PERKIN 1

Influence of ring size on the outcome of sulfide contraction reactions with thiolactams. Isolation of bicyclic ketene *S*,*N*-acetals and thioisomünchnones

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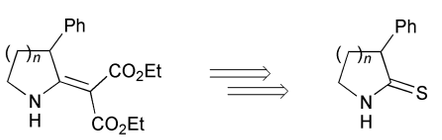
Reaction between diethyl bromomalonate and 3-phenylpyrrolidine-2-thione yielded a vinylogous urethane by the Eschenmoser sulfide contraction. However, with 3-substituted piperidine-2-thiones, sulfur was retained in the products, and a range of bicyclic heterocycles, including bicyclic ketene *S*,*N*-acetals (2-alkylidene-1,3-thiazolidin-4-ones) and stable thioisomünchnones, was isolated. A novel dimeric ketene *S*,*N*-acetal was characterised by X-ray crystallography.

Introduction

The extrusion of sulfur from organic sulfides and related systems is a useful but infrequently encountered method for the formation of carbon–carbon bonds.[1] One of the best-known variants is the Eschenmoser sulfide contraction, which was first reported in full in 1971.[2] In this reaction, thioamides or thiolactams are treated with enolisable α-halocarbonyl compounds to form α-thioiminium salts, from which sulfur is lost upon deprotonation in the presence of a suitable sulfur scavenger (usually a phosphine or a phosphite) to give β-acylated enamines (enaminones).[3] Conditions for the reaction depend on the nature of the reactants; thioiminium salts formed from tertiary thioamides undergo sulfide contraction under mild conditions (*e.g.*, at ambient temperature with triethylamine as base), while those from secondary thioamides are first deprotonated to thioimidates, which subsequently lose sulfur only in the presence of powerful bases such as potassium *tert*-butoxide, and frequently at elevated temperatures. However, when the halocarbonyl component is an activated system like dimethyl bromomalonate, the extrusion of elemental sulfur from the thioimidate intermediate may take place spontaneously with gentle warming in the absence of thiophile.

As part of our continuing explorations of β-acylated enamines and related compounds as intermediates in alkaloid synthesis,[4] we recently required the substituted vinylogous urethanes **1** and **2**, which we envisaged as arising from Eschenmoser sulfide contraction between diethyl bromomalonate and the secondary thiolactams **3** and **4**, respectively. Some unexpected results arising from this investigation are described in this article.

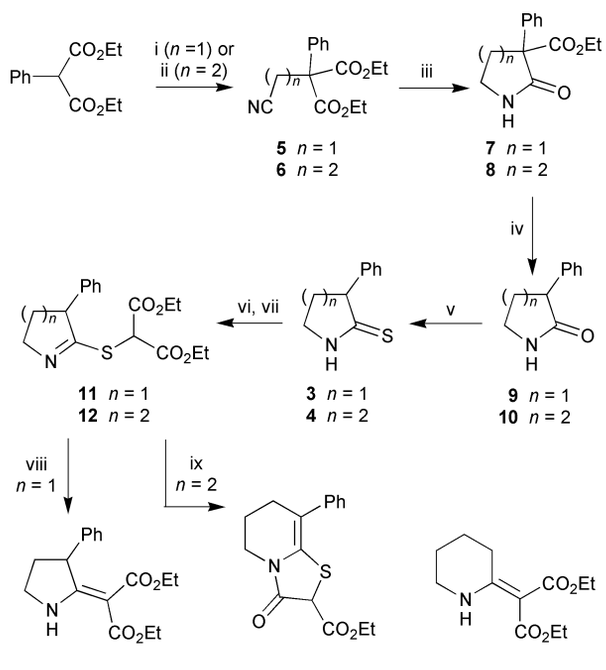


1 *n* = 1
2 *n* = 2

3 *n* = 1
4 *n* = 2

Results and discussion

The precursors **3** and **4** were prepared by the route shown in Scheme 1. Alkylation of the anion of diethyl phenylmalonate with bromoacetonitrile or acrylonitrile by reported procedures[5,6] afforded the homologous nitrilodiesters **5** and **6** in yields of 90% and 96% respectively. Hydrogenation of these products over Raney nickel (W-2 activity) in ethanol yielded lactams **7** and **8**, which were hydrolysed and decarboxylated under standard conditions to give the 3-phenyllactams **9** and **10** in overall yields of 45% and 68%, respectively. Thionation of the lactams with Lawesson's reagent[7] afforded the desired thiolactams **3** and **4** in yields of 57% and 78%, respectively.



5 *n* = 1
6 *n* = 2

7 *n* = 1
8 *n* = 2

11 *n* = 1
12 *n* = 2

3 *n* = 1
4 *n* = 2

9 *n* = 1
10 *n* = 2

1

13

14

Scheme 1 *Reagents*: i, NaH, THF, 0 °C, then $BrCH_2CN$ (90%); ii, KOH, MeOH–Bu^{t}OH, rt, then $H_2C{=}CHCN$ (96%); iii, H_2 (5–6 atm), Raney Ni, EtOH, rt; iv, NaOH or KOH, H_2O, reflux, then HCl, reflux (**9**, 45% from **5**; **10**, 68% from **6**); v, Lawesson's reagent, toluene, reflux (**3**, 57%; **4**, 78%); vi, $BrCH(CO_2Et)_2$, CH_2Cl_2, rt; vii, aq. $KHCO_3$ or K_2CO_3; viii, heat at 60 °C (84% from **3**); ix, heat at 75 °C (66% from **4**).

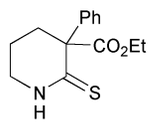
Treatment of the thiolactams **3** and **4** with diethyl bromomalonate[8] yielded *S*-alkylated salts, deprotonation of which

with aqueous potassium carbonate or potassium hydrogen carbonate solution afforded the putative thioimidates **11** and **12**. As expected, warming **11** at 60 °C resulted in deposition of elemental sulfur and the formation of the desired vinylogous urethane **1** in 84% overall yield. However, the outcome of the reaction based on the piperidinethione system **4** was completely different. Sulfur was not extruded when thioimidate **12** was heated to 75 °C, and the expected vinylogous urethane **2** was not formed; instead, the bicyclic thiazolidinone **13** was isolated in 66% yield. Leaving intermediate **12** to stand at ambient temperature also resulted in the formation of the bicyclic compound **13** (70%).

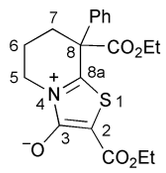
The formation of thiazoles and their oxo analogues from thioamides and α-halocarbonyl compounds (the Hantzsch synthesis[9] and variants) is a well-known process;[10] indeed, Eschenmoser himself reported that reaction of pyrrolidine-2-thione with phenacyl bromide could yield thiazolium salts if care was not taken in handling the thioimidate intermediate during sulfide contraction.[2] However, the complete divergence of reaction pathways for the five- and six-membered ring precursors in the present case is remarkable. What makes our observation even more intriguing is that when the procedure was repeated with piperidine-2-thione itself, the reaction with diethyl bromomalonate yielded the expected vinylogous urethane **14** in 91% yield, with no observable formation of a 1,3-thiazolidin-4-one or its hydroxy tautomer. This finding is in line with Eschenmoser's original report of a smooth sulfide contraction between diethyl bromomalonate and pyrrolidine-2-thione or thiocaprolactam.[2]

The phenyl substituent in intermediate **12** is clearly exerting a substantial influence in deflecting the reaction away from the sulfide contraction path, and one cannot avoid concluding that conjugation of the aromatic ring with the endocyclic double bond in bicyclic product **13** is a decisive factor in the reaction's outcome. Admittedly, a similar effect could be envisaged for the analogous product from thioimidate **11**. However, the overriding influence may well be the relative stability of exocyclic double bonds in five- and six-membered ring compounds, a phenomenon that was discussed and rationalised almost half a century ago by Brown and co-workers.[11] Although the indiscriminate application of their proposed generalisation was subsequently deprecated,[12,13] it would still seem to have validity if used cautiously. Thus, in terms of Brown's carefully worded generalisation of the observed effects,[13] the sulfide contraction of thioimidate **11**, involving the formation of a double bond that is exocyclic to a five-membered ring, is likely to be favoured in comparison with the sulfide contraction of **12**, which would entail the formation of a double bond exocyclic to a six-membered ring. The difference in stability of endocyclic double bonds in five- and six-membered rings is in general much smaller, although a preference for endocyclic double bonds in six-membered rings nevertheless seems to emerge in most cases. In the present situation, the phenyl substituent swings the outcome of the reaction with **12** towards the conjugated endocyclic double bond in the six-membered ring, perhaps for stereoelectronic reasons.

In order to exclude the possibility of forming the endocyclic ketene *S*,*N*-acetal system found in **13**, we examined the reaction between the 3,3-disubstituted piperidine-2-thione **15** and diethyl bromomalonate. In this case, the additional ester group, potentially removable at a later stage, was expected to block the formation of the endocyclic enamine and permit the sulfide contraction to take place. This thiolactam was prepared *via* lactam **8**[14] in an overall yield of 27% based on diethyl phenylmalonate (effectively 35% for the thionation step). Upon treatment of **15** with diethyl bromomalonate, however, sulfide contraction again failed to take place. Instead, the thioisomünchnone **16** was formed in 83% yield. The evidence for this unusual compound, a yellow solid, included elemental analysis and ^{13}C NMR spectroscopic signals at δ 169.60, 160.82 and 89.25 for C-8a, C-3 and C-2 of the mesoionic component of the bicyclic system, respectively. Clearly, the intermediate thioimidate shows the same reluctance to undergo sulfide contraction as did **12**, and instead an intramolecular acylation of the nucleophilic nitrogen takes place. The formation of 2-alkylidene-1,3-thiazolidin-4-one and thioisomünchnone products from 3-monosubstituted and 3,3-disubstituted thiolactams, respectively, has some precedent in the work of Padwa *et al*.[15]



15



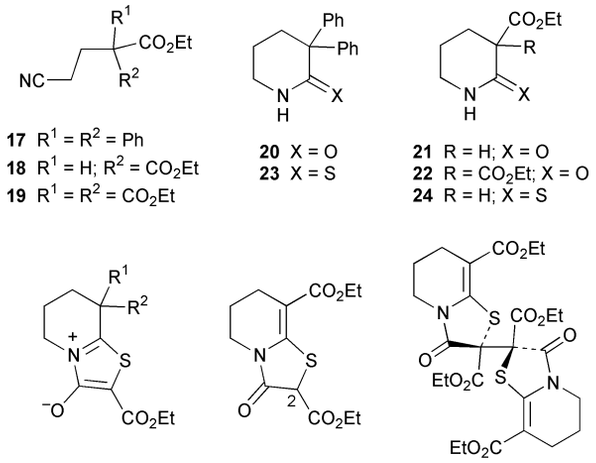
16

Thioisomünchnones are a comparatively rare class of mesoionic compounds,[16] and they tend not to be isolable unless substituted with stabilising substituents such as aryl.[17] Among the published routes to them are methods related to ours; for example, Potts and co-workers prepared a range of stable thioisomünchnones by treating secondary *N*-phenyl thiocarbamates, thioureas and thioamides with α-halo carboxylic acids followed by dehydration,[18] or, more efficiently, with α-bromoacyl chlorides.[19] Among the acyl halides employed was the monoethyl ester of α-bromomalonoyl chloride, which yielded ester-substituted heterocycles. The use of diethyl bromomalonate as the 1,2-electrophile in the synthesis of thioisomünchnones has been less often reported, *e.g.*, by Singh and Gandhi in reactions with isoquinoline-1(2*H*)-thione and quinazoline-4(3*H*)-thione,[20] and by Barton *et al*.[21] In the latter case, interestingly enough, although reaction of diethyl bromomalonate with tetrahydro-1,3-thiazine-2-thione yielded a thioisomünchnone, the use of diethyl chloromalonate in the presence of triethylamine resulted in sulfide contraction instead.

Thioisomünchnones are commonly used as transient reaction partners in 1,3-dipolar cycloadditions,[22,23] and intramolecular versions of this process have been used to good effect by Padwa and co-workers in the synthesis of alkaloids.[15] In our case, the mesoionic ring is stabilised by the electron-withdrawing ester group, and comparative inertness seems also to be conferred by the bulky substituents in the piperidine ring. Thus we were unable to isolate a product of dipolar cycloaddition from the reaction of **16** with diethyl acetylenedicarboxylate.

We undertook the synthesis of several additional thiolactams in order to test whether the formation of sulfur-containing heterocycles was likely to be a serious alternative to sulfide contraction with other piperidine-2-thione systems. The nitriloesters **17**–**19** were prepared in yields of 71–77% by alkylating the anions of the corresponding esters with acrylonitrile. Hydrogenation of these compounds over Raney nickel under pressure resulted in the direct formation of the 3-substituted piperidin-2-ones **20**–**22** in yields of 90%, 88% and 21%, respectively. Ultrasonically-promoted thionation of **20** and **21** with phosphorus pentasulfide in benzene afforded 3,3-diphenylpiperidine-2-thione **23** and ethyl 2-thioxopiperidine-3-carboxylate **24** in yields of 60% and 51%, respectively. However, attempts to prepare the corresponding thiolactam from 3,3-bis(ethoxycarbonyl)piperidin-2-one **22** failed.

We predicted that, if sulfide contraction of **23** and **24** with diethyl bromomalonate were to fail, then the former should give a thioisomünchone and the latter a thiazolidinone analogous to **13**. In the event, **23** indeed gave thioisomünchnone **25**, although in a yield of only 49%; however, thione **23** was recovered (40%). The reaction of compound **24** proved to be more puzzling. A high-melting yellow solid, shown by microanalysis and mass



17 $R^1 = R^2 = Ph$
18 $R^1 = H$; $R^2 = CO_2Et$
19 $R^1 = R^2 = CO_2Et$

20 X = O
23 X = S

21 R = H; X = O
22 R = CO_2Et; X = O
24 R = H; X = S

25 $R^1 = R^2 = Ph$
26 $R^1 = H$; $R^2 = CO_2Et$

27

meso-**28**

spectrometry to have the molecular formula $C_{26}H_{32}N_2O_{10}S_2$, was obtained in a poor yield of 17%; in addition, MS/MS studies showed clean fragmentation of the molecular ion to a moiety of formula $C_{13}H_{16}NO_5S$. These findings suggested a product formally arising from oxidative dimerisation of either the thioisomünchone **26** or the expected thiazolidinone **27**. ^{1}H NMR spectroscopy not only failed to distinguish between the two alternatives, but in fact showed the presence of at least two components in a variable ratio (5 : 2 initially, varying after further handling). A single-crystal X-ray structure determination was required to elucidate the structure, which proved to be as shown in **28**, *i.e.*, the symmetrical *meso*-dimer derived from thiazolidinone **27** by oxidative coupling at C-2. Although the crystal structure (Fig. 1) indicated a centrosymmetric molecule with a completed staggered orientation about the C-2–C-2′ bond in the solid state, restricted rotation between alternative conformations in solution would account for the observation of different species by ^{1}H NMR spectroscopy. The mechanism by which the dimerisation occurs under the reaction conditions is open to speculation.

Experimental

All solvents used for reactions and chromatography were distilled before use. Tetrahydrofuran (THF) and diethyl ether were distilled from Na–benzophenone, dichloromethane, acetonitrile and triethylamine from CaH_2, and benzene and toluene from Na. Commercially available chemicals were used as received. Melting points, recorded on a Reichert hot-stage microscope apparatus, are uncorrected. TLC was performed on aluminium-backed Alugram Sil G/UV_{254} plates pre-coated with 0.25 mm silica gel 60. Column chromatography was carried out on silica gel 60, particle size 0.063–0.200 mm (conventional columns) or Whatman Partisil Prep 40, particle size 0.040–0.063 mm (flash columns). FTIR spectra were recorded on Bruker Vector 22 or Bruker IFS 25 spectrometers. NMR spectra were recorded on a Bruker AC-200 spectrometer (200.13 MHz for ^{1}H, 50.32 MHz for ^{13}C) or a Bruker DRX 400 (400.132 MHz for ^{1}H, 100.625 MHz for ^{13}C). $CDCl_3$ was used as solvent and TMS as internal standard. DEPT and CH-correlated spectra were routinely used for assignment of signals. *J* Values are given in Hz. High-resolution mass spectra were recorded at 70 eV on a VG 70 SEQ mass spectrometer with a MASPEC II data system.

Ethyl 2-oxo-3-phenylpiperidine-3-carboxylate 8

A solution of diethyl 2-(2-cyanoethyl)-2-phenylmalonate[5,6] **6** (1.002 g, 3.46 mmol) in absolute ethanol (20 cm^3) was placed in a stainless steel autoclave. Raney nickel[24] (W-2 activity, 2.0 g), washed with absolute ethanol, was suspended in the solution.

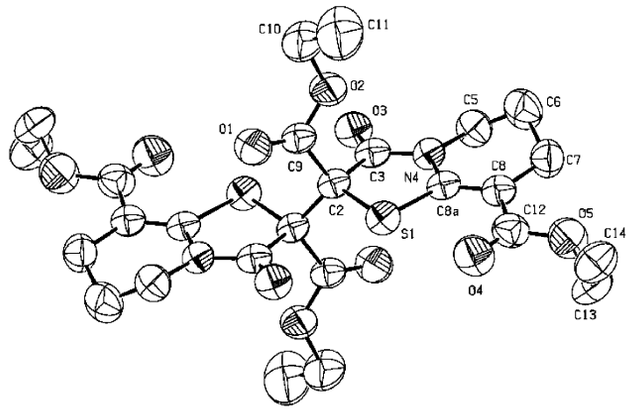


Fig. 1 ORTEP diagram of **28**. Thermal ellipsoids are at 50% probability. Hydrogen atoms have been omitted for clarity.

The autoclave was purged four times with H_2 gas (1 atm), and then sealed under H_2 (5 atm) for 18 h at rt. The opaque white suspension that resulted was filtered through a bed of Celite, and the filtered solids were washed with further portions of ethanol. The solution containing the amino diester was boiled under reflux for 24 h. Solvent was removed *in vacuo* to yield a clear oil that gradually crystallised on standing, or more rapidly on the addition of acetone. Purification by column chromatography on silica gel (EtOAc–hexane 1 : 5) yielded *ethyl 2-oxo-3-phenylpiperidine-3-carboxylate* **8** (695 mg, 81%) as colourless needles, mp 167–168.5 °C (from EtOAc–hexane) (lit.,[14] 142–143 °C from ethanol); R_f 0.25 (EtOAc–hexane 1 : 2); ν_{max}(KBr)/cm^{-1} 1724 (s, ester C=O), 1663 (s, amide C=O), 1028 (s) and 845 (s); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.40–7.23 (5H, m, Ar-H), 6.36 (variable position; 1H, br s, NH), 4.26 (2H, qd, *J* 7.1 and *ca*. 0.6, OCH_2CH_3), 3.51–3.29 (2H, m, NCH_2), 2.70 (1H, ddd, *J* 13.6, 10.2 and 3.5, CH_aH_bCPh), 2.34 (1H, ddd, *J* 13.6, 6.9 and 3.3, CH_aH_bCPh), 1.85–1.54 (2H, m, NCH_2CH_2) and 1.26 (3H, t, *J* 7.1, OCH_2CH_3); δ_C (100 MHz; $CDCl_3$) 171.59 (lactam C=O), 169.76 (ester C=O), 138.73 (arom C-1), 128.26 and 127.84 (arom C-2/C-6, C-3/C-5), 127.27 (arom C-4), 61.87 (OCH_2CH_3), 60.53 (CPh), 42.38 (NCH_2), 32.52 (CH_2CPh), 18.54 (NCH_2CH_2) and 14.00 (OCH_2CH_3). The spectroscopic data agree well with those reported for the compound prepared by a different method.[5]

3-Phenylpyrrolidin-2-one 9

Hydrogenation (6 atm, rt, 96 h) of diethyl 2-(cyanomethyl)-2-phenylmalonate[5] **5** (1.004 g, 3.65 mmol) in absolute ethanol (30 cm^3) over Raney nickel (2.0 g) as described above yielded crude ethyl 2-oxo-3-phenylpyrrolidine-3-carboxylate **7** as a white solid. This was immediately added to aq. NaOH solution (1 M, 25 cm^3) and boiled for 45 min in a preheated oil bath. The pH was adjusted to <7 with concd. HCl, which brought about rapid effervescence. The mixture was left to boil for a further 30 min. After cooling, the organic components were extracted with CH_2Cl_2 (3 × 20 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to yield *3-phenylpyrrolidin-2-one* **9** (261 mg, 45%) as a white solid, mp 88–89 (from EtOAc–hexane) [lit.,[25] 84–85 °C for racemate; lit.,[26] 104–105 °C for (3*R*) and (3*S*) enantiomers]; R_f 0.15 (EtOAc–hexane 3 : 10); ν_{max}(film)/cm^{-1} 3201 (m, br, NH), 3090 (m), 2985 (w), 2880 (w), 1694 (s, C=O), 766 (s) and 701 (s); δ_H (200 MHz; $CDCl_3$; Me_4Si) *ca*. 8.0 (1H, br s, NH), 7.47–7.20 (5H, m, Ar-H), 3.62 (1H, t, *J* 9.1, PhC*H*), 3.48–3.39 (2H, m, NCH_2), 2.58 (1H, dddd, *J* 13.0, 8.9, 6.5 and 4.1, CH_aH_bCHPh) and 2.22 (1H, dq, *J* 13.0 and 8.5, CH_aH_bCHPh); δ_C (50 MHz; $CDCl_3$) 179.04 (C=O), 139.37 (arom C-1), 128.71 and 127.96 (arom C-2/C-6, C-3/C-5), 127.01 (arom C-4), 47.59 (CHPh), 40.60 (CH_2N) and 30.67 (CH_2CHPh). Spectroscopic data are in broad agreement with those reported for the two enantiomers of **9**, prepared by a different method.[26]

3-Phenylpiperidin-2-one 10

A suspension of ethyl 2-oxo-3-phenylpiperidine-3-carboxylate **8** (106 mg, 0.43 mmol) in aq. KOH solution (2 M, 10 cm^3) was warmed to 90 °C. The solid gradually dissolved, after which the homogeneous solution was boiled for 30 min. Conc. HCl (32%) was added dropwise to the hot murky white mixture, resulting in violent effervescence. The clear acidified solution was heated for a further 30 min, cooled to rt, and extracted with EtOAc (2×20 cm^3) and CH_2Cl_2 (2×20 cm^3). The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo* to yield *3-phenylpiperidin-2-one* **10** (63 mg, 84%) as a chromatographically pure white solid, mp 166–168 °C (from ethanol) [lit.,[14] 170–170.5 °C (from acetone); lit.,[27] 171–172 °C (from toluene–hexane)]. The same product could be obtained in three steps and 63% overall yield from diethyl 2-(2-cyanoethyl)-2-phenylmalonate[5,6] **6** by sequential application of the procedures described above without purifying the intermediates. R_f 0.3 (EtOAc); ν_{max}(KBr)/cm^{-1} 3196 (s, br, NH), 3031 (m), 2938 and 2867 (s), 1665 (s, br, C=O), 1490 (s), 1414 (s), 850 (m), 755 (s) and 702 (s); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.56 (variable position, 1H, br s, NH), 7.33–7.28 (2H, m, Ar-H), 7.25–7.20 (3H, m, Ar-H), 3.62 (1H, dd, *J* 8.2 and 6.3, C*H*Ph), 3.36–3.30 (2H, m, NCH_2), 2.18–2.10 (1H, m, C$H_a$$H_b$CHPh), 1.93–1.80 (2H, m, CH_aH_bCHPh and $NCH_2CH_aH_b$) and 1.77–1.70 (1H, m, $NCH_2CH_aH_b$); δ_C (100 MHz; $CDCl_3$) 173.32 (*C*=O), 141.30 (arom C-1), 128.35 and 128.14 (arom C-2/C-6, C-3/C-5), 126.46 (arom C-4), 48.12 (*C*HPh), 42.34 (N*C*H_2), 30.46 (*C*H_2CHPh) and 20.44 (NCH_2CH_2). The spectroscopic data agree well with those reported for the compound prepared by a different method.[27]

3-Phenylpyrrolidine-2-thione 3

3-Phenylpyrrolidin-2-one **9** (151 mg, 0.93 mmol) was dissolved in toluene (20 cm^3) in a flame-dried, nitrogen-purged flask. Lawesson's reagent (0.23 g, 0.56 mmol, 0.6 eq.) was added to the clear solution, and the heterogeneous mixture was heated under reflux in a nitrogen atmosphere for 18 h. The orange–brown solution was then evaporated *in vacuo*, and the residue was purified by column chromatography on silica gel (hexane–CH_2Cl_2 1 : 5 to remove the Lawesson's reagent by-products, then EtOAc–hexane 1 : 2) to afford *3-phenylpyrrolidine-2-thione* **3** (94 mg, 57%) as a white solid, mp 174–175.5 °C (from EtOAc–hexane); R_f 0.45 (EtOAc–hexane 1 : 2); ν_{max}(KBr)/cm^{-1} 3131 (w, NH), 3028 (w), 1534 (s, C=S), 1460 (m), 1298 (m), 1145 (m) and 770 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.77 (1H, br s, NH), 7.42–7.20 (5H, m, Ar-H), 4.05 (1H, t, *J* 8.3, PhC*H*), 3.75–3.63 (2H, m, NCH_2), 2.70 (1H, dddd, *J* 12.9, 8.9, 7.1 and 5.3, C$H_a$$H_b$CHPh) and 2.29 (1H, dq, *J* 12.9 and 7.8, CH_aH_bCHPh); δ_C (50 MHz; $CDCl_3$) 208.20 (*C*=S), 140.64 (arom C-1), 128.69 and 128.12 (arom C-2/C-6, C-3/C-5), 127.30 (arom C-4), 58.86 (*C*HPh), 47.75 (*C*H_2N) and 32.57 (*C*H_2CHPh); *m*/*z* (EI) 178 (13), 177 (100%, M^+), 176 (13), 134 (5, PhCH=C=S), 118 (48), 117 (79), 115 (14) and 91 (22) (Found: M^+, 177.0612. $C_{10}H_{11}NS$ requires 177.0612).

3-Phenylpiperidine-2-thione 4

Lawesson's reagent (290 mg, 0.72 mmol, 0.7 eq.) was added to a solution of 3-phenylpiperidin-2-one **8** (178 mg, 1.01 mmol) in toluene (15 cm^3) in a flame-dried, nitrogen-purged flask, and the mixture was heated under reflux for 24 h. The solvent was evaporated *in vacuo* to yield an orange viscous oil. Purification by column chromatography on silica gel (hexane–CH_2Cl_2 1 : 5) yielded *3-phenylpiperidine-2-thione* **4** (150 mg, 78%) as a pale beige solid, mp 155–156 °C (from EtOAc–hexane) (lit.,[28] 157–158 °C) (Found: C, 69.00; H, 6.83; N, 7.33. $C_{11}H_{13}NS$ requires C, 69.07; H, 6.85; N, 7.32%); R_f 0.5 (EtOAc–hexane 1 : 2); ν_{max}(KBr)/cm^{-1} 3161 (s, br, NH), 3072 (m), 2938 and 2855 (s), 1561 (s, br, C=S), 1355 (m), 1318 (m), 1215 (m), 1125 (s), 762 (m) and 699 (s); δ_H (200 MHz; $CDCl_3$; Me_4Si) *ca*. 9.09 (variable position, 1H, br s, N–H), 7.38–7.20 (5H, m, Ar-H), 4.14 (1H, t, *J* 5.6, C*H*Ph), 3.44 (2H, br t, *J ca.*. 7.3, NCH_2), 2.14 (1H, *ca.* dddd, *J ca.* 13.1, 9.4, 9.3 and 3.7, C$H_a$$H_b$CHPh) and 1.95–1.70 (3H, m, NCH_2CH_2 and CH_aH_bCHPh); δ_C (100 MHz; $CDCl_3$) 204.68 (*C*=S), 143.01 (arom C-1), 128.47 and 128.17 (arom C-2/C-6, C-3/C-5), 126.75 (arom C-4), 53.54 (*C*HPh), 45.11 (N*C*H_2), 29.11 (*C*H_2CHPh) and 18.05 (NCH_2CH_2); *m*/*z* (EI) 193 (5, ^{34}S-M^+), 192 (14), 191 (100, ^{32}S-M^+), 190 (35), 158 (20), 134 (10), 117 (10), 104 (35), 103 (12) and 91 (27) (Found: M^+, 191.0755. $C_{11}H_{13}NS$ requires 191.0769).

Diethyl 2-(3-phenylpyrrolidin-2-ylidene)malonate 1

3-Phenylpyrrolidine-2-thione **3** (42 mg, 0.25 mmol) was dissolved in CH_2Cl_2 (1 cm^3) in a flame-dried, nitrogen-purged flask. Diethyl bromomalonate (78 mg, 0.33 mmol) was added, and the orange solution was stirred for 24 h at rt. The mixture was treated with saturated aq. $KHCO_3$ solution (5 cm^3), and the organic components were extracted with CH_2Cl_2 (3×10 cm^3). The extracts were dried (Na_2SO_4), filtered and evaporated *in vacuo* to yield the thioimidate **11** as an orange oil. This was heated at 60 °C for 35 min, and the resulting brown oil was purified by column chromatography on silica gel (EtOAc–hexane 3 : 10). *Diethyl 2-(3-phenylpyrrolidin-2-ylidene)malonate* **1** was obtained as an orange oil (65 mg, 84%); R_f 0.4 (EtOAc–hexane 3 : 10); ν_{max}(film)/cm^{-1} 3317 (m, NH), 2981 (m), 2896 (m), 1697 and 1647 (s, C=O), 1574 (s, C=C), 1434 (m), 1372 (m), 1244 (s), 1082 (s) and 764 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 9.64 (1H, br s, NH), 7.30–7.10 (5H, m, Ar-H), 4.82 (1H, dd, *J* 9.2 and 3.4, PhC*H*), 4.19 (2H, dd, *J* 13.8 and 6.8, NCH_2), 3.86–3.74 (2H, m, OC$H_2$$CH_3$), 3.74–3.57 (2H, m, OC$H_2$$CH_3$), 2.50 (1H, dq, *J* 12.7 and 8.8, C$H_a$$H_b$CHPh), 1.96 (1H, dq, *J* 12.7 and 3.5, CH_aH_bCHPh), 1.27 (3H, t, *J* 7.0, OCH_2CH_3) and 0.99 (3H, t, *J* 7.0, OCH_2CH_3); δ_C (100 MHz; $CDCl_3$) 172.57 (N*C*=C), 169.65 and 166.91 ($2 \times$ *C*=O), 141.31 (arom C-1), 128.39 and 126.90 (arom C-2/C-6, C-3/C-5), 126.41 (arom C-4), 88.47 (NC=*C*), 59.49 and 59.38 ($2 \times$ O*C*$H_2$$CH_3$), 49.96 (*C*HPh), 45.74 (N*C*H_2), 32.36 (*C*H_2CHPh), 14.18 and 13.79 ($2 \times$ OCH_2CH_3); *m*/*z* (EI) 303 (77%, M^+), 258 (69), 257 (100), 231 (23), 212 (26), 211 (55), 185 (31), 161 (44), 159 (25), 118 (75), 117 (75) and 91 (32) (Found: M^+, 303.1480, $C_{17}H_{21}NO_4$ requires 303.1471).

Ethyl 3-oxo-8-phenyl-2,3,6,7-tetrahydro-5*H*-[1,3]thiazolo[3,2-*a*]-pyridine-2-carboxylate 13

3-Phenylpiperidine-2-thione **4** (203 mg, 1.06 mmol) and diethyl bromomalonate (305 mg, 1.28 mmol) were stirred in CH_2Cl_2 solution (7 cm^3) in a flame-dried, nitrogen-purged flask at rt for 18 h. The solvent was gradually evaporated, leaving an orange oil. This was dissolved in CH_2Cl_2 (10 cm^3) and added to saturated aq. K_2CO_3 solution (10 cm^3), resulting in vigorous effervescence. The mixture was extracted with CH_2Cl_2 (3×10 cm^3), and the combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to yield the thioimidate **12** as an orange oil. This was heated neat in an oil bath preheated to *ca*. 75 °C for 90 min. Chromatographic purification of the crude product on silica gel (EtOAc–hexane 1 : 5–1 : 2) yielded *ethyl 3-oxo-8-phenyl-2,3,6,7-tetrahydro-5H-[1,3]thiazolo[3,2-a]pyridine-2-carboxylate* **13** (213 mg, 66%) as a yellow oil. (If the final heating was omitted, product **13** was obtained more slowly in 70% yield.) R_f 0.25 (EtOAc–hexane 1 : 5); ν_{max}(film)/cm^{-1} 3017 (m), 2950 and 2869 (m), 1743 (s, br, ester C=O), 1695 (s, br, amide C=O), 1633 (s), 1396 (m), 1298 (m), 1159 (m) and 1031 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.36–7.21 (5H, m, Ar-H), 4.59 (1H, s, COC*H*CO_2Et), 4.23 (2H, q, *J* 7.1, OC$H_2$$CH_3$), 3.84–3.78 and 3.73–3.67 ($2 \times$ 1H, $2 \times$ m, NCH_2), 2.58 [2H, t, *J* 6.1, =C(Ar)CH_2], 2.04 (2H, quintet, *J* 6.0, NCH_2CH_2) and 1.28 (3H, t, *J* 7.1, OCH_2CH_3); δ_C (100 MHz; $CDCl_3$) 167.34 and 165.97 ($2 \times$ *C*=O), 139.08 (arom C-1), 128.42 and 127.22

(arom C-2/C-6, C-3/C-5), 127.37 (N*C*=CAr), 126.94 (arom C-4), 112.40 (NC=*C*Ar), 62.47 (O*C*H_2CH$_3$), 48.53 (CO*C*H-CO_2Et), 41.98 (N*C*H_2), 28.40 [*C*H_2C(Ar)=], 20.71 (NCH$_2$*C*H_2) and 13.80 (OCH$_2$*C*H$_3$); *m*/*z* (EI) 305 (7%, ^{34}S-M$^+$), 304 (19), 303 (100, ^{32}S-M$^+$), 246 (15), 231 (33), 230 (98, M$^+$ − $CO_2C_2H_5$), 131 (14), 129 (14), 103 (10) and 91 (10) (Found: M$^+$, 303.0939. $C_{16}H_{17}NO_3S$ requires 303.0929).

Diethyl 2-piperidin-2-ylidenemalonate 14

A solution of piperidine-2-thione[29] (212 mg, 1.84 mmol) and diethyl bromomalonate[8] (529 mg, 2.21 mmol) in CH_2Cl_2 (10 cm^3) was stirred at ambient temperature over 18 h, and the solvent was allowed to evaporate during this time. The resulting white solid residue was dissolved in CH_2Cl_2 (25 cm^3). The organic phase was washed with saturated aq. $KHCO_3$ solution (25 cm^3), and the aqueous phase was back-extracted with CH_2Cl_2 (2 × 25 cm^3). The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo*. During evaporation, a fine yellow precipitate of sulfur began to form; the viscous orange residue formed after solvent removal was heated at 60 °C for 1.5 h to complete the extrusion of sulfur. Purification by column chromatography on silica gel (EtOAc–hexane 1 : 5–1 : 2) afforded *diethyl 2-piperidin-2-ylidenemalonate* **14** (403 mg, 91%) as a yellow oil; R_f 0.7 (EtOAc–hexane 1 : 2); ν_{max}(film)/cm^{-1} 3250 and 3144 (w, br, NH), 2980 and 2870 (m), 1699, 1644 and 1600 (s, C=O, C=C), 1279 (s), 1226 (s) and 1071 (s); δ_H (200 MHz; $CDCl_3$; Me_4Si) 10.11 (1H, br s, NH), 4.24–4.08 (4H, m, 2 × OC*H*$_2$CH$_3$), 3.37 (2H, m, NC*H*$_2$), 2.66 (2H, t, *J* 6.3, NCC*H*$_2$), 1.85–1.65 [4H, m, NCH$_2$(C*H*$_2$)$_2$], 1.29 and 1.26 (6H, overlapping t, *J* 6.6, 2 × OCH$_2$C*H*$_3$); δ_C (50 MHz; $CDCl_3$) 168.70 (N*C*=C), 165.50 (2 × *C*=O), 89.59 (NC=*C*), 59.97 and 59.07 (2 × O*C*H$_2$CH$_3$), 41.39 (N*C*H$_2$), 27.01 (*C*H$_2$C=), 21.60 (NCH$_2$*C*H$_2$), 19.16 (*C*H$_2$CH$_2$C=), 14.28 and 14.15 (2 × OCH$_2$-*C*H$_3$); *m*/*z* (EI) 241 (52, M$^+$), 196 (96, M$^+$ − OC_2H_5), 195 (100), 169 (44), 168 (33), 150 (32), 124 (23), 123 (100), 97 (55) and 82 (35) (Found: M$^+$, 241.1314. $C_{12}H_{19}NO_4$ requires 241.1303).

Ethyl 3-phenyl-2-thioxopiperidine-3-carboxylate 15

Crude ethyl 3-phenyl-2-oxopiperidine-3-carboxylate **8**, prepared as described above in three steps from diethyl phenylmalonate (5.01 g, 18.8 mmol) and acrylonitrile (1.24 cm^3, 18.8 mmol), was dissolved in toluene (75 cm^3) in a flame-dried, nitrogen-purged flask containing Lawesson's reagent (5.32 g, 13.1 mmol, 0.7 eq.). The brown solution was heated under reflux in a nitrogen atmosphere for 18 h. Evaporation *in vacuo* yielded an orange–brown malodorous oil that was purified by column chromatography on silica gel [firstly with CH_2Cl_2–hexane mixtures (7 : 10–4 : 5) to remove Lawesson's reagent by-products, followed by elution with EtOAc–hexane 1 : 2] to give *ethyl 3-phenyl-2-thioxopiperidine-3-carboxylate* **15** (1.357 g, 27% over 4 steps) as a pale yellow solid, mp 154–155 °C (from EtOAc–hexane) (Found: C, 63.40; H, 6.52; N, 5.31. $C_{14}H_{17}NO_2S$ requires C, 63.85; H, 6.51; N, 5.32%); R_f 0.65 (EtOAc–hexane 1 : 2); ν_{max}(KBr)/cm^{-1} 3439 (w, NH), 3188 (s), 1738 (s, br, C=O), 1575 (s, C=S), 1253 (m), 1031 (m), 935 (m) and 855 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 9.39 (1H, br s, NH), 7.41–7.25 (5H, m, Ar-H), 4.26 (2H, q, *J* 7.1, OC*H*$_2$-CH$_3$), 3.42–3.34 (1H, m, NC*H*$_a$H$_b$), 3.25 (1H, ddd, *J* 13.8, 6.9 and 3.4, NCH$_a$*H*$_b$), 2.68 (1H, ddd, *J* 13.6, 12.4 and 4.1, ArC-C*H*$_a$H$_b$), 2.36 (1H, dt, *J* 13.6 and 4.4, ArCC*H*$_a$H$_b$), 1.80–1.70 and 1.55–1.42 (2 × 1H, 2 × m, NCH$_2$C*H*$_2$) and 1.29 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 200.97 (*C*=S), 171.56 (*C*=O), 139.52 (arom C-1), 128.14 and 127.94 (arom C-2/C-6, C-3/C-5), 127.12 (arom C-4), 64.45 (*C*Ph), 61.86 (O*C*H$_2$CH$_3$), 44.27 (N*C*H$_2$), 31.50 (*C*H$_2$CPh), 16.55 (NCH$_2$*C*H$_2$) and 13.83 (OCH$_2$*C*H$_3$); *m*/*z* (EI) 265 (6, ^{34}S-M$^+$), 264 (17), 263 (100, ^{32}S-M$^+$), 234 (13), 191 (26), 190 (82), 189 (29), 188 (20), 162 (44), 134 (11), 104 (10), 103 (24), 91 (15) and 77 (13) (Found: M$^+$, 263.0978. $C_{14}H_{17}NO_2S$ requires 263.0980).

2,8-Bis(ethoxycarbonyl)-8-phenyl-5,6,7,8-tetrahydro[1,3]-thiazolo[3,2-*a*]pyridin-4-ium-3-olate 16

To a solution of ethyl 3-phenyl-2-thioxopiperidine-3-carboxylate **15** (200 mg, 0.76 mmol) in CH_2Cl_2 (2 cm^3) was added diethyl bromomalonate (218 mg, 0.91 mmol), and the yellow solution was left stirring for 18 h. A viscous orange oil was formed. This was suspended in CH_2Cl_2 (20 cm^3), and the mixture was added to aq. saturated K_2CO_3 (25 cm^3). After effervescence had subsided, the mixture was extracted with CH_2Cl_2 (3 × 20 cm^3), the combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to yield an orange oil. This was heated neat for 10 min in an oil bath preheated to *ca*. 60 °C. A yellow precipitate formed rapidly. Chromatographic separation of the crude product on silica gel with ethyl acetate as eluant yielded *2,8-bis(ethoxycarbonyl)-8-phenyl-5,6,7,8-tetrahydro-[1,3]thiazolo[3,2-a]pyridin-4-ium-3-olate* **16** (236 mg, 83%) as a yellow oil that solidified on standing; mp 174–175 °C (from CH_2Cl_2) (Found: C, 60.82; H, 5.58; N, 3.75. $C_{19}H_{21}NO_5S$ requires C, 60.78; H, 5.64; N, 3.73%); R_f 0.4 (MeOH–EtOAc 1 : 20); ν_{max}(KBr)/cm^{-1} 2986 and 2941 (s), 1743 (s, br, C=O), 1637 (s) and 1143 (s); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.40–7.28 (3H, m Ar-H), 7.11–7.09 (2H, m, Ar-H), 4.33 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 4.27 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 3.97 (2H, br t, *J* *ca*. 6.4, NC*H*$_2$), 2.67 (1H, *ca*. ddd, *J* *ca*. 13.6, 6.0 and 5.0, C*H*$_a$H$_b$CPh), 2.46 (1H, *ca*. ddd, *J* *ca*. 13.6, 6.2 and 4.9, CH$_a$*H*$_b$CPh), 2.02 (2H, *ca*. quintet, *J* *ca*. 6.3, NCH$_2$C*H*$_2$), 1.33 and 1.31 (6H, overlapping t, *J* 7.1, OCH$_2$C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 169.60 (mesoionic C-8a), 162.84 and 162.53 (*C*=O), 160.82 (mesoionic C-3), 139.19 (arom C-1), 129.17 and 126.29 (arom C-2/C-6, C-3/C-5), 128.83 (arom C-4), 89.25 (mesoionic *C*-CO_2Et), 63.22 and 60.09 (O*C*H$_2$CH$_3$), 56.64 (*C*Ph), 44.46 (N*C*H$_2$), 30.47 (*C*H$_2$CPh), 17.63 (NCH$_2$*C*H$_2$), 14.48 and 13.84 (OCH$_2$*C*H$_3$); *m*/*z* (EI) 377 (8%, ^{34}S-M$^+$), 376 (23), 375 (100, ^{32}S-M$^+$), 330 (15), 304 (14), 303 (54), 302 (88), 257 (28), 230 (62), 131 (16), 129 (19) and 103 (14) (Found: M$^+$, 375.1140. $C_{19}H_{21}NO_5S$ requires 375.1130).

Ethyl 4-cyano-2,2-diphenylbutanoate 17

(This compound has previously been reported only in a patent.[30]) Ethyl 2,2-diphenylacetate (911 mg, 3.79 mmol) was added to a stirred suspension of sodium hydride (60% in oil, 183 mg, 4.58 mmol) in dry THF (50 cm^3) at 0 °C, which resulted in vigorous gas evolution. The murky suspension was stirred for 1 h. Acrylonitrile (0.30 cm^3, 4.55 mmol) was added, and the reaction mixture was left for 18 h at ambient temperature. Saturated aq. NH_4Cl solution (30 cm^3) was added to the yellow reaction mixture, which was then extracted with CH_2Cl_2 (3 × 20 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to yield a yellow oil. Purification by column chromatography on silica gel (EtOAc–hexane 1 : 20–3 : 20) yielded *ethyl 4-cyano-2,2-diphenylbutanoate* **17** (790 mg, 71%) as a clear oil; R_f 0.45 (EtOAc–hexane 3 : 20); ν_{max}(film)/cm^{-1} 3060 and 3030 (m), 2982 and 2938 (m), 2248 (m, C≡N), 1729 (s, C=O), 1222 (br, s) and 701 (s); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.36–7.20 (5H, m, Ar-H), 4.17 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 2.51 (2H, *AA′*XX′ system, *J* not determined, C*H*$_2$C≡N), 2.13 (2H, AA′*XX′* system, *J* not determined, C*H*$_2$CH$_2$C≡N) and 1.16 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$); δ_C (50 MHz; $CDCl_3$) 172.84 (*C*=O), 141.11 (arom C-1), 128.44, 128.20 and 127.33 (aryl C), 119.47 (*C*≡N), 103.92 (*C*Ph$_2$), 61.52 (O*C*H$_2$CH$_3$), 34.22 (*C*H$_2$C≡N), 13.73 and 13.68 (OCH$_2$*C*H$_3$ and *C*H$_2$CH$_2$C≡N); *m*/*z* (EI) 293 (3, M$^+$), 221 (19), 220 (100), 180 (18), 179 (17), 178 (10), 165 (15) and 115 (7) (Found: M$^+$, 293.1411. $C_{19}H_{19}NO_2$ requires 293.1416).

Diethyl 2-(2-cyanoethyl)malonate 18

This compound was prepared by the method of Albertson and Fillman[31] from diethyl malonate (2.84 cm^3, 18.7 mmol),

ethanolic sodium ethoxide [prepared *in situ* from sodium metal (22 mg, 0.94 mmol) and absolute ethanol (10 cm^3)] and acrylonitrile (0.62 cm^3, 9.37 mmol). Purification by column chromatography on silica gel (EtOAc–hexane 1 : 20–1 : 2) yielded *diethyl 2-(2-cyanoethyl)malonate* **18** (1.455 g, 73%) as a clear oil; R_f 0.1 (EtOAc–hexane 1 : 20); ν_{max}(film)/cm^{-1} 2986 (s), 2249 (m, C≡N), 1730 (s, br, C=O), 1449 (m), 1372 (m), 1158 (m), 1097 (m), 1048 (m), 1024 (m) and 862 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.24 (4H, q, *J* 7.2, 2 × OC$H_2$$CH_3$), 3.51 (1H, t, *J* 7.2, $(CO)_2CH$), 2.51 (2H, t, *J* 7.2, CH_2C≡N), 2.24 (2H, q, *J* 7.2, C$H_2$$CH_2$C≡N) and 1.29 (6 H, t, *J* 7.2, 2 × OCH_2CH_3); δ_C (50 MHz; $CDCl_3$) 167.63 (*C*=O), 118.18 (*C*≡N), 61.25 (2 × O*C*$H_2$$CH_3$), 49.70 (*C*H), 23.96 (*C*H_2C≡N), 14.46 (*C*H_2-CH_2C≡N) and 13.42 (2 × OCH_2CH_3). The IR and ^{1}H-NMR spectroscopic data compared well with those reported for the compound prepared by another method.[32]

Triethyl 3-cyanopropane-1,1,1-tricarboxylate 19

This compound was prepared by the method of Skarżewski[33] from triethyl methanetricarboxylate (2.006 g, 8.64 mmol), acrylonitrile (0.63 cm^3, 9.47 mmol), tetrabutylammonium hydrogen sulfate (149 mg, 0.44 mmol) and potassium carbonate (358 mg, 2.59 mmol) in toluene (5 cm^3) at rt. Purification by column chromatography on silica gel (EtOAc–hexane 1 : 20) afforded *triethyl 3-cyanopropane-1,1,1-tricarboxylate* **19** (1.884 g, 77%) as a clear oil; R_f 0.15 (EtOAc–hexane 1 : 20); ν_{max}(film)/cm^{-1} 2986 and 2941 (m), 2250 (w, C≡N), 1737 (s, C=O), 1275 (m), 1219 (m) and 1083 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 4.28 (6H, q, *J* 7.1, 3 × OC$H_2$$CH_3$), 2.70 (2H, *AA′XX′* system, *J* not determined, CH_2C≡N), 2.51 (2H, AA′*XX′* system, *J* not determined, C$H_2$$CH_2$C≡N) and 1.30 (9H, t, *J* 7.2, 3 × OCH_2CH_3); δ_C (100 MHz; $CDCl_3$) 165.80 (*C*=O), 118.63 (*C*≡N), 64.00 [*C*H$(CO_2Et)_2$], 62.46 (3 × O*C*$H_2$$CH_3$), 28.54 (*C*$H_2$C≡N), 13.58 (3 × OCH_2CH_3) and 13.17 (*C*$H_2$$CH_2$C≡N).

3,3-Diphenylpiperidin-2-one 20

Hydrogenation (45 atm, 100 °C, 72 h) of ethyl 4-cyano-2,2-diphenylbutanoate **17** (601 mg, 2.05 mmol) in a mixture of methanol and conc. ammonia (1 : 1, 30 cm^3) over Raney nickel (1.20 g), as described above for compounds **8** and **9**, yielded spectroscopically pure *3,3-diphenylpiperidin-2-one* **20** (462 mg, 90%) as a white solid, mp 189.5–191 °C (from EtOAc–hexane) [lit.,[34] 189–190 °C (from EtOH)]; R_f 0.6 (EtOAc); ν_{max}(KBr)/cm^{-1} 3264 (m), 3197 (s), 3063 (m), 2965 (m), 2869 (m), 1668 (s, br, C=O), 1493 (s) and 843 (s); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.30–7.21 (10 H, m, Ar-H), 6.45 (1H, br s, NH), 3.36 (2H, br t, *J ca.* 5.8, NCH_2), 2.61–2.54 (2H, m, C$H_2$$CAr_2$) and 1.78–1.72 (2H, m, NCH_2CH_2); δ_C (50 MHz; $CDCl_3$) 174.12 (*C*=O), 143.85 (arom C-1), 128.54 and 128.00 (arom C-2/C-6, C-3/C-5), 126.62 (arom C-4), 56.20 (*C*Ph_2), 42.60 (NCH_2), 34.70 (*C*$H_2$$CAr_2$) and 18.91 ($NCH_2CH_2$). The spectroscopic data agree with those reported for the compound prepared by another method.[35]

Ethyl 2-oxopiperidine-3-carboxylate 21

Hydrogenation (5 atm, rt, 72 h) of diethyl 2-(2-cyanoethyl)malonate **18** (831 mg, 4.39 mmol) in absolute ethanol (30 cm^3) over Raney nickel (1.88 g), as described above for compounds **8** and **9**, yielded chromatographically pure *ethyl 2-oxopiperidine-3-carboxylate* **21** (664 mg, 88%) as a white solid, mp 72–73.5 °C (from EtOAc–hexane) [lit.,[31] >75 °C (from EtOH), lit.,[36] 78–79 °C (from benzene)]; R_f 0.3 (EtOAc); ν_{max}(film)/cm^{-1} 3240 (w, br, NH), 2947 (w), 1734 (s, ester C=O), 1665 (s, amide C=O), 1171 (m) and 1035 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.60 (1H, br s, NH), 4.21 (2H, q, *J* 7.1, O*C*H_2-CH_3), 3.40–3.26 and 3.37 (3H, superimposed m and t, *J* 7.3, COC*H*Ar and NCH_2), 2.20–2.00, 2.00–1.80 and 1.90–1.65 (4H, 3 × m, $NCH_2CH_2CH_2$) and 1.29 (3H, t, *J* 7.1, OCH_2-CH_3); δ_C (50 MHz; $CDCl_3$) 170.65 (lactam *C*=O), 168.17 (ester *C*=O), 61.03 (O*C*$H_2$$CH_3$), 48.30 (*C*H$CO_2$Et), 41.75 (NC$H_2$), 24.57 (*C*$H_2CHCO_2$Et), 20.03 ($NCH_2CH_2$) and 13.84 ($OCH_2CH_3$).

Diethyl 2-oxopiperidine-3,3-dicarboxylate 22

Hydrogenation (3 atm, rt, 72 h) of trimethyl 3-cyanopropane-1,1,1-tricarboxylate **19** (308 mg, 1.08 mmol) in absolute ethanol (10 cm^3) over Raney nickel (31 mg), as described above for compounds **8** and **9**, yielded an oil that was purified by column chromatography on silica gel (EtOAc–hexane 1 : 2) to give *diethyl 2-oxopiperidine-3,3-dicarboxylate* **22** (166 mg, 21%) as a clear yellow oil; R_f 0.4 (EtOAc–hexane 1 : 2); ν_{max}(film)/cm^{-1} 3345 (m, br, NH), 2982 and 2877 (m), 1733 (s, br, ester C=O), 1682 (s, amide C=O), 1259 (m), 1200 (m) and 1108 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.23 (1H, br s, NH), 4.28 (4H, q, *J* 7.1, O*C*$H_2$$CH_3$), 3.36 (2H, td, *J* 6.3 and 2.0, NCH_2), 2.47–2.42 (2H, m, $CH_2CH_2CH_2$), 1.83–1.70 (2H, m, NCH_2CH_2) and 1.30 (6H, t, *J* 7.1, 2 × OCH_2CH_3); δ_C (50 MHz; $CDCl_3$) 167.74 and 165.83 (3 × *C*=O), 63.02 [*C*$(CO_2Et)_2$], 62.02 (2 × O*C*$H_2$$CH_3$), 41.62 (NC$H_2$), 28.31 [*C*$H_2C(CO_2Et)_2$], 18.53 ($NCH_2CH_2$) and 13.71 (2 × OCH_2CH_3); *m/z* (EI) 244 (11%), 243 (61, M^+), 198 (28, $M^+ - OC_2H_5$), 173 (17), 170 (42, $M^+ - CO_2C_2H_5$), 152 (19), 141 (13), 127 (30), 125 (17), 124 (100) and 99 (15) (Found: M^+, 243.1112. $C_{11}H_{17}NO_5$ requires M^+, 243.1107).

3,3-Diphenylpiperidine-2-thione 23

Crushed phosphorus pentasulfide (240 mg, 1.1 mmol, 0.6 eq.) was added to a solution of 3,3-diphenylpiperidin-2-one **20** (458 mg, 1.82 mmol) in benzene (10 cm^3) in a flame-dried, nitrogen-purged flask. The flask was stoppered, and the mixture was sonicated in an ultrasound cleaning bath for 18 h. Since the reaction was incomplete, the mixture was then heated under reflux for 2 h to yield a homogeneous brown solution. The solution was evaporated *in vacuo*, and purification of the resulting viscous brown oil by column chromatography on silica gel (EtOAc–hexane 1 : 5–1 : 2) yielded *3,3-diphenylpiperidine-2-thione* **23** (290 mg, 60%) as a white solid, mp 176–178 °C (from EtOAc–hexane); R_f 0.65 (EtOAc–hexane 1 : 2); ν_{max}(KBr)/cm^{-1} 3260 (m), 3155 (m), 3057 (m), 2936 (m), 2876 (m), 1535 (m, C=S), 756 (s) and 700 (s); δ_H (400 MHz; $CDCl_3$; Me_4Si) 9.39 (1H, br s, NH), 7.33–7.24 (10H, m, Ar-H), 3.30 (2H, td, *J* 6.9 and 2.7, NCH_2), 2.65–2.60 (2H, m, C$H_2$$CAr_2$) and 1.77–1.70 (2H, m, NCH_2CH_2); δ_C (100 MHz; $CDCl_3$) 207.82 (*C*=S), 144.61 (arom C-1), 129.03 and 127.73 (arom C-2/C-6, C-3/C-5), 126.79 (arom C-4), 60.33 (*C*Ar_2), 44.27 (NCH_2), 33.41 (*C*$H_2$$CAr_2$) and 17.66 ($NCH_2CH_2$); *m/z* (EI) 268 (20), 267 (100, M^+), 266 (12), 250 (9), 201 (14), 179 (13), 178 (15), 167 (48), 165 (23) and 115 (10) (Found: M^+, 267.1076. $C_{17}H_{17}NS$ requires 267.1082).

Ethyl 2-thioxopiperidine-3-carboxylate 24

Phosphorus pentasulfide (490 mg, 2.2 mmol, 0.6 eq.) was added to a solution of ethyl 2-oxopiperidine-3-carboxylate **21** (633 mg, 3.69 mmol) in benzene (10 cm^3) in a flame-dried, nitrogen-purged flask. The flask was stoppered, and the mixture was sonicated in an ultrasound cleaning bath for 18 h. The resulting malodorous orange mixture was filtered, and the solids were washed with CH_2Cl_2 (2 × 10 cm^3) and EtOAc (2 × 10 cm^3). The combined organic phases were evaporated *in vacuo* to yield an orange oil that solidified on standing. Purification by column chromatography on silica gel (EtOAc–hexane 1 : 5–1 : 2) yielded *ethyl 2-thioxopiperidine-3-carboxylate* **24** (352 mg, 51%) as a yellow solid, mp 108–110 °C (from EtOAc–hexane) [lit.,[37] 113–114 °C (from ethanol)]; R_f 0.4 (EtOAc–hexane 1 : 2); ν_{max}(KBr)/cm^{-1} 3161 (s, v br, NH), 3082 (s), 1730 (s, C=O), 1568 (s, br, C=S), 1322 (m), 1221 (m) and 1022 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.94 (1H, br s, NH), 4.23 (2H, q, *J* 7.2, O*C*$H_2$$CH_3$), 3.83 (1H, t, *J* 6.0, C*H*C=S), 3.46–3.35 (2H, m, NCH_2), 2.18–1.95 and 1.95–1.75 (4H, 2 × m, $NCH_2CH_2CH_2$)

and 1.31 (3H, t, *J* 7.2, OCH_2CH_3); δ_C (50 MHz; $CDCl_3$) 197.83 (*C*=S), 170.85 (*C*=O), 61.54 (OCH_2CH_3), 54.05 (*C*HC=S), 44.69 (NCH_2), 24.05 (CH_2CHCS), 18.58 (NCH_2CH_2) and 14.04 (OCH_2CH_3).

2-(Ethoxycarbonyl)-8,8-diphenyl-5,6,7,8-tetrahydro[1,3]-thiazolo[3,2-*a*]pyridin-4-ium-3-olate 25

Diethyl bromomalonate (93 mg, 0.32 mmol) and 3,3-diphenylpiperidine-2-thione **23** (72 mg, 0.27 mmol) were dissolved in CH_2Cl_2 (2 cm^3) in a flame-dried, nitrogen-purged flask, and the solution was left at ambient temperature for 18 h. Evaporation of the deep orange solution *in vacuo* yielded a red solid, to which was added saturated aq. $KHCO_3$ solution (10 cm^3). The mixture was extracted with CH_2Cl_2 (3 × 10 cm^3), the extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to yield a beige solid. Purification by preparative thin-layer chromatography (EtOAc–hexane 1 : 2) yielded unreacted 3,3-diphenylpiperidine-2-thione **23** (29 mg, 40%) and *2-(ethoxycarbonyl)-8,8-diphenyl-5,6,7,8-tetrahydro[1,3]thiazolo[3,2-a]-pyridin-4-ium-3-olate* **25** (51 mg, 49%) as a yellow solid, mp 240–241 °C (from CH_2Cl_2) (Found: C, 69.34; H, 5.69; N, 3.58; S, 8.86. $C_{22}H_{21}NO_3S$ requires C, 69.63; H, 5.58; N, 3.69; S, 8.45%); R_f 0.25 (EtOAc–hexane 1 : 2); ν_{max}(KBr)/cm^{-1} 2972 (w), 1713 (s, C=O), 1645 (m), 1141 (m) and 745 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.35 (6H, br s, Ar-H), 7.05 (4H, br s, Ar-H), 4.26 (2H, br q, *J* 6.8, OCH_2CH_3), 3.95 (2H, br t, *J ca.* 6.5, NCH_2), 2.73 (2H, br s, CH_2CAr_2), 1.95 (2H, br s, NCH_2CH_2) and 1.30 (3H, br t, *J* 6.8, OCH_2CH_3); δ_C (50 MHz, $CDCl_3$) 169.29 (mesoionic C-8a), 163.16 (*C*=O), 160.98 (mesoionic C-3), 143.12 (arom C-1), 128.92 and 127.79 (arom C-2/C-6, C-3/C-5), 128.27 (arom C-4), 89.05 (mesoionic *C*-CO_2Et), 60.26 (OCH_2CH_3), 53.56 (CAr_2), 44.07 (NCH_2), 32.00 (CH_2CAr_2), 17.13 (NCH_2CH_2) and 14.58 (OCH_2CH_3); *m*/*z* (EI) 381 (8%, ^{34}S-M^+), 380 (26), 379 (100, ^{32}S-M^+), 334 (18, $M^+ - OCH_2CH_3$), 308 (22), 307 (96), 234 (39), 207 (10), 206 (52), 198 (17), 179 (13), 178 (18), 165 (22), 131 (13), 129 (11) and 91 (15) (Found: M^+, 379.1235. $C_{22}H_{21}NO_3S$ requires 379.1242. Found: $M^+ - CO_2C_2H_4$, 307.1034. $C_{19}H_{17}NOS$ requires 307.1031).

meso-Tetraethyl 3,3′-dioxo-6,7,6′,7′-tetrahydro-5*H*,5*H*′-2,2′-bi[[1,3]thiazolo[3,2-*a*]pyridinyl]-2,2′,8,8′-tetracarboxylate 28

A solution of diethyl bromomalonate (115 mg, 0.48 mmol) and ethyl 2-thioxopiperidine-3-carboxylate **24** (75 mg, 0.40 mmol) in CH_2Cl_2 (2 cm^3) was stirred at ambient temperature for 18 h. Evaporation of the resulting deep orange solution *in vacuo* yielded a red solid, to which was added saturated aq. $KHCO_3$ solution (10 cm^3). The mixture was extracted with CH_2Cl_2 (3 × 100 cm^3), and the extracts were dried ($MgSO_4$) and evaporated *in vacuo* to yield a yellow solid. Purification by preparative thin-layer chromatography on silica gel (EtOAc–hexane 1 : 2) yielded *meso-tetraethyl 3,3′-dioxo-6,7,6′,7′-tetrahydro-5H,5H′-2,2′-bi[[1,3]thiazolo[3,2-a]pyridinyl]-2,2′,8,8′-tetracarboxylate* **28** (20 mg, 17%) as a yellow solid, mp 252 °C decomp. (from acetone) (Found: C, 52.61; H, 5.65; N, 4.89; S, 10.76. $C_{26}H_{32}N_2O_{10}S_2$ requires C, 52.34; H, 5.41; N, 4.69; S, 10.75%); R_f 0.5 (EtOAc–hexane 1 : 2); ν_{max}(KBr)/cm^{-1} 2961 (w), 2931 (w), 2852 (w), 1738 (s, C=O), 1714 (s, C=O), 1675 (s, C=O), 1576 (s, br), 1270 (s), 1230 (m), 1195 (m) and 1128 (m); δ_H (400 and 200 MHz; $CDCl_3$; Me_4Si) 4.34–4.13 (4H, cluster of q, *J ca.* 7.1 Hz, OCH_2CH_3), 3.93–3.90 and 3.82–3.76 [1H (variable ratio), 2 × m, NCH_aH_b from two isomers], 3.64–3.60 and 3.53–3.47 [1H (variable ratio), 2 × *ca.* dd, *J ca.* 12.8, 9.0 and 3.6, NCH_aH_b from two isomers], 2.60–2.51 and 2.51–2.42 (2H, 2 × m, CH_2CCO_2Et), 2.15–1.95 and 1.95–1.80 (2 × 1H, 2 × m, NCH_2CH_2), 1.31, 1.24 and 1.19 (6H, cluster of t, *J ca.* 7.1, OCH_2CH_3); *m*/*z* (EI) 596 (14%, M^+), 299 (22), 298 (100), 226 (24) (Found: M^+, 596.1511, $C_{26}H_{32}N_2O_{10}S_2$ requires 596.1498. Found: $M^+/2$, 298.0745. $C_{13}H_{16}NO_5S$ requires 298.0749. Found: $M^+/2 - CO_2C_2H_4$, 226.0543. $C_{10}H_{12}NO_3S$ requires 226.0538).

Table 1 Selected bond lengths (Å) and bond angles (°) for *meso*-3,3′-dioxo-6,7,6′,7′-tetrahydro-5*H*,5*H*′-2,2′-bi[[1,3]thiazolo[3,2-*a*]pyridinyl]-2,2′,8,8′-tetracarboxylate **28**[a]

S(1)–C(2)	1.831(3)	C(2)–S(1)–C(8a)	91.66(15)
S(1)–C(8a)	1.756(3)	S(1)–C(2)–C(2)#2	112.0(3)
C(2)–C(2)#2	1.548(6)	S(1)–C(2)–C(3)	106.4(2)
C(2)–C(3)	1.543(4)	C(3)–C(2)–C(2)#2	111.8(3)
C(2)–C(9)	1.542(4)	C(2)–C(3)–N(4)	111.4(3)
C(3)–O(3)	1.209(4)	C(2)–C(3)–O(3)	123.1(3)
C(3)–N(4)	1.354(4)	N(4)–C(3)–O(3)	125.5(3)
N(4)–C(5)	1.466(4)	C(3)–N(4)–C(5)	121.4(3)
N(4)–C(8a)	1.378(4)	C(3)–N(4)–C(8a)	117.8(3)
C(5)–C(6)	1.489(5)	C(5)–N(4)–C(8a)	120.4(3)
C(6)–C(7)	1.514(5)	N(4)–C(5)–C(6)	109.2(3)
C(7)–C(8)	1.513(4)	C(5)–C(6)–C(7)	111.7(4)
C(8)–C(8a)	1.346(4)	C(6)–C(7)–C(8)	110.8(3)
C(8)–C(12)	1.460(5)	C(7)–C(8)–C(8a)	120.6(3)
C(9)–O(1)	1.179(4)	C(8)–C(8a)–N(4)	122.3(3)
C(12)–O(4)	1.210(4)	C(8)–C(8a)–S(1)	125.6(2)
		N(4)–C(8a)–S(1)	112.1(3)

[a] Equivalent position for C(2)#2: 2 − *x*, 1 − *y*, −*z*.

Crystal structure determination of 28

Single crystals of *meso*-3,3′-dioxo-6,7,6′,7′-tetrahydro-5*H*,5*H*′-2,2′-bi[[1,3]thiazolo[3,2-*a*]pyridinyl]-2,2′,8,8′-tetracarboxylate **28** were grown by slow crystallisation from acetone solution. Intensity data were collected on a small crystal (0.27 × 0.12 × 0.10 mm) on a Bruker SMART 1K CCD area detector diffractometer with graphite-monochromated Mo-Kα radiation (50 kV, 30 mA). The collection method involved ω-scans of width 0.3°. Data reduction was carried out with the program SAINT+,[38] and absorption corrections were made using the program SADABS.[39] The crystal structure was solved by direct methods using SHELXTL.[40] Non-H atoms were first refined isotropically, followed by anisotropic refinement by full-matrix least squares calculation based on F^2 using SHELXTL. Atoms C13 and C14 of the ethyl ester attached to C8 (see Fig. 1) were disordered; they were subsequently refined anisotropically over two positions with an occupancy of 0.63(2) for C13 and C14, and 0.37(2) for the alternative positions C13′ and C14′. (Only C13 and C14 are shown in Fig. 1.) All hydrogen atoms were positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using SHELXTL and PLATON.[41]

Crystal data.† Molecular formula $C_{26}H_{32}N_2O_{10}S_2$, $M = 596.66$; monoclinic; $a = 9.1807(19)$, $b = 11.696(2)$, $c = 13.880(3)$ Å; $\alpha = \gamma = 90°$, $\beta = 105.103(4)°$, $V = 1439.0(5)$ Å^3; $T = 293(2)$ K; space group $P2_1/n$ (no. 14); $Z = 2$; μ(Mo-Kα) = 0.243 mm^{-1}; 7624 reflections measured, 2528 unique ($R_{int} = 0.048$), which were used in all calculations. Refinement as described above with 203 parameters gave final *R* indices $R1 = 0.0516$ [$I > 2\sigma(I)$], $R1 = 0.1044$ and $wR2 = 0.1600$ (all data). Selected bond lengths and bond angles are shown in Table 1, and an ORTEP diagram of the structure is given in Fig. 1.

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† CCDC reference number 165356. See http://www.rsc.org/suppdata/p1/b1/b103560f/ for crystallographic files in .cif or other electronic format.

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