Novel photochemical rearrangements of dihydro-1,3-thiazines

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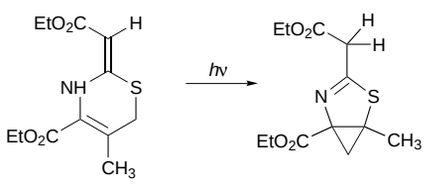
A series of 4-alkyl or 4-phenyl substituted 2,3-dihydro-6*H*-1,3-thiazine-5-carboxylates are synthesised and photolysed in toluene. The 4-methyl compound rearranges to a thiazolidine, which co-exists as an imino-tautomer in solution. The 4-ethyl derivative gives essentially a single isomer of an acyclic thioamido-diene, whilst the 4-benzyl derivative gives a mixture of all four possible thioamido-dienes. The 4-phenyl derivative gave a skeletally rearranged 2,5-dihydro-6*H*-1,3-thiazine which slowly rearranged to the corresponding 2,3-dihydro-6*H*-1,3-thiazine.

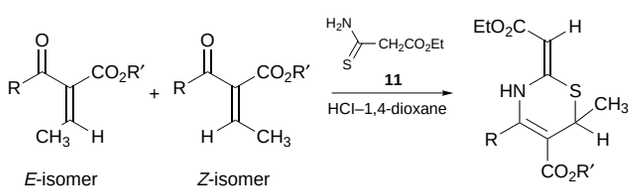
The secondary ring of cephalosporin antibiotics consists of a 2,3-dihydro-6*H*-1,3-thiazine ring. During previous studies on the effect of UV light on such systems, photolysis of the dihydrothiazine **1** in toluene using a Hanovia 125 W medium pressure mercury arc lamp and Pyrex filters was shown to give the novel bicyclic cyclopropathiazolidine system **2**.[1,2]



1 **2**

This interesting result prompted us to investigate the effects on the photolysis of varying the position and type of substituents on the dihydrothiazine. The dihydrothiazines **3**–**6** were synthesised in which the positions of the ester and the 5-alkyl substituents were interchanged relative to the original dihydrothiazine **1** and, for convenience of synthesis, one of the CH_2S protons was replaced by a methyl group. Similar dihydrothiazine structures had been reported in the literature,[3] but we felt that the synthetic route was a little cumbersome. Thus, we adapted the original method of Eggers *et al.*[4] to give the desired products **3**–**6**.

Synthesis of the dihydrothiazines **3**–**6** originally began with preparation of the corresponding α,β-unsaturated keto esters **7**–**10** by the procedure of Lenhert.[5] However, a modification of a procedure by Knoevenagel[6] was later shown to be less time consuming. Condensation of ethoxycarbonylthioacetamide **11** with the α,β-unsaturated keto esters **7**–**10** using anhydrous



E-isomer *Z*-isomer

7 R = Me, R′ = Me
8 R = Et, R′ = Me
9 R = Bz, R′ = Me
10 R = Bz, R′ = Et

3 R = Me, R′ = Me
4 R = Et, R′ = Me
5 R = Bz, R′ = Me
6 R = Ph, R′ = Et

hydrogen chloride in 1,4-dioxane,[4] gave the expected dihydrothiazines **3**–**6** in yields of 71–77%. All microanalytical and spectroscopic data were consistent with structures **3**–**6**.

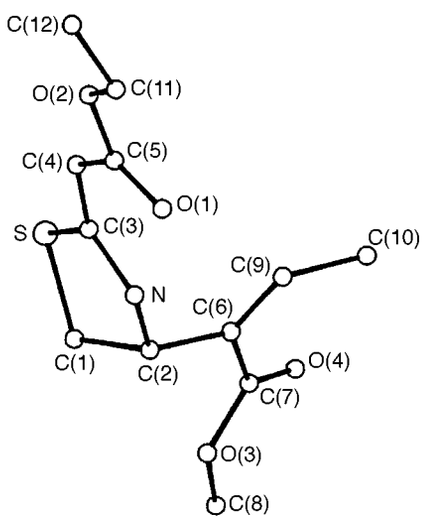


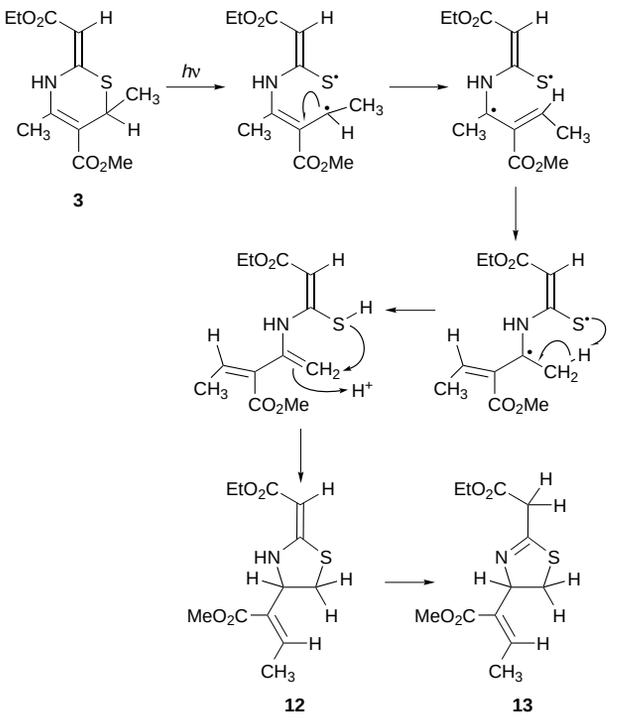
Fig. 1 X-Ray structure of photoproduct **12**. The ethyl group is disordered with two sites of occupancy 0.65 and 0.35 for C(12). Only the major site is shown.

Photolysis of the dihydrothiazine **3** under the conditions used for **1**, and also using acetone as a triplet sensitizer, gave only starting material, even after several days of photolysis. When quartz filters were used, intractable materials were obtained with a variety of solvents. However, irradiation for *ca.* 3 h, using a 400 W Photophysics medium pressure mercury arc lamp and Pyrex filters, showed loss of the chromophore at λ_{max} 338 nm and gave a white crystalline product, $C_{12}H_{17}NO_4S$, in 63% yield after evaporation of the solvent and recrystallisation of the oil.

The ^{1}H NMR spectroscopy of both the crude oil and the crystals showed two isomers in a ratio of *ca.* 2:1. X-Ray crystallography (Fig. 1) fully confirmed our NMR assignment of structure **12** for the major isomer. The second component present in solution, which did not show a NH resonance, was thus shown to be the imino-tautomer **13**. Observation of **13** is interesting, as such tautomers have not been observed in similar systems, although they have been implicated in various reaction mechanisms.[1,2] Furthermore, only *E*-isomers at the but-2-enoyl group were observed. This can be rationalized on the basis of steric hindrance between the methyl group and the thiazolidine ring during the formation of the *Z*-isomer. An interesting aspect of the ^{1}H NMR spectra of the isomers **12** and **13** is the appearance of unexpectedly strong homoallylic couplings

between the ring methine groups and the methyls of the but-2-enoyl groups (J 1.84 and 1.53 Hz respectively, confirmed by decoupling experiments). These couplings may be so pronounced due to the rigidity of the ring systems, which is further aided in the case of **12** by hydrogen bonding of the N–H to both ester carbonyls.

A reasonable mechanism for the formation of the photoproduct is illustrated in Scheme 1. Initial cleavage of the S–CH

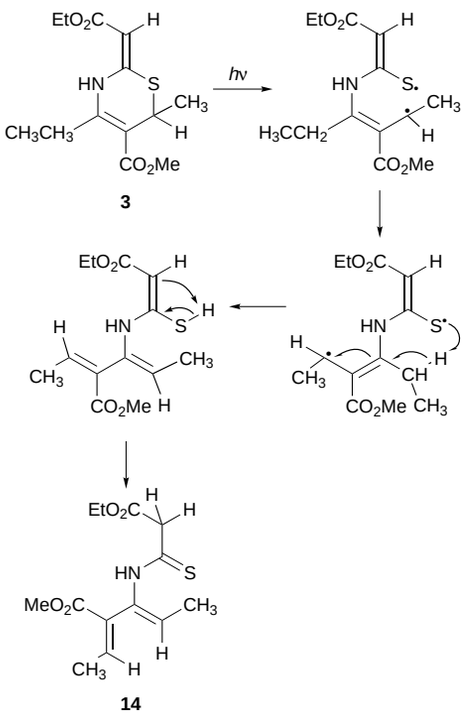


Scheme 1

bond could be followed by rotation around the N–C bond and lead to a capture of the methyl hydrogen atom by sulfur. The proposed 5-*endo-trig* ring closure to the CH_2= would not be disallowed under Baldwin's rules as the second row element, sulfur, is involved.[7] The ring closure would give a thiazolidine **12** that can undergo proton transfer to the imine tautomer **13**.

Having obtained a novel rearrangement to a thiazolidine ring system by photolysis of the methyl dihydrothiazine **3**, we now proceeded with the photolysis of the ethyl analogue **4**, using the same solvent and conditions. Initially the reaction was monitored by following the loss of the chromophore at λ_{max} 338 nm, but after 3 h TLC showed complete consumption of starting material, even though loss of the absorbance at 338 nm was not complete. The ^{1}H NMR spectrum of the liquid photoproduct (56% yield after chromatography) was much simpler than that of the photoproduct from **3**. Besides the resonances for the ester groups, the spectrum showed two one proton olefinic quartets at δ 5.70 and 6.26 (both J 7.25 Hz) coupling to a pair of three proton doublets at δ 1.67 and 1.96 (both J 7.25 Hz), a two proton singlet at δ 3.90 and a broad one proton singlet at δ 9.90, which suggested a NH group. The mass spectrum showed a molecular ion m/z 285, confirming that the product was isomeric with the starting compound. The IR spectrum showed a strong absorbance at ν_{max} 1203 cm^{-1} which strongly suggested a C=S function.[8] This suggestion was supported by the ^{13}C NMR spectrum which showed a resonance at δ 193.0 which is comparable to the C=S resonance of the thioamide **11** (δ 199.0). NOE experiments showed that irradiation of the one proton olefinic quartets, $H_3C–O_2C–C=CH–CH_3$ at δ 6.26, gave an enhancement of 2.4% to the adjacent vinylic methyl doublet at δ 1.96 as well as an enhancement of 3.1% to the other one proton olefinic quartet, HN–C=CH–CH_3 at δ 5.70. Irradiation of the methyl doublet at δ 1.67 gave an expected enhancement of 7.5% to the olefinic one proton quartet at δ 5.7 as well as an enhancement of 1.1% to the NH proton. Irradiation of the other methyl doublet at δ 1.96 gave an expected enhancement of 6.6% to the corresponding olefinic one proton quartet at δ 6.26. This evidence suggests that the diene **14** is formed and it is interesting that only the one isomer is isolated.

As with dihydrothiazine **3**, photolysis of the dihydrothiazine **4** would most probably lead to initial sulfur–carbon homolysis followed by rotation and a 1,5-hydrogen abstraction by sulfur, see Scheme 2. However, both possible alkene centres for attack



Scheme 2

are hindered by methyl substituents and so the ring closure is more restricted and the enethiol intermediate would tautomerise to give the thioamide **14**.

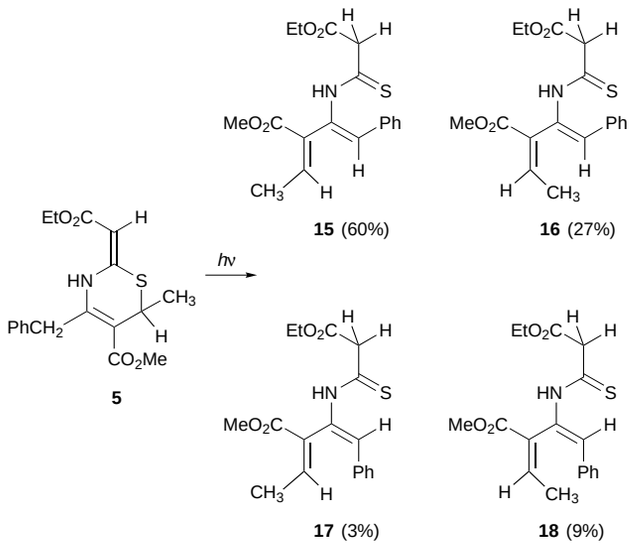
Having obtained two classes of photoproducts, we proceeded with photolysis of the benzyl dihydrothiazine **5** under the now usual conditions. As with **4**, the UV chromophore at λ_{max} 338 nm had not completely disappeared after 3 h, but TLC showed the absence of starting material and the presence of two components (isomers **18** and **15**–**17**) which could only be partially separated by chromatographic means. The ^{1}H and ^{13}C NMR spectra of both components were broadly similar to those of the photoproduct **14**, but in this case, all four possible isomers **15**–**18** had been formed.

One isomer (9%) had been almost completely separated from the others by chromatography and from the relatively high shielding (by the π-cloud of the phenyl group) of the olefinic methyl group (δ 1.69 compared to between δ 2.05 and 2.15), we assigned to this isomer structure **18**.

A similar shielding arrangement also holds true for the olefinic proton in isomer **17** (3%), which also lies above the π-cloud of a phenyl ring. Thus an olefinic quartet occurs at δ 6.4 for isomer **17**, whilst the corresponding quartets of isomers **15** (60%) and **16** (27%) were situated at *ca*. δ 7.20.

Isomer **18** also showed a large deshielding of the Ph–C*H*= proton (δ 7.45) when compared to the other isomers (δ 6.33, 6.50 and 6.52). This can be explained by the reduced conjugation arising from the interaction of the phenyl and methyl groups 'twisting' the molecule out of the plane.

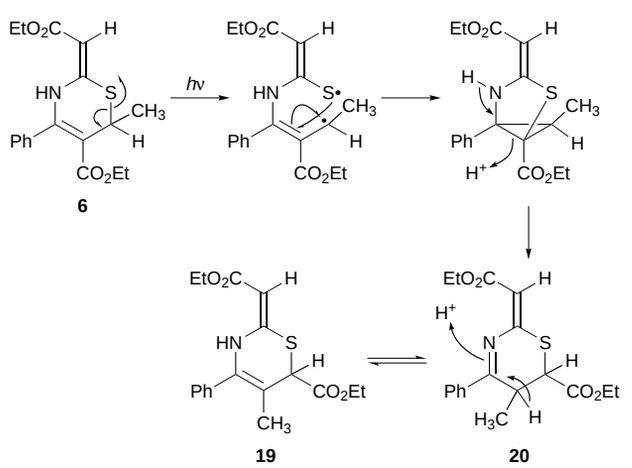
Finally, photolysis of the phenyl dihydrothiazine **6** under the usual conditions, showed loss of the chromophore at λ_{max} 344 nm within 3 h and the appearance of a new compound in a yield of 52%.



The ^{1}H NMR spectrum of the oil was unlike that of any of the previous photoproducts. The C*H*CH_3 proton, which had appeared at δ 4.20 in **6**, now appeared at δ 3.81 and showed not only a coupling of 7.09 Hz to the methyl group, but also a much smaller coupling of 2.25 Hz to a new one proton doublet at δ 3.74. The olefinic proton which appeared at δ 5.13 in **6** had now shifted downfield to δ 6.21 and the NH proton had disappeared, an observation which was confirmed by IR spectroscopy.

On storing the crude photoproduct at −20 °C for several weeks, the oil started to solidify. TLC and ^{1}H NMR spectroscopy of the solid showed it to be a further new compound. It was also found that the residual oil had not decomposed. The spectrum of the crystalline material did not show the C*H*CH_3 quartet and the corresponding CH_3 doublet that had been present for the crude oil. A new three-proton singlet appeared at δ 1.88 and the NH absorption had reappeared. The aromatic region also appeared as a single multiplet at δ 7.30. The olefinic singlet that had appeared at δ 6.21 for the oil had shifted upfield to δ 4.95. ^{13}C NMR spectroscopy showed a typical dihydrothiazine N–C–S group at δ 151.26 (*cf.* δ 151.33 for **6**).

NOE experiments conducted on a solution of the solid compound showed that irradiation of the methyl singlet at δ 1.88 gave an enhancement of 3.1% to the aromatic region and also an enhancement of 9.9% to the one proton singlet at δ 3.93. The spectroscopic data suggest the structure **19** for the solid and the structure **20** for the oil.



Scheme 3

A possible mechanism for the photochemical rearrangement of the dihydrothiazine **6** would involve the usual sulfur–carbon homolysis followed by ring-closure to the cyclopropathiazolidine which could ring-open to the photoproduct **20** (see Scheme 3). A subsequent hydrogen shift would give the dihydrothiazine **19**. Further work needs to be done to fully confirm the structures **19** and **20**.

Experimental

General

Unless otherwise stated the reagents were used as purchased. Solvents were dried over an appropriate drying agent and distilled under nitrogen.

The UV–VIS and FTIR spectra were recorded using Pye-Unicam SP8400 and Mattson Polaris Icon spectrophotometers respectively and the NMR spectra were obtained using either a Bruker WM250 or a Bruker AC 500 spectrometer. *J* Values are given in Hz. The GC–Mass spectra were obtained on a Perkin-Elmer 8500 Gas Chromatograph with an ITD Ion Trap Detector and the microanalyses were obtained as a service from the University of Sussex. Melting points were found using a Gallenkamp melting point apparatus and are uncorrected.

Methyl 2-ethylidene-3-oxobutanoate 7

The title compound was prepared by a modification of the procedure of Knoevenagel.[6] Freshly distilled acetaldehyde (4.40 g, 0.1 mol) was added, with stirring, to methyl acetoacetate (11.60 g, 0.1 mol) at −20 °C. Piperidine (0.15 g) was added over a period of 10 min ensuring that the temperature did not rise above −10 °C. After 24 h at −10 °C, the mixture was dissolved in diethyl ether and the organic layer washed with dilute aqueous acetic acid, water and dried. The solvent was removed *in vacuo* to give a clear oil which was distilled to give a clear liquid. The ^{1}H NMR spectrum showed both the *E*- and *Z*-isomers in a ratio of 29 : 71 (9.94 g, 70%); bp 61–65 °C/2 mmHg; $\delta_H(C^2HCl_3$; 250 MHz) *E*-isomer, 1.84 (3H, d, *J* 7.38, =C−C*H*$_3$), 2.29 (3 H, s, C*H*$_3$C=O), 3.70 (3H, s, C*H*$_3$O), 6.94 (1H, q, *J* 7.38, =CH); *Z*-isomer, 1.91 (3H, d, *J* 7.38, =C−C*H*$_3$), 2.24 (3H, s, C*H*$_3$C=O), 3.76 (3H, s, C*H*$_3$O), 6.94 (1H, q, *J* 7.38 =C*H*); $\delta_C(C^2HCl_3$; 62.9 MHz) 15.1 and 15.7 (2 × =C−*C*H$_3$), 26.7 and 30.9 (2 × *C*H$_3$C=O), 51.9 (2 × CH$_3$*C*H$_2$O), 136.2 and 138.0 [2 × C=*C*H(CH$_3$)], 144.1 and 144.2 [2 × *C*=CH(CH$_3$)], 164.8 and 166.6 (2 × O−*C*=O), 194.9 and 200.6 (2 × *C*=O).

Methyl 2-ethoxycarbonylmethylene-2,3-dihydro-4,6-dimethyl-6*H*-1,3-thiazine-5-carboxylate 3

Freshly prepared methyl 2-ethylidene-3-oxobutanoate **7** (1.26 g, 8.87 mmol) and ethoxycarbonylthioacetamide **11** (1.31 g, 8.91 mmol) were dissolved in dry 1,4-dioxane (25 cm^3) and the solution was saturated with dry hydrogen chloride gas at 0 °C. The solution was left at room temperature overnight and the solvent was removed *in vacuo* to give an orange gum. Chromatographic purification (silica gel, dichloromethane) gave the dihydrothiazine **3** as a yellow solid which was recrystallised from ethanol to afford yellow crystals (1.85 g, 77%); mp 77–78 °C (Found: C, 53.40; H, 6.30; N, 4.85. $C_{12}H_{17}NO_4S$ requires C, 53.11; H, 6.33; N, 5.16%); *m*/*z* 271 ($M^{+\bullet}$), 225 [(M − EtOH)$^+$], 165 {[M − (EtO + OMe + 2 × CH$_3$)]$^+$}; λ_{max}(MeOH)/nm 214 (ε/dm^3 mol^{-1} cm^{-1} 6501), 252 (ε 1717), 338 (ε 24 431); ν_{max}(Nujol mull)/cm^{-1} 1714, (O–C=O), 1660 (conjugated C=C); $\delta_H(C^2HCl_3$; 250 MHz), 1.28 (3H, t, *J* 7.25, C*H*$_3$CH$_2$O), 1.36 (3H, d, *J* 7.50, CHC*H*$_3$), 2.41 (3H, s, =C−C*H*$_3$), 3.73 (3H, s, C*H*$_3$O), 4.10 (1H, q, *J* 7.50, C*H*CH$_3$), 4.14 (2H, q, *J* 7.25, C*H*$_2$O), 5.08 (1H, br s, *H*−C=), 10.80 (1H, br s, N*H*).

2-Ethoxycarbonylmethylene-4-[(*Z*)-2-methoxycarbonylprop-1-enyl]-1,3-thiazolidine 12

The dihydrothiazine **3** (0.30 g, 1.12 mmol) was dissolved in dry toluene (*ca.* 250 cm^3) and the solution was degassed for 1 h and photolysed under N_2 using a 400 W Photophysics medium pressure mercury arc lamp, equipped with a water-cooled Pyrex jacket as a filter. The reaction was monitored by following the gradual disappearance of the absorption at λ_{max} 338 nm of the

dihydrothiazine **3** in the UV spectrum. After the reaction was complete (*ca.* 3 h) the solvent was removed *in vacuo* to give a dark oil which after column chromatography (silica gel, 1:1 diethyl ether–light petroleum, bp 60–80 °C) gave a white solid. This was recrystallised from ethanol to afford white crystals (0.19 g, 63%); mp 83–84 °C (Found: C, 53.00; H, 6.20; N, 4.90; S, 11.50. $C_{12}H_{17}NO_4S$ requires C, 53.11; H, 6.33; N, 5.16; S, 11.81%); *m/z* 271 ($M^{+\bullet}$), 225 [(M − EtOH)$^+$], 171 [(M − CH_3-CH=C−CO_2CH_3)$^+$]; λ_{max}(MeOH)/nm 216 (ε/dm^3 mol^{-1} cm^{-1} 27 215), 288 (ε 42 005); ν_{max}(liquid film)/cm^{-1} 3054 (NH), 1720 and 1704 (O−C=O); δ_H(C^3HCl_3; 500 MHz) major tautomer **12**, 1.28 (3H, t, *J* 7.22, CH_3CH$_2$O), 2.07 (3H, dd, *J* 7.24 and 1.84, CHCH_3), 2.99 (1H, dd, $J_{H^{5a},H^{5b}}$ 10.99 and J_{H^{5a},H^4} 4.95, SCH^{5a}), 3.54 (1H, dd, $J_{H^{5b},H^{5a}}$ 10.99 and J_{H^{5b},H^4} 7.24, SCH^{5b}), 3.80 (3H, s, CH_3O), 4.13 (2H, m, CH_2O), 4.78 (1H, s, C=CH), 4.97 (1H, m, H^4), 6.38 (1H, qd, *J* 7.24 and 1.63, CHCH$_3$), 8.30 (1H, s, NH); minor tautomer **13**, 1.30 (3H, t, *J* 7.15, CH_3CH$_2$O), 2.08 (3H, dd, *J* 7.31 and 1.53, CHCH_3), 3.15 (1H, dd, $J_{H^{5a},H^{5b}}$ 11.00 and J_{H^{5a},H^4} 8.24, SCH^{5a}), 3.71 (1H, dd, $J_{H^{5b},H^{5a}}$ 11.00 and J_{H^{5b},H^4} 9.26, SCH^{5b}), 3.59 (2H, m, C−CH_aH_bO), 3.79 (3H, s, CH_3O), 5.39 (1H, br t, H^4), 6.38 (1H, qd, *J* 7.31 and 1.29, CHCH$_3$); δ_C(C^2HCl_3; 125.7 MHz) 14.08 and 14.57 (2 × CH_3CH$_2$O), 15.70 and 15.76 (2 × CH_3CH=C), 35.29 (N=C−CH_2 of minor isomer), 40.27 and 40.59 (2 × CH_2S), 51.42 and 51.58 (2 × CO_2CH_3), 58.88 and 2 × 61.50 (2 × CH_2O and CH^4), 78.51 (C=CH of major isomer), 130.17 and 131.39 (2 × C=CHCH$_3$), 138.91 and 139.37 (2 × C=CHCH$_3$), 164.77 and 165.78 (N−C−S of major isomer and N=C−S of minor isomer), 166.65, 167.06, 167.88 and 169.62 (4 × O−C=O).

Methyl 2-ethylidene-3-oxopentanoate 8[9]

Freshly distilled acetaldehyde (4.40 g, 0.1 mol) was added, with stirring to methyl propionylacetate (13.10 g, 0.1 mol) at −20 °C. Piperidine (0.15 g) was added over a period of 10 min ensuring that the temperature did not rise above −10 °C. After 24 h at −10 °C, the mixture was dissolved in diethyl ether and the organic layer was washed with dilute aqueous acetic acid, water and dried. The solvent was removed *in vacuo* to give a clear oil which was distilled to give a clear liquid. The ^{1}H NMR spectrum showed both the *E*- and *Z*-isomers in a ratio of 1:1 (10.15 g, 65%); bp 60–68 °C/2 mmHg; *m/z* 156 [($M^{+\bullet}$)], 127 [(M − Et)$^+$]; δ_H(C^2HCl_3; 500 MHz) *E*-isomer, 1.09 (3H, t, *J* 7.50, CH$_2$CH_3), 1.87 (3H, d, *J* 7.44, CHCH_3), 2.63 (2H, q, *J* 7.50, CH_2CH$_3$), 3.79 (3H, s, CH_3O), 7.01 (1H, q, *J* 7.44, CHCH$_3$); *Z*-isomer, 1.09 (3H, t, *J* 7.50, CH$_2$CH_3), 1.93 (3H, d, *J* 7.44, CHCH_3), 2.63 (2H, q, *J* 7.50, CH_2CH$_3$), 3.85 (3H, s, CH_3O), 7.01 (1H, q, *J* 7.44, CHCH$_3$).

Methyl 2-ethoxycarbonylmethylene-4-ethyl-2,3-dihydro-6-methyl-6*H*-1,3-thiazine-5-carboxylate 4

Freshly prepared methyl 2-ethylidene-3-oxopentanoate **8** (1.32 g, 8.46 mmol) and ethoxycarbonylthioacetamide **11** (1.25 g, 8.50 mmol) were dissolved in dry 1,4-dioxane (25 cm^3) and the solution was saturated with dry hydrogen chloride gas at 0 °C. The solution was left at room temperature overnight and the solvent was removed *in vacuo* to give an orange gum. Chromatographic purification (silica gel, dichloromethane) gave the dihydrothiazine **4** as a yellow solid, which was recrystallised from ethanol as yellow crystals (1.78 g, 74%); mp 55–56 °C (Found: C, 54.52; H, 6.66; N, 4.56. $C_{13}H_{19}NO_4S$ requires C, 54.71; H, 6.72; N, 4.91%); *m/z* 285 ($M^{+\bullet}$), 252 {[M − (H_2O + CH_3)]$^+$}, 239 {[M − (H_2C=CH_2 + H_2O)]$^{\bullet+}$}; λ_{max}(MeOH)/nm 214 (ε/dm^3 mol^{-1} cm^{-1} 3863), 255 (ε 1741), 338 (ε 20 231); ν_{max}(Nujol mull)/cm^{-1} 1712 and 1694 (O−C=O), 1659 (conjugated C=C), 1578 (NH band); δ_H(C^2HCl_3; 500 MHz) 1.23 (3H, t, *J* 7.35 CH_3CH$_2$O), 1.28 (3H, t, *J* 7.37 CH$_2$CH_3), 1.37 (3H, d, *J* 6.95, CH_3CH), 2.66 (1H, dq, *J* 7.37 and J_{ab} 14.99, CH_aH_bCH$_3$), 2.97 (1H, dq, *J* 7.37 and J_{ab} 14.99, CH$_a$$H_bCH_3$), 3.74 (3H, s, CH$_3$O), 4.05 (1H, q, *J* 6.95 CH$_3$CH), 4.17 (2H, 2 × dq, *J* 7.35 CH_cH_dO, J_{cd} 10.75), 5.06 (1H, s, =CH), 11.01 (1H, br s, hydrogen bonded NH); δ_C(C^2HCl_3; 125.7 MHz) 12.62 (CH_3CH$_2$O), 14.38 (CH$_2$CH_3), 22.69 (CH_2CH$_3$), 27.11 (CHCH_3), 32.78 (CHCH$_3$), 51.40 (CH_2O), 59.58 (CH_3O), 90.12 (=CH), 104.11 (HN−C=C), 150.13 (HN−C=C), 152.23 (N−C−S), 165.95 and 168.99 (O−C=O).

(*Z*,*Z*)-3-(Ethoxycarbonylthioacetamido)-4-methoxycarbonylhexa-2,4-diene 14

The dihydrothiazine **4** (0.29 g, 1.02 mmol) was photolysed in a similar manner to compound **3**. The reaction was followed by the gradual disappearance of the absorption at λ_{max} 338 nm of the dihydrothiazine **4** in the UV spectrum. After the reaction was complete (3.5 h) the solvent was removed *in vacuo* to give a dark oil which after column chromatography (silica gel, diethyl ether–light petroleum 60–80 °C, 1:1) gave a pale oil which failed to crystallise, (0.16 g, 56%); *m/z* 285 ($M^{+\bullet}$), 270 [(M − CH_3)$^+$], 252 {[M − (CH_3 + H_2O)]$^+$}, 226 [(M − CO_2CH_3)$^+$]; λ_{max}(MeOH)/nm 220 (ε/dm^3 mol^{-1} cm^{-1} 9976), 272 (ε 8005) this chromophore also showed a distinct shoulder at *ca.* 325; ν_{max}(CCl_4)/cm^{-1} 3594–3188 (NH), 1728 (O−C=O), 1578 (conjugated double bond), 1203 (C=S); δ_H(C^2HCl_3; 500 MHz) 1.28 (3H, t, *J* 7.50, CH_3CH$_2$O), 1.67 and 1.96 (2 × 3H, 2 × d, *J* 7.25, CH_3CH=), 3.80 (3H, s, CH_3O), 3.88 (2H, s, CH_2C=S), 4.23 (2H, q, *J* 7.50, CH_2O), 5.70 and 6.26 (2 × 1H, 2 × q, *J* 7.25, 2 × CH$_3$CH), 9.90 (1H, br s, hydrogen bonded NH); δ_C(C^2HCl_3; 125.7 MHz) 13.5 (CH_3CH$_2$O), 13.9 and 15.5 (CH_3CH=), 49.4 (CH_2C=S), 51.6 (CH_2O), 61.7 (CH_3O), 125.4 (HN−C=CHCH$_3$), 131.3 (HN−C=CHCH$_3$), 134.8 (CH$_3$CH=C−CO_2CH_3), 136.8 (CH$_3$CH=C−CO_2CH_3), 169.6 and 167.5 (O−C=O), 193.0 (C=S).

Methyl 4-phenyl-3-oxobutyrate[10]

Under nitrogen at 0 °C, pyridine (19.75 g, 0.25 mol) was added to a solution of Meldrum's acid (14.4 g 0.1 mol) in dry dichloromethane (50 cm^3) over a period of 15 min. Phenylacetyl chloride (15.5 g, 0.1 mol) in dry dichloromethane (30 cm^3) was added over 2 h. The resulting opaque orange mixture was stirred for a further 90 min at 0 °C and then for an additional 1 h at room temperature. It was diluted with dichloromethane (20 cm^3) and poured into 2 M hydrochloric acid (70 cm^3). The organic phase was separated and the aqueous extract was washed (3 × 30 cm^3) with dichloromethane. The organic extracts were combined and washed with 2 M hydrochloric acid (2 × 25 cm^3) followed by saturated aqueous sodium chloride (50 cm^3) and the organic phase was dried. The solvent was removed *in vacuo* to give an off-white solid, which was heated under reflux in methanol for 3 h. The solvent was again removed *in vacuo* to give a pale oil which was distilled under reduced pressure to give methyl 4-phenyl-3-oxobutyrate as a clear liquid (14.33 g, 74%); bp 130–136 °C/0.6 mmHg (lit.,[10] 126–128 °C/0.6 mmHg); *m/z* 192 ($M^{+\bullet}$); δ_H(C^2HCl_3; 500 MHz) 3.48 (2H, s, C$H_2CO_2CH_3$), 3.73 (3H, s, CO_2CH_3), 3.64 (2H, s, PhCH_2), 7.20–7.36 (5H, m, aromatic protons).

Methyl 2-ethylidene-3-oxo-4-phenylbutyrate 9

Methyl 4-phenyl-3-oxobutyrate (19.20 g, 0.1 mol) was cooled to −20 °C and freshly distilled acetaldehyde (4.4 g, 0.1 mol) was added with stirring. Piperidine (0.15 g) was added dropwise over a period of 10 min keeping the temperature below −10 °C. The reaction mixture was then left at −10 °C for 24 h. The reaction mixture was dissolved in diethyl ether, washed with dilute aqueous acetic acid followed by water and the organic extracts were dried. The solvent was removed *in vacuo* to give a clear oil which was distilled to give a clear liquid. The ^{1}H NMR spectrum showed both the *Z*- and *E*-isomers in a ratio of 1:1 (15.06 g, 69%); bp 144–146 °C/2 mmHg; *m/z* 219 [($M + 1)^{+\bullet}$], 186 [(M − MeOH)$^+$], 127 [(M − C_7H_7)$^+$]; δ_H(C^2HCl_3; 500 MHz) 1.69 and 1.96 (total 3H, 2 × d, *J* 7.50, CH_3CH=, *Z*- + *E*-isomers), 3.78 (3H, s, CH_3O), 3.95 (2H, s, PhCH_2CO), 7.06 (1H, 2 × q, *J* 7.50, CH$_3$CH=), 7.26 (5H, m, aromatic protons).

Methyl 4-benzyl-2-ethoxycarbonylmethylene-2,3-dihydro-6-methyl-6*H*-1,3-thiazine-5-carboxylate 5

Freshly prepared methyl 2-ethylidene-3-oxo-4-phenylbutyrate **9** (2.07 g, 9.50 mmol) and ethoxycarbonylthioacetamide **11** (1.39 g, 9.50 mmol) were dissolved in dry 1,4-dioxane (25 cm^3) and the solution was saturated with dry hydrogen chloride gas at 0 °C. The solution was left overnight at room temperature and the solvent was removed *in vacuo* to give an orange gum. Chromatographic purification (silica gel, dichloromethane) gave the dihydrothiazine **5** as a yellow solid, which was recrystallised from ethanol to afford yellow crystals (2.35 g, 71%); mp 80–81 °C (Found: C, 62.38; H, 6.38; N, 3.71. $C_{18}H_{21}NO_4S$ requires C, 62.22; H, 6.10; N, 4.03%); *m/z* 345 $[(M - 2)^{+\bullet}]$, 256 $[(M - C_6H_7)^+]$; λ_{max}(MeOH)/nm 194 (ε/dm^3 mol^{-1} cm^{-1} 891), 338 (ε 31 520); ν_{max}(Nujol mull)/cm^{-1} 1709 and 1697 (O–C=O), 1660 (conjugated double bond), 1578 (NH bend); δ_H(C^2HCl_3; 500 MHz) 1.24 (3H, t, *J* 7.16, $CH_3CH_aH_bO$), 1.41 (3H, d, *J* 6.95 CH_3CH), 3.77 (3H, s, CH_3O), 4.11 (2H, dq, *J* 7.16 for CH_aH_bO, 1H, q partially hidden, CH_3CH=), 4.17 and 4.28 (2H, 2 × d, *J* 14.86, CH_2Ph), 5.02 (1H, s, C=CH), 7.29 (5H, m, aromatic protons), 10.97 (1H, br s, NH); δ_C(C^2HCl_3; 125.7 MHz) 14.35 (CH_3CH_2O), 22.59 ($CHCH_3$), 32.91 ($CHCH_3$), 38.51 (CH_2Ph), 51.61 (CO_2CH_3), 59.56 (CH_2O), 90.82 (exocyclic C=C–H), 105.65 (ring HN–C=C), 126.88 (aromatic *meta* and *para* carbons), 128.75 (aromatic *ortho* carbons), 136.85 (aromatic *ipso* carbons), 147.49 (ring BnC=C), 151.41 (N–C–S), 166.08 and 168.59 (2 × O–C=O).

2-(Ethoxycarbonylthioacetamido)-3-methoxycarbonyl-1-phenylpenta-2,4-dienes 15–18

The dihydrothiazine **5** (0.39 g, 1.13 mmol) was photolysed in a similar manner to compound **3**. The reaction was monitored by following reduction of the absorption at λ_{max} 338 nm in the UV spectrum due to the dihydrothiazine **5**. TLC showed the reaction to be complete within 3 h and the solvent was removed *in vacuo* to give a dark oil which, after column chromatography (silica gel, diethyl ether–light petroleum, 60–80 °C, 1:1) gave two different components **18** and **15**–**17** both as pale oils which failed to crystallise.

Isomer **18** (0.035 g, 9%); *m/z* 347 $[(M)^{+\bullet}]$, 315 $[(M - CH_3OH)^+]$, 302 $[(M - OEt)^+]$, 269 $[(M - C_6H_6)^+]$, 242 $\{[M - (Ph + C_2H_5)]^+\}$; λ_{max}(MeOH)/nm 208 (ε/dm^3 mol^{-1} cm^{-1} 9170), 270 (ε 8450) this chromophore also showed a considerable shoulder; ν_{max}(CCl_4 liquid film)/cm^{-1} 3270–2950 (NH), 1722 (O–C=O), 1634 (conjugated double bond), 1575 (aromatic C=C), 1029 (C=S); δ_H(C^2HCl_3; 500 MHz) 1.28 (3H, t, *J* 7.50, CH_3CH_2O), 1.69 (3H, d, *J* 7.50, CH_3CH=), 3.81 (3H, s, CH_3O), 3.92 (2H, s, CH_2C=S), 4.23 (2H, q, *J* 7.50, CH_2O), 7.15 (1H, q, *J* 7.50, CH_3CH), 7.27 (5H, m, *Ph*–CH=), 7.45 (1H, s, Ph–CH=), 10.40 (1H, br s, hydrogen bonded NH); δ_C(C^2HCl_3; 125.7 MHz) 13.9 (CH_3CH_2O), 16.1 (CH_3CH=), 50.2 (CH_2C=S), 52.1 (CH_2O), 61.7 (CH_3O), 127.6 (aromatic *meta* and *para* carbons), 128.3 (aromatic *ortho* carbons), 128.5 (aromatic *ipso* carbon), 129.0 [HN–C=C(H)Ph], 130.4 [HN–C=C(H)Ph], 134.9 (CH_3-CH=C–CO_2CH_3), 145.5 (CH_3CH=C–CO_2CH_3), 166.4 and 169.8 (2 × O–C=O), 191.4 (C=S).

Isomers **15**–**17** (0.13 g, 33% isolated); *m/z* 347 $[(M)^{+\bullet}]$, 315 $[(M - CH_3OH)^+]$, 302 $[(M - OEt)^+]$, 269 $[(M - C_6H_6)^+]$; λ_{max}(MeOH)/nm 212 (ε/dm^3 mol^{-1} cm^{-1} 15 903), 270 (ε 15 758) this chromophore also showed a slight shoulder; ν_{max}(CCl_4 liquid film)/cm^{-1} 3273–2908 (NH), 1725 (O–C=O), 1636 (conjugated double bond), 1048 and 1028 (C=S); δ_H(C^2HCl_3; 500 MHz) 1.29 (2 × 3H, 2 × t, *J* 7.50, 2 × CH_3CH_2O), 2.05, 2.10 and 2.15 [3 × 3H (isomer ratio **15**:**16**:**17**, 20:9:1), 3 × d, *J* 7.50, 3 × CH_3CH=], 3.80 [5H (isomer ratio **15**:**16**:**17**, 20:9:1), 6 × s, 3 × CO_2CH_3 + 3 × 2H, s, CH_2C=S], 4.19 (4H, 2 × q, *J* 7.50, 2 × CH_2O), 6.33, 6.50 and 6.65 (3 × 1H, 3 × s, 3 × PhCH=), 6.43 (1H, q, *J* 7.50, minor isomer **16** CH_3CH), 7.20 (1H, q, *J* 7.50, major isomer **15** CH_3CH), 7.34 (5H, m, *Ph*–CH=), 10.0 and 10.1 (2H, 2 × br s, 2 × hydrogen bonded NH); δ_C(C^2HCl_3; 125.7 MHz) 13.9 (CH_3CH_2O), 15.8 and 16.4 (2 × CH_3CH=), 49.8 and 49.9 (2 × CH_2C=S), 51.8 (CH_2O), 61.6 and 61.7 (2 × CH_3O), 127.7, 128.1, 128.3, 128.5 and 128.6 (aromatic carbons), 130.4 [HN–C=C(H)Ph], 130.6 [HN–C=C(H)Ph], 139.4 (CH_3CH=C–CO_2CH_3), 143.8 (CH_3CH=C–CO_2CH_3) 166.1 and 168.9 (2 × O–C=O), 193.1 (C=S).

Ethyl 2-ethylidene-3-oxo-3-phenylpropanoate 10[11]

Ethyl benzoylacetate (19.20 g, 0.1 mol) was cooled to −20 °C and freshly distilled acetaldehyde (4.40 g, 0.1 mol) was added with stirring. Piperidine (0.15 g) was added dropwise over a period of 10 min keeping the temperature below −10 °C. The reaction mixture was left at −10 °C for 24 h. The reaction mixture was dissolved in diethyl ether washed with dilute aqueous acetic acid followed by water and the organic extract was dried. The solvent was removed *in vacuo* to give a clear oil which was distilled to give a clear liquid. The ^1H NMR spectrum showed both the *Z*- and *E*-isomers in a ratio of 17:83 (14.02 g, 64%); bp 136–138 °C/2 mmHg; *m/z* 219 $[(M + H)^{+\bullet}]$, 145 $[(M - C_2H_5CO_2)^+]$, 172 $[(M - EtOH)^+]$; δ_C(C^2HCl_3; 500 MHz) *Z*-isomer (minor), 1.09 (3H, t, *J* 7.50, CH_3CH_2O), 2.14 (3H, d, *J* 7.50, $CHCH_3$), 4.14 (2H, q, *J* 7.50, CH_2O), 6.75 (1H, q, *J* 7.50, CH_3CH), 7.68 (5H, m, aromatic protons); *E*-isomer (major), 1.21 (3H, t, *J* 7.50, CH_3CH_2O), 1.75 (3H, d, *J* 7.50, $CHCH_3$), 4.14 (2H, q, *J* 7.50, CH_2O), 7.31 (1H, q, *J* 7.50, CH_3CH), 7.68 (5 H, m, aromatic protons). Some starting material was also present.

Ethyl 2-ethoxycarbonylmethylene-2,3-dihydro-6-methyl-4-phenyl-6*H*-1,3-thiazine-5-carboxylate 6

Freshly prepared ethyl 2-ethylidene-3-oxo-3-phenylpropanoate **10** (1.67 g, 7.66 mmol) and ethoxycarbonylthioacetamide **11** (1.13 g, 7.69 mmol) were dissolved in dry 1,4-dioxane (25 cm^3) and the solution was saturated with dry hydrogen chloride gas at 0 °C. The solution was left to stand overnight at room temperature and the solvent was removed *in vacuo* to give an orange gum. Chromatographic purification (silica gel, dichloromethane) gave the dihydrothiazine **6** as a yellow solid, which was recrystallised from ethanol to afford yellow crystals (2.04 g, 77%); mp 86–87 °C (Found: C, 62.23; H, 5.87; N, 3.84. $C_{18}H_{21}NO_4S$ requires C, 62.22; H, 6.10; N, 4.03%); *m/z* 347 $(M^{+\bullet})$, 314 $\{[M - (H_2O + CH_3)]^+\}$, 301 $\{[M - (C_2H_4 + H_2O)]^+\}$, 242$\{[M - (Ph + C_2H_5)]^+\}$; λ_{max}(MeOH)/nm 222 (ε/dm^3 mol^{-1} cm^{-1} 7255), 344 (ε 21 229); ν_{max}(Nujol mull)/cm^{-1} 1690 (O–C=O), 1661 (conjugated double bond), 1573 (NH bend); δ_H(C^2HCl_3; 500 MHz) 0.87 and 1.26 (2 × 3H, 2 × t, *J* 7.15, 2 × $CH_3CH_aH_bO$), 1.55 (3H, d, *J* 6.97, CH_3CH), 3.92 (2H, q, *J* 7.12, exocyclic CH_2O), 4.12 (2H, d × q, *J* 7.15 and 6.97 CH_aH_bO and 1H, q, *J* 6.97 CH_3CH), 5.13 (1H, s, C=CH), 7.35–7.44 (aromatic protons), 10.92 (1H, br s, NH); δ_C(C^2HCl_3; 125.7 MHz) 13.56 and 14.36 (2 × CH_3CH_2O), 22.71 ($CHCH_3$), 33.39 ($CHCH_3$), 59.60 and 60.12 (2 × CH_2O), 90.83 (exocyclic C=C–H), 105.47 (ring HN–C=C), 128.35 (aromatic *meta* and *para* carbons), 129.49 (aromatic *ortho* protons), 137.11 (aromatic *ipso* protons), 146.68 (ring PhC=C), 151.33 (N–C–S), 166.39 and 168.76 (2 × O–C=O).

Ethyl 2-ethoxycarbonylmethylene-5,6-dihydro-5-methyl-4-phenyl-2*H*-1,3-thiazine-6-carboxylate 20

The dihydrothiazine **6** (0.31 g, 0.89 mmol) was photolysed in a similar manner to compound **3**. The reaction was monitored by the gradual disappearance of the absorption at λ_{max} 344 nm in the UV spectrum due to the dihydrothiazine **6**. After the reaction was complete (3 h) the solvent was removed *in vacuo* to give a dark oil which after column chromatography (silica gel, diethyl ether–light petroleum 60–80 °C, 1:1) gave a pale oil which failed to crystallise (0.16 g, 46%); *m/z* 347 $(M^{+\bullet})$, 302 $[(M - OEt)^+]$, 274 $[(M - CO_2Et)^+]$; λ_{max}(MeOH)/nm 208 (ε/dm^3 mol^{-1} cm^{-1} 1332), 230 (ε 1367), 290 (ε 1799), 338 (ε 1490); ν_{max}(CH_3Cl_2 liquid film)/cm^{-1}

1735 and 1692 (O–C=O), 1650 (conjugated double bond); $\delta_H(C^2HCl_3$; 500 MHz) 1.17 and 1.32 (2 × 3H, 2 × t, *J* 7.14 and 7.16, 2 × CH_3CH$_2$O), 1.37 (3H, d, *J* 7.09, CH_3CH), 3.74 (1H, d, *J* 2.25, C*H*CO$_2$CH$_3$), 3.81 (1H, d × q, *J* 7.09 and 2.25 C*H*CH$_3$), 4.11 (2H, 2 × d × q, J_{ax} 7.14, J_{bx} 3.74 and J_{ab} 13.69 CH_2O), 4.25 (2H, q, *J* 7.16 exocyclic CH_2O), 6.21 (1H, s, C=C–*H*), 7.41 (3H, m, *meta* and *para* aromatic protons), 8.00 (2H, d, *J* 7.46, *ortho* aromatic protons); $\delta_C(C^2HCl_3$; 125.7 MHz) 13.91 and 14.38 (2 × *C*H$_3$CH$_2$O), 16.26 (*C*HCO$_2$-CH$_2$CH$_3$), 28.92 (CH*C*H$_3$), 45.37 (*C*HCH$_3$), 60.09 and 61.88 2 × *C*H$_2$O ester), 112.33 (exocyclic C=*C*–H), 127.43 (*para* aromatic carbon), 128.67 (*meta* aromatic carbons), 131.71 (*ortho* aromatic carbons), 137.64 (*ipso* aromatic carbon), 152.33 (N–*C*–S), 167.58 [ring N=*C*(Ph)–CH], 171.16 and 172.41 (2 × O –*C*=O).

Ethyl 2-ethoxycarbonylmethylene-2,3-dihydro-5-methyl-4-phenyl-6*H*-1,3-thiazine-6-carboxylate 19

On storing the crude photoproduct **20** at −20 °C for several weeks, a solid was seen to form. TLC indicated the presence of a new component, which was separated by column chromatography (silica gel, dichloromethane) to give a yellow solid that was recrystallised from ethanol (0.022 g, 7.10%); mp 100–101 °C; *m*/*z* 347 ($M^{+\bullet}$), 302 [(M − OEt)$^+$], 274 [(M − CO_2Et)$^+$], 270 [(M − Ph)$^+$]; $\delta_H(C^2HCl_3$; 500 MHz) 1.24 (3H, t, *J* 7.06 exocyclic CH_3CH$_2$O), 1.30 (3H, t, *J* 7.14 ring CH_3CH$_2$O), 1.88 (3H, s, C=C–CH_3), 3.93 (1H, s, C*H*CO$_2$Et), 4.09 (2H, 2 × d × q, *J* 7.14 and 3.42, ring CH$_3$CH_2O), 4.26 (2H, 2 × d × q, J_{ax} 7.06, J_{bx} 3.62 and J_{ab} 13.94 exocyclic CH_2O ester), 4.95 (1H, s, C=C–*H*), 7.30 (5H, m, aromatic protons), 10.47 (1H, br s, hydrogen bonded N*H*); $\delta_C(C^2HCl_3$; 125.7 MHz) 14.14 and 14.46 (2 × *C*H$_3$CH$_2$O), 19.36 (C=C–*C*H$_3$), 44.90 (*C*HCO$_2$Et), 59.15 and 62.02 (2 × *C*H$_2$O), 85.66 (exocyclic C=*C*–H), 102.35 (ring Ph–C=*C*–C–CO$_2$CH$_2$CH$_3$), 128.73, 128.78 and 128.84 (*ortho*, *meta* and *para* carbons), 134.65 (*ipso* carbon), 136.24 [ring N–*C*(Ph)=CH], 151.26 (N–*C*–S), 168.99 and 169.33 (2 × O–*C*=O).

Crystal structure determination of compound 12

Crystals of compound **12** were prepared as described above.

Crystal data. $C_{12}H_{17}NO_4S$, *M* 271.3, triclinic, *a* 7.634(3), *b* 8.165(3), *c* 11.681(4) Å, *α* 76.02(3)°, *β* 77.65(3)°, *γ* 89.72(3)°, *V* 689.3 Å^3, Mo-Kα (*λ* 0.710 69 Å), space group P$\bar{1}$, (No. 2), *Z* 2, D_c 1.31 g cm^{-3}. White crystals, size: 0.3 × 0.2 × 0.1 mm, *μ*(Mo-Kα) 2.3 cm^{-1}.

Data collection and processing. Enraf-Nonius CAD4 diffractometer, *θ*–2*θ*, monochromated Mo-Kα radiation; 2° < *θ* < 25°, *h* (0 to 9), *k* (−9 to 9), 1 (−13 to 13), 2419 unique, giving 1950 with $|F^2| > 2\sigma(F^2)$. Max. change in standard reflections −0.3%. No decay or absorption correction.

Structure analysis and refinement. Direct methods (SHELXS86). Full-matrix least-squares refinement with all non-hydrogen atoms anisotropic using Enraf-Nonius MoLEN programs and hydrogens in fixed calculated positions, $\mu_{iso} = 1.3\mu_{eq}$ for parent C(10) methyl H atoms disordered over 6 sites C(11) and C(12) atoms omitted. $(\Delta/\sigma)_{max}$ 0.04, $(\delta\rho)_{max,min}$ (e Å^{-3}) +0.56, −0.26. $\sigma(F^2) = [\sigma^2(I) + (0.04I)^2]^{\frac{1}{2}}$/Lp, $w = \sigma^2(F)$, $\Sigma w(|F_o|-|F_c|)^2$ minimised. Final *R* and R_w values are 0.066, 0.116. S 3.7, no. variables 172, observed reflections 1950.

Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web pages (http://www.rsc.org/perkin1). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/174.

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