# On the Tautomerism of 2,4-Disubstituted Thiazolones

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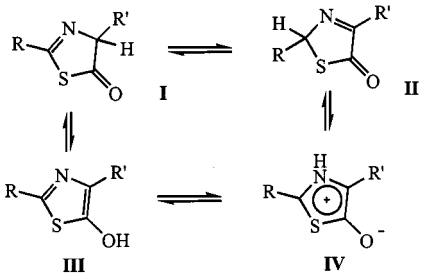
Four series of thiazolones – 2-phenyl-, 2-ethyl, 2-ethoxy, and 2-(ethylthio)thiazol-5-ones – have been synthesized. The tautomeric behavior of these thiazolones is discussed, and the keto form II, i.e. 2-ethylthiazol-5(2*H*)one has been characterized by IR, $^1$H and $^{13}$C NMR spectroscopic methods for the first time.

## Introduction

The tautomeric behavior of heterocyclic compounds has been known for many years[1,2] and is still a subject of extensive research from many different points of views. Our interest in 2,4-disubstituted thiazolones arises from the idea that these compounds might be suitable precursors for dehydrodimeric amino acids,[3] since thiazolone, as well as its analog oxazolone, encloses an α-amino acid residue.

2,4-Disubstituted thiazolones can exist in four possible structures or tautomers as depicted in Scheme 1. The keto form I and the enol form III have been detected spectroscopically in solution,[4−7] the ratio of keto to enol forms depending on the nature of the solvent. In less polar or nonpolar solvents the keto form predominates, and vice versa. The mesoionic tautomer IV has been shown to exist only in polar solvents at dilute concentration, since such solutions show significant deviations from the Lambert−Beer law.[8] However, the conjugated keto form, tautomer II, has not been detected either spectroscopically or through the interpretation of reaction pathways leading to addition products. It has been reported that in the oxazolone series, the analogous conjugated keto form II predominates if a strong electron-withdrawing group is present at the C-2 position.[9] It has also been reported that in an unsubstituted imidazol-5-one the predominant form observed, based on the $^1$H NMR spectra in DMSO, was the analogous keto form II, which was originally considered as being the less stable form with no chance of being observed experimentally.[2,10]




Scheme 1. Tautomerism of 2,4-disubstituted thiazolones

Compared to the extensive research on oxazolones,[11,12] little attention has been paid to the chemistry of thiazolones. The compounds studied are mostly derivatives of 2-phenylthiazol-5-ones.[2,13] During our research toward the synthesis of dehydrodimeric amino acids, we have synthesized a series of 2-phenyl-, 2-ethyl-, 2-ethoxy-, and 2-(ethylthio)thiazol-5-ones and have studied their properties. We have found that the nature of the substituent at the 2-position has a significant influence on the tautomeric structures of thiazolones. Based on the different substituents at the C-2 position, we will discuss in this paper the tautomerism of 2-phenyl-, 2-ethyl-, 2-ethoxy- and 2-(ethylthio)thiazolones. In particular, we would like to report evidence for the existence of the keto form II for some 2,4-disubstituted thiazolones. This keto form, which in principle exists, has never been implicated in the literature for thiazol-5-ones.

## Results and Discussion

### Synthesis of 2,4-Disubstituted Thiazolones

The synthetic pathways for the four series of thiazolones are outlined in Scheme 2. Except for the 2-phenylthiazolones, which were obtained by the cyclization of the corresponding amides of *N*-phenylthioxomethyl amino acids with $CF_3CO_2H$, all other thiazolones were synthesized by the cyclization of either *N*-ethoxy-, *N*-ethyl, or *N*-(ethylthio)-

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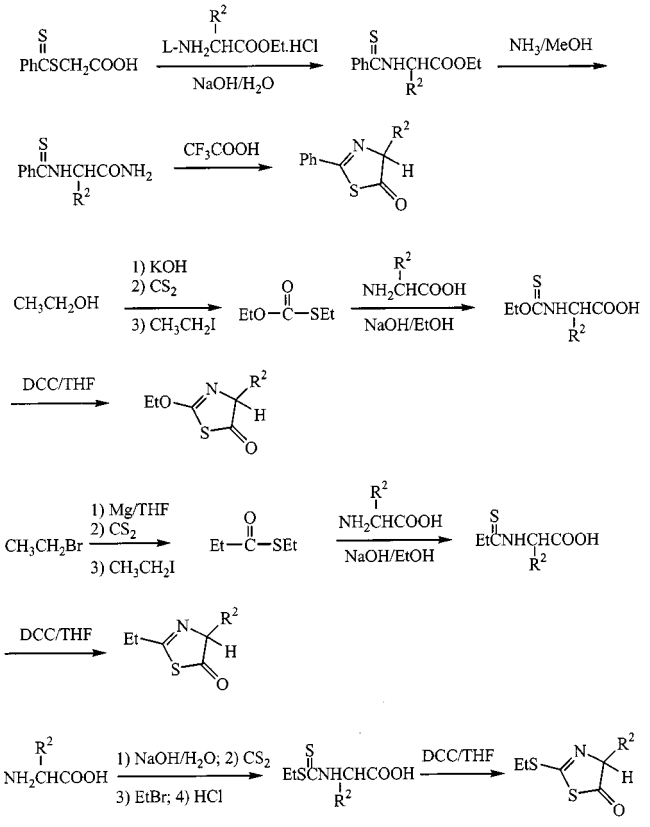
thioxomethyl amino acids with dicyclohexylcarbodiimide (DCC). Detailed synthetic procedures can be found in the Exp. Sect.



Scheme 2. Synthesis of 2,4-disubstituted thiazolones

### Tautomerism of 4-Substituted 2-Phenylthiazolones

In the 2-phenylthiazolone series, both the keto form I and the enol form III have been observed as reported earlier.[1,4,5] In the infrared spectrum (KBr), all the 2-phenylthiazolones show a weak but broad carbonyl absorption at about 1730 $cm^{-1}$. In contrast, the 2-ethyl-, 2-ethoxy-, and 2-ethylthio analogs show a very strong and sharp peak in this region. In the region of 3000−2200 $cm^{-1}$, there is a very broad absorption peak, characteristic of the OH group in the enol form III. These results indicate that the predominant tautomer for the 2-phenylthiazolones in the solid state is the enol III. However, $^1H$ NMR spectra of this series in $CDCl_3$ also show the expected keto tautomer I. The $^1H$ and $^{13}C$ NMR spectra of 4-benzyl-2-phenylthiazolone recorded in $CD_3CN$ show that this compound exists as a mixture of I and III in a ratio of about 2:1. It can therefore be concluded that the enol tautomer predominates in the solid state for the 2-phenylthiazolones, although when dissolved in nonpolar solvents they exist in the keto form, and in polar solvents they exist in both keto and enol forms.

### Tautomerism of 4-Substituted 2-Ethylthiazolones

For the 2-ethylthiazolones we have for the first time observed the existence of the second keto form, tautomer II. In the IR spectra, all the 2-ethylthiazolones show two carbonyl absorption peaks at 1730 and 1690 $cm^{-1}$, respectively. The 1730 $cm^{-1}$ peak corresponds to the carbonyl group in the keto form I, while the 1690 $cm^{-1}$ peak corresponds to the carbonyl group in the keto form II, since this carbonyl group is then conjugated with the C=N bond. There are two carbonyl carbon peaks in the $^{13}C$ NMR spectra at about $\delta = 206$ and 194. Once again, the $\delta = 206$ peak is attributed to the carbonyl carbon in I and the $\delta = 194$ peak to the carbonyl carbon in II. It should be noted that these extra peaks in the IR and NMR spectra cannot be due to impurities, since the results from the elemental analysis agreed with the proposed formula. The $^1H$ and $^{13}C$ NMR spectra also confirmed the co-existence of both keto forms I and II for the 2-ethylthiazolones. A partial $^1H$ NMR spectrum of 4-benzyl-2-ethylthiazolone is given in Figure 1. It is noteworthy that in the $^1H$ NMR spectrum the methine proton at C-4 in keto form I is coupled across five bonds to the methylene protons of the ethyl group at the C-2 position, and the proton at C-2 in keto form II is coupled across five bonds to the methylene protons of the benzyl group at the C-4 position. Such long range coupling has already been reported for thiophenes[14] and thiazolone.[4] The expanded spectrum of the methylene protons of the ethyl group at C-2 in keto form I is shown in Figure 2, together with the simulated spectrum of the same protons. Figure 3 gives the expanded spectrum of the methine proton at C-2 in keto form II, together with the simulated spectrum. As can be seen from the above two figures, the simulated spectra are in good agreement with these experimental results. According to the integration of the $^1H$ NMR spectrum, the ratio of I to II is about 88:12. The co-existence of keto forms I and II, along with the five-bond long range coupling pattern, has also been observed in 2-ethyl-4-methylthiazolone and 2-ethyl-4-(2-methylthioethyl)thiazolone. Interestingly, an early study on 4-isopropyl-2-methylthiazolone did not reveal the existence of keto form II in $CDCl_3$, although the spectrum of this compound in $[D_6]$DMSO indicated that it was 35% enolized.[4]

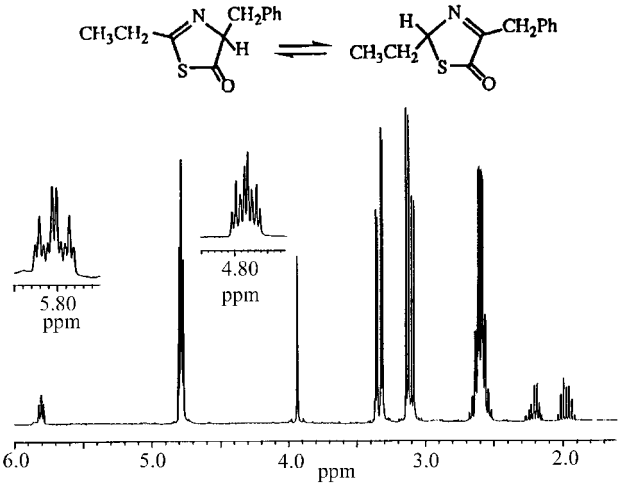



Figure 1. A partial $^1H$ NMR spectrum of 4-benzyl-2-ethylthiazolone

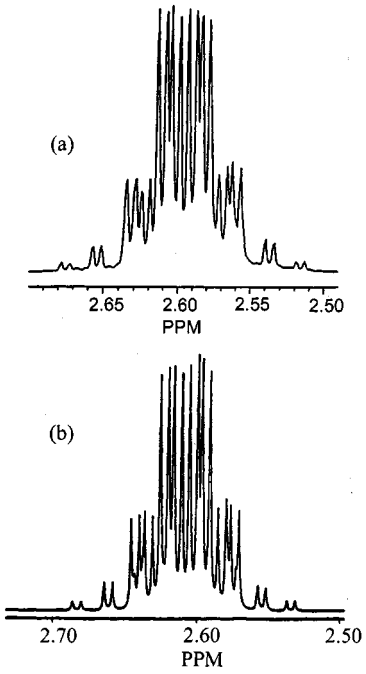



Figure 2. Experimental and simulated $^1$H NMR spectrum of the methylene protons of the ethyl group in 4-benzyl-2-ethylthiazol-5(4*H*)-one (keto form I)

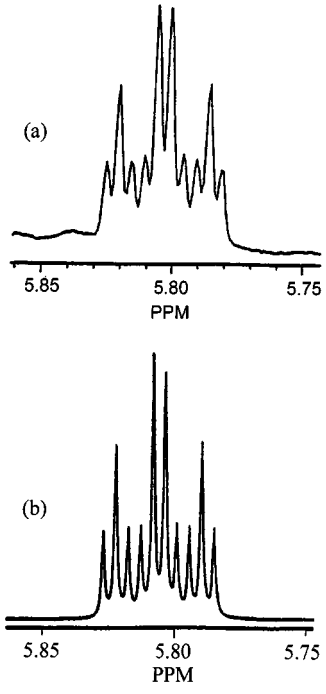



Figure 3. Experimental and simulated $^1$H NMR spectrum of the methine proton of the ethyl group in 4-benzyl-2-ethylthiazol-5(2*H*)-one (keto form II)

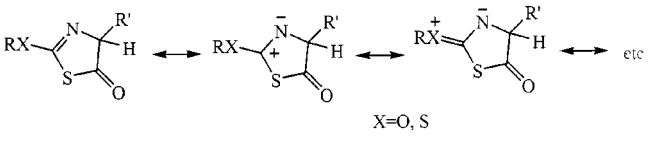
The heats of formation for 2-ethylthiazolon-5(4*H*)ones (keto form I) and 2-ethylthiazolon-5(2*H*)ones (keto form II) have been calculated at the AM1 level using the semiempirical SPARTAN program[21], the results of which are shown in Table 1. It can be seen from this table that the calculated heats of formation for keto form I are lower than those of the keto form II in all cases examined. The calculated heats of formation are consistent with our experimental results, which demonstrated that the 2-ethylthiazolin-5(4*H*)ones were the major components in the equilibrium of the two keto forms. The difference between the heat of formations $\Delta(\Delta H)$ for I and II is around 3 kJ/mol, which give a ratio of about 77:23 for I and II according to the Arrhenius equation $k = Ae^{-Ea/RT}$. This is in agreement with our experimental results, where for 2-ethyl-4-(2-methylthioethyl)thiazolone and 4-benzyl-2-ethylthiazolone the ratio is about 88:12 for I and II. Similar calculations were also performed for 2-phenyl-, 2-ethoxy-, and 2-(ethylthio)thiazolones, and it was found that $\Delta(\Delta H)$ was in the range of 10−15 kJ/mol, which gives a ratio of 99.6:0.4 for I and II according to the Arrhenius equation, indicating that keto form I for these thiazolones are far more important than keto form II. These results are also in agreement with our experimental results, since none of the keto form II was detected for these thiazolones.

Table 1. Calculated heats of formation for 2-ethylthiazol-5(4*H*)-ones and 4-benzyl-2-ethylthiazol-5(2*H*)-ones

| R (at C-4) | Thiazol-5(4*H*)-one | Thiazol-5(2*H*)-one | $\Delta(\Delta H)$ |
|---|---|---|---|
| $CH_3$ | −21.746 | −17.819 | 2.927 |
| $(CH_2)_2CH_3$ | −24.165 | −21.317 | 2.848 |
| Ph | 15.258 | 17.609 | 2.351 |
| $CH_2Ph$ | 6.303 | 9.264 | 3.321 |

### Tautomerism of 4-Substituted 2-Ethoxy- and 2-(Ethylthio)thiazolones

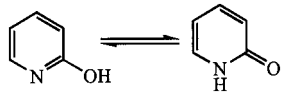
Unlike the 2-phenylthiazolones and 2-ethylthiazolones, the tautomerism of 2-ethoxythiazolones and 2-(ethylthio)-thiazolones was never observed during our studies. It seems that both 2-ethoxy- and 2-(ethylthio)thiazolones always exist in the keto form I. The $^1$H NMR spectra of 2-ethoxy-4-isopropylthiazolone in $CDCl_3$ and [$D_6$]DMSO are identical, indicating that even a highly polar solvent such as DMSO does not favor the formation of enol form III. The less likely enolization of 2-ethoxy- and 2-(ethylthio)thiazolones may be attributed to the canonical forms shown in Scheme 3. Electron-donating groups such as ethoxy and ethylthio make this resonance more favorable, and thus discourage the formation of enol form III. Furthermore, no conjugated keto form II was observed in the IR or NMR spectra for either 2-ethoxy- or 2-(ethylthio)thiazolones.




Scheme 3. Resonance of canonical forms

**Tautomerism of 2-Substituted 4-Phenylthiazolones**

The tautomerism of thiazolones is not only influenced by the choice of solvent and the electronic characteristics of the substituents at the C-2 position, but is also influenced by the electronic and steric requirements of the substituents at the C-4 position. In our previous discussion all the substituents at the C-4 position are alkyl groups. However, when the substituent at C-4 is a phenyl group, the enolization of the thiazolones is promoted markedly. For example, the IR spectrum (in KBr) of 2-phenyl-4-phenylthiazolone shows a very broad peak at 3000−2400 $cm^{-1}$, and no carbonyl absorption. The $^{13}C$ NMR spectrum of this compound in $CDCl_3$ — a nonpolar solvent — indicates an equilibrium between keto form I and enol form III. It can probably be concluded that this compound exists in the enol form in the solid state. The same conclusion is true for 2-ethyl-4-phenylthiazolone, which is a yellow solid with a melting point of 153 °C, in contrast to all other 2-ethylthiazolones which are colorless liquids at room temperature. Once again, the IR spectrum of 2-ethyl-4-phenylthiazolone shows a broad peak at 3200−2500 $cm^{-1}$, but no carbonyl absorption. The $^1H$ NMR spectrum ([$D_6$]DMSO) of this compound confirms that it exists in the enol form: the hydroxy proton appears as a broad peak at δ = 11.36, and no keto form is observed. The NMR spectrum of this compound was not recorded in $CDCl_3$ since it has very low solubility in many less polar solvents such as $CHCl_3$ and even acetone. All these properties agree with the enol form III, therefore the compound should properly be named 2-ethyl-5-hydroxy-4-phenylthiazole. A similar phenomenon was also reported in 2,4-disubstituted imidazole-5-ones, which showed that if a 4-phenyl group is present, one or both of the enol forms for imidazole-5-one predominates in the solid state and in solution in $CHCl_3$, DMSO, and pyridine.[2] This is in contrast to the well-known result that in the condensed phase the form bearing an exocyclic double bound is favored. For example, Beak et. al. reported that the predominant form of 2-hydroxypyridine in the condensed phase is the oxo form, although the aromatic hydroxy form predominates in the gas phase or in very dilute solutions (Scheme 4).[15,16]




Scheme 4. Tautomerism of 3-hydroxypyridine

The facile enolization of 2-substituted-4-phenylthiazolones is probably attributed to the conjugation of the phenyl ring with the five-membered heterocyclic ring. However, when an electron-donating group is attached to C-2, the tautomeric behavior of 4-phenylthiazolones is different from the situation when an electron-releasing group at C-2 is not present. For example, in 2-ethoxy-4-phenylthiazolone, no enol form could be detected by IR or NMR spectroscopy. It is a distillable liquid and behaves just like other 4-substituted 2-ethoxythiazolones. It should be pointed out that no NMR spectra were measured for 2-ethoxy-4-phenylthiazolone in DMSO, even though this solvent might promote the enol form. 2-Ethylthio-4-phenylthiazolone is an unstable solid. Its IR spectrum shows a very weak carbonyl peak at 1733 $cm^{-1}$ and a broad peak at around 2600$cm^{-1}$, which indicates the existence of the enol form in the solid state, although no enol form was observed in the $^1H$ and $^{13}C$ NMR spectra in $CDCl_3$.

## Conclusion

Four series of thiazolones with different substituents at both the 2- and 4-positions of the ring system have been synthesized and their tautomeric structures characterized. The keto form II, i.e. 2-ethylthiazol-5(2*H*)one, has been observed spectroscopically for the first time.

## Experimental Section

**General Remarks:** IR spectra were measured with a Nicolet FT-IR model MX-1 or a Nicolet FT-IR Model 205 unit. NMR spectra were recorded on Bruker AM 360 instrument in $CDCl_3$ using tetramethylsilane (TMS) as internal standard, unless otherwise stated. Chemical shifts are reported in parts per million (ppm) downfield from TMS. Coupling constants (*J*) are given in Hz, and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet). Mass spectra were obtained on a Hewlett Packard 5890 mass spectrometer.

**Amides of *N*-phenylthioxomethyl-D(D,L)-amino acid:** All amides of *N*-phenylthioxomethyl-D(D,L)-amino acid were synthesized according to the literature procedure.[17]

**4-(2-Methylthioethyl)-2-phenylthiazolone:** *N*-phenylthioxomethyl-L-methioninamide (1.2 g) and $CF_3CO_2H$ (7 mL) were placed into a 50 mL rounded-bottomed flask. The solution was stirred at room temp. for 12 h. Removal of $CF_3CO_2H$ on a rotary evaporator gave a residue which was neutralized with saturated $NaHCO_3$ and extracted with three 50 mL portions of ether. The combined ether layers were slowly evaporated to give the title compound as light yellow crystals, m.p. 75−77 °C; yield: 1.05 g (94%). $^1H$ NMR: δ = 2.13 (s, 3 H, $SCH_3$), 2.07−2.20 (m, 1 H, CH-C$H_2$), 2.32−2.43 (m, 1 H, CH-C$H_2$), 2.76 (t, *J* = 7.4 Hz, 2 H, $SCH_2$), 4.99 (dd, *J* = 7.9, 5.0 Hz, 1 H, CH), 7.45−7.57 (m, 3 H, Ar), 7.82−7.86 (m, 2 H, Ar). $^{13}C$ NMR: δ = 15.26, 30.59, 31.74, 82.29, 128.08, 128.84, 132.11, 133.41, 164.89, 208.79. IR (KBr): $\tilde{\nu}_{max}$ = 3061 $cm^{-1}$, 1735, 1576. $C_{12}H_{13}NOS_2$ (251.4): calcd. C 57.34, H 5.21, N 5.57; found C 57.37, H 4.81, N 5.43.

**4-Benzyl-2-phenylthiazolone:** Light yellow crystals, m.p.138−140 °C; yield: 1.10 g (79%). $^1H$ NMR: δ = 3.20 (dd, *J* = 13.8, 7.0 Hz, 1 H, $PhCH_2$), 3.47 (dd, *J* = 13.8, 4.6 Hz, 1 H, $PhCH_2$), 5.06 (dd, *J* = 7.0, 4.6 Hz, 1 H, CH), 7.1−7.8 (m, 10 H, Ar). $^{13}C$ NMR: δ = 38.37, 84.46, 126.89, 128.02, 128.19, 128.79, 129.73, 132.01, 132.37, 135.78, 164.95, 208.77. IR (neat): $\tilde{\nu}_{max}$ = 1728 $cm^{-1}$ (broad), 1595. MS (EI): *m*/*z* = 267 [$M^+$], 239, 206, 162, 121, 91. $C_{16}H_{13}NOS$ (267.3): calcd. C 71.88, H 3.74, N 5.24; found C 71.79, H 4.01, N 5.00.

**4-Methyl-2-Phenylthiazolone:** Light yellow crystals, m.p.133−135 °C (ref.[18] 135 °C); yield: 1.00 g (93%). $^1$H NMR: δ = 1.60 (d, *J* = 7.5 Hz, 3 H, $CH_3$), 4.83 (q, *J* = 7.5 Hz, 1 H, CH), 7.42−7.56 (m, 3 H, Ar), 7.81−7.84 (m, 2 H, Ar). $^{13}$C NMR: δ = 17.49, 79.56, 128.08, 128.88, 132.09, 133.50, 164.68, 209.54. IR (neat): $\tilde{\nu}_{max}$ = 1727 cm$^{-1}$, 1586. MS (EI): *m*/*z* = 191 [M$^+$], 163, 130, 121, 103, 77, 51.

**2-Phenyl-4-phenylthiazolone:** A yellow solid, m.p.132−135 °C (ref.[18] 136 °C); yield: 0.55 g (93%). $^1$H NMR: δ = 5.87 (s, 1 H, CH), 7.09−7.68 (m, overlapped, 8 H, Ar), 7.92−7.95 (m, 2 H, Ar). $^{13}$C NMR: δ = 86.25, 126.52, 126.93, 128.30, 128.40, 128.75, 128.96, 129.23, 132.47, 166.67, 206.31. IR (KBr): $\tilde{\nu}_{max}$ = 3057 cm$^{-1}$, 3000−2400 (broad), 1658. An equilibrium between 2,4-diphenylthiazolin-5-one and 2,4-diphenyl-5-hydroxythiazole was observed in the $^{13}$C NMR spectrum.

***O*-Ethyl *S*-ethyl Dithiocarbonate:** This compound was obtained in about 80% yield by a method described in the literature,[19] b.p. 195−199 °C.

***N*-Ethoxythioxomethyl-D,L-alanine:** *O*-ethyl *S*-ethyl dithiocarbonate (4.0 g, 26.6 mmol), D,L-alanine (2.14 g, 24.0 mmol), NaOH (0.96 g, 24.0 mmol), and 60 mL of absolute ethanol were placed into a 100 mL rounded-bottomed flask equipped with a reflux condenser. The mixture was refluxed for three days. Upon cooling, the solvent was removed on a rotary evaporator and the residue was dissolved in 50 mL of water. The water layer was extracted with two 20-mL portions of ethyl ether to remove unchanged dithioether. The water layer was then acidified with 6 N HCl and extracted with four 30 mL portions of diethyl ether. The combined ether layers were dried over $MgSO_4$. Removal of the ether resulted in a very thick oil which slowly solidified at room temp.; yield: 3.5 g (82%), m.p. 102−105 °C. Recrystallization from acetate/hexanes gave the pure title compound, m.p. 105−107 °C. Two rotamers in a ratio of 70:30 were observed in both the $^1$H and $^{13}$C NMR spectra. $C_6H_{11}NO_3S$ (177.2): calcd. C 40.66, H 6.26, N 7.90; found C 40.75, H 6.23, N 7.98.

All the other *N*-ethoxythioxomethyl-L(D,L)-amino acids were synthesized in the same manner. Two rotamers were observed in all cases.

**2-Ethoxy-4-(2-methylthioethyl)thiazolone:** A solution of dicyclohexylcarbodiimide (DCC) (4.34 g) in 15 mL of THF was added to a solution of *N*-ethoxythioxomethyl-L-methionine (5.0 g) in 50 mL THF. The mixture was stirred at room temp. for three days. The precipitate was then filtered off and the solvent removed on a rotary evaporator. The residue was distilled under vacuum yielding the title compound as a colorless oil, b.p. 110−120 °C/0.4−0.5Torr; yield: 2.9 g (63%). $^1$H NMR: δ = 1.40 (t, *J* = 7.1 Hz, 3 H, $CH_2$-C$H_3$), 1.99 (m, 1 H, CH-C$H_2$), 2.10 (s, 3 H, $SCH_3$), 2.20 (m, 1 H, CH-C$H_2$), 2.65 (qd, *J* = −14.1, 7.10 Hz, 2 H, $SCH_2$), 4.48−4.59 (m, 2 H, $OCH_2$), 4.66 (dd, *J* = 7.8, 4.9 Hz, CH). $^{13}$C NMR: δ = 14.12, 15.21, 30.28, 31.98, 65.62, 79.38, 160.57, 207.14. IR (neat): $\tilde{\nu}_{max}$ = 1732 cm$^{-1}$, 1637. MS (EI): *m*/*z* = 219 [M$^+$], 171, 158, 117, 82, 61. $C_8H_{13}NO_2S_2$ (219.3): calcd. C 43.81, H 5.97, N 6.39; found C 43.71, H 5.64, N 6.08.

**4-Benzyl-2-ethoxythiazolone:** Colorless oil, b.p. 134−140 °C/0.2−0.3Torr; yield: 3.80 g (51%). $^1$H NMR: δ = 1.35 (t, *J* = 7.1 Hz, 3 H, $CH_3$), 3.08 (dd, *J* = 13.7, 6.6 Hz, 1 H, $PhCH_2$), 3.24 (dd, *J* = 13.7, 4.7 Hz, 1 H, $PhCH_2$), 4.36−4.45 (m, 2 H, $OCH_2$), 4.74 (dd, *J* = 6.6, 4.7 Hz, 1 H, CH), 7.18−7.29 (m, 5 H, Ar). $^{13}$C NMR: δ = 14.13, 38.52, 65.57, 81.38, 126.79, 128.08, 129.78, 135.79, 160.63, 207.14. IR (neat): $\tilde{\nu}_{max}$ = 1731 cm$^{-1}$, 1637. MS (EI): *m*/*z* = 235 [M$^+$], 207, 128, 91, 65. $C_{12}H_{13}NO_2S$ (235.3): calcd. C 61.25, H 5.57, N 5.95; found C 61.39, H 5.37, N 6.06.

**4-Methyl-2-ethoxythiazolone:** Colorless oil, b.p. 40−45 °C/0.1−0.2Torr; yield: 3.40 g (76%). $^1$H NMR: δ = 1.40 (t, *J* = 7.2 Hz, 3 H, $CH_2$-C$H_3$), 1.46 (d, *J* = 7.3 Hz, 3 H, CH-C$H_3$), 4.44 (q, *J* = 7.2 Hz, 2 H, $OCH_2$), 4.54 (q, *J* = 7.3 Hz, CH). $^{13}$C NMR: δ = 14.02, 18.02, 66.42, 76.41, 159.96, 207.56. IR (neat): $\tilde{\nu}_{max}$ = 1735 cm$^{-1}$, 1641. MS (EI): *m*/*z* = 159 [M$^+$], 144, 116, 88, 70, 40. $C_6H_9NO_2S$ (159.2): calcd. C 45.27, H 5.69, N 8.80; found C 45.45, H 5.73, N 8.48.

**2-Ethoxy-4-phenylthiazolone:** Colorless oil, b.p. 125−135 °C/0.2−0.3Torr; yield: 1.70 g (50%). $^1$H NMR: δ = 1.46 (t, *J* = 7.1 Hz, 3 H, $CH_2$-C**H**$_3$), 4.51−4.72 (m, 2 H, $OCH_2$), 5.57 (s, 1 H, CH), 7.31−7.43 (m, 5 H, Ar). $^{13}$C NMR: δ = 14.27, 66.03, 83.46, 126.66, 128.61, 128.78, 134.79, 162.12, 204.66. IR (neat): $\tilde{\nu}_{max}$ = 1739 cm$^{-1}$, 1631. MS (EI): *m*/*z* = 220 [M$^+$], 193, 149, 132, 104, 77. $C_{11}H_{11}NO_2S$ (221.3): calcd. C 59.70, H 5.01, N 6.33; found C 59.97, H 4.59, N 6.20.

**Ethyl Ester of Propanedithioic Acid:** This compound was obtained in about 28% yield by a method described in the literature,[20] b.p. 30−35 °C/0.4−0.6 Torr.

***N*-Ethylthioxomethyl-L(D,L)-amino Acids:** All were synthesized in a similar procedure as described in the synthesis of *N*-ethoxythioxomethyl-D,L-alanine. No rotamers were observed.

**2-Ethyl-4-(2-methylthioethyl)thiazolone:** *N*-ethylthioxomethyl-L-methionine (5.4 g) and 40 mL of THF were added to a round-bottomed flask. Then, DCC (5.03 g) in 10 mL of THF was added to the flask in one portion at room temperature. This mixture was stirred at room temp. for three days. The precipitate was removed by filtration and the solution was concentrated at aspirator pressure. The residue was distilled under vacuum to give the title compound as a colorless oil, b.p. 114−120 °C/1.8−2.0Torr; yield: 4.0 g (81%). An equilibrium between 2-ethyl-4-(2-methylthioethyl)thiazolin-5(4*H*)one and 2-ethyl-4-(2-methylthioethyl)thiazolin-5(2*H*)one in a ratio of ca. 88:12 was observed in both the $^1$H and $^{13}$C NMR spectra. No separation was attempted.

**2-Ethyl-4-(2-methylthioethyl)thiazolin-5(4*H*)-one:** $^1$H NMR: δ = 1.25 (t, *J* = 7.5 Hz, 3 H, $CH_2$-C$H_3$), 1.95−2.07 (m, 1 H, CH-C$H_2$), 2.08 (s, 3 H, $SCH_3$), 2.21−2.30 (m, 1 H, CH-C$H_2$), 2.68 (t, *J* = 7.1 Hz, 2 H, $SCH_2$), 2.72 (qd, *J* = 7.5, 2.1 Hz, 2 H, $CH_3$-C$H_2$), 4.68−4.72 (m, 1 H, CH). $^{13}$C NMR: δ = 10.83, 15.07, 30.27, 30.53, 31.25, 81.29, 169.76, 209.32.

**2-Ethyl-4-(2-methylthioethyl)thiazolin-5(2*H*)-one:** $^1$H NMR: δ: Some proton signals are hidden under the major isomer except: 1.04 (t, *J* = 7.3 Hz, 3 H, $CH_2$-C$H_3$), 2.11 (s, 3 H, $SCH_3$), 2.86 (m, overlapped, 4 H, $SCH_2$ and $CH_3$-C$H_2$), 5.85 (ddt, *J* = 7.3, 5.4, and 2.0 Hz, N-CH). $^{13}$C NMR: δ = 10.16, 15.33, 28.14, 29.18, 30.33, 80.18, 169.09, 194.26. For the mixture, IR (neat): $\tilde{\nu}_{max}$ = 2974 cm$^{-1}$, 2915, 2876, 1721, 1690, 1627. MS (EI): *m*/*z* = 404 (dimer), 221, 203 [M$^+$], 142, 129, 82, 73, 61, 45. $C_8H_{13}NOS_2$ (203.3): calcd. C 47.26, H 6.44, N 6.89; found C 46.84, H 6.44, N 7.20.

**4-Benzyl-2-ethylthiazolone:** Colorless oil, b.p. 115−125 °C/0.9−1.0Torr; yield: 4.0 g (78%). An equilibrium between 2-ethyl-4-benzylthiazolin-5(4*H*)one and 2-ethyl-4-benzylthiazolin-5(2H)one in a ratio of ca. 87.8:12.2 was observed in both the $^1$H and $^{13}$C NMR spectra. No separation was attempted.

**4-Benzyl-2-ethylthiazolin-5(4*H*)-one:** $^1$H NMR: δ = 1.16 (t, *J* = 7.4 Hz, 3 H, $CH_3$), 2.59 (dqd, *J* = −14.1, 7.4, and 2.1 Hz, 1 H, $CH_3$-C*H*$_2$), 2.62 (dqd, *J* = −14.1, 7.4, and 2.1 Hz, 1 H, $CH_3$-C*H*$_2$), 3.10 (dd, *J* = 13.7, 6.6 Hz, $PhCH_2$), 3.33 (dd, *J* = 13.7, 4.7 Hz, 1 H, $PhCH_2$), 4.78 (ddt, *J* = 6.6, 4.7, and 2.1 Hz, 1 H, CH), 7.14−7.31 (m, 5 H, Ar). $^{13}$C NMR: δ = 10.75, 30.35, 37.90, 83.27, 126.80, 127.99, 129.72, 135.39, 169.86, 209.49.

**4-Benzyl-2-ethylthiazolin-5(2*H*)-one:** $^1$H NMR: δ = 1.01 (t, *J* = 7.4 Hz, 3 H, $CH_2$-C*H*$_3$), 1.91−2.03 (m, 1 H, $CH_3$-C*H*$_2$), 2.14−2.27 (m, 1 H, $CH_3$-C*H*$_2$), 3.93 (d, *J* = ≈1.8 Hz, 2 H, $PhCH_2$), 5.80 (ddt, *J* = 7.1, 5.3, and 1.8, CH), 7.14−7.31 (m, 5 H, Ar). $^{13}$C NMR: δ = 10.10, 29.13, 34.37, 79.94, 126.93, 128.54, 129.25, 135.05, 169.19, 194.17. For the mixture, IR (neat): $\tilde{\nu}_{max}$ = 3062 cm$^{-1}$, 3032, 2978, 2936, 2875, 1720, 1699. MS (EI): *m*/*z*: 219 [M$^+$], 191, 158, 130, 102, 91, 65. $C_{12}H_{13}NOS$ (219.3): calcd. C 65.72, H 5.98, N 6.39; found C 66.03, H 5.64, N 6.21.

**2-Ethyl-4-methylthiazolone:** Colorless oil, b.p. 35−40 °C/0.4−0.5Torr; yield: 1.20 g (47%). An equilibrium between 2-ethyl-4-methylthiazolin-5(4*H*)one and 2-ethyl-4-methylthiazolin-5(2*H*)one in a ratio of ca. 95.8:4.2 was observed in both the $^1$H and $^{13}$C NMR spectra. No separation was attempted.

**2-Ethyl-4-methylthiazolin-5(4*H*)-one:** $^1$H NMR: δ = 1.29 (t, *J* = 7.5 Hz, 3 H, $CH_2$-C*H*$_3$), 1.48 (d, *J* = 7.6 Hz, 3 H, CH-C*H*$_3$), 2.71 (qd, *J* = 7.5, 2.1 Hz, 2 H, $CH_2$), 4.56 (qt, *J* = 7.6, 2.1 Hz, 1 H, CH). $^{13}$C NMR: δ = 10.80, 17.16, 30.55, 78.57, 168.99, 210.15.

**2-Ethyl-4-methylthiazolin-5(2*H*)-one:** $^1$H NMR: δ = 1.08 (t, *J* = 7.4 Hz, $CH_2$-C*H*$_3$), 1.93−2.02 (m, 1 H, $CH_3$-C*H*$_2$), 2.17−2.24 (m, 1 H, $CH_3$-C*H*$_2$), 2.27 (d, *J* = 2.4 Hz, 3 H, =C-$CH_3$), 5.75−5.81 (m, 1 H, N-CH). $^{13}$C NMR: δ = 10.40, 14.45, 29.33, 79.89, the other two carbon signals were too small to be observed. For the mixture, IR (neat): $\tilde{\nu}_{max}$ = 2975 cm$^{-1}$, 2936, 2868, 1724, 1698, 1627. MS (EI): *m*/*z* = 256 (dimer-CO), 143 [M$^+$], 128, 115, 100, 73, 45, 42. $C_6H_9NOS$ (143.2): calcd. C 50.32, H 6.33, N 9.72; found C 50.03, H 5.98, N 9.82.

**2-Ethyl-4-phenylthiazolone (2-Ethyl-5-hydroxy-4-phenylthiazole):** Yellow solid, m.p. 153−155 °C; yield: 1.20 g (24%), which was identified as 2-ethyl-5-hydroxy-4-phenylthiazole instead of 2-ethyl-4-phenylthiazolin-5-one. $^1$H NMR ([D$_6$]DMSO): δ = 1.26 (t, *J* = 7.5 Hz, 3 H, $CH_3$), 2.82 (q, *J* = 7.5 Hz, 2 H, $CH_2$), 7.17 (t, *J* = 7.3 Hz, 1 H, Ar), 7.36 (t, *J* = 7.6 Hz, 2 H, Ar), 7.96 (d, *J* = 7.6 Hz, 2 H, Ar), 11.36 (s, broad, OH). IR (KBr): $\tilde{\nu}_{max}$ = 3200−2500 cm$^{-1}$ (broad), 1602, 1582, 1542. MS (EI): *m*/*z* = 205 [M$^+$], 177, 144, 121, 89, 77, 63, 51. $C_{11}H_{11}NOS$ (205.3): calcd. C 64.36, H 5.40, N 6.82; found C 64.56, H 5.88, N 7.14.

***N*-Ethylthiothioxomethyl-L-alanine:** L-alanine (4.45 g), NaOH (4.2 g), and 40 mL of water were placed into a round-bottomed flask equipped with a magnetic stirrer. $CS_2$ (3.0 mL) was added to the above solution and the mixture was stirred at room temp. until a homogeneous solution was obtained. Then, ethyl bromide (3.73 mL) was added and the mixture was stirred again at room temp. until a homogeneous yellow solution was obtained. The water layer was extracted with ether (3 × 20 mL) to remove unchanged starting materials. The water layer was then acidified with 6 N HCl and extracted with ether (4 × 30 mL). Removal of ether gave 4.96 g (51%) of a crude product. Recrystallization from $CHCl_3$/petroleum ether yielded the pure compound, m.p. 98−100 °C. $C_6H_{11}NO_2S_2$ (193.3): calcd. C 37.28, H 5.74, N 7.25; found C 37.56, H 5.92, N 7.37.

All the other *N*-ethylthiothioxomethyl-L(D,L)-amino acids were synthesized in the same manner.

**2-(Ethylthio)-4-isopropylthiazolone:** DCC (4.66 g) in 10 mL of THF was added to a solution of *N*-ethylthiothioxomethyl-L-valine (5.0 g) in 35 mL of THF and the reaction mixture was stirred at room temp. for one day. The precipitate was filtered then off and the solvent was removed on a rotary evaporator. The residue was distilled under vacuum yielding the title compound as a yellow oil, b.p. 72−78 °C/0.2−0.3 Torr; yield: 2.98 g (65%). $^1$H NMR: δ = 0.87 (d, *J* = 6.8 Hz, 3 H, CH-C*H*$_3$), 1.18 (d, *J* = 6.9 Hz, 3 H, CH-C*H*$_3$), 1.42 (t, *J* = 7.3 Hz, 3 H, $CH_2$-C*H*$_3$), 2.32−2.41 (m, 1 H, $CH_3$-C*H*), 3.12 (dq, *J* = 13.2, 7.3 Hz, 1 H, $SCH_2$), 3.28 (dq, *J* = 13.2, 7.3 Hz, 1 H, $SCH_2$), 4.45 (d, *J* = 3.7 Hz, 1 H, N-CH). $^{13}$C NMR: δ = 14.55, 16.50, 20.29, 25.14, 32.66, 87.30, 161.63, 208.37. IR (neat): $\tilde{\nu}_{max}$ = 1731 cm$^{-1}$, 1652. $C_8H_{13}NOS_2$ (203.3): calcd. C 47.26, H 6.44, N 6.89; found C 46.97, H 6.50, N 6.84.

**4-Benzyl-2-(ethylthio)thiazolone:** Yellow oil, b.p. 136−144 °C/0.05−0.1 Torr; yield: 3.45 g (65%). $^1$H NMR: δ = 1.36 (t, *J* = 7.4 Hz, 3 H, $CH_3$), 3.05−3.26 (m, overlapped, 3 H, $SCH_2$ and $PhCH_2$), 3.32 (dd, *J* = 13.8, 4.6 Hz, 1 H, $PhCH_2$), 4.77 (dd, *J* = 6.7, 4.6 Hz, 1 H, CH), 7.18−7.28 (m, 5 H, Ar). $^{13}$C NMR: δ = 14.50, 25.08, 38.33, 82.93, 126.85, 128.12, 129.65, 135.69, 162.04, 207.85. IR (neat): $\tilde{\nu}_{max}$ = 3061 cm$^{-1}$, 1730, 1560. $C_{12}H_{13}NOS_2$ (251.4): calcd. C 57.34, H 5.21, N 5.57; found C 57.21, H 5.34, N 5.61.

**2-(Ethylthio)-4-methylthiazolone:** Colorless oil, b.p. 54−60 °C/0.05−0.1 Torr; yield: 2.88 g (72%). $^1$H NMR: δ = 1.40 (t, *J* = 7.4 Hz, 3 H, $CH_2$-C*H*$_3$), 1.48 (d, *J* = 7.4 Hz, 3 H, CH-C*H*$_3$), 3.19 (q, *J* = 7.4 Hz, 2 H, $SCH_2$), 4.58 (q, *J* = 7.4 Hz, 1 H, CH). $^{13}$C NMR: δ = 14.31, 17.57, 25.12, 78.04, 161.23, 208.56. IR (neat): $\tilde{\nu}_{max}$ = 1730 cm$^{-1}$, 1562. MS (EI): *m*/*z* = 175 [M$^+$], 147, 119, 105, 86, 60, 45. $C_6H_9NOS_2$ (175.3): calcd. C 41.11, H 5.18, N 7.99; found C 41.15, H 5.30, N 7.89.

**2-(Ethylthio)-4-phenylthiazolone:** Unstable solid; yield: 1.40 g (89%). $^1$H NMR: δ = 1.44 (t, *J* = 7.4 Hz, 3 H, $CH_3$), 3.22−3.34 (m, 2 H, $SCH_2$), 5.60 (s, 1 H, CH), 7.27−7.38 (m, 5 H, Ar). $^{13}$C NMR: δ = 14.54, 25.28, 84.69, 126.69, 128.66, 128.84, 134.28, 163.94, 205.43. IR (neat): $\tilde{\nu}_{max}$ = 1733 cm$^{-1}$, 1554, 1537. Due to its instability, it was difficult to obtain good elemental analysis data.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