# Synthesis of reactive γ-lactams related to penicillins and cephalosporins[1]

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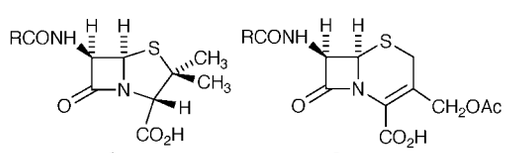
γ-Lactams with structures analogous to both penicillin (**1**) and cephalosporin (**2**) antibiotics have been synthesised. These compounds show high reactivity towards modest nucleophiles in keeping with their design as potential inhibitors of bacterial cell wall biosynthesis. Reactive γ-lactam analogues **27** and **29** of β-lactamase inhibitors such as **22** have also been prepared. An X-ray crystal structure of the cephalosporin analogue **8** has allowed structural comparisons to be made with the classical β-lactam antibiotic cephaloridine (**30**).

The antibacterial effect of β-lactam antibiotics such as penicillins (**1**) and cephalosporins (**2**) is due to their capacity to disrupt bacterial cell wall biosynthesis. This is achieved by the antibiotics acting as inhibitors of penicillin binding proteins (PBPs) which are membrane bound serine peptidases. PBPs recognise D-alanyl-D-alanine peptide termini and the structural and conformational similarity of the β-lactam antibiotics to these natural peptide substrates for PBPs is believed to ensure their acceptance by the target proteins. The high reactivity of the fused β-lactam ring towards nucleophiles then results in the formation of a covalent PBP–antibiotic complex which prevents the PBPs from taking further part in bacterial cell wall synthesis.

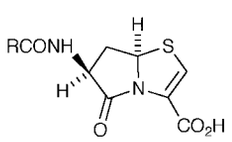
The extensive use of classical β-lactam antibiotics such as penicillin (**1**) in medicine has resulted in an increasing



**1**



**2**



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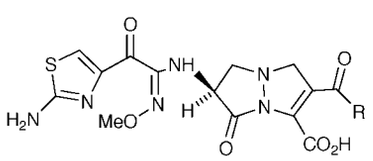

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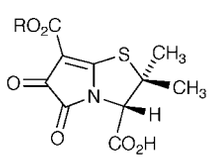
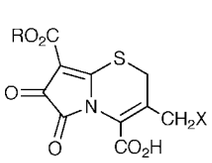


**5**



**6**

number of resistant strains of bacteria through mutation and β-lactamase gene transfer. There has, therefore, been much effort expended in recent years to prepare new structural types which will both target the PBPs and overcome the defence mechanisms of the bacteria.[2] In an attempt to move away from the β-lactam motif, several research groups have investigated the synthesis of non-β-lactam compounds, and γ-lactams and their analogues have proved popular targets.[2,3] In 1986, Baldwin *et al.*[4] prepared the compounds **3** which were γ-lactam analogues of the 6-acylaminopenems which had been prepared by Woodward and co-workers[5] who found them to be too reactive for practical use as anti-bacterial compounds. The γ-lactam analogues **3** had weak but real antibacterial activity against both Gram positive and Gram negative organisms. Pyrazolidinone-containing compounds such as the carbapenem analogues **4** prepared by the Eli Lilly group[6] have been proven to bind to bacterial PBPs[7] and to have useful *in vitro*[8] and *in vivo*[9] antibacterial properties.

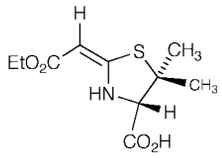
In a search for γ-lactams which would resemble the classical β-lactam antibiotics sufficiently to be accepted by PBPs and which would have a reactive amide ring, we selected compounds of the general type **5** and **6** as targets. These would structurally resemble penicillins (**1**) and cephalosporins (**2**) and the vinylogous urethane/amide properties provided by the conjugated system in the five-membered ring should compete for the lone pair on the nitrogen atom of the lactam ring. This should make the lactam carbonyl group more electrophilic. An additional destabilising feature would be the Coulombic interaction in the *cis* α-dicarbonyl system in the compounds.

We had prepared the thiazine **7**[10] and used it in a combined Michael addition–cyclisation reaction to prepare six-six and six-seven fused bicyclic compounds, and so it seemed an appropriate synthon from which to prepare a compound related to **6** above. Treatment of the thiazine **7** with oxalic acid under the phosphazo coupling conditions which had proved successful in our earlier studies[10] met with failure but when the thiazine was reacted with one equivalent of oxalyl chloride in methylene chloride containing triethylamine, a 63% yield of a solid, $C_{12}H_{11}NO_6S$, was obtained as shown in Scheme 1. There were four separate carbonyl absorptions in the IR spectrum at 1768, 1736, 1703 and 1659 $cm^{-1}$ and in the $^{13}C$ NMR spectrum at 161, 162, 172 and 181 ppm. The UV spectrum ($\lambda_{max}$ 243, 273, 318 and 427 nm) was considerably shifted from that of the starting thiazine **7** ($\lambda_{max}$ 224, 281 and 336 nm). These data were in keeping with the product being the desired bicyclic γ-lactam **8** and its lability was evident from the fact that, when it was warmed in methanol for ten minutes, the compound reacted to give the methanol adduct, $C_{13}H_{15}NO_7S$, $\lambda_{max}$ 230 and 353 nm. The $^1H$- and $^{13}C$-NMR spectra indicated that this was a mixture of the thiazine **9** and its geometric isomer **10**.

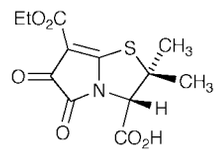
We had therefore succeeded in synthesising an extremely labile γ-lactam **8** with structural similarity to a cephalosporin antibiotic. It had no antibacterial properties as measured by an agar dilution method using surface inoculation of bacteria but, since it was an ester, this was not surprising. Various attempts to prepare the free acid from the methyl ester were unsuccessful due to the lability of the ring system. We therefore prepared the thiazine allyl ester **13** as shown in Scheme 2 by condensation of ethoxycarbonylthioacetamide (**11**)[10] with allyl 2-oxo-3-methylbut-3-enoate (**12**).[11] This was converted to the γ-lactam allyl ester **14** using oxalyl chloride but we were unable to access the free acid from this using $Pd(PPh_3)_4$ catalyst.

To obtain a thiazolidine analogue of our reactive γ-lactam, we then reacted the thiazolidine **15**[10] with oxalyl chloride as before and obtained the product **16** as an orange gum in 56% yield as shown in Scheme 3. This had the expected $^1$H- and $^{13}$C-NMR spectra, $\nu_{max}$ 1771, 1738, 1733 and 1683 cm$^{-1}$ and $\lambda_{max}$ 243, 286 and 382 nm. Reaction of this compound with ethanol at room temperature for 30 minutes gave the expected ring opened product **17** as a mixture of geometric isomers. Interestingly when the thiazolidine **15** was reacted with ethyl oxalyl chloride (2-ethoxy-2-oxoacetylchloride) in an attempt to synthesise this compound independently, the reaction gave a different product, the reaction occurring at the nitrogen atom of the enamine system rather than at carbon. The product was the single isomer **18** at 25 °C but variable temperature NMR spectroscopic experiments showed that there were two conformational isomers at −40 °C.

The free acid **20** of the penicillin analogue was finally obtained, albeit in impure form, by first reacting freshly prepared ethoxycarbonylacetimino ethyl ether hydrochloride[10] with penicillamine hydrochloride to yield the thiazolidine free acid **19** and then reacting this with oxalyl chloride. This free acid had spectra in keeping with the analogous compounds **8** and **16** but still had no useful antibacterial properties using the above agar dilution method. In view of the reactivity of the system, noted below, this might be due to the compound not surviving the time period of the MIC test.

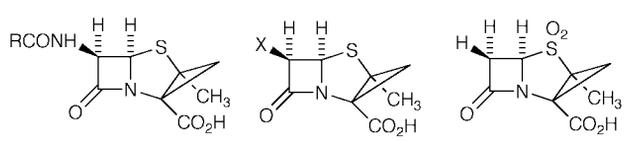


**19**

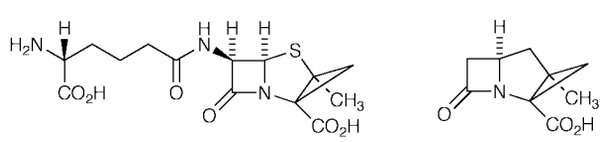


**20**

It has been reported that the tricyclic β-lactams **21** are substrates for β-lactamases[12,13] and that the β-lactams **22** and **23** are β-lactamase inhibitors.[13] Further, the tricyclic β-lactam **24** has been shown to be a potent reversible inhibitor of deacetoxycephalosporin C synthase activity[14] and an olivanic acid analogue **25** has been synthesised.[15] Since we had developed a novel synthesis of the cyclopropa[*d*]thiazoline (**26**),[16] it seemed appropriate to prepare the reactive γ-lactam analogue **27** from it by reaction with oxalyl chloride. This was readily achieved as in Scheme 4 but again conversion to a free acid proved elusive. The corresponding allyl ester **28** was therefore prepared by photolysis of the allyl ester **13** as in Scheme 5 and reaction of this with oxalyl chloride gave the desired γ-lactam analogue **29** of the β-lactams **21** to **25**. Again we were unable to access the free acid using $Pd(PPh_3)_4$ as catalyst.

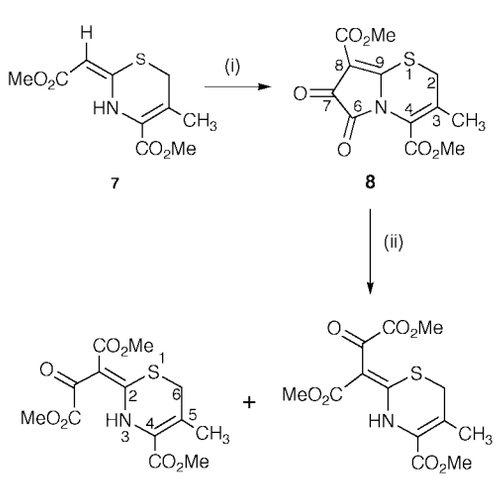


**21** **22 (X = Cl or Br)** **23**



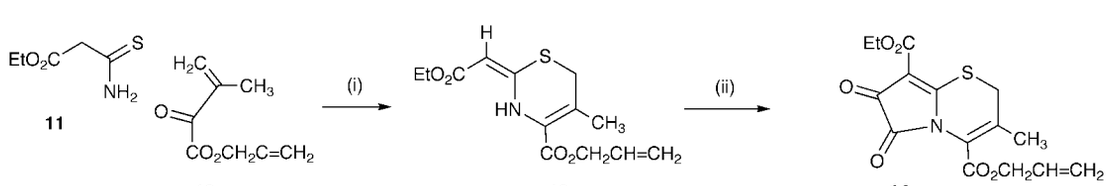
**24** **25**

Having synthesised the compounds **8**, **16** and **20** and shown that compounds **8** and **16** were reactive amides, we now felt that it would be of interest to compare the relative rates of methanolysis of these compounds. This was achieved by



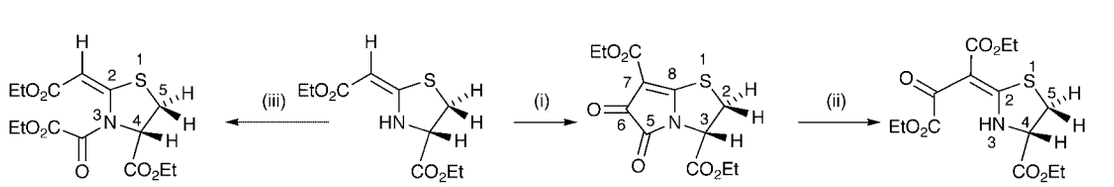
**7** **8** **9** **10**

**Scheme 1** *Reagents*, *conditions and yields*: (i) ClCOCOCl–$NEt_3$–$CH_2Cl_2$, 63%; (ii) MeOH, 90%.



**11** **12** **13** **14**

**Scheme 2** *Reagents*, *conditions and yields*: (i) HCl–dioxane, 62%; (ii) ClCOCOCl–$NEt_3$–$CH_2Cl_2$, 60%.



**18** **15** **16** **17**

**Scheme 3** *Reagents*, *conditions and yields*: (i) ClCOCOCl–$NEt_3$–$CH_2Cl_2$, 56%; (ii) EtOH, 85%; (iii) $EtO_2CCOCl$–$NEt_3$–$CH_2Cl_2$, 67%.

measuring the disappearance of the absorbance at high $\lambda_{max}$ with time on treatment of a solution in acetonitrile with an excess of methanol at room temperature. The results indicated a half-life for the thiazine **8** of 25 min, whereas the thiazolidine **16** had a half-life of 70 min. The free acid **20** had a half-life of 35 min. Further hydrolytic studies in pH 5 buffer indicated that the tricyclic compound **27** was hydrolysed at a similar rate to the bicyclic allyl ester **14**.

In an early attempt to assess the relationship between antibacterial activity and overall structure as determined by X-ray crystallography[17] an earlier suggestion by Woodward and coworkers[18] that biological activity could be ascribed to hindered amide resonance seemed to be confirmed since active compounds had an amide nitrogen with significant pyramidal character and a longer C–N bond and a shorter C–O bond than a normal amide. Later studies by Cohen[19] and Ghuysen and coworkers[20] indicated that the need for the antibacterial compound to fit the target active site was paramount for activity. We therefore recrystallised the γ-lactam **8** from benzene and determined its structure by X-ray analysis. The structure is shown in Fig. 1a from the β-face and in Fig. 1b from along the axis of the γ-lactam ring.

Cohen[19] noted that the more active compounds in his study had their carboxy group closer to the β-lactam amide with a separation distance between the oxygen atom of the amide group and the carbon atom of the carboxylate group of 3.0–3.9 Å, whereas in inactive compounds this distance was more than 4.1 Å. This distance was found to be 2.89 Å in our compound. In view of the suggested relationship between the non-planarity of the amide nitrogen in β- and γ-lactams and biological activity, it is of interest that the amide nitrogen in our compound is nearly planar (sum of the angles at nitrogen, C(1)–N–C(4) + C(1)–N–C(7) + C(4)–N–C(7), is 359.4°). The S–C(4) bond [1.705(3) Å] adjacent to the C(3)–C(4) double bond is significantly shorter than the S–C(5) bond [1.820(4) Å]. Also the C(2)–O(2) bond [1.215(4) Å] is slightly longer and the C(2)–C(3) bond [1.436(5) Å] slightly shorter than normal, perhaps indicating some delocalisation extending from O(2) to S. The C(1)–O(1) bond [1.201(4) Å] is normal. Superimposing our structure on the structure[17] of cephaloridine (**30**) showed good overlay for amide and carboxy groups but not for the sulfur atoms.

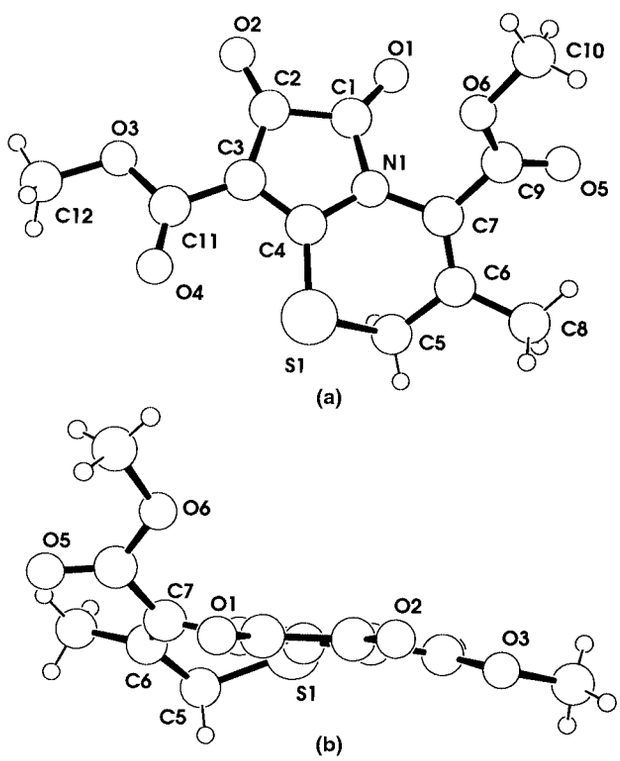
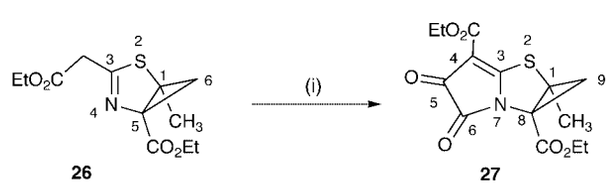
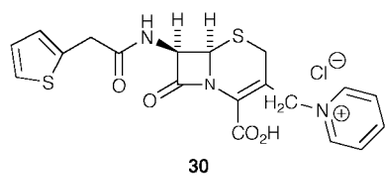



**Fig. 1** Structure of the γ-lactam **8** determined by single crystal X-ray diffraction: (a) viewed from the β-face of the molecule; (b) viewed along the axis of the γ-lactam ring.




**Scheme 4** *Reagents*, *conditions and yields*: (i) ClCOCOCl–$NEt_3$–$CH_2Cl_2$, 61%.




**30**

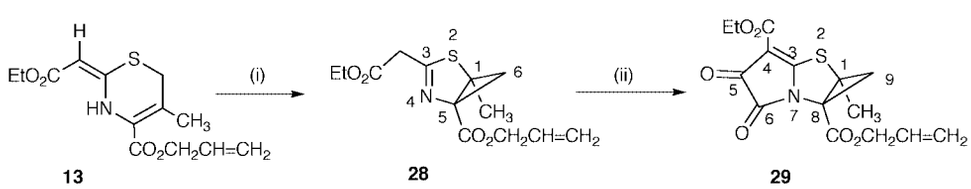
## Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Ultra-violet spectra were recorded using Pye-Unicam SP800 and Philips PU8720 spectrometers. Infra-red spectra were recorded on a Perkin-Elmer PE1710 Fourier Transform spectrometer. $^1$H-NMR spectra were recorded on a Bruker WH360 (360 MHz) spectrometer and $^{13}$C-NMR spectra on a Bruker WH360 (90.55 MHz) spectrometer. *J*-Modulated spin echo experiments were used to help characterise $^{13}$C-NMR spectra where necessary. *J* Values are given in Hz. Tetramethylsilane was used as internal standard. Mass spectra were recorded on Kratos MS80 or MS25 spectrometers at Sussex and at Zeneca Pharmaceuticals, where the accurate mass measurement was obtained. Combustion analyses were provided by Ms K. Plowman and M. Patel at Sussex and by Zeneca Pharmaceuticals. Thin layer chromatography was carried out using Kieselgel $GF_{254}$ (E. Merck), 0.25 mm analytical plates. Preparative chromatography was carried out using a chromatotron (Harrison Research) with 1, 2 or 4 mm thick plates of silica $PF_{254}$ (E. Merck) or columns packed with silica $PF_{254}$60. Petroleum ether refers throughout to a fraction of alkanes.†‡

### Dimethyl 3-methyl-6,7-dioxo-6,7-dihydro-2*H*-pyrrolo[2,1-*b*]-[1,3]thiazine-4,8-dicarboxylate (8)

To a solution of methyl 2,3-dihydro-2-methoxycarbonyl-

† Boiling range 40–60 °C.
‡ Boiling range 60–80 °C.




**Scheme 5** *Reagents*, *conditions and yields*: (i) *hv*–toluene–acetone, 47%; (ii) ClCOCOCl–$NEt_3$–$CH_2Cl_2$, 51%.

methylene-5-methyl-6*H*-1,3-thiazine-4-carboxylate (**7**)[10] (100 mg, 0.41 mmol) in dry methylene chloride (25 ml) was added triethylamine (114 μl, 0.82 mmol) and oxalyl chloride (52 mg, 0.41 mmol). The solution was stirred at room temperature under nitrogen overnight and washed with water. The organic layer was dried ($Na_2SO_4$) and the solvent was removed *in vacuo* to give an orange gum which was triturated with diethyl ether and recrystallised from benzene to yield *dimethyl 3-methyl-6,7-dioxo-6,7-dihydro-2H-pyrrolo[2,1-b][1,3]thiazine-4,8-dicarboxylate* (**8**) (77 mg, 63%), mp 196–198 °C (Found C, 48.0; H, 3.7; N, 4.7%. $C_{12}H_{11}NO_6S$ requires C, 48.5; H, 3.7; N, 4.7%); *m/z* (EI) 297 ($[M]^+$); $\lambda_{max}$ ($CHCl_3$)/nm 243, 273, 318 and 427 ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$ 10230, 10290, 7100 and 2500); $\nu_{max}$ (KBr)/cm$^{-1}$ 1768, 1736, 1703 and 1659; $\delta_H$ (360 MHz, $C^2HCl_3$) 2.04 (3H, s, $CH_3$), 3.42 (2H, s, $CH_2S$), 3.71 (3H, s, $OCH_3$) and 3.75 (3H, s, $OCH_3$); $\delta_C$ (90.55 MHz, $C^2HCl_3$) 18.71 ($CH_3$), 30.83 ($CH_2S$), 51.88 ($OCH_3$), 52.79 ($OCH_3$), 104.55 (C-3), 122.91 (C-8), 124.55 (C-4), 154.20 (N–C–S) and 161.63, 162.00, 171.87 and 180.95 (4 × C=O).

The crystal structure determination of compound **8** has been previously reported,[1] atomic coordinates, bond lengths and angles and other data have been deposited at the Cambridge Crystallographic Data Centre (CCDC) (reference number TOTCUA A8400601).

### Dimethyl 2-(4-methoxycarbonyl-5-methyl-2,3-dihydro-6*H*-1,3-thiazin-2-ylidene)-3-oxosuccinates (9) and (10)

Dimethyl 3-methyl-6,7-dioxo-6,7-dihydro-2*H*-pyrrolo[2,1-*b*]-[1,3]thiazine-4,8-dicarboxylate (**8**) (80 mg, 0.27 mmol) was dissolved in methanol (10 ml) and gently warmed on a water bath for 10 min. The solution was concentrated and cooled. The product crystallised out as a mixture of geometric isomers and was filtered and washed with cold methanol and dried *in vacuo* to yield dimethyl 2-(4-methoxycarbonyl-5-methyl-2,3-dihydro-6*H*-1,3-thiazin-2-ylidene)-3-oxosuccinates (**9**) and (**10**) (80 mg, 90%); mp 143–145 °C (Found C, 46.9; H, 4.5; N, 4.1%. $C_{13}H_{15}NO_7S$ requires C, 47.4; H, 4.6; N, 4.25%); *m/z* (EI) 329 ($[M]^+$); $\lambda_{max}$ (MeOH)/nm 230 and 353 ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$ 2560 and 3610); $\lambda_{max}$ (pH > 7, reversible)/nm, 263 and 340 ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$ 6280 and 4970); $\nu_{max}$ (KBr)/cm$^{-1}$ 1749, 1736 and 1700; $\delta_H$ (360 MHz, $C^2HCl_3$) 2.34 and 2.35 (3H, 2 × s, $CH_3$), 3.18 and 3.27 (2H, 2 × s, $CH_2S$) 3.68 and 3.74 (3H, 2 × s, $OCH_3$), 3.79 and 3.80 (3H, 2 × s, $OCH_3$) and 3.85 and 3.87 (3H, 2 × s, $OCH_3$); $\delta_C$ (90.55 MHz, $C^2HCl_3$) 19.74 and 19.82 ($CH_3$), 30.65 and 31.30 ($CH_2S$), 51.56 and 51.97 ($OCH_3$), 52.03 ($OCH_3$), 52.60 and 52.65 ($OCH_3$), 124.34 and 124.54 (C-5), 127.26 and 127.91 (C-4) and 165.21, 165.87, 170.29 and 183.78 (3 × C=O).

### Allyl 2-ethoxycarbonylmethylene-2,3-dihydro-5-methyl-6*H*-1,3-thiazine-4-carboxylate (13)

Freshly prepared allyl 2-oxo-3-methylbut-3-enoate (**12**)[11] (0.45 g, 2.92 mmol) and ethoxycarbonylthioacetamide (**11**)[10] (0.46 g, 3.45 mmol) were dissolved in dry 1,4-dioxane (20 ml) and the solution was saturated with dry hydrogen chloride gas at 0 °C. The solution was left overnight at room temperature and the solvent was removed *in vacuo* to give a dark gum. Chromatographic purification on silica gel, eluting with dichloromethane gave *allyl 2-ethoxycarbonylmethylene-2,3-dihydro-5-methyl-6H-1,3-thiazine-4-carboxylate* (**13**) as a yellow solid which was recrystallised from ethanol to give yellow crystals (0.51 g, 62%), mp 45–47 °C (Found C, 54.9; H, 6.0; N, 4.8%. $C_{13}H_{17}NO_4S$ requires C, 55.1; H, 6.0; N, 4.9%); *m/z* (EI) 283 ($[M]^+$); $\lambda_{max}$ (MeOH)/nm 225, 281 and 336 ($\varepsilon$/dm$^3$ mol cm$^{-1}$ 18300, 13000 and 31000); $\nu_{max}$ (KBr)/cm$^{-1}$ 1735 (ester) and 1664; $\delta_H$ (360 MHz, $C^2HCl_3$) 1.24 (3H, s, *J* 7.1, $CH_3$), 2.29 (3H, s, $CH_3C$=), 3.26 (2H, s, $CH_2S$), 4.13 (2H, q, *J* 7.1, $CH_2O$), 4.77 (2H, m, $OCH_2C$=), 4.87 (1H, s, HC=), 5.30 (1H, m, *cis* =$CH_2$), 5.45 (1H, m, *trans* =$CH_2$), 5.99 (1H, m, C*H*=), 11.21 (1H, br s, NH); $\delta_C$ (90.55 MHz, $C^2HCl_3$), 14.49 ($CH_3$), 20.13 ($CH_3C$=), 31.07 ($CH_2S$), 59.16 ($CH_2O$), 66.22 ($OCH_2CH$=), 85.64 (=CH), 118.88 ($OCH_2C$=), 122.72 and 125.39 (2 × C=), 131.45 (CH=), 154.40 (=C–S), 162.38 and 168.72 (ester C=O).

### 4-Allyl 8-ethyl 3-methyl-6,7-dioxo-6,7-dihydro-2*H*-pyrrolo-[2,1-*b*][1,3]thiazine-4,8-dicarboxylate (14)

Triethylamine (329 μl, 2.36 mmol) and oxalyl chloride (618 μl of a 2.00 M solution of oxalyl chloride in dichloromethane, 1.24 mmol) were added to a solution of allyl 2-ethoxycarbonylmethylene-2,3-dihydro-5-methyl-6*H*-1,3-thiazine-4-carboxylate (**13**) (0.35 g, 1.24 mmol) in dry dichloromethane (25 ml). The solution was stirred under nitrogen at room temperature overnight and washed with water. The organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo* to give *4-allyl 8-ethyl 3-methyl-6,7-dioxo-6,7-dihydro-2H-pyrrolo[2,1-b][1,3]-thiazine-4,8-dicarboxylate* (**14**) as a bright orange solid which was recrystallised from ethyl acetate and petroleum ether‡ (0.25 g, 60%), mp 124–125 °C (Found C, 53.0; H, 4.3; N, 4.1%. $C_{15}H_{15}NO_6S$ requires C, 53.4; H, 4.5; N, 4.15%); *m/z* (CI) 355 ($[M + NH_4]^+$) and 338 ($[M + H]^+$); $\lambda_{max}$ ($CHCl_3$)/nm 245, 274, 319 and 428 ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$ 5257, 6029, 3943 and 1357); $\nu_{max}$ (KBr)/cm$^{-1}$ 1762, 1728, 1678 and 1649; $\delta_H$ (360 MHz, $C^2HCl_3$) 1.37 (3H, t, *J* 7.1, $CH_3$), 2.16 (3H, s, $CH_3C$=), 3.48 (2H, s, $CH_2S$), 4.35 (2H, q, *J* 7.1, $CH_2O$), 4.74 (2H, m, $OCH_2C$=), 5.32 (2H, m, =$CH_2$) and 5.91 (1H, m, CH=).

### Diethyl 5,6-dioxo-2,3,5,6-tetrahydropyrrolo[2,1-*b*][1,3]thiazole-3,7-dicarboxylate (16)

Triethylamine (113 μl, 0.82 mmol) and oxalyl chloride (52 mg, 0.41 mmol) were added to a solution of 2-ethoxycarbonylmethylene-4-ethoxycarbonylthiazolidine (**15**)[10] (100 mg, 0.41 mmol) in dry methylene chloride (25 ml). The solution was stirred at room temperature under nitrogen overnight and washed with water. The organic layer was dried ($Na_2SO_4$) and the solvent was removed *in vacuo* to give *diethyl 5,6-dioxo-2,3,5,6-tetrahydropyrrolo[2,1-b][1,3]thiazole-3,7-dicarboxylate* (**16**) as an orange gum (68 mg, 56%); *m/z* (EI) 299 ($[M]^+$); $\lambda_{max}$ ($CHCl_3$)/nm 243, 286 and 382; $\nu_{max}$ (KBr)/cm$^{-1}$ 1771, 1738, 1733 and 1683 (amide); $\delta_H$ (360 MHz, $C^2HCl_3$) 1.17 (3H, t, *J* 7.1, $CH_3$), 1.22 (3H, t, *J* 7.1, $CH_3$), 3.76 (1H, *A*BX, $J_{AB}$ 12, $J_{AX}$ 1.6, H-2A), 4.02 (1H, A*B*X, $J_{AB}$ 12, $J_{BX}$ 12, H-2B), 4.16 (4H, m, 2 × $CH_2O$) and 5.13 (1H, AB*X*, $J_{AX}$ 12, $J_{BX}$ 1.6, H-3); $\delta_C$ (90.55 MHz, $C^2HCl_3$) 12.96 ($CH_3$), 13.36 ($CH_3$), 38.21 (C-2), 56.32 (C-3), 59.52 ($OCH_2$), 62.15 ($OCH_2$), 99.93 (C-7), 155.01 (C-8), and 159.84, 165.94, 174.04 and 185.85 (4 × C=O).

### 2-[Ethoxycarbonyl(ethoxalyl)methylene]-4-ethoxycarbonyl-1,3-thiazolidine (17)

Diethyl 5,6-dioxo-2,3,5,6-tetrahydropyrrolo[2,1-*b*][1,3]thiazole-3,7-dicarboxylate (**16**) (50 mg, 0.17 mmol) was dissolved in ethanol (10 ml) and stirred at room temperature for 30 min. The solution was concentrated and cooled and the product crystallised out of the solution. The product was filtered and washed with cold ethanol and the solid was dried *in vacuo* to yield the two geometric isomers of *2-[ethoxycarbonyl(ethoxalyl)methylene]-4-ethoxycarbonyl-1,3-thiazolidine* (**17**) as a white solid (49 mg, 85%); mp 90–91 °C (Found C, 48.8; H, 5.6; N, 4.1%. $C_{14}H_{19}NO_7S$ requires C, 48.7; H, 5.5; N, 4.1%); *m/z* (EI) 345 ($[M]^+$); $\delta_H$ (360 MHz, $C^2HCl_3$) 1.20–1.33 (9H, 6 × t, *J* 7, $CH_3$), 3.41 (2H, m, $CH_2S$), 4.14–4.28 (6H, 6 × q, *J* 7, $OCH_2$), 4.75 (0.3H, t, *J* 7.3, 0.3 H-4), 4.85 (0.7H, t, *J* 7.3, 0.7 H-4), 9.78 (0.3H, br, 0.3 N*H*) and 10.33 (0.7H, br, 0.7 N*H*).

### 2-Ethoxycarbonylmethylene-3-ethoxyoxalyl-4-ethoxycarbonyl-1,3-thiazolidine (18)

2-Ethoxycarbonylmethylene-4-ethoxycarbonyl-1,3-thiazolidine (**15**)[10] (100 mg, 0.41 mmol) was dissolved in methylene chloride (25 ml) under nitrogen, and triethylamine (57 μl, 0.41 mmol)

and ethyl oxalyl chloride (56 mg, 0.41 mmol) were added. The solution was stirred at room temperature overnight and washed with water. The organic layer was dried ($Na_2SO_4$) and the solvent was removed *in vacuo* to give a brown gum which was chromatographed using the chromatotron and diethyl ether–petroleum ether† (1:1) as eluent to give *2-ethoxycarbonylmethylene-3-ethoxyoxalyl-4-ethoxycarbonyl-1,3-thiazolidine* (**18**) as a white solid which was recrystallised from ethanol (95 mg, 67%); mp 93–96 °C (Found C, 48.6; H, 5.6; N, 3.7%. $C_{14}H_{19}NO_7S$ requires C, 48.7; H, 5.5; N, 4.1%); *m*/*z* (EI) 345 ($[M]^+$); $\delta_H$ (360 MHz, $C^2HCl_3$) 1.20 (3H, t, *J* 7.1, $CH_3$), 1.21 (3H, t, *J* 7.1, $CH_3$), 1.29 (3H, t, *J* 7.1, $CH_3$), 3.35 (2H, m, $CH_2S$), 4.11 (2H, q, *J* 7.1, $OCH_2$), 4.17 (2H, dq, *J* 7.1, $OCH_2$), 4.29 (2H, q, *J* 7.1, $OCH_2$) and 5.37 (1H, dd, *J* 6.4 and 2, H-4); at −40 °C, H-4 was observed as two signals at 5.34 and 5.39 ppm, and the olefinic C*H* as two signals at 5.71 and 7.10 ppm in a ratio of 2:3 respectively; $\delta_C$ (90.55 MHz, $C^2HCl_3$) 13.65 ($CH_3$), 13.86 ($CH_3$), 14.20 ($CH_3$), 30.51 ($CH_2S$), 60.26 ($OCH_2$), 62.08 (br, H-4), 62.66 ($OCH_2$), 63.10 ($OCH_2$), 99.79 (=CH) and 153.65, 158.34, 160.50 and 167.98 (4 × C=O); at −20 °C the olefinic C*H* appeared as two signals at 96.96 and 101.08 ppm and C-4 as two signals at 60.19 and 65.82 ppm.

### 7-Ethoxycarbonyl 2,2-dimethyl-5,6-dioxo-2,3,5,6-tetrahydropyrrolo[2,1-*b*][1,3]thiazole-3-carboxylic acid (20)

Freshly prepared ethoxycarbonylacetimino ethyl ether hydrochloride (0.63 g, 3.2 mmol)[10] was added to a solution of D-penicillamine hydrochloride (0.5 g, 2.7 mmol) in dry THF (40 ml) and dry methanol (20 ml). The solution was heated at reflux under nitrogen for 4 h, allowed to cool and filtered. The solvent was removed *in vacuo* to give *2-ethoxycarbonylmethylene-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid* (**19**) as a pale foam (0.28 g, 42%) which existed as geometric isomers in a ratio of 1:1 (*m*/*z* (CI) Found 246.08001 ($[M + H]^+$). $C_{10}H_{16}NO_4S$ requires 246.079964); $\lambda_{max}$ (MeOH)/nm 200 and 289 ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$ 3910 and 8460); $\nu_{max}$ (film)/cm$^{-1}$ 3334 (OH), 1733 and 1653; $\delta_H$ (360 MHz, $C^2HCl_3$) 1.26 (3H, t, *J* 7, $CH_3$), 1.40 (3H, s, $CH_3$), 1.54 (3H, s, $CH_3$), 3.40 (1H, 2 × s, H-4), 4.18 (2H, q, *J* 7, $OCH_2$), 4.62 (1H, 2 × s, =CH) and 8.10 (1H, 2 × s, NH). The crude 2-ethoxycarbonylmethylene-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (**19**) (100 mg, 0.41 mmol) was dissolved in dry methylene chloride (25 ml), and then triethylamine (277 µl, 1.99 mmol) and oxalyl chloride (103 mg, 0.82 mmol) were added. The solution was stirred under nitrogen at room temperature overnight and washed with water. The organic layer was dried ($Na_2SO_4$) and the solvent was removed *in vacuo* to give *7-ethoxycarbonyl-2,2-dimethyl-5,6-dioxo-2,3,5,6-tetrahydropyrrolo[2,1-b][1,3]thiazole-3-carboxylic acid* (**20**) as a brown gum. Attempts to purify the compound resulted in decomposition (53 mg, 43%); *m*/*z* (CI) 317 ($[M + NH_4]^+$) and 300 ($[M + H]^+$); $\lambda_{max}$ ($CHCl_3$)/nm 244, 286 and 370 ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$ 3020, 3350 and 1320); $\nu_{max}$ (film)/cm$^{-1}$ 3100–2800 (OH), 1771 to 1695 (br); $\delta_H$ (360 MHz, $C^2HCl_3$) 1.26 (t, $CH_3$), 1.62 (s, $CH_3$), 1.80 (s, $CH_3$), 4.18 (q, $CH_2O$) and 5.56 (s, H-4). There were peaks due to impurities in the spectrum. This crude acid had no useful antibacterial properties using the agar dilution method.

### Condensation of ethyl 3-ethoxycarbonylmethyl-l-methyl-2-thia-4-azabicyclo[3.1.0]hex-3-ene-5-carboxylate (26) with oxalyl chloride

Triethylamine (147 µl, 1.05 mmol) and oxalyl chloride (277 µl of a 2.00 M solution of oxalyl chloride in dichloromethane, 0.56 mmol) were added to a solution of ethyl 3-ethoxycarbonylmethyl-l-methyl-2-thia-4-azabicyclo[3.1.0]hex-3-ene-5-carboxylate (**26**)[16] (0.15 g, 0.56 mmol), in dry dichloromethane (25 ml). The solution was stirred under nitrogen overnight at room temperature and washed with water. The organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo* to give the product **27** as a bright orange solid which was recrystallised from ethyl acetate and petroleum ether‡ (0.11 g, 61%); mp 152–154 °C (Found C, 51.2; H, 4.5; N, 4.1%. $C_{14}H_{15}NO_6S$ requires C, 51.7; H 4.6; N, 4.3%); *m*/*z* (CI) 326 ($[M + H]^+$); $\lambda_{max}$ ($CHCl_3$)/nm 246, 294 and 396 ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$ 4460, 4207 and 1847), $\nu_{max}$ (KBr)/cm$^{-1}$ 1783, 1735, 1678 and 1656; $\delta_H$ (360 MHz, $C^2HCl_3$) 1.31 (6H, 2 × t, *J* 6.8, 2 × $CH_3$), 1.64 and 2.31 (2 × 1H, 2 × d, 2 × $J_{AB}$ 6.17, 2 × H-6), 1.72 (3H, s, $CH_3$) and 4.33 (4H, m, 2 × $CH_2O$).

### Allyl 3-ethoxycarbonylmethyl-l-methyl-2-thia-4-azabicyclo-[3.1.0]hex-3-ene-5-carboxylate (28)

Allyl 2-ethoxycarbonylmethylene-2,3-dihydro-5-methyl-6*H*-1,3-thiazine-4-carboxylate (**13**) (0.30 g, 1.06 mmol) was dissolved in dry toluene (*ca.* 200 ml) and acetone (*ca*. 20 ml) and the solution was degassed for 1 h and photolysed under nitrogen using a 125 W Hanovia immersion-type UV lamp equipped with a water-cooled Pyrex jacket as a filter. The reaction was monitored by the gradual disappearance of the absorption at $\lambda_{max}$ 337 nm from the dihydrothiazine **13** in the UV. After the reaction was complete (45–60 min) the solvent was removed *in vacuo* to give a dark oil which was chromatographed on silica gel using diethyl ether–petroleum ether‡ (1:1) as eluent to give *allyl 3-ethoxycarbonylmethyl-1-methyl-2-thia-4-azabicyclo-[3.1.0]hex-3-ene-5-carboxylate* (**28**) as a liquid (0.14 g, 47%); *m*/*z* (CI) 284 ($M + H]^+$); $\lambda_{max}$ (MeOH)/nm 243, 262 and 295 ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$ 2326, 1982 and 1374); $\nu_{max}$ (film)/cm$^{-1}$ 1735 (ester); $\delta_H$ (360 MHz, $C^2HCl_3$), 0.82 and 2.13 (2 × 1H, 2 × d, 2 × $J_{AB}$ 6.06, 2 × H-6), 1.24 (3H, t, *J* 7.1, $CH_3$), 1.69 (3H, s, $CH_3$), 3.59 (2H, s, $CH_2S$), 4.17 (2H, q, *J* 7.1, $CH_2O$), 4.70 (2H, m, $OCH_2C$=) 5.31 (2H, m, =$CH_2$) and 5.95 (1H, m, CH=); $\delta_C$ (90.55 MHz, $C^2HCl_3$), 14.00 ($CH_3$), 17.13 ($CH_3$), 25.67 (C-6), 39.78 ($CH_2C$=O), 46.65 (CS), 61.52 ($CH_2O$), 66.36 ($OCH_2C$=), 118.99 (=$CH_2$), 131.86 (CH=), 163.13 (C=N) and 165 and 167.83 (2 × C=O).

### Condensation of allyl 3-ethoxycarbonylmethyl-l-methyl-2-thia-4-azabicyclo[3.1.0]hex-3-ene-5-carboxylate (28) with oxalyl chloride

Triethylamine (235 µl, 1.69 mmol) and oxalyl chloride (442 µl of a 2.00 M solution of oxalyl chloride in dichloromethane, 0.88 mmol) were added to a solution of the thiazolidine **28** (0.25 g, 0.88 mmol), in dry dichloromethane (25 ml). The solution was stirred under nitrogen at room temperature overnight and washed with water. The organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo* to give the product **29** as a bright orange solid which was recrystallised from ethyl acetate and petroleum ether‡ (0.15 g, 51%); mp 122–123 °C (Found C, 52.7; H, 4.3; N, 4.2%. $C_{15}H_{15}NO_6S$ requires C, 53.4; H 4.5; N, 4.15%); *m*/*z* (CI) 338 ($[M + H]^+$); $\lambda_{max}$ ($CHCl_3$)/nm 244, 294 and 397 ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$ 5512, 8184 and 3803); $\nu_{max}$ (KBr)/cm$^{-1}$ 1783, 1734 and 1680; $\delta_H$ (360 MHz, $C^2HCl_3$) 1.32 (3H, t, *J* 7.5, $CH_3$), 1.72 and 2.32 (2 × 1H, 2 × d, 2 × $J_{AB}$ 7.19, 2 × H-9), 1.73 (3H, s, $CH_3$), 4.27 (2H, q, *J* 7.5, $CH_2O$), 4.76 (2H, m, $OCH_2C$=), 5.32 (2H, m, =$CH_2$) and 5.91 (1H, m, CH=).

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