# Base catalysed syntheses of the novel tetrahydropyridine-2-thione, piperidine-2-thione and 6-aza-2-oxa-3-oxo-5-thioxobicyclo-[2.2.2]octane ring systems

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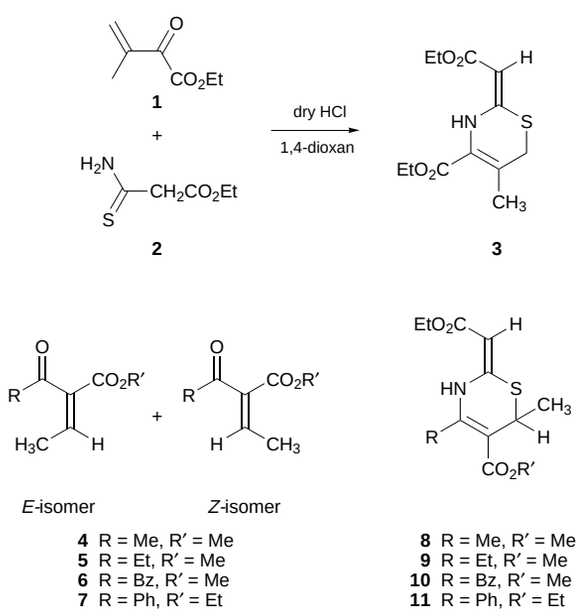
**In contrast to the acid catalysed condensations of 2-ethoxycarbonylthioamides with α,β-unsaturated ketones to dihydrothiazines, base catalysis yields 6-hydroxypiperidine-2-thiones; which can be dehydrated to tetrahydropyridine-2-thiones and, if the second substituent at the 6-position is electron releasing, the molecule can eliminate ethanol transannularly to give novel lactone bridged bicyclic systems.**

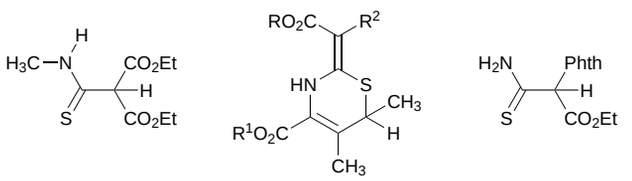
Under acid catalysed conditions (dry HCl in 1,4-dioxane), α,β-unsaturated keto ester **1**, reacts with ethoxycarbonylthioacetamide **2** to give dihydrothiazine **3** (Scheme 1).[1,2] Such ring




**Scheme 1**

systems are of interest as they form the non-β-lactam ring of cephalosporins and they also show very interesting rearrangements on irradiation with UV light.[3–5] Furthermore, the α,β-unsaturated keto esters **4**–**7** gave the dihydrothiazines **8**–**11** under similar acidic conditions.[5]

In order to examine the effects of an N-alkyl substituent on the photochemistry of these compounds an attempt was made to produce a related N-substituted dihydrothiazine from N-methylthioamide **12**[6] and the α,β-unsaturated keto esters **4**. Application of the usual acidic conditions gave only starting materials. However, base catalysis had apparently been used in the synthesis of the related dihydrothiazine **13** from thioamide **14**,[7] the intermediate hydroxytetrahydrothiazine supposedly being isolated and then dehydrated under acidic conditions. These results will be returned to near the end of the paper.




Thus catalysis of the reaction of **4** with **12** using an equimolar quantity of triethylamine in *tert*-butyl alcohol solvent was attempted, but under all conditions an intractable mixture was obtained until a catalytic amount of triethylamine (0.125 of an equivalent) was used. The clean product **15** had empirical formula $C_{14}H_{19}NO_6S$ and was formed in 59% yield. Mass spectrometry gave the molecular ion *m/z* 329, representing a loss of $C_2H_4$ relative to the expected dihydrothiazine, as well as an ion at *m/z* 285, which suggested a loss of $CO_2$. The $^1$H NMR spectrum of the product **15** showed three 3H singlets at $\delta$ 1.93, 3.46 and 3.75 and two 2H d × q at $\delta$ 4.37 (*J* 7.19 and 10.84 Hz) and $\delta$ 4.38 (*J* 7.22 and 10.84 Hz) as well as a multiplet at $\delta$ 2.80 (2H). In addition, an overlapping doublet (*J* 6.45 Hz) and triplet (*J* 7.10 Hz) at $\delta$ 1.36 (total 6H) were also observed. Selective decoupling of this methyl region simplified the multiplet at $\delta$ 2.8 to give an AB double doublet of an $ABX_3$ system ($J_{AB}$ 4.71 Hz). More interestingly the $^{13}$C NMR spectrum showed the presence of a high chemical shift resonance at $\delta$ 192.8 which was comparable to the thione C=S resonance that occurred at $\delta$ 199.0 in the starting thioamide **12** and much greater than the expected *ca.* $\delta$ 150 of a dihydrothiazine N–C–S. X-Ray diffraction confirmed the structure of **15** as the bridged lactone of Fig. 1.

A reasonable mechanism for the formation of the bicyclic compound **15** is shown in Scheme 2. Cyclisation of the intermediate **16** is a little unusual in that the sulfur should be more nucleophilic than the nitrogen, however, the nucleophilicity of the nitrogen may be enhanced by removal of the NH proton by the base catalyst.

One interesting aspect of the reaction is that only one isomer was obtained, with the methyl ester and the adjacent methyl group *trans* to each other. This may be due simply to steric hindrance between the two groups in the intermediates **16** and **17**. Since the mass spectrum showed a fragment ion at *m/z* 285, which indicated loss of $CO_2$ from the parent compound **15**, we investigated the possibility of this compound decarboxylating

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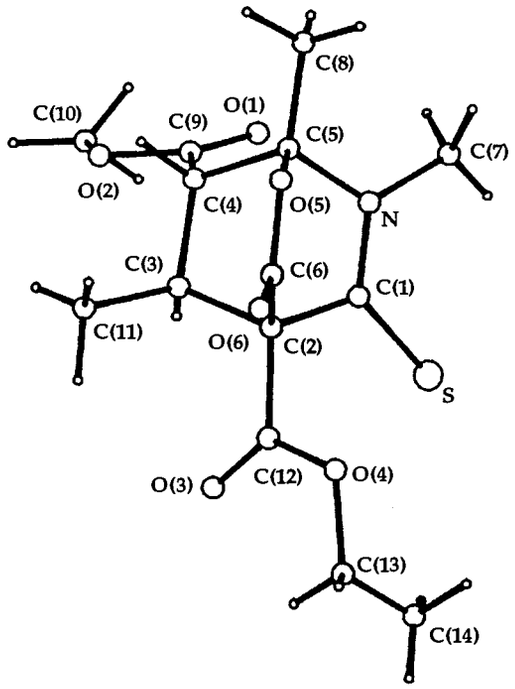
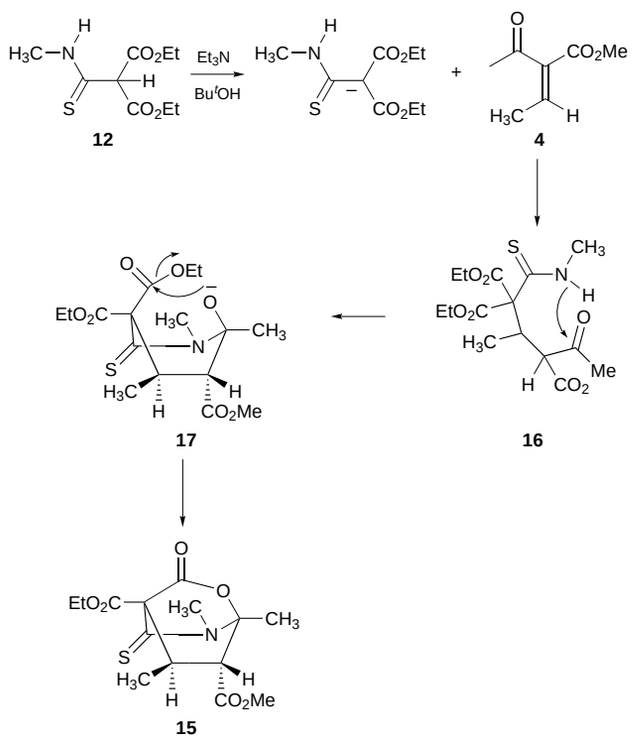


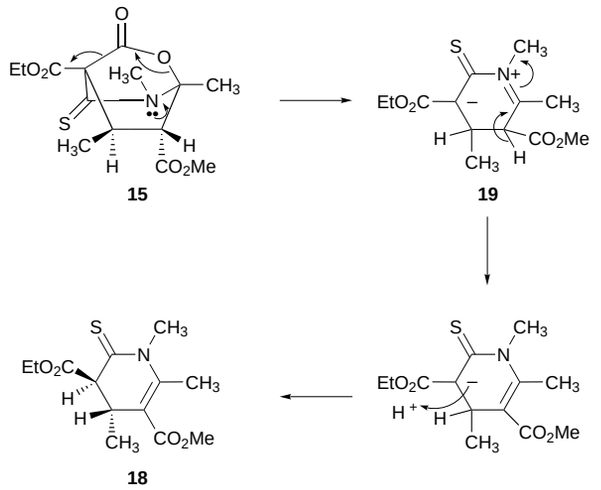

**Fig. 1** X-Ray crystal structure of compound **15**




**Scheme 2**

thermally. Heating compound **15** in a variety of solvents gave only starting material but when we heated the pure, dry crystals above their melting point, effervescence was observed and compound **18** was obtained (Scheme 3). The mass spectrum of compound **18** showed the expected molecular ion at *m*/*z* 285 and the $^{13}C$ NMR spectrum confirmed the loss of one carbonyl group. A reasonable mechanism for the reaction is given in Scheme 3. Note the loss of a relatively poorly acidic hydrogen from intermediate **19**. As will become apparent later, the ease or difficulty of such a deprotonation step appears to define the stability of these bicyclic compounds.

Simple molecular modelling treatment (Chem3DPlus on

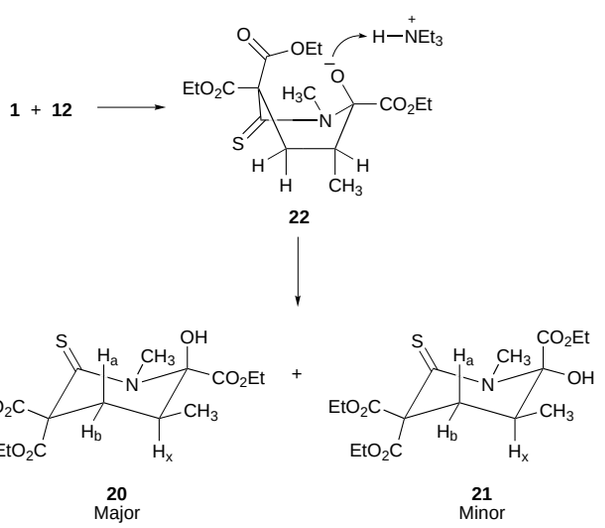



**Scheme 3**

a Macintosh) of the structure **18** showed that the three $sp^2$ carbons and the nitrogen atom of the ring are almost planar to one another. The $sp^3$ carbons of the ring are slightly puckered out of the plane. Both possible *cis*-isomers of **18** would produce dihedral angles of *ca.* 40°, giving, by the Karplus relationship, a predicted coupling constant of *ca.* 5 Hz between the *cis* $sp^3$ CHs. Similarly, a *trans*-diaxial arrangement of the CHs would give a dihedral angle of *ca.* 165° and a *J* value of *ca.* 9 Hz. Thus a *trans*-diequatorial configuration of the CHs was confirmed by a very small coupling constant (*J* 2.01 Hz, expected *ca.* 1 Hz for a dihedral angle of *ca.* 80°) in the $^1H$ NMR spectrum. Such a configuration would be favoured in the absence of transannular interactions due to the minimisation of eclipsing interactions between the carboxyethyl and 4-methyl groups.

To investigate the generality of the reaction above, we investigated the reaction of the α,β-unsaturated keto ester **1** with the N-methylthioamide **12**. Under the basic conditions described above a pale oil was isolated in 71% yield. However the mass spectrum showed a molecular ion at *m*/*z* 375 indicating that only addition had taken place.

The $^1H$ NMR spectrum showed the presence of two diastereomers in an approximate ratio of 3:2. The most interesting feature of the $^1H$ NMR spectrum included a one proton d × d × q at $\delta$ 2.18 ($J_{xa}$ 13.41, $J_{xb}$ 3.02 and *J* 6.70 Hz) and two overlapping double doublets integrating as two protons at $\delta$ 2.35 for the major isomer ($J_{ba}$ 13.42 and $J_{bx}$ 3.02 Hz) and at $\delta$ 2.38 for the minor isomer ($J_{ba}$ 13.91 and $J_{bx}$ 3.42 Hz). The

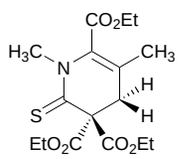



**Scheme 4**

region also included two overlapping doublets at $\delta$ 2.52 (major isomer $J_{ab}$ 13.42 and $J_{ax}$ 13.41 Hz) and at $\delta$ 2.75 (minor isomer $J_{ab}$ 13.91 and $J_{ax}$ 13.90 Hz) together integrating as one proton and appearing in a ratio of 3:2. NOE results also showed that irradiation of the hydroxy singlet at $\delta$ 4.70 showed an enhancement of 0.5% to the $\delta$ 2.52 resonance ($H_a$) showing that in the major isomer the proton is in the axial position. Thus we propose the following mechanism for the formation of the piperidines **20** and **21** (Scheme 4).

It is interesting that, while intermediate **17** forms a lactone, the intermediate **22** does not. In the case of **17** the electron donating character of the $CH_3$ group will increase the nucleophilicity of the alkoxide group. However in the case of **22** the electron withdrawing character of the ester group adjacent to the alkoxide might reduce the electron density on the alkoxide function making it less able to attack the *cis* ester and form the bridge.

Treatment of the thioamides **20** and **21** with dry hydrogen chloride in 1,4-dioxane gave a new compound whose $^1$H and $^{13}$C NMR spectroscopic data were in keeping with it being the expected dehydrated thioamide **23**. The mass spectrum also



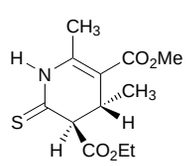

**23**

showed a molecular ion at *m*/*z* 358 ($MH^+$) and the IR spectrum showed the disappearance of the band at $\nu_{max}$ 2854–2926 $cm^{-1}$, corresponding to the loss of the OH group.

Since we had obtained novel cyclic thioamides we thought that it would be interesting to treat the α,β-unsaturated keto esters **1** and **4** with the thioamide **2**, under basic conditions, to see if similar cyclic thioamides could be obtained.

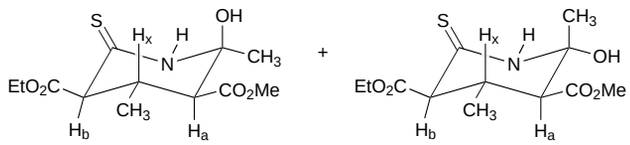
Treatment of keto ester **1** with the thioamide **2** and triethylamine in *tert*-butyl alcohol gave an intractable mixture, whilst treatment of the keto ester **4** with the thioamide **2** gave several components which were separated by chromatography.

The highest $R_f$ component was a pale yellow oil, isolated in 5% yield. The IR, UV and $^1$H and $^{13}$C NMR spectra of the compound were very similar to those of thioxopyridine **18**, except that the NH had replaced the N-methyl. As with compound **18**, the two vicinal CH groups in the ring gave a small coupling constant ($J$ 1.66 Hz), thus the structure **24**, with a *trans*-diequatorial arrangement of the vicinal CHs, was assigned to the compound.




**24**

The second component to be identified was obtained as a white crystalline solid in 42% yield. The microanalytical results gave an empirical formula of $C_{12}H_{19}NO_5S$, the mass spectrum showed a molecular ion at *m*/*z* 289 as well as a prominent ion at *m*/*z* 271 and the $^1$H NMR spectrum showed the presence of two isomers in a ratio of 9:2. The $^{13}$C NMR spectrum also showed the high field resonance typical of a thioamide at $\delta$ 198.55. Thus we proposed structures **25** and **26** for the diastereoisomeric mixture, together with the stereochemistry for three of the four chiral centres.

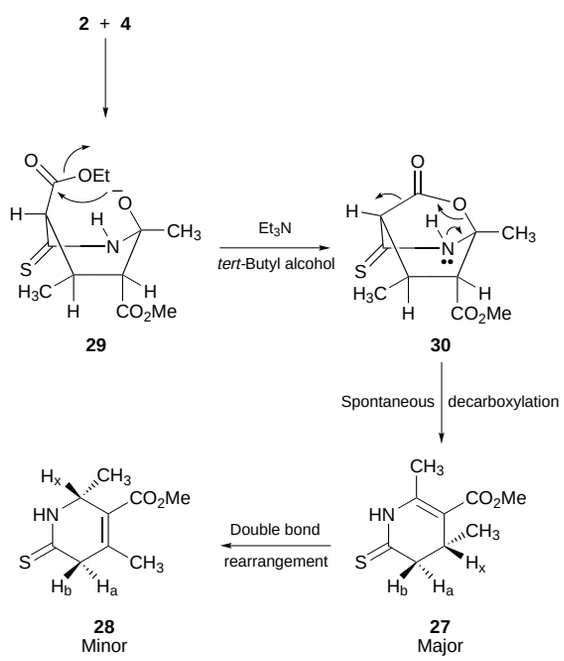



**25** Major **26** Minor

$^1$H NMR NOE experiments confirmed the stereochemistry of the isomers **25** and **26**. Irradiation of the C$H_3$COH methyl singlet of the major isomer at $\delta$ 1.58 gave an enhancement of 8.1% in the doublet at $\delta$ 2.56 ($H_a$) and an enhancement of 6.1% of the NH absorption at $\delta$ 8.71, whilst irradiation of the $CH_3$CO$H$ at $\delta$ 4.66 gave an enhancement of 5% in the C$H_x$$CH_3$ proton at $\delta$ 2.91. Irradiation of the C$H_3$COH singlet of the minor isomer gave an enhancement of 10.5% in the C$H_x$$CH_3$ proton.

Treatment of the mixture of anomers **25** and **26** with dry hydrogen chloride in 1,4-dioxane gave a yellow oil whose spectra were identical with those of compound **24**. Thus it seems likely that the highest $R_f$ component was derived from a base catalysed dehydration of **25**; **26** being less likely to dehydrate under such reaction conditions.

The third component from the reaction was isolated in a yield of 12%. The mass spectrum showed a molecular ion at *m*/*z* 199 and the $^{13}$C NMR spectrum showed a total of nine carbons, the most interesting being a resonance at $\delta$ 202.30 indicating a C=S group. $^1$H NMR spectroscopy indicated the presence of two isomers in a ratio of 6:1 and their spectra were consistent with structures **27** and **28**.

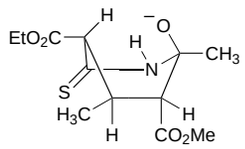



**Scheme 5**

Intermediate **29** can either protonate and form compound **25** or ring close to form intermediate **30**. Unlike compound **15**, where heating was required for decarboxylation, the presence of the NH in this structure allows spontaneous decarboxylation of **30** to give the monocyclic thioamide **27** and a further double bond rearrangement would give the isomer **28**.

The complexity of the product mixture in this case probably arises from the fact that although the alkoxide in intermediate **29** is activated by the adjacent methyl group the transannular ethoxycarbonyl group does not have the extra activation of an adjacent ethoxycarbonyl group. Thus protonation

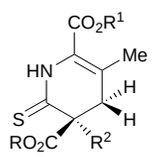
can effectively compete with ring closure with this intermediate. Furthermore, the isomeric intermediate **31** will also be formed



**31**

and this does not have a transannular ethoxycarbonyl group to cyclise with and so protonation occurs.

In the light of our results the report by Bakasse *et al.*[7] that initial base catalysis can lead eventually to the dihydrothiazines **13** must be viewed with some suspicion. It is more likely that the products are actually tetrahydropyridine-2-thiones similar to those we obtained. The analyses of such compounds **32** would



**32**

Where $R^2$ = $CO_2R$, N-Phthalimido

be identical and their spectra broadly similar, with the exceptions already noted for our compounds. However, $^{13}C$ NMR spectroscopic evidence was not presented in their communication and $^1H$ NMR spectra would not be conclusive in this instance, so a definite assessment cannot be made.

## Experimental

### General

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

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

### 4-Ethyl 7-methyl 1,6,8-trimethyl-3-oxo-5-thioxo-2-oxa-6-azabicyclo[2.2.2]octane-4,7-dicarboxylate 15

Triethylamine (0.293 $cm^3$, 2.2 mmol) was added to a stirred solution of diethyl 2-[(methylamino)carbothioyl]malonate **12**[6] (4.10 g, 17.61 mmol) in *tert*-butyl alcohol (250 $cm^3$) under nitrogen. Stirring was continued at room temperature for 0.5 hour and the α,β-unsaturated keto ester **4**[5] (2.50 g, 17.61 mmol) was added dropwise. After stirring for 24 hours TLC showed complete loss of starting materials and formation of a new component. The solvent was removed *in vacuo* to give a pale gum which was chromatographed (silica gel, diethyl ether–light petroleum, 60–80 °C, 1:1) to give a white solid which was recrystallised from ethanol (3.43 g, 59%); mp 131–132 °C (Found: C, 51.44; H, 5.74; N, 4.41. $C_{14}H_{19}NO_6S$ requires C, 51.04; H, 5.82; N, 4.25%); *m*/*z* 329 $(M)^{\bullet+}$, 285 $(M - CO_2)^{\bullet+}$, 240 $[M - (CO_2 + EtO^{\bullet})]^+$, 212 $[M - (CO_2 + S{=}C{=}NCH_3^{\bullet})]^+$; $\lambda_{max}$(MeOH)/nm 210 (ε/$dm^3$ $mol^{-1}$ $cm^{-1}$ 2519), 268 (8496) this chromophore also shows a shoulder at *ca.* 280; $\nu_{max}$(liquid film)/$cm^{-1}$ 1785 (lactone C=O), 1740 (ester C=O), 1004 (C=S); $\delta_H$($C^2HCl_3$; 500 MHz) 1.36 (2 × 3H, overlapping t and d, *J* 7.10 and 6.45, $CH_3CH_2O$ and $CHCH_3$), 1.93 (3H, s, $CH_3$), 2.80 (2H, m, $CHCH_3$ and $CHCO_2CH_3$), 3.46 (3H, s, $CH_3O$), 3.75 (3H, s, $NCH_3$), 4.37 (2H, d × q, *J* 7.19 and 10.84, $OCH_aCH_3$), 4.39 (2H, d × q, *J* 7.22 and 10.84, $OCH_bCH_3$); $\delta_C$($C^2HCl_3$; 125.7 MHz) 13.80 ($CH_2CH_2O$), 19.08 ($NCCH_3$), 21.22 ($CHCH_3$), 36.09 ($NCH_3$), 37.06 ($CHCO_2CH_3$), 52.77 ($CH_3O$), 57.84 ($CHCH_3$), 62.35 ($CH_2O$), 71.14 (S=C*C*$CO_2$Et), 92.01 ($NCCH_3$), 162.77, 164.32 and 169.96 (2 × ester C=O and bridging lactone C=O), 192.84 (C=S).

### 3-Ethyl 5-methyl 1,4,6-trimethyl-2-thioxo-1,2,3,4-tetrahydropyridine-3,5-dicarboxylate 18

The bicyclic thioamide **15** (1.15 g, 3.50 mmol) was heated with stirring above its melting point. After 1 hour effervescence was observed and after 2 hours TLC showed complete loss of starting material. The resulting crude gum was purified by chromatography (silica gel, diethyl ether–light petroleum 60–80 °C, 1:1) to give a yellow solid. Recrystallisation from ethanol afforded pale yellow crystals (0.59 g, 59%); mp 57–58 °C (Found: C, 54.63; H, 6.48; N, 4.60. $C_{13}H_{19}NO_4S$ requires C, 54.70; H, 6.72; N, 4.90%); *m*/*z* 285 $(M)^{\bullet+}$, 240 $(M - EtO^{\bullet})^+$, 212 $(M - S{=}C{=}NCH_3^{\bullet})^+$; $\lambda_{max}$(MeOH)/nm 208 (ε/$dm^3$ $mol^{-1}$ $cm^{-1}$ 6432), 236 (5150), 328 (19 370); $\nu_{max}$(liquid film)/$cm^{-1}$ 1739 and 1711 (ester C=O), 1032 (C=S); $\delta_H$($C^2HCl_3$; 500 MHz) 1.07 (3H, d, *J* 7.15, $CHCH_3$), 1.20 (3H, t, *J* 7.11, $CH_3CH_2O$), 2.48 (3H, s, $=CCH_3$), 3.32 (1H, q × d, *J* 7.15 and 2.01, $CHCH_3$), 3.71 (3H, s, $CH_3O$), 3.77 (3H, s, $NCH_3$), 4.04 (1H, d, *J* 2.01, $CHCO_2Et$), 4.12 (2H, d × q, *J* 7.10 and 10.80, $CH_aO$), 4.16 (2H, d × q, *J* 7.15 and 10.80, $CH_bO$); $\delta_C$($C^2HCl_3$; 125.7 MHz) 14.03 ($CH_3CH_2O$), 17.29 ($=CCH_3$), 17.44 ($CHCH_3$), 30.09 ($CHCO_2Et$), 37.58 ($NCH_3$), 51.71 ($CHCH_3$), 61.41 ($CH_3O$), 62.58 ($CH_2O$), 117.04 (C=*C*$CO_2CH_3$), 146.27 (*C*=$CCO_2CH_3$), 166.80 and 166.95 (2 × ester *C*=O), 196.19 (*C*=S).

### Triethyl 1,5-dimethyl-6-hydroxy-2-thioxopiperidine-3,3,6-tricarboxylates 20 and 21

Triethylamine (196 μl, 1.48 mmol) was added with stirring to a solution of diethyl 2-[(methylamino)carbothioyl]malonate **12**[6] (2.75 g, 11.80 mmol) under nitrogen in *tert*-butyl alcohol (200 $cm^3$). After 0.5 hour at room temperature ethyl 3-methyl-2-oxobutanoate **1**[2,7] (1.68 g, 11.80 mmol) was added dropwise and stirring continued. After 24 hours TLC showed complete loss of starting materials and the presence of a new component. The solvent was removed *in vacuo* to give a viscous oil which was chromatographed (silica gel, diethyl ether–light petroleum 60–80 °C, 1:1) to give a pale gum which failed to crystallise. The $^1H$ NMR spectrum showed the presence of two isomers (3.16 g, 71%); *m*/*z* 375 $(M)^{\bullet+}$, 330 $(M - EtO^{\bullet})^+$, 302 $(M - EtO_2C^{\bullet})^+$ or $(M - S{=}C{=}NCH_3^{\bullet})^+$, 273 $(M - EtO_2C - CH - OH^{\bullet})^+$; $\lambda_{max}$(MeOH)/nm 210 (ε/$dm^3$ $mol^{-1}$ $cm^{-1}$ 2542), 272 (6029); $\nu_{max}$(liquid film)/$cm^{-1}$ 3503–2873 (broad, OH), 1737 (ester C=O), 1032 or 1069 (C=S); $\delta_H$($C^2HCl_3$; 500 MHz) major isomer **20** (60%), 0.95 (3H, d, *J* 6.70, $CHCH_3$), 1.31 (9H, 3 × t, *J* 7.06, 3 × $CH_3CH_2O$), 2.18 (1H, d × d × q, $J_{CHCH_3}$ 6.70, $J_{xa}$ 13.41, $J_{xb}$ 3.02, $CH_aH_bCH_xCH_3$), 2.35 (1H, d × d, $J_{ba}$ 13.42 and $J_{bx}$ 3.02, $CH_aH_bCH_x$), 2.52 (1H, d × d, $J_{ab}$ 13.42, $J_{ax}$ 13.41, $CH_aH_bCH_x$), 3.23 (3H, s, $NCH_3$), 4.24 (6H, 3 × q, *J* 7.06, 3 × $CH_2O$), 4.70 (1H, s, OH); minor isomer **21** (40%), 0.99 (3H, d, *J* 6.77, $CHCH_3$), 1.31 (9H, 3 × t, *J* 7.06, 3 × $CH_3CH_2O$), 2.18 (1H, d × d × q, $J_{CHCH_3}$ 6.77, $J_{xa}$ 13.90, $J_{xb}$ 3.42, $CH_aH_bCH_xCH_3$), 2.38 (1H, d × d, $J_{ba}$ 13.91 and $J_{bx}$ 3.42, $CH_aH_bCH_x$), 2.75 (1H, d × d, $J_{ab}$ 13.91, $J_{ax}$ 13.90, $CH_aH_bCH_x$), 3.18 (3H, s, $NCH_3$), 4.24 (6H, 3 × q, *J* 7.06, 3 × $CH_2O$); $\delta_C$($C^2HCl_3$; 125.7 MHz) 13.71, 13.73, 13.85, 13.91, 13.94 and 14.11 (6 × $CH_3CH_2O$), 15.10 and 15.57 (2 × $CHCH_3$), 31.85 and 33.55 (2 × $CH_2$), 33.22 and 35.46 (2 × $CHCH_3$), 36.66 and

39.05 (2 × N*C*H$_3$), 62.15, 62.23, 62.26, 62.42, 64.02 and 64.10 (6 × *C*H$_2$O), 68.93 and 69.47 [2 × (EtO$_2$C)$_2$*C*], 89.26 and 90.47 (2 × *C*OH), 167.93, 167.99, 168.17, 170.02 and 171.18 (5 × ester *C*=O, sixth hidden), 195.40 and 196.24 (2 × *C*=S).

**Triethyl 1,5-dimethyl-2-thioxo-1,2,3,4-tetrahydropyridine-3,3,6-tricarboxylate 23**

The mixture of 2-thioxopiperidines **20** and **21** (3.00 g, 8.00 mmol) was dissolved in dry 1,4-dioxane (25 cm$^3$), the solution saturated with dry hydrogen chloride gas at 0 °C and left to stand overnight at room temperature. Removal of the solvent *in vacuo* gave an orange gum that was purified by chromatography (silica gel, dichloromethane) to give the 2-thioxo-tetrahydropyridine **23** as a yellow solid, which afforded pale yellow crystals on recrystallisation from ethanol (2.48 g, 87%); mp 46–48 °C (Found: C, 52.91; H, 6.55; N, 3.72. $C_{15}H_{21}NO_6S$ requires C, 52.47; H, 6.16; N, 4.08%); *m*/*z* 358 $(MH)^+$, 312 $(M - EtO^{\bullet})^+$, 284 $(M - EtO_2C^{\bullet})^+$ or $(M - S{=}C{=}NCH_3^{\bullet})^+$; $\lambda_{max}$(MeOH)/nm 210 ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$ 8012), 234 (7019), 312 (18 055); $\nu_{max}$(KBr disc)/cm$^{-1}$ 1731 (ester C=O), 1059 (C=S); $\delta_H$(C$^2$HCl$_3$; 500 MHz) 1.28 (6H, 2 overlapping t, *J* 7.11, 2 × C*H*$_3$CH$_2$O), 1.34 (3H, t *J* 7.11, C*H*$_3$CH$_2$O), 2.05 (3H, s, =CC*H*$_3$), 2.93 (2H, s, C*H*$_2$), 3.45 (3H, s, NC*H*$_3$), 4.28 (6H, 3 × q, *J* 7.11, 3 × CH$_2$O); $\delta_C$(C$^2$HCl$_3$; 125.7 MHz) 13.86 and 14.11 (2 × *C*H$_3$CH$_2$O), 19.43 (=C*C*H$_3$), 34.36 (*C*H$_2$), 40.76 (N*C*H$_3$), 61.65 and 62.50 (2 × *C*H$_2$O), 67.81 [(EtO$_2$C)$_2$*C*], 130.92 and 131.30 (H$_3$C*C*=*C*CO$_2$Et), 162.19 and 167.33 (2 × ester *C*=O), 192.29 (*C*=S).

**3-Ethyl 5-methyl 4,6-dimethyl-2-thioxo-1,2,3,4-tetrahydropyridine-3,5-dicarboxylate 24, 3-ethyl 5-methyl 4,6-dimethyl-6-hydroxy-2-thioxopiperidine-3,5-dicarboxylates 25 and 26, methyl 4,6-dimethyl-2-thioxo-1,2,3,4-tetrahydropyridine-5-carboxylate 27 and methyl 4,6-dimethyl-2-thioxo-1,2,3,6-tetrahydropyridine-5-carboxylate 28**

Triethylamine (115 μl, 0.86 mmol) was added to a solution of ethoxycarbonylthioacetamide **2**[2] (1.01 g, 6.87 mmol) in *tert*-butyl alcohol (50 cm$^3$) which was stirred at room temperature for 0.5 hour under nitrogen. The α,β-unsaturated keto ester **4**[4] (0.98 g, 6.87 mmol) was added dropwise and stirring continued for 24 hours when TLC showed complete loss of starting materials and the formation of several new components. The solvent was removed *in vacuo* to give a pale gum which after chromatography (silica gel, diethyl ether–light petroleum 60–80 °C, 1 : 1) gave three components.

First component: **24** (0.94 g, 5%); *m*/*z* 272 $(M + H)^+$; $\lambda_{max}$(MeOH)/nm 206 ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$ 4854), 240 (4398), 334 (14 821); $\nu_{max}$(liquid film)/cm$^{-1}$ 3389–2951 (broad NH), 1737 and 1713 (2 × ester C=O), 1065 or 1028 (C=S); $\delta_H$(C$^2$HCl$_3$; 500 MHz) 1.02 (3H, d, *J* 7.10, CHC*H*$_3$), 1.12 (3H, t, *J* 7.13, C*H*$_3$CH$_2$O), 2.26 (3H, s, =CCH$_3$), 3.24–3.29 (1H, d × q, *J* 7.10 and 1.66, C*H*CH$_3$), 3.67 (3H, s, CO$_2$CH$_3$), 3.73 (1H, d, *J* 1.66, EtO$_2$CC*H*), 4.07 (2H, 2 × d × q, *J* 7.13 and 3.40, CH$_2$O), 9.34 (1H, broad s, NH); $\delta_C$(C$^2$HCl$_3$; 125.7 MHz) 13.90 (*C*H$_3$CH$_2$O), 18.22 (CH*C*H$_3$), 18.47 (=C*C*H$_3$), 31.12 (*C*HCH$_3$), 51.55 (*C*HCO$_2$Et), 60.29 (*C*H$_3$O), 61.70 (*C*H$_2$O), 111.58 and 142.63 (H$_3$*C*=*C*CO$_2$CH$_3$), 166.79 and 168.23 (2 × ester C=O), 196.56 (C=S).

Second component: **25** and **26** (0.84 g, 42%); mp 147–148 °C (Found: C, 49.60; H, 6.25; N, 5.00; S, 11.40. $C_{12}H_{19}NO_5S$ requires C, 49.80; H, 6.63; N, 4.84; S, 11.08%); *m*/*z* (FAB) 312 $(M + Na)^+$, 290 $(M + H)^+$, 272 $[(M + H) - H_2O]^+$; $\lambda_{max}$(MeOH)/ nm 208 ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$ 4762), 274 (15 253); $\nu_{max}$(Nujol mull)/cm$^{-1}$ 1785 and 1739 (ester C=O), 1062 or 1035 (C=S); $\delta_H$(C$^2$HCl$_3$; 500 MHz) major isomer **25** (82%): 1.03 (3H, d, *J* 6.64, CHC*H*$_3$), 1.33 (3H, t, *J* 7.16, C*H*$_3$CH$_2$O), 1.58 (3H, s, HOCC*H*$_3$), 2.56 (1H, d, $J_{ax}$ 11.93, EtO$_2$CC*H*$_a$), 2.91 (1H, d × d × q, $J_{CH_3CH}$ 6.64, $J_{xa}$ 11.93, $J_{xb}$ 10.15, C*H*$_x$CH$_3$), 3.40 (1H, d, $J_{bx}$ 10.15, *H*$_b$CCO$_2$CH$_3$), 3.82 (3H, s, C*H*$_3$O), 4.29 (2H, q, *J* 7.16, C*H*$_2$O), 4.66 (1H, s, O*H*), 8.71 (variable) (1H, broad s, N*H*); minor isomer **26** (18%): 1.05 (3H, d, *J* 7.18, CHC*H*$_3$), 1.33 (3H, t, *J* 7.17, C*H*$_3$CH$_2$O), 1.61 (3H, s, HOCC*H*$_3$), 2.73 (1H, d, $J_{ax}$ 11.90, EtO$_2$CC*H*$_a$), 2.91 (1H, d × d × q, $J_{CH_3CH}$ 7.18, $J_{xa}$ 11.90, $J_{xb}$ 10.15, C*H*$_x$CH$_3$), 3.49 (1H, d, $J_{bx}$ 10.45, *H*$_b$CCO$_2$CH$_3$), 3.78 (3H, s, CH$_3$O), 4.29 (2H, q, *J* 7.17, C*H*$_2$O), 4.66 (1H, s, O*H*), 8.98 (variable) (1H, broad s, N*H*); $\delta_C$(C$^2$HCl$_3$; 125.7 MHz) 13.99 (*C*H$_3$CH$_2$O), 18.19 (CH*C*H$_3$), 25.52 and 28.35 (2 × *C*HCH$_3$), 30.31 and 32.44 (2 × *C*HCO$_2$CH$_3$), 52.31 and 52.48 (2 × *C*HCO$_2$Et), 54.81 (*C*H$_3$O), 61.87 (*C*H$_2$O), 62.09 and 62.39 (*C*H$_3$COH), 81.04 (*C*OH), 170.24 and 170.17 (2 × ester *C*=O), 198.55 (*C*=S).

Third component **27** and **28** (18.73 mg, 12%); mp 135–136 °C; *m*/*z* 199 $(M)^{\bullet+}$, 140 $(M - S{=}C{=}NH^{\bullet})^+$, 168 $(M - CH_3O^{\bullet})^+$; $\lambda_{max}$(MeOH)/nm 206 ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$ 1746), 278 (2953), 332 (1469); $\nu_{max}$(Nujol mull)/cm$^{-1}$ 3399–3055 (broad NH), 1699 and 1635 (ester C=O), 1070 and 1045 (C=S); $\delta_H$(C$^2$HCl$_3$; 500 MHz) major isomer **27** (85%): 1.05 (3H, d, *J* 7.03, CHC*H*$_3$), 2.28 (3H, s, =CC*H*$_3$), 2.80 (1H, d × d, $J_{ab}$ 16.83, $J_{ax}$ 6.84, S=C=C*H*$_a$H$_b$), 3.03 (1H, d × d, $J_{ba}$ 16.83, $J_{bx}$ 1.05, S=C=CH$_a$*H*$_b$), 2.96 [1H, 2 × q (appears as quintet) $J_{CH_3Hx}$ 7.03, $J_{xa}$ 1.05, H$_3$CC*H*$_x$CH$_a$H$_b$], 3.77 (3H, s, C*H*$_3$O), 8.70 (1H, broad s, N*H*); minor isomer **28** (15%): 1.09 (3H, d, *J* 7.05, CHC*H*$_3$), 2.23 (3H, s, =CC*H*$_3$), 2.63 (1H, d × d, $J_{ab}$ 16.33, $J_{ax}$ 7.02, S=CC*H*$_a$H$_b$), 2.96 (1H, hidden under major isomer, H$_3$CC*H*$_x$CH$_a$H$_b$), 3.03 (1H, hidden under major isomer, S=CCH$_a$*H*$_b$), 3.75 (3H, s, C*H*$_3$O); $\delta_C$(C$^2$HCl$_3$; 125.7 MHz) 18.13 (CH*C*H$_3$), 18.74 (=C*C*H$_3$), 26.82 (*C*HCH$_3$), 45.84 (*C*H$_2$), 51.54 (*C*H$_3$O), 113.73 (CH$_3$C=*C*CO$_2$CH$_3$), 141.68 (CH$_3$*C*=CCO$_2$CH$_3$), 167.24 (ester *C*=O), 202.30 (*C*=S).

**3-Ethyl 5-methyl 4,6-dimethyl-2-thioxo-1,2,3,4-tetrahydropyridine-3,5-dicarboxylate 24**

The mixture of hydroxy-2-thioxopiperidines **25** and **26** (0.50 g, 1.73 mmol) was 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 dehydrated thioamide **24** as a pale yellow oil which failed to crystallise (0.37 g, 79%); the spectra were identical to those of a sample of **24** obtained in the previous experiment.

**Crystal structure determination of compound 15**

Crystals of compound **15** were prepared as described above.

**Crystal data.** $C_{14}H_{19}NO_6S$, *M* 329.4, monoclinic, *a* 7.743(2), *b* 12.293(2), *c* 16.482(4) Å, *α* 90°, *β* 93.33(2)°, *γ* 90°, *V* 1566.2 Å$^3$, Mo-Kα (*λ* 0.170 69 Å), space group $P2_1/n$ (non-standard No. 14), *Z* 4, $D_c$ 1.40 g cm$^{-1}$. White crystals, size 0.3 × 0.15 × 0.05 mm, $\mu$(Mo-Kα) 2.2 cm$^{-1}$.

**Data collection and processing.** Enraf-Nonius CAD4 diffractometer, $\theta$–$2\theta$, monochromated Mo-Kα radiation; $2° < \theta < 25°$, *h* (0 to 9), *k* (0 to 14), *l* (−19 to 19), 2901 unique, giving 1417 with $|F^2| > 2\sigma(F^2)$. Max change in standard reflections was 0.5%. No decay or absorption corrections were made.

**Structure analysis and refinement.** Direct methods (SHELXS 86). Full-matrix least-squares refinement with all non-hydrogen atoms anisotropic using Enraf-Nonius SDP programs and hydrogens for C(13) and C(14) in fixed calculated positions, $\mu_{iso} = 1.3\mu_{eq}$ for parent atom, the remainder being refined isotropically. $(\Delta/\sigma)_{max}$ 0.08, $(\delta\rho)_{max,min}$ (e Å$^{-3}$) +0.43, −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 0.057, 0.066. *S* 1.7, no variables 255, observed reflections 1417.

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/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/188.

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