

β -Thioxo-esters. Part III.¹ The Spontaneous Intramolecular Cyclization of Tautomeric Diethyl Thioacetylsuccinate. Preparation and Tautomerism of 4-Ethoxycarbonyl-5-methylthiophen-2(3*H*)-one

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The acid-catalysed reaction of diethyl acetylsuccinate (1) with hydrogen sulphide in ethanolic solution yields a mixture of ethyl (*Z*)-3-ethoxycarbonyl-4-mercaptopent-3-enoate (3), 4-ethoxycarbonyl-5-methylthiophen-2(3*H*)-one (6), and 2-ethoxy-4-ethoxycarbonyl-5-methylthiophen (7), the last two products being formed by a spontaneously occurring intramolecular cyclization condensation of the non-observed ethyl (*E*)-3-ethoxycarbonyl-4-mercaptopent-3-enoate (4). In appropriate acidic media (3) can be completely converted into (6) or (7).

In connection with a general investigation of the tautomerism and other structural properties of open-chain β -thioxo-esters² attempts were made to synthesize diethyl thioacetylsuccinate (2) by acid-catalysed reaction of its oxygen analogue (1) with hydrogen sulphide. The only products that could be isolated were the unsaturated thiolactone (6) and the thiophen (7).² In an earlier paper dealing with the same reaction, Mitra and his co-workers³ reported isolation of only the thiophen (7), suggesting, however, (6) as being the likely precursor of (7). This paper reports the results of a closer study of this reaction, and on some interesting structural features of the compounds involved.

RESULTS AND DISCUSSION

In a series of experiments ethanolic solutions of diethyl acetylsuccinate (1) were treated with hydrogen sulphide and dry hydrogen chloride for periods of 4–7 h at various temperatures. Examination of the crude reaction mixtures by ¹H n.m.r. spectroscopy revealed that the most well-defined product mixture was obtained when the reaction was performed at temperatures between –40 and –30 °C. Under these conditions the product mixture was found to contain mainly the (*Z*)-enethiol (3), but appreciable quantities of the unsaturated thiolactone (6) (apparently accumulating with increasing reaction time) as well as traces of the ethoxythiophen (7) and unchanged (1) were also present. At lower reaction temperatures the reaction was incomplete, and higher reaction temperatures resulted in a more complex reaction mixture (compare with the results from the previous investigations on the synthesis of β -thioxo-esters^{2,4,5}). In no case were the β -thioxo-ester (2) or its (*E*)-enethiol tautomer (4) detected as reaction products.

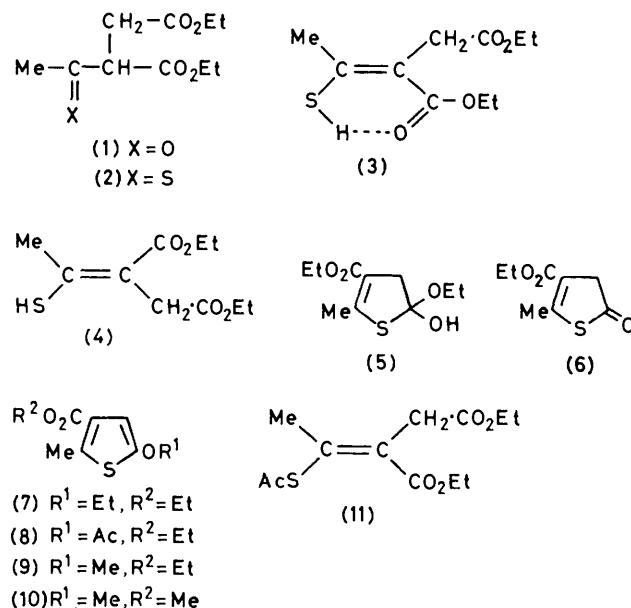
Attempts to separate the crude product mixture into its components by fractional distillation were not successful. Neither was the attempt to isolate (3) from the product mixture *via* its lead complex particularly successful, since only a smaller quantity of (3) with a purity of *ca.* 85% could be obtained by this method (see Experimental section). Nevertheless, in this state of purity (3) could be unambiguously identified and

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¹ Part II, F. Duus, *Tetrahedron*, 1974, **30**, 3753.

² F. Duus, *Tetrahedron*, 1972, **28**, 5923.

characterized by ¹H n.m.r. spectroscopy (Table 1). In order to confirm the structure of (3) as well as further to



SCHEME

TABLE 1

¹H N.m.r. spectra of ethyl (*Z*)-3-ethoxycarbonyl-4-mercaptopent-3-enoate (3) and its *S*-acetyl derivative (11)^a

	(3)	(11)
$\delta(\text{Me})^{\text{ester}}$	1.19 (t, 7)	1.24 (t, 7)
	1.21 (t, 7)	1.27 (t, 7)
$\delta(\text{Me})$	2.12 (m ^b)	2.20 (t, 0.6)
$\delta(\text{SAc})$		2.29 (s)
$\delta(\text{CH}_2)$	3.29 (m ^b)	3.39 (q, 0.6)
$\delta(\text{CH}_2)^{\text{ester}}$	4.02 (q, 7)	4.08 (q, 7)
	4.07 (q, 7)	4.14 (q, 7)
$\delta(\text{SH})^c$	6.35 ^d (q, 0.8)	

^a In CCl₄. Signal multiplicities and coupling constants are given in parentheses. ^b Narrow multiplets. ^c Concentration dependent. The signal moves towards lower field upon dilution. ^d Shift value at infinite dilution.²

verify its presence in the product mixture, a portion of this mixture, containing (3), (6), and (7) according to its ¹H n.m.r. spectrum, was treated with acetic anhydride. The resulting product mixture was separated into its

³ S. Mitra, N. K. Chakrabarty, and S. K. Mitra, *J. Chem. Soc.*, 1939, 1116.

⁴ S. Bleisch and R. Mayer, *Chem. Ber.*, 1967, **100**, 93.

⁵ F. Duus and S.-O. Lawesson, *Arkiv Kemi*, 1968, **29**, 127.

components by preparative layer chromatography (p.l.c.). In this way the *S*-acetyl derivative (11) was isolated and characterized, together with recovered (7) and another new product (8), the *O*-acetyl derivative of the enol tautomer of (6).

The application of p.l.c. directly to the non-distilled product mixture [from the reaction of (1) with hydrogen sulphide and hydrogen chloride] gave only two products, the thiolactone (6) and the thiophen (7), in 45 and 7% yields, respectively. The absence of the (*Z*)-enethiol (3) among the products suggested the possibility that (3) had been converted into (6) [or (7)] during the chromatographic process, presumably due to a catalytic effect of the silica gel. This was confirmed by experiments in which the ¹H n.m.r. spectra of ethereal solutions of crude product mixtures stirred with silica gel were monitored. However, silica gel treatment appeared to be unsatisfactory as a procedure for the synthesis of (6) in reasonable quantities. The complete conversion of (3) into mainly (6) was found to be achieved most efficiently by heating a solution of the crude product mixture in acidic acetonitrile under reflux.

It is well-known that the acid-catalysed reaction of α -substituted β -oxo-esters with hydrogen sulphide in general leads to formation of an equilibrium mixture of the (*Z*)- and (*E*)-enethiol tautomers of the derived β -thio-ester.² As noted above, the (*E*)-enethiol (4) was in no case detected as a product. Presumably, both (3) and (4) are, in fact, formed initially in the reaction of (1) with hydrogen sulphide, but the latter enethiol evidently undergoes immediate spontaneous intramolecular ring-closure condensation to yield (6) or (7), probably *via* (5). The further conversion of (3) into (6) or (7) must then depend on the spontaneity of the isomerization process (3)→(4). Under neutral conditions such a process is relatively slow.² The high proportions of (3) in the product mixtures indicate that the process is also slow in this case. Thus the ¹H n.m.r. spectrum of a tetrachloromethane solution of a mixture containing initially *ca.* 68% of (3), 26% of (6), and 6% of (7) revealed a content of *ca.* 50% of (3), 45% of (6), and 5% of (7) after 8 days at room temperature.

According to Mitra³ the thiophen (7) should be formed by reaction of (6) with the solvent (ethanol). Indeed, treatment of pure (6) with acidic ethanol at 0–20 °C was found to give a high yield of (7). The reaction of (6) with methanol under similar conditions gave a mixture of 65% of (9) and 35% of (10), the latter product being the result of a concomitant ester-interchange reaction. However, it should be noted that the thiophen (7) still appeared as a product when the lead complex of (3) was decomposed with dilute sulphuric acid, *i.e.* in the absence of ethanol. Furthermore, the reaction of (1) with hydrogen sulphide and hydrogen chloride in acetonitrile solution also afforded a low yield (*ca.* 6%) of (7). It is, therefore, reasonable to postulate that (7) is a primary product, formed directly from the intermediate (5) by elimination of water. In this connection it should be pointed out that the formation of

(7) by the ethanolsis of (6) most probably also requires the intermediacy of (5), and hence also the loss of water from (5).

All isolated products were characterized by ¹H n.m.r. and i.r. spectroscopy as well as by elemental analysis. ¹H N.m.r. data for (11) are given in Table 1. The ¹H n.m.r. data for the thiophenoid products are given in Table 2. All i.r. data are reported in the Experimental section.

TABLE 2

¹ H N.m.r. spectra of the thiophens (7)–(10) ^a				
	$\delta(\text{OR}^1)$	$\delta(\text{H}^3)$	$\delta(\text{CO}_2\text{R}^2)$	$\delta(\text{Me})$
(7)	3.99 (2 H, q, 7) 1.35 (3 H, t, 7)	6.32 (1 H, s)	4.20 (2 H, q, 7) 1.31 (3 H, t, 7)	2.56 (3 H, s)
(8)	2.22 (3 H, s)	6.80 (1 H, s)	4.21 (2 H, q, 7) 1.32 (3 H, t, 7)	2.62 (3 H, s)
(9)	3.79 (3 H, s)	6.28 (1 H, s)	4.19 (2 H, q, 7) 1.32 (3 H, t, 7)	2.55 (3 H, s)
(10)	3.79 (3 H, s)	6.28 (1 H, s)	3.74 (3 H, s)	2.55 (3 H, s)

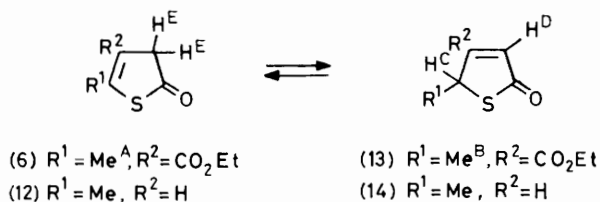
^a In CCl₄. Signal multiplicities and coupling constants are given in parentheses.

The ¹H n.m.r. spectrum of (6) in carbon disulphide shows intense signals at δ 4.13 (2 H, q, $J = 7.1$), δ 3.64 (2 H, q, $J = 2.45$), δ 2.50 (3 H, t, $J = 2.45$), and δ 1.28 (3 H, t, $J = 7.1$), consistent with the structure (6). The homoallylic coupling between the methyl protons (Me^A) and the ring protons in the 3-position (H^E) ($J = 2.45$ Hz) is similar in magnitude to that between the corresponding protons in 5-methylthiophen-2(3*H*)-one (12) ($J = 2.5$ Hz).⁶ In addition to the more intense signals already mentioned some signals of lower intensity are also present. Taken together, these signals indicate the presence of a small equilibrium percentage (8.4%) of the tautomeric 4-ethoxycarbonyl-5-methylthiophen-2(5*H*)-one (13). Whereas the methylene proton signal for the ester group of (13) apparently is coalescing with that for the ester group methylene protons of (6), the ester group methyl signal for (13) is found at δ 1.36 (3 H, t, $J = 7$). The methyl group signal (Me^B) of (13) is found at δ 1.65 (3 H, d, $J = 7.0$), and the signals from H^C and H^D at δ 4.49 (1 H, dq, $J = 1.75$ and $J = 7.0$) and δ 6.73 (1 H, d, $J = 1.75$), respectively. The couplings associated with the ring protons H^C and H^D ($J_{\text{BC}} = 7.0$ Hz, $J_{\text{CD}} = 1.75$ Hz) are of the same magnitudes as those found for 5-methylthiophen-2(5*H*)-one (14) ($J_{\text{BC}} = 7.4$ Hz, $J_{\text{CD}} = 1.9$ Hz).⁶ This type of tautomerism is not unique, although it is remarkable that (6) predominates over (13). For 5-alkylthiophen-2(3*H*)-ones the thiophen-2(5*H*)-one form is predominant (75–82%), and the unsubstituted compound exists exclusively as thiophen-2(5*H*)-one.^{6,7} However, the increased stability of (6) can easily be rationalized as the effect of an extended conjugation of the C=C–S moiety

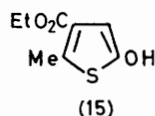
⁶ S. Gronowitz and R. A. Hoffman, *Arhiv Kemi*, 1960, **15**, 499.

⁷ A.-B. Hörnfeldt, *Arhiv Kemi*, 1964, **22**, 211.

involving the ester C=O group. Equilibrium establishment was checked by monitoring the ^1H n.m.r. spectrum of the same solution over a period of 7 days, during which the peak integration ratios did not change. The



equilibrium constant for the process (6) \rightleftharpoons (13) in carbon disulphide was thus determined as $K_{\text{eq}} = 0.09$. The interconversion between the thiophen-2(3H)-one and thiophen-2(5H)-one tautomers has been found^{6,7} to be subject to general base and acid catalysis. However, the addition of a small quantity (25 μl) of $[\text{D}_5]$ -pyridine to the n.m.r. sample had negligible effect on the tautomeric equilibrium, the proportion of (13) in this solution remaining constant at 7% during 7 days. The enol tautomer (15) was in no case detected, although its participation in the equilibrium in trace amounts seems probable due to the formation of (8) upon acetylation. In this respect (6) thus exhibits the behaviour of thiophen-2-ones having no ester group in the 4-position.⁸



EXPERIMENTAL

^1H N.m.r. spectra were recorded on Varian A-60, JEOL C-60 HL, or Varian T-60 A instruments. The chemical shifts are expressed as δ -values downfield from SiMe_4 . Coupling constants were measured on scale-expanded signals, and are quoted in Hz with an accuracy of ± 0.1 Hz. I.r. spectra were recorded for 5–20% tetrachloromethane solutions on a Perkin-Elmer 457 grating spectrophotometer. P.l.c. was carried out on silica gel PF₂₅₄₊₃₆₆ (Merck) support (450 \times 250 \times 3 mm or 1 000 \times 20 \times 1.5 mm). B.p.s and m.p.s are uncorrected. Microanalyses were carried out by the microanalytical laboratory of the department.

Acid-catalysed Reaction of Ethyl 3-Ethoxycarbonyl-4-oxopentanoate (1) with Hydrogen Sulphide.—A solution of ethyl 3-ethoxycarbonyl-4-oxopentanoate (1) (16.2 g, 75 mmol) in 99% ethanol (200 ml) was cooled to -40°C , and hydrogen sulphide and dry hydrogen chloride were passed successively through the solution, each for 1 h. Hydrogen sulphide was then again supplied for a further 2–5 h at $-35 \pm 5^\circ\text{C}$. The reaction mixture was poured cautiously into a mixture of light petroleum (200 ml) and ice-water (300 ml) with manual stirring. The layers were separated, the aqueous layer was extracted with a further portion of light petroleum (200 ml), and the combined organic layers were washed with water until neutral and then dried. The solvent was evaporated at reduced pressure leaving the crude product mixture as a reddish oil (12–15 g). ^1H N.m.r. spectro-

scopic analyses of the product mixtures from four such experiments in which the second passage of hydrogen sulphide was carried out for 2, 3, 4, and 5 h, respectively, showed the contents of (1) (0–5%), (3) (50–85%), (6) (10–40%), and (7) (0–10%), there being a clear correspondence between the prolongation of the reaction time and the increase in the content of (6) and (7). Attempted fractional distillation at reduced pressure did not lead to isolation of any of the components in acceptable purity.

Attempted Isolation of Ethyl (Z)-3-Ethoxycarbonyl-4-mercaptopent-3-enoate (3).—A distilled portion (b.p. range $81\text{--}93^\circ\text{C}$ at 0.1 mmHg) of the crude product mixture (10.0 g) was dissolved in ethanol (100 ml), and an excess of a saturated solution of lead acetate in 50% aqueous ethanol was added with manual stirring. The yellow-ochre precipitate was allowed to settle for 1 h before removal of the bulk of the liquid layer by suction. The remaining heterogeneous mixture was washed with light petroleum (3 \times 100 ml). Light petroleum (200 ml) was again added, and an excess of dilute sulphuric acid was then added in small portions with stirring. The layers were separated and the reddish organic layer was washed with water and dried. The ether was evaporated to leave a red oil [6.6 g; found by ^1H n.m.r. analysis to contain ca. 60% of (3), ca. 35% of (6), and ca. 5% of (7)]. On fractional distillation this oil distilled almost continuously within the boiling range $68\text{--}86^\circ\text{C}$ at 0.12 mmHg. The highest boiling fraction [ca. 0.9 g, b.p. $82\text{--}86^\circ\text{C}$ at 0.12 mmHg, containing ca. 85% of (3), ca. 10% of (6), and ca. 5% of (7) according to ^1H n.m.r. spectroscopy] was used for ^1H n.m.r. spectroscopic characterization of (3) (Table 1).

Preparative Layer Chromatography of the crude Product Mixture.—A portion (17.0 g) of crude product mixture, obtained as described above from (1) (24.8 g, 115 mmol), was subjected to p.l.c. (10 plates, one elution with a 1 : 4 mixture of ether and light petroleum) to give three bands. The combined material absorbed in and extracted from the 10 upper bands ($R_F = 0.5\text{--}0.6$) was isolated and distilled to give pure 5-ethoxy-3-ethoxycarbonyl-2-methylthiophen (7) [1.66 g, 7% (overall)] as a colourless liquid, b.p. $88\text{--}90^\circ\text{C}$ at 0.2 mmHg, $n_D^{25} 1.5127$ (Found: C, 56.05; H, 6.65; S, 14.95. $\text{C}_{10}\text{H}_{14}\text{O}_3\text{S}$ requires C, 56.07; H, 6.59; S, 14.94%), ν_{max} 1 712s cm^{-1} (CO).

The material extracted from the 10 middle bands ($R_F = 0.3\text{--}0.45$) was also isolated and distilled to give pure 4-ethoxycarbonyl-5-methylthiophen-2(3H)-one (6) [9.70 g, 45% (overall)] as a colourless liquid, b.p. 82°C at 0.2 mmHg, $n_D^{25} 1.5245$ (Found: C, 51.4; H, 5.5; S, 16.95. $\text{C}_8\text{H}_{10}\text{O}_3\text{S}$ requires C, 51.61; H, 5.41; S, 17.19%), ν_{max} 1 735s (CO), 1 715s (CO), and 1 615m cm^{-1} (C=C).

The isolation of the material absorbed in the more diffuse lower bands ($R_F = 0.05\text{--}0.3$) gave a liquid (3.32 g), found by ^1H n.m.r. analysis to contain ca. 70% of (6) and ca. 30% of (1).

Acetylation of the crude Product Mixture. Preparation of Ethyl 3-Ethoxycarbonyl-4-acetylthiopent-3-enoate (11) and 5-Acetoxy-3-ethoxycarbonyl-2-methylthiophen (8).—A portion of crude product mixture [12.0 g, containing ca. 40% of (3), ca. 50% of (6), and ca. 10% of (7) according to ^1H n.m.r. integrals] was dissolved in acetic anhydride (40 ml), and the solution was set aside at room temperature for 7 days. Ether (150 ml) and water (200 ml) were then added successively with stirring. The layers were separated and the organic layer was washed with aqueous sodium carbonate, then with water, and finally dried. The ether

⁸ A.-B. Hörnfeldt and S. Gronowitz, *Arkiv Kemi*, 1963, **21**, 239.

was removed by evaporation to leave a dark oil (9.3 g) which was subjected to p.l.c. (8 plates, two elutions with a 1 : 4 mixture of ether and light petroleum). Three principal bands were obtained. From the upper bands (7) (0.91 g) was isolated. The material absorbed in the 8 middle bands was extracted (ether) and recrystallized to give pure *5-acetoxy-3-ethoxycarbonyl-2-methylthiophen* (8) (2.73 g) as small white crystals, m.p. 62 °C (Found: C, 52.8; H, 5.3; S, 13.9. $C_{10}H_{12}O_4S$ requires C, 52.63; H, 5.30; S, 14.03%), ν_{\max} 1770s (CO) and 1715s cm^{-1} (CO). The material extracted from the 8 lower bands was distilled to give pure *ethyl 3-ethoxycarbonyl-4-acetylthiopent-3-enoate* (11) (1.52 g) as a colourless liquid, b.p. 132—135 °C at 0.15 mmHg (Found: C, 52.7; H, 6.6; S, 12.0. $C_{12}H_{18}O_5S$ requires C, 52.55; H, 6.62; S, 11.67), ν_{\max} 1740s (CO), 1705s (CO), and 1600w,br cm^{-1} (C=C).

Ethanolysis of 4-Ethoxycarbonyl-5-methylthiophen-2(3H)-one (6).—A solution of 4-ethoxycarbonyl-5-methylthiophen-2(3H)-one (6) (4.50 g, 24 mmol) in 99% ethanol (100 ml) was saturated with dry hydrogen chloride gas at 0 °C and then set aside at room temperature for 16 h. Ethanol was evaporated off, the residue was dissolved in ether (50 ml), and this solution was then washed with water and dried. The ether was removed by evaporation to leave pure *5-ethoxy-3-ethoxycarbonyl-2-methylthiophen* (7) (4.76 g, 92%). Physical and spectral characteristics were identical with those of the authentic compound (see above).

Methanolysis of 4-Ethoxycarbonyl-5-methylthiophen-2(3H)-one (6).—A solution of 4-ethoxycarbonyl-5-methylthiophen-2(3H)-one (6) (4.50 g, 24 mmol) in methanol (100 ml) was treated with dry hydrogen chloride and otherwise worked-up as described above to give a mixture (4.18 g) of *5-methoxy-3-ethoxycarbonyl-2-methylthiophen* (9) (65%) and *5-methoxy-3-methoxycarbonyl-2-methylthiophen* (10) (35%).

The products were not separated, since they were easily identified and characterized by the 1H n.m.r. spectrum of the mixture (Table 2).

Convenient Procedure for the Preparation of 4-Ethoxycarbonyl-5-methylthiophen-2(3H)-one (6).—Ethyl 3-ethoxycarbonyl-4-oxopentanoate (1) (16.2 g, 75 mmol) was dissolved in ethanol (200 ml) and treated with hydrogen sulphide and dry hydrogen chloride as described above. The crude product mixture (14.1 g) was dissolved in acetonitrile (150 ml) and dry hydrogen chloride gas was passed (20 min) through the solution, which was then refluxed for 24 h. Water (300 ml) and light petroleum (200 ml) were added with stirring, the layers were separated, and the aqueous layer was extracted with a further portion of light petroleum (200 ml). The combined organic extracts were washed twice with water and dried. The solvent was evaporated to leave an oil (10.8 g) which was subjected to p.l.c. (5 plates, one elution with a 1 : 4 mixture of ether and light petroleum). The material absorbed in the R_F -region 0.44—0.53 was extracted, isolated, and distilled to give analytically pure (7) (1.32 g, 8%). The material absorbed in the R_F -region 0.26—0.41 was also extracted, isolated, and distilled to give analytically pure (6) (7.57 g, 54%).

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