Synthesis of tricyclic β-lactams related to cephalosporins †[1]

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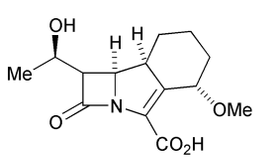
Several compounds related to the cephalosporin antibiotics and containing a novel tricyclic β-lactam system have been prepared in the expectation that they might have a more strained β-lactam ring than the parent compounds. In the event, synthetic problems required that the compounds prepared containing this system had a reduced thiazine ring. The ring strain was not exceptional as judged by the absorption frequencies in the infra red.

Tricyclic β-lactams such as Glaxo's "trinem" **1** have recently proved to be of interest.[2] One group of tricyclic β-lactam compounds which has not so far been investigated comprises analogues of penicillins or cephalosporins in which a small ring is fused across positions 5 and 6 of the penicillin nucleus or positions 6 and 7 of the cephalosporin nucleus. It seemed to us that there was a possibility that these compounds might have interesting properties due to the effect of the additional ring on the strain of the β-lactam ring. The relationship between ring strain and anti-bacterial properties was suggested at an early stage and, although this view is no longer so widely held, Morin *et al.*[3] have suggested that ring strain, as measured by infra red absorption frequency, correlates well with anti-bacterial properties.



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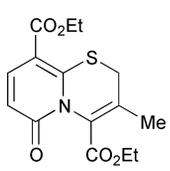

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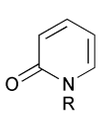

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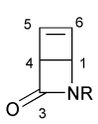

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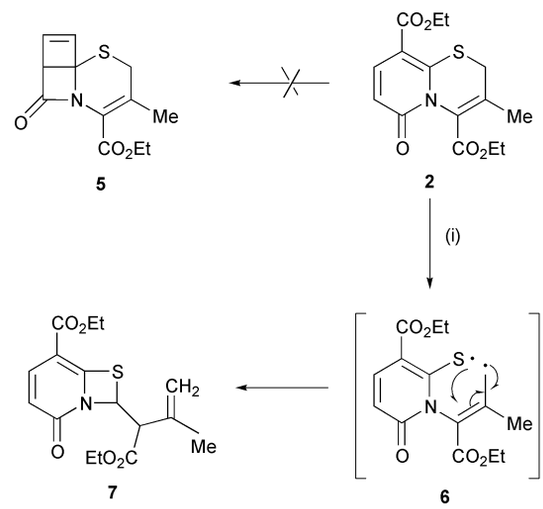
We have synthesised a series of bicyclic pyridones such as **2**[4] which are related to the cephalosporins and, since it has long been known[5] that 2-pyridones **3** will yield 2-aza-3-oxo-bicyclo[2.2.0]hex-5-enes **4** on photolysis, synthesis of the cephalosporin analogue **5** from the pyridone **2** seemed to be a worthwhile undertaking. In the event, when we photolysed the bicyclic pyridone **2**, it was the thiazine ring which underwent a high yielding and novel rearrangement by prior fission of the allylic carbon–sulfur bond as in **6** to give the product **7**.[6] The pyridone ring remained untouched, as shown in Scheme 1, and it was evident that the allylic carbon–sulfur bond in the thiazine ring was photolytically more reactive than was the pyridone ring.

† Part of the COSY spectrum of the tricyclic β-lactam **31** is available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b0/b006415g/



Scheme 1 *Reagents and conditions*: (i) *hν*, dioxane (ref. 6).

Since hydrogenation of the double bond in the thiazine ring of **2** should reduce the tendency for carbon–sulfur bond cleavage which led to the rearrangement shown in Scheme 1, we set about preparing the reduced compound **9**. The Δ^3 bond in the bicyclic thiazine **2** was extremely resistant to hydrogenation and so we treated the compound with base to rearrange the double bond to the more accessible Δ^2 position, obtaining the thiazine **8**[7] as in Scheme 2. Although this compound also proved difficult to hydrogenate, we were finally able successfully to achieve hydrogenation using rhodium on alumina as a catalyst. It was evident that the product **9** had been hydrogenated from the opposite side of the ring from the asymmetric centre at C-4, since H-4 showed a long range 'W-type' coupling of 1.5 Hz to H-2*R*, and H-3 showed *syn*-type coupling to H-2*R* (4.3 Hz) and to H-4 (4 Hz) and *anti*-type coupling to H-2*S* (12.1 Hz). When deuterium was used in the hydrogenation step, H-3 and H-2*R* were no longer evident in the ^{1}H NMR spectrum and H-2*S* and H-4 appeared as singlets, confirming our assignments, assuming *syn* addition of hydrogen to the Δ^2 bond. When the reduced compound **9** was subjected to prolonged photochemical irradiation, however, no reaction was observed. Reduction had evidently stabilised the thiazine system but it seemed that the substituted pyridone was resistant to photolysis to yield the bicyclo[2.2.0] system. A search of the literature suggested that the electron withdrawing ester group might deactivate the pyridone ring towards photolysis and so we set out to convert this to a less deactivating group.

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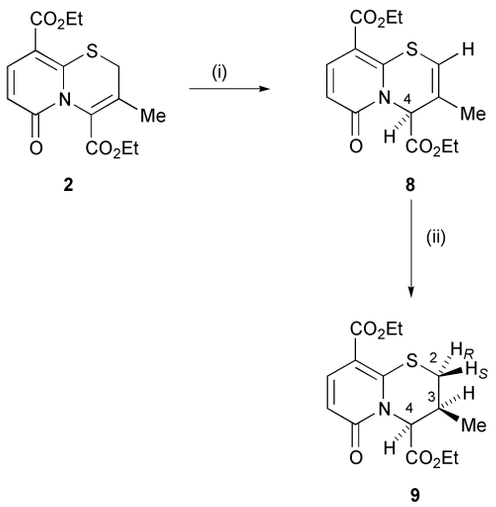
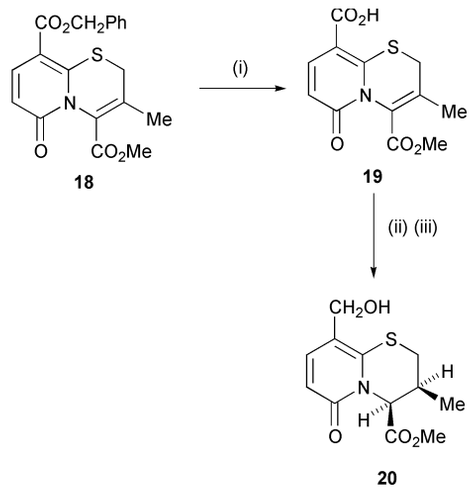


Scheme 2 *Reagents*: (i) KOH, EtOH; (ii) H_2, Rh-Al_2O_3, EtOH.

Initially this was achieved as shown in Scheme 3, using the orthogonally protected thiazine **10**,[4] which on treatment with BBr_3 in dichloromethane at −78 °C gave the acid **11**. Attempted decarboxylation of the acid **11** was unsuccessful and so it was converted to the mixed anhydride which, in initial experiments, was reduced with sodium borohydride to give the alcohol **12**. When we attempted to rearrange the Δ^3 double bond in this compound using sodium ethoxide in ethanol, the expected alcohol **13** was obtained in yields varying from 14 to 79%. On one occasion, the reduced ethyl ether **14** was also obtained as a by-product in 38% yield, presumably by elimination–addition through an intermediate such as **15** and a Meerwein–Pondorf–Verly type reduction. Reduction of the alcohol **13** in acidic methanol using rhodium on alumina as catalyst, gave two reduced compounds, the expected alcohol **16** and the methyl ether **17**. The latter compound was presumably formed by an addition–elimination sequence *via* **15** similar to that suggested for formation of the compound **14**. The ^{1}H NMR spectral coupling constants were again in keeping with hydrogenation having occurred from the less hindered side of the Δ^2-thiazine.

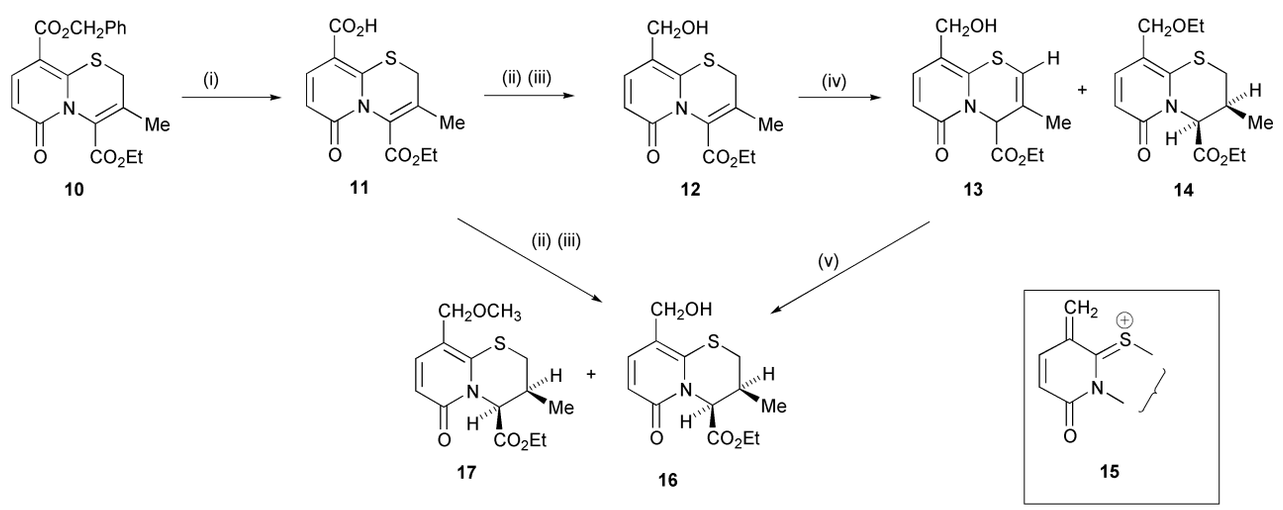
Eventually we found that the alcohol **16** could be obtained directly as, on later attempts to subject the acid **11** to the mixed anhydride–borohydride process, reduction of the conjugated Δ^3 double bond accompanied reduction of the mixed anhydride. It is interesting to note that the same stereochemistry was obtained from the borohydride reaction as from hydrogenation of the Δ^2-thiazine **13**. Although apparently being repeated under identical conditions, the borohydride reduction of the mixed anhydride seemed variable and we have tentatively ascribed the difference in its outcome to the presence or absence of residual triethylamine from formation of the mixed anhydride. We have used this direct method to prepare the alcohol methyl ester **20** conveniently in two steps from the diester **18**[4] as shown in Scheme 4. Further, when compound **2**



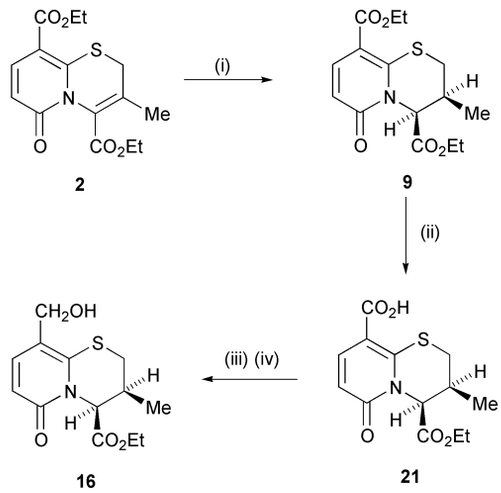
Scheme 4 *Reagents*: (i) BBr_3, CH_2Cl_2; (ii) $ClCO_2Et$, Et_3N, THF; (iii) $NaBH_4$, H_2O, THF.

was reduced with sodium borohydride, the reduced thiazine **9** could be obtained directly (Scheme 5). Hydrolysis of this diethyl ester with one equivalent of KOH gave the monoacid **21** which, on formation of the mixed anhydride and borohydride reduction, gave the reduced alcohol **16**. Thus the orthogonal protection which we had set up by using the diesters **10** and **18** proved to have been unnecessary.

We now had small quantities of the pyridone ethers **14** and **17**, obtained as by-products and so these were the first substrates for our photolysis reaction. Photolysis of the ethyl ether **14** gave a new compound in 40% yield. This no longer possessed the pyridone carbonyl absorption at 1650 cm^{-1} in the infra red but had a new carbonyl absorption at 1755 cm^{-1}. The characteristic pyridone doublets at δ 6.0 and 7.1 ppm were no longer present in the ^{1}H NMR spectrum which still showed the presence of absorptions due to the reduced thiazine system. A new doublet (J 1.4 Hz) at δ 6.37 ppm was in keeping with the olefinic proton H-5 at δ 6.65 ppm (J 1 Hz) in the known[8] bicyclic β-lactam **4** (R = H) which we prepared from the pyridone **3** (R = H) for spectral comparison. It therefore appeared that

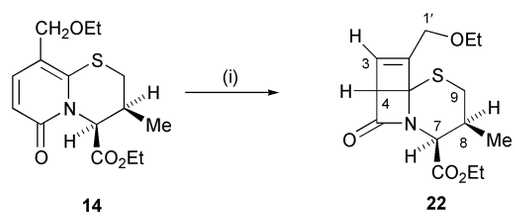


Scheme 3 *Reagents*: (i) BBr_3, CH_2Cl_2; (ii) $ClCO_2Et$, Et_3N, THF; (iii) $NaBH_4$, H_2O, THF; (iv) NaOEt, EtOH; (v) H_2, Rh-Al_2O_3, MeOH, HOAc.



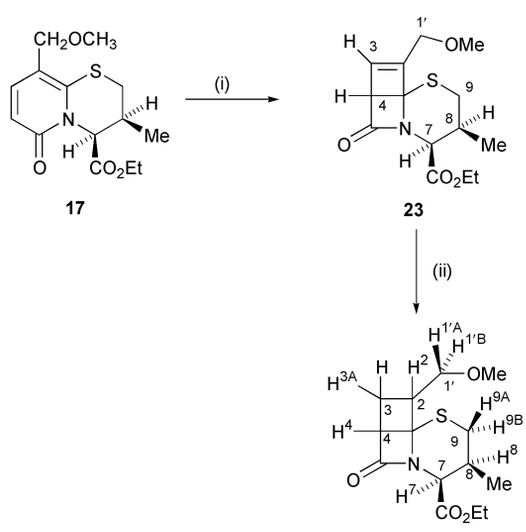
Scheme 5 *Reagents*: (i) $NaBH_4$, THF, H_2O; (ii) KOH, EtOH; (iii) $ClCO_2Et$, Et_3N, THF; (iv) $NaBH_4$, H_2O, THF.

photolysis of the pyridone **14** had given the desired β-lactam **22** as shown in Scheme 6. The product was, however, unstable, appearing to revert to the starting pyridone **14** with time.



Scheme 6 *Reagents and conditions*: (i) *hν*, toluene.

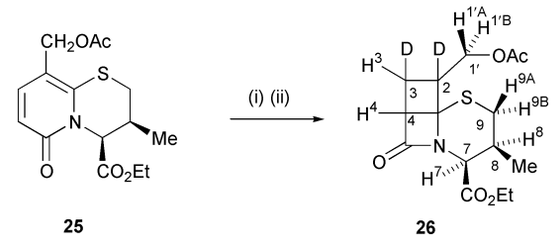
To overcome the problem of instability, we decided to hydrogenate the product of photolysis of the pyridone **17** immediately after photolysis, as shown in Scheme 7. The



Scheme 7 *Reagents and conditions*: (i) h*ν*, benzene; (ii) H_2, $Rh\text{-}Al_2O_3$, MeOH.

product from the hydrogenation had carbonyl absorptions at 1760 and 1740 cm^{-1} for β-lactam and ester carbonyl groups respectively. The ^1H NMR spectrum had complex coupling which was confirmed by a COSY spectrum which showed two systems of coupled protons, one of which represented the parent reduced 1,3-thiazine system with intact coupling between the thiazine methyl and H-8; and between H-8 and both H-7 and H-9A and H-9B. The second system could be interpreted as the bridgehead proton H-4 at δ 3.55 ppm coupling to the protons H-3 at δ 1.71 and 2.38 ppm (J 3.3 and 9 Hz), which in turn coupled to the proton H-2 at δ 2.95 ppm (J 6.9 and 10.4 Hz). The proton H-2 was further coupled to the protons H-1′ at δ 3.41 and 3.53 ppm. The ^{13}C NMR spectrum was also in keeping with the structure **24**.

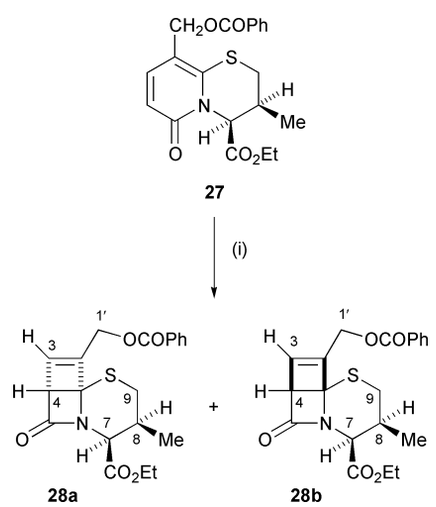
The acetate **25** was now prepared from the alcohol **16** and photolysed in benzene (Scheme 8). Reduction of the product



Scheme 8 *Reagents and conditions*: (i) *hν*, benzene; (ii) D_2, $Rh\text{-}Al_2O_3$, EtOAc.

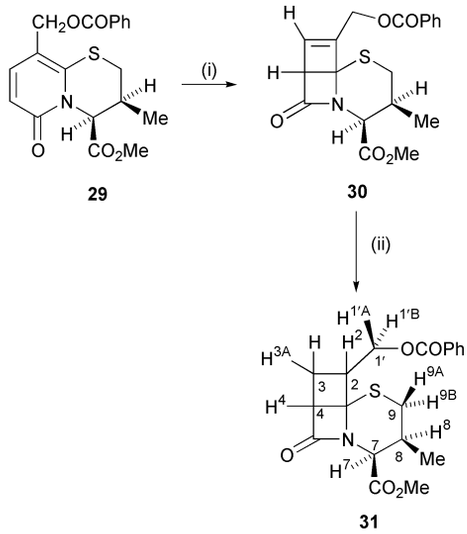
with deuterium gas gave a product with a β-lactam carbonyl absorption at 1760 cm^{-1} in the infra red and NMR spectral characteristics similar to those of the product **24** but with no resonance corresponding to H-2 and only one H-3 resonance. The structure **26** was therefore appropriate for this compound.

The benzoate ethyl ester **27** was prepared and photolysed, as shown in Scheme 9. The ^1H NMR spectrum of the product

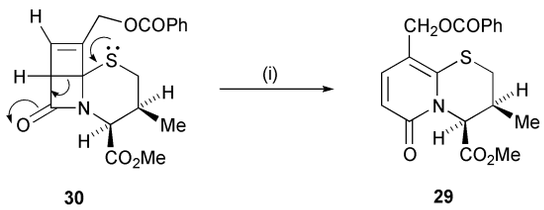


Scheme 9 *Reagents and conditions*: (i) *hν*, benzene.

indicated a 5:3 mixture of two similar products, the minor of which seemed to be the more unstable. These appeared to be the diastereoisomers **28a** and **28b** and, since the protons H-1′ were more deshielded in the minor isomer, it was assigned structure **28b** using Dreiding models to assess possible deshielding. The benzoate methyl ester **29** was also prepared and subjected to photolysis (Scheme 10) to give a product with the thiazine coupling system in the ^1H NMR spectrum together with replacement of the pyridone signals with a signal for H-4, at δ 4.21 ppm, coupled to the olefinic proton H-3 at δ 6.56 (J 2.3 Hz) and to the protons H-1′ (J 1.3 Hz). These data are compatible with structure **30** and the compound appeared to be unstable, typical pyridone peaks appearing in the ^1H NMR spectrum on standing. A similar non-concerted thermal rearrangement of bicyclic compounds of type **4** to pyridones on heating has been noted,[5d,9] and the sulfur lone pair in **30** is well placed to trigger such a rearrangement as shown in Scheme 11. To prevent loss of the tricyclic system, **30** was hydrogenated using rhodium on alumina as a catalyst. The hydrogenation product **31**, obtained in low yield on purification, had infra red bands at ν_{max} 1762 (β-lactam) and 1745 cm^{-1} (ester). The ^1H NMR spectrum had two systems of coupled protons as verified by the COSY



Scheme 10 *Reagents and conditions*: (i) *hν*, benzene; (ii) H_2, Rh-Al_2O_3, EtOH.



Scheme 11 *Conditions*: (i) Δ.

spectrum, available as electronic supplementary information. One of these coupled systems was evidently the 1,3-thiazine system. The second had new peaks which were consistent with structure **31**, the bridgehead hydrogen H-4 at δ 3.64 ppm coupling to the protons H-3 at δ 1.96 and 2.5 ppm with coupling constants 3.5 and 9 Hz respectively. These protons in turn coupled to H-2 at δ 3.12 ppm with coupling constants J 7 and 10 Hz respectively. H-2 was also coupled to the protons H-1′ at δ 4.47 ppm. These data and the ^{13}C NMR spectrum were compatible with the structure **31**.

We have therefore succeeded in synthesising a series of tricyclic bridged β-lactams related to cephalosporins. The β-lactam absorptions in the infra red were in the region 1755 to 1762 cm^{-1}, at the lower end of the range for reduced cepham systems. Bicyclic compounds analogous to **4** have been reported[9–12] to be in the range 1730 to 1772 cm^{-1}. The tricyclic reduced thiazines therefore seemed to have little additional ring strain as measured by infra red spectroscopy and their instability precluded their use as antibacterials.

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Ultra-violet spectra were recorded as solutions in methanol using Pye-Unicam SP800 and Philips PU8720 spectrometers. ε values are given in dm^3 mol^{-1} cm^{-1}. Infra red spectra were recorded on Perkin-Elmer 157G, 577 and PE1710FT spectrometers and a Pye-Unicam SP3-100 spectrometer. ^{1}H NMR spectra were recorded on Perkin-Elmer R32 (90 MHz) and R12 (60 MHz) and Bruker WH360 (360 MHz) and WP 80 (80 MHz) spectrometers. J values are in Hz. ^{13}C NMR spectra were recorded on Bruker WP80 (20.15 MHz) and Bruker WH360 (90.5 MHz) spectrometers. J-Modulated spin echo experiments were used to help characterise ^{13}C NMR spectra where necessary. Mass spectra were recorded on Kratos MS80 or MS25 spectrometers. Combustion analyses were provided by Mrs G. Olney and Miss K. Plowman of the University of Sussex and by Zeneca Pharmaceuticals. Other spectra were provided by the staff of Zeneca Pharmaceuticals, Alderley Park, Cheshire. 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. Photolyses were carried out with either a 125 W medium pressure Hanovia mercury arc lamp (internal) or a 125 W high pressure Philips mercury arc lamp (internal or external) under a nitrogen atmosphere using a Pyrex filter unless otherwise stated. All solvents were distilled prior to use. Petroleum ether refers to that fraction boiling between 40 and 60 °C.

Diethyl 3-methyl-6-oxo-4*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4,9-dicarboxylate 8[7]

A solution of diethyl 3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1-*b*]-[1,3]thiazine-4,9-dicarboxylate **2**[4] (40 mg, 0.124 mmol) in absolute ethanol (20 ml) was made strongly akaline (pH >13) with saturated ethanolic potassium hydroxide (10 drops). After standing overnight at room temperature, the solution was carefully neutralised with conc. hydrochloric acid and the solvents were removed *in vacuo* to give *diethyl 3-methyl-6-oxo-4H,6H-pyrido[2,1-b][1,3]thiazine-4,9-dicarboxylate* **8** as a solid which was recrystallised from diethyl ether as white needles (34 mg, 85%); mp 144–145 °C (Found C, 55.6; H, 5.2; N, 4.2%. $C_{15}H_{17}NO_5S$ requires C, 55.7; H, 5.3; N, 4.3%); *m/z* (EI) 323 ([M]$^+$); λ_{max} (MeOH)/nm 238, 292 and 339 (ε 3610, 9280 and 8225); ν_{max} (Nujol)/cm^{-1} 1746 (saturated ester) and 1698 (pyridone ester); δ_H (360 MHz, C^2HCl_3) 1.22 (3H, t, J 7, CH_3), 1.35 (3H, t, J 7, CH_3), 2.20 (3H, d, J 1.5, CH_3C=), 4.20 (2H, q, J 7, CH_2O), 4.35 (2H, q, J 7, CH_2O), 6.24 (1H, m, CH=), 6.48 and 7.99 (2 × 1H, d × d, J_{AB} 9.5, pyridone CH) and 6.73 (1H, br s, H-4).

Diethyl 3-methyl-6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*]-[1,3]thiazine-4,9-dicarboxylate 9

(a) Using hydrogen. A solution of diethyl 3-methyl-6-oxo-4*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4,9-dicarboxylate **8** (100 mg, 0.31 mmol) in absolute ethanol (20 ml) was hydrogenated at room temperature and pressure using 5% rhodium on alumina catalyst (20 mg). After five days at room temperature and pressure the reaction was shown to be complete by TLC. The solution was filtered through Celite and the solvent was removed *in vacuo* to yield a pale oil which was purified by chromatography using a Chromatotron with silica gel and eluting with diethyl ether–petroleum ether (3:1). The purified material was recrystallised from chloroform–petroleum ether as white prisms of *diethyl 3-methyl-6-oxo-3,4-dihydro-2H,6H-pyrido[2,1-b][1,3]thiazine-4,9-dicarboxylate* **9** (48 mg, 48%); mp 82–84 °C (Found C, 55.2; H, 5.8; N, 4.4%. $C_{15}H_{19}NO_5S$ requires C, 55.4; H, 5.9; N, 4.3%); *m/z* (EI) 325 ([M]$^+$); λ_{max} (MeOH)/nm 241, 293, 330 and 342 (sh) (ε 5400, 11600, 9600 and 8530); ν_{max} (KBr)/cm^{-1} 1740 (ester), 1700 (conjugated ester) and 1660 (pyridone); δ_H (360 MHz, C^2HCl_3) 1.26 and 1.34 (2 × 3H, t, J 7.1, 2 × CH_3), 1.41 (3H, d, J 7.0, CH_3), 2.30–2.45 (1H, m, H-3), 2.82 (1H, t, $J_{2S,2R} = J_{2,3}$ 12.1, H-2*S*), 2.82 (1H, m, $J_{2R,2S}$ 12.1, $J_{2R,3}$ 4.3, $J_{2R,4}$ 1.5, H-2*R*), 4.23 and 4.29 (2 × 2H, q, 2 × OCH_2), 5.63 (1H, dd, $J_{4,3}$ 4, $J_{4,2R}$ 1.50, H-4), 6.27 (1H, d, J 9.6, pyridone α-CH) and 7.94 (1H, d, J 9.6, pyridone β-CH). A COSY spectrum confirmed many of the couplings.

(b) Using deuterium. A solution of diethyl 3-methyl-6-oxo-4*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4,9-dicarboxylate **8** (20 mg, 0.06 mmol) in ethyl acetate (2 ml) was reduced at room temperature and pressure overnight with deuterium gas using 5% rhodium on alumina catalyst (20 mg). The solution was filtered through Celite, the solvent was removed *in vacuo* and the crude

material was chromatographed using the Chromatotron with silica gel and diethyl ether–petroleum ether (3 : 1) as eluant. The resulting oil crystallised from chloroform–petroleum ether as white prisms of *diethyl 3-methyl-6-oxo-2,3-dideuterio-4H,6H-pyrido[2,1-b][1,3]thiazine-4,9-dicarboxylate* **9**, ($H_{2R} = H_3 = {}^2H$) (8 mg, 39%); mp 81–83 °C; δ_H (360 MHz, C^2HCl_3) 1.27 and 1.35 (2 × 3H, t, *J* 7.1, CH_3), 1.41 (3H, s, CH_3), 2.88 (1H, br s, CHDS), 4.23 and 4.29 (2 × 2H, 2 × q, *J* 7.1, 2 × OCH_2), 5.65 (1H, s, H-4), 6.27 (1H, d, *J* 9.6, pyridone α-CH) and 7.94 (1H, d, *J* 9.6, pyridone β-CH).

(c) Using sodium borohydride. Diethyl 3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4,9-dicarboxylate **2** (7.75 g 23.9 mmol) was dissolved in THF (40 ml) and sodium borohydride (1.82 g, 48.1 mmol) was added. Water (2 ml) was slowly added and the solution was stirred at room temperature. After 3 h a further portion of water (20 ml) was added and the excess borohydride was destroyed with conc. hydrochloric acid. The solution was extracted with chloroform, and the organic layer was washed with water, dried (Na_2SO_4) and the solvent was removed *in vacuo* to give an orange oil. This was chromatographed on silica gel, eluting with diethyl ether to give *diethyl 3-methyl-6-oxo-3,4-dihydro-2H,6H-pyrido[2,1-b][1,3]thiazine-4,9-dicarboxylate* **9** as an off-white solid which was recrystallised from ethanol (7.2 g, 92%); mp 83–85 °C. The spectra were as described above.

4-Ethoxycarbonyl-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1-*b*]-[1,3]thiazine-9-carboxylic acid 11

A solution of boron tribromide in dichloromethane (5 ml of a 1 M solution, 5 mmol) was added *via* syringe to a stirred solution of 9-benzyloxycarbonyl-4-ethoxycarbonyl-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine **10**[4] (2 g, 5 mmol) in dry dichloromethane (40 ml) at −78 °C under nitrogen. The solution was stirred at −78 °C for 30 min and at room temperature for 1 h. It was poured into 5% aqueous sodium bicarbonate (30 ml), the organic layer was washed with further portions of aqueous sodium bicarbonate (3 × 15 ml) and the combined bicarbonate extracts were acidified to pH 1 with conc. hydrochloric acid. The product was extracted into ethyl acetate (5 × 20 ml), dried ($MgSO_4$) and the solvent was removed *in vacuo* to yield a pale red solid which was recrystallised from methanol–ether to yield *4-ethoxycarbonyl-3-methyl-6-oxo-2H,6H-pyrido[2,1-b][1,3]thiazine-9-carboxylic acid* **11** as a white microcrystalline solid (0.95 g, 62%); mp 238–240 °C (decomp.) (Found C, 52.8; H, 4.5; N, 4.5%. $C_{13}H_{13}NO_5S$ requires C, 52.9; H, 4.4; N, 4.7%); *m*/*z* (EI) 295 ($[M]^+$); λ_{max} (MeOH pH < 7)/nm 240 and 330 (ε 5580 and 4850); λ_{max} (MeOH, pH 7–14)/nm 256 (sh) and 339 (ε 4430 and 5270); ν_{max} (KBr)/cm^{-1} 2900–3100 (OH), 1740 (ester), 1705 (carboxylic acid) and 1630 (pyridone); δ_H (360 MHz, C^2HCl_3–$C^2H_3O^2H$–$(C^2H_3)_2SO$) 1.13 (3H, t, *J* 7.5, CH_3), 2.21 (3H, s, CH_3), 3.21 (2H, s, CH_2S), 4.05 (2H, q, *J* 7.5, OCH_2), 6.15 (1H, d, *J* 9, pyridone α-H) and 7.82 (1H, d, *J* 9, pyridone β-H).

Ethyl 9-hydroxymethyl-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1-*b*]-[1,3]thiazine-4-carboxylate 12

Ethyl chloroformate (0.37 g, 3.4 mmol) was added to a solution of 4-ethoxycarbonyl-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1-*b*][1,3]-thiazine-9-carboxylic acid **11** (0.5 g, 1.7 mmol) and triethylamine (0.34 g, 3.4 mmol) in dry tetrahydrofuran (20 ml) at 0 °C under argon with stirring. The solution was stirred at 0 °C for 1 h and filtered and the residue was washed with tetrahydrofuran (5 ml). The solution was added to a solution of sodium borohydride (0.26 g, 6.8 mmol) in water (15 ml) at 0 °C and stirred for 1 h at 0 °C and at room temperature for 3 h. The solution was partitioned between chloroform and dilute hydrochloric acid and the aqueous layer was extracted with further portions of chloroform (2 × 10 ml). The combined organic extracts were dried ($MgSO_4$). The solvent was removed *in vacuo* to yield *ethyl 9-hydroxymethyl-3-methyl-6-oxo-2H,6H-pyrido[2,1-b][1,3]-thiazine-4-carboxylate* **12** as an off-white solid which was recrystallised from chloroform–petroleum ether to give white plates (0.45 g, 94%); mp 154–155 °C (Found C, 55.6; H, 5.5; N, 4.9%. $C_{13}H_{15}NO_4S$ requires C, 55.5; H, 5.4; N, 5.0%); *m*/*z* (EI) 281 ($[M]^+$); λ_{max} (MeOH, pH 7–14)/nm 263, 271 (sh), 317 and 333 (sh) (ε 7840, 7250, 4510 and 3330); λ_{max} (MeOH, pH 1–7)/nm 275, 312 and 329 (sh) (ε 9470, 4440 and 2880); ν_{max} (KBr)/cm^{-1} 3300 (OH), 1730 (ester) and 1635 (pyridone); δ_H (60 MHz, C^2HCl_3) 1.18 (3H, t, *J* 7 Hz, CH_3), 2.2 (3H, s, CH_3-C=), 3.2 (2H, s, CH_2S), 4.2 (2H, q, *J* 7, OCH_2), 4.6 (2H, s, CH_2OH), 6.3 (1H, d, *J* 9.5, pyridone α-H) and 7.3 (1H, d, *J* 9.5, pyridone β-H).

Ethyl 9-hydroxymethyl-3-methyl-6-oxo-4*H*,6*H*-pyrido[2,1-*b*]-[1,3]thiazine-4-carboxylate 13

Reaction A. Sodium ethoxide (100 mg, 1.5 mmol) was added to a stirred solution of ethyl 9-hydroxymethyl-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4-carboxylate **12** (1 g, 3.6 mmol) in dry ethanol (35 ml) at 0 °C under argon. Stirring was continued at 0 °C for 1 h and at room temperature for 3 h. After cooling to 0 °C, the solution was diluted with dichloromethane and neutralised by addition of dilute hydrochloric acid. The organic layer was separated and dried ($MgSO_4$) and the solvent was removed *in vacuo* to yield an off-white solid which was used without further purification (0.79 g, 79%). Spectra were identical to those for *ethyl 9-hydroxymethyl-3-methyl-6-oxo-4H,6H-pyrido[2,1-b][1,3]thiazine-4-carboxylate* **13** prepared by Reaction B below.

Reaction B. Sodium ethoxide (10 mg, 0.15 mmol) was added to a stirred solution of ethyl 9-hydroxymethyl-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4-carboxylate **12** (100 mg, 0.36 mmol) in dry ethanol (10 ml) at −10 °C. The solution was stirred at −10 °C for 3 h and neutralised with conc. hydrochloric acid. The solution was partitioned between chloroform and water, and the organic layer was separated and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield a pale oil. The crude material was purified by chromatography on silica gel using diethyl ether–petroleum ether, (1 : 3) as eluant to yield two components. Component 1 was identified as *ethyl 9-ethoxymethyl-3-methyl-6-oxo-3,4-dihydro-2H,6H-pyrido[2,1-b][1,3]thiazine-4-carboxylate* **14** and was recrystallised from chloroform–petroleum ether (42 mg, 38%); mp 60–63 °C (Found C, 58.2; H, 7.2; N, 4.4%. $C_{15}H_{21}NO_4S$ requires C, 57.9; H, 6.8; N, 4.5%); *m*/*z* (EI) 311 ($[M]^+$); λ_{max} (MeOH)/nm 255, 338 and 350 (sh) (ε 8800, 14 500 and 11 900); ν_{max} 1730 (ester) and 1650 (pyridone); δ_H (60 MHz, C^2HCl_3) 1.03 (3H, t, *J* 7, CH_3), 1.07 (3H, t, *J* 7, CH_3), 1.24 (3H, d, *J* 7, CH_3), 2.1 (1H, m, H-3), 2.64 (1H, s, CHS), 2.8 (1H, d, *J* 1.1, CHS), 3.24 (2H, q, *J* 7, OCH_2), 4.0 (2H, q, *J* 7, OCH_2), 4.07 (2H, s, OCH_2), 5.42 (1H, d, *J* 2.7, H-4), 6.0 (1H, d, *J* 9, pyridone α-H) and 7.1 (1H, d, *J* 9, pyridone β-H); δ_C (90.55 MHz, C^2HCl_3) 13.85 (CH_3), 14.91 (CH_3), 18.53 (CH_3), 29.32 (CH_2S), 33.04 (C-3), 56.76 (C-4), 61.42 (OCH_2), 65.42 (OCH_2) 68.56 (OCH_2), 113.95 (pyridone α-C), 114.28 (C=), 140.30 (pyridone β-C), 162.36 (pyridone C=O) and 168.11 (ester). Component 2 was identified as *ethyl 9-hydroxymethyl-3-methyl-6-oxo-4H,6H-pyrido[2,1-b]-[1,3]thiazine-4-carboxylate* **13** (14 mg, 14%); mp 149–151 °C (Found C, 55.0, H, 5.5; N, 4.3%. $C_{13}H_{15}NO_4S$ requires C, 55.5; H, 5.4; N, 5.0%); *m*/*z* (EI) 281.0722 $C_{13}H_{15}NO_4S$ requires 281.17218; λ_{max} (MeOH)/nm 247, 263 and 340 (ε 5200, 5000 and 7600); ν_{max} (KBr)/cm^{-1} 3400 (OH), 1750 (ester) and 1640 (pyridone); δ_H (90 MHz, C^2HCl_3) 1.22 (3H, t, *J* 7, CH_3), 2.18 (3H, d, *J* 2, CH_3), 4.18 (2H, q, *J* 7, OCH_2), 4.4, 4.6 (2 × 1H, 2 × d, J_{AB} 12, CH_2O), 6.24 (1H, q, H-4), 6.47 (1H, d, *J* 10, pyridone α-H), 6.62 (1H, br s, H-2) and 7.42 (1H, d, *J* 10, pyridone β-H).

Ethyl 9-hydroxymethyl-3-methyl-6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4-carboxylate 16

Method A—from the thiazine 13. A solution of ethyl 9-hydroxymethyl-3-methyl-6-oxo-4*H*,6*H*-pyrido[2,1-*b*][1,3]-thiazine-4-carboxylate **13** (0.79 g, 2.8 mmol) in methanol (20 ml) containing acetic acid (1 drop) was hydrogenated with rhodium on alumina catalyst (1 g) for 15 h at room temperature and pressure. The suspension was filtered through Celite and the solvent was removed *in vacuo* to yield an oil which was found by TLC on silica gel using ethyl acetate as eluant to consist of two components. The components were separated by chromatography on a Chromatotron using silica gel with ethyl acetate as eluant. Component 1 was identified as *ethyl 9-methoxymethyl-3-methyl-6-oxo-3,4-dihydro-2H,6H-pyrido[2,1-b][1,3]thiazine-4-carboxylate* **17** which was recrystallised from chloroform–petroleum ether as white prisms (0.183 g, 22%); mp 69–71 °C (Found C, 56.6; H, 6.35; N, 4.7%. $C_{14}H_{19}NO_4S$ requires C, 56.6; H, 6.4; N, 4.7%); *m/z* (EI) 297 ([M]$^+$); λ_{max} (MeOH)/nm 245, 338 and 348 (sh) (ε 7500, 12 000 and 10 500); ν_{max} (KBr)/cm^{-1} 1735 (ester) and 1660 (pyridone); δ_H (360 MHz, C^2HCl_3) 1.25 (3H, t, *J* 7.1, CH_3), 1.45 (3H, d, *J* 7.1, CH_3), 2.3 (1H, m, H-3), 2.94 (1H, s, H-2B), 2.95 (1H, d, $J_{2A,3}$ 9.3, H-2A), 3.35 (3H, s, OCH_3), 4.21 and 4.22 (2 × 1H, 2 × q, *J* 7.1, OCH_2), 4.26 and 4.32 (2 × 1H, 2 × d, J_{AB} 11.7, OCH_2), 5.76 (1H, d, $J_{4,3}$ 3.5, H-4), 6.36 (1H, d, *J* 9.2, pyridone α-H) and 7.31 (1H, d, *J* 9.2, pyridone β-H); δ_C (90.55 MHz, C^2HCl_3) 14.10 (CH_3), 18.76 (CH_3), 29.54 (CH_2S), 33.26 (C-3), 57.00 (C-4), 57.83 (CH_2O), 61.66 (OCH_2), 70.87 (OCH_3), 114.03 (C=), 114.14 (pyridone α-C), 140.59 (pyridone β-C), 162.55 (pyridone C=O) and 168.31 (ester). Component 2 was identified as *ethyl 9-hydroxymethyl-3-methyl-6-oxo-3,4-dihydro-2H,6H-pyrido[2,1-b][1,3]thiazine-4-carboxylate* **16** which was recrystallised from chloroform–diethyl ether (95 mg, 12%); mp 143–144 °C (Found C, 54.5; H, 6.1; N, 4.9%. $C_{13}H_{17}NO_4S$ requires C, 55.1; H, 6.0; N, 4.9%); ν_{max} (KBr)/cm^{-1} 3350 (OH), 1740 (ester) and 1640 (pyridone); λ_{max} (MeOH)/nm 243 and 337 (ε 8500 and 13 400); δ_H (90 MHz, C^2HCl_3) 1.27 (3H, t, *J* 7, CH_3), 1.44 (3H, d, *J* 7, CH_3), 2.24 (1H, m, H-3), 2.93 (2H, m, CH_2S), 4.22 (2H, q, *J* 7, OCH_2), 4.49 (2H, br s, OCH_2), 5.69 (1H, d, $J_{4,3}$ 3, H-4), 6.31 (1H, d, *J* 10, pyridone α-H) and 7.38 (1H, d, *J* 10, pyridone β-H).

Method B—from the thiazine 11. Triethylamine (2.1 ml, 15.2 mmol) and ethyl chloroformate (1.5 ml, 15.7 mmol) were added to a stirred solution of 4-ethoxycarbonyl-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-9-carboxylic acid **11** (4.5 g, 15.2 mmol) in dry THF (50 ml) at −15 °C. This was stirred under nitrogen for 45 min and a solution of sodium borohydride (1.15 g, 30.4 mmol) in water (10 ml) was added. After stirring for a further 3 h the reaction was quenched with dilute hydrochloric acid and the product was extracted into chloroform. The organic layer was washed with water, dried (Na_2SO_4) and the solvent was removed *in vacuo* to give a brown gum which was chromatographed on silica gel, using chloroform–5% methanol as eluant to yield *ethyl 9-hydroxymethyl-3-methyl-6-oxo-3,4-dihydro-2H,6H-pyrido[2,1-b][1,3]thiazine-4-carboxylate* **16** as an off-white solid which was recrystallised from ethanol (2.43 g, 57%); mp 154–155 °C and had spectra in accordance with those of the sample prepared by Method A.

Method C—from the reduced thiazine acid 21. Triethylamine (2.1 ml, 15.2 mmol) and ethyl chloroformate (1.5 ml, 15.7 mmol) were added to a stirred solution of 4-ethoxycarbonyl-3,4-dihydro-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-9-carboxylic acid **21** prepared as described below (4.5 g, 15.1 mmol) in dry THF (50 ml) at −15 °C. This was stirred under nitrogen for 45 min and a solution of sodium borohydride (1.15 g, 30.4 mmol) in water (10 ml) was added. After stirring for a further 3 h, the reaction was quenched with dilute hydrochloric acid and the product was extracted into chloroform. The organic layer was washed with water, dried (Na_2SO_4) and the solvent was removed *in vacuo* to give a brown gum which was chromatographed on silica gel using chloroform–5% methanol as eluant to yield *ethyl 9-hydroxymethyl-3-methyl-6-oxo-3,4-dihydro-2H,6H-pyrido[2,1-b][1,3]thiazine-4-carboxylate* **16** as an off-white solid which was recrystallised from ethanol (2.43 g, 57%); mp 154–155 °C. The spectra were in accord with those above.

4-Methoxycarbonyl-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1-*b*]-[1,3]thiazine-9-carboxylic acid 19

A freshly prepared solution of boron tribromide (1 M in dichloromethane, 7.2 ml, 7.2 mmol) at −78 °C was added *via* syringe under nitrogen to a stirred solution of the benzyl 4-methoxycarbonyl-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1-*b*][1,3]-thiazine-9-carboxylate **18**[4] (2.69 g, 7.24 mmol) in dry methylene chloride (50 ml). The solution was stirred for 1 h at −78 °C and for 4 h at room temperature. The solution was extracted with saturated aqueous sodium bicarbonate and the combined bicarbonate extracts were acidified to pH 1 with conc. hydrochloric acid. The product was extracted into ethyl acetate and dried (Na_2SO_4). The solvent was removed *in vacuo* to yield a pale red solid which was recrystallised from methanol to yield *4-methoxycarbonyl-3-methyl-6-oxo-2H,6H-pyrido[2,1-b][1,3]-thiazine-9-carboxylic acid* **19** as a white microcrystalline solid (0.80 g, 39%); mp 227–229 °C (decomp.) (Found C, 51.05; H 4.0; N, 5.1%. $C_{12}H_{11}NO_5S$ requires C, 51.2; H, 3.9; N, 5.0%); *m/z* (EI) 281 ([M]$^+$); λ_{max} (MeOH)/nm 270 and 357 (ε 9600 and 8000); ν_{max} (KBr)/cm^{-1} 2800–3100 (OH), 1732 (CO_2H), 1705 (ester) and 1621 (pyridone); δ_H (80 MHz, C^2HCl_3–$(C^2H_3)_2SO$) 2.31 (3H, s, CH_3), 3.17 (2H, s, CH_2S), 3.73 (3H, s, OCH_3), 6.29 (1H, d, *J* 9.7, pyridone α-H) and 7.91 (1H, d, *J* 9.7, pyridone β-H); δ_C (90.55 MHz, C^2HCl_3–$(C^2H_3)_2SO$) 18.64 (CH_3), 30.09 (CH_2S), 51.94 (OCH_3), 109.80 (Ar), 113.71 (pyridone α-C), 135.81 (C=), 139.73 (pyridone β-C) and 162.85–165.90 (3 × C=O).

Methyl 3-methyl-6-oxo-9-hydroxymethyl-2*H*,6*H*-pyrido[2,1-*b*]-[1,3]thiazine-4-carboxylate 20

4-Methoxycarbonyl-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1-*b*][1,3]-thiazine-9-carboxylic acid **19** (0.68 g, 2.3 mmol) in dry THF (15 ml) was stirred at 0 °C under nitrogen. Triethylamine (0.35 ml, 2.5 mmol) and ethyl chloroformate (0.25 ml, 2.6 mmol) were added and the reaction mixture was stirred for 1 h at 0 °C. Sodium borohydride (0.55 g, 14.5 mmol) in water (10 ml) was added and the mixture was stirred at room temperature overnight, acidified with conc. hydrochloric acid and extracted with chloroform. The chloroform extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield *methyl 3-methyl-6-oxo-9-hydroxymethyl-2H,6H-pyrido[2,1-b][1,3]thiazine-4-carboxylate* **20** as a brown gum which was chromatographed on silica gel using chloroform and chloroform–10% methanol as eluants, to give an off-white solid which was recrystallised from methanol (0.41g, 65%); mp 148–151 °C (Found C, 53.1; H, 5.7; N, 5.0%. $C_{12}H_{15}NO_4S$ requires C, 53.5; H, 5.6; N, 5.2%); *m/z* (EI) 269 ([M]$^+$); λ_{max} (MeOH)/nm 243 and 339 (ε 3780 and 4280); ν_{max} (KBr)/cm^{-1} 3600–3100 (OH), 1735 (ester) and 1648 (amide); δ_H (360 MHz, C^2HCl_3) 1.19 (3H, d, *J* 7, CH_3), 2.28 (1H, m, $J_{3,2A}$ 7, $J_{3,4}$ 3.2, $J_{3,2B}$ 0.97, H-3), 2.97 (2H, ABX, $J_{2A,3}$ 9, $J_{2B,3}$ 0.97, CH_2S), 3.73 (3H, s, OCH_3), 4.52 (2H, AB, J_{AB} 12.6, CH_2Ph), 5.78 (1H, d, $J_{4,3}$ 3.2, H-4), 6.37 (1H, d, *J* 9.3, pyridone α-H) and 7.36 (1H, d, *J* 9.3, pyridone β-H).

4-Ethoxycarbonyl-3,4-dihydro-3-methyl-6-oxo-2*H*,6*H*-pyrido-[2,1-*b*][1,3]thiazine-9-carboxylic acid 21

To a solution of diethyl 3,4-dihydro-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4,9-dicarboxylate **9** (10 g, 30.9 mmol)

in ethanol (50 ml) and water (5 ml) was added potassium hydroxide (1.8 g, 32 mmol). The solution was stirred for three days at room temperature and partitioned between aqueous sodium bicarbonate and ether. The bicarbonate layer was acidified to pH 1 with conc. hydrochloric acid and extracted with ethyl acetate. The organic fraction was dried (Na_2SO_4), and the solvent was removed *in vacuo* to give *4-ethoxycarbonyl-3,4-dihydro-3-methyl-6-oxo-2H,6H-pyrido[2,1-b][1,3]thiazine-9-carboxylic acid* **21** as a tan solid. This was recrystallised from ethanol to give a white solid (5.76 g, 63%); mp 212–214 °C (Found C, 49.2; H, 5.7; H, 4.65%. $C_{13}H_{15}NO_5S{\cdot}H_2O$ requires C, 49.5; H, 5.4; N, 4.4%); *m/z* (EI) 297 ($[M]^+$); ν_{max} (KBr)/cm^{-1} 3100–2700 (OH), 1740 (ester), 1701 (acid) and 1637 (amide); δ_H (360 MHz, C^2HCl_3–$(C^2H_3)_2SO$) 1.21 (3H, t, *J* 7.1, CH_3), 1.34 (3H, d, *J* 7, CH_3), 2.33 (1H, m, $J_{3,Me}$ 7, $J_{3,2A}$ 5.9, $J_{3,2B}$ 4.8, $J_{3,4}$ 4, H-3), 2.77 (2H, m, $J_{2B,3}$ 4.8, $J_{2A,3}$ 5.9, CH_2S), 4.16 (2H, q, *J* 7.1, OCH_2), 5.51 (1H, m, $J_{4,3}$ 4, $J_{4,2}$ 1.2, H-4), 6.16 (1H, d, *J* 9.6, pyridone α-H) and 7.90 (1H, d, *J* 9.6, pyridone β-H); δ_C (90.55 MHz, C^2HCl_3–$(C^2H_3)_2SO$) 13.82 (CH_3), 16.25 (CH_3), 26.75 (CH_2S), 29.19 (C-3), 57.46 (C-4), 60.22 (OCH_2), 106.22 (N-C=), 111.24 (pyridone α-C), 139.29 (pyridone β-C), 153.70 (N-C-S), 162.60 (acid), 163.95 (amide) and 170.24 (ester).

Ethyl 2-ethoxymethyl-8-methyl-5-oxo-10-thia-6-azatricyclo-[4.4.0.0^{1,4}]dec-2-ene-7-carboxylate 22

A solution of ethyl 9-ethoxymethyl-3-methyl-6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4-carboxylate **14** (40 mg, 0.13 mmol) in toluene (50 ml) was photolysed under nitrogen with a Philips 125 W high pressure mercury arc lamp at room temperature. After 20 h, TLC showed no starting material to be present and one main new component. The solvent was removed *in vacuo* to yield a yellow oil which was purified by chromatography on a Waters sep-pak using diethyl ether–petroleum ether (1:3) to elute the impurities and diethyl ether–petroleum ether (3:1) to elute the product. The product, *ethyl 2-ethoxymethyl-8-methyl-5-oxo-10-thia-6-azatricyclo[4.4.0.0^{1,4}]dec-2-ene-7-carboxylate* **22** was obtained as an unstable pale oil (16 mg, 40%); *m/z* (EI) 311 ($[M]^+$); ν_{max} (film)/cm^{-1} 1755 (β-lactam) and 1735 (ester); δ_H (400 MHz, C^2HCl_3) 1.08 (3H, d, *J* 6.7, CH_3), 1.23 (3H, t, *J* 6.7, CH_3), 1.30 (3H, t, *J* 6.7, CH_3), 2.65 (1H, m, H-8), 2.73 (1H, dd, $J_{9A,9B}$ 13.3, $J_{9A,8}$ 2.7, CHS), 2.95 (1H, dd, $J_{9A,9B}$ 13.3, $J_{9B,8}$ 10, CHS), 3.50 (2H, 2 × q, *J* 6.7, CH_2O), 4.00 (1H, d, $J_{7,8}$ 6.7, H-7), 4.08 (1H, H-4), 4.10 (2H, d, *J* 10, CH_2O), 4.25 (2H, q, *J* 6.7, OCH_2) and 6.37 (1H, d, *J* 1.4, CH=).

Synthesis of 2-azabicyclo[2.2.0]hex-5-en-3-one 4 (R = H)[8] for spectral comparison

2-Pyridone **3** (R = H) (1 g, 11 mmol) was photolysed under nitrogen in dry degassed methanol (800 ml) with a 125 W medium pressure mercury arc lamp for seventy hours at room temperature. The solvent was removed *in vacuo* to yield a crude oil which was purified by chromatography on a Chromatotron using silica gel and eluting with diethyl ether–petroleum ether (3:1). The product was obtained as an oil which crystallised on trituration with ether (0.56 g, 56%); mp 68–69 °C; *m/z* (EI) 95 ($[M]^+$); ν_{max} (KBr/cm^{-1} 3200 (NH) and 1760 (β-lactam); δ_H (360 MHz, C^2HCl_3) 4.17 (1H, m, $J_{4,6}$ 0.85, $J_{4,5}$ 1, H-4), 4.45 (1H, m, $J_{1,6}$ 2.3, H-1), 6.54 (1H, m, $J_{5,4}$ 1, $J_{5,6}$ 2.4, H-5) and 6.65 (1H, m, $J_{6,5}$ 2.5, H-6); δ_C (90.5 MHz, C^2HCl_3) 51 (C-1), 60 (C-4), 106 (C-6) and 120 (C-5).

Photolysis of ethyl 9-methoxymethyl-3-methyl-6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4-carboxylate 17 followed by hydrogenation

A solution of ethyl 9-methoxymethyl-3-methyl-6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4-carboxylate **17** (37 mg, 0.12 mmol) in dry benzene (45 ml) was photolysed with a 125 W high pressure mercury arc lamp under nitrogen at room temperature for 20 h. The solvent was removed *in vacuo* at room temperature and the ^{1}H-NMR spectrum of the crude material showed a vinylic resonance at δ 6.4 ppm. The crude material was immediately hydrogenated in methanol (5 ml) using 5% rhodium on alumina catalyst (100 mg) at room temperature and pressure for three days. The suspension was filtered through Celite and the solvent was removed *in vacuo* to yield a pale oil. The crude oil was purified by chromatography first using a Waters sep-pak silica gel cartridge, eluting with diethyl ether–petroleum ether (3:1), and then by preparative TLC on a silica gel plate (20 × 5 cm × 0.25 mm) using diethyl ether–petroleum ether (3:1) to yield *ethyl 2-methoxymethyl-8-methyl-5-oxo-10-thia-6-azatricyclo[4.4.0.0^{1,4}]decane-7-carboxylate* **24** as an oil (7 mg, 19%); *m/z* (EI) Found 299.1191. $C_{14}H_{21}NO_4S$ requires 299.1191; *m/z* (+ve CI ammonia) 300 ($[M + H]^+$); ν_{max} ($CHCl_3$)/cm^{-1}, 1760 (β-lactam) and 1740 (ester); δ_H (360 MHz, C^2HCl_3) 1.11 (3H, d, *J* 6.8, CH_3), 1.33 (3H, t, *J* 7, CH_3), 1.71 (1H, m, $J_{3A,4}$ 3.3, $J_{3A,2}$ 6.9, $J_{3A,3B}$ 12.8, H-3A), 2.38 (1H, m, $J_{3B,4}$ 9, $J_{3B,2}$ 10.4, $J_{3B,3A}$ 12.8, H-3B), 2.55 (1H, m, H-8), 2.78 (1H, dd, $J_{9B,9A}$ 12.9, $J_{9B,8}$ 2.8, H-9B), 2.85 (1H, dd, $J_{9A,9B}$ 12.9, $J_{9A,8}$ 7.7, H-9A), 2.95 (1H, m, $J_{2,3A}$ 6.9, $J_{2,3B}$ 10.4, H-2), 3.37 (3H, s, OCH_3), 3.41 (1H, dd, $J_{1'A,1'B}$ 10.1, $J_{1'A,2}$ 5.3, H-1′A), 3.53 (1H, d, $J_{1'B,1'A}$ 10, H-1′B), 3.55 (1H, m, $J_{4,3A}$ 3.3, $J_{4,3B}$ 9, H-4), 4.11 (1H, d, $J_{7,8}$ 4.7, H-7) and 4.29 (2H, q, *J* 7.1, OCH_2)—many of the couplings were confirmed by a COSY spectrum; δ_C (90.5 MHz, C^2HCl_3) 14.17 (CH_3), 14.35 (CH_3), 20.85 (C-3), 29.85 (C-8), 31.03 (C-9), 48.69 (C-2), 55.72 (C-4), 58.38 (OCH_3), 58.55 (C-7), 61.53 (OCH_2) and 71.96 (OCH_2). The spectrum was too weak to show peaks for C-1 and the two carbonyl carbons.

Ethyl 9-acetoxymethyl-3-methyl-6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4-carboxylate 25

Ethyl 9-hydroxymethyl-3-methyl-6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4-carboxylate **16** (100 mg, 0.35 mmol) was dissolved in a mixture of pyridine (1 ml) and acetic anhydride (1 ml) and stirred at room temperature overnight. The solvent was removed *in vacuo* to yield a crude solid which was purified by medium pressure liquid chromatography using silica gel and ethyl acetate as eluant. The purified material was recrystallised from chloroform–diethyl ether to yield *ethyl 9-acetoxymethyl-3-methyl-6-oxo-3,4-dihydro-2H,6H-pyrido[2,1-b][1,3]thiazine-4-carboxylate* **25** as white prisms (70 mg, 61%); mp 99–100 °C; *m/z* (EI) Found 325.0984. $C_{15}H_{17}NO_5S$ requires 325.0984; λ_{max} (MeOH)/nm 245, 255, 336 and 348 (sh) (ε 9300, 9600, 14 000 and 11 500); ν_{max} (CH_2Cl_2)/cm^{-1} 1730 (sh) (acetyl), 1720 (ethyl ester) and 1650 (pyridone); δ_H (C^2HCl_3) 1.17 (3H, t, *J* 7.7, CH_3), 1.34 (3H, d, *J* 6.7, CH_3), 2.1 (3H, s, CH_3C=O); 2.3 (1H, m, H-3), 2.86 and 2.94 (2H, 2 × s, CH_2S), 4.14 (2H, q, *J* 7.7, OCH_2), 4.9 (2H, 2 × d, J_{AB} 12, OCH_2), 5.8 (1H, d, *J* 3.9, H-4), 6.3 (1H, d, *J* 9, pyridone α-H) and 7.3 (1H, d, *J* 9, pyridone β-H).

Photolysis and deuteriation of ethyl 9-acetoxymethyl-3-methyl-6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4-carboxylate 25

A solution of ethyl 9-acetoxymethyl-3-methyl-6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4-carboxylate **25** (40 mg, 0.12 mmol) was photolysed in dry benzene (45 ml) at room temperature overnight under nitrogen with a 125 W high pressure mercury arc lamp using a Pyrex filter. The solvent was removed *in vacuo* at room temperature to yield an oil which was dissolved in ethyl acetate (2 ml) and reduced using deuterium gas and rhodium on alumina catalyst (20 mg) at room temperature and pressure overnight. The suspension was filtered through Celite and the solvent was removed *in vacuo* to yield an oil which was purified by chromatography on a preparative

silica gel plate (20 × 5 cm × 0.25 mm) using diethyl ether–petroleum ether (3 : 1) as eluant to yield the product **26** as an oil (5 mg, 13%); *m/z* (EI) 329 ($[M]^+$); ν_{max} ($CHCl_3$)/cm^{-1} 2400 (CD), 1760 (β-lactam) and 1740 (ester); δ_H (360 MHz, C^2HCl_3) 1.11 (3H, d, *J* 6.8, CH_3), 1.33 (3H, t, *J* 7.1, CH_3), 1.8 (1H, br m, H-3), 2.10 (3H, s, $COCH_3$), 2.5 (1H, m, H-8), 2.69 (1H, dd, $J_{9B,9A}$ 12.9, $J_{9B,8}$ 2.6, H-9B), 2.93 (1H, dd, $J_{9A,9B}$ 12.9, $J_{9A,8}$ 8.3, H-9A), 3.58 (1H, m, H-4), 4.10 (1H, d, $J_{7,8}$ 4.9, H-7), 4.28 (2H, m, H-1′) and 4.30 (2H, q, *J* 6.8, OCH_2).

Ethyl 9-benzoyloxymethyl-3-methyl-6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4-carboxylate 27

Ethyl 9-hydroxymethyl-3-methyl-6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4-carboxylate **16** (90 mg, 0.32 mmol) was dissolved in dry pyridine (3 ml) and benzoic anhydride (100 mg, 0.44 mmol) was added at room temperature with stirring. The solution was stirred at room temperature under argon for two days. The solution was diluted with dichloromethane (10 ml) and washed with dilute hydrochloric acid (3 ml) and saturated aqueous sodium bicarbonate (3 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield an oil which was purified by chromatography on a Chromatotron using silica gel and eluting with diethyl ether–petroleum ether (3 : 1), for component 1 and with ethyl acetate for component 2. Component 1, *ethyl 9-benzoyloxymethyl-3-methyl-6-oxo-3,4-dihydro-2H,6H-pyrido[2,1-b][1,3]thiazine-4-carboxylate* **27** was obtained as a pale oil (45 mg, 37%); *m/z* (EI) Found 387.1134. $C_{20}H_{21}NO_5S$ requires 387.1140; ν_{max} ($CHCl_3$)/cm^{-1} 1740 (ester), 1720 (benzoyl) and 1650 (pyridone); δ_H (360 MHz, C^2HCl_3) 1.23 (3H, t, *J* 7.1, CH_3), 1.47 (3H, d, *J* 7.0, CH_3), 2.34 (1H, m, H-3), 2.97 (1H, d, *J* 1.6, CHS), 3.00 (1H, s, CHS), 4.22 (2H, d × q × q, $J_{AX} = J_{BX} = 7.1$, J_{AB} 10.5, OCH_2), 5.22 (2H, dd, J_{AB} 12.5, OCH_2), 5.77 (1H, d, $J_{4,3}$ 3.2, H-4), 6.40 (1H, d, *J* 9.3, pyridone α-H), 7.44 (1H, d, *J* 9.3, pyridone β-H), 7.4–7.5 (2H, m, ArH), 7.55 (1H, m, ArH) and 8.0–8.1 (2H, m, ArH). Component 2 was identified as unreacted starting material (30 mg).

Ethyl 2-(benzoyloxymethyl)-8-methyl-5-oxo-10-thia-6-azatricyclo[4.4.0.0^{1,4}]dec-2-ene-7-carboxylate 28

A solution of ethyl 9-benzoyloxymethyl-3-methyl-6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4-carboxylate **27** (100 mg, 0.26 mmol) in dry, degassed benzene (350 ml) was irradiated with a 125W high pressure immersion mercury arc lamp through Pyrex filters at 8 °C overnight. The benzene was removed *in vacuo* to yield a pale oil (74 mg, 74%). The ^{1}H-NMR spectroscopic data showed a crude product but it could be seen that the product existed as two isomers, the major component being the expected photoproduct **28a** in a ratio of 5 : 3 with the minor isomer **28b**. The major component was photoproduct **28a**; δ_H (360 MHz, C^2HCl_3) 1.00 (3H, d, J 7, CH_3), 1.31 (3H, t, *J* 7.1, CH_3), 2.52 (1H, m, H-8), 2.60 (1H, dd, $J_{9A,9B}$ 12.5, $J_{9B,8}$ 2.4, H-9B), 3.03 (1H, dd, $J_{9A,9B}$ 12.5, $J_{9A,8}$ 10, H-9A), 4.10 (1H, d, $J_{7,8}$ 5.5, H-7), 4.23 (1H, d, $J_{4,3}$ 2.3, H-4), 4.27 (2H, q, *J* 7, OCH_2), 4.98 (2H, 2 × d, $J_{1'A,3}$ 1.6, $J_{1'B,3}$ 1.3, H-1′), 6.59 (1H, dd, $J_{3,4}$ 2.3, $J_{3,1'}$ 1.3, H-3) and 7.49 (5H, m, ArH). The minor component was photoproduct **28b**; δ_H (360 MHz, C^2HCl_3) 1.07 (3H, d, *J* 7, CH_3), 1.30 (3H, t, *J* 7.1, CH_3), 2.45 (1H, m, H-8), 2.52 (1H, dd, $J_{9B,9A}$ 14, $J_{9B,8}$ 2.9, H-9B), 3.20 (1H, dd, $J_{9A,9B}$ 14, $J_{9A,8}$ 11.5, H-9A), 4.10 (1H, m, $J_{4,3}$ 2.8, $J_{4,1'}$ 1.8, H-4), 4.20 (1H, d, $J_{7,8}$ 7.1, H-7), 4.27 (2H, q, *J* 7, OCH_2), 5.25 (2H, ddd, $J_{1'A,1'B}$ 15, $J_{1',3}$ 1.8, $J_{1',4}$ 1.8, H-1′), 6.46 (1H, dd, $J_{3,4}$ 2.8, $J_{3,1'}$ 1.8, H-3) and 8.05 (5H, m, ArH). Spectra were in accordance for the structures **28a** and **28b**.

Methyl 9-benzoyloxymethyl-3-methyl-6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4-carboxylate 29

Methyl 9-hydroxymethyl-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1-*b*]-[1,3]thiazine-4-carboxylate **20** (200 mg, 0.74 mmol) was dissolved in dry pyridine (20 ml) and benzoic anhydride (170 mg, 0.75 mmol) was added. The solution was stirred at room temperature under nitrogen for 2 days. The solution was partitioned between chloroform and water and the organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo* to give a brown oil which was chromatographed on silica gel using diethyl ether as eluant to give *methyl 3-methyl-6-oxo-9-benzoyloxymethyl-2H,6H-pyrido[2,1-b][1,3]thiazine-4-carboxylate* **29** as a pale gum (146 mg, 53%); *m/z* (EI) Found 373.1001. $C_{19}H_{19}NO_5S$ requires 373.0984; λ_{max} (MeOH)/nm 237, 253 and 337 (ε 1850, 1100 and 1300); δ_H (360 MHz, C^2HCl_3) 1.46 (3H, d, *J* 7, CH_3), 2.32 (1H, m, H-3), 2.97–3.00 (2H, m, CH_2S), 3.74 (3H, s, OCH_3), 5.17 and 5.26 (2H, 2 × d, J_{AB} 12.6, CH_2O), 5.77 (1H, d, *J* 3, H-4), 6.39 (1H, d, *J* 9.3, pyridone α-H) and 7.41–8.05 (6H, m, pyridone β-H and ArH); δ_C (90.55 MHz, C^2HCl_3) 18.48 (CH_3), 29.41 (CH_2S), 33.13 (C-3), 52.33 (C-4), 56.89 (OCH_3), 63.46 (CH_2O), 111.97 (N-C=), 114.19 (pyridone α-C), 128.31–132.97 (Ar), 141.10 (pyridone β-C), 143.61 (N-C-S), 162.21, 166.28 and 168.62 (3 × CO).

Methyl 2-(benzoyloxymethyl)-8-methyl-5-oxo-10-thia-6-azatricyclo[4.4.0.0^{1,4}]dec-2-ene-7-carboxylate 30

A solution of the methyl 9-benzoyloxymethyl-3-methyl-6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4-carboxylate **29** (100 mg, 0.27 mmol) in dry, degassed benzene (350 ml) was irradiated with a 125 W high pressure immersion mercury arc lamp through Pyrex filters at room temperature overnight. The benzene was removed *in vacuo* to yield *methyl 2-(benzoyloxymethyl)-8-methyl-5-oxo-10-thia-6-azatricyclo[4.4.0.0^{1,4}]dec-2-ene-7-carboxylate* **30** as a pale oil (74 mg, 74%); *m/z* (EI) Found 373.0976. $C_{19}H_{19}NO_5S$ requires 373.0984; δ_H (360 MHz, C^2HCl_3) 0.98 (3H, d, *J* 7.1, CH_3), 2.50 (1H, m, $J_{8,7}$ 5.6, $J_{8,9B}$ 2.3, $J_{8,9A}$ 10, $J_{8,7}$ 7, H-8), 2.60 (1H, dd, $J_{9B,9A}$ 12.5, $J_{9B,8}$ 2.3, H-9B), 3.00 (1H, dd, $J_{9A,9B}$ 12.5, $J_{9A,8}$ 10, H-9A), 3.78 (3H, s, OCH_3), 4.10 (1H, d, $J_{7,8}$ 5.6, H-7), 4.21 (1H, dd, $J_{4,3}$ 2.3, $J_{4,1'}$ 1.3, H-4), 4.96 (2H, 2 × dd, $J_{1'B,3}$ 1.3, $J_{1'A,3}$ 1.3, H-1′), 6.56 (1H, dd, $J_{3,4}$ 2.3, $J_{3,1'}$ 1.3, H-3), 7.48, 7.62 and 8.08 (5H, m, ArH); δ_C (90.55 MHz, C^2HCl_3) 15.56 (CH_3), 28.80 (CH_2S), 31.22 (C-8), 52.21 (C-4), 57.80 (C-7), 58.74 (OCH_3), 64.20 (CH_2O), 128.40–134.7 (Ar and C=), 151.9, 164.9 and 167.6 (3 × C=O).

Methyl 2-(benzoyloxymethyl)-8-methyl-5-oxo-10-thia-6-azatricyclo[4.4.0.0^{1,4}]decane-7-carboxylate 31

Methyl 2-(benzoyloxymethyl)-8-methyl-5-oxo-10-thia-6-azatricyclo[4.4.0.0^{1,4}]dec-2-ene-7-carboxylate **30** (74 mg, 0.2 mmol) was dissolved in ethanol (25 ml) and hydrogenated using 5% rhodium on alumina (25 mg) at room temperature for 6 h. The solution was filtered and the solvent was removed *in vacuo* to give a pale brown gum which was chromatographed using a Chromatotron and silica gel with diethyl ether–petroleum ether (1 : 1) as eluant to yield *methyl 2-(benzoyloxymethyl)-8-methyl-5-oxo-10-thia-6-azatricyclo[4.4.0.0^{1,4}]decane-7-carboxylate* **31** (11 mg, 15%); *m/z* (EI) Found 375.1148. $C_{19}H_{21}NO_5S$ requires 375.1140; ν_{max} (film)/cm^{-1} 1762 (β-lactam), 1745 and 1720 (ester); δ_H (360 MHz, C^2HCl_3) 1.03 (3H, d, *J* 6.8, CH_3), 1.92–1.98 (1H, m, $J_{3B,4}$ 3.5, $J_{3B,2}$ 7, $J_{3B,3A}$ 10.5, H-3B), 2.4 (1H, m, $J_{8,9A}$ 8, $J_{8,9B}$ 3, $J_{8,7}$ 5, $J_{8,9A}$ 7, H-8), 2.48–2.54 (1H, m, $J_{3A,2}$ 10, $J_{3A,3B}$ 10.5, $J_{3A,4}$ 9, H-3A), 2.67 (1H, dd, $J_{9B,9A}$ 13, $J_{9B,8}$, 3, H-9B), 2.86 (1H, dd, $J_{9A,9B}$ 13, $J_{9A,8}$ 8, H-9A), 3.12 (1H, m, $J_{2,3B}$ 7, $J_{2,3A}$ 10, $J_{2,1'B}$ 5.5, $J_{2,1'A}$ 0.7, H-2), 3.64 (1H, dd, $J_{4,3B}$ 3.5, $J_{4,3A}$ 9, H-4), 3.81 (3H, s, OCH_3), 4.13 (1H, d, $J_{7,8}$ 5, H-7), 4.47 (2H, 2 × d, $J_{1'B,2}$ 5.5, $J_{1'A,2}$ 0.7, $J_{1'B,1'A}$ 10, H-1′), 7.45 (2H, m, ArH), 7.49 (1H, m, ArH) and 8.03 (2H, m, ArH)—the COSY spectrum is available as electronic supplementary information; δ_C (90.55 MHz, C^2HCl_3) 14.56 (CH_3), 21.07 (CH_2), 29.70 (C-8), 30.56 (CH_2S), 48.35 (C-2), 52.25 (C-4), 56.24 (C-7), 58.23 (OCH_3), 63.63 (CH_2O), 128.59 (Ar), 129.67 (Ar), 132.25 (Ar), 166.27, 166.62 and 167.67 (3 × C=O).

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