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Synthesis of Symmetrical 2,2′,4,4′-Tetrasubstituted [4,4′-Bithiazole]-5,5′(4*H*,4′*H*)-diones and Their Reactions with Some Nucleophiles

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Symmetrical 2,2′,4,4′-tetrasubstituted-[4,4′-bithiazole]-5,5′(4*H*,4′*H*)-diones were obtained in high yields by oxidation of 5(4*H*)-thiazolones by $KMnO_4$ in acetic acid. In some cases, the isomeric 2,4′- and 2,2′-bithiazolones were also formed. Results from two crossover reactions were consistent with a free radical mechanism. Four series of thiazolones were prepared, each based on a different substituent at the 2-position; i.e., phenyl, ethoxy, ethyl and ethylthio. The effects of substituents on the isomer distributions of the dehydrodimers indicated that electronic factors were less important than steric factors. X-Ray crystallography established the structure of the dehydrodimer (4*R**,4′*R**)-2,2′-diethoxy-4,4′-dibenzyl-[4,4′-bithiazole]-5,5′(4*H*,4′*H*)-dione. One stereoisomer of 2,2′-diphenyl-4,4′-dimethyl-[4,4′-bithiazole]-5,5′(4*H*,4′*H*)-dione and a mixture of the stereoisomers of 2,2′-diphenyl-4,4′-dibenzyl-[4,4′-bithiazole]-5,5′(4*H*,4′*H*)-dione were treated with nucleophiles. The former gave imide derivatives of α,α′-dehydrodimeric amino acids when the nucleophile was L-alanine ethyl ester or 1-butylamine. The structure of one of the reaction products, (4*R**,5*R**)-2,5-diphenyl-2-thiazoline-4-carboxylic acid piperidylamide, was established by X-ray crystallography. Treatment of stereoisomeric mixtures of 2,2′-diethoxy-4,4′-bithiazolones with HCl in benzene gave the corresponding *racemic* and *meso* bis(*N*-carboxythioanhydride)s. A stereoisomeric mixture of the bis(*N*-carboxythioanhydride)s of leucine treated with glycine ethyl ester gave a bicyclic derivative of the α,α′-dehydrodimeric amino acid.

Symmetrical 2,2′,4,4′-tetrasubstituted-[4,4′-bithiazole]-5,5′(4*H*,4′*H*)-diones (**1**) can be obtained by dehydrodimerization of 5(4*H*)-thiazolones (**2**),[1] well known heterocyclic compounds.[2] Since the latter may undergo ring opening when treated with nucleophiles, followed by dethioacylation, to give α-amino acids and/or their derivatives, it seemed likely that 4,4′-bithiazolones (**1**) might undergo a similar transformation to yield symmetrical α,α′-dehydrodimeric amino acids (**3**) and/or their derivatives. These little known compounds are of interest, *inter alia* because they may form when food is preserved by γ-irradiation. Indeed, irradiation of di- and tetra-peptides of alanine did yield dehydrodimers.[3] Hence, several 4,4′-bithiazolones (**1**) were synthesized and treated with nucleophiles. In the case of the closely related bioxazolones (structure **1** with S replaced by O), nucleophilic attack, presumably at a carbonyl carbon of one of the 4,4′-bioxazolone rings, was reported to cleave the 4,4′ carbon–carbon bond,[4] but our previous work showed that such cleavage was not general; i.e., some 4,4′-bioxazolones can serve as precursors to α,α′-dehydrodimeric amino acids and their derivatives.[5] The same was found to be true for the 4,4′-bithiazolones (**1**).

Results and discusssion

Dehydrodimerization of 2,4-disubstituted thiazolones. Few 4,4′-bithiazolones (**1**) are reported in the literature and only two synthetic routes leading to their formation were available when this investigation began. One used photochemically generated triplet oxygen to transform the thiazolones into their dehydrodimers.[6] The other employed iodine–triethylamine as the oxidant.[7] The photochemical method is inefficient and, in our hands, the iodine–triethylamine procedure did not yield the desired 4,4′-bithiazolones (**1**). Therefore, an alternative

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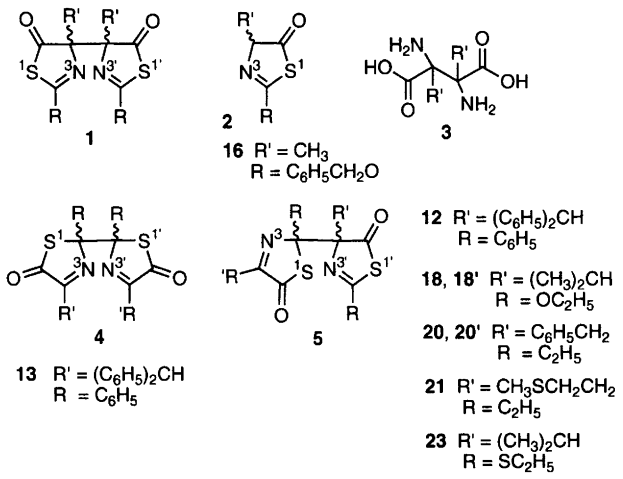
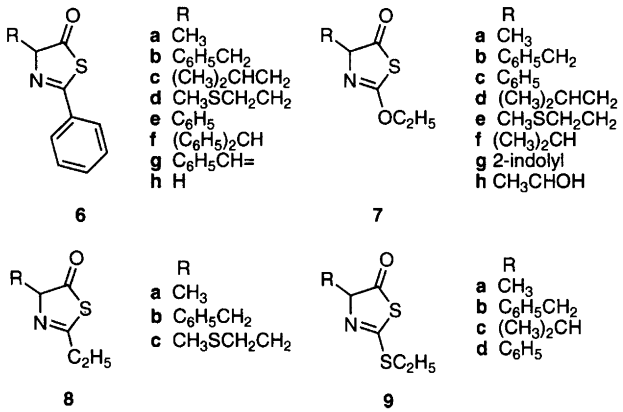


Scheme 1.

method of synthesis was sought and found. Oxidation of thiazolones by potassium permanganate in acetic acid gave excellent yields of dehydrodimers.

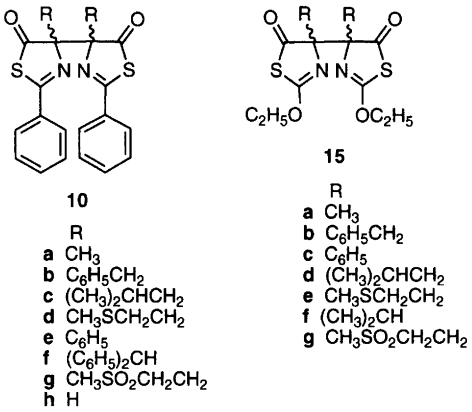
Since dehydrodimerization of heterocyclic compounds such as oxazolones, thiazolones and pyrazolones may proceed via coupling of delocalized radicals, three structural isomers – 4,4′-(**1**), 2,2′-(**4**) and 2,4′-(**5**) – each existing as stereoisomers, could, in principle, be formed. Besides investigating the reactivities of 4,4′-bithiazolones (**1**), several 2,4-disubstituted thiazolones (**2**) were prepared to study the effects of substituents at the 2 and 4 positions on the isomer distributions of the dehydrodimers. No 2,2′- or 2,4′-bithiazolones have previously been reported.

Four series of thiazolones were prepared, each based on a different substituent at the 2-position; i.e., phenyl (**6**), ethoxy (**7**), ethyl (**8**) and ethylthio (**9**).



Scheme 2.

Photochemical dehydrodimerization of 4-substituted 2-phenylthiazolones (**6**). Kato and coworkers[6] brought about dehydrodimerization of 2-phenyl-4-methylthiazolone (**6a**) to give **10a** by irradiation in the presence of oxygen and a photosensitizer. Initially, we also employed this method to prepare dehydrodimers from the 2-phenylthiazolones (**6**). Irradiation of 2-phenylthiazolones **6a**, **6b** and **6c**, dissolved in dichloromethane, for several hours in the presence of oxygen and methylene blue gave the desired 4,4′-bithiazolones **10a**, **10b** and **10c**, respectively, in yields of 46–57%. Kato *et al.* did not specify whether the 4,4′-bithiazolone (**10a**) was the *racemic* (4*R**,4*R**) or the *meso* (4*R**,4*S**) dehydrodimer, or a mixture of both. However, we found that one isomer, **10a**, (*racemic* or *meso*) was formed in great excess over the other, **10a′**, (*meso* or *racemic*). ^1H and ^{13}C NMR spectroscopy showed that the minor isomer **10a′** accounted for less than 5% of the product. When 2-phenyl-4-benzylthiazolone (**6b**) was irradiated, only one 4,4′-isomer (**10b**), either *racemic* or meso, was obtained. 2-Phenyl-4-isobutylthiazolone (**6c**) gave an 88:12 mixture of the stereoisomeric 4,4′-dehydrodimers (**10c** and **10c′**). Attempted dehydrodimerization of 2-phenyl-4-[2-(methylthio)ethyl]thiazolone (**6d**) gave a complicated mixture which defied separation and identification. Most likely the 2-methylthioethyl group was oxidized to a sulfoxide and/or a sulfone, which led to a complex mixture. Photochemical oxidation of sulfides to sulfoxides and sulfones is well known.[8] No 2,2′-or 2,4′-dehydrodimers, **4** and **5**, respectively, were detected upon irradiation of 2-phenylthiazolones **6a**, **6b** or **6c**.

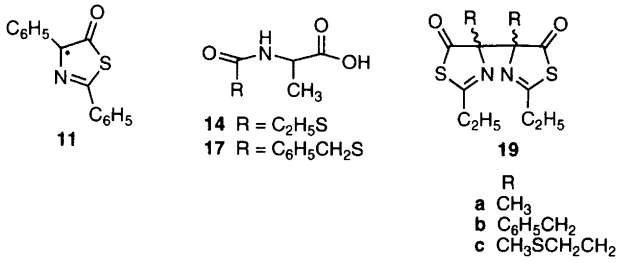


Scheme 3.

Dehydrodimerization of 2-phenylthiazolones (**6**) *by potassium permanganate.* Dehydrodimerization of 2-phenylthiazolones (**6**) using photochemistry gives modest yields and the reaction times are long. Moreover, 2-phenylthiazolones (**6**) are not very soluble in less polar solvents such as dichloromethane, necessitating the use of large amounts of solvent. For these reasons, an alternative method was sought. Potassium permanganate was found to be an excellent reagent for dehydrodimerization of many thiazolones. Dehydrodimerization of carbanions using potassium permanganate in liquid ammonia was reported by Kaiser.[9] Permanganate was thought to abstract an electron from a carbanion to give a resonance-stabilized radical intermediate which then coupled to give the product.

Dropwise addition of aqueous potassium permanganate to the 2-phenylthiazolones (**6**) in acetic acid most often led to the clean and fast formation of the 4,4′-bithiazolones (**10**) in high yields, usually greater than 90%. The work-up was simple and convenient. The results of permanganate-induced dehydrodimerizations of a series of 2-phenylthiazolones (**6**) are summarized in Table 1. Stereoisomer ratios are based on NMR spectroscopic analyses. Further details are found in the experimental section. In addition to the examples listed in Table 1, the following 2-phenylthiazolones were subjected to permanganate oxidation: (i) 2,4-diphenylthiazolone (**6e**); the ^{13}C NMR spectrum of the resulting compound(s) (**10e**) in chloroform-*d* showed only broad peaks and the ^{1}H NMR spectrum only a single broad peak at about 7.1 ppm. On the other hand, the $(M^{+}+1)$ peak expected for the dehydrodimer (**10e**) appeared in the CIMS and the C, H and N analysis agreed with the calculated values. The compound also gave an IR spectrum consistent with a 4,4′-bithiazolone. The presumed 4,4′-bi(2,4-diphenylthiazolone) (**10e**) is an almost colorless solid, stable for months as such, but giving a purple solution when dissolved in chloroform. These phenomena can be explained by the dissociation of **10e** into two thiazolone radicals **11**, probably an easy process, since the resulting radical is stabilized by the two phenyl groups at the 2- and 4-positions.

Bechgaard and coworkers[10] reported similar results in that the 1,2-dithiolyl radical, resulting from the cathodic reduction of 3,5-diphenyl-1,2-dithiolylium ion, was in equilibrium with a dimer. However, the isomeric radical from the cathodic reduction of 3,4-diphenyl-1,2-dithiolylium ion dimerized irreversibly. They attributed this result to a difference in steric interaction of the phenyl groups in the dimers. Hüttel and coworkers[11] reported that 4,4′-bipyrazolones also underwent a dissociation–reassociation equilibrium. Both groups stated that solutions of the respective dimers were deeply colored, which they thought was characteristic of radicals. Though radical **11** has not been characterized, the broad peaks in the ^{1}H and ^{13}C NMR spectra, as well as the colored chloroform solutions, are consistent with its formation. In addition, attempted recrystallization of **10e** from organic solvents such as acetone, led to decomposition. This is in contrast with the behavior of the other 4,4′-bi(2-phenylthiazolone)s (**10**), which are stable compounds both in solution and in the solid state. (ii) 2-Phenyl-4-benzhydrylthiazolone (**6f**): a complex reaction mixture was formed. However, the major product was identified as 2,4′-bithiazolone(s) **12** based on its ^{1}H and ^{13}C NMR spectra. Both 4,4′-bithiazolones **10f** and **10f′** and 2,2′-bithiazolones **13** and **13′** may also have been present in the mixture as well as hindered rotational isomers of some of these dehydrodimers. The mixture had a sharp m.p. of 171–173 °C and the C, H and N analyses were in good agreement with the values calculated for the isomeric dehydrodimers. Mass spectroscopy, however, gave only a $M^{+}/2$ (half molecular weight) peak, but no molecular ion peak. This is not unexpected, since the C4–C4′ bond is weak. In fact, no bithiazolones gave molecular ion peaks in their EIMS and sometimes not even in their CIMS. (iii) 2-Phenylthiazolone (**6h**): treatment with one equivalent of permanganate gave a complex, intractable mixture; no dehydrodimer **10h** was isolated.



Scheme 4.

Table 1. Product distribution of bithiazolones produced from 2-substituted thiazolones by oxidation with potassium permanganate in acetic acid.

Thiazolone	Product(s)	Yield (%)	Stereoisomer ratio
6a	**10a**:**10a′**	93	87[a]:13
6b	**10b**:**10b′**	96	3:1
6c	**10c**:**10c′**	92	11:1
6d	**10d**	69	99[a]:1
6d[b]	**10g**	48	≈99:1
7a	**15a**:**15a′**	81	≈1[a]:1[a]
7b	**15b**[c]:**15b′**[d]	86	≈1[a]:1[a]
7c	**15c**:**15c′**	93	≠1:1[e]
7d	**15d**:**15d′**	88	≈1:1
7e	**15e**:**15e′**	70	≈1[a]:1
7e[b]	**15g**:**15g′**	60	≈1[a]:1[a]
7f	[**15f**:**15f′**]	81	Major (3[a]:1)
	[**18**:**18′**]		Minor (1:1)
8b	[**19b**:**19b′**]	85	≠1[a,e]:1
	[**20**:**20′**]		≈1[a]:1[a]
8c	[**19c**][e]	10	
	[**21**:**21′**]		
9a	**22a**:**22a′**	93	≈1[a]:1
9b	**22b**:**22b′**	91	≈1[a]:1[a]
9c	[**22c**:**22c′**]	83	Minor
	[**23**:**23′**]		Major
9d	**22d**	68	100[a,f]:0

[a] Obtained in homogeneous state. [b] Treated with an excess of $KMnO_4$. [c] Racemic isomer (X-ray). [d] *meso* Isomer. [e] One isomer predominant. [f] Unstable in solution.

Dehydrodimerization of 2-ethoxythiazolones (**7**) *by potassium permanganate.* Before turning to $KMnO_4$, the use of iodine as an oxidant was investigated. Steglich and coworkers utilized I_2–Et_3N to form dehydrodimers from 2-benzyloxythiazolones.[7] In our hands, treatment of 2-ethoxy-4-methylthiazolone (**7a**) with I_2–Et_3N in ether gave *N*-ethylthiocarbonylalanine (**14**) as the major product plus a trace of elemental sulfur and not the expected 4,4′-bi(2-ethoxythiazolones) **15a** and **15a′**. In an attempt

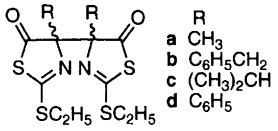
to duplicate the literature results, 2-benzyloxy-4-methylthiazolone (**16**) was treated with I_2–Et_3N. *N*-Benzylthiocarbonylalanine (**17**) was the major product and not the expected bithiazolones. These results discouraged us from pursuing this method further.

Since the photochemical method is not very efficient and the I_2–Et_3N method failed, the dehydrodimerization of all other thiazolones **7** was carried out using $KMnO_4$. As was the case for the 2-phenylthiazolones, the dehydrodimerization reaction was fast and clean. In all but one case, mixtures of *racemic* and *meso* 4,4′-bithiazolones **15** in roughly equal amounts were obtained in yields of 70–95%. Loss of products during the work-up probably accounts for the lower yields, since the ^1H and ^{13}C NMR spectra of the crude reaction mixtures showed essentially no impurities, but only peaks for the *racemic* and *meso* dehydrodimers. The results are summarized in Table 1. It is noteworthy that thiazolone **7f** differs from the others of its class by affording the stereoisomers of the 2,4′-dehydrodimers **18** and **18′** as minor constituents of the reaction mixture. Treatment of thiazolones **7g** and **7h** with potassium permanganate gave mixtures from which no products were isolated. Apparently the 2-indolyl and CH_3CHOH groups at position 4 are easily oxidized.

Dehydrodimerization of 2-ethylthiazolones (**8**) *by potassium permanganate.* Oxidation of 2-ethylthiazolones **8** by $KMnO_4$ was carried out for three cases, **8a**, **8b** and **8c**. Treatment of 2-ethyl-4-methylthiazolone **8a** with $KMnO_4$ in the usual manner gave none of the expected dehydrodimers **19a**. Instead, an intractable oil, shown by TLC to be a complex mixture, and a small amount of elemental sulfur, whose identity was confirmed by mass spectroscopy and melting point, were obtained. 2-Ethyl-4-methylthiazolone (**8a**), relatively unstable at room temperature, was apparently degraded by the strong oxidant.

The results of the other oxidations are shown in Table 1. Bithiazolones **20** and **20′** are the first examples of 2,4′-bithiazolones to be isolated. Broad peaks in the ^1H NMR spectra of 2,4′-bithiazolone **20** indicated that there was hindered rotation around the C2–C4′ bond. When the temperature was raised to 313 K, the broad peaks disappeared indicating an increase in the rate of rotation around the C2–C4′ bond. When the temperature was lowered to 203 K, peaks for two rotamers were clearly seen in the spectrum.

Dehydrodimerization of 2-ethylthiothiazolones (**9**) *by potassium permanganate.* Four 2-ethylthiothiazolones (**9**) were converted into their dehydrodimers (**22**) as summarized in Table 1. Oxidation of 2-ethylthiothiazolones (**9**) with one equivalent or with an excess of $KMnO_4$, gave the same products indicating that the sulfur of the ethylthio group remained unoxidized. Apparently, the lone electron pairs on the sulfur atom of the ethylthio group are delocalized, so the sulfur atom is not easily oxidized.



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Scheme 5.

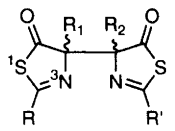
The influence of substituents on the course of dehydrodimerization. As can be seen from the above results (Table 1), dehydrodimerization of 2-phenyl-, 2-ethoxy- and 2-ethylthio-thiazolones generally gave 4,4′-bithiazolones as the major isomers rather than the 2,4′- or 2,2′-isomers. However, there are a few exceptions. Oxidation of 2-ethoxy-4-isopropylthiazolone (**7f**) or 2-ethylthio-4-isopropylthiazolone (**9c**) led to a mixture of 4,4′-bithiazolones and 2,4′-bithiazolones. The major products were still the 4,4′-dehydrodimers **15f** and **15f′** in the 2-ethoxy case (**7f**), but were the 2,4′-dehydrodimers **23** and **23′** in the 2-ethylthio case (**9c**). Again, as described above, dehydrodimerization of 2-phenyl-4-benzhydrylthiazolone (**6f**) yielded a complex mixture in which the major product was believed to be the 2,4′-bithiazolone(s) **12.**

The formation of 2,4′-bithiazolones **12**, **18**, **18′**, **23** and **23′** may be the result of steric factors, since all of the other 2-phenyl-, 2-ethoxy-, and 2-ethylthio-thiazolones gave only 4,4′-bithiazolones. Therefore, it seems that electronic factors are less important than steric factors in determining the isomer distributions if the group at the 4-position is bulky.

Crossover dehydrodimerization reactions. The oxidation of a mixture of two different thiazolones should yield a complex mixture of all possible 4,4′-bithiazolones, not to mention the possible formation of 2,4′- and 2,2′-bithiazolones. However, it was found in a crossover dehydrodimerization that the use of a large excess of one thiazolone over the other led to the formation of a specific unsymmetrical 4,4′-bithiazolone in high yield. Thus, treatment of a mixture of **6a** and **6b** (3:1 ratio) in acetic acid with aqueous $KMnO_4$ gave an 89% crude yield of a mixture of all possible diastereomeric 4,4′-bithiazolones. The crossover or mixed unsymmetrical bithiazolones **24a** and **24a′** predominated, but the symmetrical bithiazolones **10a**, **10a′**, **10b** and **10b′** were also present. The identification of the unsymmetrical bithiazolone was based on the ^1H and ^{13}C NMR spectra of the unseparated reaction products. In addition to the peaks due to symmetrical bithiazolones **10a** and **10b**, which can be easily identified by comparison with those of authentic compounds, new peaks appeared in both the ^1H and ^{13}C NMR spectra, which accounted for both diastereomers of the unsymmetrical bithiazolones. According to the integration of the ^1H NMR spectrum, 89% of **6b** went into the unsymmetrical bithiazolones **24** and **24a′** and 11% formed the symmetrical bithiazolones **10b** and **10b′**. The statistical ratio is 75:25.

Another crossover dehydrodimerization reaction was

carried out using a mixture of 2-ethylthio-4-methylthiazolone **9a** and 2-phenyl-4-benzylthiazolone **6b** (3:1 ratio). In this case, the thiazolones have different substituents at both the 2 and 4 positions. The expected unsymmetrical bithiazolones **24b** and **24b′** were produced in good yield. According to integration of the ^{1}H NMR spectrum, about 75% of **6b** formed the unsymmetrical bithiazolones **24b** and **24b′** and 25% the symmetrial bithiazolones **10b** and **10b′**, which is the statistical ratio. Some isolation of the symmetrical bithiazolones **10b** and **10b′** was achieved by recrystallization, but no further separation of this mixture was achieved. Though the unsymmetrical bithiazolones formed in both reactions were not fully characterùized, TLC indicated that it might be possible to separate them by chromatography. In any event, the results of these two crossover experiments are consistent with the proposed radical mechanism for the dehydrodimerization reactions.



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	R	R′	R_1	R_2
a	Ph	Ph	CH_3	$PhCH_2$
b	Ph	SC_2H_5	$PhCH_2$	CH_3

Scheme 6.

IR and NMR data for the bithiazolones. The spectral parameters of the bithiazolones resembled those of their precursor thiazolones and, when taken together with elemental analyses and MS data, allowed structural assignments to be made with confidence. For the 4,4′-bithiazolones, stretching frequencies for the C=O and C=N bonds were found between 1748–1711 and 1641–1553 cm^{-1}, respectively. In the ^{13}C NMR spectra, the carbonyl carbons were found between 209.5–202.1 ppm and the imino carbons between 171.8–160.1 ppm, essentially the same ranges as for the parent thiazolones. The shifts for the quaternary carbons at position 4 were between 95.5–87.3 ppm which is roughly 10 ppm higher field than for the tertiary C-4 carbons in the parent thiazolones; *viz.*, 87.3–76.4 ppm.

The spectra for the 2,4′-bithiazolones were more complicated, since there were two distinct carbonyl and two distinct imino groups in each compound; i.e., one ring is a thiazolin-5(4*H*)-one, the other a thiazolin-5(2*H*)-one. The IR stretching frequencies were in the range 1700–1681 cm^{-1} for the conjugated carbonyl groups in the thiazolin-5(2*H*)-one ring and 1738–1714 cm^{-1} for the non-conjugated carbonyl groups in the thiazolin-5(4*H*)-one ring. The IR stretching frequencies lay between 1653–1639 cm^{-1} for the conjugated imino groups and between 1630–1553 cm^{-1} for the non-conjugated imino groups. In the ^{13}C NMR spectra, the conjugated carbonyl carbons appeared at 193.9–191.8 ppm and the non-conjugated carbonyl groups between 208.7 and 204.3 ppm. The shifts for the quaternary carbons lay in the range 95.4–93.4 ppm and the imino carbons between 176.6 and 162.6 ppm; they could not be assigned to a specific ring.

Crystal structure of (4R,4′R*)-4,4′-bithiazolone* **15b**. X-Ray data were collected on an Enraf–Nonius CAD4 single crystal diffractometer. The coordinates of the non-hydrogen atoms are listed in Table 2 and a PLUTO plot of the structure is presented in Fig. 1.

X-Ray crystallography established the configuration of **15b** as *racemic* or (4*R**,4′*R**), (Fig. 1). The two halves of the molecule are almost identical regarding bond lengths and angles. A notable feature is the C4–C4′ bond length of 1.567(7) Å, longer than the usual sp^3–sp^3 bond length of 1.53 Å, indicating that this bond, which joins the two thiazolone rings, is weak. The structural data are similar to those reported for bithiazolone **25** by Foces-Foces and coworkers,[12] who found the C4–C4′ bond length to be 1.569 Å. Several analogous molecules have also had their crystal structures determined. Bioxazolone **26** has a 4,4′ carbon–carbon bond length of 1.563 Å.[13] The *racemic* and *meso* isomers, **27** and **27′**, of 1,1′,2,2′,4,4′-hexamethyl-[4,4′-biimidazole]-5,5′(4*H*,4′*H*)-dione have 4,4′ carbon–carbon bond lengths of 1.542 and 1.545 Å, respectively.[14] 4,4′-Di(phenylmethyl)-1,1′-dimethyl-2,2′-diphenyl-[4,4′-biimidazole]-5,5′-(4*H*,4′*H*)-dione (**28**) has a 4,4′ carbon–carbon bond length of 1.553 Å.[14] The shorter bond lengths for **27** and **27′** are likely due to a lesser steric interaction between the methyl substituents at the C4–C4′ positions compared with that between the 4,4′ substituents of bithiazolone **15b′**, bioxazolone **26** and bithiazolone **25**, which have benzyl or 2-phenylpropenyl groups at these positions. These larger groups are likely to cause elongation of the 4,4′-bond in order to minimize unfavorable steric interactions. This explanation is consistent with the ca. 0.01 Å increase in the 4,4′-bond length which occurs when the methyl groups of **27** and **27′** are replaced by phenylmethyl groups to give **28**.

Reactions of bithiazolones with nucleophiles. Indirect evidence indicated that the hydrolysis of 2,2′-diphenyl-4,4′-di-(2-carboxyethyl)-[4,4′-bithiazole]-5,5′(4*H*,4′*H*′)-dione under physiological conditions took place with cleavage of the C4–C4′ bond to form α-ketoglutaric acid.[15] There are no other reports of the nucleophilic ring opening of 4,4′-bithiazolones. As stated above, Steglich and coworkers[4] showed that hydrolysis of a 4,4′-bioxazolone proceeded with cleavage of the C4–C4′ bond which joined together the two heterocyclic rings, but more recently we have shown that there are exceptions to this.[5] Cleavage is not general.

Reactions of 4,4′-bithiazolone ***10a*** *with nucleophiles.* Ring opening reactions of bithiazolone **10a** were attempted with different nucleophiles. When **10a** was heated in methanol in the presence of triethylamine, *racemic N*-thiobenzoylalanine methyl ester (**29**) was obtained.

Table 2. Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2) for (4*R**,4′*R**)-2,2′-diethoxy-4,4′-dibenzyl-[4,4′-bithiazole]-5,5′(4*H*,4′*H*)-dione (**15b**).

Atom	*x*	*y*	*z*	B_{eq}[a]
S1′	0.5650(2)	0.3758(1)	0.9914(1)	6.26(4)
S1	0.5850(2)	0.5581(1)	0.7400(1)	6.48(4)
O2′	0.4633(4)	0.2532(3)	0.8641(3)	6.9(1)
O2	0.7681(4)	0.4256(3)	0.7701(3)	7.1(1)
O1′	0.7483(4)	0.5102(3)	1.0524(2)	6.8(1)
O1	0.3501(4)	0.5852(3)	0.7423(2)	5.7(1)
N3′	0.7320(4)	0.4316(3)	0.9383(30)	4.8(1)
N3	0.4390(4)	0.4399(3)	0.7712(3)	4.8(1)
C2′	0.6966(5)	0.4446(4)	0.9907(3)	5.1(2)
C2	0.4435(5)	0.5228(4)	0.7527(3)	5.3(2)
C4′	0.6548(5)	0.3541(4)	0.8806(3)	5.0(1)
C4	0.5595(5)	0.3883(4)	0.7808(3)	4.8(1)
C5′	0.5464(6)	0.3157(4)	0.9012(3)	5.5(2)
C5	0.6603(5)	0.4471(4)	0.7674(3)	5.4(2)
C6′	0.7729(6)	0.2806(4)	0.9016(4)	5.9(2)
C6	0.4934(6)	0.3133(4)	0.7088(3)	5.8(2)
C7′	0.8666(5)	0.2525(4)	0.9988(3)	5.4(2)
C7	0.4096(6)	0.3485(4)	0.6147(4)	5.8(2)
C8′	0.9890(6)	0.3021(5)	1.0646(4)	6.3(2)
C8	0.4788(7)	0.3540(5)	0.5695(4)	7.1(2)
C9′	1.0758(7)	0.2764(5)	1.1543(4)	7.7(2)
C9	0.4037(8)	0.3874(5)	0.4835(4)	8.7(2)
C10′	1.0396(8)	0.1999(6)	1.1799(5)	8.9(3)
C10	0.2593(9)	0.4167(6)	0.4412(4)	9.6(3)
C11′	0.9170(8)	0.1500(5)	1.1169(5)	9.6(3)
C11	0.1858(9)	0.4118(6)	0.4841(5)	9.2(3)
C12′	0.8287(7)	0.1744(5)	1.0237(5)	7.8(2)
C12	0.2592(7)	0.3774(5)	0.5694(4)	7.0(2)
C13′	0.8442(7)	0.5761(6)	1.0466(5)	9.7(2)
C13	0.2375(6)	0.5566(5)	0.7570(4)	6.4(2)
C14′	0.8312(9)	0.6576(9)	1.0684(7)	9.9(3)
C14	0.1564(7)	0.6388(5)	0.7553(4)	7.9(2)

[a] $B_{eq} = (4/3)\Sigma_i\Sigma_j\beta_{ij}\boldsymbol{a}_i.\boldsymbol{a}_j$.

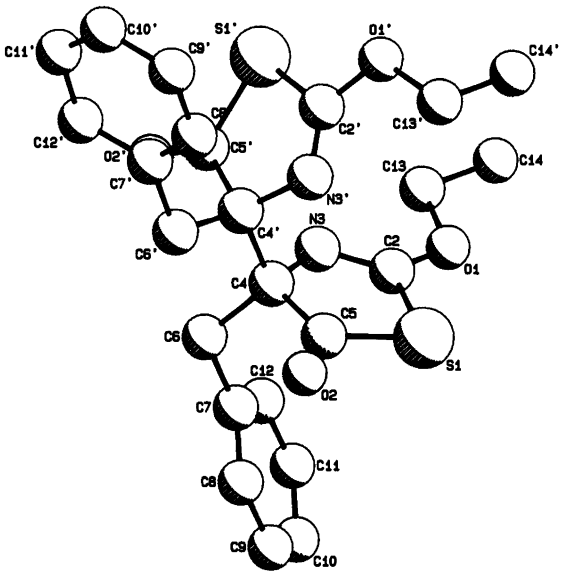
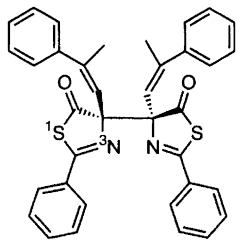
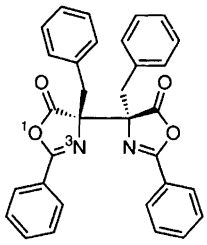


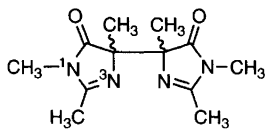
Fig. 1. PLUTO plot of **15b**.



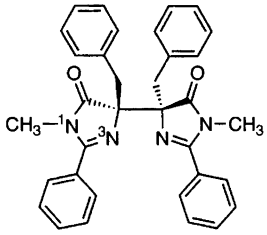
25



26



27, racemic; **27′**, meso



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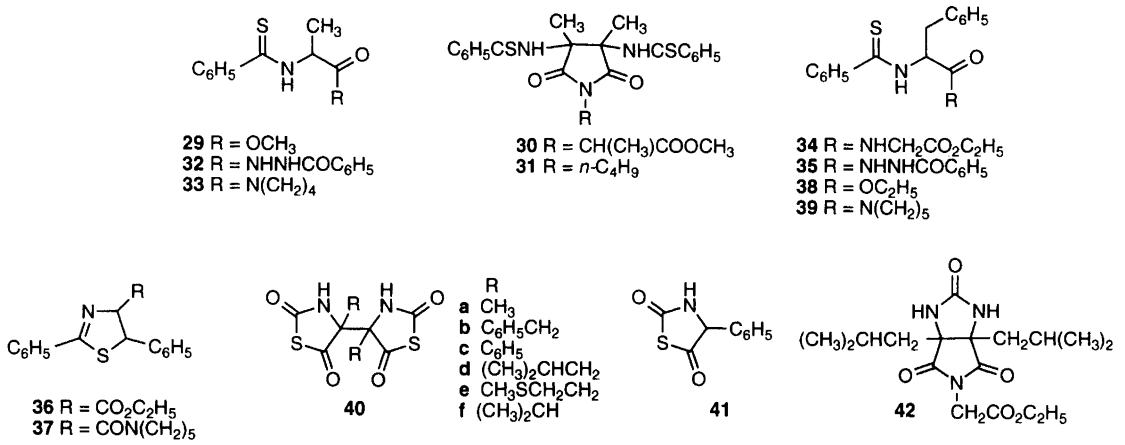
Scheme 7.



Scheme 8.

Obviously, the C4–C4′ bond was cleaved during this reaction.

Aminolysis was also examined. Treatment of **10a** with the methyl ester of L-alanine in the presence of triethylamine under reflux conditions gave two diastereomers of imide **30**. Similarly, reaction of **10a** with 1-butylamine gave imide **31** of unknown stereochemistry. No C4–C4′ cleavage took place. Surprisingly, reaction with benzoic hydrazide yielded no imide, but *racemic* **32** was formed. Aminolysis using pyrrolidine under reflux conditions gave *racemic* **33**. Both **32** and **33** probably arise from thiazolone **6a** formed in a cleavage reaction.

*Reactions of 4,4′-bithiazolones **10b** and **10b′** with nucleophiles.* Reaction of a mixture of **10b** and **10b′** with glycine ethyl ester in the presence of triethylamine yielded *racemic* **34** and **6g**. Apparently the amine acted as a base initially to form thiazolones **6g** and **6b** with compound **34** arising from aminolysis of thiazolone **6b**. A similar reaction yielded **6g** and *racemic* **35** when a mixture of **10b** and **10b′** was treated with benzoic hydrazide.

Treatment of **10b** and **10b′** with C_2H_5OH–KOH gave **6g**, and a mixture of **36** and **38**. When **10b** and **10b′** were treated with piperidine, an analogous reaction took place; *racemic* **37** and **39** plus **6g** were isolated. The structure of **37** was confirmed by an X-ray crystal structure determination (Fig. 2).

*Reactions of 4,4′-bithiazolones **15** and **15′** with HCl.* It was surprising that no reaction took place when 4,4′-bithiazolones **15b** were treated under reflux conditions with glycine ethyl ester or piperidine even when the reaction mixtures were heated for 72 h, since bithiazolones **10b** and **10b′** reacted with both primary and secondary amines quite easily. An electron-releasing ethoxy group at the 2-position of bithiazolone **15b** apparently made the carbonyl and C=N groups less electron-deficient and inert to the amine nucleophiles.

Steglich and coworkers[7] reported that 4,4′-bi(2-benzyloxythiazolone)s (**1**, R = $C_6H_5CH_2O$) could be debenzylated by treatment with dry HCl to give bis(*N*-carboxythioanhydrides) of amino acids, **40**. These thioanhydrides might serve as sources of dehydrodimeric amino acids and their derivatives. Treatment of mixtures of 4,4′-bithiazolones **15a**, **a′**, **d**, **d′**, **e** and **e′** with HCl in benzene gave the corresponding bis(*N*-carboxythioanhydride)s **40** as mixtures of the *racemic* and *meso* isomers in high yield. Pure isomers **15b** (*racemic*) and **15b′** (*meso*) gave **40b** (*racemic*) and **40b′** (*meso*), respectively. However, **15c** and **15c′** gave 4-phenyl-2,4-thiazolidinedione (**41**) as the major product and only 8% of bis(*N*-carboxythioanhydride) of phenylglycine **40c** and **40c′**. Perhaps **41** was formed via disproportionation of **15** or **40** into radicals. Koch and coworkers[16] reported a similar disproportionation reaction resulting from the dissociation of an analogous dimer.

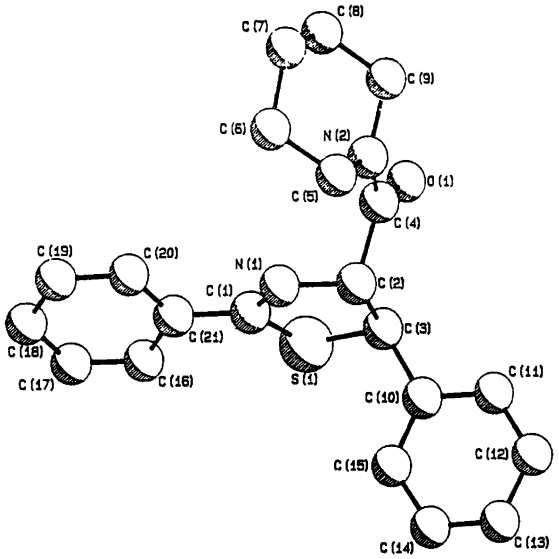


Fig. 2. PLUTO plot of **37**.

Treatment of a mixture of 2,4′- and 4,4′-bithiazolones **18** and **18′**, and **15f′** and **15f**, respectively, gave only a small amount (less than 5%) of bis(*N*-carboxythioanhydride)s **40f** and **40f′**. Since the 4,4′-bithiazolones **15f**

and **15f′** were the major components in the mixture, it was unclear why the yield of **40f** plus **40f′** was so low.

*Reaction of bis(*N*-carboxythioanhydride)s **40d** and **40d′** with nucleophiles.* When a mixture of bis(*N*-carboxythioanhydride)s **40d** and **40d′** was treated with glycine ethyl ester in the presence of triethylamine in acetonitrile, bicyclic compound **42** was obtained. The methylene protons appeared as a singlet and not an AB system, so **42** is likely the *meso* isomer. Since the C4–C4′ bond in **40d** was not cleaved, the bis(*N*-carboxythioanhydride)s (**42**) hold promise as readily available precursors to dehydrodimeric amino acids and their derivatives.

Conclusions

A method for preparing diastereomeric mixtures of 4,4′-bithiazolones (**1**) in high yield by oxidation of 5(4*H*)-thiazolones (**2**) has been developed. Separation of the isomers was possible in some cases. The configuration of one 4,4′-bithiazolone (**15b**) was established by X-ray crystallography. The influence of substituents at the 2- and 4-positions of the 5(4*H*)-thiazolones on the isomer distribution of the bithiazolones was explored. Steric factors appear to be more important than electronic factors in determining which isomers predominate. Results of crossover experiments are consistent with the radical nature of the dehydrodimerization. Several reactions of the 4,4′-bithiazolones and bis(*N*-carboxythioanhydride)s with nucleophiles indicated that these dehydrodimers may, in some cases, yield derivatives of, and subsequently, the free α,α′-dehydrodimeric amino acids (**3**).

Experimental

Melting points were obtained with a Thomas Hoover melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Nicolet FT-IR 205 spectrometer. Nuclear magnetic resonance spectra were recorded at 360 MHz for ^{1}H and 90.6 MHz for ^{13}C on a Bruker AM-360 spectrometer. All chemical shifts are reported in parts per million (ppm) downfield from a trimethylsilane (TMS) internal standard. Coupling constants (J) are given in Hertz (Hz). Mass spectra were obtained on a Hewlett Packard 5988-A GC/MS quadrupole spectrometer using electron impact (EI) and chemical ionization (CI). Elemental analyses were performed at the University Instrumentation Center.

*X-Ray crystal structure of **15b** and **37**.* Data were collected on an Enraf–Nonius CAD-4 diffractometer using a graphite monochromator. 2521 unique observed reflections with $|F_o| > 3\sigma(|F_o|)$ were measured for **15b** and 2132 for **37**. The structures were solved by direct methods (MULTAN 82; Main, Fiske, Hull, Lessinger, Germain, Declerq and Woolfson, 1982). Hydrogen atoms were located by difference Fourier synthesis. Anisotropic full-matrix least-squares refinements (on F) were done on non-hydrogen atoms; isotropic refinement on H atoms. In the last cycle, the H atoms were fixed at idealized positions. The function minimized was $\Sigma w(|F_o|-|F_c|)^2$, with $w=4F^2/[\sigma(I)^2+(pF^2)^2]$ and $p=0.04$. For **15b**, the final $R=0.070$ and $wR=0.071$, max $\Delta/\sigma=0.04$. For **37**, the final $R=0.060$ and $wR=0.074$, max $\Delta/\sigma=0.07$. Maximum peak heights in the final difference Fourier maps were: for **15**, 0.24 e Å^{-3} and $S=1.646$ for 285 variables, and for **37**, 0.27 e Å^{-3} and $S=2.817$ for 227 variables.

(2-R,4-R′)-5(4H)thiazolones were prepared in *racemic* form by standard methods. The 2-phenylthiazolones (**6**) were obtained by cyclization of *N*-thiobenzoyl amino acid amides with trifluoroacetic acid.[17,18] Cyclization of *N*-ethoxythiocarbonyl amino acids, *N*-ethylthiocarbonyl amino acids, and *N*-ethylthiothiocarbonyl amino acids with DCC in tetrahydrofuran (THF) or dichloromethane gave **7**, **8** and **9**, respectively.[19,20] Oxidation of **6**, **7**, **8** and **9** by $KMnO_4$ gave the bithiazolones described below. Dehydrodimerization of 2-ethylthiothiazolones with an equivalent of $KMnO_4$ or with an excess of $KMnO_4$ gave the same bithiazolones without oxidation of the sulfur atom of the ethylthio group. A typical synthesis is: *2,2′-diphenyl-4,4′-dimethyl-[4,4′-bithiazole]-5,5′(4H,4′H)-diones* (**10a** and **10a′**). Aqueous $KMnO_4$ (15 ml, 3%) was added with stirring over a 10–15 min period to 2-phenyl-4-methylthiazolone (**6a**) (0.40 g, 2.1 mmol) in acetic acid (10 ml) at 55–60 °C. After an additional 20 min, the excess $KMnO_4$ was decomposed using gaseous SO_2. Ice–water (30 ml) was added and the resulting ppt. was collected, washed several times with water, and finally dried, m.p. 138–140 °C (0.37 g, 0.97 mmol, 93%). The diastereomers **10a** and **10a′** were obtained in a ratio of 87:13, according to the integration of the ^{1}H NMR spectrum. The major isomer **10a**, m.p. 138–139 °C, which was identical with the dehydrodimer obtained using O_2–light, was separated from the minor one, **10a′**, by simple recrystallization from ethanol. However, **10a′** was not obtained free from **10a**. ^{1}H NMR ($CDCl_3$, major isomer **10a** reported first): δ 1.77 and 1.78 (3 H, s), 7.31–7.54 (3 H, overlapped, m), 7.64–7.68 and 7.78–7.81 (2 H, m). The ^{13}C NMR spectrum clearly showed the peaks of the minor isomer. ^{13}C NMR ($CDCl_3$, major isomer reported first): δ 17.7 and 20.0, 89.3 and 90.5, 128.1 and 128.3, 128.7 and 128.8, 132.1 and 132.2, 132.9 and 133.3, 164.8 and 163.9, 207.9 and 208.4. IR (KBr): 1723, 1600 cm^{-1}. Anal. of **10a** plus **10a′**. $C_{20}H_{16}N_2O_2S_2$: C, H, N.

*2,2′-Diphenyl-4,4′-dibenzyl-[4,4′-bithiazole]-5,5′-(4H,4′H)-diones (**10b** and **10b′**).* Reaction product mixture: m.p. 187–189 °C, (96%), diastereomeric ratio **10b**:**10b′** = 3:1 according to the integration of the benzyl protons. The major isomer (**10b**) was identical with the dehydrodimer obtained using O_2–light. No separation of **10b** and **10b′** was accomplished. ^{1}H NMR ($CDCl_3$–CD_3CN (1:1), major isomer **10b** reported first):

δ 3.61 and 3.79 (1 H, d, J=13.1 Hz), 4.11 and 3.91 (1 H, d, J=13.1 Hz), 7.10–7.20 (5 H, overlapped, m), 7.3–7.70 (5 H, overlapped, m). The aromatic protons of the minor isomer were buried under the major isomer. ^{13}C NMR ($CDCl_3$–CD_3CN (1:1), major isomer reported first): δ 36.3 and 38.6, 92.2 and 93.6, 126.18 and 126.22, 126.96 and 126.99, 127.0 and 127.2, 128.1 and 128.2, 130.1 and 130.2, 131.5 and 131.7, 131.6 and 132.1, 132.9 and 132.8, 165.2 and 164.5, 207.4 and 208.0. IR (KBr): 3061, 3028, 2941, 1726, 1720, 1601, 1578 cm^{-1}. Anal. of **10b** plus **10b′**. $C_{32}H_{24}N_2O_2S_2$: C, H, N.

*2,2′ - Diphenyl - 4,4′ - diisobutyl - [4,4′ - bithiazole] -5,5′ - (4H,4′H)-diones (**10c** and **10c′**).* Reaction product mixture: m.p. 136–138 °C (92%), **10c**:**10c′**=11:1. The diastereomeric mixture was recrystallized from 95% ethanol; however, its m.p. and composition remained unchanged. ^{1}H NMR ($CDCl_3$): δ 0.86 (3 H, d, J=7.1 Hz), 0.88 (3 H, d, J=7.0 Hz), 1.47 (1 H, m); 2.04 (1 H, dd, J=13.8, 6.5 Hz), 2.70 (1 H, dd, J=13.8, 5.8 Hz), 7.3–7.6 (5 H, m). Many proton signals of the minor component **10c′** were buried under those of the major isomer **10c** except for the two methylene protons. The chemical shifts and the coupling constants for these are 2.26 (dd, J=13.9, 5.8 Hz) and 2.51 (dd, J=13.9, 6.1 Hz). The ^{13}C NMR spectrum clearly showed the two components in the reaction mixture. ^{13}C NMR ($CDCl_3$): δ for major component: 24.1, 24.3, 25.0, 39.2, 93.6, 128.1, 128.6, 131.9, 132.86, 165.0, 208.8; δ for minor component: 24.4, 24.5, 24.5, 42.2, 94.8, 128.4, 128.8, 132.1, 133.4, 164.2, 209.2. IR (KBr): 1737, 1598, 1577 cm^{-1}. MS *m/z* (CI): 465 (M^++1), 354, 260, 234, 232 (M^+/2). Anal. of **10c** plus **10c′**. $C_{26}H_{28}N_2O_2S_2$: C, H, N.

2,2′-Diphenyl-4,4′-di(2-methylthioethyl)-[4,4′-bithiazole]-5,5′(4H,4′H)-dione (**10d**). The ^{1}H NMR spectrum showed that only one isomer was present. Recrystallization from EtOH gave **10d**, m.p. 145–147 °C, (69%). ^{1}H NMR ($CDCl_3$): δ 2.07 (3 H, s), 2.17–2.35 (2 H, m), 2.46 (1 H, ddd, J=13.3, 10.2 and 6.2 Hz), 3.03 (1 H, ddd, J=13.3, 10.7 and 4.7 Hz), 7.32–7.45 (3 H, m), 7.62–7.65 (2 H, m). ^{13}C NMR ($CDCl_3$): δ 15.4, 28.4, 30.6, 92.5, 128.2, 128.7 132.3, 132.6, 166.8, 207.6. IR (KBr): 3063, 3024, 2976, 2917, 1717, 1599, 1575 cm^{-1}. MS *m/z* (CI): 500 (M^+), 453, 372, 280, 252, 224, 250 (M^+/2), 202, 121, 61. Anal. $C_{24}H_{24}N_2O_2S_4$: C, H, N.

2,2′,4,4′ - Tetraphenyl - [4,4′ - bithiazole] - 5,5′(4H,4′H) - dione (**10e**). Reaction product mixture: m.p. 176–180 °C (decomp.), (55%). Both ^{1}H and ^{13}C NMR spectra showed only very broad peaks. IR (KBr): 3062, 3026, 1728, 1599, 1578 cm^{-1}. MS *m/z* (CI): 505 (M^++1), 358, 282, 254, 253, 226, 179, 151, 123, 105, 77. Anal. $C_{30}H_{20}N_2O_2S_2$: C, H, N. This bithiazolone was unstable in solution (chloroform, etc.) but stable in the solid state.

*2,2′ - Diphenyl - 4,4′ - dibenzhydryl - [4,4′ - bithiazole] - 5,5′ - (4H,4′H)-dione (**10f**) and 2,2′-Diphenyl-4,4′-dibenzhydryl-[2,4′-bithiazole]-5,5′(2H,4′H)-dione* (**12**). (90%). The ^{1}H and ^{13}C NMR spectra of the products were complicated. However, the major components were believed to be the 2,4′-bithiazolone (**12**) and the 4,4′-bithiazolone (**10f**) according to the spectra. Other possible components are the 2,2′-bithiazolones (**13**). Also, rotamers might exist for some of these bithiazolones. Recrystallization from $CHCl_3$–EtOH gave a mixture, m.p. 173–175 °C. Partial ^{1}H NMR ($CDCl_3$): δ 4.54 (s), 4.95 (s), 5.42 (br s), 5.61 (s), 6.70 (s), 6.72 (s). Partial ^{13}C NMR ($CDCl_3$): δ (49.8, 50.1, 50.6, 54.0, 56.1, 59.7), (94.7, 97.1, 97.3, 97.9, 98.8, 99.4), (166.6 168.1, 169.8, 170.9, 171.2, 171.6), (191.8, 192.3, 206.1, 207.1, 208.8, 209.0). IR (KBr): 3087, 3060, 3029, 1700, 1653, 1596, cm^{-1}. MS *m/z*: 510, 432, 382, 342 (M^+/2), 282, 195, 167, 121. Anal. $C_{44}H_{32}N_2O_2S_2$: C, H, N.

2,2′-Diphenyl-4,4′-di(2-methylsulfonylethyl)-[4,4′-bithiazole]-5,5′(4H,4′H)-dione (**10g**). Reaction product mixture obtained with an excess of $KMnO_4$: m.p. 185 °C (decomp.) (48%). The ^{1}H NMR spectrum of the crude product showed that it was almost homogeneous. Only a very small amount of the minor isomer could be seen in the ^{13}C NMR spectrum. Recrystallization from acetic acid left the m.p. and NMR spectra unchanged. ^{1}H NMR (DMSO-d_6): δ 2.5–3.0 (4 H, m), 3.05 (3 H, s), 7.45–7.86 (5 H, m). ^{13}C NMR (DMSO-d_6): δ 22.9, 40.5, 47.8, 91.1, 128.4, 129.5, 131.8, 133.5, 167.8, 206.8. IR (KBr): 1720, 1597, 1280, 1270 cm^{-1}. MS *m/z* (CI): 565 (M^++1), 485, 312, 284, 282 (M^+/2), 202, 126, 121, 81, 29. Anal. $C_{24}H_{24}N_2O_6S_4$: C, H, N.

*2,2′ - Diethoxy - 4,4′ - dimethyl - [4,4′ - bithiazole] - 5,5′ - (4H,4′H)-diones (**15a** and **15a′**).* Reaction product mixture: oil, (81%). The ^{1}H NMR spectrum showed that this crude product was an almost pure mixture of *racemic* and *meso* isomers. Column chromatography (silica gel; 4:1 hexanes–ethyl acetate) gave **15a**, b.p. 120–125 °C/0.4–0.5 mmHg. ^{1}H NMR ($CDCl_3$): δ 1.35 (3 H, t, J=7.20 Hz), 1.57 (3 H, s), 4.30–4.45 (2 H, m). ^{13}C NMR ($CDCl_3$): δ 14.2, 18.5, 65.9, 87.3, 160.7, 206.4. IR (neat): 1740, 1643 cm^{-1}. MS *m/z* (EI) 288 (M^+ −CO), 244, 187, 158 (M^+/2), 130, 111, 70, 42. Anal. $C_{12}H_{16}N_2O_4S_2$: C,H,N. The slower eluting isomer **15a′**, m.p. 62–65 °C. ^{1}H NMR ($CDCl_3$): δ 1.38 (6 H, t, J=7.2 Hz), 1.54 (6 H, s), 4.34–4.51 (4 H, m). ^{13}C NMR ($CDCl_3$): δ 14.1, 20.6, 65.7, 88.6, 159.7 207.1. IR (KBr): 1740, 1643 cm^{-1}. MS *m/z* (CI): 317 (M^++1), 289, 232, 188, 158 (M^+/2), 130, 57, 47. Anal. $C_{12}H_{16}N_2O_4S_2$: C, H, N.

*2,2′ - Diethoxy - 4,4′ - dibenzyl - [4,4′ - bithiazole] - 5,5′ - (4H,4′H)-diones (**15b** and **15b′**).* Reaction product mixture (86%). The isomers were separated by recrystallization. Slow evaporation of an absolute alcohol solution (3–5 days) gave isomerically pure **15b**. A single crystal X-ray analysis showed that this was the (4*R**,4′*R**); i.e., *racemic*, isomer, m.p. 124–126 °C (28%) (Fig. 1). The experimental data are given in Table 2. ^{1}H NMR

($CDCl_3$): δ 1.26 (3 H, t, J=7.1 Hz), 3.41 (1 H, d, J=13.0 Hz), 3.81 (1 H, d, J=13.0 Hz), 4.25–4.40 (2 H, m), 7.13–7.25 (5 H, m). ^{13}C NMR ($CDCl_3$): δ 14.3, 37.4, 65.9, 91.0, 126.9, 127.8, 131.0, 134.1, 161.7, 207.2. IR (KBr): 1730, 1644 cm^{-1}. MS m/z (CI): 509 (M^++41), 497 (M^++29), 469 (M^++1). Anal. $C_{24}H_{24}N_2O_4S_2$: C, H, N. The residue from the mother liquor was dissolved in hexane–ethyl acetate (5:1 v/v). Slow evaporation gave isomerically pure **15b'**, the (4*R**,4'*S**); i.e., *meso*, isomer, m.p. 120–121 °C (25%). ^1H NMR ($CDCl_3$): δ 1.36 (3 H, t, J=7.1 Hz), 3.48 (1 H, d, J=13.0 Hz), 3.59 (1 H, d, J=13.0 Hz), 4.33–4.52 (2 H, m), 7.12–7.25 (5 H, m). ^{13}C NMR ($CDCl_3$): δ 14.2, 39.5, 65.7, 92.4, 126.9, 127.8, 131.0, 134.0, 161.0, 207.5. IR (KBr): 1731, 1629 cm^{-1}. MS m/z (CI): 509 (M^++41), 497 (M^++29), 469 (M^++1). Anal. $C_{24}H_{24}N_2O_4S_2$: C, H, N.

*2,2' - Diethoxy - 4,4' - diphenyl - [4,4' - bithiazole] - 5,5' - (4H,4'H)-diones (**15c and 15c'**)*. Reaction product mixture: m.p. 152–154 °C (93%). The ^{13}C NMR spectrum showed that the product was a mixture of *racemic* and *meso* isomers. Separation by recrystallization using several solvents and by column chromatography on silica gel was unsuccessful. ^1H NMR ($CDCl_3$): δ 1.47 (3 H, t, J=7.1 Hz), 4.5–4.7 (2 H, m), 7.1–7.5 (5 H, m). Proton signals of the minor isomer were hidden under those of the major isomer. The ^{13}C NMR spectrum clearly indicated that two compounds were present with one predominating. ^{13}C NMR ($CDCl_3$): δ 14.3 and 14.4, 65.9 and 66.2; 92.0 and 92.5; 126.8 and 127.1, 128.6, 128.78, 128.81, 129.2, 132.1 and 133.2, 160.2 and 161.4, 202.1 and 202.8. IR (KBr): 1719, 1631 cm^{-1}. MS m/z (CI): 469 (M^++29), 441 (M^++1), 220 (M^+/2), 132. Anal of **15c** plus **15c'**. $C_{22}H_{20}N_2O_4S_2$: C, H, N.

*2,2' - Diethoxy - 4,4' - diisobutyl - [4,4' - bithiazole] - 5,5' - (4H,4'H)-diones (**15d and 15d'**)*. The reaction product was an oil, which was a mixture of *racemic* and *meso* isomers, (88%). No separation of the isomers was achieved. ^1H NMR ($CDCl_3$): δ 0.85 (3 H, d, J=6.6 Hz) and 0.86 (3 H, d, J=6.6 Hz), 0.90 (3 H, d, J=6.6 Hz) and 0.91 (3 H, d, J=6.6 Hz), 1.37 (3 H, t, J=7.1 Hz) and 1.40 (3 H, t, J=7.1 Hz), 1.47 (1 H, m), 1.49 (1 H, m), 1.82 (1 H, dd, J=13.9 and 6.5 Hz) and 2.02 (1 H, dd, J=14.0 and 5.8 Hz), 2.34 (1 H, dd, J=13.9 and 5.5 Hz) and 2.10 (1 H, dd, J=14.0 and 5.5 Hz), 4.36–4.55 (4 H, m). ^{13}C NMR ($CDCl_3$): δ 14.2 and 14.4, 24.0 and 24.2, 24.4, 24.7 and 24.6, 39.1 and 41.8, 65.8 and 65.6, 91.4 and 92.9, 161.2 and 160.0, 207.2 and 207.7. IR (neat): 1733, 1635 cm^{-1}. MS m/z (EI) 400 (M^+), 316, 288, 200 (M^+/2), 112, 84, 57. Anal of **15d** plus **15d'**. $C_{18}H_{28}N_2O_4S_2$: C, H, N.

*2,2'-Diethoxy-4,4'-di(2-methylthioethyl)-[4,4'-bithiazole]-5,5'(4H,4'H)-diones (**15e and 15e'**)*. The crude reaction mixture (70%) was subjected to chromatography on silica gel (4:1 hexanes–ethyl acetate) followed by recrystallization from methanol to give **15e**, m.p. 67–69 °C. ^1H NMR ($CDCl_3$): δ 1.37 (3 H, t, J=7.1 Hz), 2.07 (3 H, s), 2.16–2.41 (3 H, m), 2.63–2.76 (1 H, m), 4.43 (2 H, m). ^{13}C NMR ($CDCl_3$): δ 14.3, 15.5, 28.5, 30.7, 66.2, 90.5, 162.4, 206.1. IR (KBr): 2974, 2912, 2850, 1737, 1633 cm^{-1}. MS m/z (CI): 465 (M^++29), 437 (M^++1), 389, 362, 313, 247, 220, 218 (M^+/2), 192, 170, 144. The second fraction from the column was a mixture of **15e** and **15e'**, obtained as a deep-yellow oil. ^1H NMR ($CDCl_3$): δ 1.37 (3 H, t, J=7.1 Hz) and 1.42 (3 H, 7.0 Hz), 2.07 (3 H, s) and 2.08 (3 H, s), 2.17–2.71 (8 H, m), 4.39–4.51 (4 H, m). The ^{13}C NMR spectrum clearly showed that there were two diastereomers in the mixture. ^{13}C NMR ($CDCl_3$): δ 14.2 and 14.3, 15.46 and 15.50, 28.5 and 28.1, 30.7 and 33.3, 66.2 and 66.1, 90.5 and 91.9, 162.4 and 161.3, 206.1 and 206.5. IR (neat): 1732, 1633 cm^{-1}. MS m/z (EI) 436 (M^+), 362, 286, 259, 218 (M^+/2), 158, 142, 102, 75, 61. Anal. $C_{16}H_{24}N_2O_4S_4$: C, H, N.

*2,2' - Diethoxy - 4,4' - diisopropyl - [4,4' - bithiazole] - 5,5' - (4H,4'H)-diones (**15f and 15f'**) and 2,2'-diethoxy-4,4'-diisopropyl-[2,4'-bithiazole]-5,5'(2H,4'H)-diones (**18 and 18'**)*. A mixture of 4,4'-bithiazolones and 2,4'-bithiazolones was obtained as a colorless oil (81%). The major component **15f**, a 4,4'-bithiazolone, was obtained in a small quantity in pure form by chromatography (silica gel; 10:1 hexanes–ethyl acetate). However, the majority of the reaction product was a viscous oil containing two 4,4'-bithiazolones (major) and two diastereomeric 2,4'-bithiazolones (minor). TLC showed four closely spaced spots. No successful separation was achieved. **15f**, m.p. 75.5–77.5 °C. ^1H NMR ($CDCl_3$): δ 0.92 (3 H, d, J=6.6 Hz), 1.20 (3 H, d, J=6.7 Hz), 1.39 (3 H, t, J=7.2 Hz), 2.62 (1 H, septet, J=6.7 Hz), 4.36–4.53 (2 H, m). ^{13}C NMR ($CDCl_3$): δ 14.3, 19.0, 19.8, 33.4, 65.8, 95.1, 160.9, 206.7. IR (KBr): 2969, 2937, 2875, 1748, 1630 cm^{-1}. MS m/z (CI): 373 (M^++1), 345, 257, 215, 187, 186 (M^+/2), 160, 126, 99. Major components of the oily fraction were 4,4'-bithiazolones **15f** and **15f'**. ^1H NMR ($CDCl_3$, the major component of this pair is reported first, the ratio of major–minor is 3:1): δ 0.92 and 0.83 (3 H, d, J=6.6 Hz), 1.20 and 1.25 (3 H, d, J=6.7 Hz), 1.39 and 1.40 (3 H, t, J=7.2 Hz), 2.62 and 2.74 (1 H, septet, J=6.7 Hz), 4.36–4.54 (2 H, overlapped, m). ^{13}C NMR ($CDCl_3$, the major component of this pair is reported first): δ 14.2, 18.9 and 19.2, 19.8 and 20.2, 33.3 and 33.5, 65.7 and 65.5, 95.1 and 95.5, 160.9 and 160.1, 206.6 and 208.9. The minor components, 2,4'-bithiazolones **18** and **18'**, comprised only about 20% of the total. ^1H NMR ($CDCl_3$, the ratio of this pair is almost 1:1) most proton signals of this pair are buried under the major components except for: δ 2.80–2.88 (1 H, m), 3.02–3.11 (1 H, m), 3.36–3.42 (1 H, m), 3.44–3.53 (1 H, m). ^{13}C NMR ($CDCl_3$): δ 14.1, 14.7 and 14.8, 17.6, (18.5, 19.3, 19.6, 19.9, 19.9, 20.0), 27.6 and 27.7, 33.1 and 34.1, 60.4 and 60.8, 65.6 and 66.0, 95.0 and 95.4, 119.9, 162.6 and 163.2, 175.9 and 176.6, 192.7 and 193.1, 204.4 and 205.5. For the mixture: IR (neat): 2975, 2936,

2876, 1737, 1731, 1695, 1639, 1630 cm^{-1}. Anal. $C_{16}H_{24}N_2O_4S_2$: C, H, N.

*2,2'-Diethoxy-4,4'-di(2-methylsulfonylethyl)-[4,4'-bithiazole]-5,5'(4H,4'H)-diones (**15g** and **15g'**).* Excess $KMnO_4$ gave a mixture of **15g** and **15g'**. Recrystallization from EtOH–acetone gave **15g** (20%), m.p. 210–211 °C. ^1H NMR ($CDCl_3$): δ 1.40 (3 H, t, J=7.2 Hz), 2.4–2.9 (4 H, m), 2.94 (3 H, s), 4.38–4.52 (2 H, m). ^{13}C NMR ($CDCl_3$–CD_3CN 1:1): δ 12.9, 23.0, 39.4, 47.9, 66.2, 88.3, 162.4, 204.3. IR (KBr): 1729, 1634, 1285, 1254 cm^{-1}. MS *m/z* (CI): 501 (M^++1), 421, 252, 250 (M^+/2), 170, 127, 81, 65, 41. Anal. $C_{16}H_{24}N_2O_8S_4$: C, H, N. A second crop was obtained which was recrystallized from acetone–hexane to give **15g'** (18%), m.p. 158–162 °C . ^1H NMR ($CDCl_3$): δ 1.42 (6 H, t, J= 7.2 Hz), 2.51–2.90 (8 H, m), 2.92 (6 H, s), 4.41–4.53 (4 H, m). ^{13}C NMR ($CDCl_3$): δ 14.1, 26.8, 40.5, 49.3, 67.0, 90.3, 162.6, 205.5. IR (KBr): 1732, 1629, 1313, 1281, 1254, 1229 cm^{-1}. MS *m/z* (CI): 501 (M^++1), 421, 292, 252, 250 (M^+/2), 170, 127, 81, 65. Anal. $C_{16}H_{24}N_2O_8S_4$: C, H, N.

*2,2'-Diethyl-4,4'-dibenzyl-[4,4'-bithiazole]-5,5'(4H,4'H)-diones (**19b** and **19b'**) and 2,2'-diethyl-4,4'-dibenzyl-[2,4'-bithiazole]-5,5'(2H,4'H)-diones (**20** and **20'**).* The crude reaction mixture was obtained in 85% yield. Recrystallization from abs. ethanol first gave a pure isomer of 2,4'-bithiazolone **20**, m.p. 143–145 °C, (21%). ^1H NMR ($CDCl_3$): δ 0.66 (3 H, t, J=7.2 Hz), 0.94 (3 H, t, J=7.5 Hz), 2.28 (2 H, m), 2.43 (1 H, m), 2.80 (1 H, m), 3.35 (1 H, d, J=12.9 Hz), 3.48 (1 H, d, J=12.9 Hz), 3.93 (1 H, d, J=14.4 Hz), 4.02 (1 H, d, J=1 4.4 Hz), 7.04–7.40 (10 H, m). ^{13}C NMR ($CDCl_3$): δ 7.3, 10.5, 27.5, 30.1, 34.4, 40.8, 93.7, 95.0, 127.0 127.1, 127.8, 128.5, 129.7, 131.0, 133.7, 135.3, 169.7, 171.7, 193.9, 208.0. IR (KBr): 3060, 2977, 2936, 1714, 1681, 1645, 1630 cm^{-1}. MS *m/z* (CI): 477 (M^++41), 465 (M^++29), 437 (M^++1), 408, 317, 248, 220, 218. Anal. $C_{24}H_{24}N_2O_2S_2$: C, H, N. Slow evaporation of the solvent gave **19b** contaminated by a small amount of **20**. A second recrystallization from ethanol–hexane (2:1 v/v) gave pure **19b**, m.p. 129–131 °C, (23%). ^1H NMR ($CDCl_3$): δ 0.98 (3 H, t, J=7.4 Hz), 2.36 (2 H, q, J=7.4 Hz), 3.41 (1 H, d, J= 12.8 Hz), 3.97 (1 H, d, J=12.8 Hz), 7.10–7.20 (5 H, m). ^{13}C NMR ($CDCl_3$): δ 10.8, 29.8, 36.8, 91.5,126.9, 127.7, 131.0, 133.6, 170.9, 209.4. IR (KBr): 1711, 1628. MS *m/z* (CI): 477 (M^++41), 465 (M^+ + 29), 437 (M^++1), 421, 317, 257, 220, 218. Anal. $C_{24}H_{24}N_2O_2S_2$: C, H, N. 2,4'-Bithiazolone **20'** was obtained when the residue from the mother liquor from the second crop was crystallized from EtOH–hexane. A second recrystallization from EtOH–hexane gave pure **20'**, m.p. 93–95 °C, (15%). ^1H NMR ($CDCl_3$): δ 0.65 (3 H, t, J=7.1 Hz), 0.93 (3 H, t, J=7.5 Hz), 2.29–2.53 (4 H, overlapped, m), 3.14 (1 H, d, J=12.7 Hz), 3.43 (1 H, d, J=12.7 Hz), 4.01 (1 H, d, J=14.1 Hz), 4.07 (1 H, d, J=14.1 Hz), 7.00–7.03 (2 H, m), 7.16–7.33 (6 H, m), 7.40–7.43 (2 H, m). ^{13}C NMR ($CDCl_3$): δ 7.4 10.5, 26.6, 30.1, 34.4, 34.0, 93.4, 94.6, 127.0, 127.0, 127.7, 128.5, 129.5, 130.9, 133.5, 135.0, 169.8, 171.6, 193.9, 208.7. IR (KBr): 3053, 2977, 2939, 2917, 1738, 1691, 1623 cm^{-1}. MS *m/z* (CI): 477 (M^++41), 465 (M^++29), 437 (M^++1), 377, 349, 257, 220, 218 (M^+/2), 193, 125. Anal. $C_{24}H_{24}N_2O_2S_2$: C, H, N. Isomer **19b'** was not obtained in pure form.

2,2'-Diethyl-4,4'-di(2-methylthioethyl)-[4,4'-bithiazole]-5,5'(4H,4'H)-dione (**19c**). The oily reaction product was chromatographed (silica gel; 4:1 hexane–ethyl acetate) (10%). According to the IR and NMR spectra, the product was a mixture of one diastereomer **19c** and two diastereomers of 2,2'-diethyl-4,4'-di(2-methylthioethyl)-[2,4'-bithiazole]-5,5'(2*H*,4'*H*)-diones (**21** and **21'**), with the 4,4'-bithiazolone as the major component. No separation was achieved and their identification is tentative. IR (neat): 2974, 2936, 2915, 1721, 1693, 1625 cm^{-1}. For the 4,4'-bithiazolone: partial ^{13}C NMR ($CDCl_3$): δ 91.0, 171.8, 208.1. For the 2,4'-dehydrodimers, partial ^{13}C NMR ($CDCl_3$): δ (92.5, 92.6, 95.1, 95.4), (169.7, 169.9, 172.4, 172.5), (193.6, 193.7, 207.1, 207.7).

*2,2' - Diethylthio - 4,4' - dimethyl - [4,4' - bithiazole] - 5,5' - (4H,4'H)-diones (**22a** and **22a'**).* The NMR spectra showed that the crude product, obtained in 93% yield, was a mixture of **22a** and **22a'** in roughly equal amounts. Isomer **22a** was obtained in a small amount by column chromatography (silica gel; 4:1 EtOAc–hexanes). However, the majority of the product remained a mixture of both isomers. Isomer **22a**, ^1H NMR ($CDCl_3$): δ 1.35 (3 H, t, J=7.4 Hz), 1.59 (3 H, s), 3.04–3.22 (2 H, m). ^{13}C NMR ($CDCl_3$): δ 14.6, 17.7, 25.15, 88.0, 162.3, 207.1. IR (neat): 2979, 2931, 2872, 1728, 1557 cm^{-1}. Isomers **22a** and **22a'** gave ^1H NMR ($CDCl_3$): δ 1.35 and 1.40 (3 H, t, J=7.4 Hz), 1.59 and 1.60 (3 H, s), 3.01–3.30 (2 H, overlapped, m). ^{13}C NMR ($CDCl_3$): δ 14.55 and 14.60, 17.7 and 19.9, 25.2 and 25.4, 88.0 and 89.1, 161.4 and 162.3, 207.1 and 207.4. IR (neat): 2979, 2931, 2872, 1728, 1557 cm^{-1}. Anal. $C_{12}H_{16}N_2O_2S_4$: C, H, N.

*2,2' - Diethylthio - 4,4' - dibenzyl - [4,4' - bithiazole] - 5,5' - (4H,4'H)-diones (**22b** and **22b'**).* The reaction product was an oil (91%), whose NMR spectra showed it to be a mixture of *racemic* and *meso* isomers. Separation was accomplished by recrystallization from acetone–95% EtOH. The first crop yielded **22b**, m.p. 97–99 °C. ^1H NMR ($CDCl_3$): δ 1.31 (3 H, t, J=7.4 Hz), 3.08 (2 H, qd, J=7.4 and 1.3 Hz), 3.41 (1 H, d, J=13.0 Hz), 3.97 (1 H, d, J=13.0 Hz), 7.09–7.14 (2 H, m), 7.19–7.25 (3 H, m). ^{13}C NMR ($CDCl_3$): δ 14.8 , 25.0, 37.1, 91.8, 127.0, 127.9, 130.8, 133.6, 163.7, 207.8. IR (KBr): 3059, 3027, 2974, 2930, 2871, 1717, 1556 cm^{-1}. MS *m/z* (CI): 541 (M^++41), 529 (M^++29), 501 (M^++1), 473, 413, 252, 250 (M^+/2), 224, 162, 121, 59. Anal. $C_{24}H_{24}N_2O_2S_4$: C,H, N. The residue from the mother liquor was recrystallized from acetone–95% EtOH–water to give **22b'**,

m.p. 121–123 °C. ^{1}H NMR ($CDCl_3$): δ 1.44 (3 H, J= 7.3 Hz), 3.03 (1 H, dq, J=13.4 and 7.3 Hz), 3.32 (1 H, dq, J=13.4 and 7.3 Hz), 3.64 (1 H, d, J=13.4 Hz), 3.68 (1 H, d, J=13.4 Hz), 7.09–7.13 (2 H, m), 7.20–7.25 (3 H, m). ^{13}C NMR ($CDCl_3$): δ 14.94, 25.3, 39.5, 93.0, 127.1, 127.9, 130.8, 133.5, 163.3, 207.7. IR (KBr): 3056, 3028, 2959, 2919, 2866, 1720, 1555 cm^{-1}. Anal. $C_{24}H_{24}N_2O_2S_4$: C, H, N.

*2,2′-Diethylthio-4,4′-diisopropyl-[4,4′-bithiazole]-5,5′-(4H,4′H)-diones (**22c** and **22c′**) and 2,2′-diethylthio*-4,4′-diisopropyl-[2,4′-bithiazole]-5,5′(2H,4′H)-diones (***23** and **23′***). The oily crude reaction product (83%) was purified by chromatography (silica gel; 10:1 hexanes–EtOAc) to give a mixture of **22c** and **22c′** and the 2,4′-bithiazolones **23** and **23′**, with the 2,4′-bithiazolones as the major components. The identification of the 2,4′-bithiazolones and 4,4′-bithiazolones was based partially on the IR and ^{13}C NMR spectra. No successful separation was achieved. The ^{1}H NMR and ^{13}C NMR spectra of this mixture were very complicated. Partial ^{13}C NMR ($CDCl_3$): δ (95.0, 95.2, 95.4, 95.8, 98.4, 98.5), (161.8, 162.6, 164.7, 173.5, 175.0), (193.0, 193.4, 205.2, 206.9, 207.1, 209.0). IR (neat): 2965, 2926, 2870, 1730, 1689, 1553 cm^{-1}. Anal. $C_{16}H_{24}N_2O_2S_4$: C, H, N.

*2,2′-Diethylthio-4,4′-diphenyl-[4,4′-bithiazole]-5,5′-(4H,4′H)-dione (**22d**)*. The reaction product (68%) consisted of one isomer; m.p. 131–133 °C (acetone–95% EtOH). ^{1}H NMR ($CDCl_3$): δ 1.49 (3 H, t, J=7.4 Hz), 3.30–3.37 (2 H, m), 7.19–7.42 (5 H, m). ^{13}C NMR ($CDCl_3$): δ 14.8, 25.4, 91.7, 127.0, 129.0, 129.3, 131.3, 163.8, 202.7. IR (KBr): 3056, 2973, 2928, 2850, 1734, 1559 cm^{-1}. MS m/z (CI): 473 (M^++1), 385, 348, 298, 238, 237, 236 (M^+/2), 210, 151, 105. Anal. $C_{22}H_{20}N_2O_2S_4$: C, H, N. Although **22d** decomposed when allowed to stand in acetone–hexane soln. for several days, it was stable in the solid state for months.

Photochemical dehydrodimerization of 2-phenyl-4-methylthiazolone (**6a**). A stream of oxygen was passed through a soln. of **6a** (0.50 g, 1.32 mmol) and methylene blue (10 mg) in CH_2Cl_2 (80 ml) which was irradiated for 6 h with light from a Kodak slide projector.[6] The solvent was removed and the residue was recrystallized from 95% ethanol to give colorless crystals, m.p. 139–140 °C (lit.[6] 140 °C), (0.23 g, 0.61 mmol, 46%). The NMR spectra showed that it was mainly isomer **10a**. ^{1}H NMR ($CDCl_3$): δ 1.77 (3 H, s), 7.33–7.48 (3 H, m), 7.64–7.68 (2 H, m). ^{13}C NMR ($CDCl_3$): δ 17.7, 89.3, 128.2, 128.7, 132.1, 133.0, 164.8, 207.9. IR (KBr): 1723, 1600, 1576 cm-^{1}. MS m/z (EI) 352 (M^+−CO), 291, 259, 190 (M^+/2), 163, 121, 77.

Photochemical dehydrodimerization of 2-phenyl-4-benzylthiazolone (**6b**) was carried out as above for 8 h to give **10b**, m.p. 185–187 °C (acetone–ethanol, 2:1), (51%). ^{1}H NMR ($CDCl_3$–CD_3CN 1:1): δ 3.60 (1 H, d, J= 13.0 Hz), 4.12 (1 H, d, J=13.0 Hz), 7.10–7.20 (5 H, m), 7.3–7.5 (5 H, m). ^{13}C NMR ($CDCl_3$–CD_3CN 1:1): δ 36.3, 92.2, 126.16, 126.9, 127.0, 128.0, 130.0, 131.5, 131.6, 132.8, 165.1, 207.3. IR (KBr): 1721, 1595 cm^{-1}. MS m/z (EI) 504 (M^+−CO), 443, 266 (M^+/2), 206, 121. Anal. $C_{32}H_{24}N_2O_2S_2$: C, H, N.

Photochemical dehydrodimerization of 2-phenyl-4-isobutylthiazolone (**6c**) was carried out as above for 8 h to give a mixture of **10c** and **10c′**, m.p. 136–138 °C (acetone–ethanol 1:1), (57%). The ^{1}H NMR spectrum showed that the ratio of **10c**:**10c′** was about 10:1. The spectral data were identical with those measured for **10c** and **10c′** obtained by $KMnO_4$ oxidation of **6c**.

*Cross-coupling of 2-phenyl-4-methylthiazolone (**6a**) and 2-phenyl-4-benzylthiazolone (**6b**) by oxidation with $KMnO_4$*. Thiazolones **6a** (0.32 g, 1.68 mmol) and **6b** (0.15 g, 0.56 mmol) in acetic acid (15 ml) were treated with $KMnO_4$ (10 ml, 3%) as described above for **10a** to give a solid (0.42 g, 89%) whose NMR spectra showed it to be a mixture of **10a**, **10a′**, **10b**, **10b′** and the diastereomeric 4′-benzyl-4-methyl-2,2′-diphenyl-4,4′-bi(thiazoline)-5,5′-diones **24a** and **24a′**. According to the integration of the ^{1}H NMR spectrum, 89% of **6b** formed the cross-dehydrodimers **24a** and **24a′**. Only 11% of **6b** formed the self-dehydrodimers **10b** and **10b′**. No separation was accomplished. The NMR spectra of the mixture had peaks which matched those of authentic **10a**, **10a′**,**10b** and **10b′**. Cross-dehydrodimers: partial ^{1}H NMR ($CDCl_3$, major isomer reported first, major:minor= 77:23): δ 1.90 (3 H, s) and 1.89 (3 H, s), 3.44 (1 H, d, J=13.0) and 3.69 (1 H, d, J=13.1 Hz), 4.01 (1 H, d, J=13.0 Hz) and 3.76 (1 H, d, J=13.1 Hz). Partial ^{13}C NMR ($CDCl_3$): δ 17.7, 12.0, 37.3, 39.6, (89.6, 90.8, 92.7, 94.0), (163.8, 164.7, 165.7, 166.2), (208.18, 208.23, 208.6).

*Cross-coupling of 2-ethylthio-4-methylthiazolone (**9a**) and 2-phenyl-4-benzylthiazolone (**6b**) by oxidation with $KMnO_4$*. Thiazolones **9a** (0.39 g, 2.25 mmol) and **6b** (0.20 g, 0.75 mmol) in acetic acid (15 ml) were treated with $KMnO_4$ (9 ml, 3%) as described above for **10a** to give a solid (0.45 g, 76%), which the NMR spectra showed was a mixture of **22a**, **22a′**, **10b**, **10b′**, and diastereomeric 4′-benzyl-2′-ethylthio-4′-methyl-2-phenyl-4,4′-bi(thiazoline)-5,5′-diones **24b** and **24b′**. According to the integration of the ^{1}H NMR spectrum, 75% of **6b** formed the cross-dehydrodimers. Only 25% of **6b** formed the self-dehydrodimers **10b** and **10b′**. These were separated from the mixture by recrystallization from acetone–EtOH–water. However, no further separation of the remaining bithiazolones was achieved. The NMR spectra of the mixture had peaks which matched those of authentic **22a**, **22a′**, **10b** and **10b′**. Cross-dehydrodimers: partial ^{1}H NMR ($CDCl_3$, major isomer reported first, major:minor=57:43): δ 1.19 (3 H, t, J=7.4 Hz) and 1.21 (3 H, t, J=7.4 Hz), 1.78 (3 H, s) and 1.77 (3 H,

s), 3.35 (1 H, d, J=13.1 Hz) and 3.60 (1 H, d, J=13.1 Hz), 3.93 (1 H, d, J=13.10 and 3.67 (13.1 Hz). Partial ^{13}C NMR ($CDCl_3$): δ (14.4, 14.6), (17.6, 19.8), (25.0, 25.4), (37.3, 39.7), (88.3, 89.5, 92.7, 93.9), (161.5, 162.5, 165.4, 168.5), (207.3, 207.6, 208.1, 208.4).

Reaction of ***10a*** *with* CH_3OH–Et_3N. Triethylamine (0.4 ml) was added to bithiazolone **10a** (0.15 g, 0.39 mmol) in methanol (15 ml). The mixture was heated under reflux for 20 h. Chromatography (silica gel; 2:1 hexanes–ethyl acetate) followed by recrystallization from acetone–petroleum ether gave *racemic* **29**, m.p. 95–97 °C (lit.[18] m.p. 100–101 °C), (0.061 g, 0.27 mmol, 69%). ^{1}H NMR ($CDCl_3$): δ 1.63 (3 H, d, J=7.1 Hz), 3.83 (3 H, s), 5.30 (1 H, quintet, J=7.1 Hz), 7.38–7.51 (3 H, m), 7.78–7.81 (2 H, m), 8.12 (1 H, br s). ^{13}C NMR ($CDCl_3$): δ 17.3, 52.8, 53.9, 126.7, 128.5, 131.4, 141.3, 173.0, 198.6. IR (KBr): 3290, 3044, 2959, 2847, 1736, 1532 cm^{-1}. MS m/z (EI) 223 (M^+), 190, 163, 121, 104, 77, 59.

Reaction of ***10a*** *with* L-*alanine methyl ester.* Triethylamine (1.0 ml) and L-alanine methyl ester hydrochloride (0.165 g, 1.18 mmol) were added to bithiazolone **10a** (0.15 g, 0.39 mmol) in THF (15 ml). The mixture was heated under reflux for 36 h. Chromatography on silica gel (4:1 hexanes–ethyl acetate) followed by recrystallization from EtOH–petroleum ether gave a mixture of two diastereomers of *N*-(1-methoxycarbonylethyl)-2,3-dimethyl-2,3-di(thiobenzamido)succinimide (**30**), m.p. 190–192 °C, (0.092 g, 0.19 mmol, 49%). Attempts to separate the isomers by recrystallization were unsuccessful. ^{1}H NMR ($CDCl_3$): δ 1.74 (3 H, d, J=7.4 Hz) and 1.81 (3 H, d, J=7.4 Hz), 2.18 (12 H, s), 3.77 (3 H, s) and 3.79 (3 H, s), 4.94 (1 H, q, J=7.4 Hz) and 5.05 (1 H, q, J=7.4 Hz), 7.42–7.55 (12 H, m), 7.86–7.88 (4 H, m), 8.39 (2 H, s) and 8.40 (2 H, s). ^{13}C NMR ($CDCl_3$): δ 13.1 and 13.4, 20.9 (br), 48.7 and 49.3, 52.9 and 53.0, 68.4 (br), 126.7 and 126.7, 128.7, 131.7 and 131.8, 141.7 and 141.7, 169.2 and 169.3, 172.7 (br), 199.1(br). IR (KBr): 3339, 1792, 1750, 1722 cm^{-1}. MS m/z (EI) 483 (M^+), 446, 345, 259, 210, 189, 121, 105, 77. Anal. $C_{24}H_{25}N_3O_4S_2$: C, H, N.

Reaction of ***10a*** *with 1-butylamine.* 1-Butylamine (1.0 ml) was added to bithiazolone **10a** (0.15 g, 0.39 mmol) in THF (25 ml). The mixture was heated under reflux for 24 h. Chromatography (silica gel; 2:1 hexanes–ethyl acetate) gave *N*-butyl-2,3-dimethyl-2,3-di(thiobenzamido)succinimide (**31**). Further purification by recrystallization from acetone–hexane gave yellow crystals, m.p. 156.5–157.5 °C, (41 mg, 0.091 mmol, 24%). ^{1}H NMR ($CDCl_3$): δ 0.99 (3 H, t, J=7.4 Hz), 1.44 (2 H, m), 1.74 (2 H, m), 2.11 (6 H, s), 3.71 (2 H, m), 7.27–7.54 (6 H, m), 7.80–7.89 (4 H, m), 8.36 (2 H, s). ^{13}C NMR ($CDCl_3$): δ 13.6, 20.12, 21.1 (br), 28.8, 39.6, 68.4 (br), 126.7, 128.7, 131.7, 141.8, 173.8 (br), 199.1 (br). IR (KBr): 3353, 3058, 2957, 2938, 2827, 1722, 1696 cm^{-1}. MS m/z (EI) 453 (M^+), 317, 301, 274, 213, 189, 138, 121, 104, 77. Anal. $C_{24}H_{27}N_3O_2S_2$: C, H, N.

Reaction of ***10a*** *with benzoic hydrazide.* Benzoic hydrazide (0.16 g, 1.18 mmol) was added to bithiazolone **10a** (0.15 g, 0.39 mmol) in acetonitrile (25 ml). The mixture was heated under reflux for 24 h. Chromatography (silica gel; 1:1 hexanes–ethyl acetate) followed by recrystallization from acetonitrile gave *racemic* **32** as yellow crystals, m.p. 200–202 °C (0.085 g, 0.26 mmol, 67%). ^{1}H NMR (DMSO-d_6): δ 1.57 (3 H, d, J=7.2 Hz), 5.25 (1 H, quintet, J=7.2 Hz), 7.39–7.59 (6 H, m), 7.75–7.77 (2 H, m), 7.87–7.90 (2 H, m), 10.16 (1 H, br s), 10.31 (1 H, d, J=7.2 Hz), 10.45 (1 H, br s). ^{13}C NMR (DMSO-d_6): δ 17.7, 54.0, 127.5, 127.6, 127.9, 128.5, 130.8, 131.9, 132.4, 141.1, 165.4, 170.7, 198.0. IR (KBr): 3360, 3205, 1693. 1609 cm^{-1}. MS m/z (EI) 327 (M^+), 293, 276, 192, 164, 121, 105, 77, 51. Anal. $C_{17}H_{17}N_3O_2S$: C, H, N.

Reaction of ***10a*** *with pyrrolidine.* Pyrrolidine (0.3 ml) was added to bithiazolone **10a** (0.15 g, 0.39 mmol) in THF (20 ml). The mixture was heated under reflux for 24 h. Work-up gave *racemic N*-thiobenzoylmethylalanine pyrrolidinylamide (**33**) as yellow crystals, m.p. 174–176 °C (aqueous acetone), (55 mg, 0.21 mmol, 54%). ^{1}H NMR ($CDCl_3$): δ 1.55 (3 H, d, J=6.8 Hz), 1.88–1.94 (2 H, m), 1.97–2.07 (2 H, m), 3.45–3.60 (3 H, m), 3.71 (1 H, dt, J=10.0 and 6.5 Hz), 5.36 (1 H, quintet, J=6.8 Hz), 7.36–7.49 (3 H, m), 7.79–7.83 (2 H, m), 8.81 (1 H, br d). ^{13}C NMR ($CDCl_3$): δ 16.6, 24.1, 26.0, 46.2, 45.3, 53.3, 126.8, 128.3, 131.2, 141.2, 170.1, 197.0. IR (KBr): 3202, 1630 cm^{-1}. MS m/z (EI) 262 (M^+), 229, 191, 163, 121, 77, 55. Anal. $C_{14}H_{18}N_2OS$: C, H, N.

Reaction of ***10b*** *with glycine ethyl ester.* Triethylamine (0.2 ml) and glycine ethyl ester hydrochloride (0.165 g, 1.18 mmol) were added to a mixture of bithiazolones **10b** and **10b′** (0.216 g, 0.406 mmol) in THF (25 ml). The mixture was heated under reflux for 36 h. Chromatography (silica gel; 4:1 hexanes–ethyl acetate) gave (*Z*)-2-phenyl-4-benzylidene-5(4*H*)-thiazolone (**6g**), m.p. 128–130 °C (lit.[21] 130–132 °C), (0.066 g, 0.25 mmol, 61%) which was identified by comparison with an authentic sample. ^{1}H NMR ($CDCl_3$): δ 7.24 (1 H, s), 7.42–7.59 (6 H, m), 7.98–8.02 (2 H, m), 8.22–8.28 (2 H, m). ^{13}C NMR ($CDCl_3$): δ 128.2, 128.9, 128.9, 131.3, 131.3, 132.6, 133.2, 133.4, 133.7, 146.2, 166.7, 194.6. IR (KBr): 1695 cm^{-1}. MS m/z (EI) 265, 204, 144, 121, 102, 77, 51. Compound **34** was obtained (2:1 hexanes–ethyl acetate) as yellow crystals, m.p. 98–99 °C (acetone–hexanes), (0.105 g, 0.283 mmol, 70%). ^{1}H NMR ($CDCl_3$): δ 1.26 (3 H, t, J=7.1 Hz), 3.22 (1 H, dd, J=13.7 and 8.3 Hz), 3.47 (1 H, dd, J=13.7 and 5.3 Hz), 3.95 (1 H, dd, J=−13.8 and 6.4 Hz), 3.97 (1 H, dd, J=−13.8 and 6.4 Hz), 4.18 (2 H, q, J=7.1 Hz), 5.44 (1 H, m), 6.26 (1 H, br t), 7.26–7.48 (8 H, m), 7.69–7.71 (2 H, m), 8.43 (1 H, d, J=7.1 Hz). ^{13}C NMR ($CDCl_3$): δ 14.1, 37.2, 41.4, 60.1,

61.7, 126.8, 127.3, 128.4, 128.8, 129.3, 131.4, 136.0, 141.1, 169.0, 170.1, 198.4. IR (KBr): 3294, 1728, 1667 cm^{-1}. MS *m/z* (EI) 370 (M^+), 337, 267, 240, 131, 121, 91, 77. Anal. $C_{20}H_{22}N_2O_3S$: C, H, N.

Reaction of ***10b*** *with benzoic hydrazide.* Benzoic hydrazide (0.091 g, 0.669 mmol) was added to a mixture of bithiazolones **10b** and **10b′** (0.16 g, 0.30 mmol) in acetonitrile (30 ml). The mixture was heated under reflux for 36 h. The solvent was removed and the residue was recrystallized from acetone–EtOH–H_2O. Two crops were obtained after recrystallization. The first crop was identified as **6g** (50 mg, 0.19 mmol, 63%) by comparison with the authentic compound. The second crop was tentatively identified as **35** (42 mg, 0.10 mmol, 35%), yellow crystals, m.p. 208–211 °C. ^{1}H NMR ($CDCl_3$): δ 3.37 (1 H, dd, J=14 and 6.7 Hz), 3.41 (1 H, dd, J=14 and 6.8 Hz), 5.76 (1 H, q, J=7 Hz), 7.19–7.53 (6 H, m), 7.61–7.64 (2 H, m), 7.79–7.81 (2 H, m), 8.55 (1 H, d, J=7.6 Hz), 9.44 (1 H, br s), 10.04 (1 H, br s). IR (KBr): 3218 br, 3068, 3027, 2914, 1699, 1634, 1614 cm^{-1}.

Reaction of ***10b*** *plus* ***10b′*** *with KOH–EtOH.* A mixture of bithiazolone **10b** plus **10b′** (0.16 g, 0.30 mmol) and ethanolic KOH (3.5 ml, 0.185 M) in ethyl acetate (30 mL) was refluxed for 24 h and then acidified with 6 M HCl. Work-up followed by chromatography (silica gel; 4:1 hexanes–ethyl acetate) gave two fractions. Fraction 1 was identified as **6g**. Fraction 2 was tentatively identified as a mixture of *N*-thiobenzoylphenylalanine ethyl ester (**38**) and 2,5-diphenyl-2-thiazoline-4-carboxylic acid ethyl ester (**36**). No successful separation of these two compounds was achieved. Ester **38**: ^{1}H NMR ($CDCl_3$): δ 1.30 (3 H, t, J=7.2 Hz), 3.32 (1 H, dd, J=13.9 Hz and 4.5 Hz), 3.60 (1 H, dd, J=13.9 and 6.2 Hz), 4.25 (2 H, overlapped with the other compound), 5.53 (1 H, ddd, J=7.2, 6.2 and 4.5 Hz), 7.12–7.14 (2 H, m), 7.23–7.48 (6 H, overlapped with the other compound), 7.68–7.71 (2 H, m), 7.99 (1 H, br d). ^{13}C NMR ($CDCl_3$): δ 14.11, 36.0, 59.0, 61.9, 126.6, 127.3, 128.5, 128.6, 129.4, 131.3, 135.5, 141.3, 170.9, 198.4. MS *m/z* (CI): 354 (M^++41),342 (M^++29), 314 (M^++1). Ester **36**: ^{1}H NMR ($CDCl_3$): δ 1.30 (3 H, t, J=7.1 Hz), 4.26 (2 H, overlapped with the other compound), 5.35 (1 H, d, J=6.5 Hz), 5.43 (1 H, d, J=6.5 Hz), 7.23–7.54 (8 H, overlapped with the other compound), 7.89–7.92 (2 H, m). ^{13}C NMR ($CDCl_3$): δ 14.1, 56.6, 61.9, 86.6, 127.5, 128.1, 128.5, 128.6, 128.9, 131.8, 132.6, 140.4, 170.2. MS *m/z* (CI): 352 (M^++41), 340 (M^++29), 312 (M^++1).

Reaction of ***10b*** *plus* ***10b′*** *with piperidine.* Piperidine (0.4 ml) and bithiazolones **10b** plus **10b′** (0.16 g, 0.30 mmol) in ethyl acetate (20 ml) were heated under reflux for 16 h. The solvent was allowed to evaporate off slowly in the air. After several days, yellow needles formed, which were shown to be *racemic N*-(thiobenzoyl)phenylalanine piperidylamide (**39**), m.p. 171–172 °C, (0.051 g, 0.14 mmol, 48%). ^{1}H NMR ($CDCl_3$): δ 1.06 (1 H, m), 1.40–1.59 (5 H, m), 2.99 (1 H, ddd, J=13.3, 7.6 and 3.6 Hz), 3.29 (3 H, m), 3.53 (2 H, m), 5.83 (1 H, m), 7.22–7.46 (8 H, m), 7.75–7.78 (2 H, m), 8.67 (1 H, br d). ^{13}C NMR ($CDCl_3$): δ 24.1, 25.3, 37.6, 43.2, 46.6, 56.4, 126.8, 127.2, 128.4, 128.5, 129.7, 131.3, 135.7, 141.2, 168.5, 197.2. IR (KBr): 3212, 1617 cm^{-1}. MS *m/z* (EI) 352 (M^+), 319, 267, 216, 121, 86, 41. Anal. $C_{21}H_{24}N_2OS$: C, H, N. After the first crop had been filtered off, hexane was added to the mother liquor. Upon slow evaporation of the solvents in the open for several days, yellow crystals, identified as **6g**, formed. This second crop was filtered off, after which the mother liquor was evaporated completely and the residue was recrystallized from hexanes to give colorless crystals of *racemic* (4*R**,5*R**)-2,5-diphenyl-2-thiazoline-4-carboxylic acid piperidylamide (**37**), m.p. 135–138 °C, (0.038 g, 0.11 mmol, 36%). whose crystal structure was determined by X-ray crystallography (Fig. 2 and Table 3). ^{1}H NMR ($CDCl_3$): δ 1.54–1.72 (6 H, m), 3.35 (1 H, m), 3.51 (1 H, m), 3.86 (1 H, m), 3.98 (1 H, m), 5.50 (1 H, d, J=6.1 Hz), 5.92 (1 H, d, J=6.1 Hz), 7.24–7.51 (8 H, m), 7.85–7.89 (2 H, m). ^{13}C NMR ($CDCl_3$): δ 24.5, 25.6, 26.5, 43.7, 55.2, 86.2, 127.8, 127.9, 128.5, 128.5, 128.9, 131.4, 133.0, 141.5, 166.3, 168.3. IR (KBr): 1641, 1594, 1576 cm^{-1}. MS *m/z* (EI) 238 ($M^+ - CONC_5H_{10}$), 206, 162, 135, 112, 91, 69. Anal. $C_{21}H_{22}N_2OS$: C, H, N.

Reaction of 4,4′-bithiazolinones ***15a*** *and* ***15a′*** *with HCl gas.* A stream of HCl gas was passed through a solution of **15a** and **15a′** (0.093 g, 0.32 mmol) in benzene (5 ml) for 3 h during which time a colorless solid separated. The solid was collected, washed with ether, and dried giving a mixture of the *racemic* and *meso* isomers of the bis(*N*-carboxythioanhydrides) of alanine, (**40a** and **40a′**), (0.060 g, 0.23 mmol, 77%), m.p. 229–231 °C (decomp.). ^{1}H NMR (DMSO-d_6): δ 1.5 (3 H, overlapped, s), 9.79 and 9.92 (1 H, s). ^{13}C NMR (DMSO-d_6): δ 18.5 and 19.8, 75.0 and 76.0, 163.4 and 163.6, 198.5 and 200.0. IR (KBr): 3278, 3258, 2836, 1696, 1678 cm^{-1}. Anal. $C_8H_8N_2O_4S_2$: C, H, N.

*Reaction of (4*R**,4′*S**)-4,4′-bithiazolinone* ***15b′*** *with HCl gas* as above gave the *meso* isomer of bis(*N*-carboxythioanhydride) of phenylalanine (**40b′**) as a colorless solid, (91%), m.p. greater than 260 °C. ^{1}H NMR (DMSO-d_6): δ 3.23 (1 H, d, J=13.4 Hz), 3.53 (1 H, d, J=13.4 Hz), 7.19–7.35 (5 H, m), 10.20 (1 H, s). ^{13}C NMR (DMSO-d_6): δ 37.8, 80.4, 127.5, 128.3, 130.9, 132.7, 164.09, 199.7. IR (KBr): 3216, 3031, 2922, 2855, 1738, 1677 cm^{-1}. MS *m/z* (CI): 413 (M^++1), 381, 353, 265, 208, 206 (M^+/2), 146, 120, 91. Anal. $C_{20}H_{16}N_2O_4S_2$: C, H, N.

*Reaction of (4*R**,4′*R**)-4,4′-bithiazolinone* ***15b*** *with HCl gas* as above gave the *racemic* isomer of bis(*N*-carboxythioanhydride) of phenylalanine (**40b**) (97%), m.p. 237–239 °C (decomp.). ^{1}H NMR (DMSO-d_6): δ 3.32 (2 H, d, J=13.5 Hz), 3.51 (2 H, d, J=13.5 Hz),

Table 3. Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2) for (4*R**,5*R**)-2,5-diphenyl-2-thiazoline-4-carboxylic acid piperidylamide (**37**).

Atom	*x*	*y*	*z*	B_{eq} [a]
S1	0.9045(1)	0.2358(1)	0.5997(1)	5.38(2)
O1	0.9002(1)	0.4436(3)	0.7141(1)	5.08(5)
N1	1.0490(1)	0.3543(3)	0.6334(1)	3.88(5)
N2	1.0365(1)	0.5317(3)	0.7249(1)	4.00(5)
C1	1.0157(2)	0.2309(4)	0.6136(1)	3.87(6)
C2	0.9846(2)	0.4792(4)	0.6443(1)	3.77(6)
C3	0.8968(2)	0.4438(4)	0.6186(1)	4.08(6)
C4	0.9708(2)	0.4835(3)	0.6976(1)	3.66(6)
C5	1.1228(2)	0.5828(4)	0.7093(1)	4.64(7)
C6	1.1916(2)	0.4734(5)	0.7311(1)	5.77(9)
C7	1.1827(2)	0.4664(6)	0.7844(1)	6.31(9)
C8	1.0912(2)	0.4194(5)	0.7982(1)	5.14(8)
C9	1.0258(2)	0.5301(4)	0.7760(1)	4.72(7)
C10	0.8332(2)	0.7053(4)	0.5914(1)	4.66(7)
C12	0.8139(2)	0.8181(4)	0.5573(1)	5.89(8)
C13	0.8343(2)	0.7900(5)	0.5116(1)	6.35(9)
C14	0.8765(3)	0.6501(6)	0.4995(1)	6.34(9)
C15	0.8970(2)	0.5383(4)	0.5334(1)	5.26(8)
C17	1.0834(3)	−0.1664(5)	0.5602(1)	6.36(9)
C18	1.1623(3)	−0.1897(5)	0.6806(1)	6.11(9)
C19	1.1948(2)	−0.0782(5)	0.6114(1)	5.96(9)
C20	1.1465(2)	0.0579(4)	0.6229(1)	4.85(7)
C21	1.0666(2)	0.0836(4)	0.6023(1)	4.05(6)

[a] $B_{eq} = (4/3)\Sigma_i\Sigma_j\beta_{ij}\boldsymbol{a}_i.\boldsymbol{a}_j$.

7.19–7.34 (10 H, m), 10.09 (2 H, s). ^{13}C NMR (DMSO-d_6): δ 36.9, 79.3, 127.4, 128.3, 130.9, 132.9, 164.2, 198.2. IR (KBr): 3167, 3069, 2885, 1697, 1667 cm^{-1}. MS *m/z* (EI) 441(M^++29), 415, 413 (M^++1), 353, 296, 234, 208, 206 (M^+/2), 180, 120, 91. Anal. $C_{20}H_{16}N_2O_4S_2$: C, H, N.

*Reaction of 4,4'-bithiazolinones **15c** and **15c'** with HCl gas* as above gave a mixture of the *racemic* and *meso* isomers of the bis(*N*-carboxythioanhydride)s of phenylglycine (**40c** and **40c'**) (11%), m.p. 209–210 °C (decomp.). ^{1}H NMR (DMSO-d_6): δ 7.24–7.52 (5 H, overlapped m), 9.91 and 10.30 (1 H, s). ^{13}C NMR (DMSO-d_6): δ 70.1 and 93.0, 125.9, 126.8, 128.0, 128.5, 129.0, 129.2, 135.1 and 137.3, 162.9 and 164.8, 198.1 and 198.7. IR (KBr): 3222, 3095, 1737, 1672 cm^{-1}. MS *m/z* (CI): 385 (M^++1), 281, 234, 194, 192 (M^+/2), 166, 123, 104, 79. The solvent (benzene) of the mother liquor was removed and the residue was recrystallized from $CHCl_3$–petroleum ether giving 4-phenyl-2,5-thiazolidinedione (**41**), m.p. 129–131 °C (lit.[7] 125–127 °C), (0.23 g, 1.19 mmol, 52%). ^{1}H NMR ($CDCl_3$): δ 5.29 (1 H, s), 7.08 (1 H, br s), 7.34–7.45 (5 H, m). ^{13}C ($CDCl_3$): δ 70.3, 126.5, 129.3, 129.7, 133.6, 167.4, 195.7. IR (KBr): 3146, 3071, 2857, 1747, 1682 cm^{-1}. MS *m/z* (CI): 193 (M^+), 165, 136, 121, 104, 77, 51.

*Reaction of 4, 4'-bithiazolinones **15d** and **15d'** with HCl gas* as above gave a mixture of the *racemic* and *meso* isomers of the bis(*N*-carboxythioanhydride)s of leucine (**40d** and **40d'**) (80%), m.p. 215–217 °C (decomp.). ^{1}H NMR (DMSO-d_6): δ 0.80 and 0.81 (3 H, d, *J*=6.5 Hz), 0.90 and 0.92 (3 H, d, *J*=6.7 Hz), 1.57 (1 H, overlapped, m), 1.73 (1 H, dd, *J*=14.3 and 5.4 Hz), 1.94 (1 H, dd, *J*=6.4 Hz) This diastereomeric pair of methylene protons for the other isomer appears as a doublet at 1.87 ppm, (2 H, *J*=6.2 Hz), 9.79 and 9.94 (1 H, s). ^{13}C NMR (DMSO-d_6): δ 23.3 and 23.8, 23.8, 24.0 and 24.3, 38.3 and 39.8, 79.3 and 80.4, 164.0 and 164.1, 198.7 and 200.1. IR (KBr): 3288, 2959, 2931, 2872, 1701, 1683 cm^{-1}. MS *m/z* (CI): 385 (M^++41), 373 (M^++29), 345 (M^++1), 285, 202, 174, 172 (M^+/2), 146, 84. Anal. $C_{14}H_{20}N_2O_4S_2$: C, H, N.

*Reaction of 4,4'-bithiazolinones **15e** and **15e'** with HCl gas* as above gave a mixture of the *racemic* and *meso* isomers of the bis(*N*-carboxythioanhydride)s of methionine (**40e** and **40e'**) (97%), m.p. 214–216 °C (decomp.). ^{1}H NMR (DMSO-d_6): δ 2.02 and 2.03 (3 H, s), 2.07–2.47 (4 H, overlapped, m), 9.83 and 9.94 (1 H, br s). ^{13}C NMR (DMSO-d_6): δ: 14.6 and 14.7, 26.9 and 27.4, 30.1 and 31.5, 78.4 and 79.4, 164.1 and 164.3, 197.9 and 199.3. IR (KBr): 3277, 3255, 2975, 2914, 2830, 1696, 1684 cm^{-1}. MS *m/z* (CI): 281, 232, 192, 190 (M^+/2), 142, 104, 61. Anal. $C_{12}H_{16}N_2O_4S_4$: C, H, N.

*Reaction of a mixture of 4,4'- and 2,4'-bi(2-ethoxy-4-isopropylthiazolin-5-one)s (**15f** and **15f'**; **18** and **18'**) with HCl gas* as above gave a mixture of the *racemic* and *meso* isomers of bis(*N*-carboxythioanhydride)s of valine (**40f** and **40f'**) with a ratio of about 93:7 (0.080 g, 0.25 mmol, 8%). ^{1}H NMR (DMSO-d_6): δ (major isomer reported first) 0.89 and 0.96 (3 H, d, *J*=6.6 Hz), 1.15 and 1.09 (3 H, d, *J*=6.8 Hz), 2.54 and 2.48 (1 H, septet,

$J=6.7$ Hz), 9.57 and 9.50 (1 H, s). ^{13}C NMR (DMSO-d_6): δ (major isomer reported first) 18.5 and 18.6, 18.8 and 19.1, 33.4 and 33.8, 82.8 and 81.2, 165.0 and 165.0, 200.5 and 198.6. IR (KBr): 3242, 2978, 2938, 2880, 1743, 1676 cm^{-1}. MS *m/z* (CI): 357 ($M^+ +41$), 345 ($M^+ +29$), 317 ($M^+ +1$)257, 169, 160, 158 ($M^+/2$), 132, 98. Anal. $C_{12}H_{16}N_2O_4S_2$: C, H, N.

*Reaction of the bis(N-carboxythioanhydride)s of leucine (**40d** and **40d′**) with glycine ethyl ester.* Triethylamine (0.5 ml) was added to a mixture of the *racemic* and *meso* bis(thioanhydrides) **40d** and **40d′** (0.26 g, 0.76 mmol) and glycine ethyl ester hydrochloride (0.24 g, 1.72 mmol) in acetonitrile (25 ml). The mixture was heated at reflux for 12 h, then the solvent was removed and the residue was acidified with 6 M HCl (0.25 ml) and extracted with EtOAc (3 × 10 ml). The combined organic layers were dried over $MgSO_4$. Removal of the EtOAc gave an oily solid which was recrystallized from acetone–water and then from acetone–petroleum ether to give *1,3,3a,6a-tetrahydro - 3a,6a - diisobutyl - 5 - ethoxycarbonylmethyl-pyrrolo[3,4-d]-imidazole-2,4,6-trione* (**42**), m.p. 124–126 °C, (105 mg, 0.297 mmol, 39%). ^{1}H NMR ($CDCl_3$): δ 1.02 (6 H, d, $J=6.6$ Hz), 1.03 (6 H, d, $J=6.6$ Hz), 1.27 (3 H, t, $J=7.2$ Hz), 1.68 (2 H, dd, $J=14.8$ and 6.5 Hz), 1.87 (2 H, dd, $J=14.8$ and 5.1 Hz), 1.94–2.05 (2 H, m), 4.20 (2 H, q, $J=7.2$ Hz), 4.27 (2 H, s), 6.00 (2 H, s). ^{13}C NMR ($CDCl_3$): δ 14.0, 23.9, 24.17, 24.9, 38.8, 39.7, 62.1, 66.6, 1593, 166.1, 175.3. IR (KBr): 3194, 3079, 2952, 1715 cm^{-1}. MS *m/z* (EI) 353 (M^+), 325, 310, 297, 269, 241, 196, 153, 111, 96, 68. Anal. $C_{17}H_{27}N_3O_5$: C, H, N.

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