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THE CHEMISTRY OF 1,3-THIAZOLINONE ⇌ HYDROXY-1,3-THIAZOLE SYSTEMS

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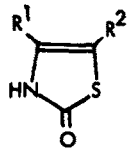
INTRODUCTION

This Report follows the style adopted for most of its predecessors, since it aims to provide a critical survey of the topic with emphasis on useful contributions to synthesis, reaction mechanisms, and structure determinations, with only brief discussion of routine work. Therefore, although examples of all

the isomeric 1,3-thiazolinones and some sulphur analogues are included in this Report, viz. compounds (1)–(7), the coverage concerns the thiazolin-4-ones (2) and particularly the thiazolin-5-ones (3), almost exclusively; those five ring systems (1)–(5) which are capable of tautomerism, and therefore fall strictly within the scope of this Report, are reviewed; compound types (6) and (7) are also included to the extent that they serve as starting materials in synthesis of the other thiazolinones.

A recently-published review of hydroxythiazoles[1] covers the literature to December 1976, and the same period has been surveyed for thiazolethiols,[1] aminothiazoles,[2] and mesoionic thiazoles.[3]



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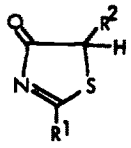

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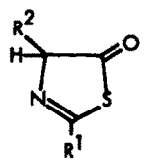

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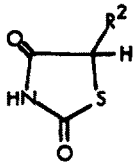

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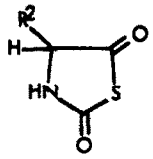

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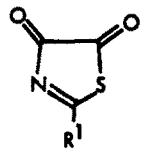

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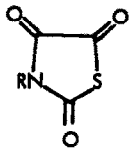

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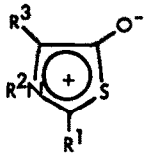

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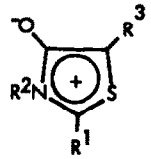

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Mesoionic tautomers have been implicated in reactions of thiazolinones, and comparisons with non-tautomerising mesoionic thiazolinones[3] (8) and (9) have been included in this Report. Recent comprehensive coverage of mesoionic heterocyclic compounds is available;[4] the tautomerism of heterocycles has been surveyed.[5]

GENERAL SURVEY

The thiazolin-5-one ring encloses the α-amino-acid residue =N–CHR^2–CO–, and the most widely-used method for peptide structure determination (Edman degradation)[6] involves 2-anilinothiazolin-5-ones (3; R^1 = PhNH) as intermediates. Nearly all alternative methods for peptide sequence analysis depend on the clean formation and identification of thiazolin-5-ones, and the devising of improved modifications of established techniques, to allow unambiguous structure determinations for long polypeptides, will depend on advances in thiazolinone chemistry.

Thiazolin-5-ones have been used in an early tetracycline synthesis[7] and in the synthesis of penicillin analogues.[8] A new β-lactam synthesis[9] is based on thiazolin-5-ones, and a differently conceived route with the same objective uses thiazolin-4-ones.[10,145]

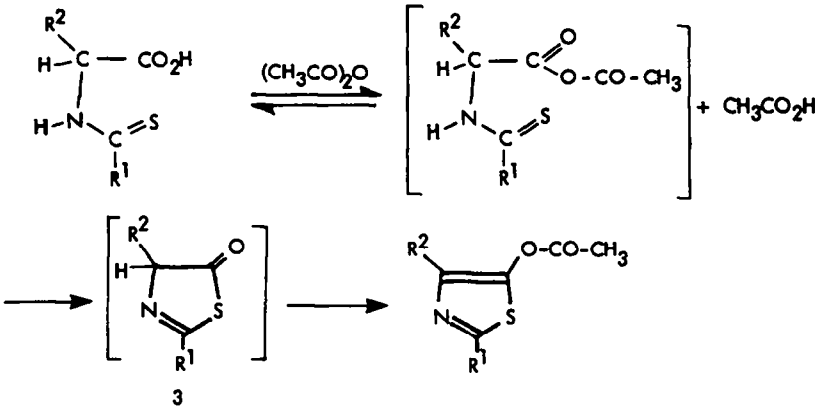
Methods for the synthesis of thiazolin-4-ones (2) provide more features of mechanistic interest, perhaps, than those used for the synthesis of the other thiazolinones. The long-known thiazolin-2-ones (1) and rhodanines (4; S in place of exocyclic O at C-2) exhibit relatively routine chemical behaviour in comparison with the wide variety of ring-cleavage, substitution, and cycloaddition reactions undergone by thiazolin-4-ones and thiazolin-5-ones.

THIAZOLIN-5-ONES (3)

The earliest work on this ring system stems from the penicillin project undertaken in the early 1940s.[11] Studies made at that time were apparently incidental extensions of the substantial amount of work devoted to the oxazolin-5-ones, a well-reviewed area of heterocyclic chemistry.[12] These early results for thiazolin-5-ones, published in full at later times,[13-20] indicated a close similarity with the general behaviour of the oxazolin-5-ones. However, the limited range of thiazolin-5-ones studied in the pioneering work was not sufficiently representative, particularly since very few 4-substituted compounds were included. It now appears that it is frequently a naive assumption that the behaviour of sulphur heterocycles can be predicted from that of their oxygen analogues. In the present context, the erroneous claim[21] that 2-phenylthiazolin-5-ones are formed by acetic anhydride cyclisation of *N*-thiobenzoylamino-acids, by analogy with the standard procedure for the synthesis of oxazolin-5-ones, was based on a coincidental similarity between elemental compositions of the 5-acetoxy-2-phenylthiazoles actually obtained (Scheme 1),[22] and those of the corresponding 2-phenylthiazolin-5-ones which were too confidently expected. Only 2-phenylthiazolin-5-one itself (3; R^1=Ph, R^2=H) can be prepared in this way,[7,22] and these results illustrate the greater nucleophilicity of the exocyclic oxygen atom of 2,4-disubstituted thiazolin-5-ones compared with that of the corresponding oxygen atom of analogous oxazolin-5-ones,[23] since the thiazolin-5-one is undoubtedly an intermediate in the 5-acetoxythiazole synthesis.

Preparations of thiazolin-5-ones

Cyclization of *N*-thioaroyl- or *N*-thioacylamino-acids X·CS·NH·CHR²·CO_2H with dicyclohexylcarbodi-imide,[23,26] phosphorus tribromide,[21,23-25] or trifluoroacetic acid,[22,24] and the cleavage of their amides and peptides with hydrogen chloride in dioxan[6,28] or trifluoroacetic acid,[6,24] are convenient general methods for the synthesis of 2-aryl- or -alkyl-thiazolin-5-ones (3; X=aryl, alkyl) (Scheme 2). Analogous thionocarbamates (X=RO–) and dithiocarbamates (X=RS–) yield 2-alkoxy- and -alkylthiothiazolin-5-ones when dicyclohexylcarbodi-imide is used as reagent,[23,49] but the acidic reagents give thiazolidin-2,5-diones with the same starting materials. Conversion of an *N*-thiobenzoylamino-acid ester with trifluoroacetic acid into the corresponding thiazolin-5-one is a slow reaction,[26] compared with the reactions of analogous acids and amides.



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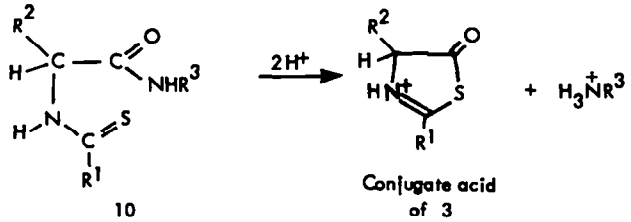
Scheme 1.



10 Conjugate acid of 3

Scheme 2.

4-Benzhydryl-2-phenyloxazolin-5-one is converted into the corresponding thiazolin-5-one by reaction with thioacetic acid,[27] but this is not a generally applicable reaction since oxazolin-5-ones can undergo further condensation with thioacetic acid[85] leading to 2,4-disubstituted 5-acetylmercaptothiazoles in most cases.

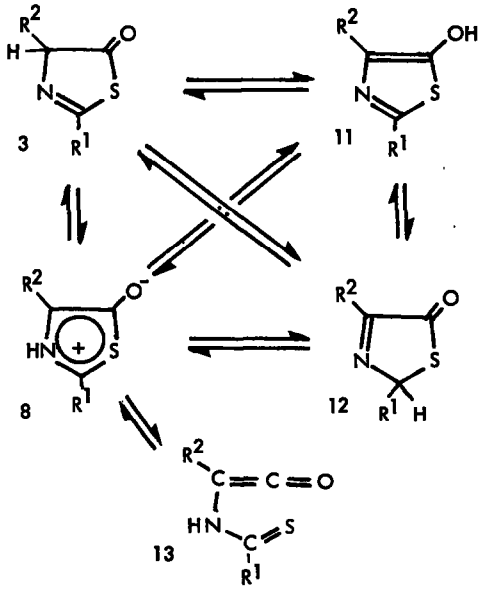
The fact that the cleavage of an *N*-phenylthiocarbamoyl-peptide (**10**; R^1=Ph·NH) with acid is the basis of the Edman sequence analysis of polypeptides[6] has encouraged the search for alternative reagents for this reaction (hydrogen chloride in nitromethane[28] and perfluoroalkanoic acids[6] have been used). Preliminary observations[29] indicate that thermolytic cleavage of **10** can occur in inert solvents. Similar peptide derivatives (**10**; R^1=HS, R^1=RO, R^1=RS) yield thiazolidin-2,5-diones and 2-thiono-thiazolidin-5-ones on treatment with anhydrous acids.[18-20,32-35]

Trifluoroacetic anhydride has been advocated[30] for the conversion of *N*-(benzylthio)thiocarbonyl-glycine and its amides into 2-(benzylthio)thiazolin-5-one, but alternative products are formed using this reagent with analogous starting materials (**10**; R^1=Ph, PhNH).[69]

Tautomerism of thiazolin-5-ones

The behaviour of thiazolin-5-ones in addition reactions, discussed in the following section, reveals the existence of three tautomeric species **3**, **11** and **8**, in solution. The "keto" and "enol" forms, **3** and **11**, respectively, have been detected in solutions through spectrometric studies,[36-38] in ratios determined by solvent characteristics. The mesoionic tautomer **8** has been shown to exist in increasing proportions as solutions of 2-phenylthiazolin-5-ones in polar solvents are diluted, since such solutions show substantial deviations from the Bouguer–Beer–Lambert law.[36]

The remaining tautomer **12**, which is in principle capable of existence, has not so far been detected through spectrometric studies, or through the interpretation of reaction pathways leading to addition products. In the oxazolin-5-one series, the analogous tautomer (the "pseudo-oxazolinone") is the predominating form where a strongly electron-withdrawing group (e.g. trifluoromethyl) is located at C-2.[39] The displacement of the methylthio-group of a 2-(methylthio)thiazolin-5-one by an alkylamine indicates the formation of an intermediate of type **12**.[40] The formation of benzaldehyde in solutions of 2-phenylthiazolin-5-ones in cold aqueous sodium hydrogen carbonate,[41] is best explained on the basis of tautomer **12** as starting material. Recent literature summarised in Ref. 42 describes the isolation of tautomers of oxazolin-5-ones corresponding to **8** and **12**.



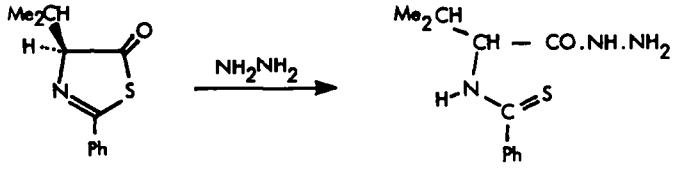
Scheme 3.

Adopting Katritzky's precept,[5] that tautomeric systems should be referred to according to the systematic name of their predominant tautomer, most "2-phenyl-thiazolin-5-ones" are 5-hydroxy-2-phenylthiazoles, while the 4-isopropyl-, 4-s-butyl-, and 4-unsubstituted compounds are 2-phenylthiazolin-5-ones. These are the forms taken by these compounds in the solid or liquid states, while other 5-hydroxy-2-phenylthiazoles exist as such in the solid state, and in polar solvents to a predominant

extent, as judged by spectroscopic data. For example, the keto:enol ratio for 4-methyl-2-phenyl-thiazolin-5-one in various solvents is: chloroform 100:0, nitrobenzene 95:5, acetonitrile 85:15, acetone 65:35, cyclohexanone 50:50, methanol 20:80, and dimethyl sulphoxide 0:100.[36,37]

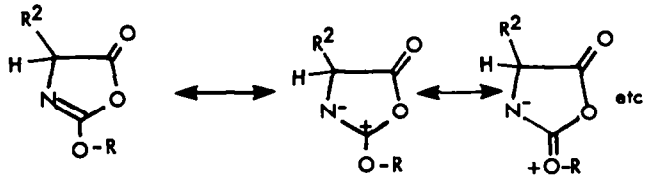
Comparison with the tautomeric behaviour of analogous 2-phenyloxazolin-5-ones shows that substitution of ring oxygen by sulphur causes a substantial trend away from a preference for the keto form (oxazolin-5-one) into a preference for the enol form (5-hydroxythiazole), except for thiazolin-5-ones carrying bulky 4-substituents. The demonstration that 2,4-diphenyloxazolin-5-one can be crystallized as its mesoionic tautomer[42] has not been matched for the corresponding hydroxythiazole.

The chiral stability of 2-phenyloxazolin-5-ones formed by the cyclization of *N*-benzoyl-L-amino-acids has been studied in considerable detail,[43] because of the crucial role played by partly-racemized oxazolin-5-ones as the source of unwanted diastereoisomers in peptide synthesis. Whereas many oxazolin-5-ones have been isolated in optically-pure, crystalline form, as have corresponding oxazolin-5-onium perchlorates,[44] even those thiazolin-5-ones for which the keto-tautomeric form is favoured in non-polar solvents are racemized during isolation from reaction mixtures, and undergo relatively rapid racemization in chloroform in the absence of base; $t_{1/2}$ for 4-isobutyl-2-phenylthiazolin-5-one is 20 min; $t_{1/2}$ for the corresponding 4-s-butyl isomer is 300 min in chloroform at room temperature.[26] Reaction of a chiral 2-phenyloxazolin-5-one with hydrazine gives an optically-pure *N*-benzoylamino-acid hydrazide,[45,46] whereas the corresponding reaction with (−)-2-phenyl-4-isopropylthiazolin-5-one involves almost instantaneous racemisation and yields N^{α}-thiobenzoyl-DL-valyl hydrazide (Scheme 4).[26]



Scheme 4.

Relative rates of racemisation of oxazolin-5-ones and thiazolin-5-ones in the absence of added bases are determined by the relative basicities of the various thiazolin-5-one tautomers ("autoracemisation") in solutions and by their proportions, as well as by structural features influencing the acidity of the proton at C-4 (electronic characteristics of the substituent at C-2 and C-4; steric influence of the substituent at C-4). The various factors operating in the case of 4-substituted oxazolin-5-ones carrying an electron-releasing group at C-2 combine to promote high chiral stability. 2-Benzyloxy-oxazolin-5-ones, isolated recently for the first time,[47,48] but which may have been involved unknowingly in racemisation-free peptide coupling experiments employing *N*-benzyloxycarbonyl-L-amino-acids, are substantially more resistant to racemisation than their 2-phenyl analogues. 2-Benzylthio-thiazolin-5-ones are correspondingly more prone to adopt the keto-tautomeric form, rather than the enolic form, compared with their 2-phenyl analogues.[49,50] The effect of the electron-releasing 2-substituent on lowering the acidity of the 4-proton in these series may be attributed to the greater importance of canonical forms which discourage anion formation at C-4 (Scheme 5). 2,4-Dialkylthiazolin-5-ones are less completely enolized than their 2-phenyl analogues; in $^2H_6$-dimethyl sulphoxide at 34°, 4-isopropyl-2-methylthiazolin-5-one exists as a 65:35 keto-enol mixture, the corresponding ratio for 4-isopropyl-2-phenyl-thiazolin-5-one being 20:80.[23]



Scheme 5.

2-Alkoxythiazolin-5-ones appear to exist in the keto-tautomeric form in solution in $^2H_6$-dimethyl sulphoxide or in ^2H-chloroform, since ^1H NMR spectra of these solutions are identical, and no exchange with deuterium oxide is observed, in contrast to the behaviour of a 2,4-dialkylthiazolin-5-one in ^2H-chloroform.[23] While there is considerable scope here for more detailed studies, the order aryl > alkyl > alkylthio > alkoxy applies for the effect of the 2-substituent in a 2,4-disubstituted thiazolin-5-one on the promotion of the hydroxythiazole structure relative to the thiazolinone form. All members of a series

of 2-benzyloxythiazolin-5-ones exist as such, except the 4-unsubstituted compound, which is partly enolized, and the 4-phenyl compound, which is largely enolized, in hexamethylphosphoric triamide.[51]

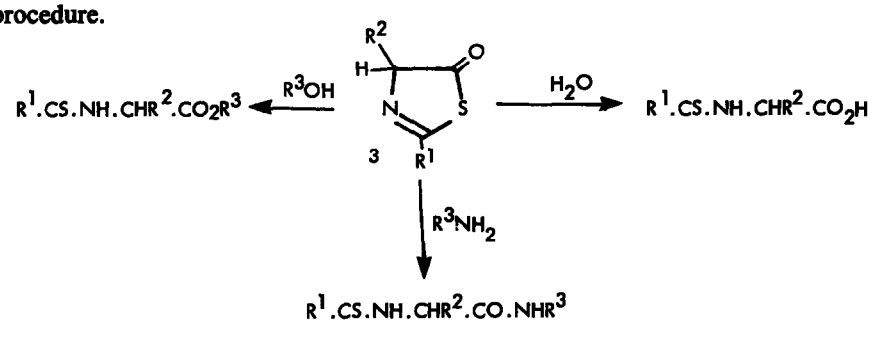
Siemion *et al.*[52] report that the condensation of *N*-benzyloxythiocarbonyl-L-phenylalanine with p-nitrophenol, mediated by dicyclohexylcarbodi-imide, gives the DL-p-nitrophenyl ester. This can only be interpreted as due to the racemization of the intermediate thiazolin-5-one prior to nucleophilic ring cleavage, and stands in contrast to the formation of optically-pure aminolysis products yielded by the analogous 2-benzyloxy-oxazolin-5-one.[47] In the oxazolin-5-one series, since chiral 2-aryloxazolin-5-ones are easily racemized during aminolysis, the nature of the 2-substituent appears to influence the keto-enol tautomer ratio in the same way as in the thiazolin-5-one series.[47]

The easy *O*-acylation reaction undergone by 2-phenylthiazolin-5-ones (Scheme 1) is shared with 2-methyl-, but not with 2-alkoxy-, analogues.[23] A strong base (sodium hydride) is needed to de-protonate a 2-benzyloxythiazolin-5-one, and a low yield of a 5-(carbamoyloxy)thiazole can then be obtained. There is therefore the expected correlation between ease of enolization and ease of enol acetate formation in this series. 4-Substituted 2-phenyloxazolin-5-ones yield analogous 5-acyloxyoxazoles with an acyl chloride in the presence of one molar equivalent of triethylamine, but the rearrangement of these compounds to 4-acyloxyoxazolin-5-ones[53] in pyridine is not undergone by corresponding thiazoles, and Dakin–West products are not formed from thioacylamido-acids.

Reactions of thiazolin-5-ones

A range of characteristic reactions has been described including examples which illustrate the presence in reaction mixtures of anionic and mesoionic forms.

Addition reactions. Nucleophilic addition to C-5 of the keto-tautomeric form is involved in hydrolysis, alcoholysis, and aminolysis reactions, demonstrated for 2-phenyl (**3**; R^1=Ph),[25,26] 2-benzylthio[30] (**3**; R^1=$PhCH_2S$), and 2-anilinothiazolin-5-ones (**3**; R^1=PhNH) (Scheme 6).[54] The hydrazinolysis shown in Scheme 4 is a further example. In all these reactions, except in failing to sustain chiral integrity, these thiazolin-5-ones behave like analogous oxazolin-5-ones. Their participation in a peptide synthesis (**3** + NH_2·CHR·CO_2H → **10**; R^3 = CHR·CO_2H) which is entirely analogous to a classical method using oxazolin-5-ones, has been established,[26] but the racemization of the amino-acid residue added at the *N*-terminus of a peptide in this way renders the method of little direct interest in the general field. A further difference in the stereochemical aspect of the aminolysis reaction arises in the formation of equal amounts of pairs of diastereoisomeric *N*-thiobenzoyldipeptides when an L-α-amino-acid is used for the aminolysis of a 4-substituted 2-phenylthiazolin-5-one, in contrast to the often substantial enantiomeric excess of the L,L-diastereoisomer obtained through the corresponding reaction with a DL-4-substituted-2-phenyloxazolin-5-one.[55] Separation of diastereoisomeric products can be accomplished in representative chiral aminolysis reactions of L-amino-acids with 2-phenyl-4-substituted thiazolin-5-ones,[26] and the reaction is suitable for modifying physiologically-active peptides for testing structure-activity relationships, for example, since it can be brought about very effectively in acetic acid, a solvent in which peptides and amino-acids are generally soluble. The process has been proposed as a method for protection of the primary or secondary amino-group.[30] De-protection, the reversal of the reaction, regenerates the thiazolin-5-one as well as the amine. All these nucleophilic ring-opening processes are the reverse of the principal methods available for the synthesis of thiazolin-5-ones from amino-acid derivatives, and have been the subjects of study both for their possible applications in synthesis, as just described, and for the mechanistic interest associated with the formation of 3-phenyl-thiohydantoins via hydrolytic ring-opening of 2-anilinothiazolin-5-ones which is a stage in the Edman polypeptide sequence analysis procedure.



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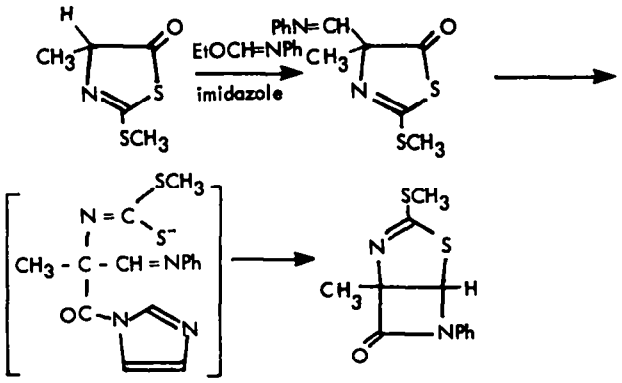
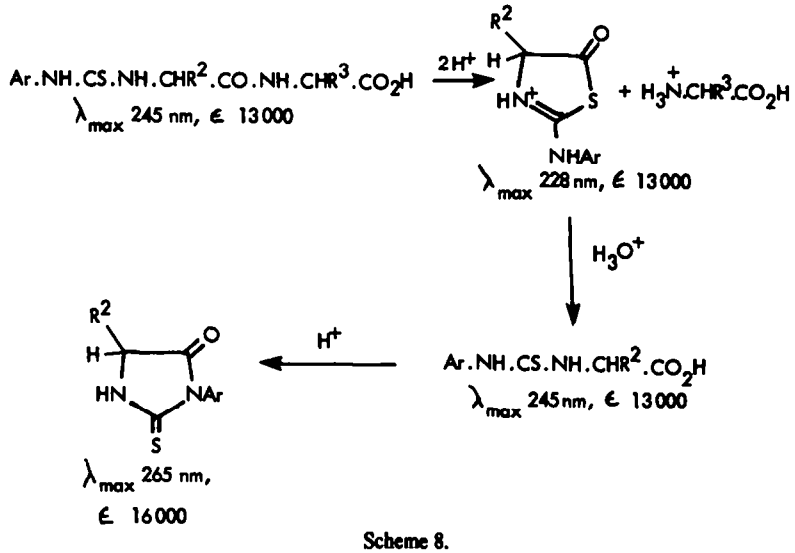
Scheme 6.



Scheme 7.

The novel β-lactam synthesis[9] shown in Scheme 7 depends on the nucleophilic ring-opening of a 4,4-disubstituted thiazolin-5-one, possibly by imidazole as shown, or alternatively by water and an alternative ring-closure mechanism.

Hydrolysis of thiazolin-5-ones is readily effected in weakly alkaline solutions. Interesting examples of asymmetric synthesis have been described[56] in which a racemic 4-substituted 2-phenylthiazolin-5-one is entirely converted into the corresponding *N*-thiobenzoyl-L-α-amino-acid through trypsin- or chymotrypsin-catalysed hydrolysis as a consequence of the facile tautomeric interconversion of the ring system. The mechanism proposed by Edman for the rearrangement of 2-anilinothiazolin-5-ones[6,28] into 3-phenylthiohydantoins and supported by Bethell, Metcalfe and Sheppard[57] (Scheme 8), implies that acid-catalysed hydrolysis is very easily accomplished in this case. A kinetic study of the hydrolysis step (Scheme 8) has shown that in perchloric acid solutions (pH less than 1.0), the reaction is inhibited as the pH drops to *ca.* −10, but that the rate is independent of pH over the range pH 3 to pH −2 if constant ionic strength is maintained through the addition of sodium perchlorate. Similar univalent salt effects have been noted for the acid-catalysed hydrolysis of succinic anhydride,[58] but these facts cannot be interpreted to give further support to the mechanistic scheme (Scheme 8), which is largely based on UV-spectrometric data and which may involve alternative intermediate stages.



Scheme 8.

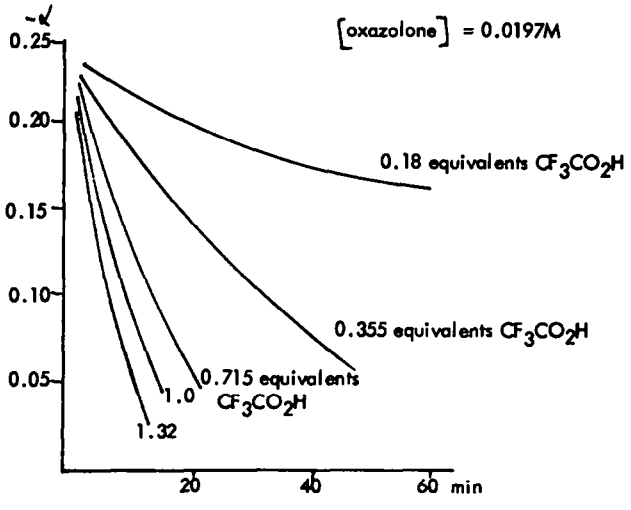
Transient absorption increases at 230 nm and at a later stage around 245 nm during the course of the reaction are consistent with the intermediacy of the thiazolin-5-one and its hydrolysis product, the *N*-phenylthiocarbamoylamino-acid.[57] Each of the steps in the mechanistic scheme has been studied separately, the information obtained leading to proposals for optimized reaction conditions for the Edman procedure.

There are aspects of the chemistry of thiazolin-5-ones which suggest that variations of the accepted mechanism of the Edman sequence analysis shown in Scheme 8 should be considered. In any case, it

was recognized at an early stage[28] that an alternative rearrangement pathway might exist for the conversion of a 2-anilinothiazolin-5-one into a 3-phenylthiohydantoin. Recent papers advocate thermal rearrangement, e.g. at 80° during 30 min,[59] or at 140° for samples on a silica gel TLC plate.[60] Although there has been insufficient experimental rigour in these studies to allow mechanistic speculation, there is a group of heterocyclic rearrangements of the same type: R-NH-C(=N-)-S- → S=C(-NH-)-NR- for which several examples involving base catalysis have been described.[61] The mechanistic details of the Gewald rearrangement of 2-aminothiophens[61] may also apply to aza-analogues.

The Edman degradation of proline-containing peptides is known to proceed with low yields at the proline cleavage stage.[62] The chemistry involved with this particular imino-acid residue is a significant variation of that for an *N*-terminal amino-acid residue (Scheme 8); the intermediate thiazolin-5-one must be formulated either as a mesoionic 2-phenylaminothiazolin-5-one, protonated presumably on the exocyclic nitrogen atom, or a 2-phenyliminothiazolin-5-one protonated on the ring nitrogen atom. The ultimate product of the cleavage of a proline residue by the Edman method is a 3-phenylthiohydantoin, as with other amino-acid residues, but the structural differences of the thiazolinone intermediates imply that the competing paths to the phenylthiohydantoin in the proline case may show a greater preference for the thermal (non-hydrolytic) intermediates, rather than the path shown in Scheme 8, whereas the preference may be the other way round for other amino-acid residues. Unusual chemistry has been uncovered in studies of the preparation of *N*-phenylthiocarbamoyl derivatives of sarcosine and pipecolic acid;[63] these imino-acids are close relatives of proline, and this work may explain the need for modified reaction conditions in the Edman degradation with peptides carrying an *N*-terminal proline residue.[62] 3-Phenylthiohydantoins formed from optically-pure peptides through these reactions are largely racemized, a fact which can be accounted for on the basis of tautomerization of the thiazolin-5-onium cation, although chiral thiazolin-5-ones which carry an electron-releasing 2-substituent must be considered to be resistant to racemization. Studies on chiral thiazolin-5-ones are represented only in two studies,[26,50] while many more results have been accumulated for analogous racemization studies on oxazolin-5-ones. Although specific comparisons between these two heterocyclic series may be inappropriate, the general trend observed in the oxazolin-5-one series (increasing optical stability in moving from 4-substituted-2-

Table 1. Racemisation of 4-isobutyl-2-phenyloxazol-5(4H)-one in CH_2Cl_2 at 25°

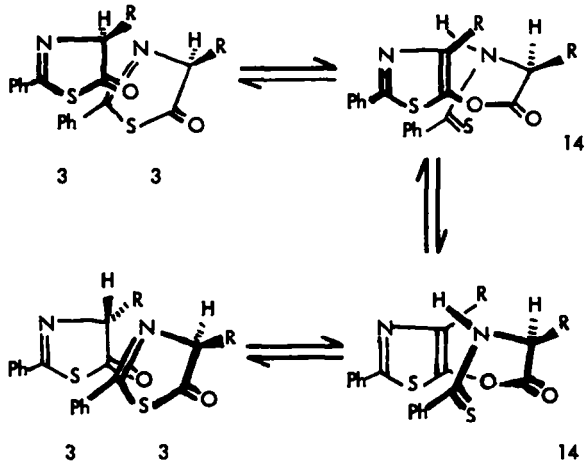


$t_{\frac{1}{2}}$ (min)	equivalents CF_3CO_2H
91	0.18
22.5	0.355
8.5	0.71
7	1.0
5.1	1.32

phenyl- to -2-benzyloxythiazolin-5-ones; high optical stability of 2-phenyloxazolin-5-on-4-ylium cations) can be assumed to hold for the thiazolin-5-one series also.

A mechanism can be proposed to account for the acid-catalysed racemisation of oxazolin-5-ones.[64] Carboxylic acids effectively catalyse the racemization in dichloromethane of (−)-2-phenyl-4-isobutyloxazolin-5-one (Table 1),[64] and this effect can be seen in the published data[65] describing the preparation of this compound; a rapid initial change in α_D is observed during the acetic anhydride cyclisation of *N*-benzoyl-L-leucine, followed by a slow first order decrease from a maximum optical rotation. Goodman and Levine[65] recommend polarimetric monitoring, the reaction mixture being evaporated under reduced pressure at the point where α_D is at a maximum, giving the optimum yield of optically-pure oxazolin-5-one.

A mechanism to account for acid-catalysed racemisation in these series, based on an established role of a carboxylic acid as an esterification catalyst,[66] and on the fact that the exocyclic oxygen atom is susceptible to acylation in both oxazolin-5-one and (especially) in thiazolin-5-one series, is shown in Scheme 9.



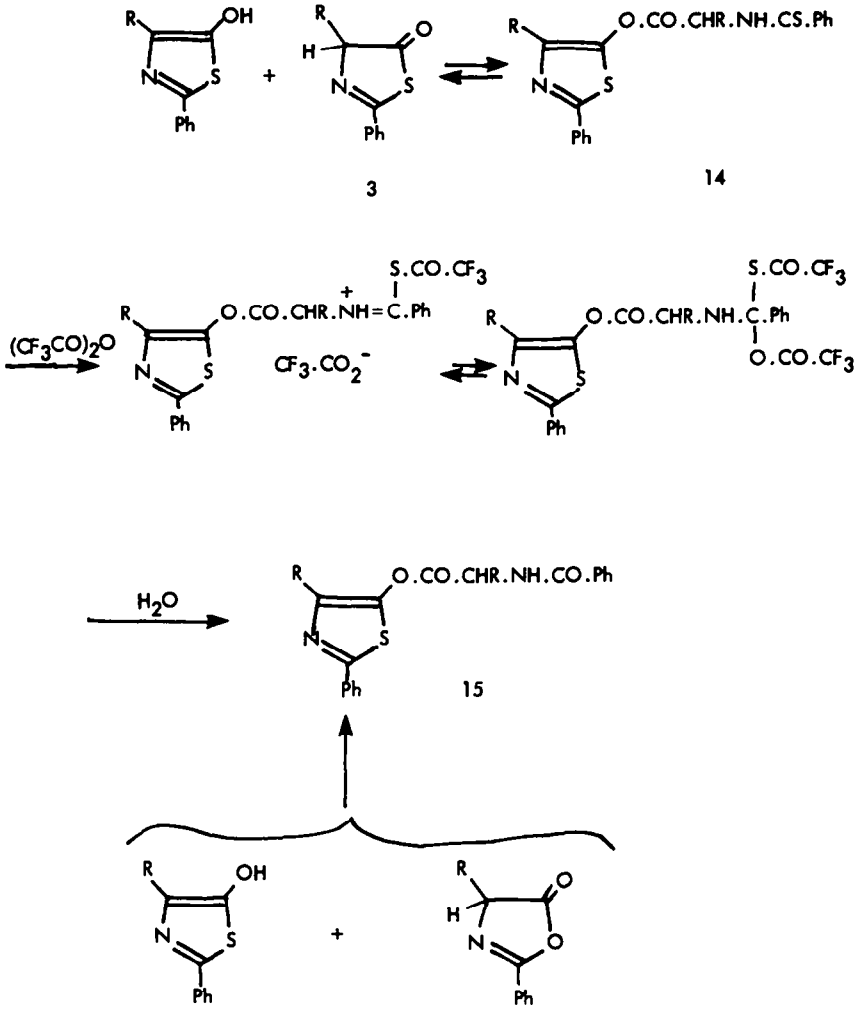
Scheme 9.

The interpretation of the role of acid in the racemization of compounds carrying a chiral centre adjacent to a carbonyl function is frequently problematical. With one exception, the amino-acids obtained by the hydrolysis of proteins in 6M-hydrochloric acid are not racemized; for the exceptional case, L-cystine, a mechanism involving enolization has been proposed,[67] involving the hetero-atom in the stabilization of charge so as to facilitate enolization. Protonation of the carbonyl group in the acid hydrolysis of proteins would be expected, as well as protonation of the amino-group in the hydrolysis product, tending to prevent the departure of the proton from the chiral centre. Protonation of the ring nitrogen atom has been reported to protect a chiral oxazolin-5-one from racemization,[68] since oxazolin-5-onium cations formed from *N*-benzoyl-L-amino-acids with perchloric acid can be hydrolysed to the starting materials with only slight racemization, and de-protonated without racemization. The role of a carboxylic acid in promoting racemization of a chiral oxazolin-5-one or thiazolin-5-one therefore calls for an alternative interpretation, and the mechanism displayed in Scheme 9 is supported by the finding that adding an oxazolin-5-one to the dichloromethane solution of an optically-active thiazolin-5-one causes a 50% increase in the rate of racemization.[64]

This can be accounted for by the fact that an oxazolin-5-one is a better acylating agent than a thiazolin-5-one,[26] and is therefore consistent with the proposed mechanism. Raude and Hoppe have recently reported[9] that a 2-benzylthio-thiazolin-5-one exists as the dimer (**14**; $PhCH_2S$ in place of Ph), but that on distillation it reverts into the "monomeric" thiazolin-5-one (**3**; $R^1 = PhCH_2S$); it was found that a 2-phenylthiazolin-5-one which adopts the keto-tautomeric form in the condensed state, 4-isopropyl-2-phenylthiazolin-5-one (a liquid at room temperature), slowly deposits colourless crystals during a period of 3–4 weeks.[69] This compound is the corresponding 5-(2′-benzamidoalkyloxy)thiazole (**15** in Scheme 10), easily obtained from *N*-thiobenzoyl-DL-valine by brief treatment with trifluoroacetic anhydride.[69] The formation of this compound can be accounted for from either the thiazolinone "dimer" **14**, or from an initially-formed thiazolinone, whose enol tautomer undergoes acylation by a mixed anhydride ($PhCO{\cdot}NH{\cdot}CHR{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CF_3$ or its thiobenzoyl analogue) or by the corresponding

oxazolin-5-one. Although the acylation of a thiazolin-5-one by an oxazolin-5-one is very easily accomplished,[69] by mixing the reactants in acetone solution and dilution with petrol, so too is the conversion of an *N*-thiobenzoylamino-acid ester into the *N*-benzoyl-analogue by trifluoroacetic anhydride via an S-trifluoroacetylthiobenzimidate intermediate.[69]

The conversion of *N*-thiobenzoyl-L- or DL-amino-acids into 5-(2′-benzamidoalkyloxy)thiazoles (Scheme 10) has been shown to be a general reaction.[69] However, 2-phenylthiazolin-5-ones do not react with trifluoroacetic anhydride to give these products; the thiazolin-5-ones are undoubtedly converted into 5-trifluoroacetyloxythiazoles by the reagent, but on aqueous work-up these esters revert to the starting materials.



Scheme 10.

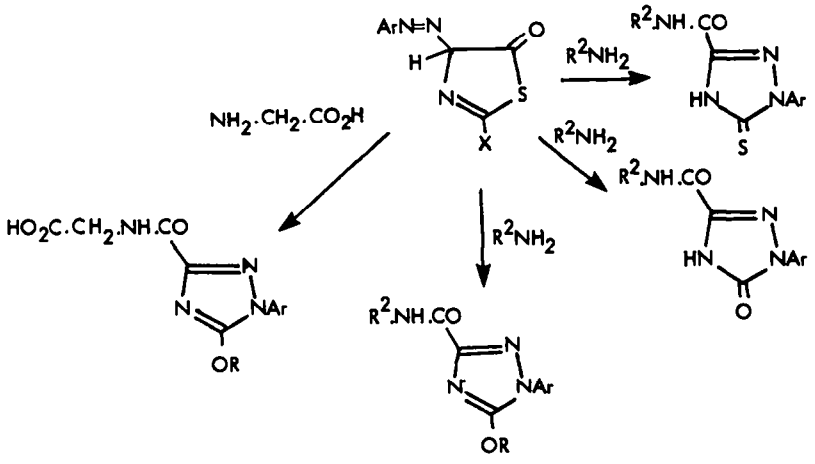
Analytical data reported[70] for the unidentified compound obtained from *N*-(benzylthio)thiocarbonyl-DL-phenylalanine through reaction with thionyl chloride probably indicate it to be the analogous 5-(2′-benzylthiocarbonyl-1′-phenylpropionyloxy)thiazole.

Returning to the mechanism of the Edman degradation, the dimerization established for thiazolin-5-ones carrying a 2-phenyl- or 2-benzylthio-substituent can be carried over to the 2-anilinothiazolin-5-ones formed from *N*-phenylthiocarbamoylpeptides in the first stage (the "coupling" stage) of an Edman cycle. The putative dimers, 5-(2′-phenylthiocarbamoylamino-acyloxy)-2-anilinothiazoles, are "activated esters", and can be envisaged to be transformed readily into the 3-phenylthiohydantoin, the product of the "conversion" step of the Edman cycle. The dimers carry the phenylthiocarbamate chromophore, and the thiazole chromophore, and should show the same UV absorption characteristics as a phenylthiocarbamoylamino-acid (for thiazole itself, λ_{max} 240 nm, ϵ 4000 in hexane). The experimental support for the two-stage Edman mechanism (Scheme 8) is therefore also consistent with a mechanism incorporating the

thiazolinone dimer as well as, or instead of, the phenylthiocarbamoylamino-acid. This revised mechanism rationalizes the observations that racemization is substantial, and that some oxidative desulphurisation has been found to occur. There have been many reports of the formation of side-products in the Edman polypeptide sequence analysis,[71] artefacts appearing at an early stage in the repetitive use of the "coupling–conversion" cycle in an extended sequence determination; yields of 3-phenylthiohydantoins often fall to about 20% after a few cycles.[72]

There is a growing realisation[31,57] that reagents and conditions used in the Edman procedure can be improved, following the improved understanding of the reactivity profile of thiazolin-5-ones which has now emerged.[31] A method for polypeptide sequence analysis has been established, which is closely related to the Edman procedure but which employs *N*-thiobenzoyl[73,74] or *N*-thioacetyl-peptides[75] and therefore yields a 2-phenyl- or a 2-methylthiazolin-5-one during a cycle. In contrast to their 2-anilino-analogues, 2-phenyl- or -methyl-thiazolin-5-ones are not susceptible to rearrangement during isolation from reaction mixtures, and fewer artefacts are formed since this reaction pathway is not open.

The first-formed aminolysis adduct from a 4-arylazothiazolin-5-one undergoes condensation or isomerization to a triazole (Scheme 11).[76]

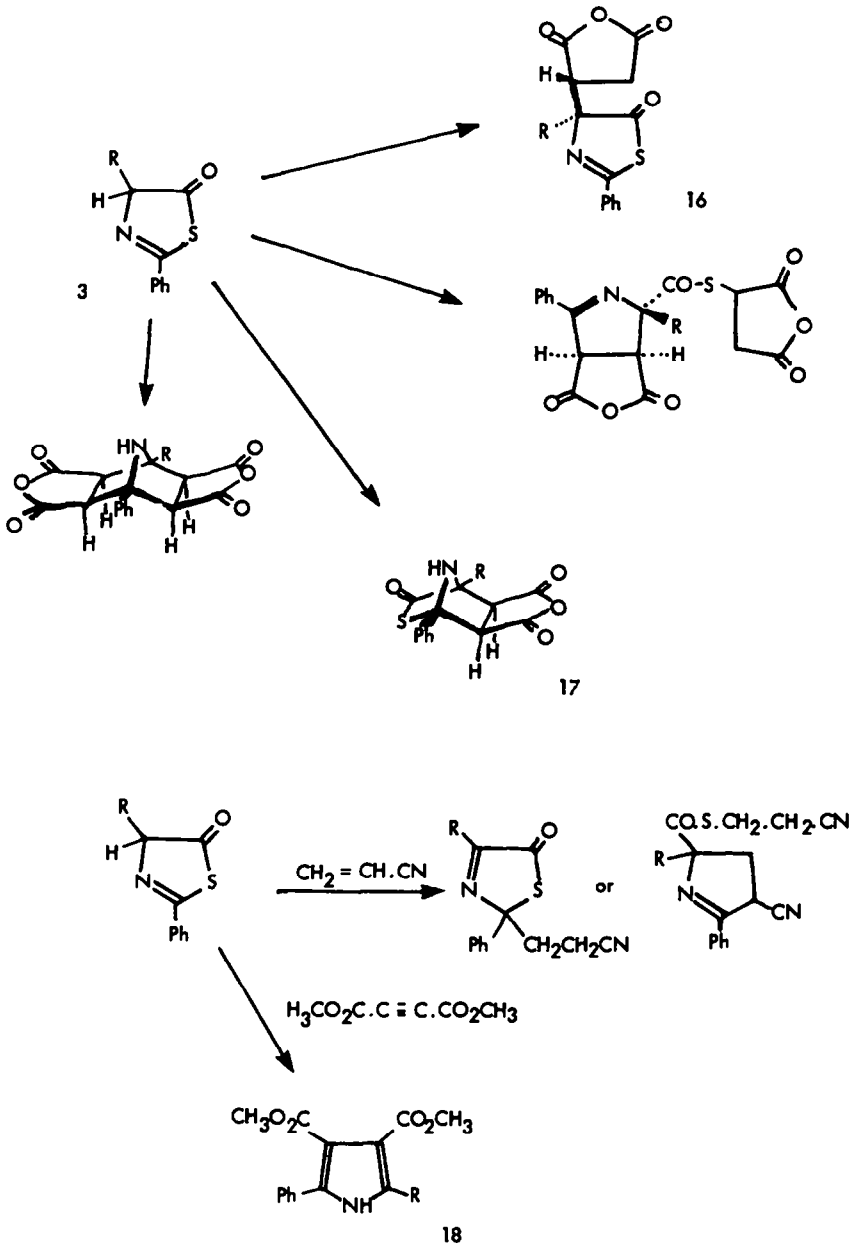


Scheme 11.

Hydrolysis of thiazolin-5-ones to α-amino-acids. Addition of water at C-5 leading to ring opening is followed by hydrolysis of the resulting *N*-thiocarbonyl-substituted amino-acid, when a 2-methyl or phenylthiazolin-5-one is treated with 6M hydrochloric acid at 120° during 2–3 hr.[75,77,78] The formation of the corresponding 3-phenylthiohydantoin, which resists hydrolysis under these conditions, occurs when a 2-anilinothiazolin-5-one is treated in the same way, and conversion into the aminoacid in this case[77,77a] requires treatment with 6M hydrochloric acid during more than 16 hr at 150°.

Addition of thiazolin-5-ones to unsaturated systems. The greater acidity of the proton at C-4 in 2-phenyl-4-substituted thiazolin-5-ones relative to the corresponding oxazolin-5-ones accounts for the easy formation of Michael adducts **16** as well as cycloadducts, with electron-deficient alkenes (Scheme 12),[79] under conditions in which oxazolin-5-ones give only cyclo-adducts or their cleavage products.[78] Michael addition reactivity has also been demonstrated for oxazolin-5-ones,[80] but the presence of strong base was mandatory. The ratios of products formed between thiazolin-5-ones and acceptors are solvent-dependent, and reflect both the different tautomeric populations expected in different solvents on the basis of spectroscopic studies, and adoption of a role by (presumably) the hydroxythiazole tautomer as base for catalysis of the Michael addition pathway.[79] Differences between the addition products of thiazolin-5-ones with those from corresponding oxazolin-5-ones also reflect the different stabilities of the initially-formed cycloadducts in the two series. The thiazolinone–alkene cycloadduct (**17**) can be isolated from reaction mixtures, whereas the product of extrusion of CO_2 from the oxygen analogue is rapidly reached in the corresponding oxazolinone reaction.

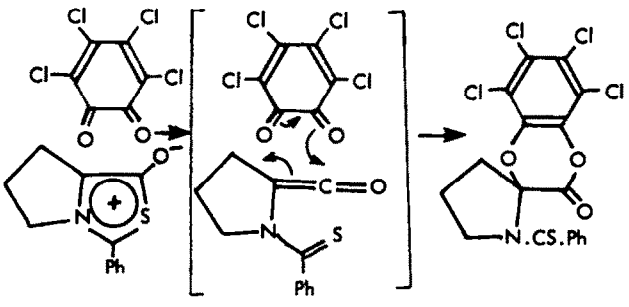
Analogous cycloadducts formed by both series with alkynes, however, are unstable under the conditions of the reaction or of work-up, and pyrroles (**18**) are easily accessible from either starting material. All the addition reactions with thiazolinones were carried out using reaction conditions which are substantially less forcing than those reported in the earlier studies involving oxazolin-5-one cycloadditions.[78]



Scheme 12.

Adducts formed between thiazolin-5-ones and tetrachloro-o-benzoquinone[41] (Scheme 13) are analogous to those obtained from corresponding oxazolin-5-ones.[81] Their formation is rationalized on the basis of tautomerization into the mesoionic form, and thiazolium-5-olates themselves readily undergo the addition reaction;[82] the suggestion has been made, however, that valence isomerization of the thiozolinone into the thioacylamido-ketene (13 in Scheme 3; see also Scheme 20) precedes addition.[82] No evidence was provided for this extra stage in the mechanism, but the formation of the analogous ketene has been advocated[83] to account for the course of the cycloaddition of a carbodi-imide to a mesoionic oxazolin-5-one, leading to an azetidine.

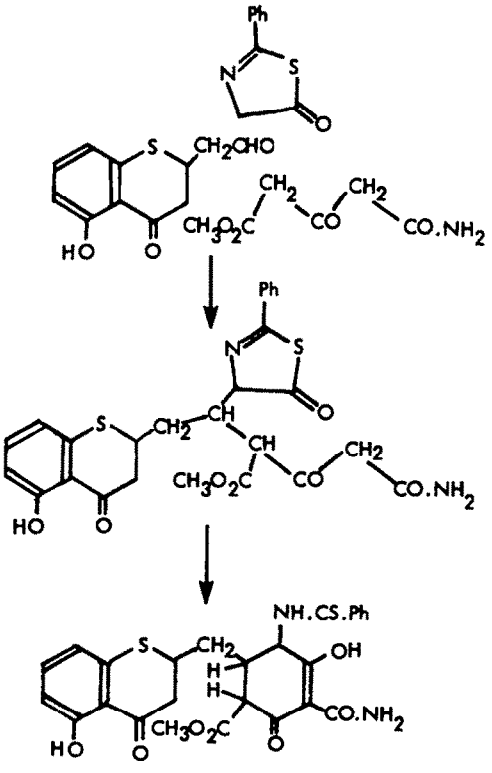
Condensation reactions of thiazolin-5-ones. 2-Phenylthiazolin-5-one reacts as a typical active methylene compound, giving condensation products with carbonyl compounds.[8,21] The overall process is equivalent to the Erlenmeyer reaction undergone by *N*-acylamino acids, leading to 4-alkylideneoxazolin-5-ones. 4-Unsubstituted thiazolin-5-ones have been described as unstable,[7,16,30] though this refers to their behaviour in reaction solutions, which rapidly discolour, rather than implying that they have only short shelf life.



Scheme 13.

The use of 2-phenylthiazolin-5-one in a synthesis of tetracycline analogues[7] (the later stages are shown in Scheme 14) illustrates a useful application in synthesis. The advantage of using the thiazolin-5-one in this synthesis, rather than the corresponding oxazolin-5-one, lies in the fact that the thiobenzamide group which appears in the condensation product **19** can be cleaved to unmask the nitrogen function in ring A under mild conditions, whereas the benzamide analogue could not be cleaved without degradation elsewhere in the molecule. A series of patents has appeared, covering tetracycline analogues obtained by the route based on this reaction.[84] Condensation of the aldehyde with the thiazolinone (lead(II) acetate/THF) precedes the Michael addition of methyl 3-oxoglutaramate (NaH/dioxan).[7]

The synthesis of 5-acetylmercaptothiazoles from amino-acids and thioacetic acid has been established,[85] and the process has been broken down into its constituent steps (Scheme 15). As well as the *N*-acetylamino-acid, other obvious intermediates were shown to be capable of condensation with thioacetic acid, including the thiazolin-5-one, and the use of an *N*-thioacylated amino-acid as starting material provides a general synthesis of thiazoles substituted by sulphur functional groups at C-5. One exception has been uncovered[41] where the process does not go beyond the 5-acetoxythiazole in the case

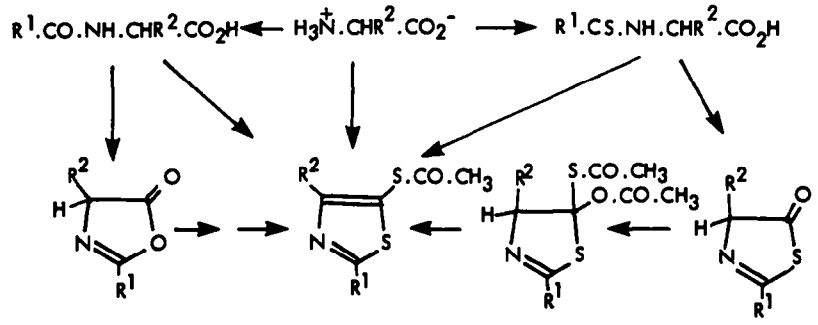


19

Scheme 14.

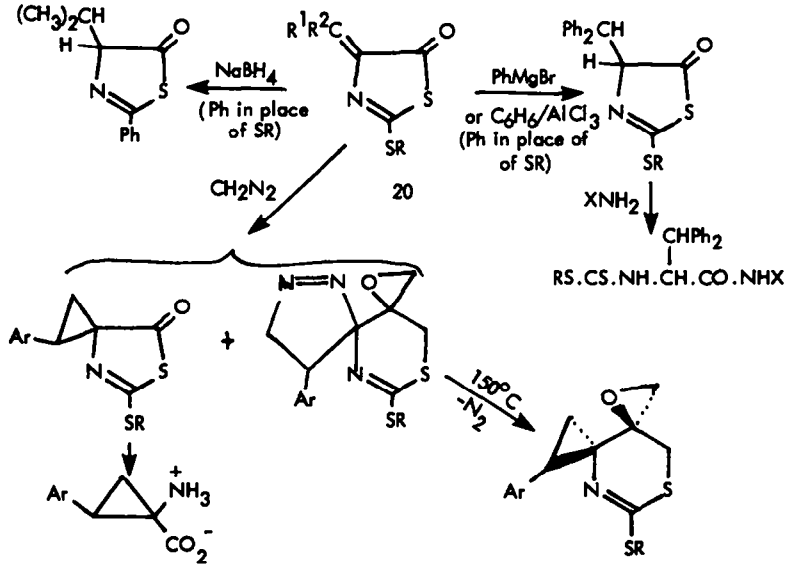
of *N*-thiobenzoyl-*C*-phenylglycine, and a significant factor here is the almost complete adoption of the enol tautomeric form by the "thiazolin-5-one" intermediate (the formation of 4-benzhydryl-2-phenylthiazolin-5-one from the corresponding oxazolin-5-one and thioacetic acid has been described,[27] indicating that the thiazolin-5-one is an intermediate in the overall process leading to 5-acetylmercaptothiazoles). Lurye and Gatsenko[87] believed that the product which they obtained in a similar reaction was 4-benzyl-2-phenylthiazolin-5-one, but this was shown later[85] to be the corresponding 5-acetylmercaptothiazole.

Behringer and Kuchinka[90] showed that 2-acetylamino-thiazolin-5-ones reacted with thioacetic acid to give 5-acetylmercaptothiazoles, but that 2-(benzylthio)thiocarbonyl- and *N*-phenylthiocarbamoylamino-acids did not react.



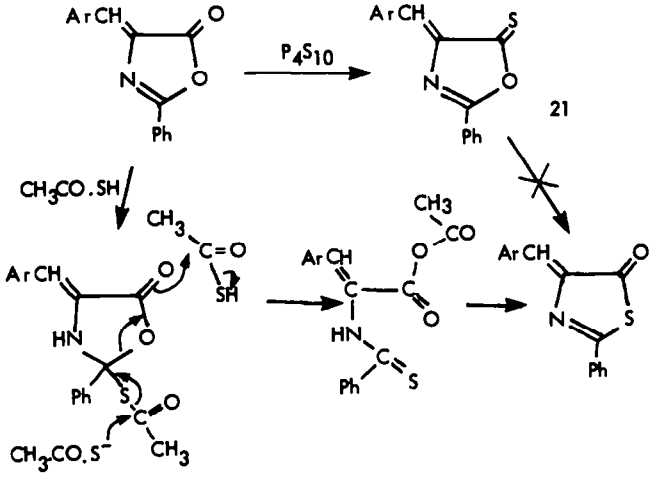
Scheme 15.

Conversion of 2-substituted thiazolin-5-ones into 2,4-disubstituted thiazolin-5-ones. Condensation of 2-phenylthiazolin-5-one with acetone gives the 4-isopropylidenethiazolin-5-one, which on reduction with sodium borohydride gives the 4-isopropyl analogue.[8] Michael addition reactions of 4-alkylidenethiazolin-5-one were studied intensively as part of the penicillin project,[11] and the process was used for the synthesis of unusual amino-acids via the usual 1,4-addition mechanism; for example,[16,17] 2-alkyl 4-benzylidenethiazolin-5-ones **20** yield 4-benzhydrylthiazolin-5-ones with phenylmagnesium bromide from which, by aminolysis, the corresponding amino-acid amides can be obtained (Scheme 16).[16] Filler and Rao[27] have described the same general approach to amino-acids, but in an exceptional example,[89] ring-opening by a Grignard reagent is considered to precede 1,4-addition, to account for the formation of an α-thiobenzamido-ketone Ar·CHR·CH(NH·CS·Ph)·CO·R from 4-benzylidene-2-phenylthiazolin-5-one.



Scheme 16.

Access to 4-alkylidenethiazolin-5-ones is best gained through the Erlenmeyer-type condensation reaction of a thiazolin-5-one with an aldehyde or ketone, but an alternative route involving the treatment of the analogous alkylideneoxazolin-5-ones with thioacetic acid has been extensively illustrated,[86,90] again because of the relevance these ring systems were believed to have to the structure of penicilin[11] (for a recent example, supplementing many earlier examples of the formation of 4-alkylidenethiazolin-5-ones from penicillins, see Ref. 90a). The deceptively simple isosteric S–O exchange reaction involved is not a matter of thionation of the carbonyl group followed by rearrangement, since 4-alkylidene-oxazolin-5-thiones (21; Scheme 17) formed using P_4S_{10} do not rearrange during work-up. A mixed thiocarboxylic anhydride formed from the oxazolin-5-one through ring-opening with thioacetic acid is possibly a key intermediate in the process, but an alternative route involving addition of thioacetic acid at C-2, followed by ring-opening, is more likely.



Scheme 17.

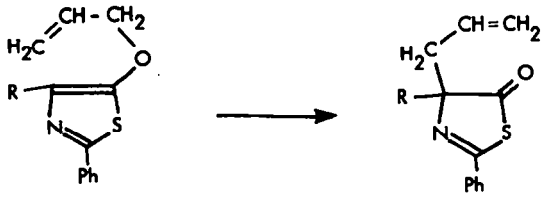
Reactions leading to 4,4-disubstituted thiazolin-5-ones; oxidative dimerization of thiazolin-5-ones. Rearrangement of 5-(2′-alkenyloxy)thiazoles, formed from a thiazolin-5-one, an allylic halide, and base, places allyl substituent on C-4 through a Claisen rearrangement (Scheme 18).[90b] A single example of this reaction was reported as a detail in a paper covering the consecutive Claisen and Cope rearrangements of analogous 5-(2′-alkenyloxy)oxazoles, but unpublished results[41] can be mentioned which support the presumption that there is a general process illustrated here.

An alternative approach to 4,4-disubstituted thiazolin-5-ones is involved in the addition of diazomethane to a 4-arylidenethiazolin-5-one (Scheme 16). As described in the preceding section, these compounds behave as normal α,β-unsaturated ketones in undergoing 1,4-addition (Michael addition), but alternative products are reached through diazomethane addition, depending on the reaction conditions.[91] There is an interesting contrast again, with 4-arylideneoxazolin-5-ones, which yield only the corresponding ring-expansion products (the 1,3-oxazines) with diazomethane.[92]

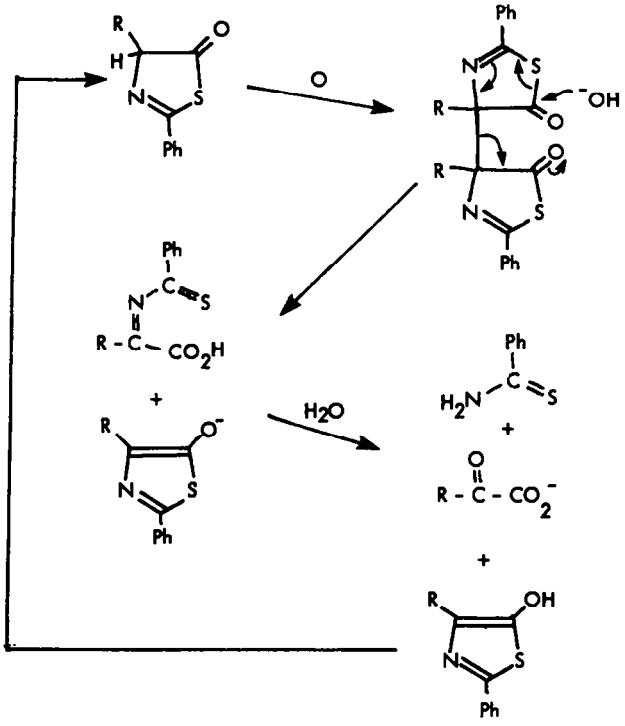
Any substitution reaction placing a substituent at C-4 in these ring systems has a particular importance in that the hydrolysis of the product yields the corresponding α-amino-acid. The synthesis of cyclopropane-based α-amino-acids from 4-arylidenethiazolin-5-ones has emerged from these studies[93] (Scheme 16). Rae and Umbrasas[37] attempted to synthesise a 2,5-epidithiopiperazine-3,6-dione as a model for the condensed amino-acid system which is a characteristic feature of the structures of fungal metabolites of the sporidesmin and gliotoxin types. The synthetic challenge amounts to the construction of an α-*S*-substituted amino-acid, and the conversion of a 2,4-disubstituted thiazolin-5-one into the 4-acetylthio-analogue via the 4-chloro-4-substituted thiazolin-5-one (prepared using sulphuryl chloride) was found to be feasible. However, this was a less serviceable route than the corresponding use of an oxazolinone since selective hydrolysis of the thiazolinone ring in the presence of the thiolacetate grouping was not possible.[37]

Oxidative dimerization of a 2,4-disubstituted thiazolin-5-one is easily brought about by iodine.[49] Indirect evidence that the same process is brought about by aeration in aqueous dioxan has been derived from the demonstration[94] that the blue pigment trichotomine is formed under physiological conditions from 2-phenyl-4-(2′-carboxyethyl)thiazolin-5-one and L-tryptophan in this solvent during a period of

several days. It was shown[95] that the pigment is formed from L-tryptophan and α-ketoglutaric acid under these conditions, and the formation of the keto-acid from the thiazolin-5-one depends on the oxidation of the thiazolinone to the dimer, and its conversion into the keto-acid through the hydrolysis mechanism established for corresponding oxazolinone dimers (Scheme 19).



Scheme 18.



Scheme 19.

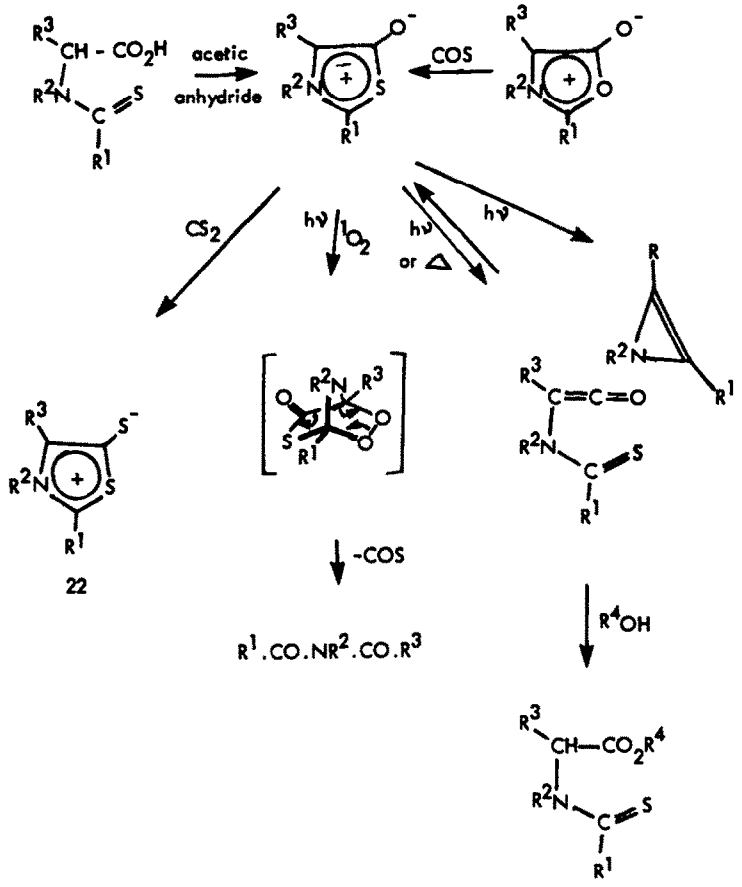
Unequal amounts of meso- and (±)-diastereoisomeric forms are produced through iodine oxidation of a 2-alkylthio-4-benzylthiazolin-5-one.[49]

Mesoionic thiazolin-5-ones

Brief coverage of the recent literature on these compounds deserves a place in this Report, so that the behaviour of tautomeric thiazolin-5-ones can be set in context against that of one of their contributing forms.

Cyclization reactions analogous to those used for the synthesis of members of the tautomeric series have been illustrated in several papers.[96,97] In contrast, conversion of a mesoionic oxazolin-5-one (a "münchnone") with carbonyl sulphide (Scheme 20)[98,99] has no parallel in the synthesis of tautomeric thiazolin-5-ones; the mesoionic sulphur analogue is formed analogously with carbon disulphide,[85] and the same compound is formed from an *N*-thioacyl-*N*-alkylamino-acid and thioacetic acid.[85]

The main reactions of mesoionic thiazolin-5-ones are cycloaddition,[100] and substitution reactions for the special case of the 4-unsubstituted compounds.[96] Cycloadducts corresponding to those illustrated in earlier sections of this Report (Schemes 12 and 13) are formed under mild conditions[100] compared with the conditions reported for analogous reactions with münchnones.[98,99] Greater stability of the cycloadducts formed by mesoionic thiazolin-5-ones, compared with oxazolin-5-ones, has been found in a



Scheme 20.

number of cases. The mesoionic thiazolin-5-thione (22) is less reactive towards dipolarophiles than its exocyclic oxygen analogue, but the expected reaction products are obtained with phenyl isothiocyanate and with dimethyl fumarate,[100] thus over-riding the conclusion[98,99] that these thiones are devoid of cycloaddition reactivity.

THIAZOLIN-4-ONES (2)

A parallel can be found with the thiazolin-5-one series, in the non-typical behaviour of 2-substituted thiazolin-4-ones compared with their 2,5-disubstituted homologues.

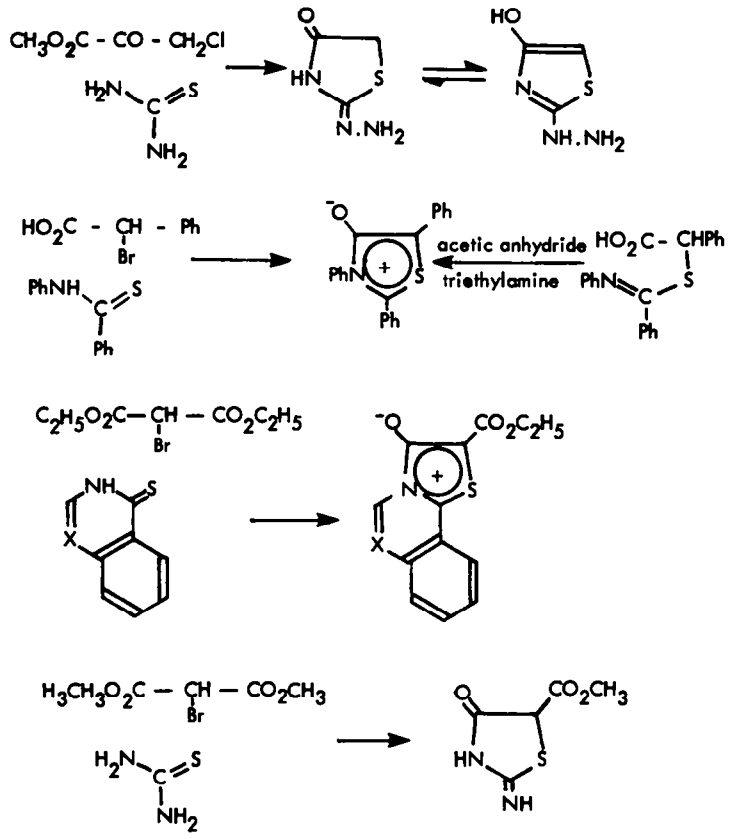
Although the importance of the thiazolin-5-ones, due to their involvement in the chemistry of amino-acids and peptides, is not shared with the thiazolin-4-ones, there are applications in synthesis and an isolated example of physiological importance in the dependence of firefly bioluminescence on the formation of an excited thiazolin-4-one. The same interest, in tautomeric behaviour and in cycloaddition reactivity, has been committed to the literature dealing with thiazolin-4-ones during the last few years.

Preparations of thiazolin-4-ones (2)

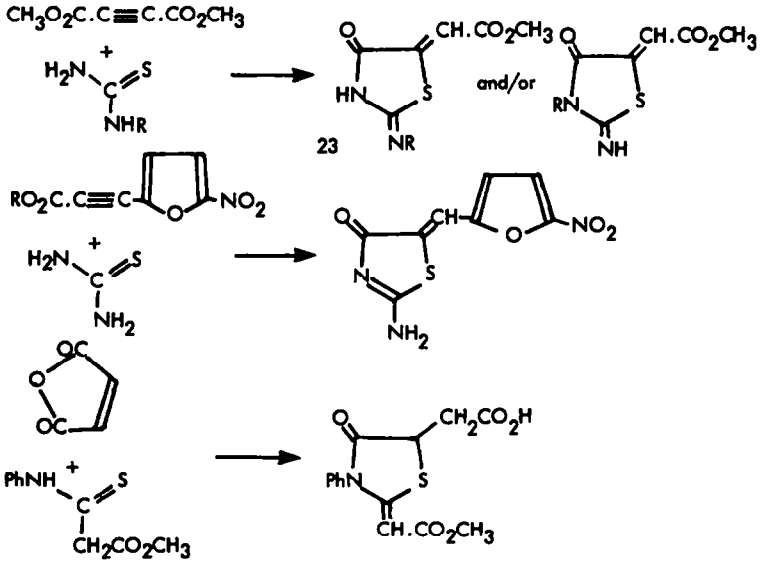
Many more routes have been shown to exist to thiazolin-4-ones than to their thiazolin-5-one isomers, and these are summarised in Schemes 21–28.

Synthesis from thioamides and α-halogenocarbonyl compounds. This variant of the Hantzsch thiazole synthesis has been widely used (Scheme 21),[101–106] and also succeeds with dithiocarbamic acids and dithiocarbamates.

Synthesis from thioamides and α,β-unsaturated carbonyl compounds. The reactions illustrated in Scheme 22 for dimethyl acetylenedicarboxylate[107–109] and for the unsymmetrical alkyne[110] are further examples of the S–C–N + C–CO approach to this ring system. Maleic anhydride can be used,[111] the process then amounting to an addition reaction.



Scheme 21.

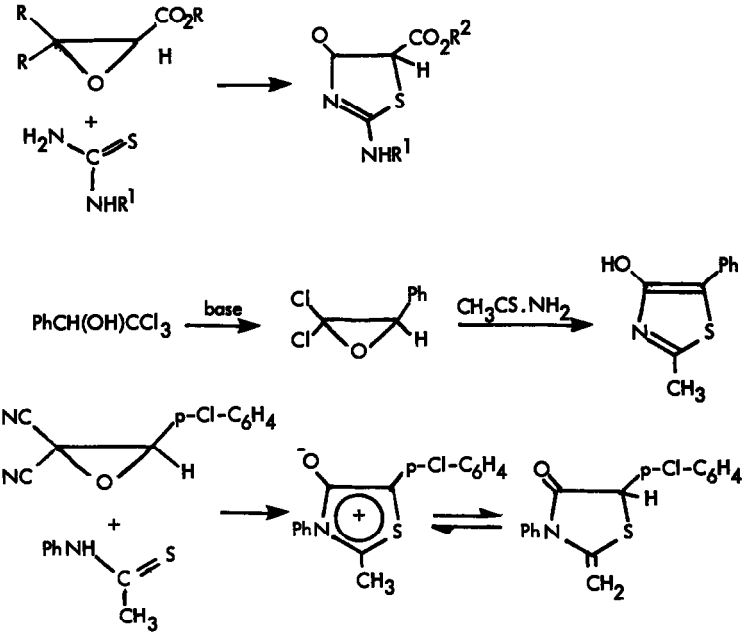


Scheme 22.

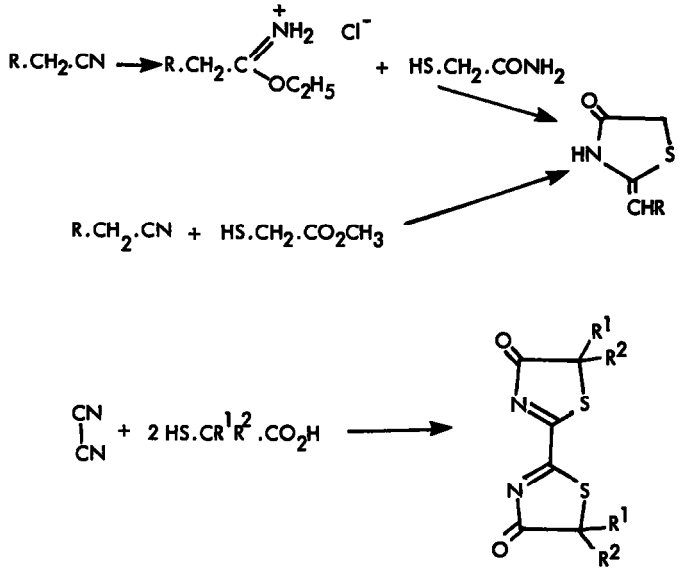
Synthesis from thioamides and oxiranes. Early work[112] demonstrating the use of glycidic esters in thiazolin-4-one synthesis (Scheme 23) through condensation with a thiourea or a dithiocarbamate has been supplemented recently, with the introduction of gem-dichloro-[113] or gem-dicyano-oxiranes[114–117] for the purpose.

Synthesis from α-mercaptoalkanoic acids. This route (Scheme 24)[118–120] also represents the C–N + S–C–CO approach. The use of α-isothiocyanatoalkanoic acids described in the next section is a hidden form of the same process.

Synthesis from α-thiocyanatoalkanoic acids. A crop of papers[121–123] illustrate "one-pot" processes leading to 5-arylidenethiazolin-4-ones (Scheme 25).



Scheme 23.

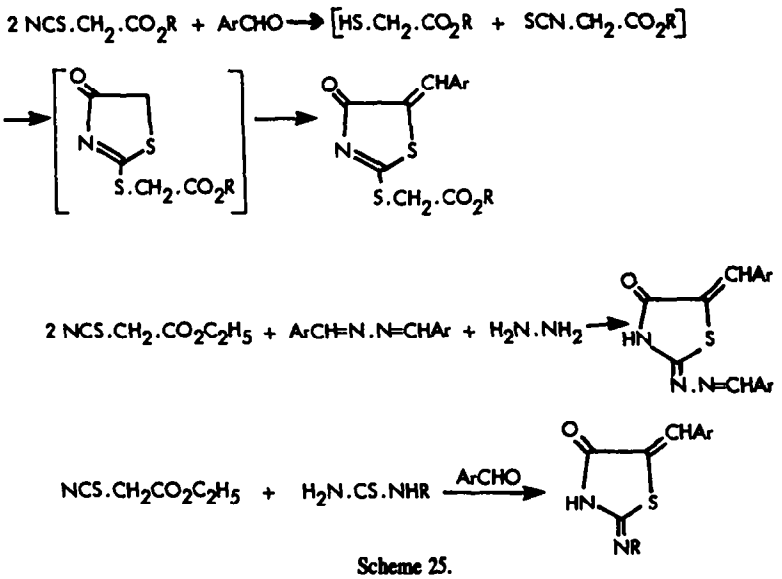


Scheme 24.

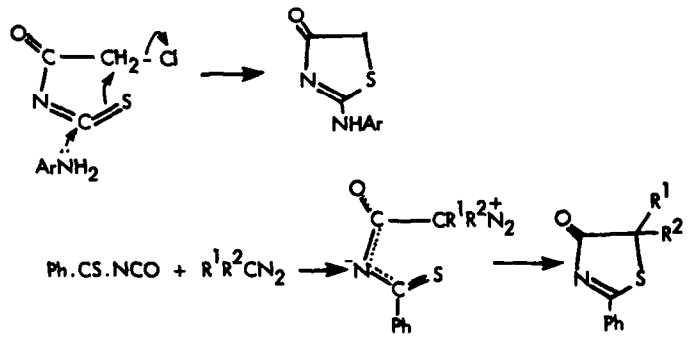
Synthesis from acylisothiocyanates and from thioacylisocyanates. Low yields (10–25%) of 2-anilinothiazolin-4-ones are obtained from the condensation of chloroacetylisothiocyanate $Cl{\cdot}CH_2{\cdot}CO{\cdot}NCS$ with anilines.[124] The 1,4-dipole formed between thiobenzoyl isocyanate and a diazoalkane is smoothly transformed into the corresponding 2-phenyl-4-substituted thiazolin-4-one (Scheme 26).[125]

Synthesis from rhodanines. One of the longest-known heterocyclic systems,[126] most conveniently prepared by the condensation of an isothiocyanate with mercaptoacetic acid, yields the 5-acyl derivative with an acyl chloride and base,[10] or the *S*-alkyl derivative with an alkylating agent (Scheme 27).[10]

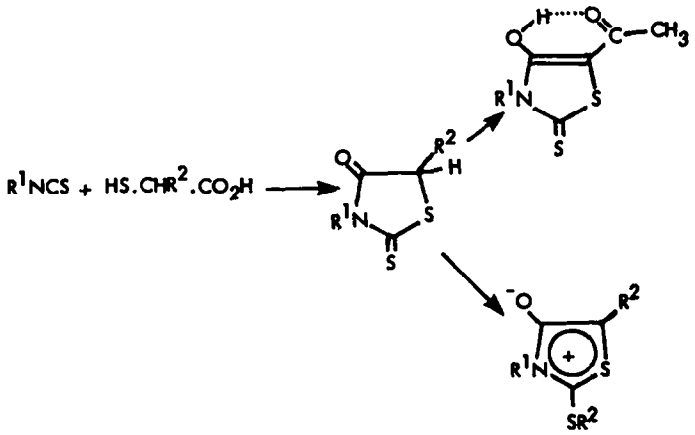
Synthesis in vivo (*oxyluciferin from luciferin*). Oxygenation of firefly luciferin, a 2-benzthiazolylthiazoline-4-carboxylic acid (Scheme 28) is considered to proceed through several steps in yielding a light-emitting thiazolin-4-one[127] (or a radical derived from it[128]).[127–130]



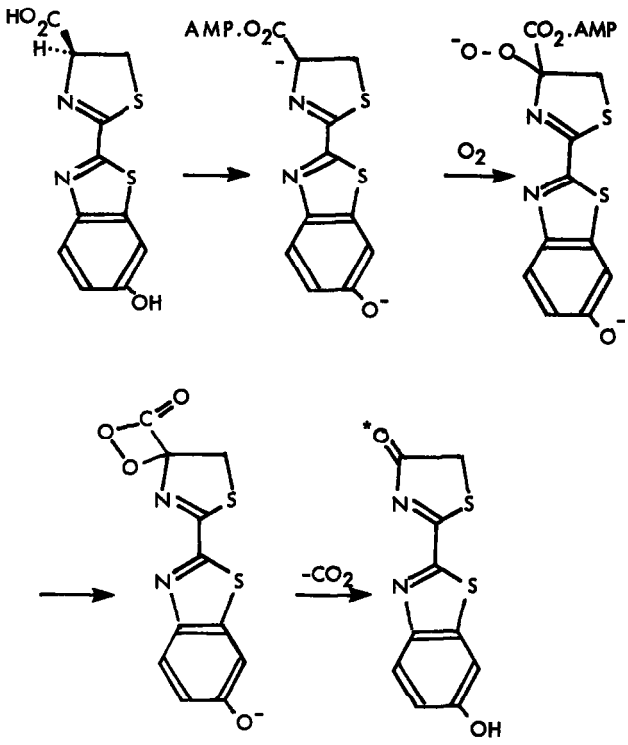
Scheme 25.



Scheme 26.



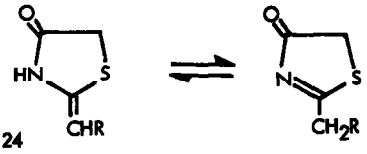
Scheme 27.



Scheme 28.

Tautomerism of thiazolin-4-ones

Relatively little knowledge has been gathered on this aspect of thiazolin-4-one chemistry. Interpretation of physical data and of the course of addition reactions has provided this knowledge, amounting to generalizations that "unlike most 4-hydroxythiazoles, which adopt the keto-form, 2-methyl-5-phenylthiazolin-4-one exists as the enol";[113] and converse statements asserting the general predominance of the enol form in this series,[131] based on the intepretation of *N*-(α-alkoxyalkyl)ation by vinyl ethers as an ene reaction involving the enol form of a thiazolin-4-one. Reactions of thiazolin-4-ones include cycloaddition to dimethyl fumarate,[132] thus indicating the existence of the mesoionic tautomer in solutions of thiazolin-4-ones. 2-Phenylthiazolin-4-one exists in acetone as a 50:50 keto:enol mixture, while in dimethyl sulphoxide it is 90% enolized.[133] Oxyluciferin adopts predominantly the enolic form, in solution in acetone or in dimethyl sulphoxide as well as in the solid state.[130] In the thiazolin-5-one series, the 4-unsubstituted compounds tend to adopt the keto-tautomeric form preferentially, whereas the 5-unsubstituted thiazolin-4-ones clearly favour the enolic form unless a doubly-bonded hetero-atom or singly-bonded hetero-atom substituent (=S, =O, =NR; -SR, -OR, $-NR^1R^2$) is placed at C-2. This is emphasised by the fact that reaction of rhodanine (2-thiono-thiazolidin-4-one) with an acyl halide and an organic base gives the 5-acyl derivative, and not the enol ester.[10] However, the nature of the 5-substituent in a 5-substituted thiazolin-4-one has an important influence on the keto:enol equilibrium, as is clearly shown in just this example;[10] the introduction of a 5-acetyl group into a rhodanine switches the tautomeric equilibrium in favour of the 2-thiono-4-hydroxythiazoline, as demonstrated by UV and NMR data.



24

Scheme 29.

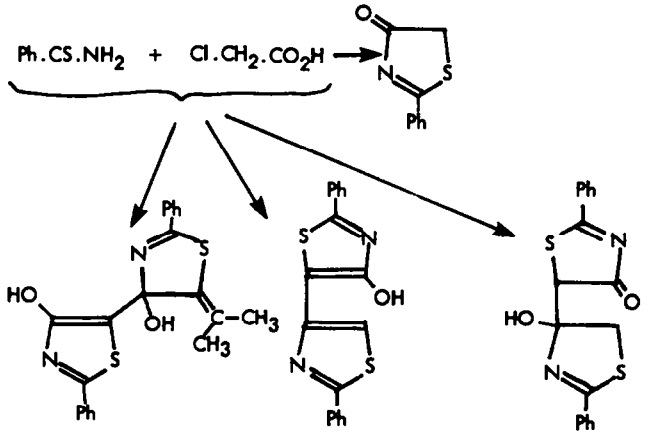
The double tautomerization of 2-hydrazinylthiazolin-4-one shown in Scheme 21 has been illustrated in Ref. 101, and the analogous tautomeric 2-alkylthiazolin-4-one (Scheme 29) has been shown[118] to exist as the 2-alkylidenethiazolin-4-one (24) since two geometrical isomers can be isolated.

X-Ray crystal analysis studies have been reported for thiourea-dimethylacetylenedicarboxylate condensation products,[108] revealing the all-exocyclic unsaturation pattern shown in compound (23) in Scheme 22, and for 2-amino-4-carboxymethylthiazolin-4-one, in which partial double bond character in the C-2–S and bonds has been revealed.[134] 5-Phenyl-2-phenylmethylaminothiazolin-4-one exists as such in the solid state.[135]

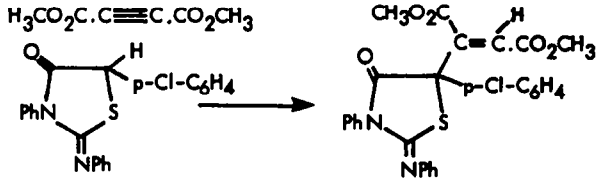
Reactions of thiazolin-4-ones

Specific reactions of mesoionic thiazolin-4-ones are reviewed briefly in the following section, providing a perspective for the behaviour of the tautomeric thiazolin-4-ones described in this section. The various addition, substitution, and oxidation reactions undergone by analogous thiazolin-5-ones are all represented (Schemes 31–33), but the novel *N*-(α-alkoxyalkyl)ation procedure displayed in Scheme 32 has no parallel, for structural reasons, in the thiazolin-5-one series.

A range of dimeric products may be obtained in attempted preparations of 2-substituted thiazolin-4-ones unless experimental procedures are carefully followed, due to the high reactivity of the "activated methylene group" (C-5).[136] The confused situation concerning the correct labelling of samples prepared in attempts to synthesise 2-phenylthiazolin-4-one was resolved by Gronowitz *et al.*,[137] who have assigned structures (Scheme 30) to preparations reported earlier.[138]



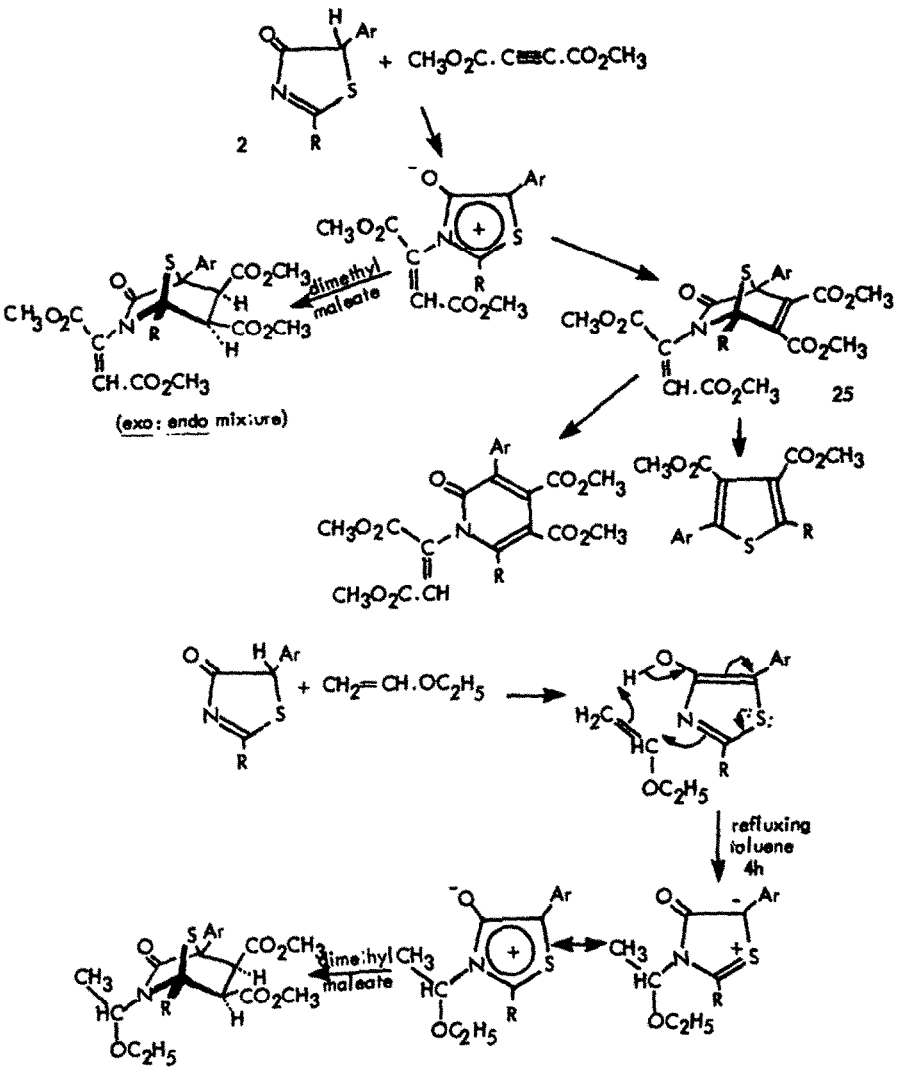
Scheme 30.



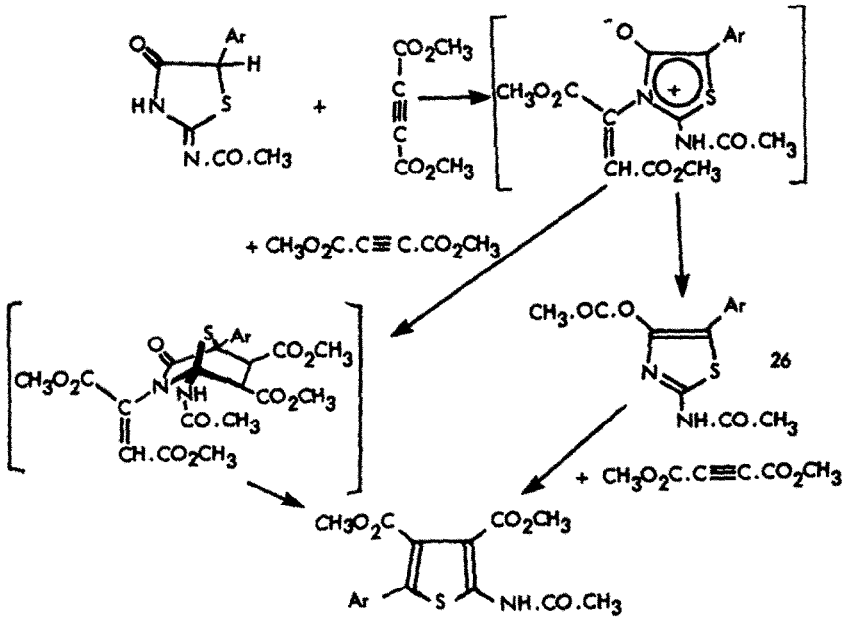
Scheme 31.

2-Phenylthiazolin-4-ones yield 4-acyloxy-2-phenylthiazoles through reaction with an acyl anhydride in the presence of pyridine.[130]

Addition reactions. Michael addition has been reported for an *N*-phenyl-2-phenyliminothiazolidin-4-one to dimethyl acetylenedicarboxylate in benzene in the presence of triethylamine (Scheme 31).[131] The 1:2-cycloadduct **25** (Scheme 32) formed between dimethylacetylenedicarboxylate and a 2,5-di-arylthiazolin-4-one **2** is considered to arise through an ene reaction resulting in *N*-alkenylation, followed by cycloaddition of the resulting mesoionic thiazolin-4-one to a second molecule of the alkyne.[131] The *N*-alkylation step is also brought about when ethyl vinyl ether, dimethyl maleate, and the 2,5-diarylthiazolin-4-one are reacted in refluxing toluene during 4 hr,[131] the fact that the vinyl ether is not a good dipolarophile accounting for the particular course of the reaction in this case. In the absence of the vinyl ether, there is no reaction between dimethyl maleate and the thiazolinone in the same reaction time, but after some 15 hr the expected exo:endo mixture is obtained. The greater reactivity of mesoionic thiazolinones compared with tautomeric thiazolinones implied in these studies is consistent with other results, particularly the behaviour of the corresponding thiazolin-5-ones. The mechanism for the formation of the acetoxythiazole (**26**) in Scheme 33 has not been established, though in view of the low yields and the easy formation of enol acetates from many thiazolinones, it is likely that the starting material acts as the acetylating agent.



Scheme 32.



Scheme 33.

The cycloaddition process illustrated for tautomeric thiazolin-4-ones in Scheme 32 is the main reaction characterizing their mesoionic homologues.

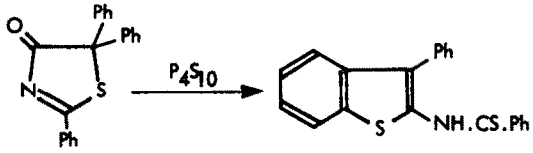
Other reactions of thiazolin-4-ones. Specific reactions with mechanistic interest include the C-5–S cleavage involved in the conversion of 2,5,5-triphenylthiazolin-4-one into a benzothiazole (Scheme 34),[139] and the C-2 addition–elimination reaction of a rhodanine shown in Scheme 35.[140]

Mesoionic thiazolin-4-ones

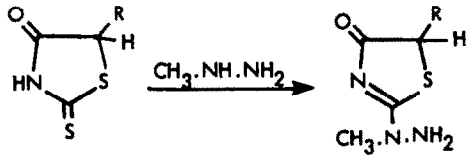
Preparations and cycloaddition reactions have already been referred to, though the examples given (formation of thiophens and pyridones) illustrate only part of the range of cycloaddition studies which have been reported.

Further indications of the greater stability of the cycloadducts formed by mesoionic sulphur heterocycles, compared with their oxygen analogues, are provided in the thiazolin-4-one series. 2,3,5-Triphenylthiazolium-4-olate gives a 78% yield of the cycloadduct with benzyne, which decomposes (Scheme 36) through one of two routes depending on the conditions.[141] Many examples of reactions following the same general pathway have been described, mainly by three research groups,[131,142] including comparative studies with other mesoionic systems.[143] Cycloaddition reaction studies of a selenium analogue show it to be a reluctant dipolarophile.[103]

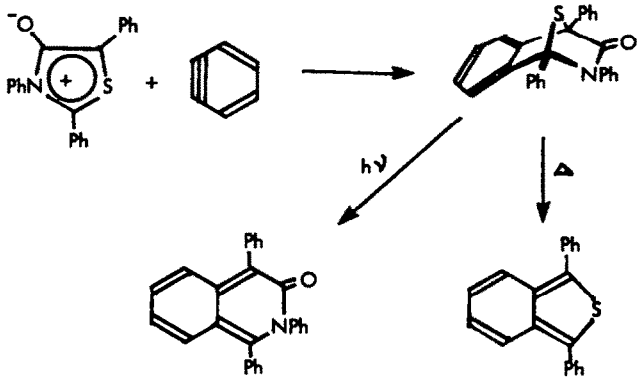
The novel photorearrangement shown in Scheme 37[144] illustrates the continuing theme of interesting and untypical reactions shown by hetero-atom substituted thiazolinones. The potential for this process in azetidinone synthesis has been realized;[10,145] photo-induced ring contraction of mesoionic thiazolin-4-



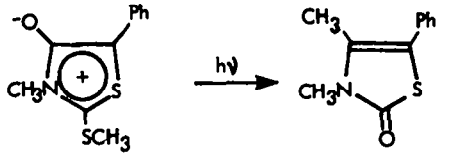
Scheme 34.



Scheme 35.



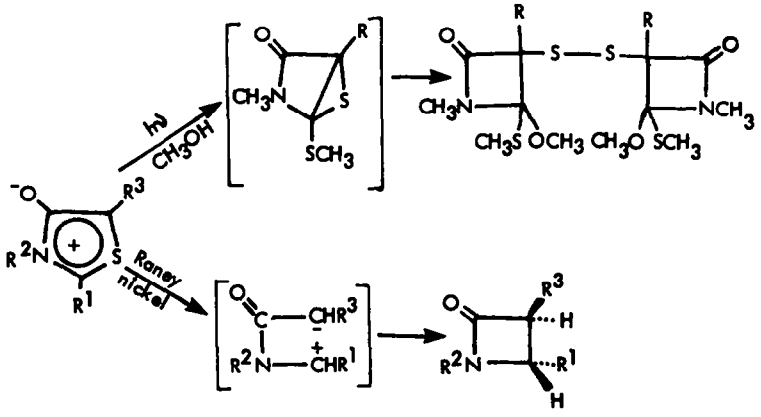
Scheme 36.



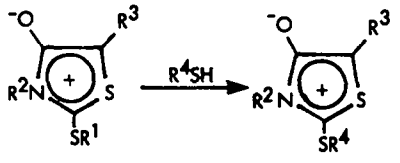
Scheme 37.

ones in methanol has been demonstrated (Scheme 38),[10] but yields of methoxy-substituted azetidinones are low (21–25%) and the alternative rearrangement product shown in Scheme 37 is also formed (14%).[10] There is the basis in this reaction for a synthesis of 6-alkoxycephalosporins, but the relative inaccessibility of mesoionic 5-amino-thiazolin-4-ones and the low yields of ring-contracted products suggest that the route is not particularly promising.[10] The same ring-contraction, but with extraordinary stereospecificity, is induced by treatment of a 2,3,5-triarylthiazolin-4-one with Raney nickel;[145] of a variety of intermediates, the zwitterion is considered to be most consistent with the stereospecificity and the influence of triphenylphosphine on the cis/trans ratio.[145]

Conversion of one mesoionic 2-alkylthio-thiazolin-4-one into another (Scheme 39) illustrates a C-2 addition-elimination sequence in this series.[10]



Scheme 38.



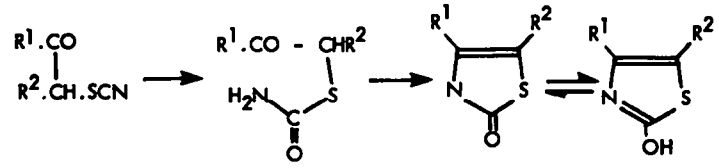
Scheme 39.

THIAZOLIN-2-ONES (1)

These, the longest-known tautomeric thiazolinones, receive the briefest survey in this Report. Two forms, corresponding to amide ⇌ imidol tautomers, are represented in this series, and no mesoionic structure accommodating charge delocalisation involving all ring atoms is possible.[3,146] Except for isolated examples, the chemistry is relatively routine. Sulphur analogues (thiazol-2-thiones) have been at least as fully studied over the years, and mention is made of these where gaps in thiazolin-2-one chemistry seem to exist.

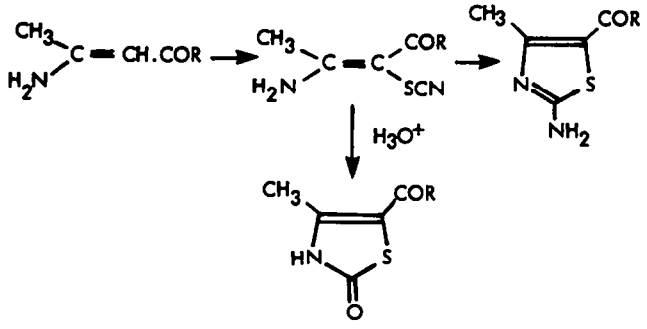
Preparations of thiazolin-2-ones

Rearrangement of α-thiocyanato-alkyl ketones (Scheme 40) is the major route to thiazolin-2-ones.[147] The reaction can be brought about for the simplest structures in aqueous solutions containing acid or base,[148,149] but alternative solvents and a modified reaction intermediate are conceivable[150,151] (e.g. ethanol saturated with hydrogen chloride) for substrates insoluble in water. This route can be directed towards thiazolin-2-imines[149] through the use of amines (Scheme 41); cyclization of enamines derived from α-thiocyanato-alkyl-ketones gives thiazolin-2-ones in acid solutions, or thiazolin-2-imines in aqueous alkali.[152]



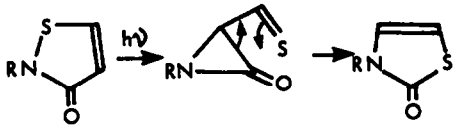
Scheme 40.

Thiazolin-2-thiones can be prepared through a variant of the Hantzsch synthesis, in which an α-halogenocarbonyl compound is condensed with ammonium dithiocarbamate.[153]

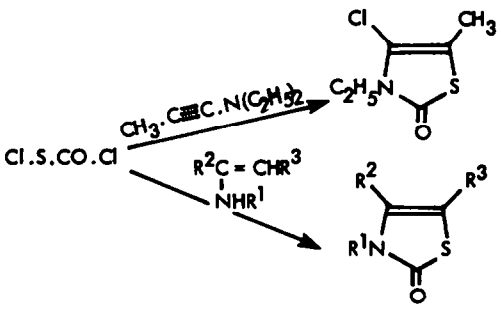


Scheme 41.

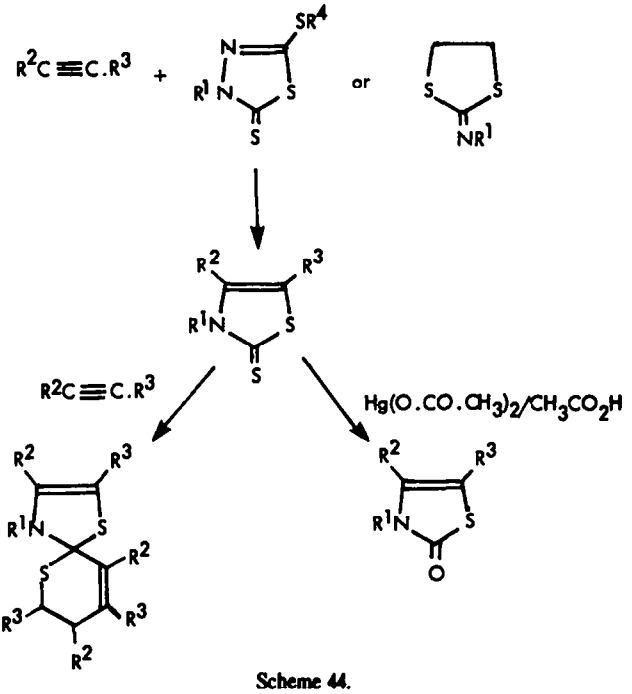
Photorearrangement of an *N*-alkylisothiazolin-5-one gives the corresponding thiazol-2-one (Scheme 42). Members of the *N*-substituted series are available from chlorocarbonylsulphenyl chloride (Scheme 43),[155,156] and are formed in small amounts in dimethylsulphoxide solutions of 4,4-dialkylthiazolium bromides.[157] Cycloaddition reactions leading to thiazolin-2-thiones (Scheme 44)[158] have been described, this Scheme also states the conditions recommended for the conversion of a thiazolin-2-thione into the 2-one.[158] Routes to thiazolin-2-thiones employing isothiocyanates are summarised in Scheme 45.[159,160] The rearrangement of a 5,5-disubstituted rhodanine into a tautomeric thiazolin-2-thione (Scheme 46) is notable.[161] Conversion of thiazolidin-2,4-dione into 4-chloro-5-formylthiazolidin-2-one with phosphorus oxychloride in *N*,*N*-dimethylformamide[165] illustrates another approach to thiazolin-2-ones.



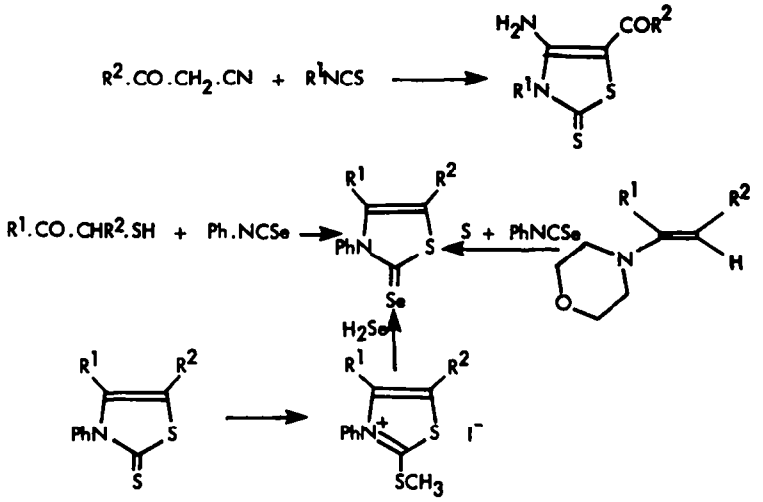
Scheme 42.



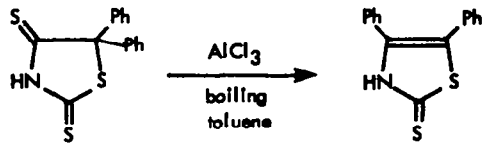
Scheme 43.



Scheme 44.



Scheme 45.



Scheme 46.

Tautomerism of thiazolin-2-ones

The restricted range of tautomeric possibilities open to thiazolin-2-ones, compared with the other thiazolinones, limits the interest in this topic to comparisons with other amide systems, and a substantial amount of work continues to be reported at this level, based on spectroscopic studies.[162] Only selective coverage of this area is intended here.

2-Hydroxythiazoles undergo conventional reactions of phenols,[147] surviving 5-substitution by electrophiles (e.g. sulphonation with fuming sulphuric acid) and thereby showing the high chemical stability which is typical of 2,4-dialkylthiazoles. While the thiazole-2-thiol tautomer is favoured in alkaline solution for the parent member of the thiazolin-2-thione series,[163] as for the 2-hydroxythiazoles, most thiazolin-2-ones exist as such in the solid state[162] (although zwitterionic formulations are important contributing forms[164]). The *N*-protonated thiazolin-2-thione exists in strongly acidic aqueous solutions of 4,5-disubstituted thiazolin-2-thiones,[163] and while 4,5-dimethylthiazolin-2-thione exists as a thiol-thione mixture in the solid state and in aprotic solvents, thiazolin-2-thione itself and its 4-methyl- and 4-phenyl homologues exist as such in these media.[163]

Reactions of thiazolin-2-ones and thiazolin-2-thiones

The main reactions, since cycloaddition processes are excluded, are alkylation at nitrogen and at the exocyclic 2-substituent (Michael-type addition of a 4,5-disubstituted thiazolin-2-thione to electron-deficient alkenes CH_2=CHX in the presence of base gives a mixture of *N*-alkylthiazolin-2-thione and 2-alkylthiothiazole[166]) and ring-opening.[167] While 2-hydroxy-, 2-amino-, 2-methylamino- and 2-dimethylamino-4-methylthiazole are unaffected by treatment in liquid ammonia with dissolved sodium, the 2-mercapto analogue gives the di-anion $^-$S·CH=N·CMe=CH·S$^-$.[167] This is probably a reflection of the formation of the exocyclic sulphur-centred radical anion from which the cleavage is initiated,[167] while the corresponding intermediate is not formed in the 2-hydroxy- and 2-amino- series.

THIAZOLIDIN-2,5-DIONES (5)

These compounds show all the reactions of thiazolin-5-ones which exist mainly in the keto-form, although there are four possible tautomers of the keto-enol type. These compounds are therefore effective aminoacylating agents and the main features of interest in their chemistry are in synthesis of amino-acids and peptides. Their oxazolidine analogues are important in the synthesis of polypeptides and poly(α-amino-acid)s, and the predominance of the di-keto tautomeric form in these compounds and the structural resemblance to a carboxylic acid anhydride, has led to the adoption of the name "*N*-carboxylic anhydride" for these compounds. This has been carried over to the thiazolidine analogues, which become "*N*-thiocarboxylic anhydrides"[169] or "*N*-carboxy-thioanhydrides".[51]

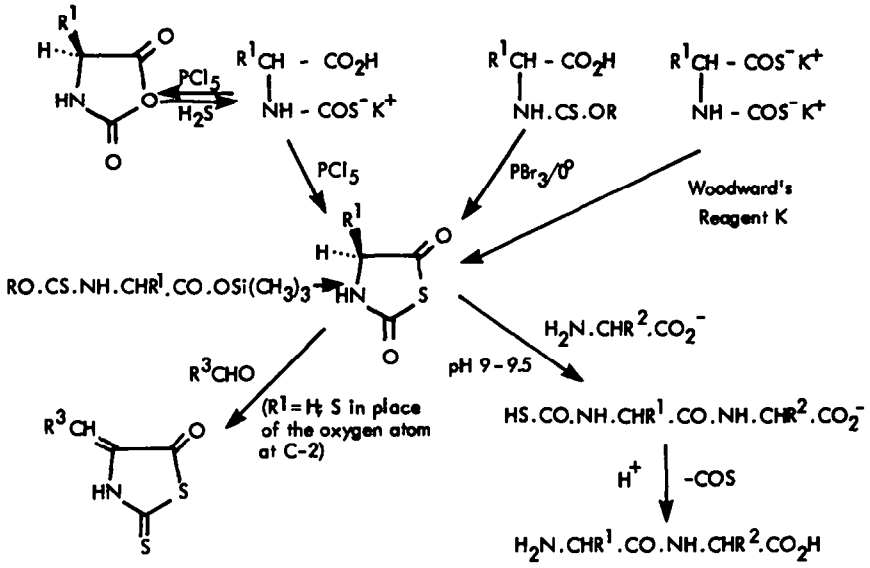
Preparations of thiazolidin-2,5-diones and 2-thionothiazolidin-5-ones

The cyclization of an *N*-alkoxythiocarbonyl-α-amino-acid with acid, or under conditions where acid is liberated by the interaction of the reagent with the carboxyl group of the substrate, leads to the thiazolidin-2,5-dione by cleavage of the alkoxy group in the initially-formed 2-alkoxythiazolin-5-one. Phosphorus tribromide is the recommended reagent for the cyclization reaction,[169] leading to crystalline, optically-pure thiazolidin-2,5-diones from L-amino-acids; thionyl chloride is also effective but tends to lead to oils as reaction products.[169] The preparation can be conducted in separate steps, employing dicyclohexylcarbodi-imide or acetic anhydride for the cyclization, and using hydrogen chloride in benzene for alkyl-oxygen fission.[51] Racemisation occurs during the 2-alkoxythiazolin-5-one isolation procedure in the two-step route, rather than at the alkyl-oxygen fission stage, since representative thiazolin-2,5-diones are not racemized in contact with HCl[169] (strangely, contact with HBr does cause some loss of optical activity[169]).

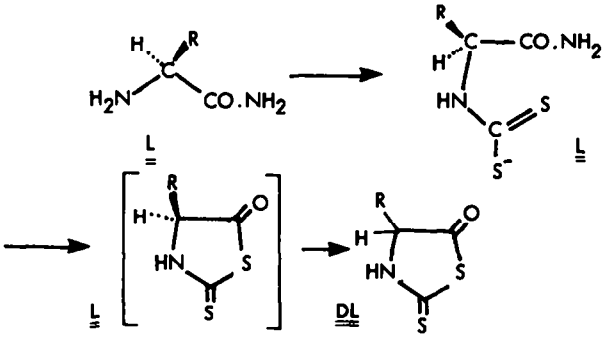
The use of alkoxythiocarbonylamino-acid trimethylsilyl esters has been advocated for the synthesis of thiazolidin-2,5-diones under anhydrous conditions, using phosphorus tribromide as cyclization agent.[170] Alternative routes are shown in Scheme 47.[169]

Corresponding 2-thionothiazolidin-5-ones are prepared by cyclization of thiocarbamic acids formed between amino-acid amides and carbon disulphide (Scheme 48).[18-20,32,33] Crystalline products obtained in this way from L-amino-acid amides are racemic, in contrast with thiazolidin-2,5-diones formed analogously under acid conditions. Several papers appeared, extending the work of the penicillin project on this ring system, and describing their use in peptide synthesis and stepwise degradation.[32-34] The currently-used preparative methods[169] are based on the work described in the earlier literature.[34]

α-Isothiocyanato-alkanoic acids exist in equilibrium with 2-thiono-oxazolidin-5-ones, which do not show, through their reactions, any tendency to isomerise into thiazolidin-2,5-diones.[171]



Scheme 47.



Scheme 48.

Tautomerism of thiazolidin-2,5-diones and 2-thionothiazolidin-5-ones

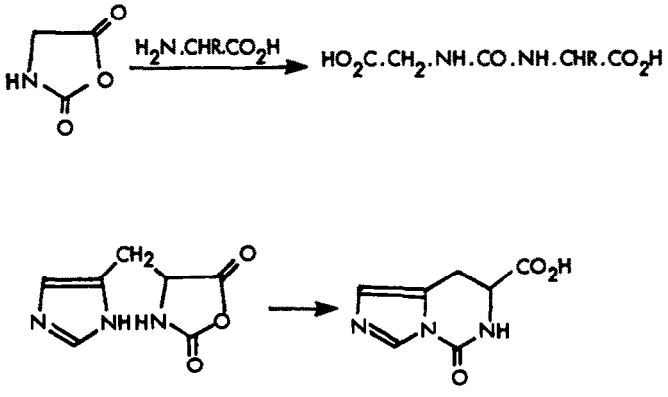
The optical stability of thiazolidin-2,5-diones in solution is less than that of corresponding oxazolidin-2,5-diones,[169] but nevertheless is sufficiently high that their use in peptide synthesis can lead to optically-pure products when aminolysed in aqueous reaction media at pH 10.[169] The tendency towards enolization shown by certain thiazolin-5-ones is therefore almost extinguished in these compounds, which extend the trend towards the predominance of the keto-tautomeric form which is initiated by replacing a 2-alkyl- or -phenyl- substituent by an alkoxy-substituent. A 2-hydroxy group would be expected to have a similar influence to an alkoxy-group, if the inductive effect of the 2-substituent controls the keto-enol equilibrium,[51] but infrared spectroscopic data[51] indicate the presence of a 2-keto-substituent in this series, both for solid samples and for solutions in polar solvents. By analogy, both amide and imidate moieties involving positions 2 and 3 of a thiazolidin-2,5-dione are capable of stabilizing the keto-tautomer involving positions 4 and 5, to an extent greater than resonance stabilization which should be expected to operate for the fully enolized form.

2-Thionothiazolidin-5-ones are commonly depicted as such, e.g. **18**, but more correctly as 2-mercaptothiazolin-5-ones when drawn to illustrate their applications in synthesis.[172] The greater propensity towards the thiolimidate form, which contrasts with the behaviour of the thiazolidin-2,5-diones, may account for the greater tendency of 2-mercaptothiazolin-5-ones to undergo racemization. Optically-active 4-(p-hydroxybenzyl)-2-mercaptothiazolin-5-one is completely racemized after 2–3h in solution in methanol. An identical solution containing 0.1 equivalents of hydrogen chloride shows a much slower racemization rate and, surprisingly, racemization was extremely slow in ethyl acetate as solvent.[18]

Reactions of thiazolidin-2,5-diones and 2-thionothiazolin-5-ones

Ring cleavage by nucleophiles, and condensation reactions involving the "active methylene group" in the 4-unsubstituted compounds, are the main reactions of these compounds, as for other thiazolin-5-ones (Scheme 47). The particular nucleophilic cleavage reaction with considerable value in synthesis is aminolysis by an amino-acid or a peptide, leading to a dipeptide or a polypeptide respectively. In contrast to the products formed in this way with other thiazolin-5-ones, thiolcarbamates are relatively unstable, and reaction conditions can be adopted so that the net result of the aminolysis of a thiazolidin-2,5-dione by a peptide is the addition of an amino-acid residue to the *N*-terminus of the peptide. Thus, a "one-pot" stepwise peptide synthesis involving sequential addition of amino-acids as the appropriately 4-substituted thiazolidin-2,5-diones is feasible, and has been investigated as a possible improvement over the analogous use of oxazolidin-2,5-diones.[168]

The use of thiazolidin-2,5-diones in peptide synthesis shows some equality with, or advantages over, the use of oxazolidin-2,5-diones in the cases of glycine and alanine derivatives, where aminolysis proceeds without significant racemization, and in the case of histidine, where a troublesome side-reaction in the oxazolidin-2,5-dione series (shown also in the case of glycine, Scheme 49) is not a problem with the thiazolidin-2,5-dione analogues, since intermediate thiolcarbamates formed from these compounds on aminolysis do not rearrange readily. The compounds shown in Scheme 49 arise via a side-reaction involving a carbamate-isocyanate rearrangement.[169]



Scheme 49.

Optically-pure thiazolidin-2,5-diones are not racemized in contact with HCl, but the mildly basic conditions accompanying aminolysis lead to unacceptably high proportions of unwanted diastereoisomers during peptide synthesis in nearly all cases.[169] An explanation for the higher acidity at C-4 in this series, relative to corresponding oxazolidin-2,5-diones, has been found[169] in the higher resonance energy of hydroxythiazole anions relative to their oxazole analogues. A further relevant factor[169] may be the smaller bond angle strain at the sp^2 C-4 centre resulting from the different geometry of the two ring systems (C–S bonds are longer than C–O bonds). The factor controlling racemization in the thiazolin-5-one series is the nature of the 2-substituent, and the lower bond order of the carbonyl groups in thiazolin-5-ones and thiazolidin-2,5-diones shown by IR spectroscopic studies[173] indicates the greater contribution of canonical forms with high electron density in the ring, compared with oxazolinones.

Condensation of 2-mercaptothiazolin-5-one with aldehydes and ketones, followed by hydrolysis, is a standard route for the synthesis of amino-acids,[172] and is illustrated in Scheme 47. Many condensation reactions of the same type were investigated by Cook *et al.*[14,15] on the basis of the possible relevance of the reaction, and its products, to the chemistry of penicillin.

THIAZOLIDIN-2,4-DIONES (4)

This long-known[174] ring system has sustained a steady trickle of research papers, because of its pharmaceutical potential (low level hypnotic activity, structural similarity with barbiturates). Their sulphur analogues, rhodanines (2-thionothiazolidin-4-ones; the name rhodanic acid is frequently used in the earlier literature for these compounds), isorhodanines (2-oxothiazolidin-4-thiones), and thiorhodanines (thiazolidin-2,4-dithiones) have an even longer history. Further potential uses of these compounds (antiviral properties of rhodanines,[175] metal corrosion inhibition properties of thiazolidin-2,4-dione,[176] for example) are being uncovered.

Nitrogen analogues (2-iminothiazolidin-4-ones) are encountered as intermediates in standard syntheses of these compounds, and have received brief mention earlier in this Report. 2-Iminothiazolidin-2,4-diones continue to be named "pseudothiohydantoins" in *Chemical Abstracts.*

Tautomerism of thiazolidin-2,4-diones and their sulphur and nitrogen analogues

These compounds are named according to their predominant tautomers, i.e. all-exocyclic double bonds, in the preceding paragraphs. Differences in reactions at C-2 and C-4 in thiazolidin-2,4-diones reflect the different environments of the two carbonyl groups (S–CO–NH– vs C–CO–NH–) rather than any significant contribution of an enolic form involving one of these positions. The X-ray structure of 2-imino-5-phenylthiazolidin-4-one[177] reveals the enhanced acidity of the proton at position 3 which is consistent with the structural similarity of a tautomer containing the O=C·NH·C=X moiety with imides, well known as *N*-acids. 2-Aminothiazolin-4-onyl-5-acetic acid is shown by X-ray crystal analysis to adopt the amino-tautomeric form, and not the iminothiazolidinone alternative[134] in the solid state.

Preparations of thiazolidin-2,4-diones and their sulphur and nitrogen analogues

Reactions of thioureas with α-halogeno-acid derivatives[174] or with dimethylacetylenedicarboxylate[178] yield 2-iminothiazolidin-4-ones (Scheme 22) which are easily hydrolysed to the thiazolidin-2,4-diones. α-Isothiocyanatoalkanoic acid amides similarly yield the imines,[179] as do α-isothiocyanatoacylureas.[180] Rhodanines are easily prepared from an α-halogeno-acid and ammonium dithiocarbamate $NH_2{\cdot}CS{\cdot}S^-NH_4^+$,[153] and *N*-substituted rhodanines are formed in the same way from ammonium alkyldithiocarbamates,[181] or through the most frequently-used route, from an isothiocyanate and an α-mercaptoalkanoic acid.[182]

Reactions of thiazolidin-2,4-diones and their sulphur and nitrogen analogues

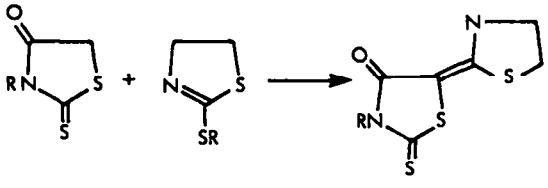
N-Alkylation leading to *N*-alkylaminomethylthiazolidin-2,4-diones is easily accomplished under the usual Mannich reaction conditions.[183] *N*-Ethylation occurs, using iodoethane in solvents of low polarity, while *O*-alkylation involving the carbonyl group at position 2 accompanies *N*-alkylation when the more reactive alkylating agents are used.[184] Alkylation of a rhodanine occurs exclusively on the exocyclic sulphur atom.[10] The fact that enol ethers are not formed in this reaction is consistent with the behaviour of other thiazolinones which are reluctant to enolise. Alkylation of 3,5-disubstituted rhodanines yields the corresponding S-alkylated mesoionic thiazolin-4-ones.[10,144,185]

Sodium borohydride reduction of 3,5,5-trisubstituted thiazolidin-2,4-diones gives the 4-hydroxythiazolidin-2-ones.[186] The same carbonyl group is the site of reaction with 5-substituted thiazolidin-2,5-dione with P_4S_{10}, aminolysis of the resulting 4-thione giving 4-imines.[187]

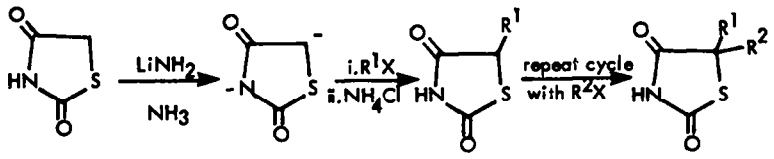
Rhodanines lacking a 5-substituent show the typical "active methylene" condensation reactions undergone by other thiazolinones with this structural feature.

A large number of papers, mostly from Russian laboratories, have appeared describing the incorporation of thiazolidinethiones and dithiones into cyanine dyes, and into other dye structures, based on the condensation of the thiazolidine with an aldehyde or ketone to give the corresponding 5-alkylidenethiazolidin-2,4-dithione or its 2-oxo-analogue.[188] Condensation with a 2-alkylthiothiazoline (Scheme 50) is effected in boiling acetic acid,[188,189] whereas the other aldol-type condensations described employ the usual basic reaction media.

Alkylation of the di-anion of thiazolidin-2,5-dione, created in liquid ammonia (Scheme 51) with lithium amide, yields the 5,5-di-alkylated thiazolidin-4-one; remarkably, no *N*-alkylation was observed,[190] in contrast to results with this compound involving alternative base-induced alkylation procedures.[183]



Scheme 50.

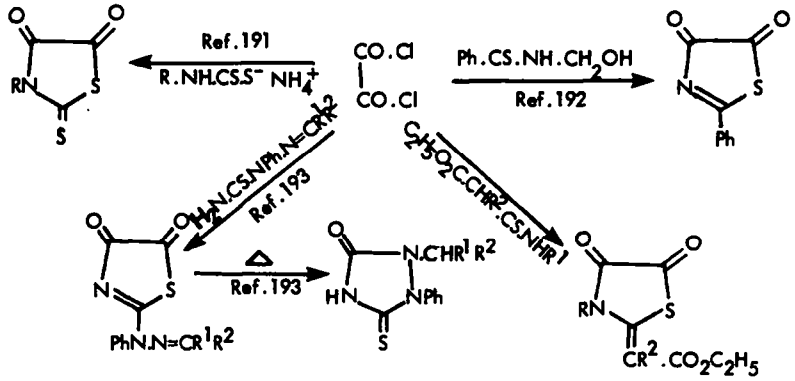


Scheme 51.

THIAZOLIDIN-4,5-DIONES (6) AND THIAZOLIDIN-2,4,5-TRIONES (7)

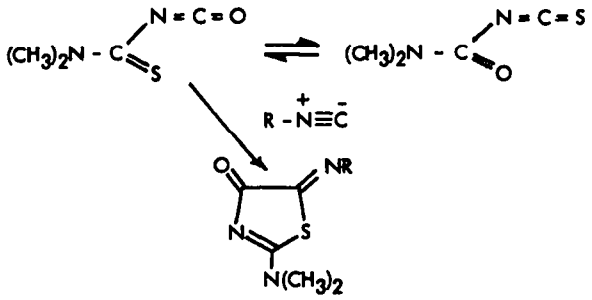
These compounds, although incapable of tautomerism, are given a brief mention in this Report since their reactions may include redox processes through which they are brought to lower oxidation level thiazolinones capable of tautomerism. They are also potential starting materials for alternative syntheses of the other thiazolinones.

The use of oxalyl chloride in different syntheses, based on standard routes to other thiazolinones, is illustrated in Scheme 52.[191-193]

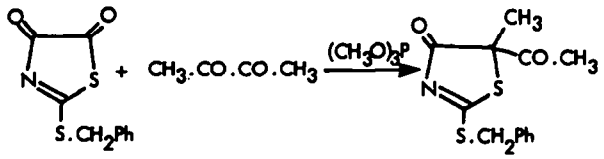


Scheme 52.

Reaction of a thioacylisocyanate with an isonitrile yields a 2-substituted 5-alkylimino-thiazolidin-4-one (Scheme 53).[194] The reaction of a thiazolidin-4,5-dione shown in Scheme 54[195] is a superficial analogy to the reversal of this synthesis.



Scheme 53.



Scheme 54.

Conversion of a 2-hetero-atom substituted thiazolidin-4,5-dione into a thiazolidin-2,4,5-trione seems feasible by analogy with the reactions of analogous thiazolinones, but does not appear to have been described.

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