Synthesis of Bicyclic Pyridone and Dihydropyridone Analogues of β-Lactam Antibiotics[1]

Nigel K. Capps,[a] Gareth M. Davies,[b] David Loakes,[a] Richard W. McCabe[a] and Douglas W. Young*[,a]

[a] *School of Chemistry and Molecular Sciences, University of Sussex, Falmer, Brighton BN1 9QJ, UK*
[b] *ICI Pharmaceuticals, Mereside, Alderley Park, Macclesfield SK10 4TG, UK*

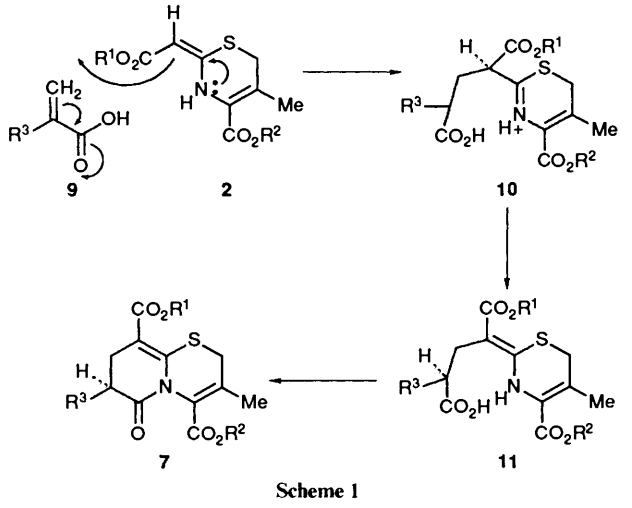
Condensation of the vinylogous urethanes **2**, **26**, **28** and **29** with acrylates, haloacrylates and propiolic acid has afforded easy access to bicyclic dihydropyridone and pyridone analogues of cephalosporins, carbapenams, penicillins and bisnorpenicillins. Synthesis of the pyridone is accompanied, in one instance, by an interesting cyclisation to the glutaconic anhydride **23** and significant differences in tautomeric behaviour have been found between the five-membered vinylogous urethanes **28** and **29** and their six-membered counterparts **2**.

The interest in non-β-lactam bicyclic compounds related to cephalosporins and penicillins as potential antibacterial compounds[2] and the potential of bicyclic pyrido[2,1-*b*]thiazines and related compounds as intermediates for the synthesis of strained tricyclic analogues of β-lactam antibiotics[3] has prompted us to investigate the use of vinylogous urethanes of general formula **1** in a one step synthesis of bicyclic compounds containing one of the rings present in β-lactam antibiotics.

The vinylogous urethane **2** contains a thiazine ring similar to that present in cephalosporin C. The dibenzyl ester **2** (R^1 = R^2 = $PhCH_2$) had already been prepared[4a] by reaction of the thioamide **3** (R^1 = $PhCH_2$) with freshly prepared benzyl 3-methyl-2-oxobut-3-enoate **4** (R^2 = $PhCH_2$)[4] and, although, in our hands, this led to intractable oils, reduction of the reported reaction time led to reasonable yields of the desired dihydrothiazine **2** (R^1 = R^2 = $PhCH_2$). The dihydrothiazines **2** (R^1 = R^2 = Et), **2** (R^1 = R^2 = Me), **2**(R^1 = $PhCH_2$, R^2 = Et) and **2** (R^1 = $PhCH_2$, R^2 = Me) were prepared in a similar manner. The ^1H and ^{13}C NMR spectra of the dihydrothiazines **2** indicated that only one of the two possible geometric isomers was present in each case. This was assumed to be the (*E*)-isomer shown, as it would be stabilized by hydrogen bonding between the NH group and the ester carbonyl group. This would not be possible in the alternative (*Z*)-isomer. In some instances, the olefinic and NH protons integrated as less than one proton in C^2HCl_3, presumably due to exchange *via* imine ⇌ enamine tautomerism.

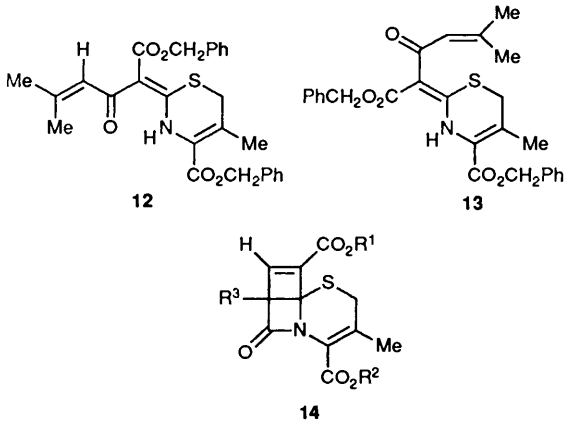
Interestingly, a by-product was obtained from the condensation of the benzyloxythioacetamide **3** (R^1 = $PhCH_2$) with methyl 3-methyl-2-oxobut-3-enoate **4** (R^2 = Me) in addition to the thiazine **2** (R^1 = $PhCH_2$, R^2 = Me). This had analytical and spectral data consistent with the bicyclic structure **6** which would be formed by annelation resulting from reaction of the first-formed thiazine **2** (R^1 = $PhCH_2$, R^2 = Me) with the keto ester **4** (R^2 = Me).

Having prepared the dihydrothiazines **2**, we were now in a position to examine the possibility of synthesising bicyclic compounds from them. The acid chloride of 2-phthalimidoacrylic acid[5] was, therefore, treated with the thiazine **2** (R^1 = R^2 = $PhCH_2$) to give a product, $C_{33}H_{26}N_2O_7S$, m.p. 112 °C, in 30% yield. The UV spectrum, λ_{max} 313 nm, showed a blue shift from that of the starting thiazine **2** (R^1 = R^2 = $PhCH_2$) (λ_{max} 336 nm) and the CH_2S and $PhCH_2$ protons, which had been singlets in the ^1H NMR spectrum of the starting thiazine **2** (R^1 = R^2 = $PhCH_2$) were AB systems in the ^1H NMR spectrum of the product. This indicated that an asymmetric centre had been created in the reaction. An additional ABX system at δ 3.09, 3.69 and 5.09 confirmed that ring closure had occurred. The product was assigned the structure **7** (R^1 = R^2 = $PhCH_2$, R^3 = phthalimido) rather than the alternative structure **8** which would not have been expected to have a much lower UV absorption than the starting thiazine and which would have been expected to show a ketonic carbonyl absorption to lower field in the ^{13}C NMR spectrum than the lowest field signal at 167 ppm. The yield of the condensation was improved to 92% by treating the thiazine **2** (R^1 = R^2 = $PhCH_2$) with phthalimidoacrylic acid and PCl_3. This method was also used to prepare the diethyl ester **7** (R^1 = R^2 = Et, R^3 = phthalimido), the 2-phenylacetamidoacrylate adducts **7** (R^1 = R^2 = $PhCH_2$, R^3 = $PhCH_2CONH$) and **7** (R^1 = R^2 = Et, R^3 = $PhCH_2$-CONH) and the acrylate adducts **7** (R^1 = R^2 = $PhCH_2$, R^3 = H) and **7** (R^1 = R^2 = Et, R^3 = H).



Scheme 1

The most likely mechanism for the ring closure, outlined in Scheme 1, is Michael reaction by the enamine system of the thiazine **2** on the acrylate **9** to yield the intermediate **11**. This would then ring close to give the product **7**. The propensity for the ambident vinylogous urethane system of thiazine **2** to react on carbon rather than nitrogen was shown when the hindered acrylate, 3,3-dimethylacrylic acid, was used in the reaction with the thiazine **2** ($R^1 = R^2 = PhCH_2$). The product was a pale yellow oil, $C_{27}H_{27}NO_5S$, λ_{max} 358 nm. It was evidently a mixture of the geometric isomers **12** and **13** at room



temperature from both ^1H and ^{13}C NMR spectra, and the isomers were shown to equilibrate at 140 °C in [$^2H_6$]-DMSO by an 'averaging' of the ^1H NMR spectrum. The ketonic carbonyl signals in the ^{13}C NMR spectra at room temperature, δ_C 188.6 and 189, were to lower field than the amide carbonyl signal of the bicyclic compounds **7**.

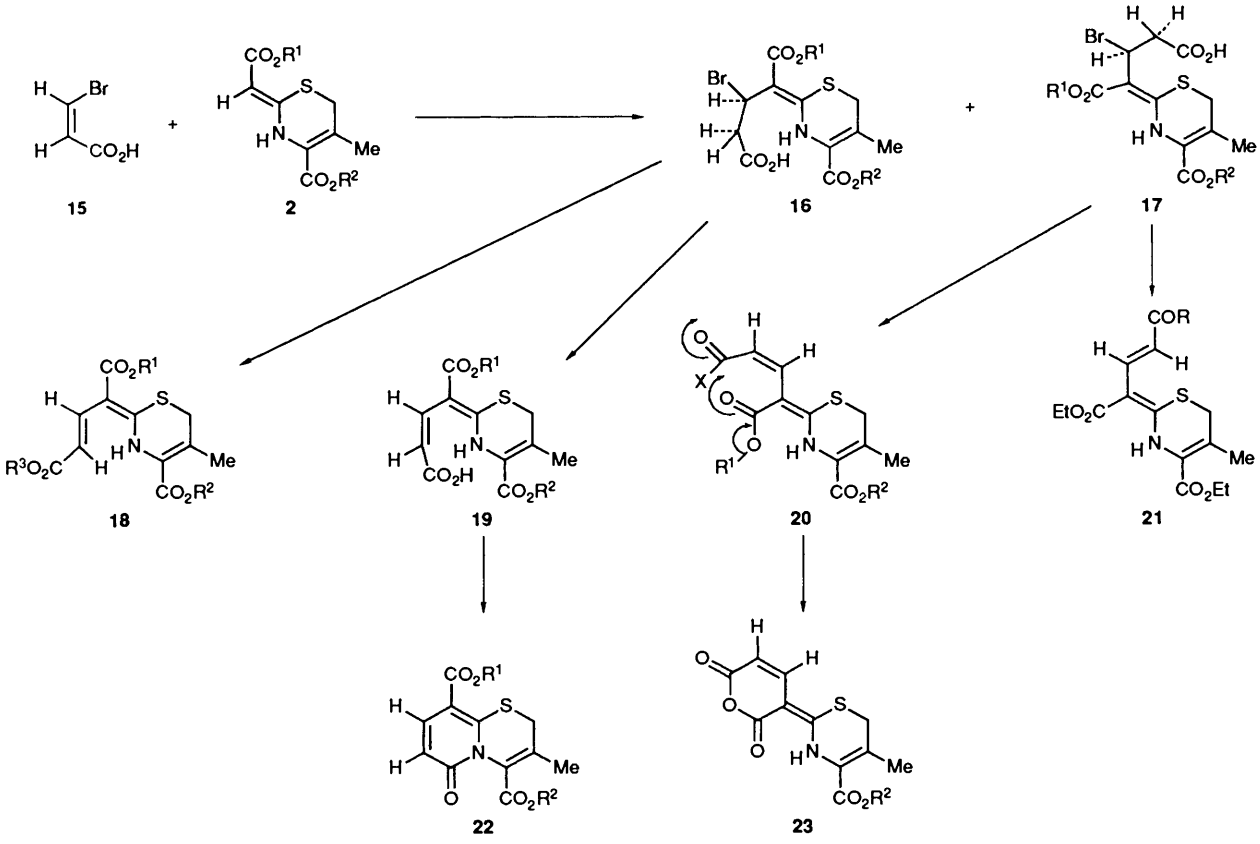
Having developed a synthesis of dihydropyridones fused to a 1,3-thiazine which is substituted in a similar manner to a cephalosporin, we decided to extend the synthesis to the corresponding pyridones. These compounds were of interest as precursors of the tricyclic β-lactams **14**.[3] (*Z*)-3-Bromoacrylic acid **15**[6] was therefore allowed to react with the dihydrothiazine **2** ($R^1 = R^2 = Et$). Use of PCl_3, so successful in the preparation of the dihydrothiazines, resulted in complex mixtures but when dicyclohexylcarbodiimide (DCC) was used in the presence of 4 Å molecular sieves to remove the hydrogen bromide formed, three isolable products were obtained. The first of these, $C_{13}H_{13}NO_5S$, m.p. 225–227 °C, was obtained in 14% yield, being separated by its relative insolubility in diethyl ether. It had an extended chromophore, λ_{max} 390 nm, and spectra were in keeping with its assignment as the hydrogen bonded geometrical isomer of the glutaconic anhydride **23**. The IR spectrum was in accord with expectation,[7,8] and an X-ray crystal structure of a derivative[9] confirmed its structure and stereochemistry. A mechanism for formation of the anhydride **23** is shown in Scheme 2. Here initial Michael attack may lead either to the *E*-adduct **16** or the *Z*-adduct **17**. Assuming dehydrobromination to be the next step, **16** will give either the *Z,E*-isomer **18** or the *Z,Z*-isomer **19**, whereas **17** will give the *E,Z*-isomer **20** or the *E,E*-isomer **21**. Cyclisation of the *E,Z*-isomer **20** as shown, will result in the glutaconic anhydride **23**.

Chromatography of the diethyl ether soluble fraction of the reaction gave two further products. The first of these, $C_{28}H_{41}N_3O_6S$, m.p. 183–186 °C, λ_{max} 379 nm, was obtained in 22% yield and was evidently a single geometric isomer of the adduct **21** [$R = N(C_6H_{11})CONHC_6H_{11}$]. This would be formed by trapping the *E,E*-isomer **21** (R = OH) and the *trans* nature of the olefinic protons was evident from the coupling constant (*J* 14.5 Hz). The second product from the column, $C_{15}H_{17}NO_5S$, m.p. 151–153 °C, was the major product of the reaction, being obtained in 50% yield. It proved to be the desired pyridone **22** ($R^1 = R^2 = Et$).

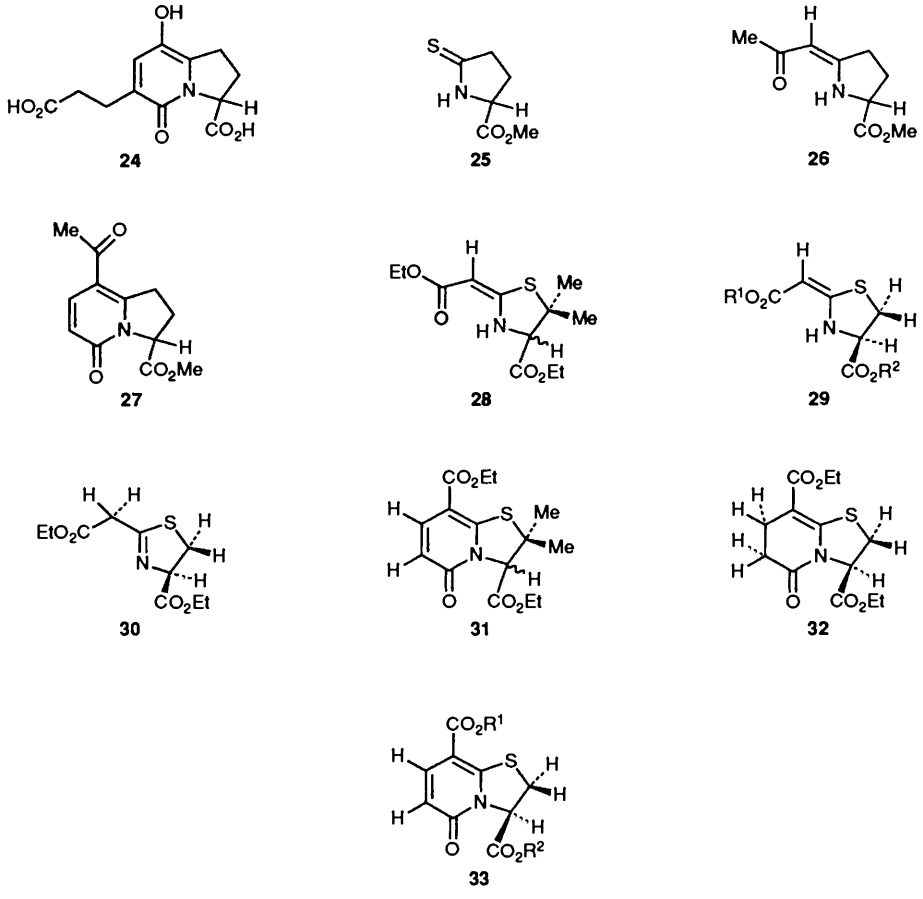
Since *Z*-3-bromoacrylate had given a mixture, we decided to investigate the reaction of *Z*-3-chloroacrylic acid[10] in this reaction. Use of dicyclohexylcarbodiimide (DCC) gave the pyridone **22** ($R^1 = R^2 = Et$) in slightly reduced yield compared to the reaction of thiazine with 3-bromoacrylic acid but little contamination from other products was observed. The PCl_3 conditions which had been so successful in the synthesis of the dihydropyridones but which had failed in the preparation of the pyridone from bromoacrylic acid, gave a 35% yield of the pyridone **22** ($R^1 = R^2 = Et$) when (*Z*)-3-chloroacrylic acid was used. A similar yield of the pyridone was obtained when the thiazine **2** ($R^1 = R^2 = Et$) was allowed to react with propiolic acid and DCC. The pyridone mixed esters **22** ($R^1 = PhCH_2$, $R^2 = Et$) and **22** ($R^1 = PhCH_2$, $R^2 = Me$) were also prepared from the reaction of propiolic acid with the appropriate thiazines in the presence of DCC. Interestingly, by-products were obtained in these reactions in 17 and 19% yields respectively. These proved to be the dibenzyl esters **18** ($R^1 = R^3 = PhCH_2$, $R^2 = Et$) and **18** ($R^1 = R^3 = PhCH_2$, $R^2 = Me$) and had presumably arisen by transesterification of the intermediate *Z,E*-acids **18** ($R^3 = H$). None of the corresponding diesters **18** ($R^1 = PhCH_2$, $R^2 = R^3 = Et$) or **18** ($R^1 = PhCH_2$, $R^2 = R^3 = CH_3$) was obtained.

Having synthesised bicyclic compounds related to cephalosporins, we next investigated application of the method to the synthesis of compounds in which the pyridone was linked to a five-membered carbocyclic ring such as is found in the carbapenam antibiotics. The pyridone analogues had added interest in view of the fact that compounds such as A58365A **24** from *Streptomyces chromofuscus* have been shown to be angiotensin-converting enzyme (ACE) inhibitors.[11,12] Methyl 5-thioxoproline **25** was therefore prepared[13] and treated with bromoacetone[14] to give the enethiol ether which was reacted directly with triphenylphosphine to give a modest yield of the desired enaminone **26**. Condensation with propiolic acid then gave the pyridone **27** as an oil which was characterised as its tosyl hydrazone. Subsequent to completion of this work,[1,15] Danishefsky[16] used this approach to synthesise the ACE inhibitor **24**.

The vinylogous urethane **28** required for the penicillin series was prepared by reaction of ethoxycarbonylacetimino ethyl ether hydrochloride with (±)-penicillamine ethyl ester and the corresponding bisnorpenicillin analogues **29** ($R^1 = R^2 = Et$) and **29** ($R^1 = PhCH_2$, $R^2 = Me$) were prepared in like manner, using the appropriate imino ether and an L-cysteine ester. Interestingly, although the compounds **2** in the six-membered series had been shown to exist as single geometric isomers, ^1H and ^{13}C NMR spectra indicated that the compounds **28** and **29**



Scheme 2



in the five-membered series existed as mixtures of isomers. The ^{1}H NMR spectrum of the thiazolidine **29** ($R^1 = R^2 = Et$) in $C_6{}^2H_6$ at 65 °C was well resolved and a saturation transfer experiment suggested that the enamine **29** ($R^1 = R^2 = Et$) was in equilibrium with the imine **30**. Irradiation of the downfield methyl triplet of the major isomer caused transfer of saturation

to one of the methyl triplets of the minor isomer. Further, irradiation of the olefinic signal at δ 5.1 caused transfer of saturation to an AB system at δ 3.2.

Reaction of the penicillin analogue **28** with propiolic acid and DCC gave the bicyclic pyridine **31** and the bisnorpenicillin analogues, dihydropyridone **32** and pyridones **33** ($R^1 = R^2 =$ Et) and **33** ($R^1 = PhCH_2$, $R^2 =$ Me) were also prepared using our annelation procedures.

Experimental

M.p.s were determined on a Kofler hot stage apparatus. Optical rotations were determined on a Perkin-Elmer PE241 polarimeter using a 1dm path cell and $[\alpha]$ values are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on Perkin-Elmer 257, 457, 477 and PE1710 FT instruments and UV spectra on Pye-Unicam SP800 and Phillips PU8720 spectrophotometers. ^1H NMR spectra were recorded on Perkin-Elmer R32 (90 MHz), Bruker WP80 (80 MHz) and Bruker WH360 (360 MHz) instruments and ^{13}C NMR spectra on Bruker WP80 (20.15 MHz) and WH360 (90.55 MHz) instruments; J values are given in Hz. Combustion analyses were recorded by Mrs. G. Olney and Miss K. Plowman, University of Sussex and by the microanalytical laboratory, I.C.I. Pharmaceuticals plc. Mass spectra were obtained by Mr. A. Greenway on Kratos MS25 and MS80 instruments using electron impact (EI) ionisation unless otherwise stated. Thin layer chromatography was carried out using Merck Kieselgel GF_{254} 0.25 mm analytical plates, and flash chromatography on PF_{254} silica.

Benzyl 2-Benzyloxycarbonylmethylene-2,3-dihydro-5-methyl-6H-1-3-thiazine-4-carboxylate **2** ($R^1 = R^2 = PhCH_2$) was prepared by the method of Lowe *et al.*[4] using freshly prepared benzyl 3-methyl-2-oxobut-3-enoate **4** ($R^2 = PhCH_2$) and benzyloxycarbonylthioacetamide **3** ($R^1 = PhCH_2$). In our hands shorter reaction times (12–18 h) than the 2 d recommended were found to be necessary. The product, m.p. 107–108 °C (lit.,[4] 107–108 °C) was obtained in 49% yield and had spectra similar to those reported.[4]

Ethyl 2-Ethoxycarbonylmethylene-2,3-dihydro-5-methyl-6H-1-3-thiazine-4-carboxylate **2** ($R^1 = R^2 =$ Et).—Freshly prepared ethyl 3-methyl-2-oxobut-3-enoate **4** ($R^2 =$ Et)[17] (3.2 g, 22.5 mmol) and ethoxycarbonylthioacetamide **3** ($R^1 =$ Et)[4] (3.6 g, 24.5 mmol) were dissolved in dry dioxane (30 cm^3) and saturated with anhydrous HCl at 0 °C. The solution was left at room temperature overnight and then the solvent was removed under reduced pressure to yield an orange syrup which was flash chromatographed (silica:ether–hexane, 3:1) to yield the *thiazine* as a pale oil which crystallised with time and was recrystallised from ethanol (4.8 g, 78%), m.p. 69–71 °C (Found: C, 52.7; H, 6.4; N, 5.05. $C_{12}H_{17}NO_4S$ requires C, 53.1; H, 6.3; N, 5.2%); m/z 271 (M^+); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1725, 1705 (unsaturated esters) and 1655 (olefinic); λ_{max}(MeOH)/nm 224, 281 and 336 (log ε 3.97, 3.78 and 4.20); $\delta_H(C^2HCl_3$; 60 MHz) 1.27 and 1.39 (6 H, 2t, J 7, CH_3), 2.30 (3 H, s, CH_3C=), 3.28 (2 H, s, CH_2S), 4.17 and 4.35 (4 H, 2 q, J 7, CH_2O), 4.85 (1 H, s, olefinic) and 12.10 (1 H, br s, NH); the δ 4.85 and 12.10 resonances could only be observed in very pure C^2HCl_3 and disappeared on addition of ^2H_2O; $\delta_C(C^2HCl_3$; 25.15 MHz) 14.2 and 14.6 (2q, 2 × CH_3), 20.0 (q, *Me*C), 30.9 (t, CH_2S), 59.0 and 61.7 (2t, 2 × CH_2O), 85.2 (d, =CH–), 122.4 and 125.3 (2s, 2 × C=), 154.5 (s, SCN) and 162.5 and 168.5 (2s, 2 × C=O).

Methyl 3-Methyl-2-oxobut-3-enoate **4** ($R^2 = CH_3$).—Methyl 2-hydroxy-3-methylbut-3-enoate **5** ($R^2 = CH_3$)* (10 g, 0.08 mol) was shaken with manganese dioxide (BDH, precipitated, 40 g) in diethyl ether (500 cm^3) at room temperature. After 2 h a further portion of manganese dioxide (40 g) was added. After shaking for a further 6 h at room temperature, the suspension was filtered. The solid was washed with ether and the solvent was removed under reduced pressure to yield a pale yellow liquid, which was used without further purification (9.02 g, 92%), $\delta_H(C^2HCl_3$; 90 MHz), 1.89 (3 H, d, J 2, CH_3C=), 3.80 (3 H, s, OCH_3), 6.09 (1 H, s, olefinic) and 6.18 (1 H, d, J 2, olefinic).

Methyl 2,3-Dihydro-2-methoxycarbonylmethylene-5-methyl-6H-1,3-thiazine-4-carboxylate **2** ($R^1 = R^2 = CH_3$).—Freshly prepared methyl 3-methyl-2-oxobut-3-enoate **4** ($R^2 = CH_3$) (8.7 g, 68 mmol) and methoxycarbonylthioacetamide **3** ($R^1 = CH_3$) (9.1 g, 68 mmol) were dissolved in dry dioxane (50 cm^3) and the solution was saturated with hydrogen chloride gas at 0 °C. The solution was left overnight at room temperature, and then the solvent was removed under reduced pressure to give an orange oil. This was chromatographed (silica:ether–hexane, 1:1) to give a yellow solid which was recrystallised from methanol to yield the *thiazine* (8.2 g, 50%), m.p. 76–78 °C (Found: C, 49.4; H, 5.5; N, 5.5. $C_{10}H_{13}NO_4S$ requires C, 49.4; H, 5.4; N, 5.8); m/z 243 (M^+); λ_{max}/nm 224, 281 and 336 (log ε 3.66, 3.46 and 3.92); ν_{max}(KBr)/cm^{-1} 1728 and 1656; $\delta_H(C^2HCl_3$; 360 MHz) 2.27 (3 H, s, CH_3), 3.24 (2 H, s, CH_2S), 3.65 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 4.86 (1 H, s, CH) and 11.14 (1 H, br, NH); $\delta_C(C^2HCl_3$; 90.55 MHz), 19.70 (CH_3), 30.77 (CH_2S), 50.30 (OCH_3), 52.17 (OCH_3), 84.95 (C=), 122.49 (=C), 125.15 (NC), 154.50 (NCS) and 162.71 and 168.88 (2 × C=O).

Ethyl 2-Benzyloxycarbonylmethylene-2,3-dihydro-5-methyl-6H-1,3-thiazine-4-carboxylate **2** ($R^1 = PhCH_2$, $R^2 =$ Et).—A solution of freshly prepared ethyl 3-methyl-2-oxobut-3-enoate **4** ($R^2 =$ Et)[17] (14 g, 0.1 mol) and benzyloxycarbonylthioacetamide **3** ($R^1 = PhCH_2$)[4] (23 g, 0.11 mol) in dry dioxane (100 cm^3) was saturated at 0 °C with dry hydrogen chloride gas. The solution was left overnight at room temperature and then the solvent was removed under reduced pressure to yield a yellow oil which crystallised from chloroform–hexane as yellow prisms (19 g, 57%), m.p. 98–99 °C (Found: C, 61.55; H, 5.7; N, 4.1. $C_{17}H_{19}NO_4S$ requires C, 61.3; H, 5.7; N, 4.2%); m/z 333 (M^+); λ_{max}(MeOH)/nm 280 and 337 (log ε 4.47 and 4.83); ν_{max}(KBr)/cm^{-1} 3120 (NH) and 1700 (esters); $\delta_H(C^2HCl_3$; 90 MHz), 1.38 (3 H, t, J 7, CH_3), 2.24 (3 H, s, CH_3C=), 3.2 (2 H, s, CH_2S), 4.31 (2 H, q, J 7, CH_2O), 4.93 (1 H, s, HC=), 5.16 (2 H, s, benzyl CH_2) and 7.33 (5 H, s, aromatics); $\delta_C(C^2HCl_3$; 20.15 MHz), 14.16 (q, CH_3), 19.93 (q, CH_3C=), 31.02 (t, CH_2S), 61.75 (t, CH_2O), 64.89 (t, Ph*C*H_2O), 85.11 (d, olefinic), 127.88 (m, aromatics) and 155.11 (C=O).

Methyl 2-Benzyloxycarbonylmethylene-2,3-dihydro-5-methyl-6H-1,3-thiazine-4-carboxylate **2** ($R^1 = PhCH_2$, $R^2 = CH_3$).—Freshly prepared methyl 3-methyl-2-oxobut-3-enoate **4** ($R^2 = CH_3$) (12.19 g, 0.095 mol) and benzyloxycarbonylthioacetamide **3** ($R^1 = PhCH_2$) (19.92 g, 0.095 mol) were dissolved in dry dioxane (100 cm^3) and the solution was saturated with dry hydrogen chloride gas at 0 °C. The solution was then allowed to warm to room temperature overnight when the solvent was removed under reduced pressure to yield an orange gum. This was flash chromatographed (silica:ether–hexane, 1:1) to yield the thiazine as a yellow solid which was recrystallised from methanol (23.0 g, 76%), m.p. 86.5–88 °C (Found: C, 60.1; H, 5.3; N, 4.1. $C_{16}N_{17}NO_4S$ requires C, 60.2; H, 5.4; N, 4.4%); m/z 319 (M^+); λ_{max}(MeOH)/nm 222, 283 and 336 (log ε 4.03, 3.75 and 4.27); ν_{max}(KBr)/cm^{-1} 1740 and 1700 (esters); $\delta_H(C^2HCl_3$; 90 MHz) 2.27 (3 H, s, CH_3C=), 3.24 (2 H, s,

* Prepared by I.C.I. Pharmaceuticals using the method described,[18] for preparing the ethyl ester.

CH_2S), 3.84 (3 H, s, CH_3O), 4.95 (1 H, s, HC=), 5.15 (2 H, s, OCH_2Ph) and 7.35 (5 H, br, aromatics); $\delta_C(C^2HCl_3$; 90.55 MHz) 19.95 (CH_3C=), 31.00 (CH_2S), 52.40 (OCH_3), 64.98 (OCH_2Ph), 85.36, 122.73 and 125.43 (olefinics), 127.8–128.5 (aromatics), 155.06 (NCS) and 162.95 and 168.46 (2 × C=O).

Methyl 10-Benzyloxycarbonyl-6,7,8,9-tetrahydro-3,8-dimethyl-6,7-dioxo-2H-[1,3]thiazino[3,2-a]azepine-4-carboxylate **6**.—This *compound* was always present from the above reaction and, in one instance, was isolated from the flash chromatography column, eluting after the thiazine and in the same solvent system (5.12 g, 17%), m.p. 150–152 °C (Found: C, 60.5; H, 5.3; N, 3.9. $C_{21}H_{21}NO_6S$ requires C, 60.7; H, 5.1; N, 3.4%); *m/z* 415 (M^+); λ_{max}(MeOH)/nm 224, 291 and 338 (log ε 4.10, 4.04 and 4.09); ν_{max}(KBr)/cm^{-1} 1791, 1744 and 1679; $\delta_H(C^2HCl_3$; 360 MHz) 1.22 (3 H, d, *J* 6.7, 8-CH_3), 1.96 (1 H, m, *J* 6.7, 5.6 and 12.5, 8-H), 2.32 (3 H, d, *J* 1.3, 3-CH_3), 2.64 (2 H, ABX, *J* 17, 12.5 and 5.6, 9-CH_2), 3.05 and 3.46 (2 H, ABX, *J* 15 and 1.2, CH_2S), 3.80 (3 H, s, CH_3O), 5.19 (2 H, AB, *J* 12.5, CH_2Ph) and 7.26–7.40 (5 H, m, aromatics); $\delta_C(C^2HCl_3$; 90.55 MHz) 14.24 (8-CH_3), 15.61 (3-CH_3), 28.01 (C-9), 30.46 (CH_2S), 33.73 (C-8), 52.86 (OCH_3), 65.45 (CH_2Ph), 93.39 (C-10), 96.86 (C-3), 120.49 (C-4), 127.57, 128.09 and 136.33 (aromatics), 145.78 (C-6), and 161.13, 165.57 and 165.68 (3 × C=O).

2-Phthalimidoacryloyl Chloride.—Phthalimidoacrylic acid[5] (33 mg, 0.152 mmol) was dissolved in redistilled thionyl chloride (2 cm^3) and heated to reflux under nitrogen for 2 h. The thionyl chloride was removed under reduced pressure to give a white crystalline, easily hydrolysable solid; $\nu_{max}(CH_2Cl_2)$/cm^{-1} 1785 and 1725 (imide) and 1755 (acid chloride).

Dibenzyl 7,8-Dihydro-3-methyl-6-oxo-7-phthalimido-2H,6H-pyrido[2,1-b][1,3]thiazine-4,9-dicarboxylate **7** ($R^1 = R^2 = PhCH_2$, R^3 = *phthalimido*).—*Method A*. To a solution of benzyl 2-benzyloxycarbonylmethylene-2,3-dihydro-5-methyl-6*H*-1,3-thiazine-4-carboxylate **2** ($R^1 = R^2 = PhCH_2$) (50 mg, 0.127 mmol) and triethylamine (30 mm^3, *ca.* 0.22 mmol) in dry chloroform (5 cm^3) was added 2-phthalimidoacryloyl chloride (36 mg, 0.154 mmol) in chloroform (2 cm^3). The mixture was heated to reflux under nitrogen and aliquots were monitored by TLC and by UV and IR spectroscopy. After 8 h, the reaction mixture was allowed to stand for 2 d at room temperature and the mixture was then washed with saturated aqueous sodium hydrogen carbonate and water and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product (64 mg) was subjected to preparative TLC (silica: $CHCl_3$–EtOAc, 1:1). The major component (23 mg, R_f *ca.* 0.6) was obtained as an oil which had spectra identical with those of the crystalline compound **7** ($R^1 = R^2 = PhCH_2$, R^3 = phthalimido) prepared in method B below.

Method B. Phthalimidoacrylic acid[5] (1 g, 4.6 mmol) and benzyl 2-benzyloxycarbonylmethylene-2,3-dihydro-5-methyl-1,3-thiazine-4-carboxylate **2** ($R^1 = R^2 = PhCH_2$) (1.7 g, 4.3 mmol) were dissolved in dry benzene (10 cm^3) and dry dioxane (20 cm^3) and phosphorus trichloride (0.64 g, 4.66 mmol) was added. The solution was heated to reflux under nitrogen until TLC (silica: $CHCl_3$–EtOAc, 1:1) showed that the dihydrothiazine was no longer present (*ca.* 2 h). The solvent was removed under reduced pressure and the orange foam was dissolved in ethyl acetate and washed successively with saturated aqueous sodium hydrogen carbonate, 1 mol dm^{-3} hydrochloric acid, water and saturated aqueous sodium chloride. The ethyl acetate solution was dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield an orange foam, which was recrystallised from hot ethyl acetate to give white crystals of the bicyclic product **7**($R^1 = R^2 = PhCH_2$, R^3 = phthalimido) (2.35 g, 92%), m.p. 112 °C (Found: C, 66.4; H, 4.5; N, 4.55. $C_{33}H_{26}N_2O_7S$ requires C, 66.7; H, 4.4; N, 4.7%); *m/z* 594 (M^+); λ_{max}(MeOH)/nm 231sh, 240sh, 249sh and 313 (log ε 4.48, 4.37, 4.04 and 4.01); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 1780, 1720 and 1678; $\delta_H(C^2HCl_3$; 220 MHz) 2.27 (3 H, s, CH_3C=) 2.95 (1 H, d, *J* 13.7, CHS), 3.04 (1 H, dd, *J* 15.5 and 5.5, HCC=), 3.5 (1 H, d, *J* 13.7, CHS), 3.67 (1 H, q, *J* 15.5 and 14, HCC=), 5.06 (1 H, dd, *J* 14 and 5.5, NCH), 5.30 (2 H, AB, *J* 12, $PhCH_2O$), 5.15 (2 H, AB, *J* 12, $PhCH_2O$), 7.34 (10 H, br m, aromatics) and 7.82 (4 H, m, aromatics); $\delta_C(C^2HCl_3$; 25.15 MHz) 18.69 (q, *Me*C=), 24.45 (t, CH_2C=), 31.61 (t, CH_2S), 49.20 (d, NCH), 66.92 (t, 2 × OCH_2Ph), 105.75 (s, CCO_2), 123.47 (d, aromatic), 126.62 (s, $MeCCH_2$), 128.38–128.69, 131.72, 134.15 and 135.66 and 135.78 (aromatics), 141.49 (s, $NCCO_2$), 152.04 (s, NCS) and 161.87, 165.09, 165.59 and 167.15 (4s, 4 × C=O).

Method C. Phthalimidoacrylic acid (27.5 mg, 0.127 mmol) benzyl 2-benzyloxycarbonylmethylene-2,3-dihydro-5-methyl-6*H*-1,3-thiazine-4-carboxylate **2** ($R^1 = R^2 = PhCH_2$) (50 mg, 0.127 mmol) and DCC (29 mg, 0.141 mmol) were dissolved in dichloromethane (5 cm^3) and stirred overnight at room temperature. The precipitated urea was filtered off and the solvent was removed under reduced pressure. The remaining solid was washed with a minimum of dichloromethane and again filtered. Pentane was added to the filtrate to give white crystals of the product, the ^{1}H NMR spectrum of which was identical with that of the product obtained by methods A and B above (21 mg, 28%).

Diethyl 7,8-Dihydro-3-methyl-6-oxo-7-phthalimido-2H,6H-pyrido[2,1-b][1,3]thiazine-4,9-dicarboxylate **7** ($R^1 = R^2$ = Et, R^3 = *phthalimido*).—Phthalimidoacrylic acid[5] (1.08 g, 4.98 mmol), phosphorus trichloride (0.69 g, 5.02 mmol) and ethyl 2-ethoxycarbonylmethylene-2,3-dihydro-5-methyl-6*H*-1,3-thiazine-4-carboxylate **2** ($R^1 = R^2$ = Et) (1.35 g, 4.98 mmol) were dissolved in dry dioxane (10 cm^3) and dry benzene (5 cm^3) and heated to reflux under nitrogen for 4 h. The solvent was removed under reduced pressure and the yellow foam was dissolved in dichloromethane. The extract was washed successively with saturated aqueous sodium hydrogen carbonate, hydrochloric acid (1 mol dm^{-3}) and saturated aqueous sodium chloride and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield an off-white foam (2.12 g, 90%) which was fairly pure by ^{1}H NMR spectroscopy.

Recrystallisation from dichloromethane and diethyl ether gave the white crystalline *product* **7** ($R^1 = R^2$ = Et) (1.56 g, 66%), m.p. 105–108 °C (Found: C, 58.7; H, 4.7; N, 5.9. $C_{23}H_{22}N_2O_7S$ requires C, 58.7; H, 4.7; N, 5.95%); *m/z* 470 (M^+); λ_{max}(MeOH)/nm 306 (log ε 3.98); ν_{max}(Nujol)/cm^{-1} 1780, 1720 and 1678; $\delta_H(C^2HCl_3$; 220 MHz), 1.31 (3 H, t, *J* 7, CH_3), 1.39 (3 H, t, *J* 7, CH_3), 2.30 (3 H, s, CH_3C=), 2.96 and 3.49 (2 H, AB, *J* 13.7, CH_2S), 3.13 (1 H, dd, *J* 15 and 5.5, CHC=), 3.72 (1 H, t, *J* 15, CHC=), 4.3 (4 H, m, 2 × CH_2O), 5.13 (1 H, dd, *J* 15 and 5.5, NCH) and 7.84 (4 H, m, aromatics); $\delta_C(C^2HCl_3$; 25.15 MHz) 13.8 and 14.4 (2q, 2 × CH_3), 18.5 (q, CH_3C=), 24.3 (t, CH_2C), 31.6 (t, CH_2S), 49.3 (d, NCH), 61.0 and 61.5 (2t, 2 × CH_2O), 106.2 (s, CCO_2), 123.5 (aromatic), 126.7 (s, $MeCCH_2$), 131.7 and 134.3 (aromatics), 141.55 (s, $NCCO_2$); 151.6 (s, NCS) and 162.1, 165.3, 165.6 and 167.2 (4s, 4 × C=O).

Dibenzyl 7,8-Dihydro-3-methyl-6-oxo-7-phenylacetamido-2H,6H-pyrido[2,1-b][1,3]thiazine-4,9-dicarboxylate **7** ($R^1 = R^2 = PhCH_2$, $R^3 = PhCH_2CONH$).—2-Phenylacetamidoacrylic acid[19] (30 mg, 0.146 mmol), phosphorus trichloride (*ca.* 15 mg, 0.11 mmol) and benzyl 2-benzyloxycarbonylmethylene-2,3-dihydro-5-methyl-6*H*-1,3-thiazine-4-carboxylate **2** ($R^1 = R^2 = PhCH_2$) (60 mg, 0.152 mmol) were heated to reflux in dry dioxane (1.5 cm^3) and dry benzene (2 cm^3) for 1.5 h when TLC showed that little dihydrothiazine remained. The

solvent was removed under reduced pressure to give an orange solid which was extracted with dichloromethane (15 cm^3) and filtered. The solvent was removed under reduced pressure to give an orange solid (81 mg). Recrystallisation from ethyl acetate gave white crystals of the *product* **7** (R^1 = R^2 = $PhCH_2$, R^3 = $PhCH_2CONH$) (68 mg, 80%), m.p. 175–177 °C (Found: C, 68.4; H, 5.1; N, 5.0. $C_{33}H_{30}N_2O_6S$ requires C, 68.0; H, 5.15; N, 4.8%); *m/z* 582 $(M)^+$; $\nu_{max}(CHCl_3)/cm^{-1}$ 1725, 1710 and 1680; λ_{max}(MeOH)/nm 232 and 316 (log ε 4.05 and 3.95); $\delta_H(C^2HCl_3$; 90 MHz) 2.00 (1 H, t, *J* 15, CHC=), 2.26 (3 H, CH_3C=), 2.80 and 3.42 (2 H, AB, *J* 14, CH_2S), 3.27 (1 H, dd, *J* 15 and 6, CHC=), 3.57 (2 H, s, $PhCH_2CO$), 4.58 (1 H, dt, *J* 15 and 6, NHCH), 4.94 and 5.28 (2 H, AB, *J* 12, OCH_2Ph), 5.17 (2 H, br s, OCH_2Ph), 5.93 (1 H, br d, *J* 6, NH; slowly exchanges with ^2H_2O) and 7.3 (15 H, m, aromatics).

Diethyl 7,8-*Dihydro*-3-*methyl*-6-*oxo*-7-*phenylacetamido*-2H,6H-*pyrido*[2,1-b][1,3]*thiazine*-4,9-*dicarboxylate* **7** (R^1 = R^2 = Et, R^3 = $PhCH_2CONH$).—2-Phenylacetamidoacrylic acid[19] (1.81 g, 8.83 mmol), phosphorus trichloride (1.21 g, 8.8 mmol) and ethyl 2-ethoxycarbonylmethylene-2,3-dihydro-5-methyl-6*H*-1,3-thiazine-4-carboxylate **2** (R^1 = R^2 = Et) (2.4 g, 8.86 mmol) were heated to reflux under nitrogen in dry dioxane (15 cm^3) and dry benzene (10 cm^3) for 4 h. The solvent was removed under reduced pressure and the orange residue was taken up in ethyl acetate (*ca.* 100 cm^3). This was washed with saturated aqueous sodium hydrogen carbonate, hydrochloric acid (1 mol dm^{-3}) and saturated aqueous sodium chloride, and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a crude yellow product (3.7 g). Recrystallisation from dichloromethane and diethyl ether gave a white crystalline solid (3.1 g, 81%), m.p. 130–132 °C and 172–174 °C (Found: C, 59.85; H, 5.95; N, 6.1. $C_{23}H_{26}N_2O_6S$ requires C, 60.25; H, 5.7; N, 6.1%); *m/z* 458 (M^+); ν_{max}(Nujol)/cm^{-1} 3270 NH, 1725sh, 1715, 1680 and 1655; λ_{max}(MeOH)/nm 235 and 315 (log ε 4.45 and 3.96); $\delta_H(C^2HCl_3$; 220 MHz) 1.11 (3 H, t, *J* 7, CH_3), 1.29 (3 H, t, *J* 7, CH_3), 2.28 (1 H, dd, *J* 15 and 15, CHC=), 2.82 and 3.43 (2 H, AB, *J* 14, CH_2S), 3.35 and 3.59 (1 H, dd, *J* 15 and 6, CHC=), 3.63 (2 H, s, $PhCH_2CO$), 4.08 and 4.47 (2 H, qq, *J* 7 and 10, OCH_2), 4.25 (2 H, q, *J* 7, OCH_2), 4.60 (1 H, dt, *J* 15 and 6, NHCH), 6.25 (1 H, br d, *J* 6, NH; slowly exchanges with ^2H_2O) and 7.32 (5 H, br s, aromatics).

Dibenzyl 7,8-*Dihydro*-3-*methyl*-6-*oxo*-2H,6H-*pyrido*[2,1-b][1,3]*thiazine*-4,9-*dicarboxylate* **7** (R^1 = R^2 = $PhCH_2$, R^3 = H).—Acrylic acid (15.6 mg, 0.217 mmol), phosphorus trichloride (16 mg, 0.116 mmol) and benzyl 2-benzyloxycarbonylmethylene-2,3-dihydro-5-methyl-6*H*-1,3-thiazine-4-carboxylate **2** (R^1 = R^2 = $PhCH_2$) (85 mg, 0.215 mmol) were heated to reflux under nitrogen in dry dioxane (2 cm^3) and dry benzene (1 cm^3) for 3.5 h when TLC showed that no acrylic acid remained, but that thiazine was still present. A further portion of acrylic acid (15 mg, 0.208 mmol) was added and heating was continued at reflux for a further 3 h, when TLC showed that all of the thiazine had been consumed. The solvent was removed under reduced pressure, and the orange-red residue was taken up in ethyl acetate (*ca.* 25 cm^3). This solution was washed with saturated aqueous sodium hydrogen carbonate, hydrochloric acid (1 mol dm^{-3}) and saturated aqueous sodium chloride and dried ($MgSO_4$). The solvent was removed under reduced pressure to give a dark oil (90 mg) which was separated by TLC (silica:$CHCl_3$–EtOAc, 1:1), to give the product **7** (R^1 = R^2 = $PhCH_2$, R^3 = H) (R_f *ca.* 0.7) as a yellow oil (54 mg, 56%). Distillation of a portion of this oil at 140 °C and 0.2 mmHg gave *needles* which melted at room temperature (Found: C, 65.4; H, 5.3; N, 3.1. $C_{25}H_{23}NO_5S$ requires C, 66.8; H, 5.1; N, 3.1%); *m/z* 449.129 72 ($C_{25}H_{23}NO_5S$ requires 449.129 68); λ_{max}(MeOH)/nm 318; $\delta_H(C^2HCl_3$; 90 MHz) 2.25 (3 H, s, CH_3C=), 2.53 (4 H, s, 2 × CH_2), 3.09 (2 H, s, CH_2S), 5.12 (2 H, s, OCH_2Ph), 5.16 (2 H, s, OCH_2Ph) and 7.31 (10 H, s, aromatics).

Diethyl 7,8-*Dihydro*-3-*methyl*-6-*oxo*-2H,6H-*pyrido*[2,1-b][1,3]*thiazine*-4,9-*dicarboxylate* **7** (R^1 = R^2 = Et, R^3 = H).—Phosphorus trichloride (500 mg, 3.6 mmol) was added to ethyl 2-ethoxycarbonylmethylene-2,3-dihydro-5-methyl-6*H*-1,3-thiazine-4-carboxylate **2** (R^1 = R^2 = Et) (2 g, 7.4 mmol) in dry benzene (20 cm^3) and dry dioxane (40 cm^3) and the solution was stirred under nitrogen at room temperature for 30 min. Acrylic acid (0.57 g, 7.9 mmol) in dry dioxane (10 cm^3) was added dropwise and the solution was heated to reflux for 2 h when TLC (silica:ether–hexane, 3:1) showed thiazine still to be present.

A further portion of acrylic acid (0.1 g, 1.4 mmol) was added and heating was continued at reflux for a further 30 min. The solvent was removed under reduced pressure and the crude material was taken up in chloroform and washed successively with saturated aqueous sodium hydrogen carbonate and water and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield an orange oil which was crystallised from chloroform–hexane to yield yellow prisms (0.94 g, 39%), m.p. 117–118 °C (Found: C, 55.35; H, 5.8; N, 4.5. $C_{15}H_{19}NO_5S$ requires C, 55.4; H, 5.85; N, 4.3%); *m/z* 325 (M^+); λ_{max}(MeOH)/nm 237 and 317 (log ε 4.02 and 3.99); $\lambda_{max}(H^+$/MeOH)/nm 292 and 349 (log ε 3.69 and 4.14); ν_{max}(KBr)/cm^{-1} 1720 and 1705 (esters), 1672 (amide) and 1560; $\delta_H(C^2HCl_3$; 360 MHz) 1.28 and 1.33 (2 × 3 H, 2t, *J* 7.1, 2 × CH_3) 2.28 (3 H, s, CH_3), 2.62 (2 H, m, β-CH_2), 2.77 (2 H, m, α-CH_2), 3.14 (2 H, s, CH_2S) and 4.23 and 4.25 (4 H, 2q, *J* 7.1, 2 × CH_2); $\delta_C(C^2HCl_3$; 90.55 MHz) 14.05 and 14.44 (2q, CH_3), 18.65 (q, CH_3), 20.36 (t, $2CH_2$), 31.77 (t, CH_2S), 60.85 and 61.23 (2t, 2 × CH_2O), 107.74, 127.24, 140.22 and 151.75 (4s, olefinic) and 162.55, 166.06 and 170.15 (3s, C=O).

Benzyl-2-(1-*Benzyloxycarbonyl*-4-*methyl*-2-*oxopent*-3-*enylidene*)-2,3-*dihydro*-5-*methyl*-6H,1,3-*thiazine*-4-*carboxylate* **12** + **13**.—A solution of 3,3-dimethylacrylic acid (100 mg, 1.0 mmol), benzyl 2-benzyloxycarbonylmethylene-2,3-dihydro-5-methyl-6*H*-1,3-thiazine-4-carboxylate **2** (R^1 = R^2 = $PhCH_2$) (200 mg, 0.5 mmol) and phosphorus trichloride (*ca.* 70 mg, 44 mm^3, 0.5 mmol) was heated at reflux under nitrogen in dry dioxane (5 cm^3) and dry benzene (3 cm^3) until TLC (silica; $CHCl_3$) showed no thiazine remaining (*ca.* 4 h). The solvent was removed under reduced pressure to give an orange foam which was taken up in ethyl acetate (10 cm^3) and washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride. The ethyl acetate solution was dried (Na_2SO_4) and the solvent was removed under reduced pressure to give an orange oil. Preparative TLC (silica; $CHCl_3$) gave a mixture of the geometric isomers **12** and **13** as a pale yellow oil (R_f *ca.* 0.5); 113.5 mg, 45%; *m/z* 477.1632 ($C_{27}H_{27}NO_5S$ requires 477.1610); λ_{max}(MeOH)/nm 250, 335sh and 358 (log ε 4.07, 3.97 and 4.03); ν_{max}(film)/cm^{-1} 1730, 1715 and 1640 (carbonyl); $\delta_H(C^2HCl_3$; 90 MHz) 1.69 (3 H, br s, sharpens on irradiation at δ 6.30, CH_3C=), 2.05 (3 H, br s, sharpens on irradiation at δ 6.30, CH_3C=), 2.31 (3 H, br s, CH_3C=), 3.06 and 3.17 (2 × 1 H, 2s, geometric isomers, CH_2S), 5.26 (2 H, s, OCH_2Ph), 5.33 (2 H, s, OCH_2Ph), 6.24 and 6.35 (2 × ½ H, dq, both *J* 1.2, sharpens to br dd on irradiation at either δ 1.69 or 2.05, olefinic), 7.38 (10 H, br, aromatics) and 12.97 and 15.10 (2 × ½ H, 2 br s, NH, exchanges with ^2H_2O).

Variable temperature ^1H *NMR spectrum* ([$^2H_6$]-*DMSO*). The change of solvent altered chemical shifts and the relative ratio of the geometric isomers from *ca.* 1:1 in C^2HCl_3 to *ca.* 2:1 in [$^2H_6$]-DMSO. The minor isomer had resonances at δ 3.23 (CH_2S), 6.30 (HC=) and 12.63 (NH); whilst the major isomer had resonances at δ 3.40 (CH_2S), 6.15 (HC=) and 14.65 (NH). The resonances at δ 2.3 (ring CH_3C=), 5.2 (OCH_2Ph), 5.3

(OCH_2Ph) and 7.4 (aromatics) sharpened slightly as the temperature was increased but were otherwise unchanged. The resonances at δ 1.7 and 2.0 [$(CH_3)_2C$=] sharpened as the temperature was raised. The resonances at δ 12.63 and 14.65 (both NH) became broader and flatter as the temperature was increased, until at 95 °C they had completely disappeared. The CH_2S resonances, δ 3.23 and 3.40, began to collapse at 60 °C, had coalesced into a broad resonance at 70 °C and a fairly sharp singlet was seen, δ *ca.* 3.3 at 120 °C. A similar process occurred with the two multiplets at δ 6.15 and 6.3 which had coalesced to a single resonance, δ *ca.* 6.23 at 70 °C and began to sharpen at 80 °C. At 140 °C the fine-structure of the quartet was again visible.

δ_C(C^2HCl_3; 25.15 MHz) 19.96 (2q, CH_3C=), 20.52 and 20.78 (2q, CH_3C=), 27.20 and 27.37 (2q, CH_3C=), 31.23 and 32.22 (2t, CH_2S), 66.06, 66.71, 67.35 and 67.46 (4t, 2 × OCH_2Ph), 103.08 and 103.57 (2s, $OCHCO_2$), 124.92 and 125.47 (2s, Me*C*=), 125.77 and 126.93 (2d, H*C*CO), 127.35 and 127.65 (2s, Me*C*=), 128.56, 135.24 and 136.15 (aromatics), 149.37 and 149.80 (2s, 2 × $NCCO_2$), 161.63 and 162.12 (2s, 2NCS), 165.76, 166.86, 167.70 and 168.37 (4s, 4 × CO) and 188.6 and 189 (2s).

Reaction of (*Z*)-3-*Bromoacrylic Acid with Ethyl* 2-*Ethoxycarbonylmethylene*-2,3-*dihydro*-5-*methyl*-6H-1,3-*thiazine*-4-*carboxylate* **2** (R^1 = R^2 = Et).—A mixture of DCC (3.84 g, 18.6 mmol), (*Z*)-3-bromoacrylic acid (0.9 g, 5.96 mmol), ethyl 2-ethoxycarbonylmethylene-2,3-dihydro-5-methyl-6*H*-1,3-thiazine-4-carboxylate **2** (R^1 = R^2 = Et) (1.28 g, 4.72 mmol) and 4 Å molecular sieve powder (unconditioned) (*ca.* 5 g) was stirred in dichloromethane (300 cm^3) under nitrogen at room temperature in the dark for periods of up to 2 weeks, until the reaction was judged to be complete by the disappearance of bromoacrylic acid from the TLC (silica: Et_2O–hexane, 1:2). The suspended matter was filtered off and washed with small portions of dichloromethane until the washings were only faintly yellow. Approximately twice the volume of diethyl ether was added to the filtrate and combined washings. The yellow precipitate was filtered off and purified by extracting several times with chloroform to remove soluble impurities. The insoluble product was the microcrystalline 4-(4-*ethoxycarbonyl*-2,3-*dihydro*-5-*methyl*-6H-1,3-*thiazin*-2-*ylidene*)*glutaconic anhydride* **23** (R^2 = Et) (195 mg, 14%), m.p. 225–227 °C (Found: C, 52.7; H, 4.4; N, 4.8. $C_{13}H_{13}NO_5S$ requires C, 52.9; H, 4.4; N, 4.7%); *m*/*z* 295 (M^+); λ_{max}(MeOH)/nm 224, 305 and 390 (log ε 3.85, 3.70 and 4.50); ν_{max}(Nujol)/cm^{-1} 3325 (NH), 1745sh, 1718 and 1670 (carbonyls); δ_H(C^2HCl_3; 90 MHz) 1.42 (3 H, t, *J* 7.3, CH_3), 2.44 (3 H, s, H_3CC=), 3.50 (2 H, s, CH_2S), 4.42 (2 H, q, *J* 7.3, CH_2O), 5.74 (1 H, d, *J* 9.5, OCCH=), 7.57 (1 H, d, *J* 9.5, OCC=CH) and 10.85 (1 H, br, NH; exchangeable with ^2H_2O).

The solvent from the mother liquors remaining after preparation of the glutaconic anhydride **23** (R^2 = Et) was removed under reduced pressure and the residue was subjected to preparative medium pressure liquid chromatography on silica gel using diethyl ether–hexane (2:3) as eluent. Unchanged dihydrothiazine (*ca.* 100 mg) separated near the solvent front and this was followed by two fractions with similar retention times (*ca.* 20–30 min). The compound with the shorter retention time was recrystallised from hot ethanol and proved to be yellow crystals of *ethyl* 2-(N,N′-*dicyclohexyl*-1-*ethoxycarbonyl*-4,6-*dioxo*-5,7-*diazahept*-2E-*enylidene*)-2,3-*dihydro*-5-*methyl*-6H,1,3-*thiazine*-4-*carboxylate* **21** [R = $N(C_6H_{11})CONHC_6H_{11}$] (560 mg, 22%), m.p. 183–185 °C (Found: C, 60.7; H, 7.8; N, 7.3%. $C_{28}H_{41}N_3O_6S$ requires C, 61.4; H, 7.5; N, 7.7%); *m*/*z* 547 (M^+); λ_{max}(MeOH)/nm 228, 312 and 379 (log ε 3.98, 4.04 and 4.31); ν_{max}(Nujol)/cm^{-1} 1705sh, 1690, 1670sh and 1640; δ_H(C^2HCl_3; 90 MHz) 1.36 (3 H, t, *J* 7, CH_3), 1.38 (3 H, t, *J* 7, CH_3), 1.1–2.5 and 3.4–4.2 (22 H, br m, 2 × cyclohexyl), 2.35 (3 H, s, H_3CC=), 3.32 (2 H, s, CH_2S), 4.33 (2 H, q, *J* 7, CH_2O), 4.36 (2 H, q, *J* 7, CH_2O), 6.70 (1 H, d, *J* 15, =CHCO), 7.87 (1 H, d, *J* 15, CH=CCO), 8.33 (1 H, dm, *J ca.* 7, urea NH) and *ca.* 12.6 (1 H, br s, enamine NH).

The second new compound from the preparative medium pressure liquid chromatography was recrystallised from either methanol or diethyl ether as yellow needles of *diethyl* 3-*methyl*-6-*oxo*-2H,6H-*pyrido*[2,1-b][1,3]*thiazine*-4,9-*dicarboxylate* **22** (R^1 = R^2 = Et) (760 mg, 50%), m.p. 151–153 °C (Found: C, 55.5; H, 5.4; N, 4.4. $C_{15}H_{17}NO_5S$ requires C, 55.7; H, 5.3; N, 4.3%); *m*/*z* 323 (M^+); λ_{max}(MeOH)/nm 221, 290, 349 and 360sh (log ε 4.09, 3.97, 3.90 and 3.83); ν_{max}(Nujol)/cm^{-1} 1717, 1692 and 1663; δ_H(C^2HCl_3; 90 MHz) 1.23 (3 H, *J* 7, CH_3), 1.36 (3 H, t, *J* 7, CH_3), 2.31 (3 H, s, H_3CC=), 3.17 (2 H, s, CH_2S), 4.23 (2 H, q, *J* 7, CH_2O), 4.36 (2 H, q, *J* 7, CH_2O), 6.32 (1 H, d, *J* 10, pyridone α-CH) and 7.90 (1 H, d, *J* 10, pyridone β-CH); δ_C(C^2HCl_3; 25.15 MHz) 13.77 (q, CH_3), 14.20 (q, CH_3), 18.64 (q, H_3CC=), 30.12 (t, CH_2S), 61.27 (t, 2 × CH_2O), 109.06 (s, NC=), 113.99 (d, pyridone α-CH), 128.18 and 135.7 (2s, olefinics), 138.91 (d, pyridone β-CH), 155.59 (s, NCS) and 162.20, 162.47 and 164.10 (3s, 3 × CO).

Diethyl 3-*Methyl*-6-*oxo*-2H,6H-*pyrido*[2,1-b][1,3]*thiazine*-4,9-*dicarboxylate* **22** (R^1 = R^2 = Et).—*Method B.* Ethyl 2-ethoxycarbonylmethylene-2,3-dihydro-5-methyl-6*H*-1,3-thiazine-4-carboxylate **2** (R^1 = R^2 = Et) (2.5 g, 9.2 mmol), 3-chloroacrylic acid[10] (1.0 g, 9.4 mmol) and freshly distilled phosphorus trichloride (1.3 g, 9.5 mmol) in dry dioxane (10 cm^3) and dry benzene (5 cm^3) were heated to reflux under nitrogen for 3 h until TLC (silica:ether–hexane, 3:1) showed that the thiazine had reacted. The solvent was removed under reduced pressure and the residue was taken up in ethyl acetate and washed with saturated aqueous sodium hydrogen carbonate and water and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude solid was recrystallised from ethyl acetate to yield the pyridone **20** (R^1 = R^2 = Et) as yellow prisms (1.03 g, 34%), m.p. 149–151 °C; with spectra identical with those of the sample prepared above.

Method C. Propiolic acid (260 mg, 3.7 mmol) and DCC (770 mg, 3.74 mmol) in dry dichloromethane (5 cm^3) were added to a stirred solution of ethyl 2-ethoxycarbonylmethylene-2,3-dihydro-5-methyl-6*H*-1,3-thiazine-4-carboxylate **2** (R^1 = R^2 = Et) (1 g, 3.7 mmol) in dry dichloromethane (10 cm^3). The solution was stirred under nitrogen for 70 h at room temperature and then filtered through grade I alumina (Woelm, neutral) to remove precipitated dicyclohexylurea which was washed with dichloromethane. The solvent was removed under reduced pressure to yield a crude solid, which was recrystallised from chloroform–hexane to yield yellow prisms (0.40 g, 34%), m.p. 149–151 °C; with spectra identical with those of the sample above.

9-*Benzyl* 4-*Ethyl* 3-*Methyl*-6-*oxo*-2H-*pyrido*[2,1-b][1,3]*thiazine*-4,9-*dicarboxylate* **22** (R^1 = $PhCH_2$, R^2 = Et).—A solution of DCC (7.23 g, 0.033 mol) in dry dichloromethane (50 cm^3) was added dropwise to a stirred solution of ethyl 2-benzyloxycarbonylmethylene-2,3-dihydro-5-methyl-6*H*-1,3-thiazine-4-carboxylate **2** (R^1 = $PhCH_2$, R^2 = Et) (10 g, 0.03 mol) and propiolic acid (2.3 g, 0.033 mol) in dry dichloromethane (200 cm^3) under an atmosphere of nitrogen at room temperature. The solution was stirred for 3 d at room temperature during which time it turned from orange to dark brown. It was then filtered through Celite to remove precipitated dicyclohexylurea. The solvent was removed under reduced pressure to yield a dark gum which was purified by flash chromatography (silica) to yield two components, the first, eluting with ether–hexane (1:3) proving to be unchanged starting material (3.7 g). The second component eluted with ether–hexane (2:1) as a pale oil which crystallised from chloroform–hexane as pale yellow prisms (5.35

g, 73%), m.p. 106–109 °C (Found: C, 62.6; H, 5.2; N, 3.6. $C_{20}H_{19}NO_5S$ requires C, 62.3; H, 4.9; N, 3.6%); *m/z* 385 (M^+); λ_{max}(MeOH)/nm 277, 298sh, 313sh, 328sh and 348 (log ε 3.74, 3.50, 3.34, 3.28 and 3.10); ν_{max}(KBr)/cm^{-1} 1735 and 1700 (esters) and 1655 (pyridone); δ_H(C^2HCl_3; 90 MHz) 1.2 (3 H, t, *J* 7, CH_3), 2.3 (3 H, s, CH_3C=), 3.15 (2 H, s, CH_2S), 4.2 (2 H, q, *J* 7, CH_2O), 5.3 (2 H, s, $PhCH_2O$), 6.25 (1 H, d, *J* 9, pyridone α-CH), 7.35 (5 H, br s, aromatics) and 7.9 (1 H, d, *J* 9, pyridone β-CH); δ_C(C^2HCl_3; 20.15 MHz) 13.86 (q, CH_3), 18.76 (q, CH_3C=), 30.15 (t, CH_2S), 61.39 (t, CH_2O), 67.89 (CH_2Ph), 108.76 (s, *C*CO_2Bz), 114.89 (d, pyridone α-CH), 128.32–128.61 (aromatics), 135.84 (s, NC=), 139.00 (d, pyridone β-CH), 156.28 (s, NCS) and 162.26, 162.48 and 163.94 (3s, C=O).

Ethyl 2-[(1Z,2E)-1,3-*Dibenzyloxycarbonylprop*-2-*enylidene*]-3,6-*dihydro*-5-*methyl*-2H-1,3-*thiazine*-4-*carboxylate* **18** (R^1 = R^3 = $PhCH_2$, R^2 = Et) was always present and was isolated on one occasion in 16% yield by chromatography, eluting before the pyridone **20** (R^1 = $PhCH_2$, R^2 = Et) using the same solvent system; m.p. 116–117 °C (Found: C, 65.5; H, 5.4; N, 2.7. $C_{27}H_{27}NO_6S$ requires C, 65.7; H, 5.5; N, 2.8%); *m/z* (CI) 494 (M^+ + 1); λ_{max}(MeOH)/nm 224, 310 and 370 (log ε 4.08, 4.12 and 4.41); δ_H(C^2HCl_3; 360 MHz), 1.39 (3 H, t, *J* 7, CH_3), 2.35 (3 H, s, CH_3C=), 3.31 (2 H, s, CH_2S), 4.35 (2 H, q, *J* 7, CH_2O), 5.19 (2 H, s, CH_2Ph), 5.33 (2 H, s, CH_2Ph), 6.32 (1 H, d, *J* 15, olefinic), 7.25–7.40 (10 H, m, aromatics), 7.84 (1 H, d, *J* 15, olefinic) and 12.79 (1 H, s, NH); δ_C(C^2HCl_3; 90.55 MHz) 14.12 (CH_3), 19.84 (CH_3C=), 31.49 (CH_2S), 62.02 (CH_2O), 65.56 (CH_2Ph), 66.15 (CH_2Ph), 96.43 (NC=C), 113.97 (olefinic), 124.30 (CH_2CCH_3), 125.86 (HN*C*CO_2Et), 127.81–137.05 (aromatics), 139.52 (olefinic), 161.03 (NCS) and 162.30, 168.02 and 168.56 (3 × CO).

Methyl 9-*Benzyloxycarbonyl*-3-*methyl*-6-*oxo*-2H,6H-*pyrido*-[2,1-b]-1,3-*thiazine*-4-*carboxylate* **22** (R^1 = $PhCH_2$, R^2 = CH_3).—DCC (6.5 g, 31.5 mmol) in dichloromethane (50 cm^3) was added dropwise to a stirred solution of methyl 2-benzyloxycarbonylmethylene-2,3-dihydro-5-methyl-6*H*-1,3-thiazine-4-carboxylate **2** (R^1 = $PhCH_2$, R^2 = CH_3) (10.0 g, 31.3 mmol) and propiolic acid (2.20 g, 31.3 mmol) in dry methylene dichloride (200 cm^3). The solution was stirred under nitrogen for 4 d at room temperature and then filtered through Celite to remove the precipitated dicyclohexylurea. The solvent was removed under reduced pressure to yield an orange solid, which was flash chromatographed (silica gel: ether–hexane, 1:1) to yield a yellow solid. This was recrystallised from methanol (6.31 g, 54%), m.p. 145–147 °C (Found: C, 61.1; H, 4.7; N, 3.5. $C_{19}H_{17}NO_5S$ requires C, 61.4; H, 4.6; N, 3.8%); *m/z* 371 (M^+); λ_{max}(MeOH)/nm 213, 278, 296 and 348 (log ε 3.70, 3.63, 3.54 and 3.30); ν_{max}(KBr)/cm^{-1} 1724 and 1698 (esters) and 1651 (pyridone); δ_H(C^2HCl_3; 90 MHz) 2.31 (3 H, s, CH_3C=), 3.16 (2 H, s, CH_2S), 3.71 (3 H, s, OCH_3), 5.42 (2 H, s, CH_2Ph), 6.31 (1 H, d, *J* 10, pyridone α-CH), 7.42 (5 H, m, aromatics) and 7.93 (1 H, d, *J* 10, pyridone β-CH); δ_C(C^2HCl_3; 90.55 MHz) 18.82 (CH_3), 30.18 (CH_2S), 52.16 (OCH_3), 67.13 (CH_2Ph), 108.99 (*C*CO_2Bz), 114.19 (pyridone α-C), 127.97–128.68 (aromatics), 135.74 (C=*C*CH_3), 136.15 (C=*C*CO_2CH_3), 139.05 (pyridone β-C), 156.12 (NCS) and 162.44, 162.82 and 163.94 (3 × C=O).

Methyl 2-[(1Z,2E)-1,3-*Bis*(*benzyloxycarbonyl*)*prop*-2-*enylidene*]-3,6-*dihydro*-5-*methyl*-2H-1,3-*thiazine*-4-*carboxylate* **18** (R^1 = R^3 = $PhCH_2$, R^2 = CH_3).—This compound was always present from the above reaction and in one instance was isoated by chromatography, eluting before the pyridone **20** (R^1 = $PhCH_2$, R^2 = CH_3) using the same solvent system (2.9 g, 19%), m.p. 126–127 °C; *m/z* 479.1399 (M^+) ($C_{26}H_{25}NO_6S$ requires 479.1402); λ_{max}(MeOH)/nm 229, 307 and 376 (log ε 4.05, 4.12 and 4.7); δ_H(C^2HCl_3; 80 MHz), 2.34 (3 H, s, CH_3), 3.30 (2 H, s, CH_2S), 3.88 (3 H, s, OCH_3), 5.17 (2 H, s, CH_2Ph), 5.32 (2 H, s, CH_2Ph), 6.30 (1 H, d, *J* 15.4, olefinic), 7.36 (10 H, m, aromatics) and 7.84 (1 H, d, *J* 15.4, olefinic); δ_C(C^2HCl_3; 90.55 MHz) 19.81 (CH_3), 31.36 (CH_2S), 52.53 (OCH_3), 65.44 and 66.08 (2 × CH_2Ph), 96.34 (NC=*C*CO_2CH_2Ph), 113.99 (olefinic), 127.74–128.47 (aromatics), 136.18, 136.93, 139.41 and 160.92 (olefinics) and 162.73, 167.88 and 168.38 (3 × C=O).

5-(2-*Oxopropylidene*)*pyrrolidine*-2-*carboxylate* **26**.—A solution of bromoacetone[14] (1.3 g, 9.5 mmol) in dry dichloromethane (10 cm^3) was added in one portion to a solution of methyl 5-thioxoproline **25**[13] (1.5 g, 9.4 mmol) in dry dichloromethane (10 cm^3) at room temperature. The solvent was immediately removed under reduced pressure at room temperature and the residue was left under high vacuum for 4 h. The resulting syrup was suspended in dichloromethane and washed with saturated aqueous sodium hydrogen carbonate and dried (Na_2SO_4). The solvent was removed under reduced pressure to yield the enethiol ether as an oil which was used without further purification (1.76 g, 87%), *m/z* 215 (M^+); ν_{max}(KBr)/cm^{-1} 1735 (ester) and 1710 (ketone); δ_H(C^2HCl_3; 90 MHz) 2.23 (3 H, s, CH_3), 2.3–2.9 (4 H, m, CH_2), 3.70 (3 H, s, OCH_3), 4.02 (2 H, s, CH_2S) and 4.65 (1 H, t, *J* 8, CH).

The enethiol ether was heated to reflux in dry benzene (15 cm^3) with triphenylphosphine (10 g, 38 mmol) under nitrogen for 20 h. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane. The compound was extracted into orthophosphoric acid (1 mol dm^{-3}) which was then neutralised with aqueous sodium hydrogen carbonate and extracted with chloroform and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude material was purified by chromatography (chromatotron silica: ether–hexane, 1:3) to yield a pale oil (6.96 mg, 47%), *m/z* 183.0885 ($C_9H_{13}NO_3$ requires 183.0895); ν_{max}(liquid film)/cm^{-1} 3250 (NH), 1740 (ester) and 1700 (enone); δ_H(C^2HCl_3; 90 MHz) 2.04 (3 H, s, CH_3), 2.1–2.8 (4 H, m, CH_2), 3.76 (3 H, s, OCH_3), 4.42 (1 H, dd, *J* 5.4 and 8.1, CH) and 5.14 (1 H, s, olefinic).

Methyl 5-*Oxo*-8-(2-*oxoethyl*)-1,2,3,5-*tetrahydroindolizine*-3-*carboxylate* **27**.—Propiolic acid (0.55 g, 7.9 mmol) was added to a stirred solution of the enaminone **26** (1.3 g, 7.1 mmol) in dry dichloromethane (10 cm^3) at 0 °C under argon followed by DCC (1.61 g, 7.8 mmol) in dry dichloromethane (5 cm^3). The solution was stirred at 0 °C for 1 h and at room temperature for 2 d. The suspension was filtered through Celite to remove precipitated dicyclohexylurea and the solvent was removed under reduced pressure to yield a dark syrup. The crude material was purified by medium pressure liquid chromatography (silica; ethyl acetate) to yield the pyridone **27** as a pale oil (350 mg, 22%), *m/z* 235.084 45 ($C_{12}H_{13}NO_4$ requires 235.0845); ν_{max}(CH_2Cl_2)/cm^{-1} 1745 (ester), 1690 (ketone) and 1650 (pyridone); δ_H(C^2HCl_3; 90 MHz) 2.49 (3 H, s, CH_3), 3.64–4.11 (4 H, m, CH_2), 3.78 (3 H, s, OCH_3), 5.16 (1 H, dd, *J* 5 and 9, NCH), 6.44 (1 H, d, *J* 10, pyridone α-CH) and 7.82 (1 H, d, *J* 10, pyridone β-CH); δ_C(C^2HCl_3; 90.55 MHz) 25.58 (CH_2), 27.78 (CH_3), 33.21 (CH_2), 52.81 (OCH_3), 61.54 (CH), 116.91 (pyridone α-CH) and 140.5 (pyridone β-CH).

Tosyl Hydrazone.—*p*-Toluenesulphonylhydrazine (160 mg, 0.86 mmol) was added to a solution of the pyridone **27** (134 mg, 0.57 mmol) in absolute ethanol (1 cm^3) with stirring under argon at room temperature. The solution was stirred at reflux under argon for 2 h and allowed to cool. The solvent was removed under reduced pressure to yield a pale foam which was purified by medium pressure liquid chromatography (silica; ethyl acetate) to yield a white crystalline solid (132 mg, 57%), m.p. 80–87 °C; *m/z* (positive CI, NH_3) 404 (M^+ + 1); ν_{max}(CH_2Cl_2)/cm^{-1} 1740 (ester) and 1660 (pyridone); δ_H(C^2HCl_3; 90 MHz) 2.1 (3 H, s, CH_3) 2.25 (2 H, m, CH_2), 2.4 (3 H, s, CH_3), 3.18 (2 H, t, *J* 7.7, CH_2), 3.76 (3 H, s, OCH_3), 5.09 (1 H,

dd, *J* 3.9 and 9, CH), 6.37 (1 H, d, *J* 10, pyridone α-CH), 7.26 (2 H, d, *J* 7.7, aromatic), 7.37 (1 H, d, *J* 10, pyridone β-CH), 7.77 (2 H, d, *J* 7.7, aromatic) and 8.34 (1 H, br, s, NH).

Ethoxycarbonylacetimino Ethyl Ether Hydrochloride.—A solution of freshly distilled ethyl cyanoacetate (5 g, 44 mmol) in dry ether (40 cm^3) and dry ethanol (2.3 g, 50 mmol) was saturated with dry hydrogen chloride gas at −5 °C over a period of 10 min and stirred for a further 1.5 h. The solvent was removed under reduced pressure to yield a white solid which was washed with dry ether and dried under reduced pressure (7.9 g, 92%), m.p. 100–102 °C; $\delta_H([^2H_6]$-DMSO; 90 MHz) 1.2 (6 H, m, 2 × CH_3), 4.0 (4 H, m, CH_2) and 4.4 (2 H, d, CH_2).

Ethyl 2-Ethoxycarbonylmethylene-5,5-dimethylthiazolidine-4-carboxylate **28**.—Ethoxycarbonylacetimino ethyl ether hydrochloride (120 mg, 0.61 mmol) was added to a solution of (±)-penicillamine ethyl ester (90 mg, 0.62 mmol) in dry tetrahydrofuran (THF) (10 cm^3) and dry methanol (5 cm^3). The solution was heated to reflux under nitrogen for 2.5 h, allowed to cool and filtered to remove precipitated ammonium chloride. The solvent was removed under reduced pressure to yield a pale oil which was purified by chromatography (chromatotron silica:ether–hexane, 1:5). The *product* was an oil which yielded white flakes on trituration with diethyl ether (78 mg, 46%), m.p. 103–105 C (Found: C, 52.6; H, 6.9; N, 5.3. $C_{12}H_{19}NO_4S$ requires C, 52.75; H, 6.9; N, 5.1%); *m/z* 273 (M^+); λ_{max}(MeOH)/nm 287 (log ε 3.91); ν_{max}(KBr)/cm^{-1} 3260 (NH) and 1750 (ester); $\delta_H(C^2HCl_3$; 360 MHz, mixture of *E*- and *Z*-isomers) 1.26 and 1.32 (3 H, 2t, *J* 7.2, 2 × CH_3), 1.40 and 1.43 (3 H, 2s, 2 × CH_3), 1.68 and 1.73 (3 H, 2s, 2 × CH_3), 4.12 and 4.28 (2 H, 2q, *J* 7, 2 × CH_2), 4.35 (1 H, s, CH) and 4.63 and 4.73 (2s, olefinics); $\delta_C(C^2HCl_3$; 90.55 MHz), 14.24 and 14.63 (2 × CH_3), 25.22 and 27.15 (CH_3), 25.37 and 28.15 (CH_3), 53.68 (C), 58.89 and 61.78 (2 × CH_2), 71.43 (CHN), 79.50 (CH), 85.25 (CH) and 162.86, 168.08 and 169.30 (C=O).

Ethyl 2-Ethoxycarbonylmethylenethiazolidine-4-carboxylate **29** ($R^1 = R^2$ = Et).—Ethyl L-cysteinate hydrochloride (18.5 g, 0.1 mol), ethoxycarbonylacetimino ethyl ether hydrochloride (19.5 g, 0.1 mol) and potassium acetate (11.36 g) were dissolved in water (58 cm^3) and diethyl ether (58 cm^3). The clear two phase solution was shaken at room temperature for 4 h and the aqueous phase was extracted with chloroform. The organic layers were washed with water and dilute hydrochloric acid and dried (Na_2SO_4). The solvent was removed under reduced pressure to give an off-white *solid* which was recrystallised from diethyl ether (14.27 g, 58%), m.p. 72–73.5 °C; $[\alpha]_D$ −84.6 (*c* 1.5, $CHCl_3$) (Found: C, 48.9; H, 6.4; N, 5.9. $C_{10}H_{15}NO_4S$ requires C, 49.0; H, 6.1 and N, 5.7%); *m/z* 245 (M^+); λ_{max}(MeOH)/nm 285 (log ε 4.33); ν_{max}(KBr)/cm^{-1} 3300 (NH) and 1730 (ester); $\delta_H(C^2HCl_3$; 360 MHz) 1.22–1.34 (6 H, m, 2 × CH_3), 3.55–3.67 (2 H, m, CH_2S), 4.08–4.30 (4 H, m, 2 × CH_2); major isomer: 4.79 (1 H, s, HC=), 5.05–5.11 (1 H, tt, *J* 1.3 and 9.4, NCH=) and 8.6 (1 H, s, NH); minor isomer: 4.62 (1 H, td, *J* 1 and 6.6, NCH=); $\delta_H(C_6{}^2H_6$; 360 MHz) major isomer: δ 0.81 and 1.0 (2 × 3 H, 2t, *J* 7, 2 × CH_3), 2.5 (1 H, dd, *J* 7.5 and 11, CHS), 2.8 (1 H, dd, *J* 4.4 and 11, CHS), 3.6 (1 H, q, *J* 4.4 and 7.5, NCH), 3.7 (2 H, q, *J* 7, CH_2O), 4.1 (2 H, dq, *J* 1.6 and 7, CH_2O) and 5.1 (1 H, s, NC=CH); minor isomer: δ 0.84 and 0.86 (6 H, 2t, *J* 7, 2 × CH_3), 2.8 (1 H, m, *J* 4.4 and 11, CHS), 3.2–3.3 (2 H, dd, CH_2), 3.4 (1 H, d, *J* 8.8, CHS), 3.9 (4 H, 2q, 2 × CH_2) and 4.8 (1 H, m, *J* 8.8 and 11, NCH); $\delta_C(C^2HCl_3$; 90.5 MHz) 14.09, 14.12, 14.17 and 14.59 (4 × CH_3), 31.42, 36.29, 40.2 and 58.94 (4 × CH_2), 61.48, 61.75 and 62.1 (3 × CH_2S), 62.25 (NC=CH), 77.98 and 80.07 (NC), 164.2 and 166.72 (NC=) and 167.57, 169.14, 169.71 and 170.39 (4 × C=O).

Methyl 2-Benzyloxymethylenethiazolidine-4-carboxylate **29** ($R^1 = PhCH_2$, $R^2 = CH_3$).—A solution of methyl L-cysteinate hydrochloride (0.75 g, 4.3 mmol) benzyloxycarbonylacetimino ethyl ether hydrochloride (1.1 g, 4.1 mmol) and potassium acetate (0.5 g) in water (1 cm^3) and ether (1 cm^3) was shaken for 4 h at room temperature. The solution was extracted with chloroform, washed with water and dilute hydrochloric acid and dried (Na_2SO_4). The solvent was removed under reduced pressure. The resulting oil was purified by chromatography (silica:ether–hexane, 1:3) to give the thiazolidine as a pale yellow oil (0.45 g, 35%), *m/z* 294 ($M + 1^+$); λ_{max}(MeOH)/nm 285; ν_{max}(liquid film)/cm^{-1} 3350 (NH) and 1750 and 1730 (ester); $\delta_H(C^2HCl_3$; 360 MHz) 3.40–3.50 (2 H, m, CH_2S), 3.79 and 3.80 (3 H, 2s, OCH_3), 4.62 (1 H, dd, *J* 6.5 and 7.5, CH), 4.70 and 4.89 (1 H, 2s, olefinic), 5.06 and 5.21 (2 H, m, OCH_2) and 7.36 (5 H, m, aromatics). *N.B.* The sample was essentially a mixture of *E*-and *Z*-isomers in an approximate ratio of 2:1.

Diethyl 2,3-Dihydro-2,2-dimethyl-5-oxo-5H-thiazolo[3,2-a]pyridine-3,8-dicarboxylate **31**.—DCC (0.4 g, 1.9 mmol) was added to a stirred solution of ethyl 2-ethoxycarbonylmethylene-5,5-dimethylthiazolidine-4-carboxylate **28** ($R^1 = R^2$ = Et) (0.4 g, 1.5 mmol) in dry dichloromethane (5 cm^3) at room temperature under nitrogen followed by propiolic acid (0.16 g, 2.2 mmol) in dry dichloromethane (2 cm^3). The solution was stirred overnight and the solvent was removed under reduced pressure to yield a residue which was taken up in chloroform and filtered through a short column of alumina (Woelm, neutral, grade I) to remove the urea. The residue was then purified by chromatography (chromatotron silica:ether–hexane, 4:1) to yield an off-white solid which was recrystallised from chloroform–hexane to yield white *prisms* (0.30 g, 63%), m.p. 106–108 °C (Found: C, 54.9; H, 6.2; N, 4.3. $C_{15}H_{19}NO_5S$ requires C, 55.4; H, 5.85; N, 4.3%); *m/z* 325 (M^+); λ_{max}(MeOH, pH 7)/nm 279sh, 286, 311sh, 323 and 336sh (log ε 3.90, 3.93, 3.70, 3.76 and 3.67); ν_{max}(KBr)/cm^{-1} 1740 and 1700 (esters) and 1660 (pyridone); $\delta_H(C^2HCl_3$; 360 MHz) 1.29 and 1.36 (2 × 3 H, t, *J* 7.1, 2 × CH_3), 1.58 (3 H, s, CH_3), 1.68 (3 H, s, CH_3), 4.27 and 4.33 (2 × 2 H, q, *J* 7.1, 2 × CH_2), 5.12 (1 H, s, CH), 6.24 (1 H, d, *J* 9.5, pyridone α-CH) and 7.87 (1 H, d, *J* 9.5, pyridone β-CH); $\delta_C(C^2HCl_3$; 20.15 MHz) 14.09 and 14.38 (2q, 2 × CH_3), 23.80 (q, CH_3), 33.14 (q, CH_3), 51.24 (s, CMe_2S), 61.17 and 62.12 (2t, 2 × CH_2), 72.04 (d, CH), 114.01 (d, pyridone α-CH), 140.15 (d, pyridone β-CH) and 166.42 (C=O).

Diethyl 2,3,6,7-Tetrahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3,8-dicarboxylate **32**.—Phosphorus trichloride (600 mg, 4.3 mmol) was added to ethyl 2-ethoxycarbonylmethylene-thiazolidine-4-carboxylate **29** ($R^1 = R^2$ = Et) (2 g, 8.1 mmol) in dry benzene (20 cm^3) and dry dioxane (40 cm^3) and the solution was stirred under nitrogen at room temperature for 30 min. Acrylic acid (0.7 g, 9.7 mmol) in dry dioxane (10 cm^3) was added dropwise and the solution was heated to reflux for 2.5 h. The solvent was removed under reduced pressure and the crude product was extracted with chloroform and washed successively with saturated aqueous sodium hydrogen carbonate and water, and dried ($MgSO_4$). The solvent was removed under reduced pressure to give a yellow solid which was recrystallised from methanol to give a white *solid* (1.11 g, 45%), m.p. 108–109 °C; $[\alpha]_D^{25}$ −325 (*c* 2, $CHCl_3$) (Found: C, 52.5; H, 5.7; N, 4.4. $C_{13}H_{17}NO_5S$ requires C, 52.2; H, 5.7 and N, 4.7%); *m/z* 299 (M^+); ν_{max}(KBr)/cm^{-1} 1735 and 1708 (esters) and 1676 (pyridone); λ_{max}(MeOH)/nm 240 and 298 (log ε 4.19 and 4.31); $\delta_H(C^2HCl_3$; 360 MHz) 1.28 and 1.31 (6 H, 2t, *J* 7, CH_3), 2.6–2.9 (4 H, m, CH_2), 3.32–3.49 (2 H, ABX, *J* 12, 2 and 7.7, CH_2S), 4.25 (4 H, m, CH_2O) and 5.32 (1 H, dd, *J* 7.7 and 2, NCH); $\delta_C(C^2HCl_3$; 90.55 MHz) 14.1 and 14.5 (2 × CH_3), 21.46 and

30.97 (2 × CH_2), 31.36 (CH_2S), 60.54 and 62.27 (2 × CH_2O), 60.16 (NCH), 100.08 and 151.03 (olefinic), and 166.54, 168.38 and 168.63 (3 × carbonyl).

Diethyl 2,3-*Dihydro*-5-*oxo*-5H-*thiazolo*[3,2-a]*pyridine*-3,8-*dicarboxylate* **33** (R^1 = R^2 = Et).—A solution of DCC (2.4 g, 11.6 mmol) in dry dichloromethane (20 cm^3) was added dropwise to a stirred solution of ethyl 2-ethoxycarbonylmethylenethiazolidine-4-carboxylate **29** (R^1 = R^2 = Et) (4 g, 16 mmol) and propiolic acid (1.2 g, 17.1 mmol) in dry dichloromethane (30 cm^3) under nitrogen at room temperature. The solution was stirred at room temperature for 4 d. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (silica:diethyl ether–hexane, 3:1) to give a yellow *solid* (1.28 g, 27%), m.p. 165–172 °C; $[\alpha]_D$ −324.7 (*c* 1.5, $CHCl_3$) (Found: C, 52.4; H, 5.5; N, 4.6. $C_{13}H_{15}NO_5S$ requires C, 52.5; H, 5.1; N, 4.7%); *m/z* 297 (M^+); λ_{max}(MeOH)/nm 290, 319 and 334sh (log ε 4.09, 3.87 and 3.76); ν_{max}(KBr)/cm^{-1} 1735 and 1694 (esters) and 1661 (pyridone); δ_H($C_5{}^2H_5N$; 360 MHz) 1.09 and 1.21 (2 × 3 H, 2t, 2 × CH_3), 3.7–3.88 (2 H, ABX, *J* 2.5, 9.7 and 12.0, CH_2S), 4.17–4.29 (4 H, m, 2 × CH_2), 5.9 (1 H, dd, *J* 2.5 and 9.7, NCH), 6.4 (1 H, d, *J* 9.5, CH=) and 7.8 (1 H, d, *J* 9.5, CH=).

3-*Methyl* 8-*Benzyl* 2,3-*Dihydro*-5-*oxo*-5H-*thiazolo*[3,2-a]*pyridine*-3,8-*dicarboxylate* **33** (R^1 = $PhCH_2$, R^2 = CH_3).—A solution of DCC (0.6 g, 2.9 mmol) in dry dichloromethane (5 cm^3) was added to a stirred solution of the thiazolidine **29** (R^1 = $PhCH_2$, R^2 = CH_3) (1 g, 3.4 mmol) and propiolic acid (0.3 g, 4.3 mmol) in dry dichloromethane (20 cm^3) under nitrogen at room temperature. The solution was stirred for 4 d at room temperature and filtered through Celite to remove precipitated dicyclohexylurea. The solvent was removed under reduced pressure to yield a crude product which was chromatographed (silica:ether–hexane, 3:1). The resulting solid recrystallised from chloroform–hexane as yellow prisms (0.24 g, 20%), m.p. 134–136 °C; $[\alpha]_D^{24}$ −222.5 (*c* 1.24, THF) (Found: C, 58.9; H, 4.6; N, 4.2. $C_{17}H_{15}NO_5S$ requires C, 59.1; H, 4.35; N, 4.1%); *m/z* 345 (M^+); λ_{max}(MeOH)/nm 275sh, 284, 318 and 334sh (log ε 4.15, 4.24, 3.99 and 3.80); ν_{max}(KBr)/cm^{-1} 1740 and 1700 (ester) and 1660 (pyridone); δ_H(C^2HCl_3; 90 MHz) 3.58 (2 H, m, CH_2S), 3.78 (3 H, s, OCH_3), 5.30 (2 H, s, CH_2O), 5.62 (1 H, dd, *J* 3 and 8, CH), 6.27 (1 H, d, *J* 9, pyridone α-CH), 7.38 (5 H, s, aromatics) and 7.89 (1 H, d, *J* 9, pyridone β-CH).

Acknowledgements

We thank Miss Ong Swee Kim for experimental assistance, ICI Pharmaceuticals plc and SERC for CASE studentships (to N. K. C., D. L. and R. W. McC.); and Dr. A. G. Avent for the saturation transfer experiment.

References

1 Published in part as a preliminary communication: R. W. McCabe, D. W. Young and G. M. Davies, *J. Chem. Soc., Chem. Commun.*, 1981, 395.
2 J. E. Baldwin, G. P. Lynch and J. Pitlik, *J. Antibiot.*, 1991, **44**, 1.
3 D. W. Young, in *Molecular Recognition—Chemical and Biochemical Problems*, ed. S. M. Roberts, RSC. London, 1989, p. 56.
4 (*a*) S. H. Eggers, V. V. Kane and G. Lowe, *J. Chem. Soc.*, 1965, 1262; (*b*) G. C. Barrett, S. H. Eggers, T. R. Emerson and G. Lowe, *J. Chem. Soc.*, 1964, 788.
5 M. H. Benn and R. E. Mitchell, *Can. J. Chem.*, 1972, **50**, 2195.
6 C. Rappe, *Acta Chem. Scand.*, 1965, **19**, 31.
7 D. Smith and P. J. Taylor, *Spectrochim. Acta, Part A*, 1976, **32**, 1503.
8 D. Smith and P. J. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1979, 1376.
9 P. B. Hitchcock, R. W. McCabe, D. W. Young and G. M. Davies, *J. Chem. Soc., Chem. Commun.*, 1981, 608.
10 A. N. Kurtz, W. E. Billups, R. B. Greenlee, H. F. Hamil and W. T. Pace, *J. Org. Chem.*, 1965, **30**, 3141.
11 J. S. Mynderse, S. K. Samlaska, D. S. Fukuda, R. H. Dubus and P. J. Baker, *J. Antibiot.*, 1985, **38**, 1003.
12 A. H. Hunt, J. S. Mynderse, S. K. Samlaska, D. S. Fukuda, G. M. Maciak, H. A. Kirst, J. L. Occolowitz, J. K. Schwartzendruber and N. D. Jones, *J. Antibiot.*, 1988, **41**, 771.
13 J. S. Petersen, G. Fels and H. Rapoport, *J. Am. Chem. Soc.*, 1984, **106**, 4539.
14 P. A. Levene, in *Organic Synthesis*, Coll. Vol. 2, ed. A. H. Blatt, Wiley, New York, 1943, p. 88.
15 N. K. Capps, D.Phil. Thesis, Sussex, 1984.
16 F. G. Fang and S. J. Danishefsky, *Tetrahedron Lett.*, 1989, **30**, 3621.
17 D. M. Green, A. G. Long, P. J. May and A. F. Turner, *J. Chem. Soc.*, 1964, 766.
18 E. Vogel and H. Schinz, *Helv. Chim. Acta*, 1950, **33**, 116.
19 T. Wieland, G. Ohnacker and W. Ziegler, *Chem. Ber.*, 1957, **90**, 194.

Paper 1/03604A
Received 15*th July* 1991
Accepted 2*nd August* 1991