone 1,1-dioxides[204] (190).



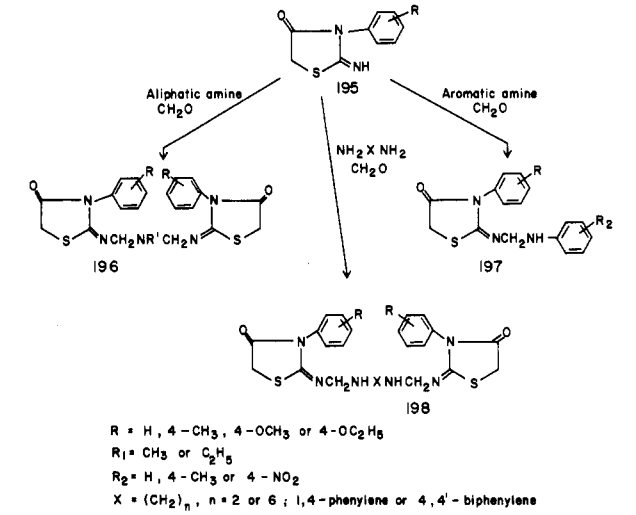
However, Chizhevskaya et al.[205] have reported Mannich reactions at nitrogen at position 3 of 2-(arylimino)-4-thiazolidinones with formaldehyde and secondary amines (191).



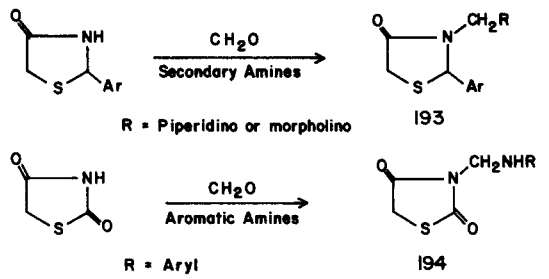
Zubenko[206] carried out Mannich reactions of unsubstituted 2-imino-4-thiazolidinones with primary aromatic amines and formaldehyde in methanol at room temperature and concluded that the reaction occurs at the N-3 position with 70–100% yields (192).



SCHEME X

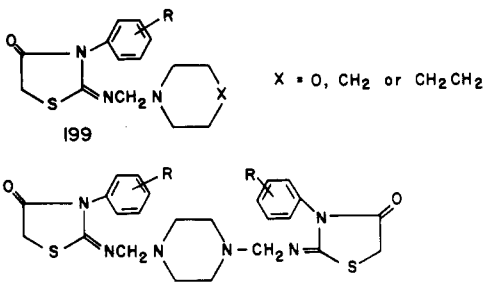


Kononenko et al.[207] have reported aminomethylation reactions of 2-aryl-4-thiazolidinones and 2,4-thiazolidinediones with formaldehyde and amines by heating in alcohol (193, 194).

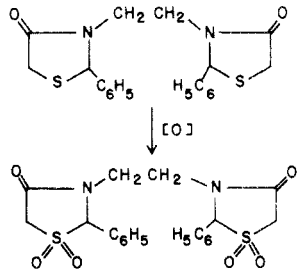


2-Imino-3-aryl-4-thiazolidinones (195) undergo Mannich reactions[208] with primary aliphatic amines and formaldehyde to give the bis[(thiazolidinylideneamino)methyl]amines (196) whereas the reaction of 195 with formaldehyde and primary aromatic amines gives *N*-[(thiazolidinylideneamino)methyl]anilines (197). Similarly, the reaction of 195 with diamines NH_2XNH_2 yields bisthiazolidinylidene derivatives (198) (Scheme X).

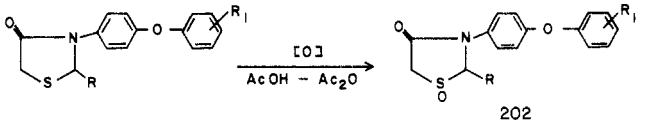
Svetkin et al.[209] further reported the Mannich reaction of 2-imino-3-aryl-4-thiazolidinones with secondary amines and formaldehyde, giving products of type 199 and 200.



1,2-Bis(2-phenyl-4-oxothiazolidin-3-yl)ethane obtained by the reaction of dibenzal ethylenediamine with thioglycolic acid in dry benzene is oxidized to dioxides 201 by heating in AcOH and 33% hydrogen peroxide.[117] However, 4-thiazolidinones on treatment with 30% H_2O_2 in a mixture of cold acetic acid and acetic anhydride give the 4-thiazolidinone *S*-monooxide derivatives[210] (202).



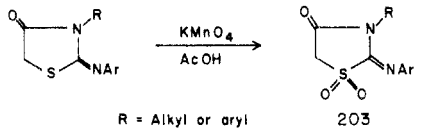
201



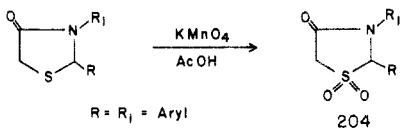
202

R = CCl_3, Ph, 3-$NO_2C_6H_4$ or 4-$NO_2C_6H_4$
R = H, 2-Cl, 4-Cl, 2-Me, 3-Me or 4-Me

2-(Arylimino)-3-substituted-4-thiazolidinones and 2,3-disubstituted-4-thiazolidinones are oxidized to the corresponding 1,1-dioxides (**203, 204**) on treatment with $KMnO_4$ in glacial acetic acid at 0 °C.[39,52,53,119]

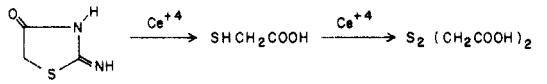


R = Alkyl or aryl 203

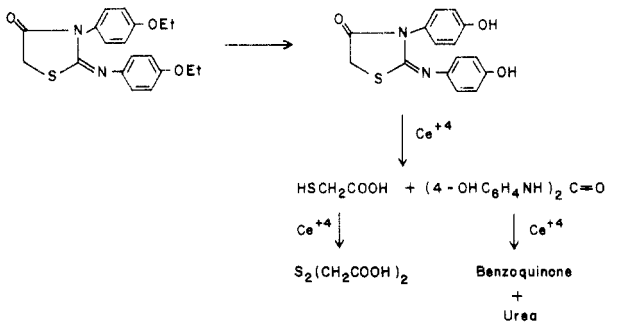


R = R_1 = Aryl 204

Oxidation of 2-imino-4-thiazolidinone by a solution of cerium(IV) sulfate[211] in aqueous methanol proceeds via initial hydrolysis to give thioglycolic acid followed by its Ce^{4+} oxidation to $S_2(CH_2COOH)_2$.

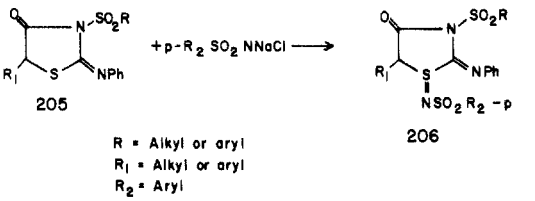


2-(4-Ethoxyphenyl)imino-3-(4-ethoxyphenyl)-4-thiazolidinone, under similar conditions, is first converted to corresponding 4-hydroxyphenyl derivative which is oxidized to $HSCH_2COOH$ and $(p\text{-}OHC_6H_4NH)_2CO$. Both are further oxidized to $S_2(CH_2COOH)_2$, benzoquinone, and urea.



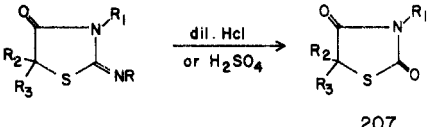
4-Thiazolidinones of type **205** undergo oxidative imination[212] to afford *S*-imino derivatives (**206**) on treatment with $p\text{-}R_2C_6H_4SO_2NNaCl$ compounds. Compound **205**, R_1 = H, is unreactive to the oxidative imination.

Various 2-(substituted-imino)-4-thiazolidinones undergo hydrolysis at position 2 on treatment with dilute hydrochloric acid or sulfuric acid to give 2,4-thiazolidinediones and amines (**207**).[33,34,59,213,214]



205 206

R = Alkyl or aryl
R_1 = Alkyl or aryl
R_2 = Aryl

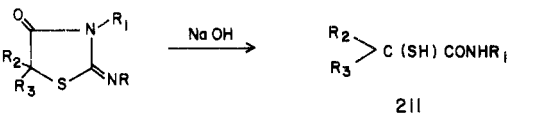


207

R = R_1 = H or aryl
R_2 = R_3 = H, CH_3 or Ph
R_2R_3 = Arylidene

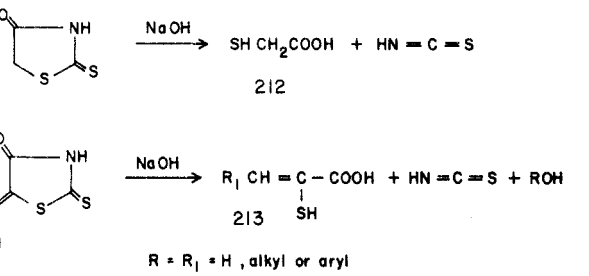
Svetkin et al.[215] carried out reactions with phenyl isothiocyanate and 2-imino-3-aryl-4-thiazolidinones and obtained 2-[(phenylthiocarbamido)imino]-3-aryl-4-thiazolidinones (**208**) in good yields. These compounds on treatment with 36% hydrochloric acid were found to undergo hydrolytic ring cleavage to give **209** which on cyclodehydration followed by hydrolysis yields 2,4-thiazolidinonedione (**210**) (Scheme XI).

2-(Substituted-imino)-4-thiazolidinones on treatment with 1 N NaOH alone, in alcoholic solution at room temperature, or at reflex temperature undergo ring opening to give corresponding substituted-carbamoyl thioglycolic acids[33,34] (**211**).



211

Similarly, rhodanine and its alkylidene or aylidene derivatives undergo ring cleavage[216] on alkaline hydrolysis to give mercaptoacetic acid (**212**) and α-mercapto-α,β-unsaturated acids (**213**), respectively.

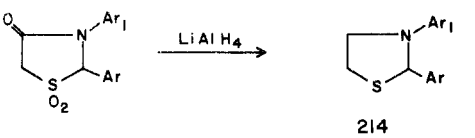


212

213

R = R_1 = H, alkyl or aryl

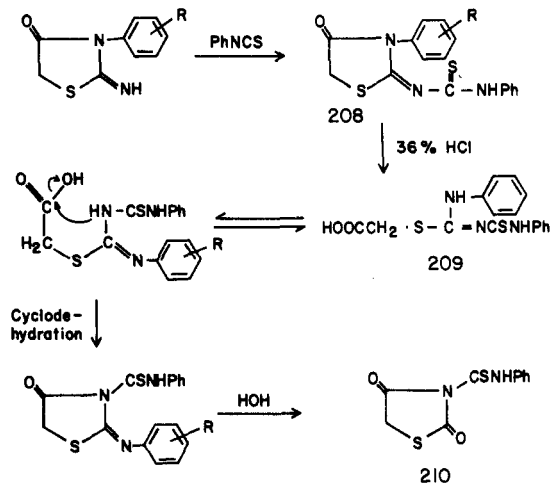
Various 4-thiazolidinone 1,1-dioxides undergo reduction[151] with lithium aluminum hydride, leading to the formation of corresponding thiazolidines (**214**).



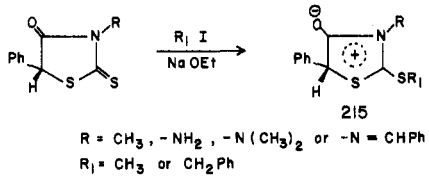
214

The term "mesoionic" has been proposed for the compounds in which a negative charge is associated with an atom or groups of atoms covalently bonded to a five- or six-membered heteroaromatic ring, which carries a positive charge and for which no single satisfactory covalent or polar structure can be written. 3,5-Substituted-2-thiono-4-thiazolidinones can be converted to their mesoionic derivatives,[26] anhydro-2-(al-

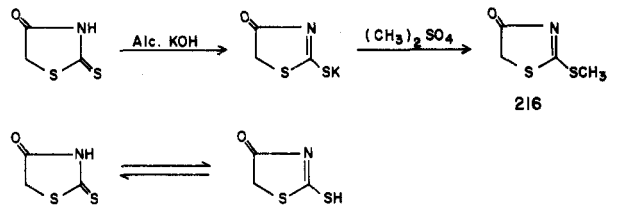
SCHEME XI



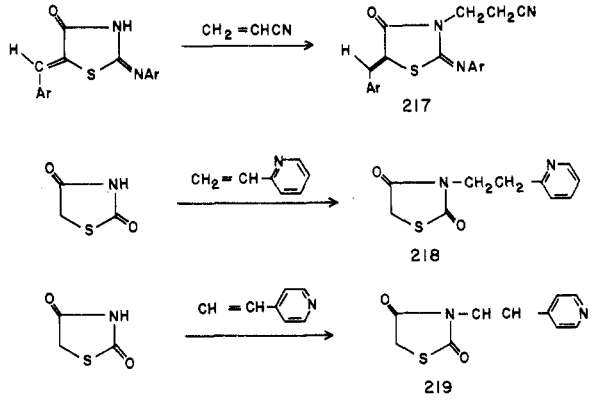
kylthio)-3-substituted-4-hydroxy-5-substituted-thiazolium hydroxides (**215**), by alkylation with alkyl iodide in the presence of NaOEt in absolute alcohol under cold conditions.



However, unsubstituted 2-thiono-4-thiazolidinone on treatment with saturated alcoholic KOH followed by the reaction with dimethyl sulfate gives 2-(methylthio)thiazolin-4-one (**216**) via the intermediate formation of the potassium thio salt.[216] This reaction supports existence of a thione–thiol tautomeric equilibrium.

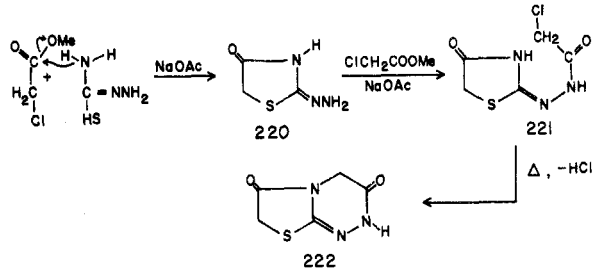


2-(Arylimino)-5-arylidene-4-thiazolidinones react at position 3 with acrylonitrile to give 2-(arylimino)-3-(cyanoethyl)-5-arylidene-4-thiazolidinones[217] (**217**). Similarly, 2,4-thiazolidinediones react with equimolar amounts of 4- or 2-vinylpyridines to form *N*-[β-(2- or 4-pyridyl)ethyl]thiazolidine-2,4-diones[218] (**218**, **219**).

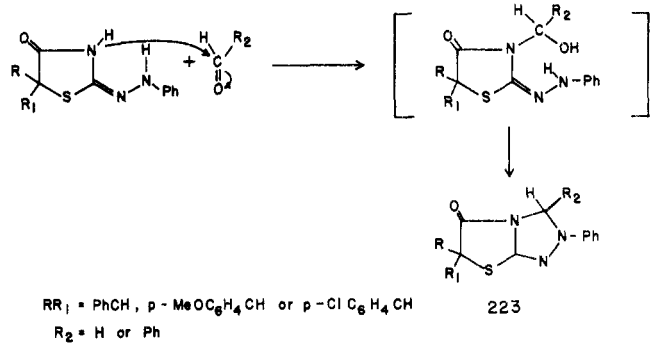


A large variety of 4-thiazolidinones has been used for the synthesis of many other heterocyclic compounds.

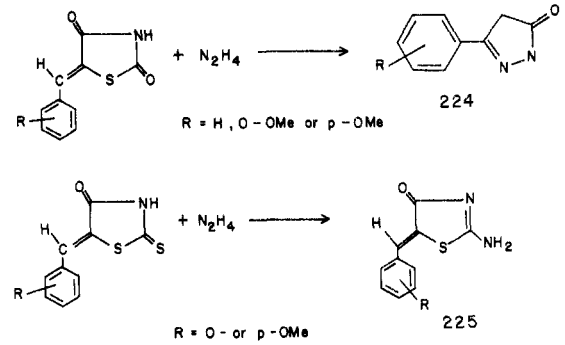
2-Hydrazono-4-thiazolidinones, obtained by the reaction of thiosemicarbazide and methyl chloroacetate, further reacts with methyl chloroacetate in the presence of NaOAc to give 2-chloroacetyl derivative **221** which on heating cyclizes to give theinotriazine[69] (**222**).



2-(Phenylhydrazono)-4-thiazolidinones, on reaction with formaldehyde or aromatic aldehydes, undergo cyclization, giving rise to 2-phenyltetrahydrothiazolo-[2,3-*c*]-1,2,4-triazol-5-ones[219] (**223**).



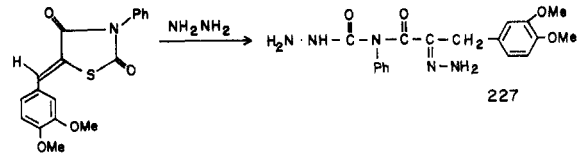
2-Oxo-5-arylidene-4-thiazolidinones react with hydrazine to undergo ring cleavage followed by cyclization to give 5-aryl-3-pyrazolinones[172] (**224**) in 55–70% yields.



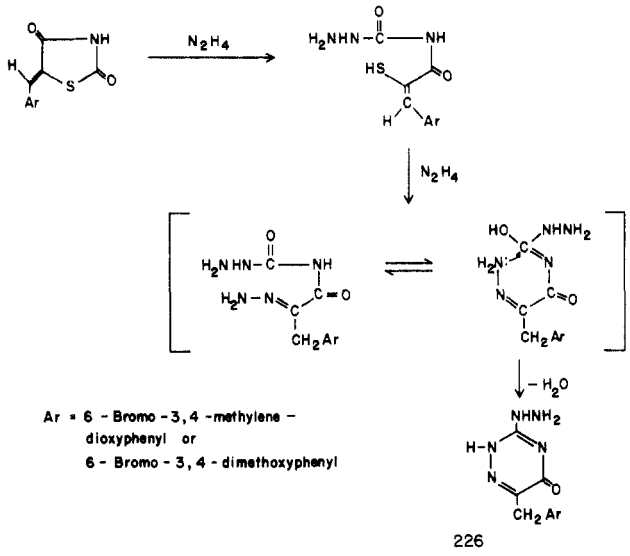
On the other hand, 2-thiono-5-arylidene-4-thiazolidinones on treatment with hydrazine give 2-amino-5-arylidene-4-thiazolinones (**225**) in 35–50% yields.

However, Raouf et al.[184] have reported the synthesis of triazinones (**226**) by the reaction of 5-(substituted-benzylidene)-2,4-thiazolidinediones with hydrazine. The route through which the transformation occurs may be presented as in Scheme XII.

But hydrazine cleaves the ring of 5-(3,4-dimethoxybenzylidene)-3-phenyl-2,4-thiazolidenedione to give 1-amino-3-phenyl-5β-[[(3,4-dimethoxyphenyl)-ethylidene]amino]biuret (**227**) with the evolution of H_2S.

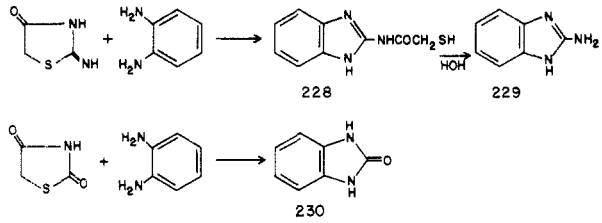


SCHEME XII



226

2-Imino-4-thiazolidinone undergoes ring cleavage to Schiff bases on treatment with *o*-phenylenediamine and further recyclizes into a benzimidazole derivative[181] (**228**). This on hydrolysis gives 2-aminobenzimidazole

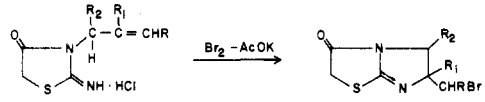


228 229

230

(**229**). 2-Oxo-4-thiazolidinone under similar conditions leads to the formation of 2-benzimidazolone (**230**).

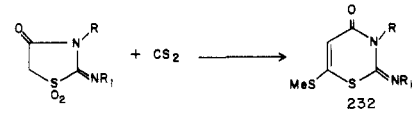
Krasnitskaya et al.[220] have synthesized substituted imidazothiazolones (**231**) from the corresponding 2-imino-3-substituted-4-thiazolidinones on treatment with Br_2–AcOK.



$R = R_2 = H$
$R_1 = H$ or CH_3
$RR_2 = CH_2CH_2$ or $(CH_2)_3$

231

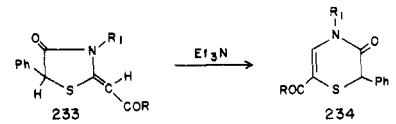
2-Imino-4-oxothiazolidine 1,1-dioxides,[155] prepared from carbodiimides, ketenes, and liquid SO_2, react with carbon disulfide to give 45–79% yields of heterocycles of type **232**.



232

$R = R_1$ = $PhCH_2$, p-tolyl, 3,5-$Me_2C_6H_3$ or p-ClC_6H_4

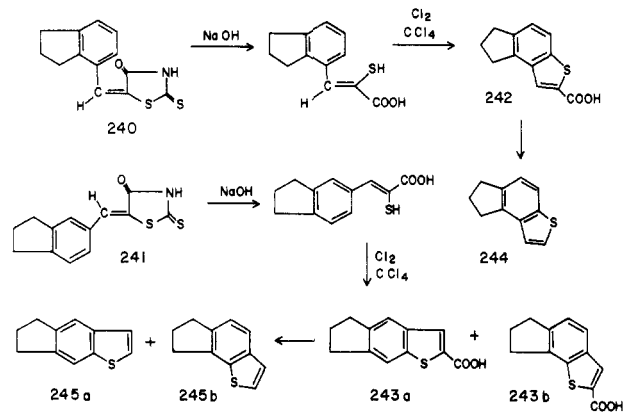
Satzinger[148] has reported the ring expansion of 2-substituted methylene-3,5-disubstituted-4-thiazolidines (**233**) on prolonged contact with triethylamine, giving compounds **234**.



233 234

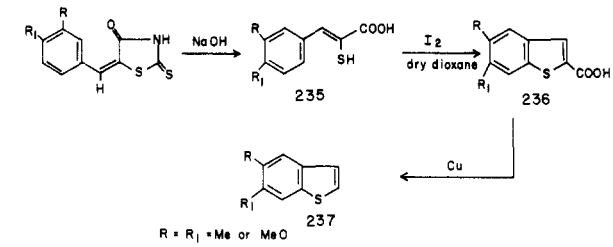
R = EtO, BuO or Ph
R_1 = Me, $Me_2NCH_2CH_2$ or 2-piperidinoethyl

SCHEME XIII



240 241 242 243a 243b 244 245a 245b

5-(Substituted-benzylidene)-2-thiono-4-thiazolidinones undergo hydrolytic ring cleavage[216] on treatment with NaOH, giving β-substituted-α-mercaptoacrylic acid (**235**). The α-mercaptoacrylic acids are recyclized into

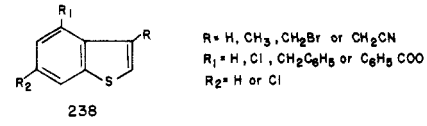


235 236 237

R = R_1 = Me or MeO

2-carboxyl-5,6-disubstituted-benzo[*b*]thiophenes (**236**) in the presence of iodine and dry dioxane at refluxing temperature.[221] The benzothiophenecarboxylic acids are readily decarboxylated to benzothiophenes (**237**) by copper in quinoline. Substituents in the phenyl moiety of acrylic acids markedly affect the yield of cyclized products.

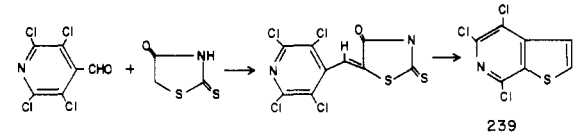
Various other benzothiophene derivatives (**238**) have been synthesized[222,223] by using the above method.



238

R = H, CH_3, CH_2Br or CH_2CN
R_1 = H, Cl, $CH_2C_6H_5$ or C_6H_5COO
R_2 = H or Cl

Under similar conditions, polyhalothienopyridine (**239**) is synthesized from tetrachloropyridine-4-carboxaldehyde and rhodanine.[224]

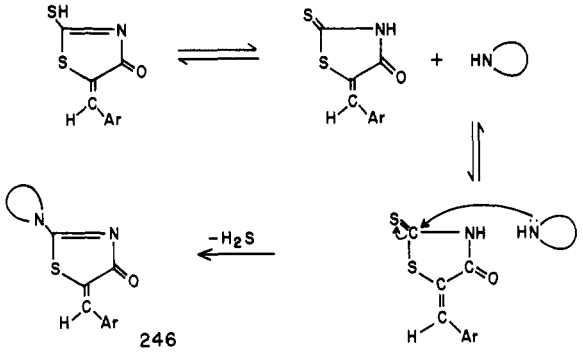


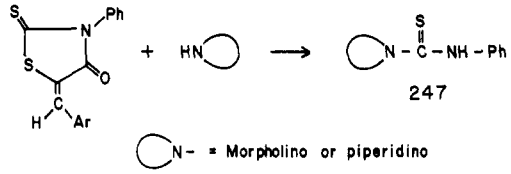
239

Grüenhaus et al.[225] have synthesized indenothiophenes from isomeric indancarboxaldehydes and 2-thiono-4-thiazolidinone through the intermediates 5-(4-indanylidene)- and 5-(5-indanylidene)rhodanine (**240, 241**). These substituted rhodanines undergo hydrolytic ring cleavage followed by ring closure in the presence of chlorine in dry carbon tetrachloride, giving rise to indenothiophenecarboxylic acids (**242, 243**) which on decarboxylation give indenothiophenes (**244, 245**) (Scheme XIII).

Raouf et al.[184,226] have studied the reaction of 5-arylidene-2-thiono-4-thiazolidinones with secondary amines and reported the formation of 2-thiazolin-4-ones (**246**) and amine salt. The reaction may be represented

SCHEME XIV

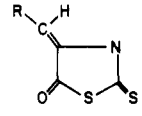




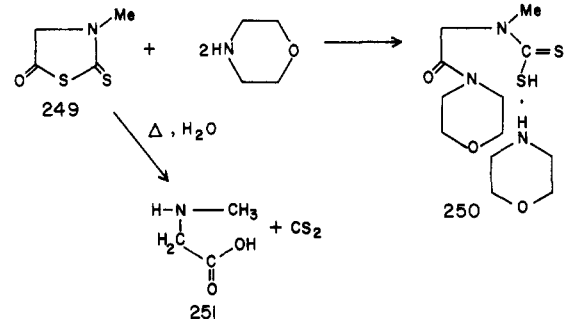
as in Scheme XIV. On the other hand, 5-arylidene-3-phenyl-2-thiono-4-thiazolidinones on treatment with secondary amines undergo ring cleavage leading to the formation of the corresponding thioureas (247).

C. 5-Thiazolidinones

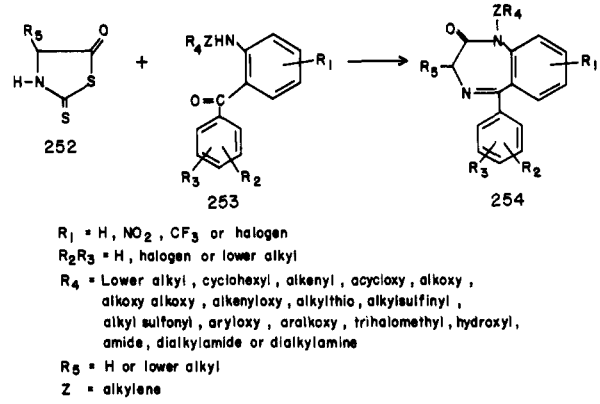
Phenylacrolein, furylacrolein, aromatic aldehydes, and furfural and their α-bromo derivatives undergo Aldol condensation[161,227,228] reaction with 2-thiono-5-thiazolidinone and give the corresponding compounds (248).



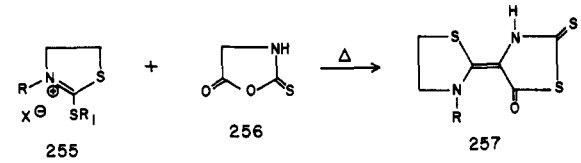
2-Thiono-3-methyl-5-thiazolidinone (249) on treatment with 2 equiv of morpholine in acetone leads to the formation of morpholinium salt (250). The 5-thiazolidinone 249 on boiling in water undergoes ring cleavage, giving sarcosine (251) and carbon disulfide.[160]



The reaction[229] of 2-thiono-5-thiazolidinone (252) with amino ketones (253) in dichloromethane in the presence of ethereal HCl gives an excellent route for the preparation of various substituted benzodiazepines (254) which belong to an important group of psychopharmacological agents.

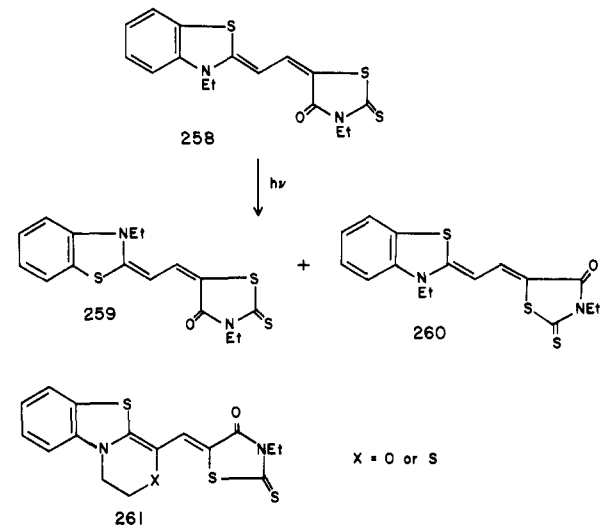


Thermal condensation[230] of 2-(alkylthio)thiazolidine quaternary salts (255) with 2-thiono-5-thiazolidinone (256) in pyridine or triethylamine gives various thiazolidines (257).



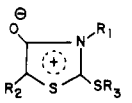
IV. Photochemistry of Thiazolidinones

Merocyanine (258), 4-thiazolidinone derivative, in toluene undergoes photoisomerization, giving rise to two isomers from the excited singlet state during irradiation in the visible region.[231,232] The isomers were identified



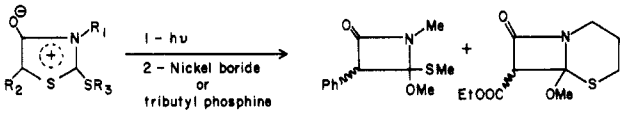
spectroscopically as longer lived isomer 259 and shorter-lived isomer 260 by comparison with the systems (261) in which one double bond is prevented from isomerizing. Compounds 258 and 259 are stabilized by H-bonding between the carbonyl and the methine H, and 258 and 260 are stabilized by including the benzothiazole N in an all-trans conjugated system. Photoisomerization through the excited triplet state in the presence of fluorene as triplet donor gives only 259. Irradiation of 261 gives a single isomer in each case, both through a singlet and a triplet intermediate.

Barton et al.[233] have explored the possibility of a new route for β-lactam synthesis by the photolytic ring contraction of mesoionic 2-(alkylthio)thiazol-4-ones (262–268), the derivatives of 4-thiazolidinone prepared by the alkylation of 3,5-disubstituted-2-thiono-4-thiazolidinones.



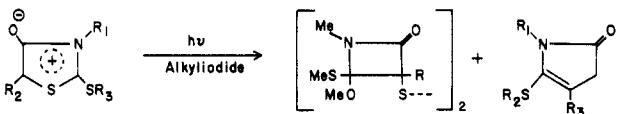
262 - R_1 = R_3 = Me ; R_2 = Ph
263 - R_1 = R_3 = Me ; R_2 = COOEt
264 - R_1 = R_3 = CH_2COOEt ; R_2 = COOEt
265 - R_1 = $CH_2CH=CH_2$; R_2 = CO·COOEt ; R_3 = Me
266 - R_1 = $CH_2CH(OMe)_2$; R_2 = CO·COOEt ; R_3 = Me
267 - R_1R_3 = $(CH_2)_3$; R_2 = COOEt
268 - R_1R_3 = $(CH_2)_3$; R_2 = CO·CH_2Ph

Photolysis of methanolic solutions of mesoions **262–267** under argon gives a crude mixture which on treatment with nickel boride or tributylphosphine gives desulfurized β-lactam **269** and **270**.



262 and 267 269 270

Photolysis of methanolic solutions of **262** and **263** in the presence of alkyl iodide affords cleaner reaction, possibly due to a heavy atom effect, giving β-lactams **271** along with isomeric thiazol-2-one (**272**).



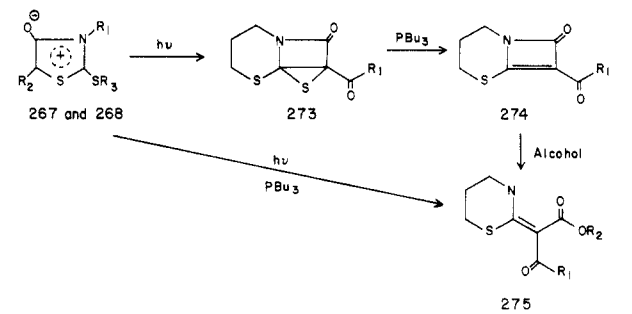
262 and 263 271 272

R_1 = R_3 = Me
R_2 = Ph or COOEt

R = Ph or COOEt

R_1 = R_2 = Me
R_3 = COOEt

Under identical conditions, the mesoions **267** and **268** undergo slow photolysis and give lower yields of β-lactams. The additional ring increases the strain in β-



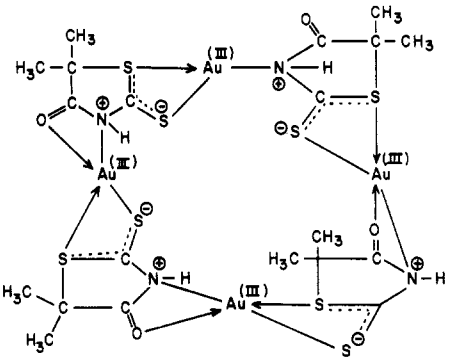
267 and 268 273 274 275

lactam thiiran intermediate **273** with consequent ready loss of sulfur in the presence of tributylphosphine, giving rise to unsaturated lactams **274**. These compounds undergo ring opening in methanolic solution, giving β-aminoacrylates (**275**). These compounds (**275**) are formed in good yields from the mesoions **267** and **268** on photolysis in the presence of phosphines. These results strongly suggest the formation of a four-membered bicyclic ring-contraction product of type **273** on photolysis of mesoions. Compounds **273** rearrange to thiazolin-2-ones (**272**), lose sulfur, and afford β-aminoacrylates (**275**) or are trapped by methanol, yielding β-lactams (**269–271**).

V. Metal Complexes of Thiazolidinones

Coordination complexes of rhodanine (2-thiono-4-thiazolidinone) and its 3-substituted derivatives as ligand[234-238] have been studied with copper(I), silver(I), gold(I), palladium(II), and platinum(II). On the basis of molar conductivity and infrared and nuclear magnetic resonance spectral analysis it is believed that the coordination in these complexes takes place through the thiocarbonyl group of the ligand.[234-236] Moers et al.[239] studied the X-ray crystal structure of (3-methylrhodanine)copper(I) iodide and proposed a polymeric structure in which the iodine atoms act as bridges and the ligand 3-methylrhodanine is terminally coordinated with the thiocarbonyl group of the ligand.

Gold forms a 1:1 complex with 2-thiono-5,5-dimethyl-4-thiazolidinone. Molecular weight determination and elemental analysis indicate a tetramer. On the basis of UV, IR, ^1H NMR, ESR, and mass spectral analysis, X-ray diffraction, electron microscope, and polarographic studies, the structure of gold complex with 2-thiono-5,5-dimethyl-4-thiazolidinone is proposed as A. The binding sites in the complex are through



A

nitrogen, oxygen, and two sulfur atoms.[240]

Several 1:1 or 1:2 complexes of 2-thiazolidinone with zinc(II), cadmium(II), and mercury(II) halides have been prepared and characterized by molecular conductance and IR spectral data measurements where 1:1 complexes have been proposed to be dimeric tetrahedral structures with halogen bridges and 1:2 derivatives a monomeric tetrahedral structures.[241] 2-Thiazolidinone is O-bonded in the zinc derivatives and N-bonded in cadmium ones, while in the mercury complexes the sulfur atom is clearly involved in the coordination to the metal. The general formula of 2-thiazolidinone complexes is given as $Mt_2O_2X_2$ (M = Zn, X = Cl, Br, I; M = Hg, X = Cl, Br) and Cdt_2OX_2 (X = Cl, Br, I), where t_2O represents 2-thiazolidinone.

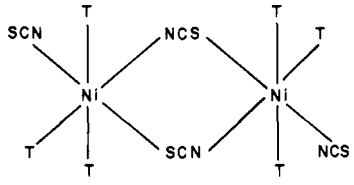
Metal carbonyl complexes of 2-thiazolidinone were prepared by irradiating ethereal solution of the appropriate metal hexacarbonyl [$M(CO)_6$, M = Mo, Cr, or W] and 2-thiazolidinone.[242] In all cases the yield was very poor because complexes decompose quickly. Molybdenum complex with 2-thiazolidinone could not be isolated, while the chromium and tungsten derivatives were characterized by infrared spectroscopy. It is concluded that the ligands are bonded through sulfur which is consistent with their very low stability.

The halide complexes of cobalt(II) with 2-imino-4-thiazolidinone as ligand (L) were prepared by refluxing alcoholic solution of 1:2 anhydrous cobalt(II) halide and ligand for about 30 min. These were characterized by elemental analyses, infrared spectral analyses, electronic spectral data, and magnetic susceptibility values.[243] The ligand has four different possible coordinating sites, such as cyclic NH, imino NH, C=O, and S. The electronic data and magnetic susceptibility indicated the

tetrahedral stereochemistry for Co(II) and IR spectra indicated that the cyclic NH is coordinated with metal atom.

Deprotonated 2-imino-4-thiazolidinone complexes of copper(I), silver(I), gold(I), zinc(II), cadmium(II), and mercury(I) have been prepared and characterized by their elemental and infrared spectral analyses.[244] All the complexes were found to be diamagnetic for Cu(I), Ag(I), Au(I), Zn(II), Cd(II), and Hg(II). The infrared spectra revealed the deprotonation of the cyclic NH and its bonding to the metal and nonbonding of either exocyclic NH or C=O. The sulfur of 2-imino-4-thiazolidinone is also bonded with metal.

Thiocyanate complexes of Zn(II), Cd(II), Hg(II), Co(II), and Ni(II) with 2-imino-4-thiazolidinone have been reported.[245] Their structural characterization is based on molar conductance, magnetic moment, infrared, and electronic spectral studies. A negative shift of 100-cm^{-1} magnitude for the C=O group in the complexes as compared to ligand indicates that the coordination takes place through carbonyl oxygen.[246] The positions and the nature of CN, CS, and NCS bands in the infrared spectra indicate that the thiocyanates unit is N-bonded in Zn(II) and Co(II) complexes and S-bonded in Cd(II) and Hg(II).[247,248] However, thiocyanate is a bridge type in the Ni(II) complex. Studies have shown that Ni(II) in this complex is octahedral. Structure B for the Ni(II) complex was proposed.

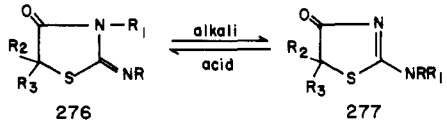


B

VI. Molecular Spectroscopy of Thiazolidinones

A. Ultraviolet Absorption Spectroscopy

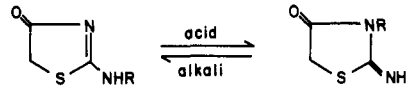
Ultraviolet absorption spectra of 2-iminothiazolidin-4-ones (**276**) and 2-amino-Δ^2-thiazolin-4-ones (**277**) in aqueous solution showed absorption maxima (λ_{max}) at about 220 and 245 nm, respectively.[249] In compounds **277**, the peak at 245 nm exhibited a hypsochromic shift to 220 nm in strong acidic medium and reappeared when the solution was neutralized. The hypsochromic shift in **277** is due to the protonation of the doubly bonded nitrogen atom and consequently rearrangement of the endocyclic to exocyclic double-bond and thus destroying the conjugation with the ring carbonyl.[250,251]



276 277

R = R_1 = CH_3 or C_2H_5
R_2 = H, C_2H_5 or C_6H_5
R_3 = H

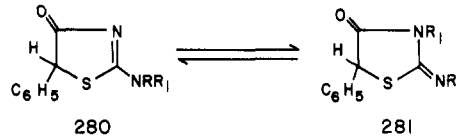
Compounds having both unsubstituted nitrogen (**276** or **277**; R = R_1 = H) are potentially capable of tautomerism and showed λ_{max} at 220 and 250 nm. Furthermore, the λ_{max} at 250 nm shifted to 220 nm in strong acidic solution and reappeared on neutralization. The intensity of λ_{max} at 220 nm was found to be the same in model compounds as well as in compounds having both nitrogen atoms unsubstituted. These results indicated that the both tautomeric forms are present in aqueous solution.[251-253] Similarly, in acidic medium, 2-alkylamino compounds (**278**) rearranged to 3-alkyl-2-imino derivatives (**279**), while under alkaline condi-



278 279

tions, the reaction was reversed. However, 2-isopropylamino derivative **278** could not undergo the rearrangement. In aqueous solution these compounds exist in their amino form.[31,254] Furthermore, Ramsh et al.[255] studied the UV spectra of 2-amino-Δ^2-thiazolin-4-one and some model compounds and determined their basicity. They also found that the 2-amino-Δ^2-thiazolin-4-one exists in the amino form in water solution. They determined the tautomeric equilibrium constant, K_t = amino form/imino form $\sim 10^3$.

Najer et al.[32] studied the UV spectra of several 5-phenyl-2-amino-Δ^2-thiazolin-4-ones (**280**) and 5-phenyl-3-methyl-2-iminothiazolidin-4-ones (**281**) in ethanol. They found that the equilibrium of tautomers **280** $\rightleftharpoons$ **281** is dependent on the nature of substituent



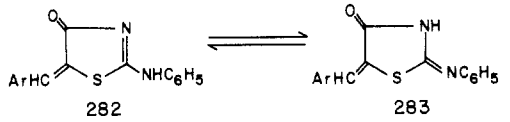
280 281

R = R_1 = H, CH_3, C_2H_5, iso-C_3H_7, C_6H_5 or $C_6H_5CH_2$

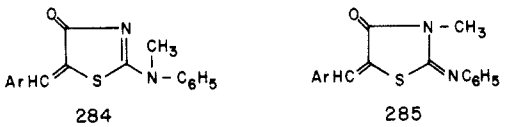
present at the exocyclic nitrogen atom. Thus, if R is a hydrogen, alkyl, or arylalkyl group, tautomer **280** is predominant, and if R is a phenyl group, tautomer **281** is predominant.

The ultraviolet absorption spectra of a series of 2-(arylimino)-4-thiazolidinones containing electron-donor and electron-acceptor substituents in the phenyl ring were studied.[256,257] When substituents are present in the para position of the phenyl ring, the position of the characteristic thione absorption is shifted. A bathochromic shift occurs with the substituents CH_3, NO_2, and $(CH_3)_2N$. If the substituent has an unshared pair of electrons or a multiple bond, a new band appears in the 222–274-nm region. A hypsochromic shift occurs with ortho substitution of the OCH_3 group.

The UV spectra of the potentially tautomeric 2-(phenylamino)-5-arylidene-Δ^2-thiazolin-4-ones (**282**) and 2-(phenylimino)-5-arylidenethiazolidin-4-ones (**283**) and their methylated analogues 2-(methylphenylamino)-5-aryliden-Δ^2-thiazolin-4-ones (**284**) and 2-(phenylimino)-3-methyl-5-aryliden-Δ^2-thiazolin-4-ones (**284**) and 2-(phenylimino)-3-methyl-5-arylidenethiazolidin-4-ones (**285**) were recorded in solvents with various polarities such as dioxane, 70% aqueous dioxane, and methanol.[258] All compounds showed a strong band in the region 320–430 nm, explained by the presence of a long-chain conjugation, i.e., K band. The bathochromic shift in hydroxyl-containing solvents indicates that this band is due to π–π^* transitions. The introduction of both electron-donating and -accepting substituents into



282 283



284 285

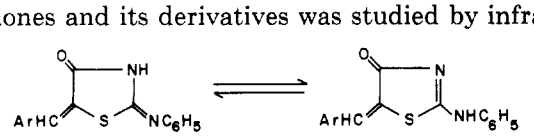
the phenyl ring present at position 5 also leads to a bathochromic shift of the K band. 2-(Methylphenylamino)-5-arylidene-Δ^2-thiazolin-4-ones (**284**) have a strong absorption band at 270–330 nm which is only separated from K band in the case of compounds with electron-donating substituents. Electron-donating substituents have been shown to cause a hypsochromic shift while electron-accepting substituents cause a bathochromic shift of this band. The characteristic bands in the region 230–260 nm in the spectra of 2-(phenylimino)-3-methyl-5-arylidenethiazolidin-4-ones (**285**) undergo a bathochromic shift on the introduction of various types of substituents into the phenyl ring present at position 5 and also in hydroxyl-containing solvents. The UV spectra of **283** in dioxane are of the same nature to a considerable degree as that of the spectra of **285**. In hydroxyl solvents (methanol, 70% aqueous dioxane) the spectra of **283** and **285** differ from each other to some degree, and this difference increases with the increase in the polarity of the solvents. In a given solvent it is greater with the higher electron-donating properties of the substituent present in the phenyl ring of position 5. In dioxane and 70% aqueous dioxane, the value of the factor λ, which characterizes the relative contribution from the resonance and induction effects, for compound **283** practically coincides with the λ of the models of the imino form (**285**) and differs considerably from the λ value of the models of the amino form (**284**). These findings lead to the confirmation that the imino form **283** predominates in solvents with various polarities.

The λ_{max} in the UV spectra of various substituted 2-thiazolidinones and 4-thiazolidinones have been reported by several other workers (ref 26, 105, 109, 184, 187, 225, 259).

B. Infrared Spectroscopy

Taylor[260,261] reported the complete assignment of the characteristic bands in the infrared spectra of several 2-substituted-4-thiazolidinones. He described the criteria for determining the cis and trans configurations of the above compounds. The cis isomer is favored when hydrogen bonding is otherwise impossible. In nearly other circumstances the trans is the stable form.[20] A combination of pK_a and spectroscopic evidence has been used to define the conjugated system present in these thiazolidinones.

The imino–amino tautomerism of 2-imino-4-thiazolidinones and its derivatives was studied by infrared

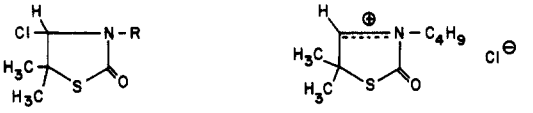


spectroscopy.[262] The spectral data showed that in crystal state imino isomer is predominant whereas in solution amino isomer[262] predominates. However, the infrared spectral studies showed that both in the crystalline state and in solution in dioxane the 5-arylidene-2-(phenylimino)thiazolidin-4-ones exist in the imino form, and only in the case of compounds with electron-donating substituents present in the phenyl ring of arylidene group the amino form possibly exists to a small extent in dioxane.[263]

The frequencies of the characteristic bands in the infrared absorption spectra of various thiazolidinones and 4-thiazolidinones have been reported by other workers (ref 105, 110, 119, 123, 134, 149–151, 164, 176, 179, 184, 225, 258, 259, 264–267).

C. Nuclear Magnetic Resonance Spectroscopy

The nuclear magnetic resonance spectrum of **286** (R = n-C_4H_9) showed only one methyl resonance of relative

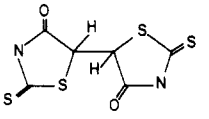


288

286, R = n-C_4H_9
287, R = C_6H_5

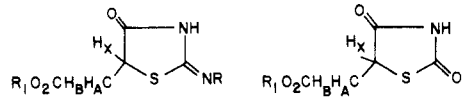
intensity 6, while that of **287** (R = C_6H_5) has two expected methyl signals (relative ratio 3:3). The equivalency of methyl groups in **286** is lost when chlorine group is replaced by other substituents such as hydroxyl or methoxyl. These results, in conjunction with the higher reactivity of **286** relative to **287** toward nucleophiles, indicate that the butyl derivative may be best represented by structure **288** in which the carbonium ion formed by ionization of chlorine atom is stabilized by delocalization of the positive charge. This will force the hydrogen atom at C-4 into the plane of the ring and thus create the same magnetic environment for both methyl groups as indicated by the single resonance.[13]

The protons present at the 5- and 5′-positions in 2,2′-dithioxo-5,5′-bi-4-thiazolidinones (**289**) appear as a sharp singlet[105] equivalent to two protons in the nuclear magnetic resonance spectrum of **289**.



289

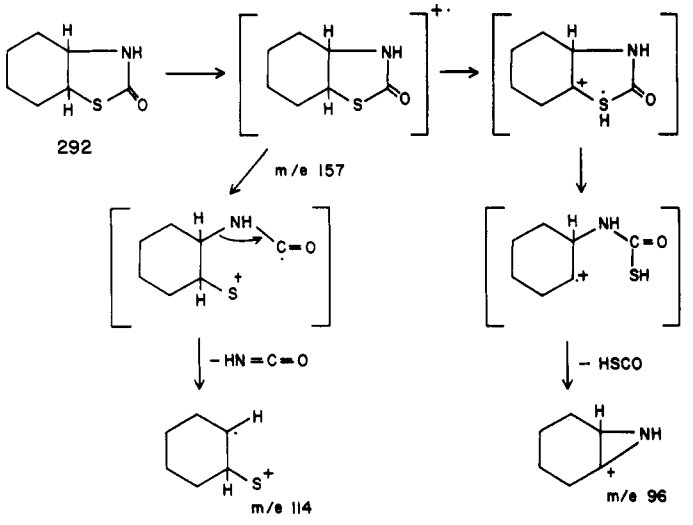
The nuclear magnetic resonance spectra[104] of 2-imino-4-oxothiazolidinyl-5-acetates (**290**) and 2,4-dioxothiazolidine 5-acetates (**291**) show characteristic pat-



290 291

terns of an ABX system with approximate coupling constants of J_{AB} = 17.0–18.0, J_{AX} = 5.0–7.5, and J_{BX} = 4.0–5.0 Hz. The large values of J_{AB}'s were referred to as "carbonyl effect" on the coupling constants for the methylene groups by Takahashi[268] in the structurally related 2-thiono-5-(carboxylmethyl)-4-thiazolidinones. The chemical shifts of the protons H_A, H_B, and H_X have been assigned at about 3.09–3.35, 2.78–3.07, and

SCHEME XV

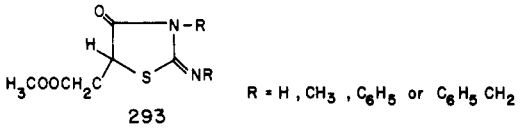


4.36–4.60 ppm, respectively, and indicate that the methylene protons adjacent to an asymmetric center are magnetically nonequivalent.[269] Furthermore, the readers are advised to see the following references where the chemical shift of the various types of proton resonances of different thiazolidinones have been reported (ref 110, 119, 123, 134, 149–151, 164, 176, 183, 259, 264).

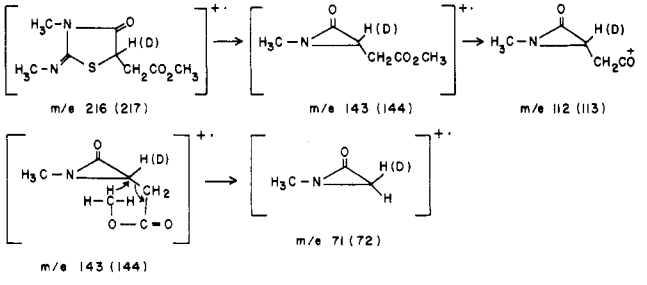
D. Mass Spectroscopy

The molecular ion peaks[21] in the mass spectrum of *cis*-octahydro-1,3-benzothiazol-2-one (**292**) are observed at 157, 114, 96, and 81. The fragmentation patterns of this compound is represented as in Scheme XV.

The molecular ion peaks in the mass spectra of 2-imino-4-oxothiazolidinyl-5-acetates (**293**) have been

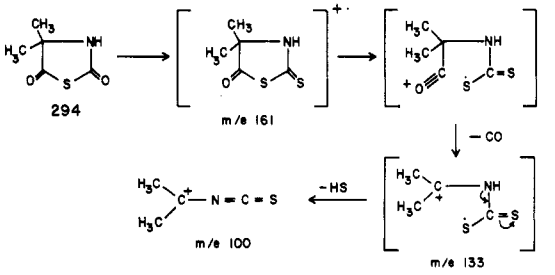


assigned.[104] The principal daughter ion peaks were determined by means of deuterium exchange and high-resolution mass spectroscopy. In the mass spectrum of methyl 2-(methylimino)-3-methyl-4-oxothiazolidinyl-5-acetate, the fragments at *m/e* 71 and 112 support the five-membered ring structure. These peaks appear in the deuterium spectrum at *m/e* 72 and 113, respectively.



The mass spectrum[164] of 4,4-dimethyl-2-thiono-5-thiazolidinone (**294**) gave the molecular ion peaks at 161 (M^+, 100), 133 (M^+ – CO, 57) and 100 (M^+ – CO – SH, 37). The cleavage of the ring's weakest bond would labilize the ring carbonyl for expulsion and give the M – CO ion. The fragmentation patterns of **294** may be

SCHEME XVI

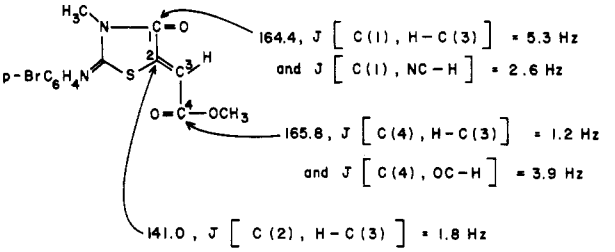


represented as in Scheme XVI.

Other workers have also reported the assignment of the various molecular ion peaks in the mass spectra of 4-thiazolidinone[149] and the mesoionic derivatives[270] of 4-thiazolidinone and 5-thiazolidinone.

E. Carbon-13 Nuclear Magnetic Resonance Spectroscopy

Vögeli et al.[271] studied the carbon-13 NMR spectra of a series of substituted 4-thiazolidinones in $CDCl_3$. The chemical shifts and C,H spin-coupling constants are given. Various constitutional isomers have been differentiated, and the configuration of trisubstituted exocyclic C=C double bonds have been established on the basis of C,H spin-coupling constants over two and three bonds.



VII. Biological Activity of Thiazolidinones

A. Anticonvulsant Activity

The anticonvulsant activity of several series of 2-(arylimino)/(arylhydrazono)-3-aryl/(alkylaryl)/furfuryl/2-pyrimidyl/cycloalkyl/(substituted amino)/(3-(*N*-morpholino)propyl)-4-thiazolidinones has been studied against pentylenetetrazol-induced seizures[75,85–92,94] in albino mice of either sex at a dose of 100 mg/kg. Most of the compounds were found to exhibit protection against pentylenetetrazole-induced seizures, and the degree of protection ranged up to 80%. However, no definite structure activity relationship could be observed regarding the anticonvulsant activity possessed by thiazolidinones.

B. Hypnotic Activity

Several 2-(arylimino)-3-(2-pyrimidyl)-4-thiazolidinones[92] and 2-(arylimino)-3-(3-(*N*-morpholino)-propyl)-4-thiazolidinones[90] were evaluated for their ability to potentiate pentobarbital-induced hypnosis in mice at a dose of 100 mg/kg. All thiazolidinones were found to potentiate pentobarbital sleeping time. The increase in the duration of sleep ranged from 10 ± 3 min in untreated control to 98.6 ± 10 min in mice pretreated with substituted thiazolidinones.

C. Respiratory Activity

A number of 4-thiazolidinones were investigated for their inhibitory effects on the oxidation of the substrates of the tricarboxylic acid cycle and β-hydroxybutyrate by rat brain homogenates.[87,90-92] All thiazolidinones selectively inhibited NAD-dependent in vitro oxidation of various substrates, whereas NAD-independent oxidation of succinate remained unaltered. The presence of added NAD not only increased the cellular respiratory activity of rat brain homogenates during oxidation of pyruvate but also decreased the inhibitory effectiveness of substituted thiazolidinones.[87,92] These results have provided evidence for a possible competition between the thiazolidinones and NAD for the active site(s) on the enzyme molecules.

D. Antiinflammatory, Antiproteolytic, and Antihemolytic Properties

Newbould[272] studied the antiinflammatory activity of 2-[(butoxycarbonyl)methylene]-4-thiazolidinone. The compound was found to be devoid of activity against most models of acute inflammation. However, it partially inhibited carrageenin-induced edema in the rat and prevented completely the development of secondary lesions in the rats injected with adjuvant (a fine suspension of dead tubercle bacilli in liquid paraffin) in the footpad. A group of 2,3,5-trisubstituted-4-thiazolidinones were studied by Patel et al.[143] where 2-(4-methoxyphenyl)-3-(3-methylphenyl)-5-methyl-4-thiazolidinone was found to exhibit inhibition of edema by 13.5% after 24 h. A few 2-aryl-3β-(aryloxyethyl)-4-thiazolidinones and their corresponding 1,1-dioxides have been shown[128] to exhibit antiinflammatory activity. Various 2-(substituted imino)-3-[(3,4-dimethoxyphenyl)ethyl]-4-thiazolidinones were also studied[273] for their antiinflammatory activity against carrageenin-induced edema. The antiinflammatory activity of these thiazolidinones was correlated with their antiproteolytic activity and their ability to inhibit trypsin-induced hydrolysis of bovine serum albumin. A large number of substituted oxothiazolylacetic acids have also been reported[100,101] to possess antiinflammatory and antiproteolytic activity.

Antiproteolytic and antihemolytic properties of several 4-thiazolidinones were investigated by Chaudhari et al.[274] The in vitro protection of the hypoosmotic hemolysis of human red blood cells and the inhibition of trypsin-induced hydrolysis of bovine serum albumin by these thiazolidinones were found to be concentration-dependent.

E. Antitubercular Activity

Litvinchuk[275] reported antitubercular activity with low toxicity associated with a few derivatives of 2-imino-4-thiazolidinones. Repeated therapeutic doses were found to possess antituberculous activity comparable to streptomycin or phthivazid. Kapustyak[276] has studied structure–tuberculostatic activity relationship of some 4-thiazolidinones. Fujikawa et al.[54] reported chemotherapeutic effectiveness against *Myobacterium tuberculosis*. A few derivatives were found to inhibit the growth of human tubercle bacilli, H37Rv strain, in a concentration of 12.5 μg/mL. Several other derivatives of thiazolidinones have also been found[277,278] to inhibit the growth of *Myobacterium tuberculosis* H37Rv strain. The effect of thiazolidinone derivatives on other *Myobacterium* strains have also been studied.[279-281] Turkevich et al.[66] reported few 2-imino-4-thiazolidinone derivatives as possible antitubercular compounds. In other study, 5-(5-nitrofurfurylidene)-3-ethylrhodanine has been found to be a promising tuberculostatic compound.[282] Danila[283] reported the antimicrobial activity of several 2-thiono-4-thiazolidinone derivatives.

F. Anthelmintic Activity

3-Methyl-5-[(4-nitrophenyl)azo]rhodanine, nitrodan, was reported as a potent anthelmintic compound[284-286] which was effective when administered in feed against *Hymenolepis nana* and *Syphacia obvelata* infections in mice, *Asceridia galli* infections in chickens, and *Toxocera canis*, *Ancylostoma caninum*, and *Uncinaria stenocephala* infections in dogs, pigs, and horses. 2-Imino-3-(2-acetamidophenyl)-4-thiazolidinone derivatives have been found to be effective in vitro against horse Strongyloids at concentrations[287] of 10^{-3} to 10^{-6} M. Hussain et al.[199] synthesized a few azorhodanine derivatives in search of potent anthelmintics and found only 2-thiono-3-(4-chlorophenyl)-5-[[4-(4-methylpiperazino)phenyl]azo]-4-thiazolidinone possessing anthelmintic activity against *N. dubius* in mice. Aries[288,289] reported various 2-thiono-3-substituted-5-[(2-methyl-4-nitrophenyl)azo]-4-thiazolidinones and 2-thiono-3-methyl-5-[(2,4-dinitrophenyl)azo]-4-thiazolidinone as potent anthelmintic agents which were not only effective alone but also showed activity as well with other parasiticides. Nemeseri[290] reported 2-thiono-3-(3,4-dichlorophenyl)-4-thiazolidinone as an antiparasitic agent which prevented infections caused by *Asceridia galli* in chickens.

G. Cardiovascular Effects

Nagar et al.[88] studied the cardiovascular effects of a series of 2-cyclopentyl/(cyclohexylimino)-3-aryl-4-thiazolidinone-5-ylacetic acids on adult cats of either sex. All substituted thiazolidinones induced hypotension of varying degree. The duration of hypotensive activity observed with most of these compounds was less than 15 min.

H. Antibacterial Activity

Several 2-[(dichlorophenyl)imino]-4-thiazolidinones and 2-(arylhydrazono)-4-thiazolidinones and their corresponding 5-arylidene derivatives were tested against *Staphylococcus aureus*. The antibacterial activity of 5-arylidene derivatives of both 2-[(dichlorophenyl)imino]/2-(arylhydrazono)-4-thiazolidinones was found to be greater than that of the parent compounds.[185] The screening data of more than 50 thiazole and thiazolidinone derivatives against some common bacteria revealed that the thiazolidinones were more active than the thiazoles.[291] An enhancement in activity was observed with mercurated thiazolidinone derivatives as compared to nonmercurated derivatives. Akerblom[292] investigated the antibacterial activity of a series of 5-(5-nitro-2-furfurylidene)-2-(substituted-imino)-4-thiazolidinones and 5-(5-nitro-2-furylpropenylidene)-2,4-thiazolidinediones against *Staphylococcus aureus*, β-

Haemolytic streptococcus, E. coli, K. aerogenes, and *P. vulgaris*. All of them showed a high activity against *S. aureus*. The activity against *E. coli* and *K. aerogenes* was dependent on the size of the substituents. Among several 4-thiazolidinones evaluated in vitro against eight bacterial species, 3-(morpholinomethyl)-2-phenyl-4-thiazolidinone hydrochloride was found to be most active antibacterial agent.[293] Recently Fennech et al.[134] screened 3-substituted-2-adamantyl-4-thiazolidinones against 12 bacterial strains (5 Gram-positive: *S. pneumoniae, S. pyogenes, S. aureus, S. aureus Pen. Res.*, and *S. faecalis*; 7 Gram-negative: *E. coli, K. penumoniae, P. mirabilis, P. vulgaris, S. marcescens, E. cloacae*, and *P. aeruginosa*). The minimal inhibitory concentration (MIC $\geq$ 125 μg/mL) indicated that these compounds were poor antibacterial agents. 2-Aryl-3-benzothiazolyl-4-thiazolidinones exhibited[294] 35–56% inhibition of Gram-positive and Gram-negative bacteria at a final concentration of 10^{-3} M. Some 2-spiro-3-aryl-5-methyl-4-thiazolidinones were found to be bactericidal against *E. coli* and *Staphylococcus aureus*.[136,295] 3-Ethyl-5-(5-nitrofurfurylidene)-2-thiono-4-thiazolidinone inhibited[136,295] *Staphylococcus londonii* at a concentration of 0.2 μg/mL. The antibactericidal data of several substituted-4-thiazolidinones are reported by other investigators.[296] Several *N*-glycosyl- or *N*-glucopyranosyl-5-aralkylidenerhodanines were found to possess antibacterial activity.[297,298]

I. Antifungal Activity

Rao[299] reported high antifungal activity of some mercurated derivatives of 4-thiazolidinones against *Aspergillus niger* at a dilution of 1:10 000. Various 2-(4′-arylthiazolyl-2′-imino)-3-aryl-4-thiazolidinones have also been found to be sufficiently active against *Aspergillus niger* and *Alternaria tenius*[38] at a dilution of 1:10 000. Matolcsy et al.[300] have found very high antifungal activity associated with the derivatives of 2-thiono-4-thiazolidinones against *Alternaria tenius* and *Botrytis allii*. Several 2-[(*o*-methylphenyl)imino]-3-aryl-4-thiazolidinones and their 5-phenylazo derivatives have been found to be very good fungicidal agents against *Helminthosporium euphorbiae*.[37] Chaubey et al.[39] screened various 1,1-dioxides and 5-phenylazo derivatives of 2-(arylimino)-3-aryl-4-thiazolidinones against *Aspergillus niger* and found the compounds to be fungistatic and not fungicidal. 3-Ethyl-5-methyl-2-[(4-chlorobenzothiazol-2-yl)imino]-4-thiazolidinone and 3-ethyl-5-methyl-2-[(5-chlorobenzothiazol-2-yl)imino]-4-thiazolidinone were found to exhibit 100% inhibition of spore germination[79] of *Alternaria tenius* at concentrations of 1:1000, 1:5000, and 1:10 000. But 3-benzyl-5-methyl-2-[(5-methylbenzothiazol-2-yl)imino]-4-thiazolidinone has been found to exhibit[72] only 40.5% inhibition of *Alternaria tenius* at a concentration of 1:5000. Fifty percent inhibition of *Alternaria tenius* was exhibited by 3-(2,4-dinitrophenyl)-2-thiono-6-thiazolilidinone[301] at a concentration of 90 μg/cm^2. Gupta and Rani[302] have tested various 5-substituted-3-(polynitrophenyl)-2-thiono-4-thiazolidinones against *Aspergillus niger, Alternaria tenius, Helminthosporium sativm*, and *Fusarium oxysporum* by spore germination method and established a relationship between fungitoxicity and their molecular structure. A large number of other derivatives of 4-thiazolidinone have also been tested for their antifugal activity against variety of fungi, and some of them were found to be good antifungal agents (ref 73, 129, 134, 136, 139, 142, 197, 226, 282, 291).

J. Insecticidal Activity

[(3,5,5-Trimethyl-4-oxo-2-thiazolidinylidene)amino]-methyl carbamate has been reported[303] to control the growth of *Blaniulus guttulatus*. Several other derivatives of thiazolidinones are also reported to be insecticides.[304-307]

Tong et al.[308] have reported 2-thiono-4-thiazolidinone and 2,4-thiazolidinone derivatives as the repellants against female *Aedes aegypti* mosquitoes on human skin.

K. Antiviral Activity

2,4-Dioxo-5-thiazolidinylacetic acid prevents in high dilution (2×10^{-4} M) the cytopathogenic changes in cell culture of human embryonic kidneys infected with Herpes simplex virus and poliovirus type I. This compound prevented the cytopathogenic changes with these viruses if added simultaneously with virus to the cell culture medium or even if added at different time intervals after the cells have been infected.[309]

Schauer et al.[310] investigated a number of 4-oxo-5-thiazolidinylacetic acid derivatives for their activity against Herpes simplex in order to find out a relationship between their antiviral activity and chemical structure. The substituents present at position 2 and 3 of the 4-oxo-5-thiazolidinylacetic acid were found to play an important role during the inhibition of viral multiplication. Among 12 compounds tested, 3-(*p*-tolyl)-2-(methylphenylhyrazono)-4-oxo-5-thiazolidinylacetic acid was found to be the most active against viral multiplication. Several 2-[cyano(alkoxycarbonyl)-methylene]-4-thiazolidinones were tested and used as virustatic agents in pharmaceutical compositions.[311]

N-Glucosyl-5-(*p*-nitrobenzylidene)rhodanine at a final concentration of 150 μg/mL inhibited RNA synthesis of both host cells and virus cell to a similar extent.[297,298] At concentrations of 50 and 100 μg/mL, this compound inhibited 10% of cellular RNA synthesis but 40% of viral RNA synthesis. This difference in inhibition of RNA synthesis revealed that rhodanine derivatives possess antiviral activity.

Rhodanine was found to be a selective inhibitor[312,313] of the multiplication of Echovirus type 12. Coxsackievirus A9, Echovirus 7, the prototype strain of Echovirus 9, and influenza virus 13 strain were slightly susceptible to rhodanine. Eighteen derivatives and analogues of rhodanine were also tested against Echovirus 12. These compounds were considerably less active than rhodanine or were inactive without possessing antiviral activity, and some of them were more toxic to host cells than rhodanine.[312]

L. Herbicidal Activity

Several substituted rhodanine derivatives were found to inhibit the germination and early growth of weeds without giving damage to rice plants.[314,315] The use of 5-(2-chlorobenzylidene)rhodanine at 1000 g/10 acres completely inhibited the growth of barnyard grass and broadleaf weeds in pots containing 3- or 4-leaf-stage rice

plants after 30 days. Some 3-arylrhodanines were reported to be useful as herbicides by the barley leaf segment test.[316]

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