Determination of Tautomeric Phenotypes of β-Thioxo Esters and Characterization of the Tautomeric Enethiolic Constituents by Means of ^{13}C NMR Spectroscopy†

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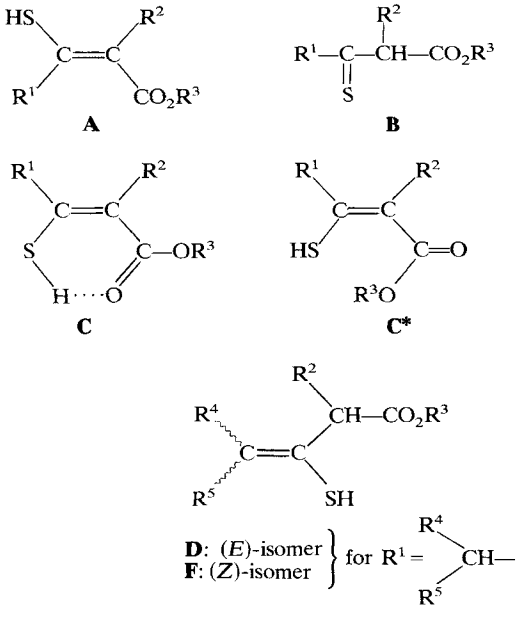
The ^{13}C NMR spectra of 28 enethiolizable β-thioxo esters and 6 enethiolizable β-thioxo thioloesters have been recorded in order to establish the tautomeric phenotypes of these compounds. All compounds investigated are essentially enethiolic. The carbonyl-conjugated (*Z*)-enethiol form is the exclusive or predominant tautomer of open-chain β-thioxo esters and thioloesters, thioacylmalonates and medium-sized 2-alkoxycarbonylcycloalkanethiones. The carbonyl-conjugated (*E*)-enethiol form is identifiable for open-chain α-unsubstituted β-thioxo esters and thioloesters, and abundant for open-chain α-substituted β-thioxo esters. Non-conjugated enethiol forms [i.e. (*Z*)- and (*E*)-isomeric β,γ-unsaturated β-mercapto esters] are abundant tautomeric constituents of ω-substituted and higher 2-alkoxycarbonylcycloalkanethiones. The chemical shifts of the carbon atoms directly involved in the tautomeric change have been rationalized in terms of substituent screening contributions. Deuterium isotope effects on the central carbon atoms of selected deuterio-enethiolic compounds have been measured in order to depict the ester group rotamerism in CO-conjugated (*Z*)-enethiols. The abundance of the CO-conjugated (*E*)-enethiols, as well as the preferred population of the non-conjugated (*Z*)-enethiol form relative to the non-conjugated (*E*)-enethiol form, is rationalized in terms of the occurrence of a no-bond interaction between the lone-pair electrons of the enethiolic sulphur atom and the 'chelating' methylene hydrogen atoms of *cis*-alkyl groups.

INTRODUCTION

^1H NMR, IR and UV spectroscopic studies of enethiolizable β-thioxo esters (the β-thioxo esters are named as such for simplicity, regardless of which possible tautomer is predominant) have demonstrated that such compounds, both in solution and as neat liquids, exist exclusively or predominantly as tautomeric enethiols, unless they are subject to particular steric requirements.[1–3] However, several enethiolic structures are possible (Scheme 1). As long as steric interactions between R^1, R^2 and OR^3 in the planar proton-chelating *cis*-enethiol form **C** are insignificant (i.e. for $R^2 = H$), this form predominates not only in solution and in the neat liquid state,[1] but also in the gas phase.[4] The introduction of an α-substituent (i.e. $R^2 \neq H$) in general gives rise to a simultaneous increased population of the rotameric *cis*-enethiol form **C*** (discernible from **C** in the IR spectrum, but not in the ^1H NMR spectrum) and the *trans*-enethiol form **A** (discernible from **C** by both IR and ^1H NMR spectroscopy).[1] Furthermore, five- to nine-membered 2-alkoxycarbonylcycloalkanethiones, a special class of α-substituted β-thioxo esters that cannot exist in the **A** form, merely show a relatively enhanced population of the rotameric **C*** form.[3] Thioacylmalonates (R^2 = CO_2R) necessarily exist as enethiols merely in the **C** form,[1] otherwise the simultaneously increased bulkiness of R^1 and R^2 effects population of the 'anomalous' enethiol forms **D** and **F** ($R^1 = CHR^4R^5 \neq$ Me, R^2 = alkyl)[5] or, in extreme cases, eventually the thioxo form **B** (e.g. R^1 = Me, $R^2 = Pr^i$ or cyclopentyl).[1]



Scheme 1

† β-Thioxo Esters, Part 5. For Part 4, see Ref. 4.
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This paper reports a ^{13}C NMR spectroscopic study carried out in a search for corroboration of the above findings and, in particular, in order to test the ^{13}C NMR spectroscopic method as a tool for detection of, and distinguishing between, the different tautomeric forms involved in thioketone–enethiol tautomerism.[6]

Features not easily determined by means of ^{1}H NMR are the geometric isomerism of the 'anomalous' enethiol form (**D** and/or **F**) and the relative abundances of the rotamers **C** and **C***. The former point may be settled by means of ^{13}C chemical shifts, the latter by investigation of deuterium isotope effects on the ^{13}C chemical shifts.

Finally, the stabilizing interactions in the different tautomers and rotamers are discussed, and an explanation for the relative abundances of the tautomeric forms is offered.

RESULTS AND DISCUSSION

Tautomeric interconversion processes usually proceed at rates allowing the tautomeric constituents present in measurable concentrations to be recognized as individual species by NMR spectroscopy. The previous ^{1}H NMR spectroscopic findings[1–3,5] predict that any of the tautomeric forms, **A**, **B**, **C** and **D** (and/or **F**), should be discernible individually in the ^{13}C NMR spectra of β-thioxo esters, whereas the population of different rotameric forms of a given tautomer cannot be perceived immediately owing to the rapidity of the rotameric interconversion (e.g. **C**⇄**C***, Scheme 1). Therefore, if not specifically stated otherwise, the (*Z*)-enethiol form is henceforward designated by **C**, irrespective of the extent of population of its rotameric form **C***.

The β-thioxo esters studies are listed in Table 1, which also contains a survey of the tautomeric and isomeric forms that were unambiguously detectable for each β-thioxo ester by ^{13}C NMR spectroscopy. A series of open-chain α-unsubstituted β-thioxo thioloesters known from recent ^{1}H NMR and IR studies[7] to exist, like their ester relatives, predominantly in the (*Z*)-enethiol form **C**, are also included. From previous knowledge of the structural features of most of the compounds under investigation, the interpretations of their proton-decoupled ^{13}C NMR spectra in terms of the carbon resonances of the individual tautomeric or isomeric forms actually existing were made without severe difficulties. However, a complete assignment was not possible in all cases, mostly owing to too low concentrations of the species and/or to overlapping lines in the region of sp^3 hybridized carbon resonance signals. SFORD spectra were recorded in a few relevant cases to ensure signal assignment; in other cases of doubt assignments have been made tentatively on the basis of analogy considerations.

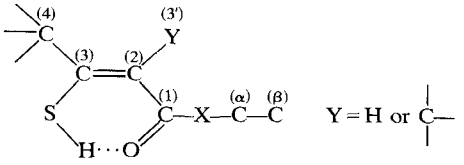
For the sake of clarity and comparability, the ^{13}C NMR chemical shifts measured, instead of being presented as the tabulated spectra of the investigated compounds with their varied tautomeric phenotypes, have been arranged in tables according to their affiliation to tautomeric structure. Thus, ^{13}C NMR shifts of the (*Z*)-enethiol forms **C**, which are the prevailing tautomeric constituents for all compounds investigated with the exceptions of **31** and **33**, are collected in Table 2. Tables 3 and 4 contain the ^{13}C NMR shifts

Table 1. Survey of the β-thioxo esters and β-thioxo thioloesters (R^1—CS—CHR^2—CO—XR^3) investigated, and the tautomeric forms detected in $CDCl_3$ solution by ^{13}C NMR spectroscopy

Compound	R^1	R^2	X	R^3	Observed tautomer(s)[a]
1	Me	H	O	Et	**A**[b], **C**
2	Me	H	O	Pr^i	**A**[b], **C**
3	Me	H	O	Bu	**A**[c], **C**
4	Me	H	O	Bu^i	**A**[b], **C**
5	Me	H	O	Bu^{sec}	**A**[b], **C**
6	Me	H	S	Et	**C**[d]
7	Me	H	S	Pr^i	**A**[b], **C**
8	Me	H	S	Bu	**A**[b], **C**
9	Me	H	S	Bu^i	**C**[d]
10	Me	H	S	Bu^{sec}	**A**[b], **C**
11	Me	H	S	Bu^t	**A**[b], **C**
12	Et	H	O	Et	**C**[d]
13	Pr	H	O	Et	**C**[d]
14	Pr^i	H	O	Et	**C**[d]
15	Bu^t	H	O	Et	**C**[d]
16	Ph	H	O	Et	**C**[d]
17	$EtOCOCH_2$	H	O	Et	**C**[d]
18	Me	CO_2Et	O	Et	**C**
19	Et	CO_2Et	O	Et	**C**
20	Pr	CO_2Et	O	Et	**C**
21	Pr^i	CO_2Et	O	Et	**C**
22	$-(CH_2)_3-$		O	Et	**C**[e]
23	$-(CH_2)_4-$		O	Et	**C**[e]
24	$-(CH_2)_5-$		O	Et	**C**[e]
25	$-(CH_2)_6-$		O	Et	**C**[e]
26	$-(CH_2)_7-$		O	Et	**C**[e]
27[f]	Me	Me	O	Et	**A**, **C**[e]
28[f]	Me	Et	O	Et	**A**, **C**[e]
29[f]	Me	Pr	O	Et	**A**, **C**[e]
30[f]	Ph	Me	O	Et	**A**, **C**[e]
31[f]	$-CH(Me)(CH_2)_3-$		O	Et	**C**[e], **D**[g]
32[f]	$-(CH_2)_8-$		O	Et	**C**[e], **F**[h]
33[f]	$-(CH_2)_9-$		O	Et	**A**, **C**[e], **D**[g], **F**[h]
34[f]	$-(CH_2)_{10}-$		O	Et	**A**, **C**[e], **D**[g], **F**[h]

[a] Compare with Scheme 1. The spectra of **1**, **12–19** and **31–33** were recorded on a Bruker Spectrospin WH 90 spectrometer, and those of **2–11**, **30** and **34** on a JEOL FX 90Q spectrometer.
[b] The existence of *ca* 5% of the (*E*)-enethiol form **A** was indicated only by the relatively intense C-2 resonance signal (Table 3).
[c] The existence of *ca* 5% of the (*E*)-enethiol form **A** was indicated clearly by several unambiguously assignable carbon resonance signals in the ^{13}C NMR spectrum on the basis of 60 000 transients.
[d] The low percentages (*ca* 5%) of the (*E*)-enethiol form **A** co-existing at tautomeric equilibrium with the (*Z*)-enethiol form **C**, according to the ^{1}H NMR spectrum,[1,7] were not unambiguously detectable in the proton-decoupled ^{13}C NMR spectrum.
[e] Two rotameric forms (C⇄C*, see Scheme 1) have been identified by IR spectroscopy.[1,3]
[f] Approximate equilibrium percentages (±5%) of the detected tautomeric constituents, as estimated from signal area ratios between comparable signals, are: **27A**, 35%; **27C**, 65%; **28A**, 38%; **28C**, 62%; **29A**, 37%; **29C**, 63%; **30A**, 20%; **30C**, 80%; **31C**, 25%; **31D**, 75%; **32C**, 80%; **32F**, 20%; **33A**, 9%; **33C**, 21%; **33D**, 9%; **33F**, 61%; **34A**, 12%; **34C**, 44%, **34D**, 15%; **34F**, 29%.
[g] (*E*)-isomeric form.
[h] (*Z*)-isomeric form.

Table 2. ^{13}C NMR chemical shifts of (*Z*)-enethiol forms C of β-thioxo esters and β-thioxo thioloesters (in $CDCl_3$ solution)



Compound[a]	C-1	C-2	C-3	C-4	C-3'	C-α	C-β	Other carbons
1C	167.7	111.4	154.6	27.9	—	59.9	14.4	—
2C	167.2	111.8	154.0	27.8	—	67.1	21.9	—
3C	167.8	111.4	154.4	27.9	—	63.8	30.8	19.3, 13.8
4C	167.8	111.4	154.5	27.9	—	70.1	27.9	19.1
5C	167.4	111.8	154.1	27.9	—	71.7	28.9, 19.6	9.7
6C	189.4	118.6	150.9	27.9	—	23.1	14.9	—
7C	189.6	118.7	150.7	27.9	—	34.4	23.0	—
8C	189.6	118.7	150.9	28.0	—	31.8	28.5	22.1, 13.6
9C	189.3	118.7	150.9	27.9	—	37.0	28.8	21.7
10C	189.6	118.8	150.5	28.0	—	40.7	29.6, 20.9	11.4
11C	190.5	118.9	149.9	28.1	—	48.0	29.9	—
12C	168.1	109.8	161.1	34.8	—	59.9	14.4	13.5
13C	168.0	110.6	159.6	43.5	—	59.9	14.4	22.1, 13.3
14C	168.5	108.1	166.8	39.6	—	59.9	14.4	22.2
15C	169.0	107.0	171.0	39.7	—	59.9	14.3	29.9
16C	168.3	111.2	156.9	140.8	—	60.3	14.4	130.1, 128.8, 126.8
17C	168.6[b]	114.3	149.9	46.4	—	60.3[d]	14.2	167.5,[b] 61.6[c,d]
18C	166.1[b]	119.8	155.7	26.0	165.2[b]	61.0[d]	14.0	61.4[c,d]
19C	166.1[b]	118.9	162.0	33.2	165.4[b]	61.0[d]	14.0	61.4,[c,d] 14.0
20C	166.2[b]	119.4	160.6	41.5	165.5[b]	61.0[d]	14.1	61.4,[c,d] 22.8, 13.7
21C	166.6[b]	117.8	167.5	36.1	165.9[b]	61.1[d]	14.1	61.4,[c,d] 21.8
22C[e]	166.4	123.7	150.9	41.5	32.6	60.0	14.4	21.8[f]
23C[e]	167.8	120.7	148.9	37.7	26.4	60.3	14.4	23.3,[f] 22.4[f]
24C[e]	168.6	124.9	154.2	42.7	31.7[g]	60.4	14.4	28.6,[f] 26.1,[f] 25.7[f]
25C[e]	168.0	122.8	151.2	39.9	30.4[g]	60.3	14.4	29.6,[f] 27.8,[f] 26.6[f] 26.0[f]
26C[e]	168.2	123.9	150.6	39.2	28.4[g]	60.3	14.4	26.8,[f] 26.7,[f] 26.1[f] 25.1,[f] 23.7[f]
27C[e]	168.3	118.1	145.4	27.0	15.0	60.4	14.3	—
28C[e]	168.2	124.9	145.3	26.3	22.6	60.3	14.4	13.7
29C[e]	168.3	123.7	145.4	26.6	31.2	60.3	14.3	22.6, 13.9
30C[e]	168.1	119.7	147.9	143.7	16.6	60.6	14.3	128.6, 118.0, 127.0
31C[e,h]	168.2	120.2	152.1	40.1	30.4[g]	60.3	14.3	26.9,[f] 21.6,[f] 18.2
32C[e]	168.0	124.4	148.7	36.4	27.7[g]	60.3	14.4	—[i]
33C[e,i]	168.6	126.3	147.4	36.9[d]	—[k]	60.4	14.2	—[i]
34C[e,l]	168.5	124.5	149.4	36.6[d]	—[k]	60.4	14.4	—[i]

[a] See Table 1 and Scheme 1.
[b] Tentative ^{13}CO assignment.
[c] C-α of non-chelating ester ethyl group.
[d] Tentative assignment.
[e] Co-existence of rotameric (*Z*)-enethiol forms (**C**⇄**C***) according to IR spectroscopic findings.[1,3]
[f] ^{13}C NMR shifts of ring methylene groups.
[g] Tentative ring methylene group ^{13}C NMR shift assignment.
[h] The (*Z*)-enethiol form is a minor constituent (*ca* 25%) of the tautomeric system.[5]
[i] Presentation and assignment of ^{13}C NMR signals other than the most informative have been omitted owing to lack of relevance.
[j] The (*Z*)-enethiol form is a minor constituent (*ca* 21%) of the tautomeric system.
[k] Assignment has not been made.
[l] The (*Z*)-enethiol form is the most abundant tautomeric constituent (*ca* 44%).

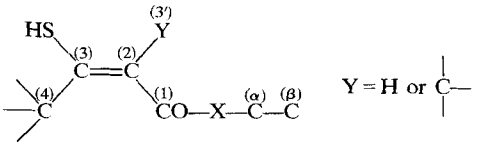
characterizing the (*E*)-enethiol forms **A** and the non-conjugated enethiol forms **D** and **F**, respectively. In no case were ^{13}C NMR signals assignable to the potentially existing thioketone form **B** observed.

Spectral characteristics of tautomeric forms

The ^{13}C NMR spectra of open-chain α-unsubstituted β-thioxo esters (**1–5**, **12–17**) and the related β-thioxo thioloesters (**6–11**) show exclusively, or almost exclusively, one tautomeric form, the (*Z*)-enethiol form **C** (Table 2).

For compounds **1**, **12** and **13**, the substituent effects of the SH group can be evaluated from the ^{13}C chemical shifts of the corresponding acids:[8,9] $\Delta(C\text{-}3)_{SH} = +7.3$, $+8.5$ and $+8.5$ ppm, $\Delta(C\text{-}2)_{SH} = -10.6$, -9.8 and -10.0 ppm, and $\Delta(C\text{-}4)_{SH} = +10.1$, $+11.5$

Table 3. ^{13}C NMR chemical shifts of (*E*)-enethiol forms A of β-thioxo esters and β-thioxo thioloesters (in $CDCl_3$ solution)



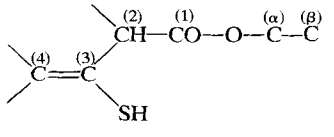
Compound[a]	C-1	C-2	C-3	C-4	C-3'	C-α	C-β	Other carbons
1A[b]	—	114.4	—	—	—	—	—	—
2A[b]	—	114.3	—	—	—	—	—	—
3A[b,c]	165.0	114.1	153.2	—	—	—	—	—
4A[b]	—	114.2	—	—	—	—	—	—
5A[b]	—	114.3	—	—	—	—	—	—
7A[b]	—	121.0	—	—	—	—	—	—
8A[b,d]	168.8	120.9	—	—	—	—	—	—
10A[b]	—	121.1	—	—	—	—	—	—
11A[b]	—	121.3	—	—	—	—	—	—
27A[e]	166.6	120.8	143.9	26.2	17.5	60.2	14.3[f]	
28A[e]	166.7	127.9	141.9	26.5	25.6	60.2	14.4[f]	12.2
29A[e]	167.0	126.9	141.9	26.6[f]	34.3	60.2	14.3[f]	21.1, 13.9
30A[e]	167.0	123.3	143.2[g]	—[h]	18.0	60.1	13.4	133.4, 128.3, 127.7
33A[e]	166.7	128.2	148.7	—[h]	—[h]	60.3	14.2[f]	—[h]
34A[e]	—[h]	128.3	155.0	—[h]	—[h]	60.4[f]	14.2[f]	—[h]

[a] See Table 1 and Scheme 1.
[b] Other signals of the (*E*)-enethiol form **A** were not clearly recognizable under the recording conditions (commonly 2000–4000 transients), owing to the low equilibrium percentages of this form (*ca* 5%, estimated from signal intensities).
[c] Spectrum recorded on the basis of 60 000 transients.
[d] Spectrum recorded on the basis of 50 000 transients.
[e] For equilibrium percentages estimated from signal area measurements, see Table 1, footnote f.
[f] The signal merges with the corresponding signal of the (*Z*)-enethiol form **C**.
[g] Tentative assignment.
[h] Signal assignment has not been made.

and +9.5 ppm, respectively. However, in most other cases the chemical shifts of the corresponding carboxylic acid are not known. It is hence also necessary to give composite substituent effects by comparing with the corresponding olefins.[10–13] For **1** and **12–15** the following substituent effects are obtained: $\Delta(C\text{-}3)_{SH,CO}$ = +20.6, +20.9, +20.6, +20.8 and +21.2 ppm, $\Delta(C\text{-}2)_{SH,CO}$ = −4.6, −3.7, −3.9, −3.2 and −2.0 ppm and $\Delta(C\text{-}4)_{SH,CO}$ = +8.0, +8.0, +7.3, +7.3 and +6.0 ppm, respectively.

The small equilibrium percentages (*ca* 5%) of the (*E*)-enethiol form **A**, normally detectable by ^1H NMR

Table 4. ^{13}C NMR chemical shifts of non-conjugated ('anomalous') enethiol forms D[a] and F[a] of β-thioxo esters (in $CDCl_3$ solution)



Compound[a]	C-1	C-2	C-3	C-4	C-α	C-β	Other carbons
31D[b]	174.0	50.0	116.7	136.0	60.8	14.3	32.4,[c] 27.8, 21.1, 20.2
32F[d]	172.9	57.9	126.3	134.6	60.8	14.4	30.2[c,e]
33F[f]	173.2	57.0	126.8	131.8[g]	60.8	14.2	30.2[c,e]
33D[f]	—[h]	—[h]	—[h]	137.8[g]	—[h]	—[h]	—[e]
34F[f]	173.2[i]	53.9[i]	126.2[i]	133.6[g,i]	60.8	14.4	—[e]
34D[f]	173.7[i]	57.5[i]	128.3[i]	134.3[g,i]	—[h]	—[h]	—[e]

[a] See Table 1 and Scheme 1.
[b] Predominant tautomeric form. Equilibrium percentages of **31D** (co-existing alone with **31C**): 75%.
[c] C-5.
[d] Equilibrium percentages of **32F** (co-existing alone with **32C**): 20%.
[e] Further documentation of the ring methylene carbon resonances has been omitted owing to assignment difficulties.
[f] For equilibrium percentages see Table 1, footnote f.
[g] These signals are doublets in the SFORD ^{13}C NMR spectra.
[h] Not assigned owing to ambiguities and/or insufficient signal intensity.
[i] Assignments are made tentatively on the basis of signal area comparison.

spectroscopy,[1,7] either avoid recognition or are detectable unambiguously only from the α-carbon signal (C-2), deshielded relative to the C-2 signal of the (*Z*)-enethiol form **C** by 2.5–3.0 ppm (esters) or 2.2–2.4 ppm (thioloesters) (compare Tables 2 and 3). The less intense, hydrogen-deficient ester carbonyl carbon (C-1) and the sulphur-linked enethiol carbon (C-3) resonance signals were detectable, and were shielded by 2.8 and 1.2 ppm, respectively, relative to the corresponding signals of the (*Z*)-enethiol form (Table 3). The assignment of signals from the sparsely populated (*E*)-enethiol form **A** in the region of the sp^3 hybridized carbon resonances, however, was abandoned owing to ambiguities.

Only one carbonyl-conjugated enethiol form is feasible for the thioacylmalonates **18–21** (i.e. **A**≡**C**). Since enethiol hydrogen chelation is consistently present, this form is best considered as a (*Z*)-enethiol form (**C**). The ^{13}C NMR spectra of the thioacylmalonates are clearly in accord with the exclusive existence of this tautomer (Table 2), as also deduced from their ^1H NMR spectra (see Experimental). The assignments of the carbonyl and ester alkyl carbon resonances as presented in Table 2 are based on analogy considerations.

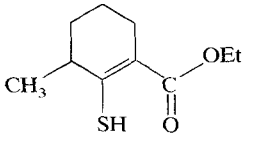
The SH-group promoted substituent effects found for **18** are $\Delta(C\text{-}3)_{SH} = +7.8$ ppm and $\Delta(C\text{-}2)_{SH} = -7.6$ ppm as derived from standard parameters for the acid.[14]

In accord with the previous ^1H NMR spectroscopic findings,[3] the ^{13}C NMR spectra of the 5–9-membered 2-ethoxycarbonylcycloalkanethiones **22–26** clearly demonstrate the existence of only the (*Z*)-enethiol form **C**, no other tautomeric form being traceable. Compared with the corresponding cycloalkenes,[15–18] the substituent effects of the SH, CO pair are found to be close to 20 ppm (+19.6 to +22.7 ppm) for C-3 and close to −7 ppm (−6.4 to −7.1 ppm) for C-2. The slight variation of the former is possibly due to varying abundances of the **C*** form (see below). $\Delta(C\text{-}4)_{SH,CO}$ varies from +9.9 to +12.1 ppm. The substituent effects observed in the cyclic compounds are thus very similar to those of the open-chain compounds.

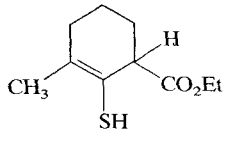
Contrary to the β-thioxo esters discussed above, the open-chain α-substituted β-thioxo esters **27–30** ($R^2 \neq H$, Scheme 1) display ^{13}C NMR spectra which clearly disclose the co-existence of two tautomeric enethiol forms, easily and unambiguously characterizable as the (*Z*)-enethiol form **C** and its geometrical isomer, the (*E*)-enethiol form **A**, respectively (see Tables 2 and 3). Fairly concordant signal area ratios for all pairs of corresponding signals allowed easy determination (within ±5%) of equilibrium percentages of the respective enethiolic forms (see Table 1, footnote f).

In the case of α-substituted compounds, data for the corresponding carboxylic acid are also available.[19] For **27C** $\Delta(C\text{-}3)_{SH} = +7.5$ ppm, $\Delta(C\text{-}2)_{SH} = -10.1$ ppm and $\Delta(C\text{-}4)_{SH} = +13.5$ ppm. For **27A** the substituent effects are $\Delta(C\text{-}3)_{SH} = +7.3$ ppm, $\Delta(C\text{-}2)_{SH} = -6.6$ ppm and $\Delta(C\text{-}4)_{SH} = +11.0$ ppm. The substituent effects are therefore very similar for the **A** and **C** forms. Likewise, the substituent effects in the non-substituted and α-substituted compounds are similar.

The ^{13}C NMR spectrum of 2-ethoxycarbonyl-6-methylcyclohexanethione (**31**) also shows the co-existence of two tautomeric species, the minor constituent (*ca* 25%) being easily identified as the (*Z*)-enethiol form (**31C**) (Tables 1 and 2). Since tautomeric forms possessing a *trans*-cyclohexenic structure are physically impossible, no other structure than that of 6-ethoxycarbonyl-1-mercapto-2-methylcyclohexene (**31D**) is compatible with the ^{13}C NMR spectral pattern (Table 4) of the second, major constituent (*ca* 75%), in full agreement with ^1H NMR spectroscopic findings.[5]



31C



31D

The substituent effects observed for **31C** as measured from standard chemical shift values[14] are similar to those observed for **23**. However, for **31D** the substituent effects are very different, $\Delta(C\text{-}3)_{SH} = -2.4$ ppm and $\Delta(C\text{-}4)_{SH} = +0.5$ ppm. It could be speculated that the difference originates in the different conformations of the ring in **31D** and in the related cycloalkene.

A related tautomeric situation is found for 2-ethoxycarbonylcyclodecanethione (**32**). However, in **32** the carbonyl-conjugated (*Z*)-enethiol form **32C** is the prevailing tautomeric constituent, an 'anomalous' non-conjugated enethiol form (either **32D** or **32F**) constituting only about 20% of the tautomeric equilibrium system (Tables 1, 2 and 4). This unambiguous determination of the tautomeric phenotype of **32** is significant, since no definitive conclusion could be reached on the basis of the ^1H NMR spectrum of **32** alone.[3] The consistent interpretation of the ^1H NMR spectrum of **32** hence implies the assignment of the low-intensity signals at δ5.69 and 2.96 to the vinylic and the non-chelated mercapto group proton resonances, respectively, of **32D**.[3] Characterized by similar inconclusive ^1H NMR spectra, the next higher homologues, 2-ethoxycarbonylcycloundecanethione (**33**) and 2-ethoxycarbonylcyclododecanethione (**34**),[3] display relatively complicated ^{13}C NMR spectra, clearly suggesting the existence of multicomponent tautomeric systems. Unfortunately, the region of the more shielded sp^3 carbon resonances is, in both cases, very complex and practically unapproachable for signal assignment. However, from analogy considerations, from comparison of signal intensities and with the aid of additionally recorded SFORD ^{13}C NMR spectra, it is possible, in both cases, to assign the signals characterizing the tautomeric forms **C** and **D** (Tables 2 and 4). Since the existence of detectable concentrations of the thioketonic tautomers (i.e. **33B** and **34B**) is out of the question owing to the definitive absence of thiocarbonyl and α-carbon ^{13}C resonance signals, interpretation of the remaining signals can be made only in terms of the additional existence of tautomeric forms possessing *trans*-cycloalkene structures, i.e. the carbonyl-conjugated enethiol form **A** and the geometrical isomer **F** of the 'anomalous' non-conjugated enethiol form (see Tables 3 and 4). Thus,

both **33** and **34** are found to be represented in $CDCl_3$ solution by tautomeric equilibrium systems composed of four detectable forms, i.e. **A**, **C**, **D** and **F** (Table 1, Scheme 2). (The ^{13}C NMR spectra of **33** and **34** were recorded on samples purified by PLC and subsequent distillation, and should contain no impurities.)

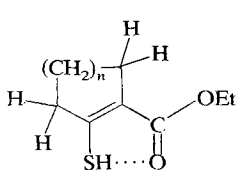
As seen above, distinction has already been made between the (*E*)- and (*Z*)-forms of the 10-, 11- and 12-membered rings. Data from (*E*)- and (*Z*)-cyclooctene[17] and from 10–12-membered 1-trimethylsilyloxycycloalkenes[20] were found to be suitable for this purpose. The most useful shifts are those of C-1 and C-3, since these appear at relatively lower field in rings linked from *trans*-positions than in those linked from the *cis*-positions.

The assignment of **34F** to a (*Z*)-isomer is further confirmed, as the chemical shift of C-3 and C-4 are predicted very accurately using the substituent effects of **31D** and the chemical shifts of (*E*)-cyclododecene.[18]

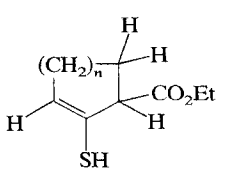
Thiolic deuterium isotope effects

The isotope effect is defined as $^{n}\Delta C = \delta C(H) - \delta C(D)$.[21] Thiolic deuterium isotope effects on pertinent ^{13}C NMR chemical shifts are given in Table 5. $^{2}\Delta$ varies from 0.0 to 0.25 ppm. Further, $^{2}\Delta$ evidently varies with the capability of the species to form intramolecular hydrogen bonds. The magnitude of $^{2}\Delta$ thus indicates that the efficiency of the intramolecular hydrogen bond is similar to that found for methyl salicylate,[21] i.e. the hydrogen bond is of intermediate strength. This finding is in accord with theoretical predictions.[22]

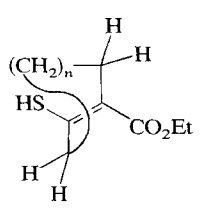
The α-substituted esters **22–34** exist as mixtures of the two rotamers **C** and **C***. Hydrogen bonding is unlikely in **C***, and the isotope effect is hence small



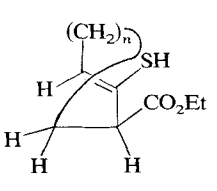
25C: $n = 4$ (100%)
26C: $n = 5$ (100%)
32C: $n = 6$ (80%)
33C: $n = 7$ (21%)
34C: $n = 8$ (44%)



25D: $n = 4$ (not detected)
26D: $n = 5$ (not detected)
32D: $n = 6$ (not detected)
33D: $n = 7$ (9%)
34D: $n = 8$ (15%)



25A: $n = 4$ (not detected)
26A: $n = 5$ (not detected)
32A: $n = 6$ (not detected)
33A: $n = 7$ (9%)
34A: $n = 8$ (12%)



25F: $n = 4$ (not detected)
26F: $n = 5$ (not detected)
32F: $n = 6$ (20%)
33F: $n = 7$ (61%)
34F: $n = 8$ (29%)

Scheme 2

Table 5. Thiolic deuterium isotope effects on ^{13}C NMR chemical shifts (in ppm) of selected enethiolic β-thioxo esters

Compound[a]	$^{4}\Delta$(C-1)	$^{3}\Delta$(C-2)	$^{2}\Delta$(C-3)	Other carbons	% C-form	% C-form[b]
15C	+0.09	0	+0.25	—	100[c]	100
22C	+0.05	0	+0.155	—	62	73
24C	+0.07	+0.03	+0.17	+0.02[d]	68	66
26C	+0.04	0	+0.09	—	36	50
27C	+0.06	0	+0.13	+0.02[d]	52	—
27A	+0.01	+0.07	0	+0.07[d] +0.02[e]	0[c]	—

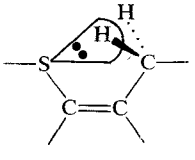
[a] See Scheme 1 and Table 1.
[b] From Ref. 3.
[c] By definition.
[d] C-4.
[e] C-3'.

and judged from **27A** (Table 5) to be of the order of 0 ppm. As the magnitude of $^{2}\Delta$ for the apparently fully hydrogen-bonded species **15C** is 0.25 ppm, intermediates between these two extremes are assumed to reflect reduced percentages of the **C**-rotamer. The isotope effects measured and the C-rotamer percentages calculated are given in Table 5, where the latter are compared with those obtained from ^{1}H NMR and IR measurements.[3]

Configurational implications

The abundance of a given tautomer is governed by its energy content. The hydrogen bond between the thiolic proton and the carbonyl oxygen atom of the ester group stabilizes the enethiol form **C**. Although this interaction as estimated from deuterium isotope effects is of intermediate strength, compounds of the $R^1CSCHR^2CO_2R^3$ type, with $R^2 = H$, are expected to exist mainly in the enethiol form **C**.

An increase of R^2 effects increased steric interaction between R^1 and R^2, and hence destabilization of the enethiol form **C** relative to the enethiol form **A**. The **A** form presumably becomes populated also because of the formation of an attractive no-bond interaction between the α-hydrogen atoms of the α-alkyl group and the lone pair of the sulphur ($CH_2\cdots\cdots S$) as depicted below.



The interaction is likely to involve two C—H bonds to give a 'pseudo-aromatic' system.[23] Such an interaction may occur in the **A** forms of **27–30**, in which the α-substituents are methyl, ethyl and propyl groups, whereas it is less likely in the α-isopropyl compound where only one C—H bond is available. In agreement with this finding, the α-isopropyl compound exists practically exclusively in the thioketone form **B**.[1]

C-2 of the deuterated **27A** is clearly split into a triplet with a coupling constant of 0.83 Hz. The corresponding ^{3}J(C-2, C-3, S, H) is thus 5.4 Hz, which

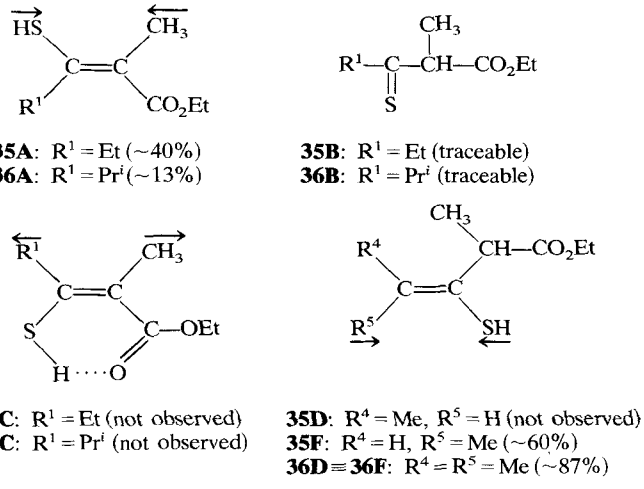
shows that the geometry of the coupling path is transoid.[24,25] No similar splitting was observed for **27C**, in which the coupling path is cisoid. The observation of a large three-bond coupling in **27A** strongly supports the idea of the non-bonding interaction (see above) suggested for this type of compound, where the SH proton for steric reasons is directed away from C-2. In this context it is worth mentioning that **27A–30A**, in their ^{1}H NMR spectra, display a distinct 'through space' coupling between the SH proton and the α-alkyl α-methylene protons (J = 0.6–0.7 Hz), and that a corresponding coupling is absent in **27C–30C**.[1] Further, the observation of a deuterium isotope effect in a mixture of deuterium-labelled and non-deuterium labelled **A**-form indicates that the exchange rate is much slower than normal for a thiolic proton not engaged in intramolecular hydrogen bonding. This decrease in the exchange rate is also in accord with the idea of a no-bond interaction. Both lone pairs of the sulphur atom are partly engaged (by lone-pair 'chelation' and enethiolic conjugation, respectively), and blocking of the lone pairs inevitably effects a reduction in the exchange rate.

Compound **31** cannot exist in the enethiol form **A**. However, the 'anomalous' enethiol form **31D** is abundant, in line with the fact that a no-bond CH_2·····S interaction similar to that observed for the open-chain α-substituted enethiol forms is possible.

Cycloalkenes with up to 10-membered rings are more stable in the *cis*- than in the *trans*-form [i.e. (*Z*)- and (*E*)-forms, respectively]. However, for larger rings the *trans*-form becomes the more stable.[26] In the case of the 10-membered cyclic β-thioxo ester **32** the tautomeric form **32C** (further stabilized by intramolecular mercapto group hydrogen bonding) accordingly predominates (80%), whereas its geometrical isomer **32A** is not observed. On the other hand, of the two possible 'anomalous' enethiol forms, **32F** (the *trans*-cycloalkene derivative) rather than **32D** (the *cis*-cycloalkene derivative) is observed (20%), as a clear corroboration of the idea of the CH_2·····S interaction as a stabilizing factor.

For the 11- and 12-membered cyclic β-thioxo esters, **A**-, **C**-, **D**- and **F**-forms are observed. Although somewhat destabilized by ring strain, the **C** form is fairly abundant (**33C**, 21%; **34C**, 44%; Table 1) owing to stabilization by intramolecular CSH·····OC hydrogen bonding. The **F**-form is also abundant (**33F**, 61%; **34F**, 29%; Table 1) as a favoured geometrical isomer further stabilized by no-bond CH_2·····S interaction. The recognition of the **D**-form is remarkable considering its apparent lack of stabilization possibilities. However, variation in ring conformation governed by ring size and/or substitution (e.g. the CO_2Et group) also probably plays a part as a regulator of the stability in the individual cases.

In general, the CSH·····OC hydrogen bonding provides better stabilization than the no-bond CH_2·····S interaction. However, if even a small steric repulsive interaction is present, other forms than the hydrogen-bonded CO-conjugated enethiol form **C** become abundant. This is particularly well demonstrated in the case of ethyl 2-methyl-3-thioxopentanoate (**35**), a compound recently shown by Paquer and Smadja[5] to exist as a tautomeric mixture of essentially two ^{1}H NMR characterizable enethiol forms (the thioxoketone form **35B** reported to be co-admixtured was not further determined). Distinction between the geometric isomeric forms was not made.[5] However, on the basis of the above considerations and the ^{1}H NMR data available,[5] the two abundant enethiol forms are easily identified as **35A** and **35F** (Scheme 3). The conspicuous feature is that the CO-conjugated (*Z*)-enethiol form **35C** is absent, evidently destabilized by repulsive steric interactions. Both **35A** and **35F** are potentially stabilized by the no-bond CH_2·····S interaction. The second known open-chain α-substituted β-thioxo ester having $R^1 > CH_3$, ethyl 2,4-dimethyl-3-thioxopentanoate (**36**), exists according to the data of Paquer and Smadja[5] preponderantly in the **F** form (≡**D** form), with a subsidiary fraction in the **A** form (Scheme 3).



Scheme 3

To conclude, depending on their individual nature, β-thioxo esters can exist in several (up to four) different enethiolic tautomeric forms. The relative abundances of these are determined by the destabilizing effect of steric interactions, the stabilization obtainable by the formation of intramolecular CSH·····OC hydrogen bonding or no-bond CH_2·····S interaction, and stabilization/destabilization owing to ring strain and conformational preferences.

EXPERIMENTAL

Spectra

^{13}C NMR spectra were recorded on a Bruker Spectrospin WH 90 spectrometer at 22.63 MHz with a digital resolution of 0.04 ppm per point at 303 K, a Jeol FX 90Q spectrometer at 22.5 MHz with a digital resolution of 0.03 ppm per point at 308 K, a Bruker HX 270 spectrometer at 67.889 MHz with a digital resolution of 0.015 ppm per point at 300 K or a Bruker WM 400E spectrometer at 100.61 MHz with a digital resolution of 0.012 ppm per point at 310 K. All spectra were recorded with broad-band ^{1}H decoupling

and, whenever assignment was questionable, also in the single-frequency off-resonance (SFORD) decoupling mode. For the deuterium isotope effect studies, spectra of both deuteriated, non-deuteriated and mixtures of the two species were recorded. In no cases were significant discrepancies observed between the spectra of the pure compounds and those of the mixtures. TMS served as a reference standard. Concentrations were *ca* 20% w/v in $CDCl_3$.

^1H NMR spectra were recorded on *ca* 20% w/v solutions at 60 MHz on a Varian A-60 spectrometer at ambient temperature using TMS as internal reference standard.

Compounds

The β-thioxocarbonyl compounds investigated were synthesized by reaction of the corresponding β-oxocarbonyl compounds with hydrogen sulphide in acidic media as described previously.[1,3,6] The β-thioxo esters **19**, **20** and **21** have not been reported previously.

Diethyl thiopropionylmalonate (19). This was prepared analogously to **18**.[1] Yield: 49%, pale pink oil, b.p. 85 °C (0.16 mmHg). Elemental analysis: found C, 52.00; H, 6.95; S, 13.58%; $C_{10}H_{16}O_4S$ requires C, 51.72; H, 6.94; S, 13.78%. ^1H NMR (CCl_4): δ (ppm) = 6.97 (1H, t, J = 1.2 Hz), 4.23 (4H, q, J = 7 Hz) 2.42 (2H, m), 1.29 (6H, t, J = 7 Hz), 1.22 (3H, t, J = 7 Hz).

Diethyl thiobutyroylmalonate (20). This was prepared analogously to **18**.[1] Yield: 64%, pale pink oil, b.p. 105 °C (0.3 mmHg). Elemental analysis: found C, 53.70; H, 7.22; S, 11.98%; $C_{11}H_{18}O_4S$ requires C, 53.65; H, 7.37; S, 12.99%. ^1H NMR (CCl_4): δ (ppm) = 6.99 (1H, t, J = 1.2 Hz), 4.21 (4H, q, J = 7 Hz), 2.39 (2H, m), 1.65 (2H, m), 1.30 (6H, t, J = 7 Hz), 0.95 (3H, t, J = 7 Hz).

Diethyl thioisobutyroylmalonate (21). This was prepared analogously to **18**,[1] except that the final H_2S supply was prolonged to 72 h at room temperature and purification by the lead salt method[1] was necessary. Yield: 9%, pale pink oil, b.p. 88 °C (0.13 mmHg). Elemental analysis: found C, 53.85; H, 7.45; S, 12.80%; $C_{11}H_{18}O_4S$ requires C, 53.65; H, 7.37; S, 12.99%. ^1H NMR (CCl_4): δ (ppm) = 7.65 (1H, d, J = 0.8 Hz), 4.21 (4H, q, J = 7 Hz), 2.88 (1H, m), 1.29 (6H, t, J = 7 Hz), 1.20 (6H, d, J = 7 Hz).

Preparation of enethiolic deuteriated β-thioxo esters

A 10-ml volume of a 10% solution of the β-thioxo ester in $CDCl_3$ was stirred vigorously with 10 ml of D_2O for 2.5–3 h, then the layers were separated. The $CDCl_3$ layer was dried (Na_2SO_4), filtered and used directly for the NMR measurements.

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