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.
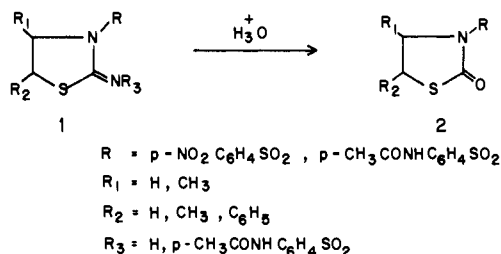
Diverse biological activities such as bactericidal, pesticidal, fungicidal, insecticidal, anticonvulsant, tuberculostatic, antiinflammatory, antithyroidal, potentiation of pentobarbital-induced sleeping time, etc., have been found to be associated with thiazolidinone derivatives. In recent years, several 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]

$R = p\text{-}NO_2C_6H_4SO_2$, $p\text{-}CH_3CONHC_6H_4SO_2$
$R_1 = H, CH_3$
$R_2 = H, CH_3, C_6H_5$
$R_3 = H, p\text{-}CH_3CONHC_6H_4SO_2$

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).

$R = R_1 = H$ or CH_3
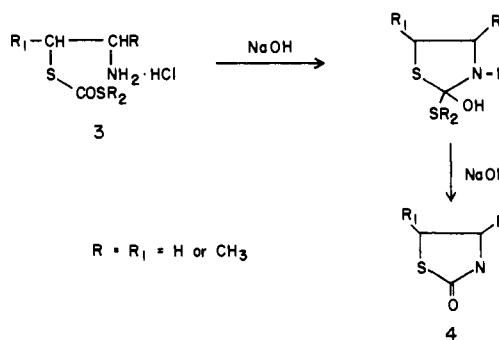
2-Thiothiazolidinones (5), on refluxing with mercuric oxide[8] in acetic acid, give 2-thiazolidinone (6).

$R = CH_3$ or C_2H_5
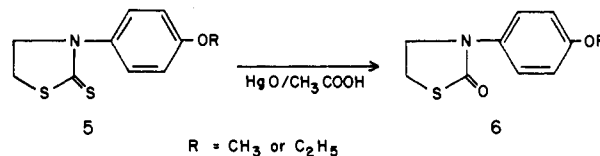
The reaction of N-(β-mercaptoethyl)arylamines with phosgene in toluene[9,10] yields 3-aryl-2-thiazolidinones (7).

$R = Aryl$
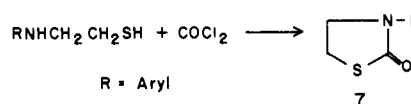
The synthesis of several substituted 2-thiazolidinones (8) is reported by the condensation of α-aminoalkenes,
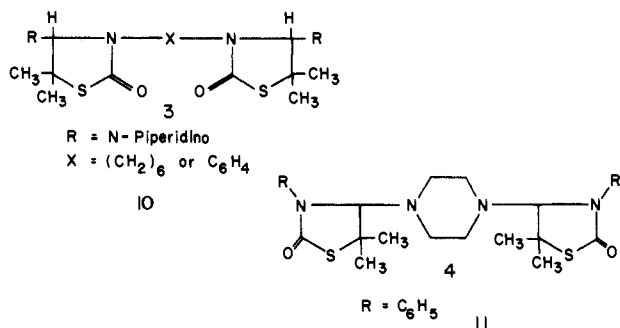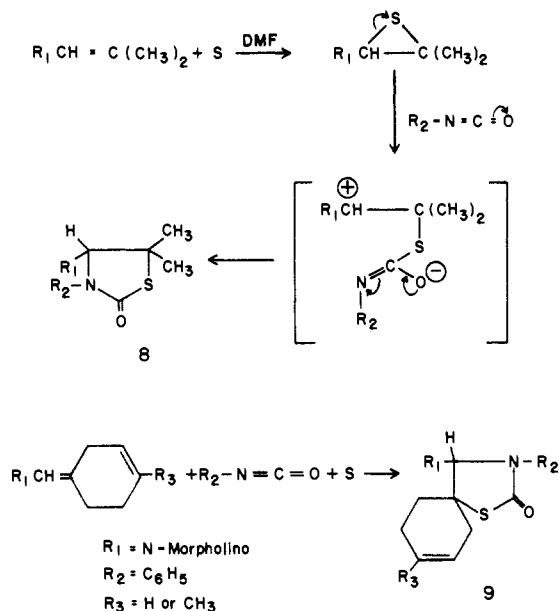
sulfur, and isocyanates.[11] The optimum yield is obtained when sulfur is first condensed with the amino-alkene in a solvent containing carbonyl group, preferably dimethylformamide, and the adduct thus obtained is treated with the appropriate is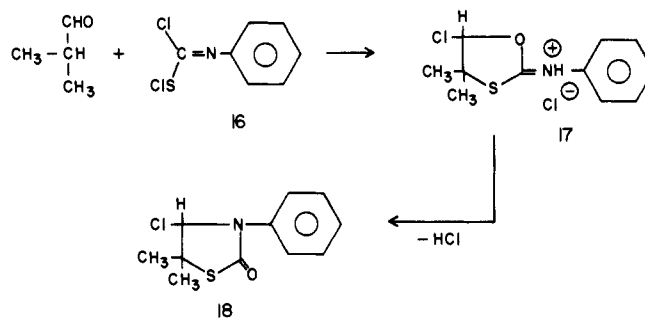ocyanate. The derivatives of (aminomethylene)cyclohexane or (amino-methylene)cyclohexene, on condensation with sulfur and isocyanates, give their corresponding spiro compounds (9). Under similar conditions, reaction of diisocyanates or diaminodienes yield the corresponding bicyclic derivatives 10 and 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.
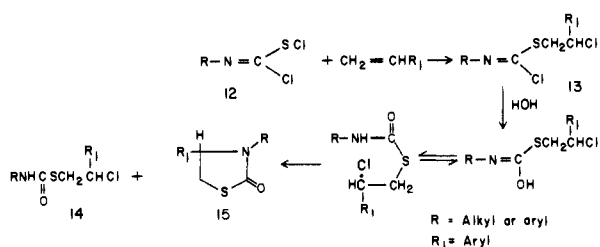

The addition of N-alkyl- or N-aryl-S-chloroisothio-carbamoyl chloride (16) to the ethereal solution of iso-butyraldehyde at 25–30 °C leads to the formation of an adduct (17) which is of limited stability at room tem-

perature 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]
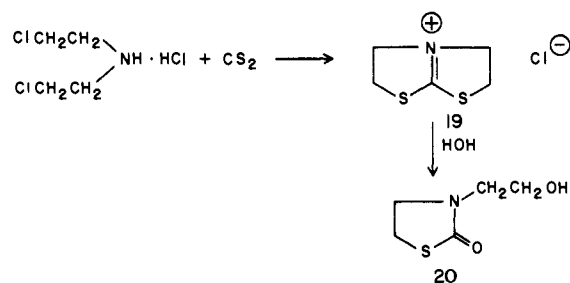
The reaction of 3-alkyl-2-iminothiazolidines (21) with aqueous NaNO₂ at 0 °C in the presence of hydrochloric acid or acetic acid produces 3-alkyl-2-nitrosoimino-thiazolidines (22) which on refluxing in n-butyl alcohol
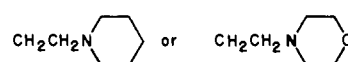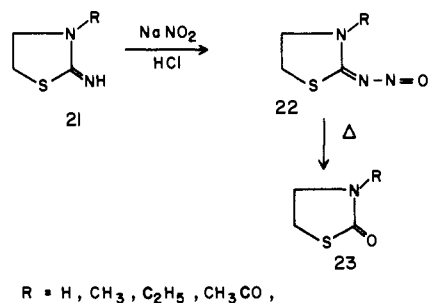
give the corresponding 3-alkyl-2-thiazolidinones[15] (23). Brown et al.[16] reexamined the thermal decomposition of 22 and noticed that the 3-methyl-2-(nitrosoimino)-thiazolidine decomposed smoothly in pyridine within 10 min to give 3-methyl-2-thiazolidinone in 87% yield. Decomposition also occurred in p-xylene, toluene, o-dichlorobenzene, and dimethyl sulfoxide.

Shiva P. Singh is a research associate at the University of North Dakota, Grand Forks, ND. He was born in India in 1947. He received his B.Sc. and M.Sc. degrees from Agra University, Agra, India, and was lecturer in the postgraduate college, Gyanpur, before joining the Ph.D. program at King G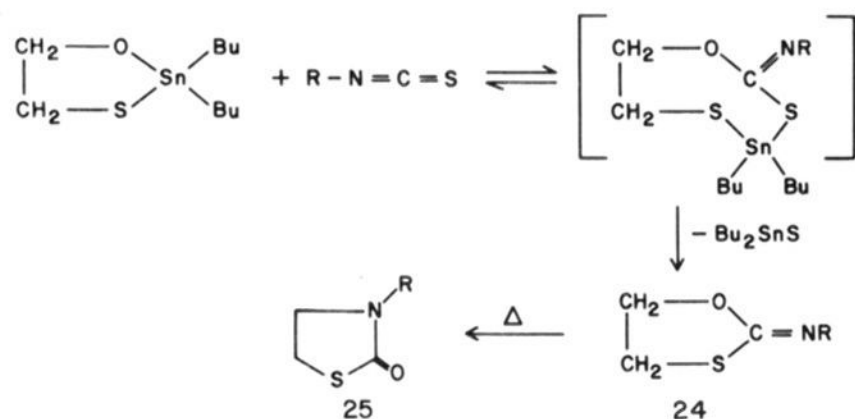eorge's Medical College, Lucknow, India. He received his Ph.D. degree under the guidance of Dr. Surendra S. Parmar from Lucknow University in 1976. His research interests are in the field of medicinal chemistry, photochemistry, and carbon-12 NMR spectroscopy.
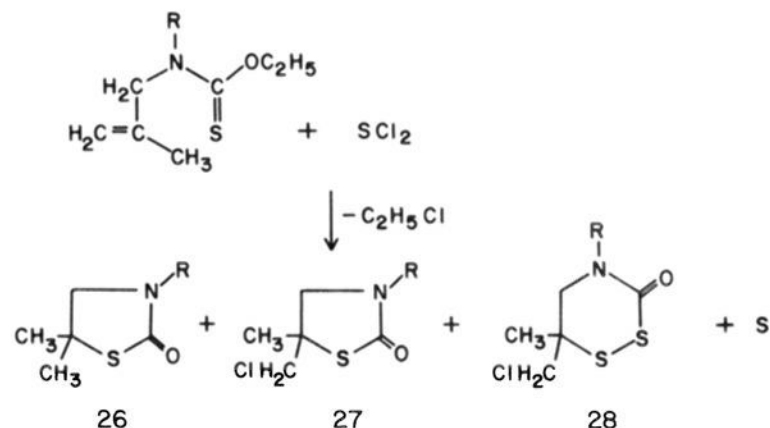
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Cyclic organostannyl sulfides such as 2,2-dibutyl-1,3,2-oxathiastannolane react with phenyl or alkyl isothiocyanate to give 2-iminooxathiolane (24) with the

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

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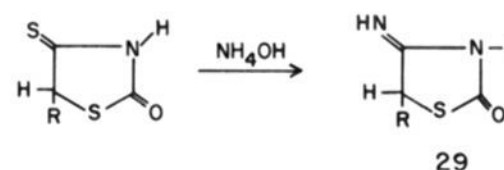
A convenient one-step cyclization reaction leading to the synthesis of 2-thiazolidinone derivatives from 2-iodoalkyl isothiocyanates has been recently reported.[21] Refluxing of vic-iodo isothiocyanates (30) with anhydrous methanol in tetrachloroethylene in the dark gives

R_1 = H or CH_3 R_2-R_3 = $(CH_2)_2-$ (cis) or

R_2 = C_6H_5

R_3 = H or CH_3 (trans - indano)

$R_1 R_2 R_3$ = 5 α - androstano

SCHEME I
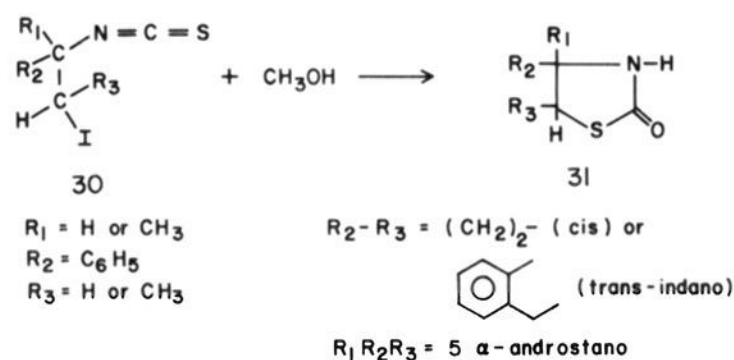
SCHEME II

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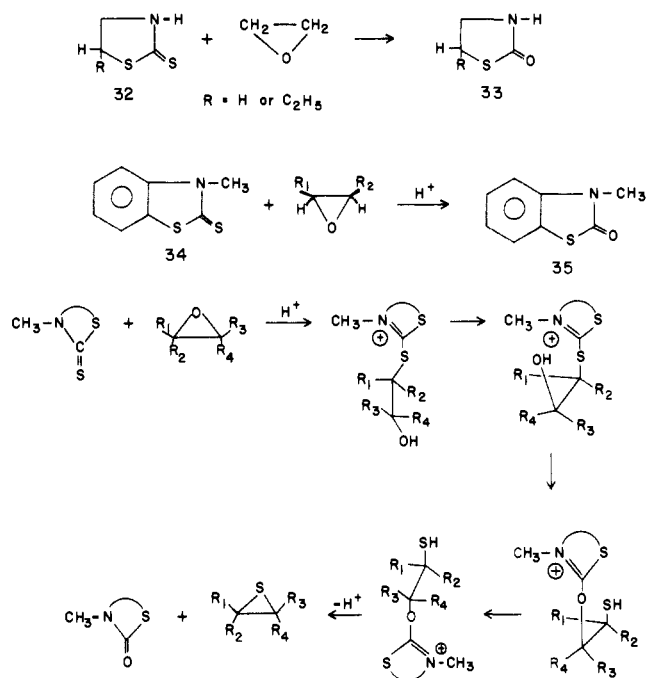
various substituted 2-thiazolidinones (**31**) in good yields.

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

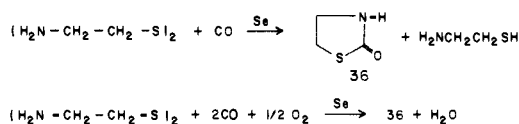1 mol of disulfide gives 1 mol of 2-thiazolidinone and 1 mol of amino thiol. However, only 2-thiazolidinone is obtained when the above reaction is carried out in the presence of oxygen which reoxidizes the thiol to disulfide.[24]

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
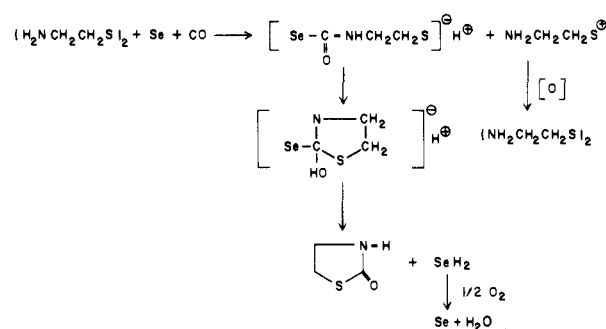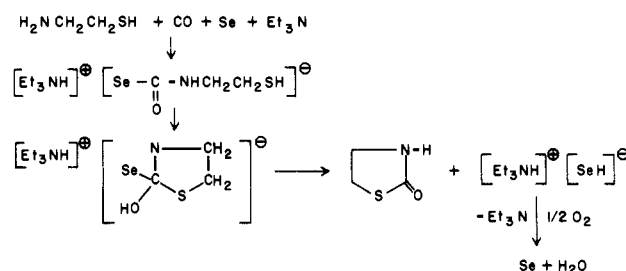
of NaHCO$_3$ to give substituted 2-thiono-4-thiazolidinones[26,27] (**37**).

R = CH$_3$, NH$_2$
R$_2$ = Ph. H
X = Halogen
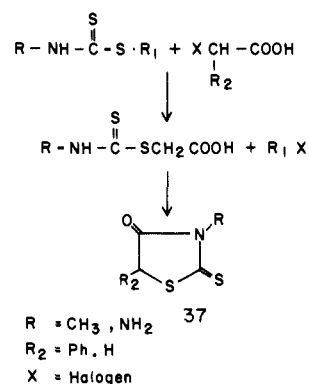
Ammonium dithiocarbamates condense with the glycidic esters **38** to give 2-thiono-3-substituted-5-(hydroxyalkyl)-4-thiazolidinones (**39**) which are readily dehydrated in refluxing acetic acid to 2-thiono-3-substituted-5-alkylidene-4-thiazolidinones[28] (**40**).

R = CH$_3$, C$_2$H$_5$ or Ph
R$_1$ = CH$_3$ or C$_2$H$_5$
R$_2$ = Ph
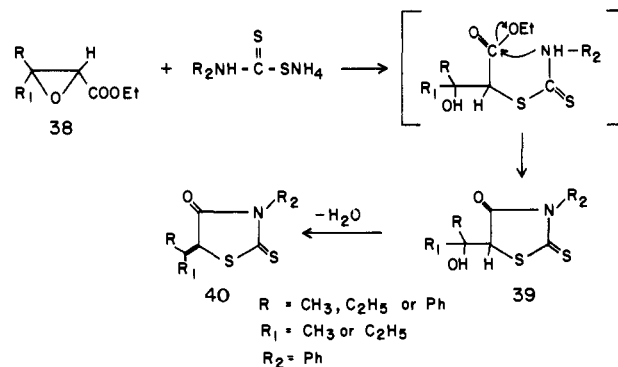
Substituted 2-imino-4-thiazolidinones (**41**) are obtained in good yields by the reaction of symmetrical and unsymmetrical thioureas with various substituted and unsubstituted α-haloalkanoic acids, their esters, acid chlorides, amides, or carbamates.[29-95] The reaction proceeds via the intermediate isothiourea which cyclizes in refluxing acetic acid, ethanol, or benzene in the

presence of sodium acetate or pyridine.

41
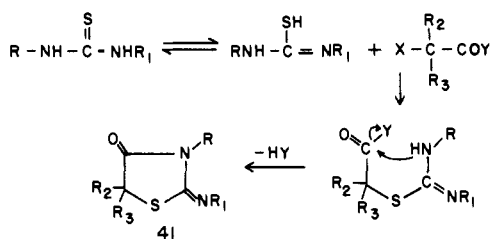
R   = Alkyl, aryl or heterocyclic

R₁ = Alkyl, aryl or heterocyclic

R₂ = H or alkyl

R₃ = H or alkyl

R₂R₃= 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]
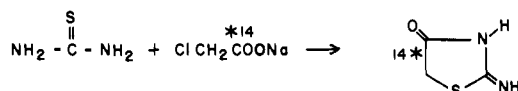
Various N-substituted acetylthioacetamides on treatment with monochloroacetic acid in the presence of sodium acetate in refluxing acetic acid yield 2-acetylmethylene-3-substituted-4-thiazolidinones[97] (42).

R = Aryl   42
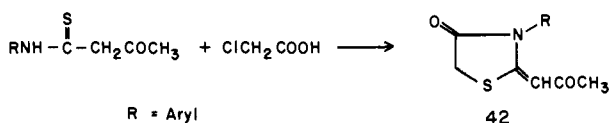
4-Oxo-5-thiazolidineacetic acids can be conveniently prepared from dicarboxylic acids.[98] α-Bromosuccinic acid mixed with dithiocarbaminates on neutralization with NaHCO₃ followed by acidification and boiling yields 2-thiono-4-oxo-5-thiazolidineacetic acids (43). However, α-bromosuccinic acid on treatment with thioureas in the presence of sodium acetate in methanol yields 2-imino-4-oxo-5-thiazolidineacetic acids (44).

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]
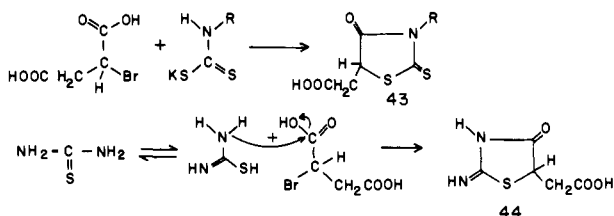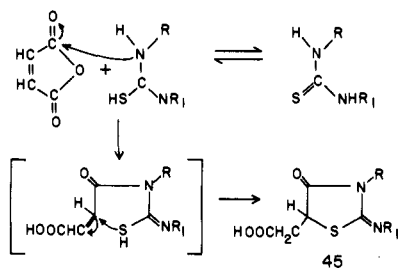

45

3-Carboxyalkyl-2-thiono-4-thiazolidinones have been synthesized from long-chain amino acids,[102,103] NH₂-(CH₂)ₙCOOH. The amino acids react with CS₂ 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
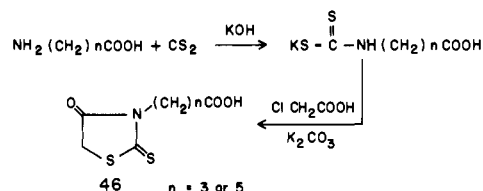
Dimethyl acetylenedicarboxylate (DMAD) reacts readily with substituted and unsubstituted thioureas, dithiocarbamates, thiocarbamates, thiosemicarbazides, and thiosemicarbazones to give 4-thiazolidinones.[104,105] Lown et al.[106] have proposed the six-membered structure, 2,3-dihydro-1,3-thiazine-4-one (47), for the reaction

47

R₁ = H , CH₃ , (CH₃)₂CH , C₆H₅CH₂ or C₆H₅

R₂ = H , CH₃ , C₆H₅CH₂ , C₆H₅ or O-CH₃OC₆H₄
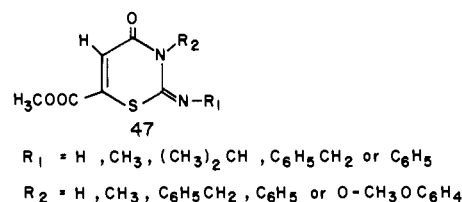
products of DMAD and thioureas on the basis of NMR and mass spectra. Structure 47 was supported by Winterfeldt et al.[107] and Kishida et al.[108] but is without any chemical evidence. Products 47 were, however, proved to have the five-membered structure 48 by chemical reactions and spectroscopic data.[104] 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, CH₃ , C₆H₅CH₂ or C₆H₅
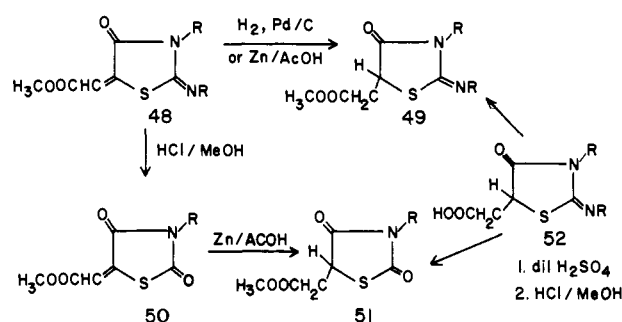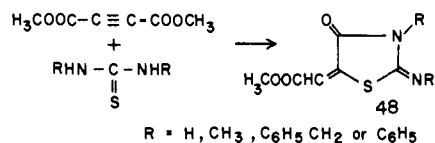
DMAD on reaction with monosubstituted thioureas gives isomeric mixtures of 2-imino-4-thiazolidinones 53 and 54.

53   54

R = CH₃ or C₆H₅
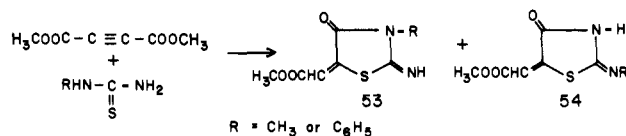
DMAD reacts readily with dithiocarbamates in methanol at room temperature to give 2-thiono-4-thiazolidinones.[104,105] The course of the reaction was, however, found to be markedly influenced by the reaction conditions. When DMAD is added to the methanolic

SCHEME IV

$$CH_2-COOC_2H_5 \atop SCN + NH_2-C(=S)-NH_2 \xrightarrow{-C_2H_5OH} CH_2-CONH-C(=S)-NH_2 \atop S-CN$$

$$C_6H_5-CH=C(SCN)-CONH-C(SH)=NH \xleftarrow{C_6H_5CHO} CH_2(SCN)-CONH-C(SH)=NH$$

$$\downarrow -HSCN$$

65

solution of ammonium N-substituted dithiocarbamate, 3,3′-disubstituted-2,2′-dithiono-Δ⁵,⁵′-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-Δ⁵,⁵′-bi-4-thiazolidinones (**57**).

$$H_3COOC-C\equiv C-COOCH_3 \atop + \atop R-HN-C(=S)-SH\cdot Base \longrightarrow 55$$

$$\downarrow RNH-C(=S)-SH\cdot Base$$

57   56

R = CH₃, C₂H₅, C₃H₇, C₄H₉ or C₆H₅CH₂

DMAD reacts with methylammonium N-methyl-thiocarbamate in methanol at room temperature to give 3-substituted-5-[(methoxycarbonyl)methylidene]-2,4-thiazolidinediones (**58**).
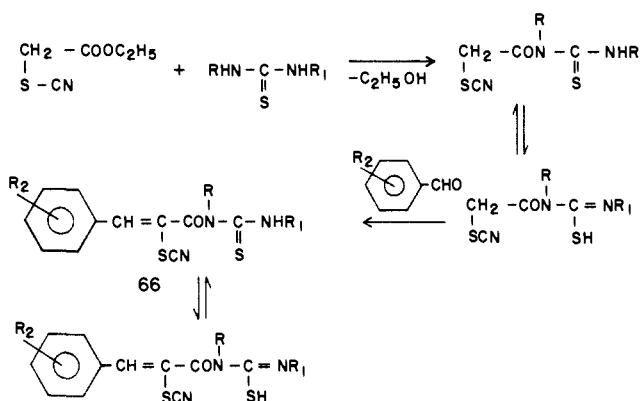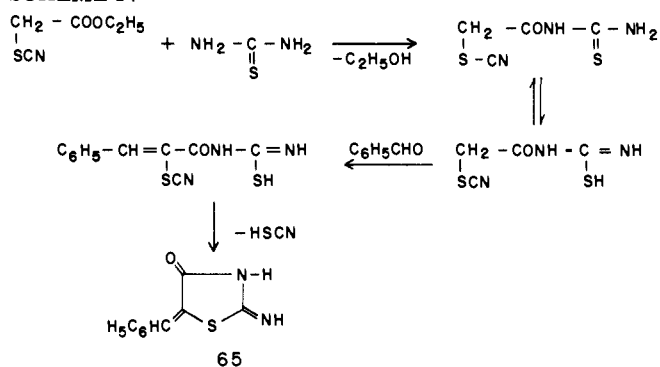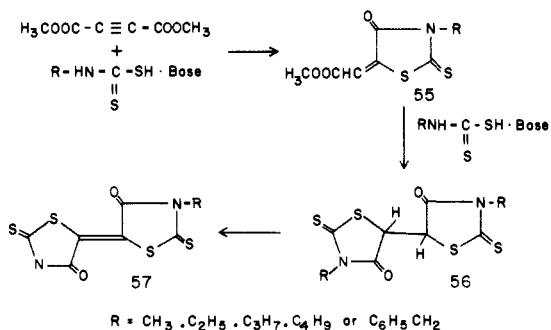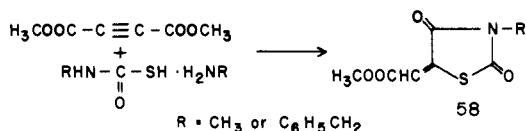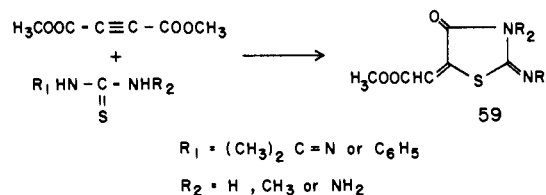
$$H_3COOC-C\equiv C-COOCH_3 \atop + \atop RHN-C(=O)-SH\cdot H_2NR \longrightarrow 58$$

R = CH₃ or C₆H₅CH₂

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

$$H_3COOC-C\equiv C-COOCH_3 \atop + \atop R_1HN-C(=S)-NHR_2 \longrightarrow 59$$

R₁ = (CH₃)₂C=N or C₆H₅

R₂ = H, CH₃ or NH₂

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

$$NC-CH=CH-CN + RNHC(=S)-SH\cdot NEt_3 \longrightarrow 60$$

$$\swarrow MeOH/H_2O \qquad \downarrow H_2O/HCl$$

63   62

$$R_1S-C(=C(SR_2))-CN \atop NC + RNH-C(=S)-SH\cdot NEt_3 \longrightarrow 61$$

$$\downarrow 50\% H_2SO_4$$

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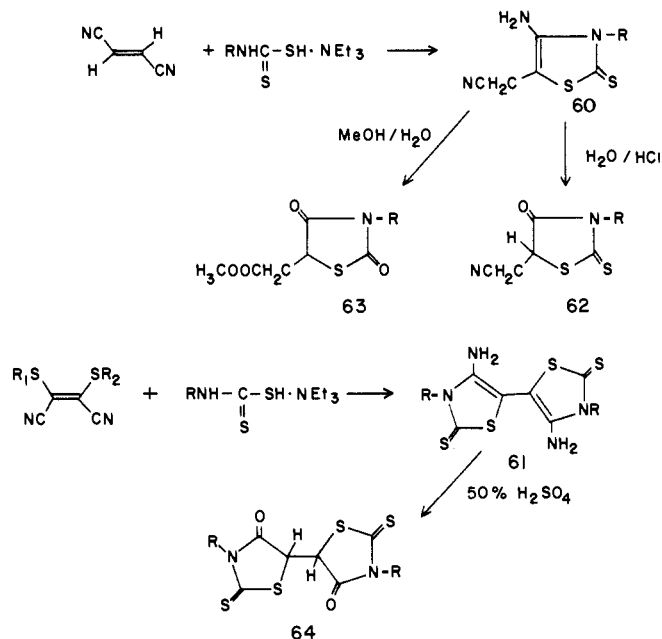
resulted into the formation of 4-thiazolidinones (**62–64**). The double bonds of the nitriles are activated by cyano groups which react readily with nucleophiles.

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**).

$$CH_2=C=O + ClCH_2COOH \xrightarrow{CHCl_3} 67$$

$$\downarrow \atop + S \atop R-NH-C(=S)-NHR_1 \longrightarrow 68$$

R = R₁ = H or Ar
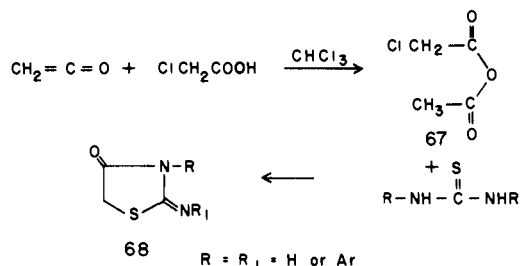
Various 3-substituted-2-thiono-4-thiazolidinones (**69**) can be conveniently prepared by the reaction of substituted isothiocyanates with α-mercaptoacetic acid or its ester followed by acid cyclization of the resulting (thiocarbamoyl)mercaptoacetic acids and acetates.[113]

$$RNCS + SHCH_2COOR_1 \longrightarrow RNH\overset{\overset{S}{\|}}{C}-SCH_2COOR_1$$

R = Alkyl or aryl

69
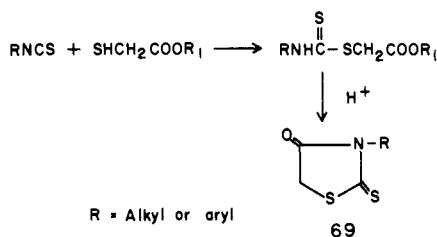
α-Mercaptoalkanoic acids have been extensively used for the synthesis of 4-thiazolidinones. The substituted and unsubstituted α-mercaptoalkanoic acids react conveniently with Schiff bases of aromatic or heterocyclic aldehydes and aliphatic or aromatic amines in different solvents to give a variety of 2-substituted-4-thiazolidinones[114-143] (**70**).

R = Alkyl or aryl
R₁ = Aryl or heterocyclic
R₂ = H or alkyl
R₃ = H or alkyl
R₂R₃ = Arylidene

70

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**).

R = Aryl
R₁ = Alkyl
R₂ = Alkyl

71

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.

R₁ = H or alkyl
R₂ = R₃ = 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**).
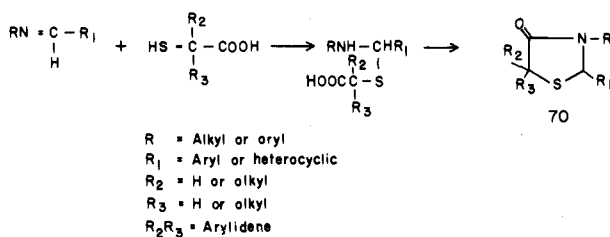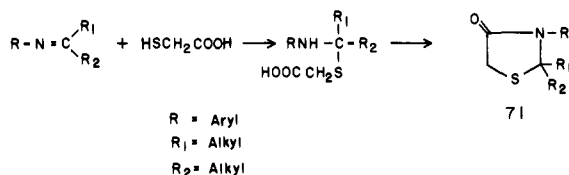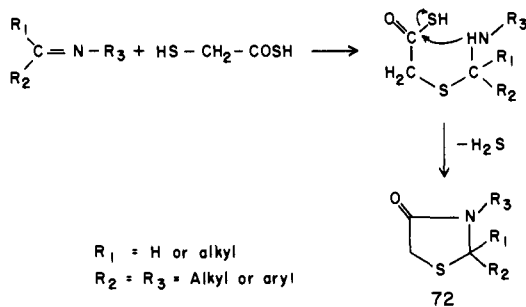
Substituted and unsubstituted α-mercaptoacetic acid esters react smoothly with the compounds containing activated nitrile groups in the presence of an equivalent

73
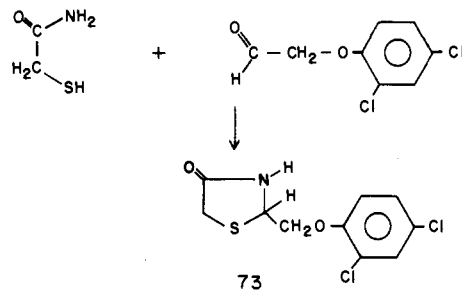
amount of alcoholate to give 4-thiazolidinones[147,148] (**74**).

R = CH₃ or C₂H₅
R₁ = H or C₂H₅
R₂ = H, C₂H₅, Ph or O-CH₃C₆H₄
R₃ = H or Ph
R₄ = -COOEt, -CONH₂, -CN.Bz.Ph, Pyridyl or indoyl

74
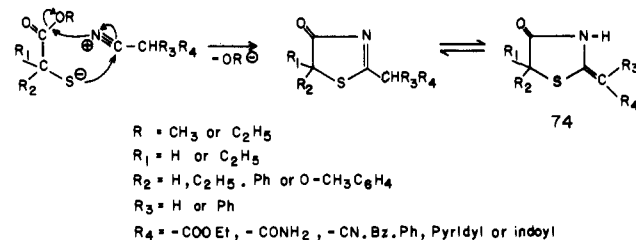
Monforte et al.[149] have recently synthesized 4-thiazolidinones (**75**) and 2,4-thiazolidinediones (**76**) by reacting carbodiimides with α-mercaptopropionic acid.

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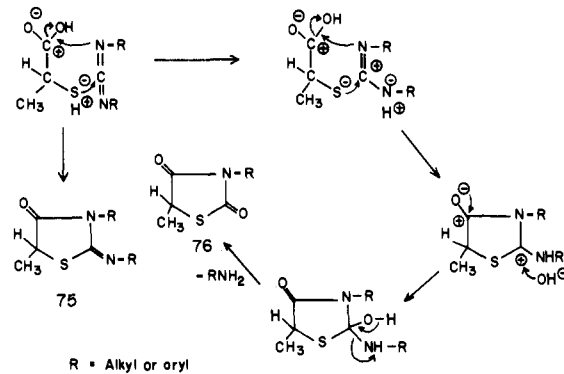
The acid reacts with one of the two carbodiimidic C=N groups to give 3-substituted 2-imino-5-methyl-4-thiazolidinones (**75**). The related 3-substituted 5-methyl-2,4-thiazolidinediones are also formed except in the reaction with dicyclohexylcarbodiimide.

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

$$Ph-CH=N-Ph + H_2C=C=O + SO_2$$

77
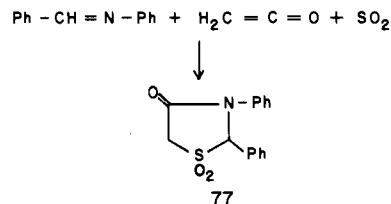
with benzylideneaniline with ketene in liquid SO₂ at -70 °C. The cycloaddition may proceed through a concerted mechanism (**78**) or through the reaction of 1,4-dipole intermediate, formed from ketene and the imine with sulfur dioxide (**79**).

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

78   79

80
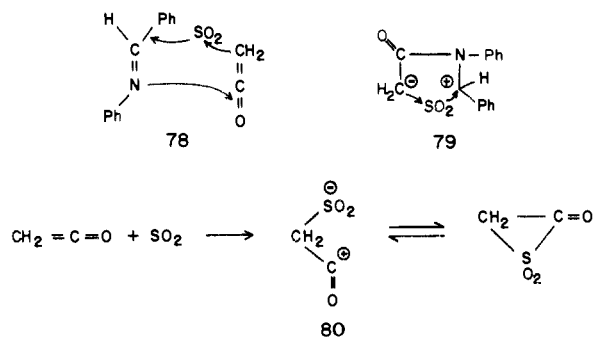
ketene and sulfur dioxide, though not by isolation but by interception with appropriate reagents and low-temperature NMR study. They have studied 1,3-dipolar additions of the intermediate with benzylideneaniline and its derivatives to give 2,3-disubstituted-4-thiazolidinones (81) and demonstrated the reaction to be sensitive to electronic effects. Electron-withdrawing

81
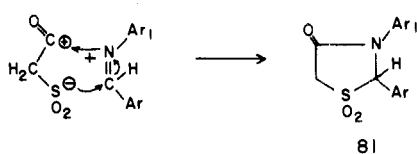
groups in the benzylidene ring favored the reaction while the same groups in the aniline ring of the Schiff base hindered the reaction. They have shown that other ketenes such as dimethyl-, ethylbutyl-, and diphenylketenes do not form adducts with sulfur dioxide. The lack of reactivity of diphenylketene 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,SCH₃ or SC₂H₅   84
R₁ = H ,Cl , Br, n-C₄H₉, C₆H₉ or SC₂H₅
RR₁ = -S (CH₂)₂ S-
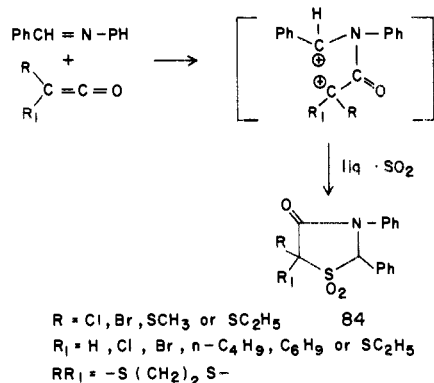
The 5-halogenated and 5-alkylthio derivatives of 84 are conveniently dehalogenated and desulfurized by

SCHEME V

83   +   82

R = CH₃ , C₂H₅ or iso-C₃H₇

SCHEME VI

R₁ = Cl or Br
R₂ = H, Cl or Br

85

R₁ R₂ = -S(CH₂)₂ S-
R₁ = SCH₃ or SC₂H₅
R₂ = H or SC₂H₅

SCHEME VII

88   R = 2-Furyl, 5-methyl-2-furyl, 2-thienyl, 3,4-dimethoxyphenyl,
       3-methoxyphenyl or styryl
     R₁ = H or CH₃
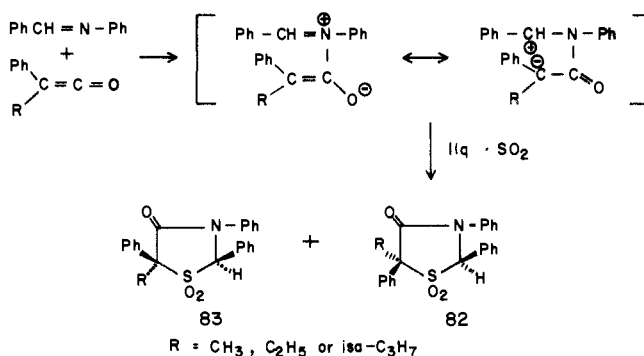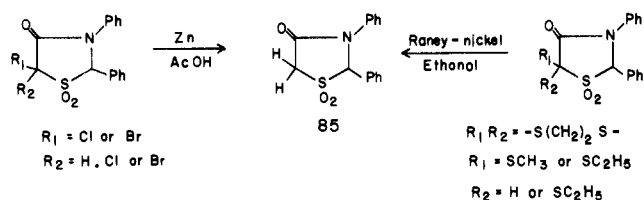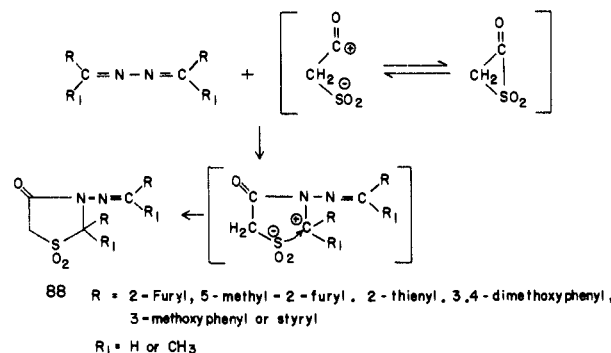
treatment with zinc in acetic acid and Raney nickel in ethanol, respectively, to 85.

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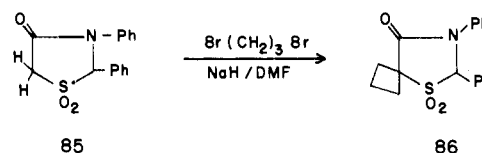
The product 85 is easily dialkylated in the 5-position, leading to the formation of spiro compound 86 using dibromopropane in the presence of NaH in dimethylformamide.

R = Aryl   87
R₁ = H or aryl
R₂ = Alkyl or aryl
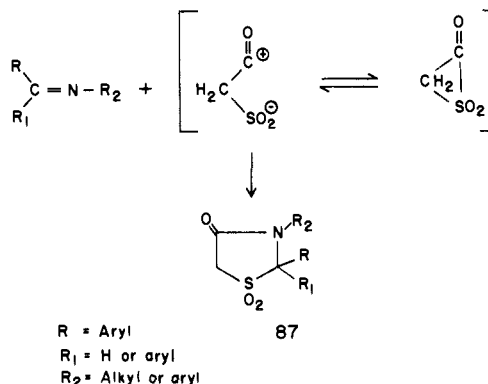
Lysenko and Joullié[154] have reported the reaction of ketene–SO₂ adduct with different compounds containing the imino function, thereby illustrating the gener-

SCHEME VIII

R = Bz, 4-tolxyl , 4-anisyl , 3,5-Me$_2$C$_6$H$_3$ or 2,4,5-Me$_3$C$_6$H
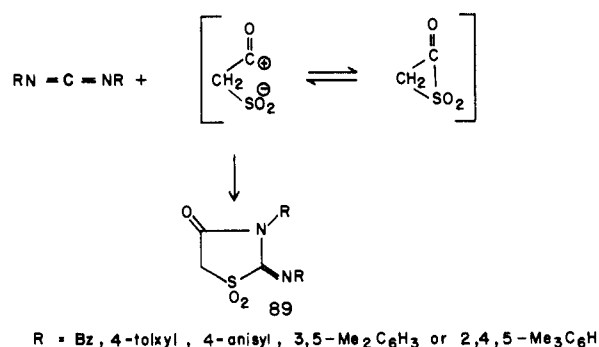
ality of this reaction (Scheme VI).

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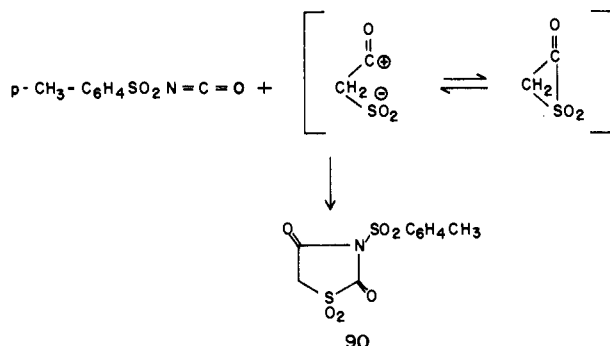
Baudy and Robert[157] have synthesized mesoionic thiazoles, anhydro-5-hydroxythiazolium hydroxides (**92**), in good yields by the reaction of *gem*-dicyano epoxides (**91**) with thioamides in neutral medium. In most

X = H, Cl or NO$_2$

R$_1$ = Ph or CH$_3$

R$_2$ = Ph or PhCH$_2$
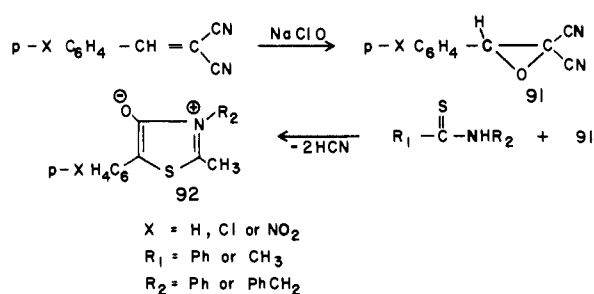
cases the reaction is complete after 2 h at room temperature.

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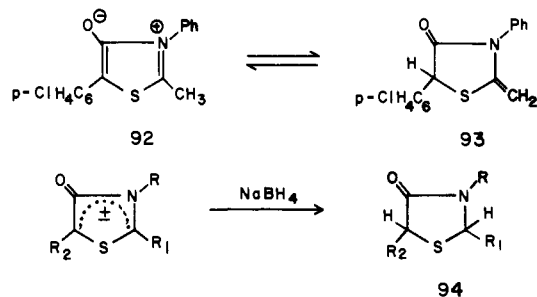
5-Aryl-3-(phenylimino)-1,2-dithioles (**95**) react easily with various ketenes[159] to give 2-(2-aryl-2-thioxoethylidene)-3-phenyl-5,5-disubstituted-4-thiazolidinones (**96**). Sulfur atom in the side chain at position 2 of **96** is readily exchanged by oxygen on treatment with mercuric acetate.

R = H, CH$_3$ or C$_6$H$_5$
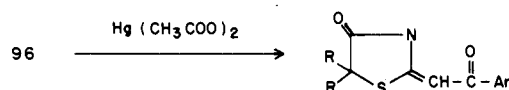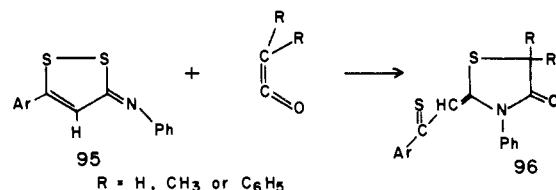
Compounds **96** are fragmented to their starting materials on pyrolysis. However, such compounds loose phenyl isocyanate on oxidation and give 1-aryl-3,4-epithio-4,4-disubstituted-butene-2-thione (**97**) which quickly rearranges to a new product, 3-(disubstituted methylene)-5-aryl-1,2-dithioles (**98**).
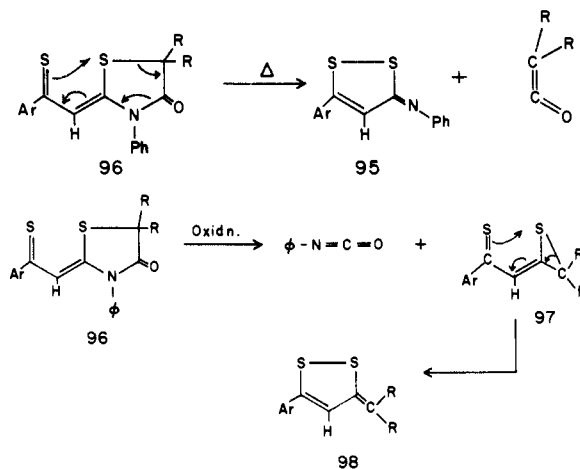
C. 5-Thiazolidinones

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**).
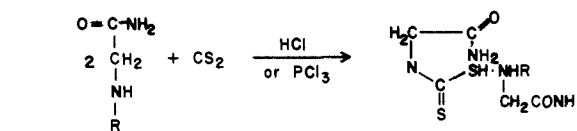
R = CH₃, C₂H₅, cyclohexyl or
n-heptyl

99

R = CH₃ or C₆H₅

100   101
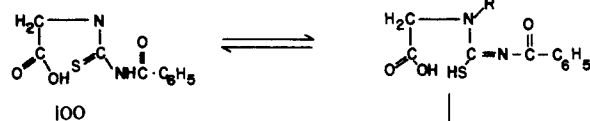
3-(Dimethylamino)-2,2-dimethyl-2*H*-azirine (102) reacts with carbon disulfide to give crystalline product which have the dipolar structure 103 [4,4-dimethyl-5-(dimethyliminium)-2-thiazoline-2-thiolate]. In solu-

102

105   103   104

106   107
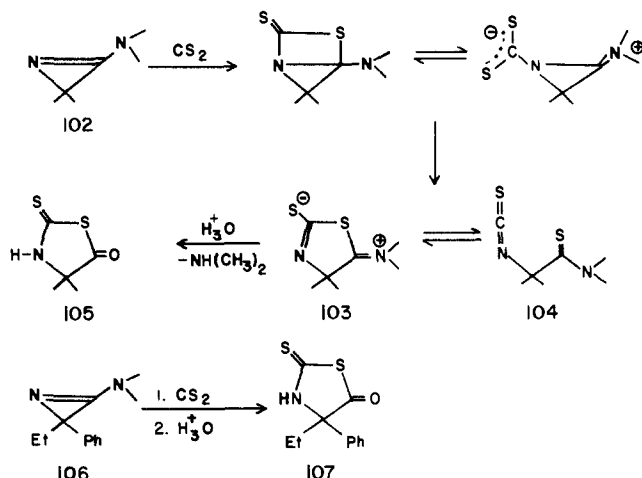
tion, nondipolar (charge-free) isomeric form 104 (1-(dimethylthiocarbamoyl)-1-methylethyl isothiocyanate) is almost exclusively populated. The hydrolysis of 103 with 3 N hydrochloric acid results in the formation of 4,4-dimethyl-2-thiono-5-thiazolidinone (105) in 84% yield. The structure of 105 is confirmed 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-(dimethyl-amino/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-

108   109

110   111
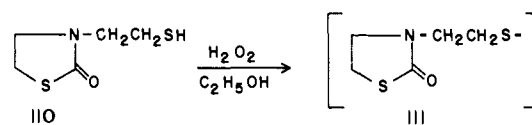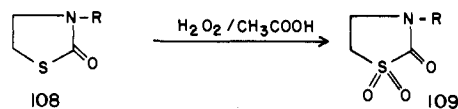
thiazolidinon-3-yl)ethyl disulfide (111).

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
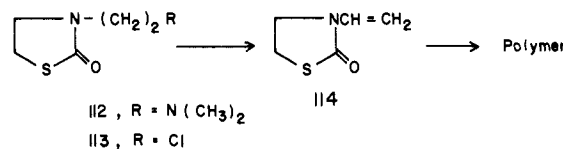
112 , R = N(CH₃)₂
113 , R = Cl   114

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]

115   116

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

117   118   119
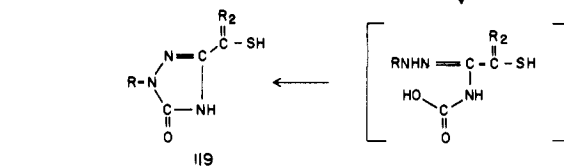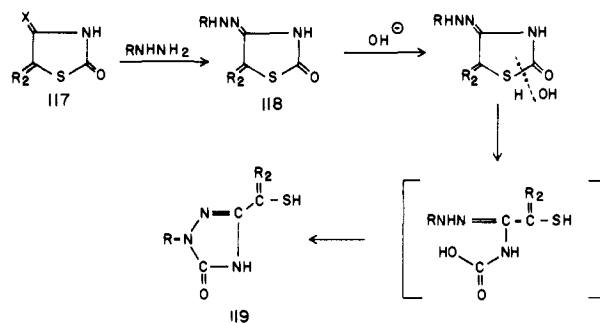
X = S, O or NH
R₂ = 2H, C₆H₅CH or 4-OCH₃C₆H₃CH
R = H, CH₃, C₆H₅CO, NH₂CO, NH₂NHCO

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).
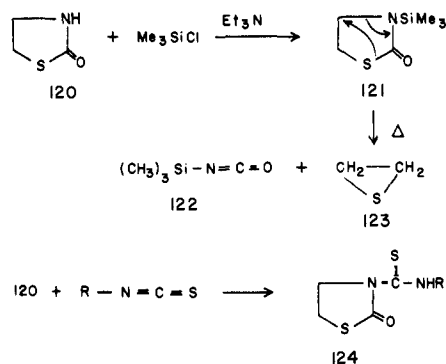
SCHEME IX

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

X = CH₂ or O

135 – R₁ = H, R₂ = CN
136 – R₁ = H, R₂ = COOC₂H₅
137 – R₁ = C₆H₅, R₂ = NO₂
138 – R₁ = C₆H₅, R₂ = COC₆H₅
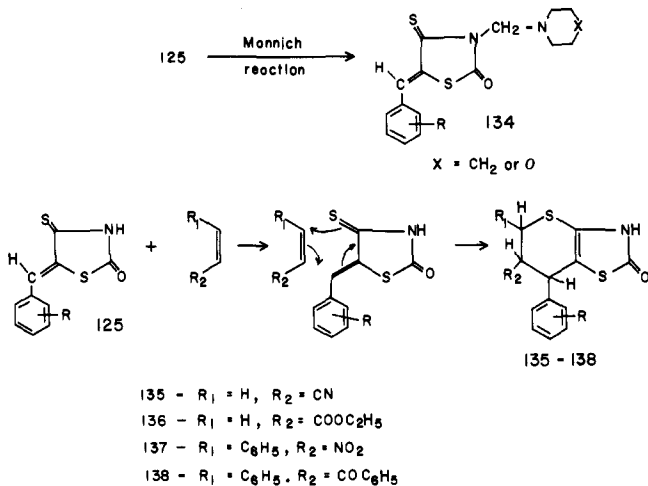
reaction of 125 with acrylonitrile, ethyl acrylate, ω-nitrostyrene, or β-styryl ethyl ketone at room temperature in benzene or ether solution in the presence of pyridine as a catalyst gives the corresponding tetrahydro-7H-thiopyrano[2,3-d]thiazol-2-one derivatives 135, 136, 137, and 138, respectively. 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-7H-thiopyrano[2,3-d]thiazol-2-one N-arylimides (139).
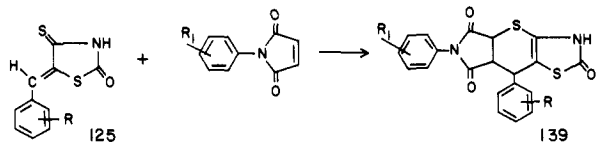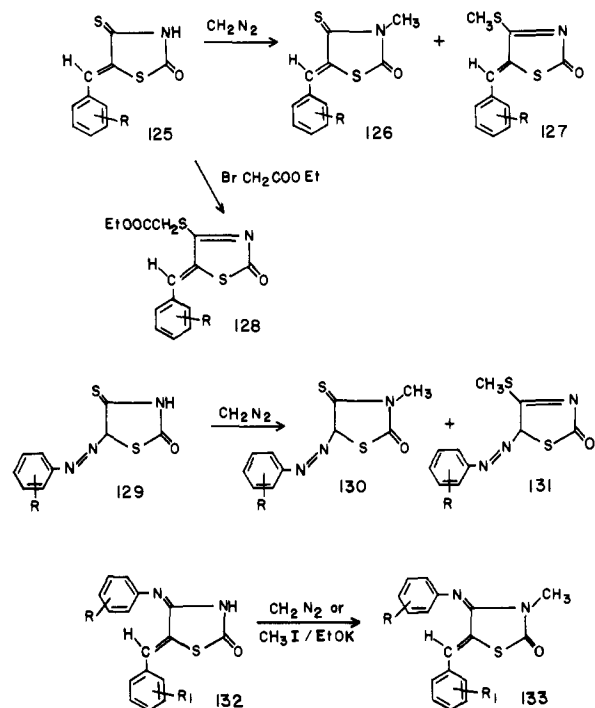
The reaction of Grignard's reagents[177–179] with various substituted-2-thiazolidinones 125, 132, and 133 gives 5-substituted-4-thiono-2-thiazolidinones (140), 5-substituted-4-(arylimino)-2-thiazolidinones (141), and 5-substituted-4-(arylimino)-3-methyl-2-thiazolidinones (142), respectively. In this reaction, the carbanion of

R₁ = H or C₆H₅
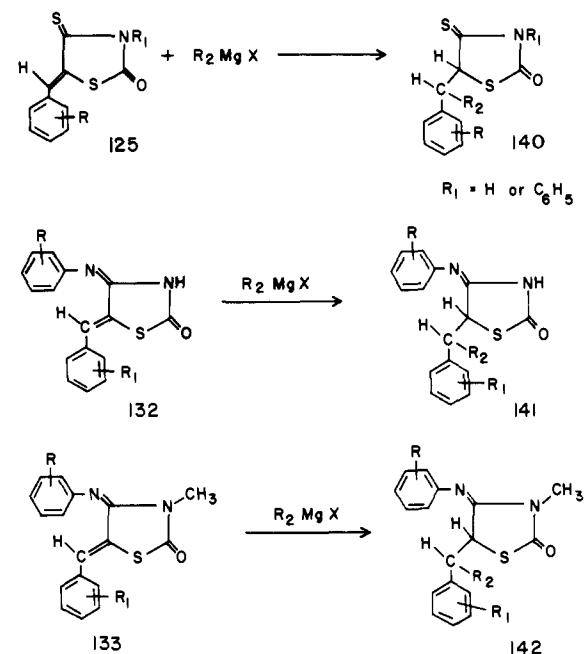
the reagent attacks the exocyclic electrophilic carbon atom of 125, 132, and 133.

4-(Arylimino)-2-thiazolidinones (143) undergo diazo-coupling 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]
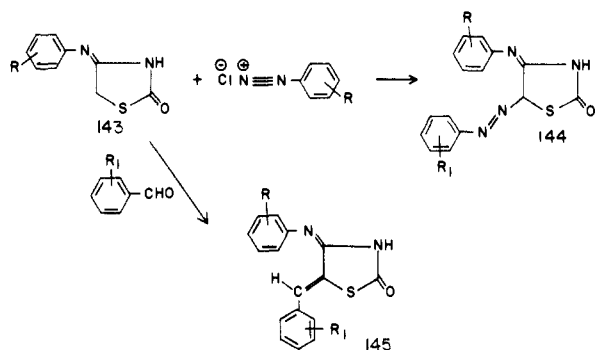
2-Thiazolidinone reacts with 1-chloro-4-nitroiso-quinoline[180] in the presence of NaH in DMF to yield 3-(4-nitroisoquinolin-1-yl)-2-thiazolidinone (**146**).
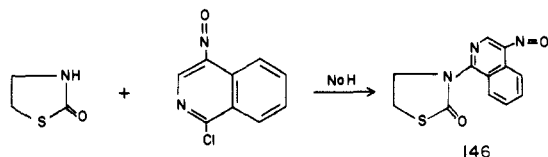
4-Chloro-5,5-dialkyl-2-thiazolidinones (**147**) possessing an exceptionally reactive chlorine atom are very susceptible to nucleophilic attack.[13] These compounds react readily with water, alcohols, amines, etc. The
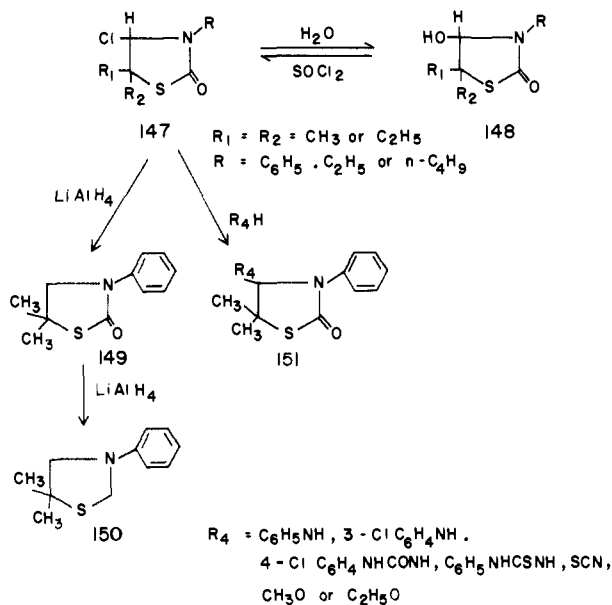
4-hydroxy-5,5-dialkyl-2-thiazolidinone (**148**), obtained by the reaction of **147** with water, is converted back to **147** by reaction with thionyl chloride. In other reactions, N-phenyl-4-chloro-5,5-dimethyl-2-thiazolidinone gives dehalogenated derivative **149** in the first step and N-phenyl-5,5-dimethylthiazolidine (**150**) in the second step when treated with lithium aluminium hydride. Replacement of chlorine of N-phenyl-4-chloro-5,5-di-methyl-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
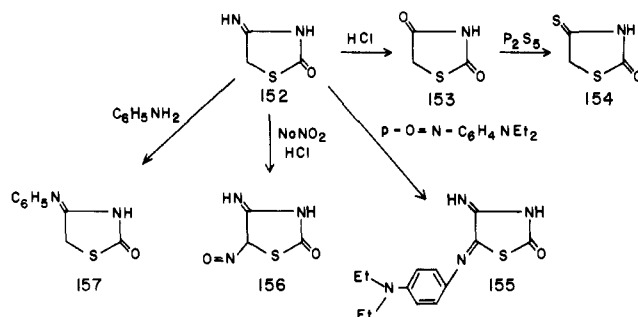
the presence of 5% HCl at 0 °C to give 5-nitroso-4-im-ino-2-thiazolidinone (**156**). Treatment of **152** with aniline in the presence of sodium acetate and glacial acetic acid gives 4-(phenylimino)-2-thiazolidinone (**157**).

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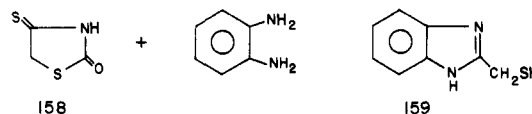
B. 4-Thiazolidinones

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

R₁ = Alkyl or aryl
R₂ = Alkyl, aryl or heterocyclic
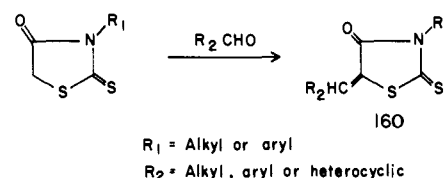
very useful synthetic reagents which will be discussed elsewhere. The reactions have mostly been carried out in the presence of anhydrous sodium acetate in benzene or acetic acid.

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

R₁ = Alkyl, aryl or heterocyclic
R₂ = Alkyl, aryl or heterocyclic
R₃ = Alkyl, aryl or heterocyclic
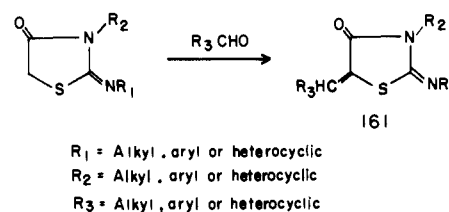
variety of aliphatic, aromatic, and heterocyclic aldehydes (ref 36, 49, 54, 59, 64, 67, 68, 73, 74, 182, 185–187) have been reported to react with the 4-thiazolidinones. The

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).

R = Aromatic   162

R₁CHO

163

R = [structure] or [structure]

R₁ = Aromatic
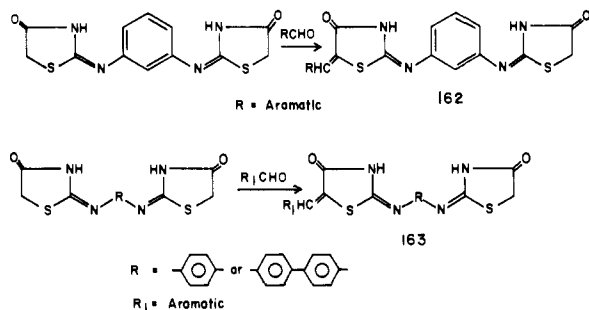
2-Substituted-4-thiazolidinones, prepared by the Schiff bases and mercaptoacetic acids, react with aldehydes in the presence of anhydrous sodium ethoxide in dry benzene to give 5-arylidene or alkylidene derivatives[135,188,189] (164) in good yields.

R₄CHO

164

R₁ = H, alkyl or aryl
R₂ = H, alkyl or aryl
R₃ = Alkyl or aryl
R₄ = Alkyl or aryl
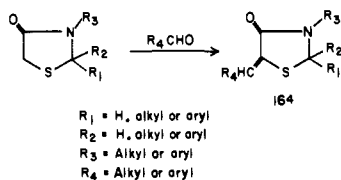
The condensation of aldehydes with the 2-alkyl- or -aryl-4-thiazolidinones in the presence of sodium acetate and acetic acid does not occur, possibly because of the decreased reactivity of the methylene group due to the absence of thioxo or imino groups at position 2. Karishin and Samusenko[190] have 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).

X = H or halogen   165
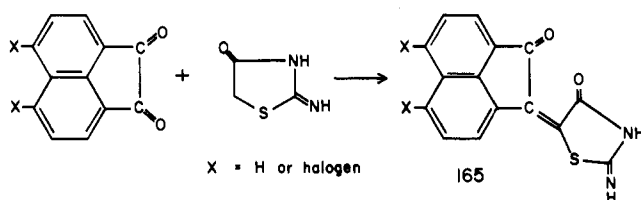
Similarly, isatin also condenses only with one of its carbonyl groups at the 5-position of various 2-imino-4-thiazolidinones, giving thioindigoid dyes of type[191,192] **166**.

166

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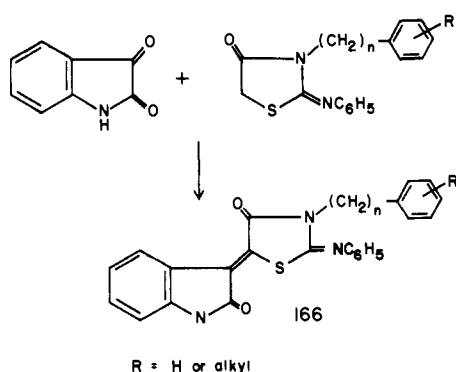
5-Arylidene derivatives, obtained by the aldol condensation, react with bromine in chloroform at the carbon–carbon double bond to give dibromo compounds[60,61,73,74] (167, 168).

R = Heterocyclic
R₁ = Alkyl or aryl
R₂ = Aryl

Br₂

168

R = [structure] or [structure]

R₁ = Aryl
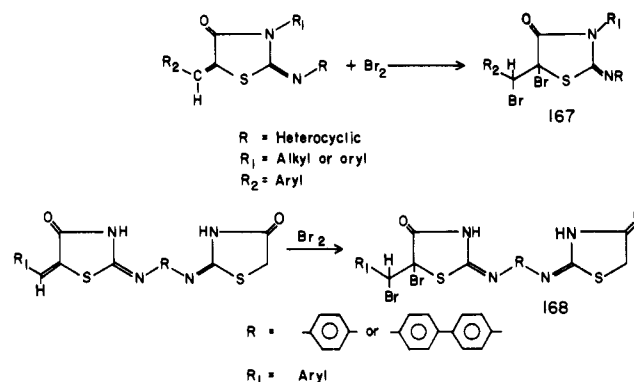
Snider et al.[189] have reported Friedel–Craft reactions with 5-arylidene-4-thiazolidinones using benzene and anhydrous aluminum chloride. The reaction of 5-arylidenerhodanines with benzene and ≥4 mol of aluminum chloride cleaves the arylidene substituent to give rhodanine (169) and triphenylcarbinol.

$\frac{C_6H_6}{AlCl_3}$ + Ph₃COH

R = Alkyl or alkoxy   169
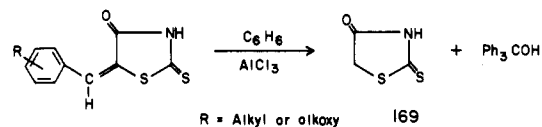
However, 2,3-diphenyl-5-arylidene-4-thiazolidinones under similar conditions add benzene to the unsaturated linkage to give 2,3,5-triphenyl-5-benzyl-4-thiazolidinones (170).

$\frac{C_6H_6}{AlCl_3}$

R = Alkyl   170
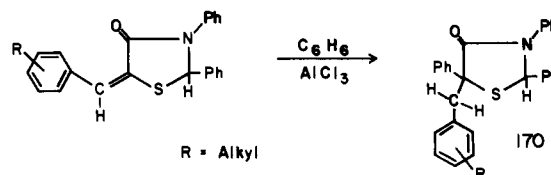
2,3-Dimethylbutadiene reacts at the carbon–carbon double bond of 5-(aroylmethylidene)-2-thiono-4-thiazolidinones to give thiazolidinone spirocyclohexenes[193] (171).

171

R = Aryl
R₁ = C₆H₅ or CH₃OC₆H₄
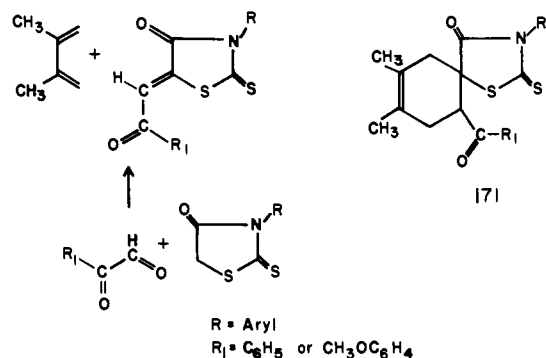
5-Arylidenerhodanines on treatment with gaseous diazomethane give mixtures of N-methyl and S-methyl derivatives[194] (172, 173). Linear correlation exists between the log of the relative yields (N-methyl/S-methyl) and substituent constants of substitution groups R. Increasing the dielectric constants of the solvents increased the relative yields of N-methyl derivatives; in amines like triethylamine and aniline, only
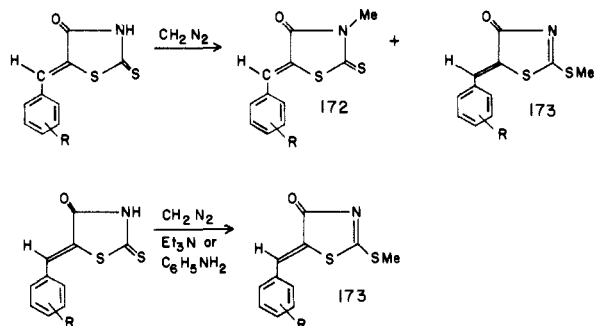
S-methylthiazolone derivatives are formed (173).

Lugovkin[196] has reported phosphorylation of 5-aryl-idenerhodanines (174) by substituted phosphorus acids.
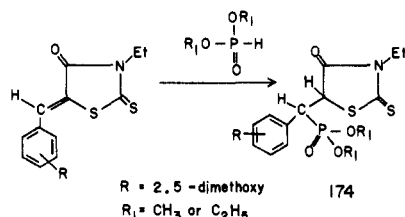
5-Arylidene-2-(alkylthio)-4-thiazolones easily condense with aniline to give 2-imino-4-thiazolidinones[195] (175). This reaction can be used as a good method for
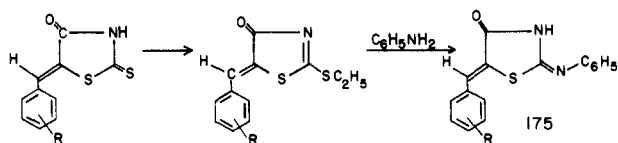
the conversion of rhodanines to 2-imino-4-thiazolidinones.

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).
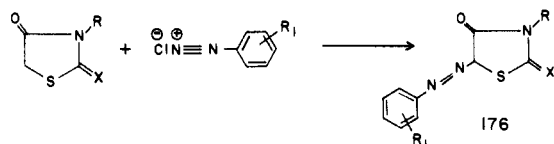
R = Alkyl or oryl
R₁= Alkyl. olkoxy. holo or heterocyclic
X = S or O
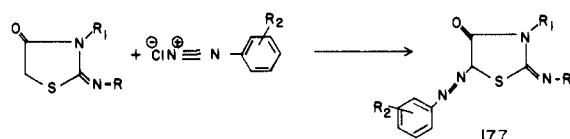
R = Alkyl. oryl or heterocyclic
R₁= Alkyl. oryl or heterocyclic
R₂= Alkyl

2-(Carbethoxymethylene)-3-methyl-4-thiazolidinone reacts with bromine[147] to give 2-(carbethoxy-methylene)-3-methyl-5-bromo-4-thiazolidinone (178). The bromo compound on treatment with triethylamine gives 179.
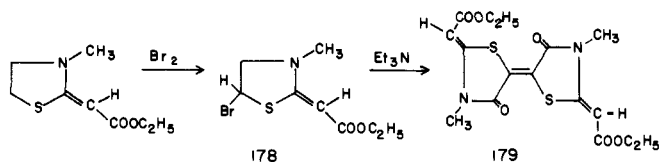
Kvitko et al.[200] have reported the reaction of substituted benzoyl chlorides with various 2-thiono-4-thiazolidinones, giving 5-aroyl-4-thiazolidinones (180).
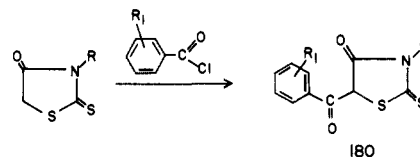
Nakayama[201] has studied the introduction of cyclic dithioacetal functions into activated methylene compounds by treatment with 2-alkoxy-1,3-benzodithioles. 2-(3-Methylbutoxy)-1,3-benzodithiole on treatment with rhodanine in anhydrous acetic acid gives 5-bis(1,3-benzodithiol-2-yl)rhodanine in high yields (181).

R = (CH₂)₂ CH (CH₃)₂
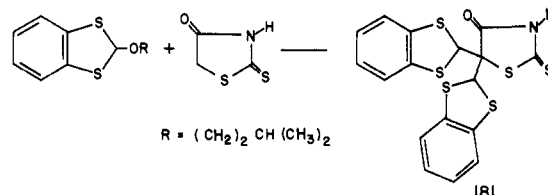
Phthalic anhydride undergoes condensation[202] at the 5-position of various 2-substituted imino-4-thiazolidinones in acetic anhydride and triethylamine to give 2-substituted imino-5-phthalyl-4-thiazolidinones (182).

R = R₁ = Aryl
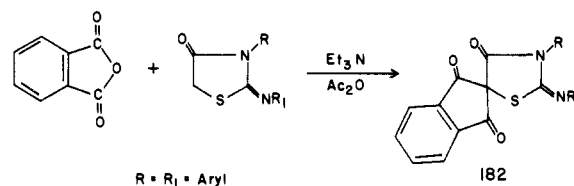
However, mixed anhydride reacts spontaneously with 2-imino-3-aryl-4-thiazolidinones at room temperature to give *N*-chloroacetyl derivatives[111] (183).
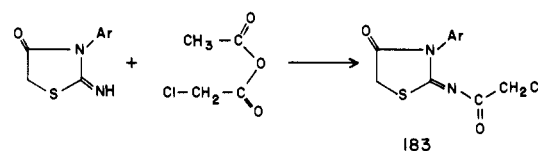
Tominaga et al.[203] have reported the reaction of 3-ethylrhodanine with carbon disulfide in the presence of sodium hydroxide in dimethyl sulfoxide, giving 3-ethyl-5-[bis(methylthio)methylene]-2-thioxo-4-thiazo-lidinone (184). This on treatment with nucleophilic
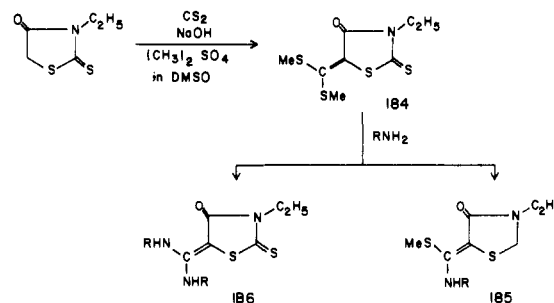
reagents such as amines or active methylenes yields the corresponding replacement products of one (185) or two (186) methylthio group in good yields, respectively.

The active ketene thioacetal group of 184 reacts with active methylene compounds in the presence of K₂CO₃ in dimethyl sulfoxide; this results in the corresponding

replacement product (187) of one methylthio group of

X = H, -CN or -COOCH₃ ; Y = NO₂, -CONH₂ or -COOCH₃

XY = (structure)

R = NHCH₂C₆H₅ , -NHC (CH₃)₃ , -NH-CH₂CH₂N(C₂H₅)₂ , -NH (CH₂)₂CN or
-NH (CH₂)₂OH
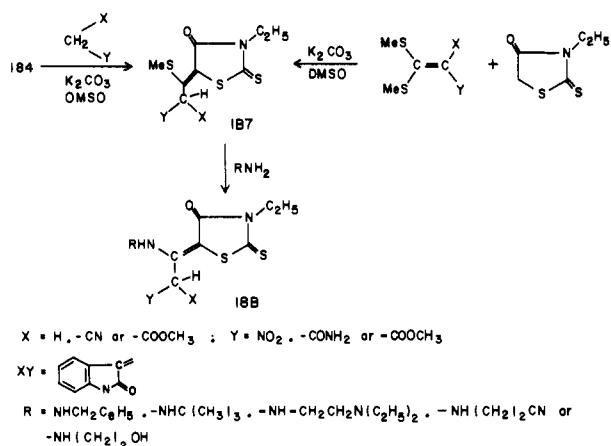
184 in good yields. 3-Ethylrhodanine also reacts with ketene thioacetal in the presence of K₂CO₃ in dimethyl sulfoxide to give 187. The compounds (187) having an active methylthio group react with amines to give the amine derivatives (188).

Fisher et al.[155] synthesized 2-imino-3-substituted-5-[bis(methylthio)methylene]-4-thiazolidinones (189) in
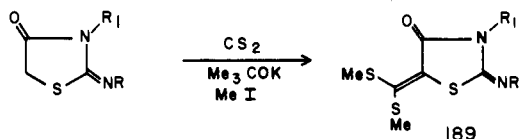
27–43% yields by the reaction of 2-imino-3-substituted-4-thiazolidinones with carbon disulfide, potassium–trimethyl methoxide, and methyl iodide.

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).

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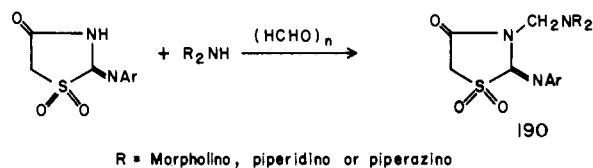
However, Chizhevskaya et al.[205] have reported Mannich reactions at nitrogen at position 3 of 2-(arylimino)-4-thiazolidinones with formaldehyde and secondary amines (191).

R₂ = Piperidino or morpholino   191
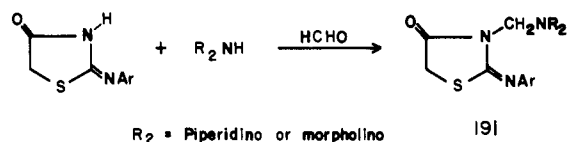
Zubenko[206] carried out Mannich reactions of unsubstituted 2-imino-4-thiazolidinones with primary aromatic amines and formaldehyde in methanol at room temperature and concluded that the reaction occurs at the N-3 position with 70–100% yields (192).

R = Ph , O - CH₃ C₆ H₄ , p -CH₃OC₆H₄ , p - EtOC₆H₄ or
p - Br C₆H₄

SCHEME X

R = H, 4 - CH₃, 4 -OCH₃ or 4 -OC₂H₅
R₁ = CH₃ or C₂H₅
R₂ = H, 4 - CH₃ or 4 - NO₂
X = (CH₂)ₙ , n = 2 or 6 ; 1,4-phenylene or 4,4'- biphenylene
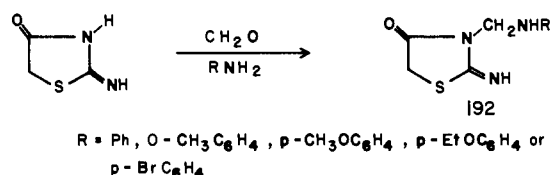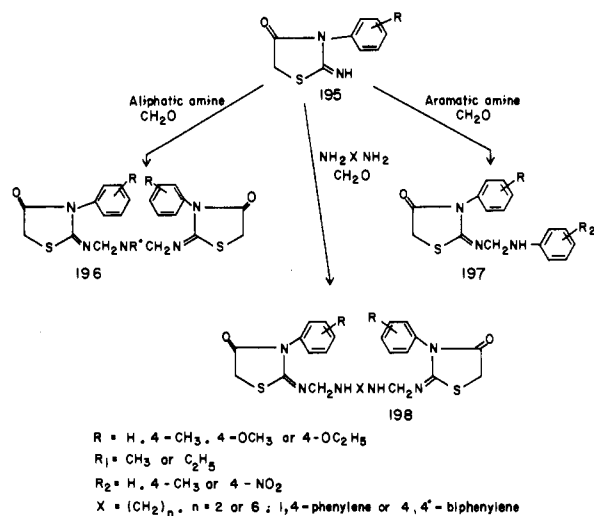
Kononenko et al.[207] have reported aminomethylation reactions of 2-aryl-4-thiazolidinones and 2,4-thiazolidinediones with formaldehyde and amines by heating in alcohol (193, 194).

R = Piperidino or morpholino   193

R = Aryl   194
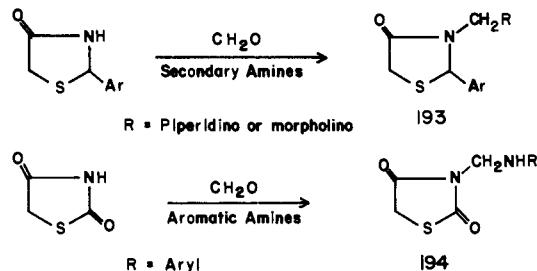
2-Imino-3-aryl-4-thiazolidinones (195) undergo Mannich reactions[208] with primary aliphatic amines and formaldehyde to give the bis[(thiazolidinylidene-amino)methyl]amines (196) whereas the reaction of 195 with formaldehyde and primary aromatic amines gives N-[(thiazolidinylideneamino)methyl]anilines (197). Similarly, the reaction of 195 with diamines NH₂XNH₂ 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.

X = O, CH₂ or CH₂CH₂

199

200
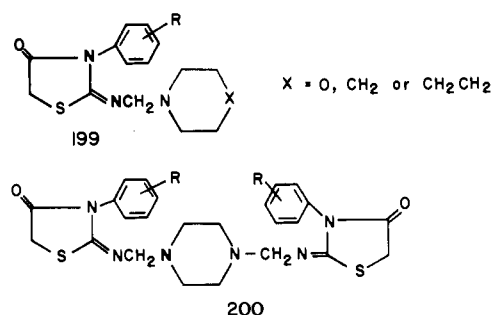
1,2-Bis(2-phenyl-4-oxothiazolidin-3-yl)ethane obtained by the reaction of dibenzal ethylenediamine with thioglycolic acid in dry benzene is oxidized to dioxides 201 by heating in AcOH and 33% hydrogen peroxide.[117] However, 4-thiazolidinones on treatment with 30% H₂O₂ in a mixture of cold acetic acid and acetic anhydride give the 4-thiazolidinone S-monooxide derivatives[210] (202).

201

R = CCl₃. Ph. 3-NO₂ C₆H₄ or 4-NO₂ C₆H₄

R = H. 2-Cl. 4-Cl. 2-Me , 3-Me or 4-Me

202
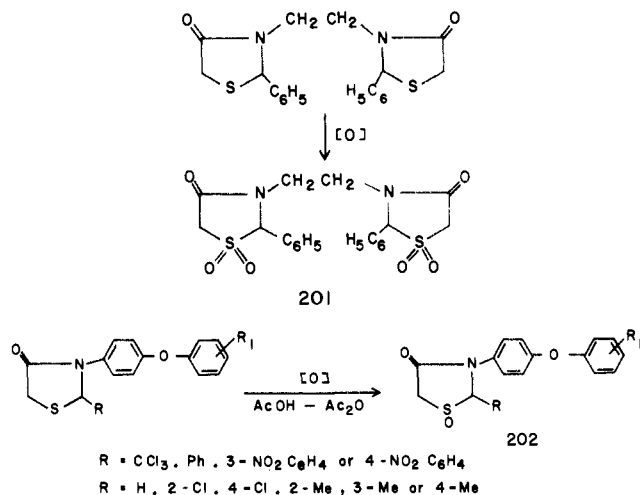
2-(Arylimino)-3-substituted-4-thiazolidinones and 2,3-disubstituted-4-thiazolidinones are oxidized to the corresponding 1,1-dioxides (**203, 204**) on treatment with KMnO₄ in glacial acetic acid at 0 °C.[39,52,53,119]

R = Alkyl or aryl   **203**

R = R₁ = Aryl   **204**
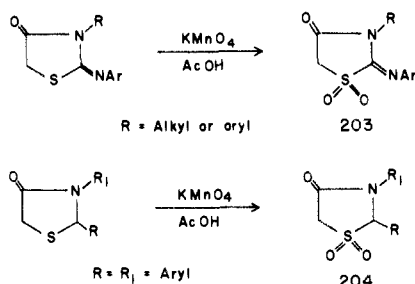
Oxidation of 2-imino-4-thiazolidinone by a solution of cerium(IV) sulfate[211] in aqueous methanol proceeds via initial hydrolysis to give thioglycolic acid followed by its Ce^{4+} oxidation to $S_2(CH_2COOH)_2$.
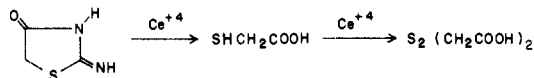
2-(4-Ethoxyphenyl)imino-3-(4-ethoxyphenyl)-4-thiazolidinone, under similar conditions, is first converted to corresponding 4-hydroxyphenyl derivative which is oxidized to $HSCH_2COOH$ and $(p\text{-}OHC_6H_4NH)_2CO$. Both are further oxidized to $S_2(CH_2COOH)_2$, benzoquinone, and urea.

HSCH₂COOH + (4-OHC₆H₄NH)₂ C=O

S₂(CH₂COOH)₂   Benzoquinone
+
Urea
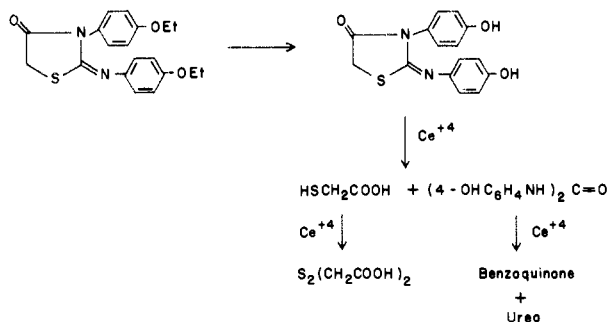
4-Thiazolidinones of type **205** undergo oxidative imination[212] to afford S-imino derivatives (**206**) on treatment with $p\text{-}R_2C_6H_4SO_2NNaCl$ compounds. Compound **205**, R₁ = H, is unreactive to the oxidative imination.

Various 2-(substituted-imino)-4-thiazolidinones undergo hydrolysis at position 2 on treatment with dilute hydrochloric acid or sulfuric acid to give 2,4-thiazoli-

+p-R₂ SO₂ NNaCl ⟶

205   **206**

R = Alkyl or aryl
R₁ = Alkyl or aryl
R₂ = Aryl
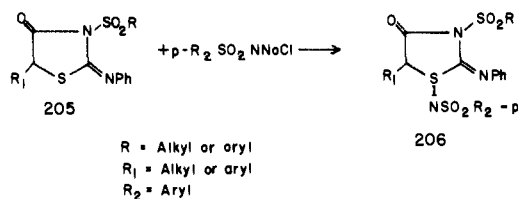
dinediones and amines (**207**).[33,34,59,213,214]

207

R = R₁ = H or aryl
R₂ = R₃ = H, CH₃ or Ph
R₂R₃ = Arylidene
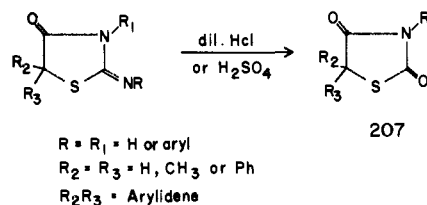
Svetkin et al.[215] carried out reactions with phenyl isothiocyanate and 2-imino-3-aryl-4-thiazolidinones and obtained 2-[(phenylthiocarbamido)imino]-3-aryl-4-thiazolidinones (**208**) in good yields. These compounds on treatment with 36% hydrochloric acid were found to undergo hydrolytic ring cleavage 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
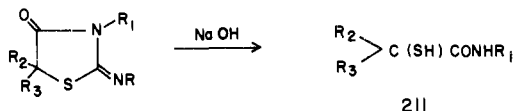
Similarly, rhodanine and its alkylidene or aylidene derivatives undergo ring cleavage[216] on alkaline hydrolysis to give mercaptoacetic acid (**212**) and α-mercapto-α,β-unsaturated acids (**213**), respectively.

SH CH₂COOH + HN=C=S
212

R₁ CH=C—COOH + HN=C=S + ROH
          |
213   SH

R = R₁ = H , alkyl or aryl
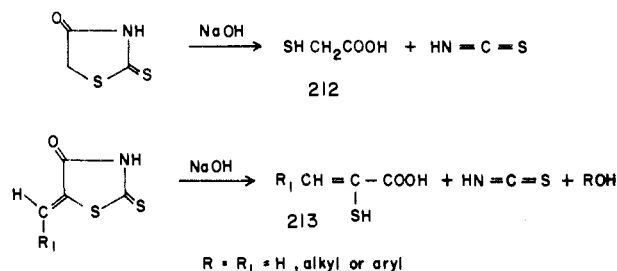
Various 4-thiazolidinone 1,1-dioxides undergo reduction[151] with lithium aluminum hydride, leading to the formation of corresponding thiazolidines (**214**).

214
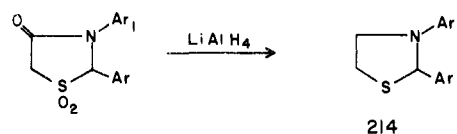
The term "mesoionic" has been proposed for the compounds in which a negative charge is associated with an atom or groups of atoms covalently bonded to a five- or six-membered heteroaromatic ring, which carries a positive charge and for which no single satisfactory covalent or polar structure can be written. 3,5-Substituted-2-thiono-4-thiazolidinones can be converted to their mesoionic derivatives,[26] anhydro-2-(al-

SCHEME XI

208

36% HCl

209

Cyclode-
hydration

210
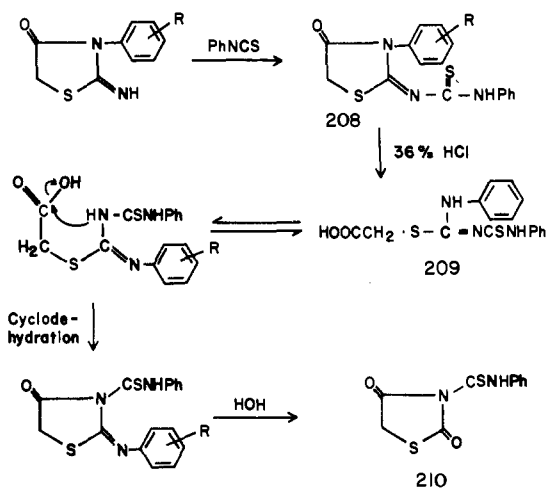
kylthio)-3-substituted-4-hydroxy-5-substituted-thiazo-
lium hydroxides (**215**), by alkylation with alkyl iodide
in the presence of NaOEt in absolute alcohol under cold
conditions.

215

$R = CH_3, -NH_2, -N(CH_3)_2$ or $-N=CHPh$
$R_1 = CH_3$ or CH_2Ph
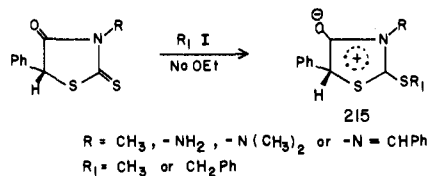
However, unsubstituted 2-thiono-4-thiazolidinone on
treatment with saturated alcoholic KOH followed by
the reaction with dimethyl sulfate gives 2-(methyl-
thio)thiazolin-4-one (**216**) via the intermediate forma-
tion of the potassium thio salt.[216] This reaction sup-
ports existence of a thione-thiol tautomeric equilibrium.

216
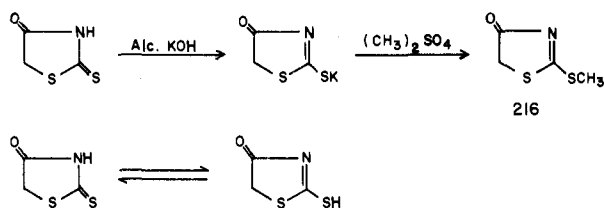
2-(Arylimino)-5-arylidene-4-thiazolidinones react at
position 3 with acrylonitrile to give 2-(arylimino)-3-
(cyanoethyl)-5-arylidene-4-thiazolidinones[217] (**217**).
Similarly, 2,4-thiazolidinediones react with equimolar
amounts of 4- or 2-vinylpyridines to form N-[β-(2- or
4-pyridyl)ethyl]thiazolidine-2,4-diones[218] (**218, 219**).

217

218

219
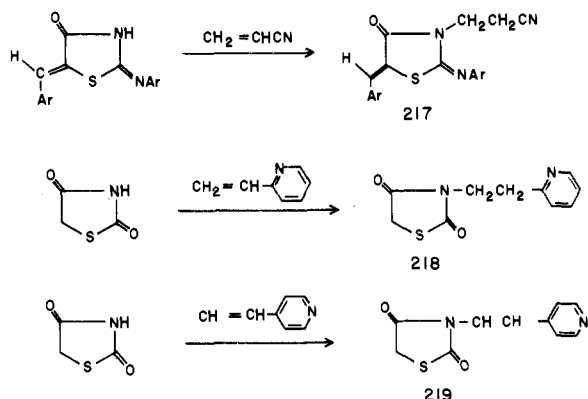
A large variety of 4-thiazolidinones has been used for
the synthesis of many other heterocyclic compounds.

2-Hydrazono-4-thiazolidinones, obtained by the re-
action 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**).

220   221

Δ, $-HCl$

222
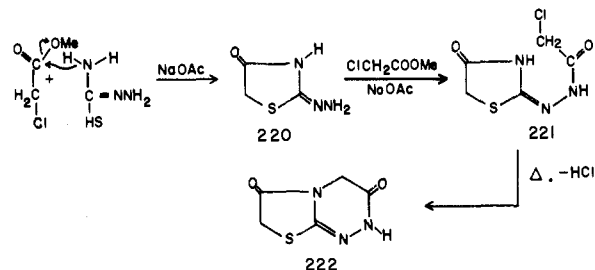
2-(Phenylhydrazono)-4-thiazolidinones, on reaction
with formaldehyde or aromatic aldehydes, undergo cy-
clization, giving rise to 2-phenyltetrahydrothiazolo-
[2,3-c]-1,2,4-triazol-5-ones[219] (**223**).

$RR_1 = PhCH, p-MeOC_6H_4CH$ or $p-ClC_6H_4CH$ 223
$R_2 = H$ or Ph
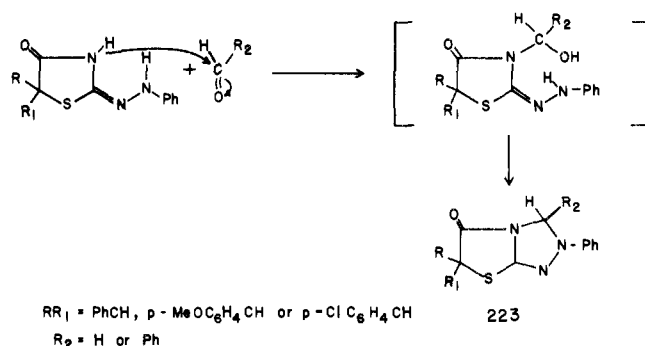
2-Oxo-5-arylidene-4-thiazolidinones react with hy-
drazine to undergo ring cleavage followed by cyclization
to give 5-aryl-3-pyrazolinones[172] (**224**) in 55-70% yields.

$R = H, o-OMe$ or $p-OMe$ 224

$R = o-$ or $p-OMe$ 225
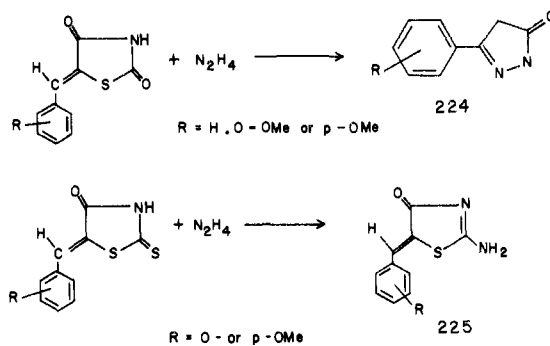
On the other hand, 2-thiono-5-arylidene-4-thiazolidi-
nones on treatment with hydrazine give 2-amino-5-
arylidene-4-thiazolinones (**225**) in 35-50% yields.

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-dimethoxy-
benzylidene)-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.

227
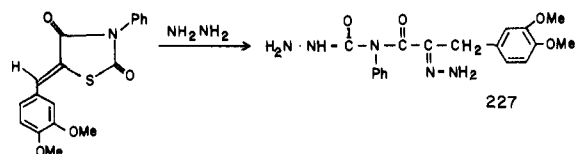
SCHEME XII
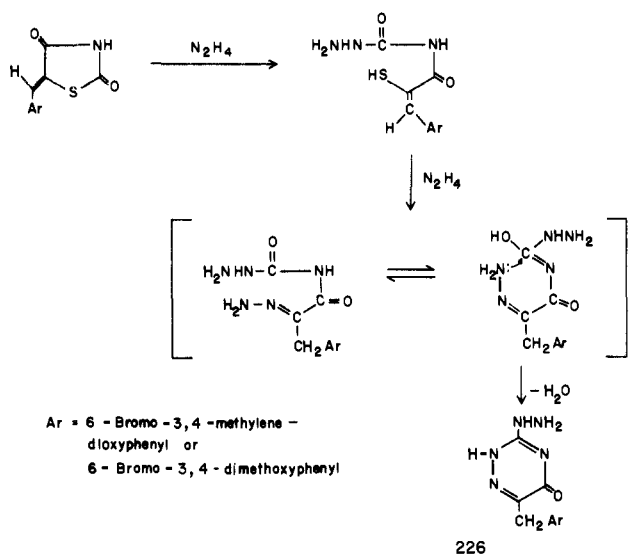
2-Imino-4-thiazolidinone undergoes ring cleavage to Schiff bases on treatment with o-phenylenediamine and further recyclizes into a benzimidazole derivative[181] (228). This on hydrolysis gives 2-aminobenzimidazole
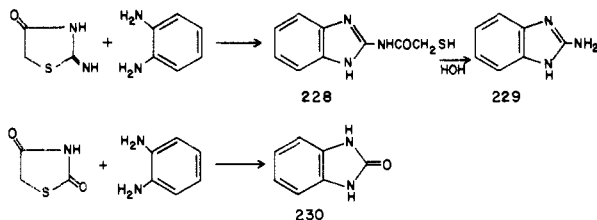
(229). 2-Oxo-4-thiazolidinone under similar conditions leads to the formation of 2-benzimidazolone (230).

Krasnitskaya et al.[220] have synthesized substituted imidazothiazolones (231) from the corresponding 2-imino-3-substituted-4-thiazolidinones on treatment with Br₂–AcOK.
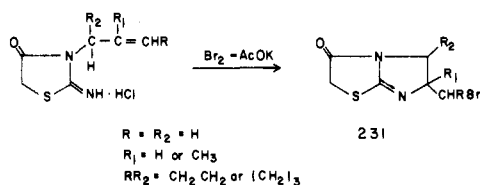
2-Imino-4-oxothiazolidine 1,1-dioxides,[155] prepared from carbodiimides, ketenes, and liquid SO₂, react with carbon disulfide to give 45–79% yields of heterocycles of type 232.
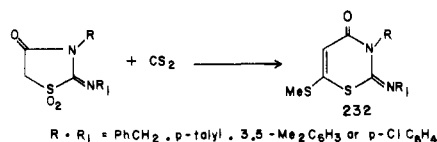
Satzinger[148] has reported the ring expansion of 2-substituted methylene-3,5-disubstituted-4-thiazolidines (233) on prolonged contact with triethylamine, giving compounds 234.
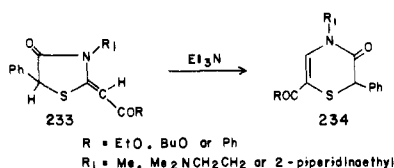
SCHEME XIII
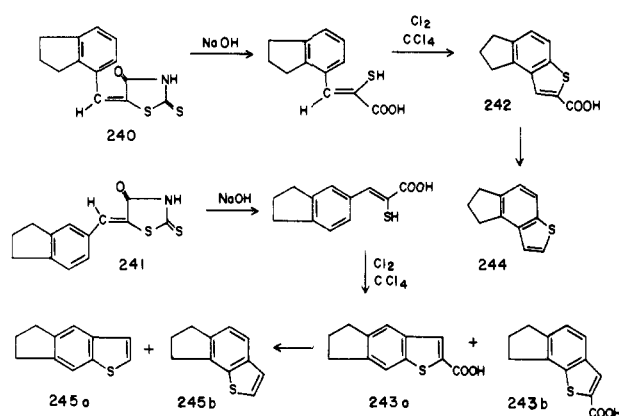
5-(Substituted-benzylidene)-2-thiono-4-thiazolidinones undergo hydrolytic ring cleavage[216] on treatment with NaOH, giving β-substituted-α-mercaptoacrylic acid (235). The α-mercaptoacrylic acids are recyclized into
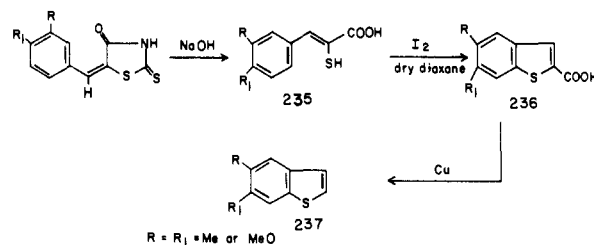
2-carboxyl-5,6-disubstituted-benzo[b]thiophenes (236) in the presence of iodine and dry dioxane at refluxing temperature.[221] The benzothiophenecarboxylic acids are readily decarboxylated to benzothiophenes (237) by copper in quinoline. Substituents in the phenyl moiety of acrylic acids markedly affect the yield of cyclized products.

Various other benzothiophene derivatives (238) have been synthesized[222,223] by using the above method.
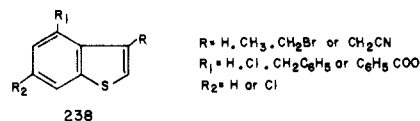
Under similar conditions, polyhalothienopyridine (239) is synthesized from tetrachloropyridine-4-carboxaldehyde and rhodanine.[224]
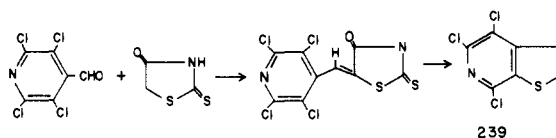
Grüenhaus et al.[225] have synthesized indenothiophenes from isomeric indancarboxaldehydes and 2-thiono-4-thiazolidinone through the intermediates 5-(4-indanylidene)- and 5-(5-indanylidene)rhodanine (240, 241). These substituted rhodanines undergo hydrolytic ring cleavage followed by ring closure in 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

246

⟨N- ⟩ = Piperidino, morpholino or pyrrolidino

247

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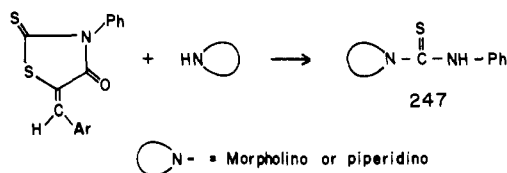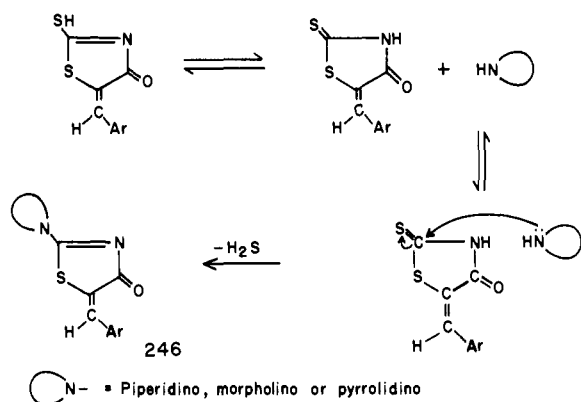
as in Scheme XIV. On the other hand, 5-arylidene-3-phenyl-2-thiono-4-thiazolidinones on treatment with secondary amines undergo ring cleavage leading to the formation of the corresponding thioureas (247).

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).

248
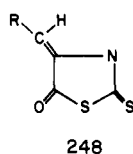
2-Thiono-3-methyl-5-thiazolidinone (249) on treatment with 2 equiv of morpholine in acetone leads to the formation of morpholinium salt (250). The 5-thiazolidinone 249 on boiling in water undergoes ring cleavage, giving sarcosine (251) and carbon disulfide.[160]
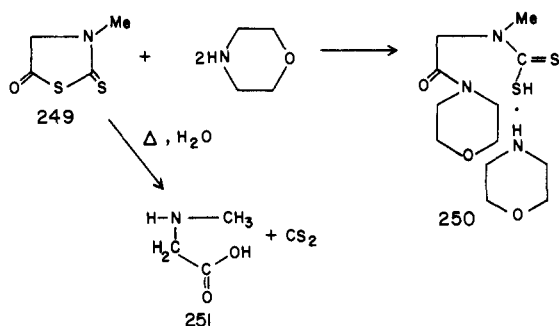
The reaction[229] of 2-thiono-5-thiazolidinone (252) with amino ketones (253) in dichloromethane in the presence of ethereal HCl gives an excellent route for the preparation of various substituted benzodiazepines (254) which belong to an important group of psychopharmacological agents.

252   253   254

R_1 = H, NO_2, CF_3 or halogen

R_2R_3 = H, halogen or lower alkyl

R_4 = Lower alkyl, cyclohexyl, alkenyl, acycloxy, alkoxy, alkoxy alkoxy, alkenyloxy, alkylthio, alkylsulfinyl, alkyl sulfonyl, aryloxy, oralkoxy, trihalomethyl, hydroxyl, amide, dialkylamide or dialkylamine

R_5 = H or lower alkyl

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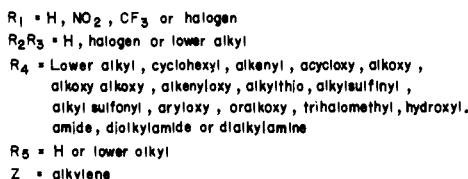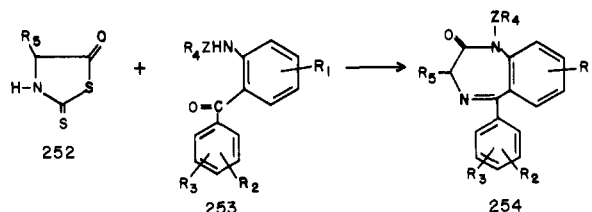
Thermal condensation[230] of 2-(alkylthio)thiazolidine quaternary salts (255) with 2-thiono-5-thiazolidinone (256) in pyridine or triethylamine gives various thiazolidines (257).

255   256   257
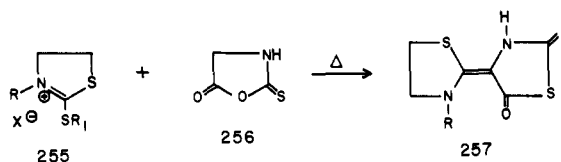
IV. Photochemistry of Thiazolidinones

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

258

259   +   260

261

X = O or S
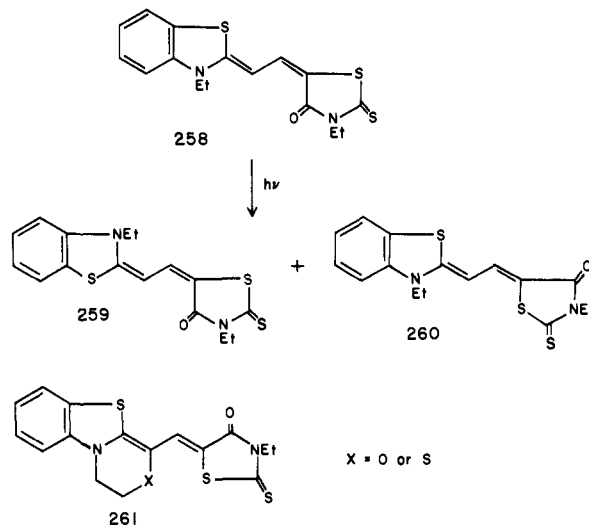
spectroscopically as longer lived isomer 259 and shorter-lived isomer 260 by comparison with the systems (261) in which one double bond is prevented from isomerizing. Compounds 258 and 259 are stabilized by H-bonding between the carbonyl and the methine H, and 258 and 260 are stabilized by including 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.
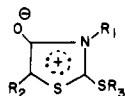
262 - R_1 = R_3 = Me ; R_2 = Ph
263 - R_1 = R_3 = Me ; R_2 = COOEt
264 - R_1 = R_3 = CH$_2$COOEt ; R_2 = COOEt
265 - R_1 = CH$_2$CH = CH$_2$; R_2 = CO·COOEt ; R_3 = Me
266 - R_1 = CH$_2$CH(OMe)$_2$; R_2 = CO·COOEt ; R_3 = Me
267 - R_1 R_3 = (CH$_2$)$_3$; R_2 = COOEt
268 - R_1 R_3 = (CH$_2$)$_3$; R_2 = CO·CH$_2$Ph

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.
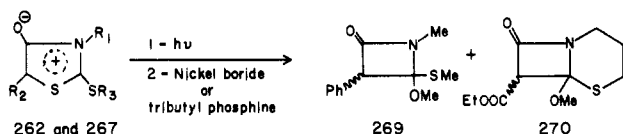
Photolysis of methanolic solutions of 262 and 263 in the presence of alkyl iodide affords cleaner reaction, possibly due to a heavy atom effect, giving β-lactams 271 along with isomeric thiazol-2-one (272).
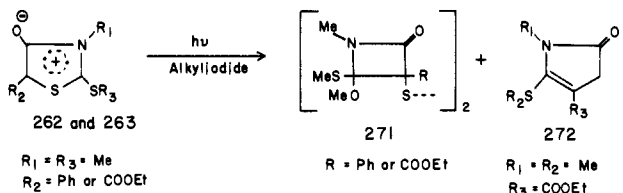
Under identical conditions, the mesoions 267 and 268 undergo slow photolysis and give lower yields of β-lactams. The additional ring increases the strain in β-

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).
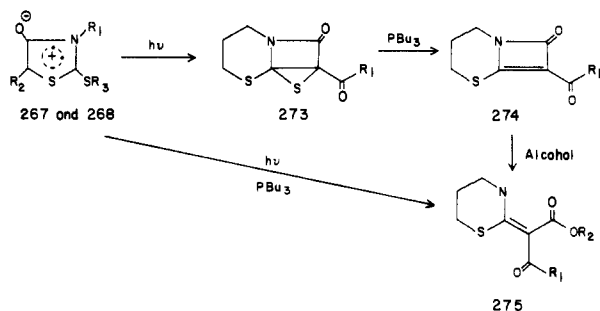
V. Metal Complexes of Thiazolidinones

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, ^{1}H 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
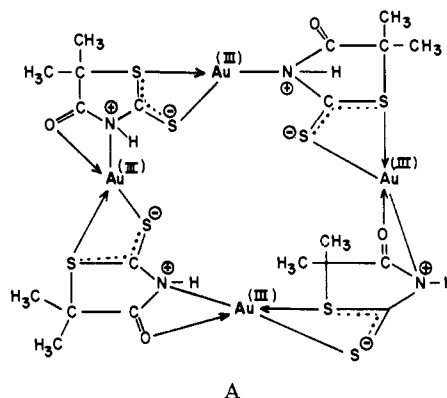
nitrogen, oxygen, and two sulfur atoms.[240]

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$_2$O$_2$X$_2$ (M = Zn, X = Cl, Br, I; M = Hg, X = Cl, Br) and Cdt$_2$OX$_2$ (X = Cl, Br, I), where t$_2$O 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.

T = 2 - Imino - 4 - thiozolidinone

B
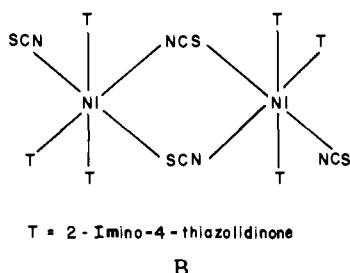
VI. Molecular Spectroscopy of Thiazolidinones

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]

R = R$_1$ = CH$_3$ or C$_2$H$_5$
R$_2$ = H, C$_2$H$_5$ or C$_6$H$_5$
R$_3$ = H
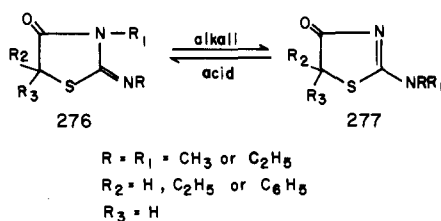
Compounds having both unsubstituted nitrogen (276 or 277; R = R$_1$ = H) are potentially capable of tautomerism and showed λ_{max} at 220 and 250 nm. Furthermore, the λ_{max} at 250 nm shifted to 220 nm in strong

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-

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 $\sim 10^3$.
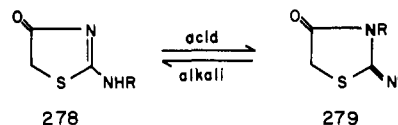
Najer et al.[32] studied the UV spectra of several 5-phenyl-2-amino-Δ^2-thiazolin-4-ones (280) and 5-phenyl-3-methyl-2-iminothiazolidin-4-ones (281) in ethanol. They found that the equilibrium of tautomers 280 $\rightleftharpoons$ 281 is dependent on the nature of substituent

R = R$_1$ = H, CH$_3$, C$_2$H$_5$, iso-C$_3$H$_7$, C$_6$H$_5$ or C$_6$H$_5$CH$_2$
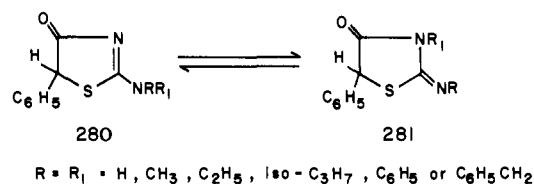
present at the exocyclic nitrogen atom. Thus, if R is a hydrogen, alkyl, or arylalkyl group, tautomer 280 is predominant, and if R is a phenyl group, tautomer 281 is predominant.

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$_3$)$_2$N. 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
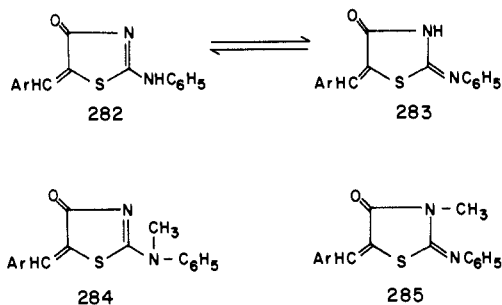
the phenyl ring present at position 5 also leads to a bathochromic shift of the K band. 2-(Methylphenyl-amino)-5-arylidene-Δ^2-thiazolin-4-ones (284) have a strong absorption band at 270–330 nm which is only separated from K band in the case of compounds with electron-donating substituents. Electron-donating 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-(phenyl-imino)-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
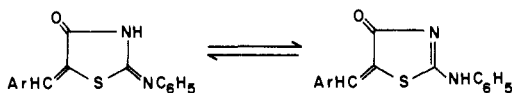
spectroscopy.[262] The spectral data showed that in

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-aryl-idene-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

286, R = n-C_4H_9
287, R = C_6H_5
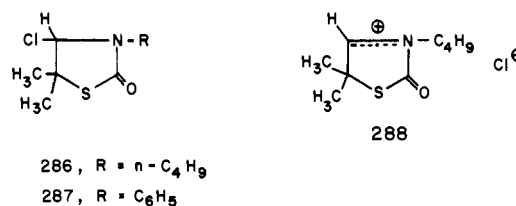
intensity 6, while that of 287 (R = C_6H_5) has two expected methyl signals (relative ratio 3:3). The equivalency of methyl groups in 286 is lost when chlorine group is replaced by other substituents such as hydroxyl or methoxyl. These results, in conjunction with the higher reactivity of 286 relative 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
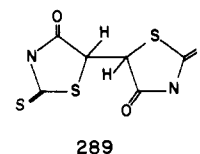
The nuclear magnetic resonance spectra[104] of 2-imino-4-oxothiazolidinyl-5-acetates (290) and 2,4-dioxo-thiazolidine 5-acetates (291) show characteristic pat-

290   291
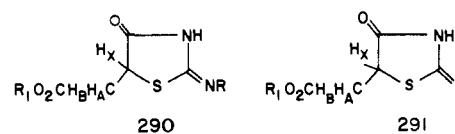
terns of an ABX system with approximate coupling constants of J_{AB} = 17.0–18.0, J_{AX} = 5.0–7.5, and J_{BX} = 4.0–5.0 Hz. The large values of J_{AB}'s were referred to as "carbonyl effect" on the coupling constants for the methylene groups by Takahashi[268] in the structurally related 2-thiono-5-(carboxylmethyl)-4-thiazolidinones. 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

SCHEME XVI
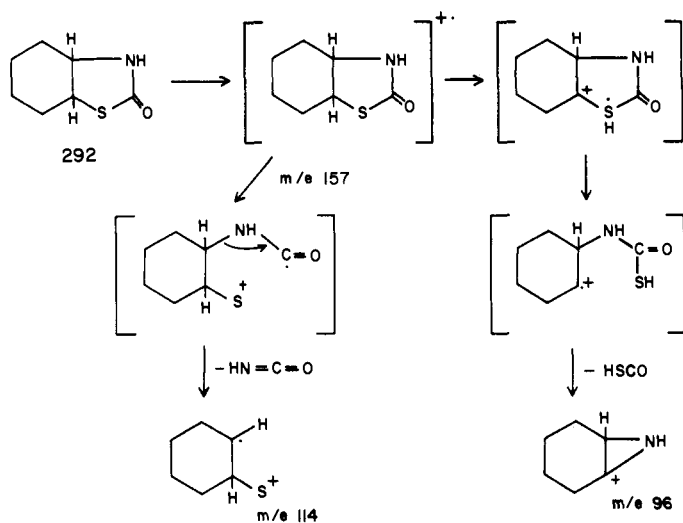
4.36–4.60 ppm, respectively, and indicate that the methylene protons adjacent to an asymmetric center are magnetically nonequivalent.[269] Furthermore, the readers are advised to see the following references where the chemical shift of the various types of proton resonances of different thiazolidinones 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

$$R = H, CH_3, C_6H_5 \text{ or } C_6H_5CH_2$$

293
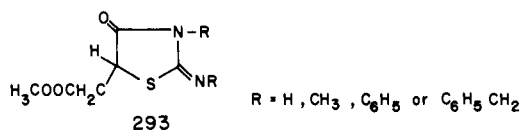
assigned.[104] The principal daughter ion peaks were determined by means of deuterium exchange and high-resolution mass spectroscopy. In the mass spectrum of methyl 2-(methylimino)-3-methyl-4-oxothiazolidinyl-5-acetate, the fragments at m/e 71 and 112 support the five-membered ring structure. These peaks appear in the deuterium spectrum at m/e 72 and 113, respectively.
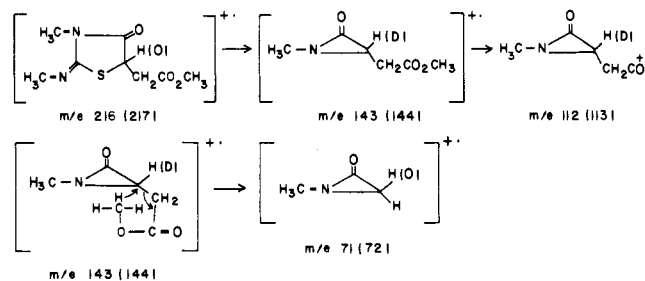
The mass spectrum[164] of 4,4-dimethyl-2-thiono-5-thiazolidinone (**294**) gave the molecular ion peaks at 161 (M^+, 100), 133 ($M^+ - CO$, 57) and 100 ($M^+ - CO - SH$, 37). The cleavage of the ring's weakest bond would labilize the ring carbonyl for expulsion and give the M – CO ion. The fragmentation patterns of **294** may be
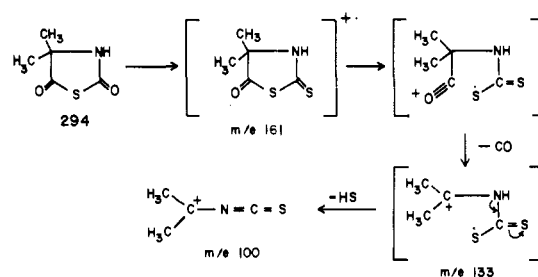
represented as in Scheme XVI.

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.
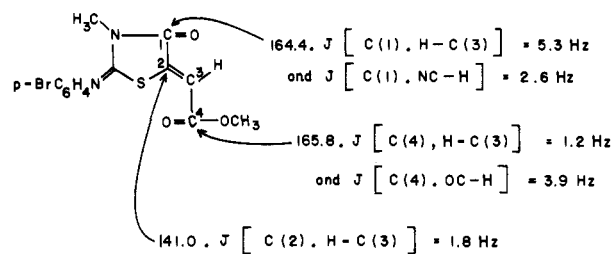
VII. Biological Activity of Thiazolidinones

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-hydroxy-butyrate 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-thia-zolidinones were studied by Patel et al.[143] where 2-(4-methoxyphenyl)-3-(3-methylphenyl)-5-methyl-4-thia-zolidinone 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-dimethoxy-phenyl)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-im-ino-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-thiazolidi-none 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 deriva-tives 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-methyl-piperazino)phenyl]azo]-4-thiazolidinone possessing an-thelmintic 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 effec-tive 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 hypoten-sion 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 cor-responding 5-arylidene derivatives were tested against *Staphylococcus aureus*. The antibacterial activity of 5-arylidene derivatives of both 2-[(dichlorophenyl)im-ino]/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 thiazoli-dinone derivatives against some common bacteria re-vealed that the thiazolidinones were more active than the thiazoles.[291] An enhancement in activity was ob-served 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-thia-zolidinones 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 ≥ 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/cm². Gupta and Rani[302] have tested various 5-substituted-3-(polynitrophenyl)-2-thiono-4-thiazolidinones against *Aspergillus niger, Alternaria tenius, Helminthosporium sativum*, 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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