Tetrahedron Vol. 37, No. 15, pp. 2633 to 2640, 1981
Printed in Great Britain

0040-4020/81/152633-08$02.00/0

A STUDY OF THE TAUTOMERISM OF 2- AND 4-ETHOXYCARBONYLTHIOLAN-3-ONES IMPLICATING STEREOCHEMICAL EFFECTS OF RING-SUBSTITUTION

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(*Received in UK 4 December* 1980)

Abstract—A series of 2- and 4-ethoxycarbonylthiolan-3-ones have been synthesized and studied by ^{1}H NMR and IR spectroscopy. Under conditions of tautomeric equilibrium in tetrachloromethane solution the 4-ethoxycarbonylthiolan-3-ones are generally more enolized (40–74%) than the 2-ethoxycarbonylthiolan-3-ones (6–34%), and both series of compounds generally are less enolized than six-membered ring analogues. The extent of enolization of the title compounds is highly influenced by the nature and position of the ring-substitutents. Provable differencies in population of diastereomeric ketone forms related to the same, common enol forms are discussed in terms of stereochemical qualifications.

Special attention has been drawn to 2- and 4-alkoxycarbonylthiolan-3-ones owing to their often reported applicability as building materials in the syntheses of a variety of heteropolycyclic compounds. Thus suitably substituted 4-alkoxycarbonylthiolan-3-ones have been reported as precursors in the total synthesis of the coenzym biotin[1] and in syntheses of 9-thiaprostaglandins.[2] A convenient route to thieno[3,2-*c*]pyridazines depends on the synthetic availability of 2-ethoxycarbonylmethyl-4-ethoxycarbonylthiolan-3-one,[3] and several recent papers have demonstrated the utility of 2- and 4-ethoxycarbonylthiolan-3-ones in drug syntheses.[4] Our interest in these compounds arose at first because of their potential utility in the synthesis of new heterocyclic β-thioxo esters, designed for the investigation of "anomalous" enethiolization[5] in connection with our current studies of the tautomeric properties of β-thioxo esters.[5,6] However, during the course of our investigations it turned out that 2- and 4-alkoxycarbonylthiolan-3-ones, in spite of their extensive use in synthesis, are known exemplarily rather than as classes of compounds with reactive and structural characteristics of their own. Apart from a single paper[7] discussing solvents effects on the keto-enol equilibria of a series of β-oxo esters containing heterocyclic rings (including the thiolane ring) in terms of dissimilar solvation of the heterocyclic fragment in the ketone and the enol form, respectively, this paper apparently is the first to report comprehensively on tautomeric properties of 2- and 4-alkoxycarbonylthiolan-3-ones.

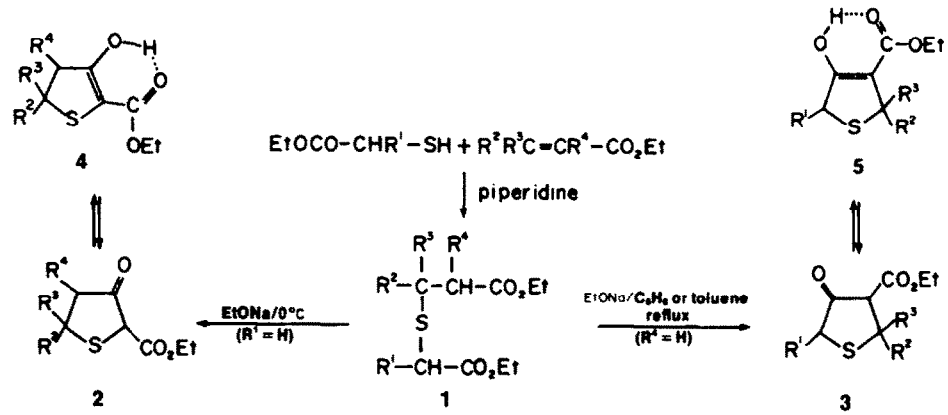
RESULTS AND DISCUSSION

Synthesis. The synthetic routes to the 2- and 4-ethoxycarbonylthiolan-3-ones under investigation are outlined in Scheme 1. The dicarboxylic esters **1** were easily obtained in high yields by addition of thioglycolic or thiolactic esters to the appropriately substituted acrylic esters in the presence of catalytic quantities of piperidine.[8–12] Cylizations of **1** (R^1 = H) into thiolanone **2** were performed without difficulties under Dieckmann conditions at 0°C (at room temperature for **2e**), using sodium ethanolate as base.[9–12] As expected,[9] similar cyclization of dicarboxylic esters **1** having R^1 = Me turned out not to take place satisfactorily. When the ring-closure condensation reactions were carried out by means of sodium ethanolate in boiling benzene or toluene[8,9,11–13] the alternative 3-thiolanones **3** could be obtained in good yields in several cases (**3a**, **3b**, **3h**, and **3i**). Under the latter conditions, however, **1c** did not react satisfactorily, and **1d** again gave a high yield (59%) of **2d**. No attempts were made to synthesize the 3-thiolanones **3** derived from the dicarboxylic esters having R^4 = Me,[9] i.e. **1e** and **1f**. The 3-thiolanone **3g** was obtained by reaction of the diester **1g** with sodium amide in ethereal solution at room temperature.[14]

The dual potentiality of the sulphidic dicarboxylic esters **1** to undergo cyclization condensation has been discussed by Woodward and Eastman,[9] who interpreted the formation of **2** in terms of a kinetically controlled reaction course, and the formation of **3** in terms of a thermodynamically controlled reaction course. Several years later Hromatka and his coworkers,[13] on the basis of experimental evidence, concluded that the formation of **3** may also depend on the ability of the isomer **2** to undergo temperature dependent retro-Claisen cleavage, anion isomerization, and alternative recyclization.

Competitionally conditioned formation of isomeric ethoxycarbonylthiolan-3-ones was actually observed only in three cases. Thus, whereas **3a** was obtained virtually pure from **1a** by performing the cyclization reaction at 110°C, cyclization of **1a** at 0°C inevitably lead to **2a** contaminated by 5–10% of **3a** (**2a** containing less than 3% of **3a** could be obtained by fractional distillation). On the other hand, cyclization of **1b** at 0°C lead to pure **2b**, whereas at 110°C **3b** contaminated by 15–20% of **2b** was obtained (in the latter case the attempted purification by fractional distillation afforded **3b** of *ca.* 92% purity). Finally, the conversion of **1c** purely into **2c** easily took place at 0°C, but at 110°C a complex reaction mixture containing also appreciable quantities of **2c** was obtained and isolation of **3c** from this reaction mixture was not achieved.

Pilot experiments clearly revealed that **2a** as well as **2b** can not survive treatment with sodium ethanolate in boiling toluene for 18–24 hr. In accordance with the observation of Hromatka,[13] retro-Claisen cleavage took place to completeness, but alternative recyclizations were found practically negligible. Thus the claimed[13] possibility of conversion of 2-alkoxycarbonylthiolan-3-



2a, 4a: $R^2 = R^3 = R^4 = H$
2b, 4b: $R^3 = R^4 = H, R^2 = Me$
2c, 4c: $R^3 = R^4 = H, R^2 = Ph$
2d, 4d: $R^4 = H, R^2 = R^3 = Me$
2e, 4e: $R^2 = H, R^3 = R^4 = Me$
2f, 4f: $R^2 = R^3 = H, R^4 = Me$

1a: $R^1 = R^2 = R^3 = R^4 = H$
1b: $R^1 = R^3 = R^4 = H, R^2 = Me$
1c: $R^1 = R^3 = R^4 = H, R^2 = Ph$
1d: $R^1 = R^4 = H, R^2 = R^3 = Me$
1e: $R^1 = R^2 = H, R^3 = R^4 = Me$
1f: $R^1 = R^2 = R^3 = H, R^4 = Me$
1g: $R^2 = R^3 = R^4 = H, R^1 = Me$
1h: $R^3 = R^4 = H, R^1 = R^2 = Me$
1i: $R^4 = H, R^1 = R^2 = R^3 = Me$

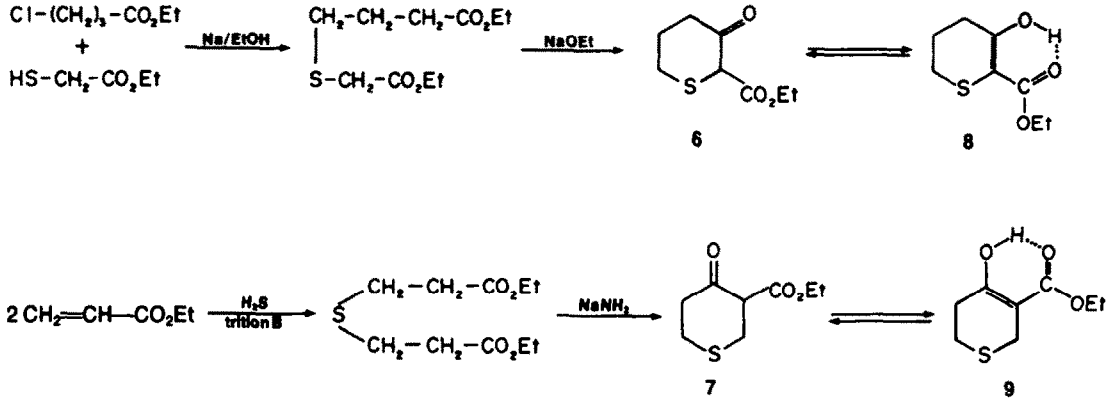
3a, 5a: $R^1 = R^2 = R^3 = H$
3b, 5b: $R^1 = R^3 = H, R^2 = Me$
3g, 5g: $R^2 = R^3 = H, R^1 = Me$
3h, 5h: $R^3 = H, R^1 = R^2 = Me$
3i, 5i: $R^1 = R^2 = R^3 = Me$

Scheme 1.

ones 2 into 4-alkoxycarbonylthiolan-3-ones 3 via retro-Claisen cleavage seems to have little practical importance.

The six-membered heterocyclic β-oxo esters 6 and 7 were as comparative compounds synthesized without difficulties by routes fundamentally similar to those leading to the thiolan-ones 2 and 3 (Scheme 2).[15-21]

nition in several cases, the enolic proton signal otherwise appears as a relatively broad peak of low intensity at around δ 10.5 as an indication of the occurrence of an intramolecular hydrogen-bonded enol form (visualized in Scheme 1).[22,23] The presence of the enol tautomer 4 is furthermore unambigously reflected in the IR spectra (Fig. 1, Table 3), which besides the dominating strong



Scheme 2.

Structure. The ^1H NMR spectra of the 2-ethoxycarbonylthiolan-3-ones 2 in tetrachloromethane solution (Table 1) indicate *a priori* that enolization is not a very prevailing feature of these compounds. The often rather complicated spectra exhibit clearly in all cases the dominating signal pattern of the ketonic form 2, but a double set of easily identified ester group proton signals admits of no doubt that minor equilibrium concentrations of enol form 4 are present. Although it escapes recog-

bands in the carbonyl region at around 1760 cm^{-1} (ketonic C=O stretching) and around 1740 cm^{-1} (ester C=O stretching), for all investigated compounds exhibit medium intensity bands at around 1660 cm^{-1} (chelated, conjugated ester C=O stretching) and around 1610 cm^{-1} (conjugated C=C stretching).[24] The apparent absence of distinct IR enolic O–H stretching vibration bands in the region above 3000 cm^{-1} is not unexpected, owing to the relatively low enol concentrations and the fact that

Table 1. ^{1}H NMR spectral data of 2-ethoxycarbonylthiolan-3-ones, 2-ethoxycarbonylthian-3-one, and their enol forms under conditions of tautomeric equilibrium in tetrachloromethane at ambient temperature.[a] Enol contents[b] and tautomeric equilibrium constants[c]

	$\delta(Me^k)$[d]	$\delta(Me^e)$[d]	$\delta(CH_2{}^k)$[d]	$\delta(CH_2{}^e)$[d]	$\delta(S\text{-}CH\lessdot^k)$	$\delta(OH^e)$	% Enol	K_{eq}[c]
2a⇄4a[f]	1.28(t,7)	1.32(t,7)	4.16(q,7)	4.22(q,7)	3.85(s)	-[g]	19.5±1	0.24
2b⇄4b[h]	1.29(t,7)	1.32(t,7)	4.15(q,7)[i]	4.21(q,7)	3.97(s)[j] 4.02(s)[j]	10.45(br.s)	17±2	0.2[l]
2c⇄4c[m]	1.28(t,7)	1.26(t,7)	4.18(q,7)	4.20(q,7)	4.11(s)[j] 4.14(s)[j]	-[g]	30±2	0.4[l]
2d⇄4d[n]	1.28(t,7)	1.31(t,7)	4.16(q,7)	4.21(q,7)	4.19(s)	10.45(br.s)	34±1	0.52
2e⇄4e[p]	1.27(t,7)	-[q]	4.13(q,7)[j] 4.15(q,7)[j]	4.21(q,7)	3.99(s)[j] 4.03(s)[j,r]	9.69(s)[s] 10.53(br.s)[s]	13±1[t]	-
2f⇄4f[u]	1.28(t,7)	1.32(t,7)	4.15(q,7)	4.23(q,7)	3.88(s)[j] 3.93(s)[j]	-[g]	6±3	0.06[l]
6⇄8[v]	1.32(t,7)	1.35(t,7)	4.25(q,7)	4.28(q,7)	3.84(s)	12.16(s)	68.5±1	2.17

[a] Chemical shifts are given as δ-values in p.p.m. relative to TMS. Relevant signal characteristics (signal multiplicity, coupling constants (Hz)) are given in parantheses. Abbreviations: s (singulet), d (doublet), t (triplet), q (quartet), m (multiplet), br. (broad). [b] Determined by signal integration. [c] K_{eq} = [enol] / [ketone]. [d] Ester group protons. [k] Ketone form. [e] Enol form. [f] Ring proton signals at δ 2.2-3.5 ($4H^{e+k}$,m). [g] Signal not recognizable. [h] Ring proton signals at δ 1.9-3.1 ($2H^{e+k}$,m) and 3.2-4.0 ($1H^{e+k}$,m). Methyl signals (d,6.5) at δ 1.40 and 1.47 (diastereomeric ketone forms, the methyl signal from the enol form apparently coalesces with the former). [i] Recorded at 90 MHz this signal appears as two very close-lying quartets, separation less than 0.01 p.p.m. [j] Diastereomeric ketone forms. [l] Pseudo equilibrium constants, since in fact two equilibria are involved: ketone⇄enol ⇄diastereomeric ketone. [m] Additional signals at δ 2.4-3.5 ($2H^{e+k}$,m), 4.2-5.0 ($1H^{e+k}$,m), and 7.27 ($5H^{e+k}$,m). [n] Additional ketone form signals at δ 1.48 ($3H^k$,s), 1.57 ($3H^k$,s), and 2.52/2.68 ($2H^k$, AB-system, J_{AB} = 16.3). Enol form signals at δ 1.50 ($6H^e$,s) and 2.70 ($2H^e$,s). [p] Mixture of stereoisomeric ketone and enol forms. Ring proton signals at δ 1.7-3.8 ($2H^{e+k}$,m). Methyl signals (d,6.5) of high intensity at δ 1.17 and 1.41, of lower intensity at δ 1.10, 1.13, 1.40, and 1.45. [q] Signal apparently masked. [r] Recorded at 90 MHz this signal resolves into two very close-lying singulets. [s] Signals of very low intensity (integral ratio ca. 1:2), probably from diastereomeric enol forms. [t] Total contents of enol forms. [u] Ring proton signals at δ 2.1-3.4 ($3H^{e+k}$,m). Methyl signals at δ 1.22 ($3H^k$, d,7) and 1.26 ($3H^e$,d,7). [v] Ring proton signals at δ 1.9-3.2 ($6H^{e+k}$,m).

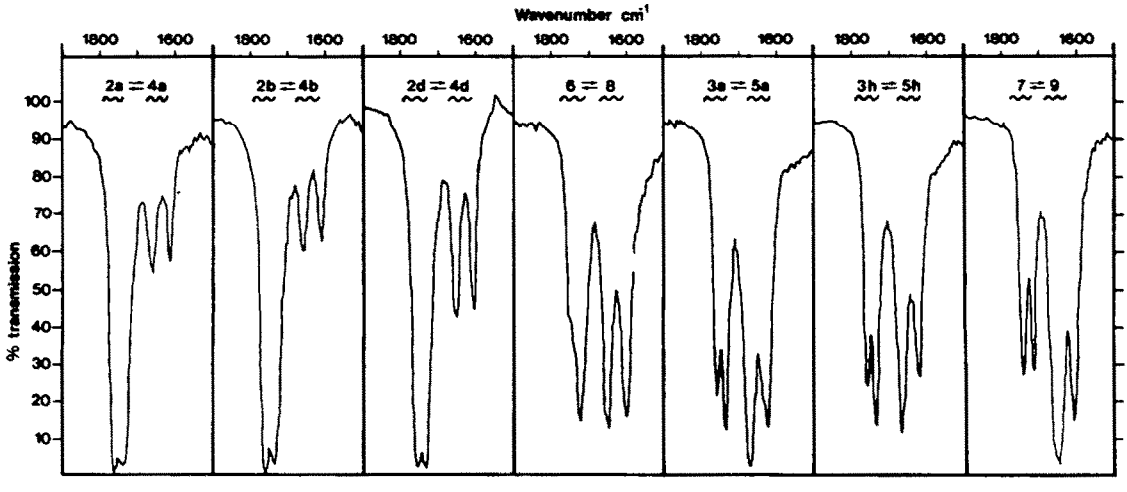


Fig. 1. IR absorption in the C=O/C=C stretching vibration region of some representative 2- and 4-ethoxycarbonylthiolan-3-ones and related six-membered ring compounds, demonstrating co-existence of tautomeric ketone and enol forms (solvent: CCl_4).

hydroxylic stretching vibration bands of enols engaged in intramolecular hydrogen–bonding with a carbonyl group usually are broad and of low intensity.[25]

In contrast to the above findings for the 2-ethoxycarbonylthiolan-3-ones, the isomeric 4-ethoxycarbonylthiolan-3-ones **3** exist under the same conditions mainly in their chelated enolic form **5**. Both of the tautomeric forms are recognizable in the ^{1}H NMR spectra, which in all cases display double sets of ester group proton signals and a distinct enolic hydroxyl proton signal at δ 10.9–11.5 (Table 2).[22,23] The general prevalence of the enol form **5** is also clearly indicated by the IR spectra, which exhibit their most intense absorption bands in the carbonyl olefin stretching region at 1660–1673 cm^{-1} (chelated, conjugated ester carbonyl group stretchings) and at 1617–1628 cm^{-1} (conjugated C=C stretching).[24] The general appearance of a broad, less intense band at 3000–3050 cm^{-1}, unambigously assignable to a chelated enolic O–H stretching vibration, confirms the presence of significant equilibrium concentrations of the enol form.[25] The ketonic form documents its general presence and co-existence with the enol form by displaying rather strong bands at around 1760 cm^{-1} (ketonic C=O stretchings) and 1740 cm^{-1} (ester C=O stretchings) (Fig. 1, Table 3).

It may perhaps give rise to surprise that enolization is found more prevailing for 4-ethoxycarbonylthiolan-3-ones **3** than for 2-ethoxycarbonylthiolan-3-ones **2**, since reflections concerning the relative stabilities of the 3- and 2-thiolene systems (the respective enolic framings) supposedly would lead to a prediction endowing the higher stability with the 2-thiolene system owing to the potentiality of conjugative interaction between the C=C double bond and the sulphur atom of the ring. Nevertheless, the observed trend is in good agreement with a recent observation[26] that 4-acetylthiolan-3-one is completely enolic in tetrachloromethane solution, whereas 2-acetylthiolan-3-one is enolized to an extent of 80% under the same conditions. That the contents of enol in the six-membered heterocyclic β-oxo esters **6** and **7** generally are higher than in the related five-membered ring compounds is consistent with observations within the corresponding homocyclic series.[23,24]

The discussion of the tautomerism of 2- and 4-ethoxycarbonylthiolan-3-ones has hitherto not included stereochemical considerations. However, even when no centre of chirality is introduced by additional ring-substitution, i.e. in the cases of systems **2a**⇄**4a** and **3a**⇄**5a**, the enol form must co-exist with two enantiomeric ketone forms, but these will be equally populated and

Table 2. ^{1}H NMR spectral data of 4-ethoxycarbonylthiolan-3-ones, 3-ethoxycarbonylthian-4-one, and their enol forms under conditions of tautomeric equilibrium in tetrachloromethane at ambient temperature.[a] Enol contents[b] and tautomeric equilibrium constants[c]

	δ(Me^k)[d]	δ(Me^e)[d]	δ(CH$_2^k$)[d]	δ(CH$_2^e$)[d]	δ(-CH<^{k})	δ(OH^e)	% Enol[b]	K_{eq}[c]
3a⇄**5a**[f]	1.28(t,7)	1.30(t,7)	4.17(q,7)	4.22(q,7)	-[g]	10.92(br.s)	74±2	2.8
3b⇄**5b**[h]	1.29(t,7)	1.31(t,7)	4.18(q,7)	4.24(q,7)	3.04(d,10.4)[i]	11.10(br.s)	40±4	0.7
3g⇄**5g**[j]	1.30(t,7)	1.30(t,7)	4.18(q,7)	4.22(q,7)	-[l]	10.88(br.s)	69±2	2.2
3h⇄**5h**[m]	1.29(t,7)	1.32(t,7)	4.17(q,7)[n]	4.23(q,7)[n]	2.99(d,10.2)[i] 3.11(d,10.2)[i]	11.18(br.s)	63±3	1.7[p]
3i⇄**5i**[q]	1.30(t,7)	1.33(t,7)	4.08(q,7)	4.26(q,7)	3.28(s)[r] 3.38(s)[r]	11.52(s)	71±2	2.4
7⇄**9**[s]	1.28(t,7)	1.31(t,7)	4.18(q,7)	4.20(q,7)	-[s]	12.41(s)	76±2	3.2

[a-e,k] See corresponding footnotes of table 1. [f] Ring proton signals, enol form: δ 3.72 (4H^e,m (narrow AA'BB'-system)); ketone form: δ(H^2) 3.25 (2H^k,s), δ(H^4,H^5) 2.9-3.6 (3H^k,m). [g] Chemical shift not determined, see footnote f. [h] Mixture of one pair of enantiomeric enol forms and one pair of enantiomeric ketone forms. Ring proton signals at δ 3.38 (2H^k,s), 3.5-4.0 (2H^e+1H^k,m), and 4.0-4.3 (1H^e,m). Ring methyl group signals at δ 1.41 (3H^k,d,6.5) and 1.46 (3H^e,d,6.5). [i] Assignment was verified by deuterium exchange experiments. [j] Ring proton signals at δ 3.63 (2H^e,m), 2.9-3.7 (3H^k,m), and 3.9-4.4 (1H^{e+k},m). Ring methyl group signals at δ 1.37 (3H^k,d, 6.5) and 1.49 (3H^e,d,6.5). [l] Chemical shift not determined, resonance signal included in the multiplet at δ 2.9-3.7. [m] Apparently a mixture of four stereoisomeric enol forms and four stereoisomeric ketone forms, forming four pairs of NMR indistinguishable enantiomers. Ring proton resonance signals at δ 3.35-4.35 (2H^e+2H^k, overlapping m's). Five discernable close-lying doublet methyl signals at δ 1.38, 1.39, 1.44, 1.47, and 1.53 (J's = 6.5-7) integrate as 6H^{e+k}. [n] Recorded at 90 MHz this signal appears as two close-lying quartets. [p] Pseudo equilibrium constant, since evidently at least four equilibria are to be considered. [q] Ring methine proton signals, diastereomeric ketone forms, at δ 3.58 (q,7) and 3.67 (q,7); enol form methine proton signal at δ 4.04 (q,7). Ring methyl signals at δ 1.47 (3H^k,d,7), 1.49 (3H^e,d,7), 1.57 (3H^e,s), and 1.61 (3H^e,s); signals from ketone form methyl groups at 5-position are masked. [r] Signals from diastereomeric ketone forms, integral ratio ca. 2:1. [s] Resonance signals of ring methylene protons and ketonic methine proton (not extractable) within δ 2.3-3.8 (6H^e+7H^k, m).

Table 3. Characteristic IR absorption bands of tautomeric 2- and 4-ethoxycarbonylthiolan-3-ones and related six-membered ring compounds[a]

	ν[O–H][b]	ν[C=O][c]	ν[C=O][c]	ν[C=O][b]	ν[C=C][b]
2a⇄4a	-[d]	1760(s)	1738(s)	1660(m)	1612(m)
2b⇄4b	-[d]	1760(s)	1736(s)	1660(m)	1610(m)
2c⇄4c	-[d]	1761(s)	1740(s)	1663(m)	1613(m)
2d⇄4d	-[d]	1758(s)	1738(s)	1654(m)	1608(m)
2e⇄4e	-[d]	1757(s)	1738(s)	1653(m)	1607(m)
2f⇄4f	-[d]	1757(s)	1737(s)	1656(m)	1607(m)
3a⇄5a	~3050(br.)	1760(s)	1738(s)	1673(s)	1626(s)
3b⇄5b	~3000(br.)	1760(s)	1738(s)	1669(s)	1625(s)
3g⇄5g	~3050(br.)	1759(s)	1737(s)	1672(s)	1628(s)
3h⇄5h	~3050(br.)	1759(s)	1735(s)	1667(s)	1621(s)
3i⇄5i	~3000(br.)	1760(sh)	1740(s)	1660(s)	1617(s)
6⇄8	~2950(br.)	1750(sh)	1723(s)	1649(s)	1600(s)
7⇄9	~2950(br.)	1746(s)	1718(s)	1654(s)	1611(s)

[a] The spectra were recorded on 2–4% tetrachloromethane solutions. Absorption band maxima are expressed as wavenumbers in cm^{-1}. Band intensities are indicated in parantheses as s (strong) and m (medium); sh denotes shoulder. [b] Enol form. [c] Ketone form. [d] Absorption bands are not discernable.

indistinguishable by NMR. Hence the ^1H NMR spectra can still be interpreted simply in terms of superimpositions of the spectra of one enol and "one" ketone form. The same situation holds for the systems **2d⇄4d**, **6⇄8**, and **7⇄9**.

In the cases **2b⇄4b**, **2c⇄4c**, **2f⇄4f**, **3b⇄5b**, **3g⇄5g**, and **3i⇄5i** one centre of chirality exists owing to ring-substitution. We may therefore here expect to observe two enantiomeric enol forms and four stereosiomeric ketone forms, the latter being pairwise enantiomeric and otherwise diastereomeric. This situation is outlined by an example in Fig. 2. Again enantiomeric forms will be indistinguishable by NMR, whereas diastereomeric forms should be distinguishable. Thus the ^1H NMR spectra of the compounds under consideration should be interpreted in terms of possible superimpositions of

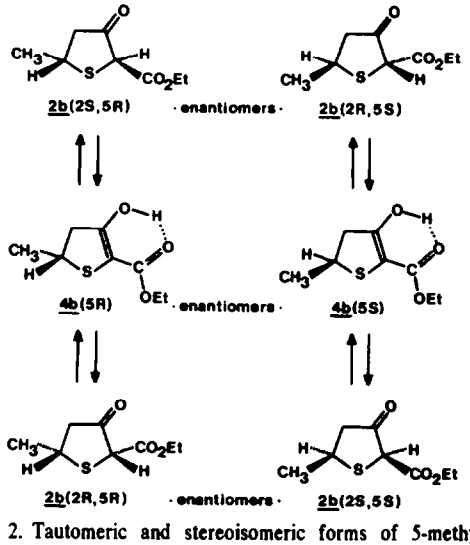
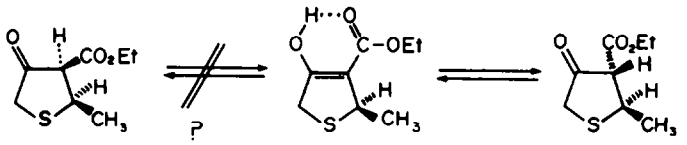


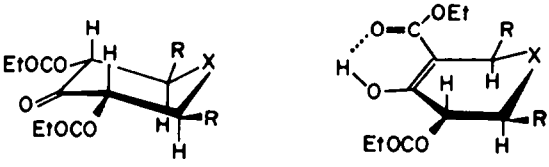
Fig. 2. Tautomeric and stereoisomeric forms of 5-methyl-2-ethoxycarbonylthiolan-3-one and possible pathways of interconversion.

the spectra of "one" enol form and "two" diastereomeric ketone forms. The latter may not necessarily be equally populated, depending on the stereochemical conditions. In accord with expections the ^1H NMR spectra of **2b⇄4b**, **2c⇄4c**, **2f⇄4f**, and **3i⇄5i** in fact display the pattern of three superimposed spectra (Tables 1 and 2). Of course, the equilibrium constants tabulated for these systems are not "true" equilibrium constants (see Fig. 2), but rather reflect extents of enolization. In case of **3g⇄5g** the complexity of the observed ^1H NMR spectrum does not allow for a conclusion regarding the number of actually existing diastereomeric ketone forms. However, the observed ^1H NMR spectrum of **3b⇄5b** distinctly display the combined pattern of spectra from the enol form and only one ketonic species, thus indicating existence of merely one pair of enantiomeric ketone forms. The coupling constant measured for the vicinal coupling between the ketonic α-hydrogen nucleus and the ring-proton at 5-position (10.4 Hz) indicates a nearly *trans*-coplanar (aa)-location of the two hydrogen atoms,[27] and, as a corollary, *trans* (ee)-location of the space-filing methyl and ethoxycarbonyl groups. This is consistent with a preferred, if not exclusive, population of the sterically less hindered of the two possible diastereomeric ketone forms, as exemplified by the **3b⇄5b**(5R)[28] system (Scheme 3). The preferred population of one of two more possible ketone forms, interconvertible via their common enol form has precedent. 2,6-Dialkyl-3,5-*bis*(ethoxycarbonyloxan-4-ones, as well as their thia- and aza-analogues, have been shown by ^1H NMR spectroscopy to exist preferentially in the symmetrical ketone form **10**,[29] co-existing at tautomeric equilibrium in solution with traces of the enol form **11**.[30] Coupling constants of 10.5–11.5 Hz were determined for the coupling between the (aa)-vicinal ring protons.[29]

With two centres of chirality innated by ring-substitution both of the system **2e⇄4e** and **3h⇄5h** are predicted to display ^1H NMR spectra composed by the spectra of four stereoisomeric enol forms (pairwise

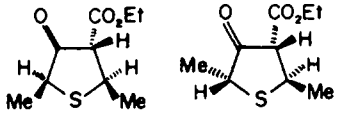


Scheme 3.



Scheme 4.

enantiomeric, otherwise diastereomeric) and eight stereoisomeric ketone forms (pairwise enantiomeric, otherwise diastereomeric), i.e. assignment must be carried out taking into account two spectroscopically different enol forms and four spectroscopically different ketone forms. Indeed, the observed spectra are very complex, and a complete line assignment turned out to be unfeasible. However, in both cases the observed spectra furnished sufficient information to allow for a reliable description of the tautomeric situation. Thus, as regards the system **2e**⇄**4e**, evidently at least three of the four possible NMR-distinguishable ketone forms co-exist with two NMR-different enol forms to varied extents. However, in the case of the system **3h**⇄**5h** apparently only two different ketonic species co-exist in detectable concentrations with the two expectedly observed enolic forms (Table 2). Two, and merely two, distinct doublet resonance signals, at δ 2.99 and 3.11, respectively, unambigously assignable to the acidic[31] ring-protons at 4-position of two different ketonic forms, are observed. The measured coupling constants for the coupling between the ring-protons located at 4- and 5-positions (both 10.2 Hz) suggest nearly *trans*-coplanar (aa)-location of these, hence identifying the observed ketonic forms as **3h**(2S, 4R, 5R) and **3h**(2R, 4R, 5R) (and, of course, their mirror images **3h**(2R, 4S, 5S) and **3h**(2S, 4S, 5S)).



Scheme 5.

Conclusion. Compared with 2-ethoxycarbonylcyclopentanone, the homocyclic relative which under conditions of tautomeric equilibrium in tetrachloromethane solution is enolized to the extent of 11.5%,[23] 2- and 4-ethoxycarbonylthiolan-3-ones show a clearly enhanced tendency to exist in the enol form. Probably, the replacement of a carbon atom by a sulphur atom in the five-membered ring effects an enlargement as well as an added puckering of the ring, endowing the thiolane ring with a shape character directed towards that of the six-membered homocyclic ring. 2-Ethoxycarbonylcyclohexanone is enolized in tetrachloromethane solution to the extent of 85%.[23] That substitution of a carbon with a sulphur atom in the six-membered ring evidently leads to decreased enolization (Tables 1 and 2) is also in accord with the above picture, since 2-ethoxycarbonylcycloheptanone, the next higher homologue in the homocyclic series, is enolized to 31% in tetrachloromethane solution.[23]

The position of the sulphur atom in the thiolanone ring relative to the β-oxo ester moiety decisively influences the extent of enolization, 2-ethoxycarbonylthiolan-3-ones 2 being generally less enolized (6–34%, Table 1) than 4-ethoxycarbonylthiolan-3-ones **3** (40–74%, Table 2). Furthermore, the above findings clearly underline the important influence of ring-substitution on the tautomeric equilibria of 2- and 4-ethoxycarbonylthiolan-3-ones, both as regards the site of the keto-enol equilibrium in general, and the population of competing stereoisomeric ketone forms, related to the same common enol form, in particular. The effect of ring-substitution on the population of competing ketone forms is especially pronounced, whenever the ester group is located at a carbon atom neighbouring a centre of chirality.

EXPERIMENTAL

^1H NMR spectra were recorded on 2–20% solns on a Varian A-60, supplementary a Jeol FX 90Q spectrometer, using TMS as internal reference standard. *IR spectra* were recorded on 2–4% solns (CCl_4) on a Beckman IR 18 spectrophotometer.

For all synthesized compounds the purity was checked by NMR. Elemantal analyses were carried out on all new heterocyclic compounds by the Microanalytical Laboratory of the Department of General and Organic Chemistry of the H. C. Ørsted Institute, the University of Copenhagen. B.ps are uncorrected. Unless stated otherwise, yields refer to the isolated quantities of the pure products.

The dicarboxylic esters **1** were synthesized according to a known procedure.[8-12] Relevant characteristics are given below.

Ethyl 3-(ethoxycarbonylmethylmercapto) propanoate (**1a**): Yield: 88%; $b.p._{0.12}$: 98° (lit[12] $b.p._{12}$: 154–155°). ^1H NMR (CCl_4): δ 1.25 (3H, t, J = 7 Hz), 1.27 (3H, t, J = 7 Hz), 2.4–3.0 (4H, m), 3.13 (2H, s), 4.09 (2H, q, J = 7 Hz), 4.13 (2H, q, J = 7 Hz).

Ethyl 3-(ethoxycarbonylmethylmercapto) butanoate (**1b**): Yield: 94%; $b.p._{0.12}$: 96–98° (lit[32] $b.p._1$: 109–110°). ^1H NMR (CCl_4): δ 1.25 (3H, t, J = 7 Hz), 1.26 (3H, t, J = 7 Hz), 1.33 (3H, d, J = 6 Hz), 2.1–2.85 (2H, m, AB-part of ABX-system), 3.17 (2H, s), 3.0–3.6 (1H, m, X-part of ABX-system), 4.09 (2H, q, J = 7 Hz), 4.13 (2H, q, J = 7 Hz).

Ethyl 3-(ethoxycarbonylmethylmercapto)-3-phenylpropanoate (**1c**): Yield: 97%; $b.p._{0.15}$: 142° (lit[10] $b.p._2$: 163–165°). ^1H NMR (CCl_4): δ 1.11 (3H, t, J = 7 Hz), 1.24 (3H, t, J = 7 Hz), 2.6–3.1 (2H, m, AB-part of ABX-system), 2.85 (2H, s), 3.98 (2H, q, J = 7 Hz), 4.07 (2H, q, J = 7 Hz), 4.43 (1H, q, X-part of ABX-system), 7.24 (5H, m).

Ethyl 3-(ethoxycarbonylmethylmercapto)-3-methylbutanoate (**1d**): Yield: 66%; $b.p._{0.17}$: 106–107°. ^1H NMR (CCl_4): δ 1.25 (3H, t, J = 7 Hz), 1.27 (3H, t, J = 7 Hz), 1.41 (6H, s), 2.52 (2H, s), 3.19 (2H, s), 4.08 (2H, q, J = 7 Hz), 4.11 (2H, q, J = 7 Hz).

Ethyl 3-(ethoxycarbonylmethylmercapto)-2-methylbutanoate (**1e**): Yield: 83%; $b.p._{0.27}$: 104–106°. ^1H NMR (CCl_4): δ 1.25 (6H, m),

1.26 (3H, t, $J = 7$ Hz), 1.29 (3H, t, $J = 7$ Hz), 2.51 (1H, 5'tet, $J = 6.8$ Hz), 3.14 (2H, s), 3.14 (1H, 5'tet, $J = 6.8$ Hz), 4.10 (2H, q, $J = 7$ Hz), 4.13 (2H, q, $J = 7$ Hz).

Ethyl 3-(ethoxycarbonylmethylmercapto)-2-methylpropanoate (**1f**): Yield: 93%; b.p.$_{0.12}$: 95° (lit[33] b.p.$_6$: 140–144°). ^{1}H NMR (CCl_4): δ 1.21 (3H,d, $J = 7$ Hz), (3H, t, $J = 7$ Hz), 1.27 (3H, t, $J = 7$ Hz), 2.3–3.0 (3H, m), 3.10 (2H, s), 4.10 (2H, q, $J = 7$ Hz), 4.13 (2H, q, $J = 7$ Hz).

Ethyl 3-[(1-ethoxycarbonyl)ethylmercapto]propanoate (**1g**): Yield: 89%; b.p.$_{0.14}$: 100–107° (lit[14] b.p.$_{10.5}$: 149–153°). ^{1}H NMR (CCl_4): δ 1.25 (3H, t, $J = 7$ Hz), 1.28 (3H, t, $J = 7$ Hz), 1.38 (3H, d, $J = 7$ Hz), 2.3–3.0 (4H, m, AA'BB'-system), 3.31 (1H, q, $J = 7$ Hz), 4.08 (2H, q, $J = 7$ Hz), 4.12 (2H, q, $J = 7$ Hz).

Ethyl 3-[(1-ethoxycarbonyl)ethylmercapto]butanoate (**1h**): Yield: 91%; b.p.$_{0.15}$: 103–108°. ^{1}H NMR (CCl_4) suggests mixture of stereoisomers: δ 1.25 (3H, t, $J = 7$ Hz), 1.28 (3H, t, $J = 7$ Hz), 1.28 (~ 1.5H, d, $J = 7$ Hz), 1.32 (~ 1.5H, d, $J = 7$ Hz), 1.36 (~ 1.5H, d, $J = 7$ Hz), 1.40 (~ 1.5H, d, $J = 7$ Hz), 2.0–2.9 (2H, m), 3.1–3.6 (2H, m), 4.09 (2H, q, $J = 7$ Hz), 4.13 (2H, q, $J = 7$ Hz).

Ethyl 3-[(1-ethoxycarbonyl)ethylmercapto]-3-methylbutanoate (**1i**): Yield: 61%; b.p.$_{0.2}$: 101–102°. ^{1}H NMR (CCl_4): δ 1.25 (3H, t, $J = 7$ Hz), 1.26 (3H, t, $J = 7$ Hz), 1.37 (3H, d, $J = 7$ Hz), 1.41 (6H, s), 2.54 (2H, s), 3.38 (1H, q, $J = 7$ Hz), 4.07 (2H, q, $J = 7$ Hz), 4.11 (2H, q, $J = 7$ Hz).

General procedure for the preparation of 2- and 4-ethoxycarbonylthiolan-3-ones (worked out on the basis of earlier described procedures[8–13]): A stirred suspension of sodium ethanolate (0.3 mole) in 200–250 ml of the appropriate dried solvent (ether, ethanol, benzene, or toluene) is brought to the desired reaction temperature, and the sulphidic dicarboxylic ester **1** (0.25 mole) is added dropwise during 1–2 hr under stirring at that temperature. Keeping the temperature constant, the reaction mixture is stirred for additional 4–6 hr. For reactions to be carried out in ether at 0° a further occasional supply of ether (200–300 ml) may be needed to keep the reaction mixture mobile. The reaction mixture is then poured into a mixture of 200 g of acetic acid and 200 g of crushed ice under manual stirring (in the syntheses of **2e**, **2f**, **3a**, **3b**, **3h**, and **3i** the reaction mixture was allowed to stand overnight, incidentally with stirring (**3b**, **3h**, **3i**), before being poured into the ice-acetic acid mixture). The layers are separated, if convenient after a further supply of ether, chloroform (**2a**), or water. The aqueous layer is extracted twice with ether or chloroform (**2a**), and the combined organic layers are washed with aqueous $NaHCO_3$, then with water, and finally dried ($CaSO_4$). The solvent is removed by evaporation, and the remaining oil distilled to give the product as a colourless oil.

2-Ethoxycarbonylthiolan-3-one (**2a**): Prepared according to the above general procedure. The reaction was performed at 0° using ethanol as solvent and chloroform as extraction medium. Yield: 23–43%, b.p.$_{10}$: 119–122° (lit[11] b.p.$_{3-4}$: 98–101°).

2-Ethoxycarbonyl-5-methylthiolan-3-one (**2b**): Prepared according to the above procedure in ethereal medium at 0°. Yield: 66%, b.p.$_{0.2}$: 84–87° (lit[32] b.p.$_{0.1}$: 78–81°, lit[34] b.p.$_{17}$: 134–137°).

2-Ethoxycarbonyl-5-phenylthiolan-3-one (**2c**): Prepared according to the general procedure in ethereal medium at 0°. Yield: 31%, b.p.$_{0.12}$: 132–137° (lit[10] b.p.$_1$: 158–160°).

2-Ethoxycarbonyl-5,5-dimethylthiolan-3-one (**2d**): Prepared according to the general procedure, in ethereal medium at 0° in 75% yield, in boiling toluene in 59% yield. B.p.$_{0.17}$: 90°. (Found: C, 53.65; H, 7.09; S, 15.27. $C_9H_{14}O_3S$ requires: C, 53.46; H, 6.98; S, 15.82%).

2-Ethoxycarbonyl-4,5-dimethylthiolan-3-one (**2e**): Prepared by Dieckmann condensation reaction at room temperature in benzene following the above general procedure. Yield: 75%, b.p.$_{0.15}$: 83–88°. (Found: C, 53.95; H, 7.15; S, 15.25. $C_9H_{14}O_3S$ requires: C, 53.46; H, 6.98; S, 15.82%).

2-Ethoxycarbonyl-4-methylthiolan-3-one (**2f**): Prepared by Dieckmann condensation in ether at 0° according to the above general procedure. Yield: 71%, b.p.$_9$: 122–123° (lit[33] b.p.$_{13}$: 128–131).

4-Ethoxycarbonylthiolan-3-one (**3a**): Prepared by Dieckmann reaction in boiling toluene according to the general procedure. Yield: 35%, b.p.$_9$: 116–117° (lit[8] b.p.$_4$: 96°, lit[12] b.p.$_1$: 90–93°).

4-Ethoxycarbonyl-5-methylthiolan-3-one (**3b**): By Dieckmann reaction in boiling toluene according to the general procedure. Yield: 59%. The product was contaminated by 15–20% of **2b**. Fractional redistillation gave a product of 92% purity, b.p.$_9$: 117–120°. (Found: C, 51.20; H, 6.58; S, 16.64. $C_8H_{12}O_3S$ requires: C, 51.06; H, 6.43; S, 17.00%).

4-Ethoxycarbonyl-2-methylthiolan-3-one (**3g**): Prepared as described by Karrer and Schmid.[14] Yield: 33%, b.p.$_{0.15}$: 70–71° (lit[14] b.p.$_9$: 125–128°).

4-Ethoxycarbonyl-2,5-dimethylthiolan-3-one (**3h**): Prepared by Dieckmann condensation reaction in boiling dry toluene according to the above general procedure. Yield: 80%, b.p.$_{0.18}$: 62–68°. (Found: C, 54.12; H, 7.12; S, 15.16. $C_9H_{14}O_3S$ requires: C, 53.46; H, 6.98; S, 15.82%).

4-Ethoxycarbonyl-2,5,5-trimethylthiolan-3-one (**3i**): Prepared by Dieckmann condensation reaction in boiling dry benzene according to the above general procedure. Yield: 25%, b.p.$_1$: 78°. (Found: C, 55.43; H, 7.61; S, 14.91. $C_{10}H_{16}O_3S$ requires: C, 55.54; H, 7.46; S, 14.80%).

2-Ethoxycarbonylthian-3-one (**6**): Prepared by Dieckmann condensation reaction as described in lit.[15–17] Yield: 48%, b.p.$_{0.2}$: 74–75° (lit[15] b.p.$_{0.09}$: 65°, lit[17] b.p.$_{12}$: 139–141°).

3-Ethoxycarbonylthian-4-one (**7**): Prepared by Dieckmann condensation reaction as described in lit.[20] Yield: 28%, b.p.$_{0.17}$: 77–80° (lit[20] b.p.$_{16}$: 150–151°).

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