# On the Synthesis and Structure of 2-Methylenethiazolidin-4-ones.* Carbalkoxy Derivatives and Isolation of Geometrical Isomers

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An alternative synthesis of 2-carbalkoxymethylenethiazolidin-4-ones ** and the separation of the two geometrical isomers in pure form from the reaction mixture by fractional crystallization is described. Attempts to assign configuration to the two isomers based on NMR data are also discussed.

In connection with investigations on the pharmacological activity of certain thiazolines, which have been the subject of much synthetic effort since it was recognized that penicillin contains such a moiety, it was of interest to prepare 2-methylenethiazolidin-4-ones of type *1*, having an exocyclic double bond in the 2 position.
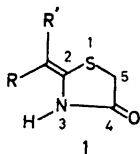
R′ = H, R = COOEt or COOMe

R′ = COOEt or COOMe, R = H

At the time our work was initiated, compounds of this type had not been described. Since then reports concerning this system have been published by

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* Presented in part at "Organikerdagarna", Göteborg, June 14— 16, 1967; *cf. Svensk Kem. Tidskr.* 79 (1967) 578.
** According to the IUPAC recommendations[1] these compounds should be named alkyl 4-thiazolidone-$\Delta^{2,\alpha}$-acetates. We have chosen to retain the nomenclature used by Satzinger[2] and by Taylor[3] since this enables direct comparisons to be made.

Satzinger[2] and by Taylor.[3] The purpose of the present and the following[4] communication is to describe a different and probably general synthesis for compounds of type *1*, to verify the observations by Taylor[3] that they exist in two forms, both containing an exocyclic double bond, to confirm that they are geometrical isomers, which are readily interconvertible, and to propose a mechanism for the interconversions, based on deuterium-exchange experiments.

Our synthesis was based on the following observations. Condensation of the hydrochlorides of imidic esters with esters of 2-amino-3-mercaptocarboxylic acids have been reported to yield Δ^2-thiazolidines [5-7] of type *2* (R = alkyl or aryl).
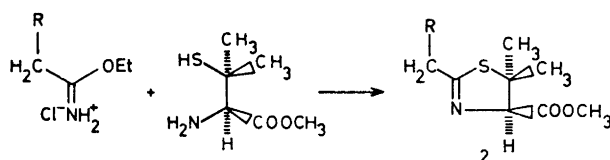

It is well-known that heterocyclic compounds of the general type *3*, with X = NH, O, or S, often exist in the tautomeric form *4*.[8]
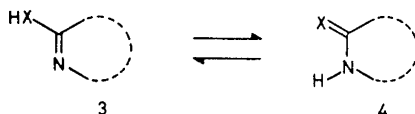
Consequently we reacted mercaptoacetamide with the hydrochlorides of different imidic esters, expecting to obtain *5a*, which would then tautomerize to *5b*.
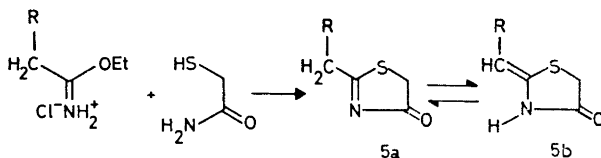

We have carried out condensations with R = COOEt, COOMe, and CN,[4] and in all cases compounds of type *5b* have been isolated. When R = H no reaction took place. The reaction product of mercaptoacetamide and carbethoxyacetimidic ethyl ester hydrochloride (R = COOEt) yielded, when isolated and purified by fractional crystallization, the two isomeric compounds *6* and *7*.[3]
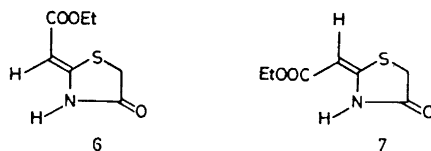
The lower melting, here called "L", and the higher melting, here called "H", carbethoxy compounds gave very similar elemental analysis values and molecular weights (182 and 186, respectively) by the Rast method. Mass spectrometry proved them to be isomers with a molecular ion at $m/e = 187$ and an $M + 2$ isotope peak of 5.4 %, which corresponds to the molecular formula $C_7H_9NO_3S$. The mass spectra of "L" and of "H", discussed in an accompanying communication,[4] displayed almost identical fragmentation patterns, which is often characteristic of stereoisomers.[9]

The spectral data for 6 and 7 (cf. Experimental) are the same as those reported [3] for the compounds Taylor refers to as the "stable" and "metastable" isomers.

Since internally hydrogen-bonded protons suffer a paramagnetic shift,[10-12] and since a lowering of the ester $C = O$ and NH infrared-absorption frequences in dilute solution are characteristic of intramolecular hydrogen bonding, we believe that "L" should be represented by structure 8 and "H" by 9.
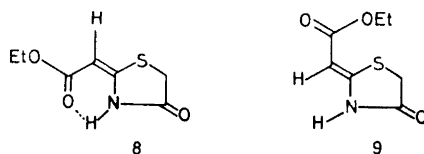

Simon et al.[13] have published a semi-empirical rule for the calculation of the chemical shifts of olefinic protons, which, when applied to these compounds, leads to close agreement with the observed values and also supports the conclusion that the hydrogen-bonded formula 8 represents "L" (cf. Table

Table 1. Observed (in chloroform-d) and calculated [13] values for the chemcal shifts of the olefinic proton in the methyl and ethyl ester compounds.

| Compound | Observed | | Calculated | | Difference |
	Isomer	δ, ppm	Isomer	δ, ppm	δ, ppm
2-Carbethoxymethylene-	"H"	5.54	Z	5.33	0.21
thiazolidin-4-one	"L"	5.07	E	5.02	0.05
2-Carbomethoxymethylene-	"H"	5.58	Z	5.33	0.25
thiazolidin-4-one	"L"	5.13	E	5.02	0.11

1). These proposals will later be supported by additional observations. When carbomethoxyacetimidic ethyl ester hydrochloride is condensed with mercaptoacetamide a corresponding pair of high- and low-melting methyl esters is obtained. The structures of these two isomers were determined in the way described for the ethyl esters. Pertinent data can be found in Experimental and in Table 1.

While our work was in progress, Satzinger [2] described the synthesis of the same compounds by the following different route.
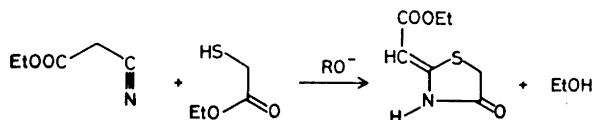
He did not notice the presence of two forms, probably because a different isolation and condensation procedure was used. We have repeated the Satzinger synthesis and have found that the products are identical with those obtained by our procedure. Satzinger's method is probably more convenient than ours. Taylor [3] has since proposed what can be regarded as a modification of the Satzinger method, using ethyl cyanoacetate and mercaptoacetic acid in acid toluene solution.[14]

Investigations on a thiazolidine system similar to *1* (or *5*) have also been reported by Cook, Elvidge, Graham, and Harris.[15-17] They describe two compounds, having identical UV spectra ($\lambda_{max} = 290$ nm), which they first assumed to have structure *10a* (R = H and CH_3) but since attempts to nitrosate one of them (R = CH_3) in the side chain failed, they proposed that these compounds were instead the 2-methylene tautomers of type *10b*.

10a 10b
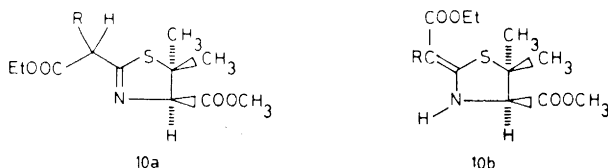
The same authors also report [15] two isomeric compounds, displaying almost identical UV spectra, which they propose to be the *cis* and *trans* isomers *11* and *12*.

11 12
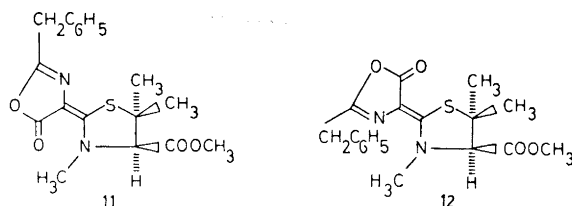
The true character of these thiazolines has not been established with modern spectroscopic methods.[17]

With the gross structures of "L" and "H" ethyl esters verified we wish to discuss briefly some details in their NMR spectra and the change in their UV spectra on addition of base.

In an NMR spectrum (*cf.* Fig. 1) at 100 MHz of a sample containing both "L" and "H" the CH_2S resonance signals are very close, $\delta = 3.69$ and 3.65, respectively. Expansion of this region revealed that the band in "L" was a doublet ($J = 0.4$ Hz), while the same absorption in "H" was a singlet within the experimental accuracy. Since this CH_2 group has no adjacent protons
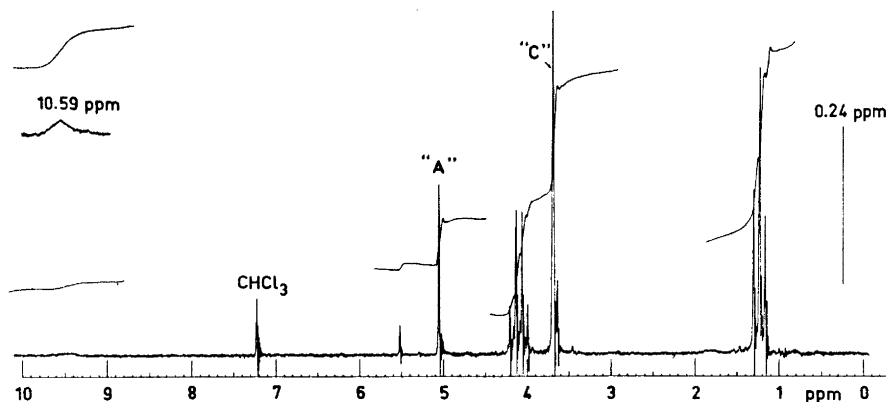
Fig. 1. NMR spectrum (100 MHz, CDCl₃) of a mixture (*ca.* 85:15) of *8* and *9*.

and the five-membered ring probably is planar, long-range coupling is likely to exist with either the olefinic or the amide protons. After addition of heavy water to the solution, the amide proton had exchanged, but the resonance from the CH_2S protons remained a doublet. Expansion of the olefinic proton region showed that the olefinic proton in "L" appeared as a triplet ($\delta = 5.07$, $J = 0.4$ Hz), while the same proton in "H" ($\delta = 5.54$) was a singlet with a bandwidth of 0.5 Hz. No change in the appearance of the signals from these protons took place on addition of heavy water. Irradiation of the olefinic proton signal "A" (*cf.* Fig. 1) reduced the CH_2S signal "C" to a singlet, and this shows that long-range coupling exists between these protons in "L". Identical measurements on "H" showed that the coupling constant between the same protons is less than 0.05 Hz. These findings are in agreement with the proposal that "L" is the hydrogen-bonded form where all protons are held in a more rigid position, resulting in a shorter distance between the olefinic and methylene protons. The methyl esters (*5b*, R = COOMe) were prepared with the hope that their NMR spectra would be simpler to analyze than those of the ethyl esters. This, however, did not materialize since the chemical shifts of the CH_3 and CH_2S protons are almost the same (*cf.* Experimental), giving rise to overlapping signals. The long-range coupling ($J = 0.4$ Hz) between the methylene protons and the olefinic proton was also present in the low-melting methyl ester, but not in the corresponding high-melting isomer.

The dissociation constants for "L" and "H", which are very close (pK_a ("L") = 10.7 and pK_a("H") = 10.1, in methanol-water, 9:1)* do not allow a definite conclusion to be drawn as to which isomer contains an intramolecular bond, since "L" and "H" both form the same anion.

As was pointed out earlier, the UV spectra of "L" and "H" are virtually identical and of a type expected for the proposed chromophore.[15,16] The spectra of "L" and "H" in ethanol solution both remained unchanged on addition of acid. If, instead, base was added to a neutral ethanol solution, new maxima

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* Taylor[3] reports 9.80 and 8.60 respectively, in 60 % aqueous methanol.

developed at 308 nm ($\varepsilon = 30\,000$) for both "L" and "H". When the basic solutions were acidified with an excess of hydrochloric acid, the original maximum at 283 nm reappeared. This reversible process can be pictured in terms of the following transformation:
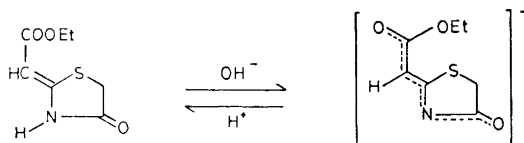
When the experiment was carried out on a preparative scale, it was discovered that pure "H" was isolated when a solution of "L" was first treated with base and then neutralized with acid. The ionization-reprotonation process of the amide system was therefore accompanied by a *cis-trans* isomerization of the exocyclic double bond.

In order to illuminate this process, the NMR spectra of the two isomers were recorded in different media. The transformations reported below were followed by means of the olefinic proton signal at $\delta = 5.23$ (pyridine-d_5) and 5.07 (chloroform-d) for the E isomer,[18] *8*, and at $\delta = 5.82$ (pyridine-d_5) and at 5.54 (chloroform-d) for the Z izomer,[18] *9*.

The present NMR studies were carried out under conditions slightly different from those of Taylor,[3] but the results and conclusions are essentially identical with his.

Addition of a few drops of trifluoroacetic acid to a chloroform solution of the synthetic product, which contained a 60:40 mixture of the two isomers, caused an immediate rearrangement to a 25:75 mixture of the Z and E isomers, respectively. Addition of excess pyridine-d_5 to the same trifluoroacetic acid-containing solution caused a change in the $Z{:}E$ ratio to 70:30. It was also observed that the dissolution rate was increased considerably when a drop of trifluoroacetic acid was added. The reason for this behavior is a fast rearrangement of Z into the more soluble low-melting isomer. The positions of the NMR signals of the two isomers were not changed by the above additions. This fact excludes the formation of appreciable quantities of charged species.

Similar experiments with the two isomerically pure (melting point and infrared studies) Z and E isomers gave the following results. The Z isomer, dissolved in chloroform which was allowed to evaporate slowly, was completely converted to the E isomer after 24 h. If, however, the Z isomer was dissolved in chloroform and kept in a closed vessel at room temperature for 72 h, an NMR spectrum showed that 75 % had rearranged to the E isomer. When this mixture was left for a longer period of time in the same solvent, no further change in the isomer ratio could be detected. If pure E was dissolved in pyridine, an NMR spectrum, recorded immediately, showed the presence of 90 % of Z (and 10 % of E). When pure E was dissolved in dimethyl sulfoxide and an NMR spectrum was recorded immediately, only signals from the Z isomer could be detected. It was also observed that the NMR spectra of the pyridine and dimethyl sulfoxide solutions had not changed after 48 h. These results are summarized in Chart 1.
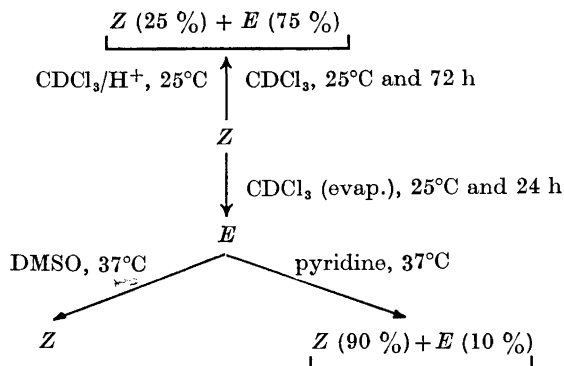
Z (25 %) + E (75 %)

CDCl$_3$/H$^+$, 25°C   CDCl$_3$, 25°C and 72 h

Z

CDCl$_3$ (evap.), 25°C and 24 h

E

DMSO, 37°C   pyridine, 37°C

Z Z (90 %) + E (10 %)

Chart 1.

EXPERIMENTAL

IR spectra were determined in chloroform solution (*ca.* 2 %), when not otherwise stated, with a Beckman model IR-9 spectrophotometer. NMR spectra were obtained with a Varian A-60 and a Varian HA-100 spectrometer. The chemical shifts are reported in δ-values, using tetramethylsilane as internal standard. UV spectra were measured in ethanol with a Beckman DB spectrophotometer and dissociation constants with an automatic titrator, model Titrigraph TTT1. Mass spectra were recorded with an LKB 9000 instrument. Melting points were determined with a Reichert melting-point microscope. Thin-layer chromatography was carried out on Silica Gel GF$_{254}$ (Merck) according to Stahl.

Preparation of 2-carbethoxymethylenethiazolidin-4-one. In a 1 1 three-necked flask, equipped with a reflux condenser, a gas inlet tube and a mechanical stirrer, 600 ml of chloroform, 56 g (0.62 mol) of mercaptoacetamide and 123 g (0.62 mol) of carbethoxy-acetimidic ethyl ester hydrochloride were introduced. The suspension was stirred and refluxed under dry carbon dioxide for 6 h. The reactants had then dissolved and ammonium chloride had precipitated. The reaction mixture was cooled to room temperature, and the solid was removed by filtration and washed with chloroform. The filtrates were concentrated under reduced pressure to a volume of *ca.* 65 ml. After the solution had been cooled in ice water, 27.0 g of ester mixture (m.p. 161 − 162°C, dried at room temperature at 2 torr) was removed by filtration and washed with chloroform. Concentration of the mother liquor yielded another 23.6 g, m.p. 145 − 148°C. The two fractions were combined and pure "H" and "L" were obtained by fractional crystallizations from ethanol and ethyl acetate at different temperatures.

Solvent (ethanol) Volume ml	Temp. °C	Yield g	M.p. °C	
80	35	21.8	164 − 166	(a)
80	25	7.4	109 and 161 − 162	(b)
80	15	2.2	109 and 162	(c)
80	5	1.2	110 and 160	(d)
40	5	1.2	110 and 163	(e)
20	5	0.6	110 and 156	(f)
5	5	1.2	163 − 165	(g)

Fractions (a) and (g) were then combined and recrystallized from ethanol, yielding 16.9 g of "H", m.p. 164 — 166°C. A final recrystallization from ethanol-ether (1:1) gave 10.0 g of "H", m.p. 163 — 165°C.

Fractions (b) — (f) were then combined and fractionated from ethanol: yield, m.p., (fraction); 8.0 g, 109 — 159°C, (a'); 3.0 g, 109 — 159°C, (b'); 0.5 g, 158 — 160°C, (c').

Fractions (a') and (b') were then combined and recrystallized from ethyl acetate: yield, m.p., (fraction); 2.8 g, 138 — 159°C, (a''); 2.3 g, 152 — 158°C, (b''); 5.1 g, 108 — 111 and 155°C, (c'').

Of these, fraction (c'') was recrystallized from ethyl acetate: yield, m.p., (fraction); 2.5 g, 108 and 155°C, (a'''); 0.9 g, 108°C, (b'''). Recrystallization of (b''') from ethyl acetate gave 0.46 g of "L", m.p. 105 — 108°C.

When the melting point of already melted and solidified "L" was retaken, it had changed to 155 — 160°C. Consequently "L" is partially converted to "H" at this high temperature.

The following properties were recorded for the *high-melting* isomer. IR: 3420 (NH), 1714 (amide $C=O$), 1682 (ester $C=O$), and 1595 cm^{-1} ($C=C$). UV: $\lambda_{max}=283$ nm ($\varepsilon=$ 21 500). NMR (CDCl$_3$): triplet ($J=7.0$ Hz) at 1.21 (3H, CH$_3$), singlet at 3.56 (2H, SCH$_2$), quartet ($J=7.0$ Hz) at 4.10 (2H, OCH$_2$), singlet at 5.54 (1H, $=$CH), and broad NH absorption at 9.48 ppm. *Anal.* (Found: C 45.01; H 4.91; N 7.53; S 17.15. Calc. for C$_7$H$_9$NO$_3$S: C 44.92; H 4.85; N 7.48; S 17.10.) MS: M$^+=187$. For the *low-melting* isomer the following properties were recorded. IR: 3290 (NH), 1732 (amide $C=O$), 1668 (ester $C=O$), and 1602 cm^{-1} ($C=C$). UV: $\lambda_{max}=283$ nm ($\varepsilon=21$ 500). NMR (CDCl$_3$): triplet ($J=7.0$ Hz) at 1.21 (3H, CH$_3$), doublet ($J=0.4$ Hz) at 3.69 (2H, SCH$_2$), quartet ($J=7.0$ Hz) at 4.10 (2H, OCH$_2$), triplet ($J=0.4$ Hz) at 5.07 (1H, $=$CH), and broad NH absorption at 10.59 ppm. *Anal.* (Found: C 44.98; H 4.82; N 7.55; S 17.16. Calc. for C$_7$H$_9$NO$_3$S: C 44.92; H 4.85; N 7.48; S 17.10.) MS: M$^+=187$.

2-Carbomethoxymethylenethiazolidin-4-one was obtained from carbomethoxyacetimidic ethyl ester hydrochloride and mercaptoacetamide according to the procedure described above. Fractional crystallization of the crude mixture in the way described for the ethyl ester mixture, but instead with acetone-methanol-petroleum ether (60 — 80°), 10:1:10, as the solvent, eventually yielded two isomeric methyl esters. The following properties were recorded for the *high-melting* isomer. M.p. 182 — 186°C. IR: 3430 (NH), 1718 (amide $C=O$), 1680 (ester $C=O$), and 1600 cm^{-1} ($C=C$). UV: $\lambda_{max}=283$ nm ($\varepsilon=19$ 940). NMR (pyridine-d_5): singlet at 3.70 (3H, OCH$_3$), singlet at 3.85 (2H, SCH$_2$), singlet at 5.80 (1H, $=$CH), and NH absorption at 10.58 ppm. *Anal.* (Found: C 41.68; H 4.13; N 8.07; S 18.60. Calc. for C$_6$H$_7$NO$_3$S: C 41.61; H 4.05; N 8.09; S 18.50.) MS: M$^+=173$. For the *low-melting* isomer the following properties were recorded. M.p. 146 — 148°C. IR: 3260 (NH), 1730 (amide $C=O$), 1668 (ester $C=O$), and 1605 cm^{-1} ($C=C$). UV: $\lambda_{max}=283$ nm ($\varepsilon=21$ 020), NMR (pyridine-d_5): singlet at 3.62 (3H, OCH$_3$), doublet ($J=0.4$ Hz) at 3.89 (2H, SCH$_2$), and triplet ($J=0.4$ Hz) at 5.25 ppm (1H, $=$CH), the NH proton absorption could not be found. *Anal.* (Found: C 41.61; H 4.09; N 8.14; S 18.60. Calc. for C$_6$H$_7$NO$_3$S: C 41.62; H 4.05; N 8.09; S 18.50.) MS: M$^+=173$.

The rule of Simon *et al.*,[13] applied to the chemical shifts for the olefinic protons, predicts (*cf.* Table 1) the low-melting methyl ester to be the E isomer and the high-melting methyl ester to be the Z isomer, as was the case with the ethyl ester isomers.

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