Photochemical Transformations of Cephalosporins [1]

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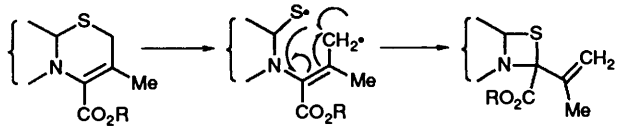
Two new photochemical reactions of the ceph-3-em **4** have been discovered. In methanol, rearrangement to the 2-isopropenyl-6-methoxy-4-oxotetrahydro-1,3-thiazine **14** occurs, whilst in tetrahydrofuran–acetone, regio- and stereo-specific addition leads to the tricyclic lactone **25**.

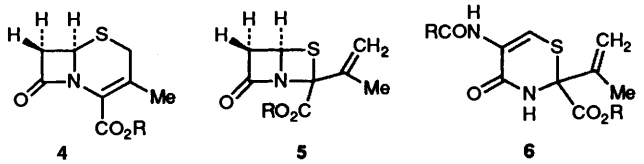
In studies of the photochemistry of 1,3-thiazine derivatives, we have discovered[2] that irradiation of thiazines of general formula **1** gives excellent yields of the corresponding thiazetidines **3** *via* the possible intermediacy of the diradicals **2** (Scheme 1). Since



1 **2** **3**

Scheme 1

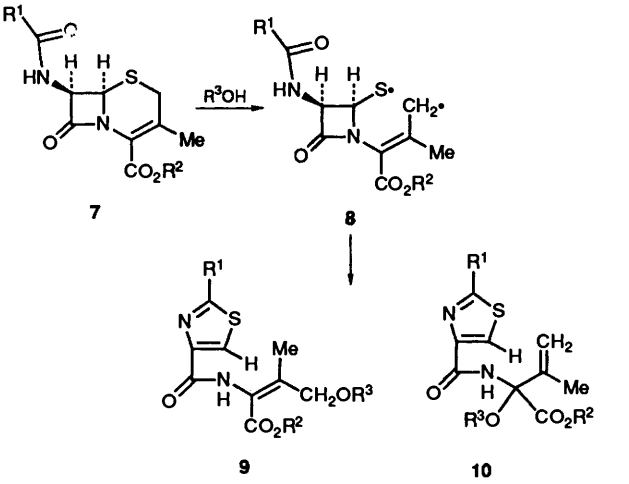
cephalosporins have a similar 1,3-thiazine ring system to the compounds undergoing the rearrangement, we were intrigued by the possibility that irradiation of the cephalosporin **4** might lead to the new β-lactam system **5**. This ring system may be



4 **5** **6**

regarded, with penicillins and cephalosporins, as part of a 'homologous series' of β-lactams fused to four-, five- and six-membered rings. This, the most strained member of the series, has never been prepared, although the structural type has been suggested for an intermediate in the rearrangement of penicillin sulfoxides to thiazines **6**.[3]

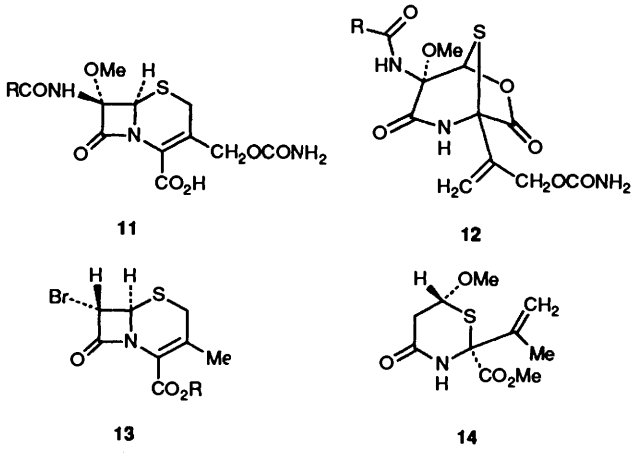
Previous work on the photochemistry of cephalosporin derivatives has involved 7-acylamino derivatives. When the ester **7** was irradiated in either methanol or ethanol, the products were shown[4] to be the thiazoles **9** and **10** (Scheme 2).



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

Scheme 2

The diradical **8**, analogous to our putative diradical **2**, was suggested as the first-formed intermediate in this reaction. This was encouraging but it was evident that the presence of the side chain had caused further rearrangement. A further photochemical rearrangement was observed when cefoxitin **11** was



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

irradiated in methanol to yield the bridged compound **12**.[5] Again a diradical analogous to **2** was suggested as being the first-formed intermediate but the free carboxylic acid group had evidently become involved in the reaction, forming a bicyclic product.

We therefore decided to photolyse the 7-unsubstituted 4-ester **4** (R=Me). Reaction of the 4-bromo-trichloroethyl ester **13** (R=CH_2CCl_3) with zinc in tetrahydrofuran (THF) containing dipotassium phosphate buffer to cleave the trichloroethyl ester and reduce the 7-bromide, followed by treatment with ethereal diazomethane gave the desired product **4** (R=Me) in 46% yield, accompanied by a 14% yield of the dichloroethyl ester **4** (R=CH_2CHCl_2) formed by reductive monodechlorination and debromination of the ester **13**. Photolysis was carried out in a variety of solvents giving, in the main, intractable mixtures. In three cases, however, identifiable products were obtained.

Photolysis in methanol at −10 °C gave a methanol adduct in which the characteristic pattern for the desired methylvinyl system was present in the ^1H NMR spectrum. However, characteristic absorptions for the β-lactam system were absent in both IR and ^1H NMR spectra, and two methoxy singlets were present in the ^1H NMR spectrum. The structure was finally solved by X-ray crystallographic analysis (Fig. 1) and the compound was shown to be the 1,3-thiazine **14**. The relative stereochemistry of the methoxy and ester groups was *cis* but the *C*2/*c* space group indicated that the compound was racemic.

Possible mechanisms for formation of the thiazine **14** are shown in Scheme 3. Literature precedence [2,4,5] suggests that the diradical **15** will be the first-formed intermediate. This may rearrange to yield the desired β-lactam-thiazetidine **5** (R=Me)

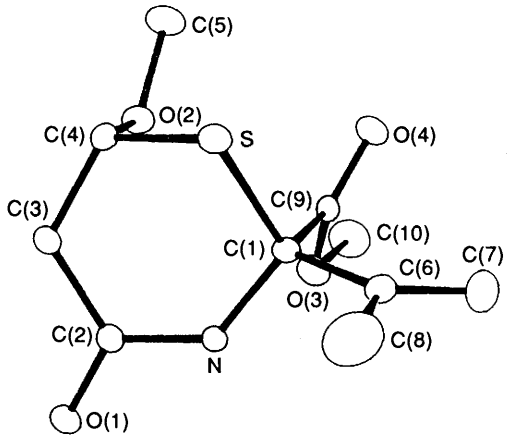
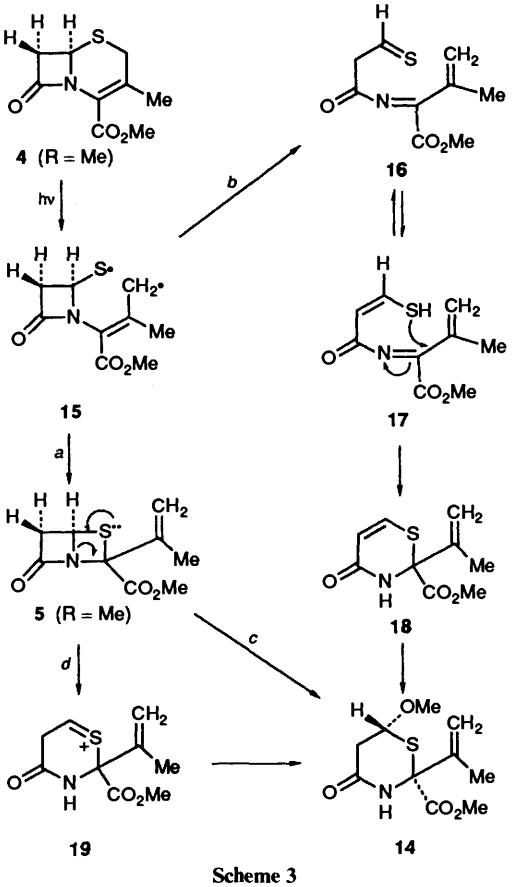


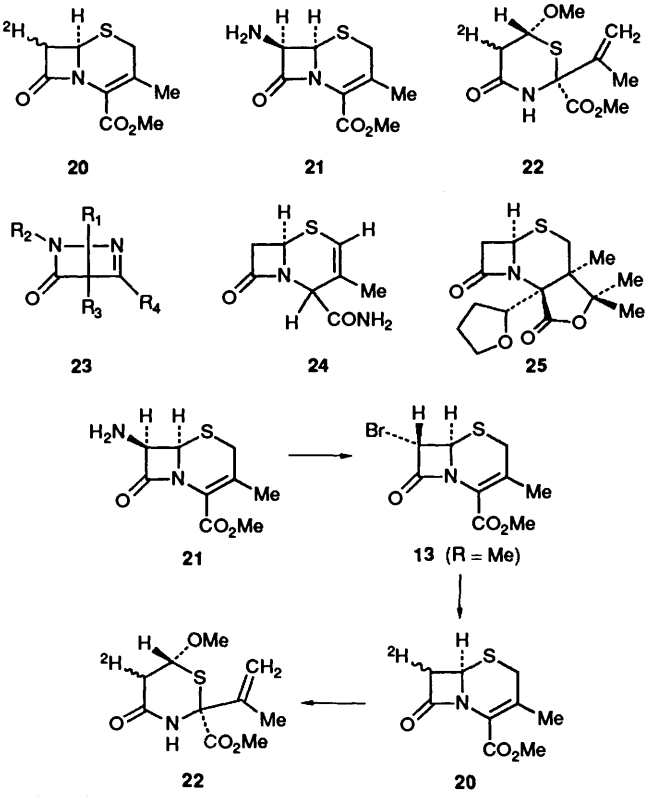
Fig. 1 Molecular structure of the 1,3-thiazine **14**



Scheme 3

or the thioaldehyde ⇌ thioenol, **16** ⇌ **17** which might cyclise as shown to the thiazine **18**. Methanolysis would then give the product **14**. Since this route would involve loss of hydrogen from C-7 of the starting cephalosporin, we prepared the 7-deuteriated compound **20** by conversion of 7-amino-deacetoxycephalosporanic acid **21** into the bromide **13** (R=Me) and use of ^2H_2O in the zinc reduction (Scheme 4). Deuterium incorporation was not fully stereospecific but on photolysis, the product **22** retained all of the deuterium, indicating that, unless a very large kinetic isotope effect operates against this loss, the mechanism *b* in Scheme 3 is unlikely.

It is thus possible that the diradical **15** yields the hoped-for β-lactam-thiazetidinone **5** (R=Me) but that this will be subject to methanolysis either directly as in route *c* or *via* participation of the sulfur lone pair as in route *d*. The fact that, whilst **4** is optically active, **14** is racemic would favour route *d*. It is conceivable that the bridged product **12**, obtained by photolysis



Scheme 4

of the free acid **11**, is formed by an analogous but intramolecular reaction on a β-lactam-thiazetidinone.

Because of Yamazaki's success in isolating the highly unstable β-lactam **23** by photolysis of a pyrimidin-4-one in diethyl ether and liquid ammonia,[6] we irradiated the ceph-3-em **4** (R=Me) in this solvent system. The sole clean product isolated was evidently a β-lactam from its IR and ^1H NMR spectroscopic data. The CH_2S protons were, however, no longer apparent in the ^1H NMR spectrum, being replaced by a one proton singlet at δ 4.61 and a one proton multiplet at δ 6.07 which was coupled to the methyl group at δ 1.91. The other data were in accord with the ceph-2-em structure **24**, a 1,3-hydrogen shift having occurred.

When the ceph-3-em **4** (R=Me) was irradiated in THF, reaction occurred only in the presence of acetone as a triplet sensitiser. The product had an extremely well-resolved ^1H NMR spectrum and it was evident that addition of both solvents to the double bond had occurred. The structure and stereochemistry of the product was shown to be that of the tricyclic adduct **25** by X-ray structure analysis (Fig. 2). This compound would be formed by attack of a THF radical from the less hindered side of the ring followed by reaction of acetone at the β-face of C-3 and subsequent lactonisation.

Experimental

M.p.s were determined on a Kofler hot stage apparatus, optical rotations on a Perkin Elmer PE241 polarimeter ($[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}), IR spectra on Perkin Elmer 257, 457 and 477 instruments and UV spectra on a Pye Unicam SP800 spectrophotometer. ^1H NMR spectra were recorded on Perkin Elmer R12 (60 MHz) and R32 (90 MHz) and Bruker WH 360 (360 MHz) instruments and ^{13}C NMR spectra on a Bruker WH 360 (90.5 MHz) instrument (*J* values are given in Hz). Mass spectra were recorded on Kratos MS 80 or MS 25 instruments by Mr. A. Greenway using electron

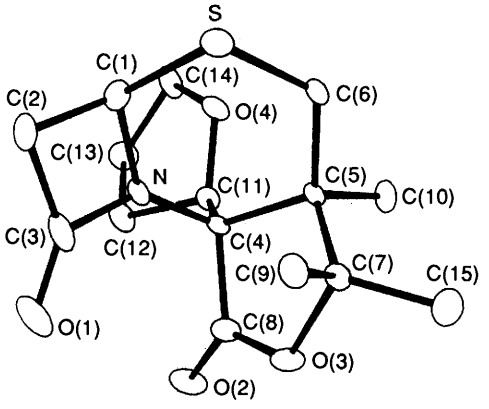


Fig. 2 Molecular structure of the tricyclic lactone **25**

impact ionisation (EI) unless otherwise stated. Combustion analyses were carried out by Mrs. G. Olney, the University of Sussex.

Methyl 3-*Methyl*-8-*oxo*-5-*thia*-1-*azabicyclo*[4.2.0]*oct*-2-*ene*-2-*carboxylate* **4** (R=Me).—A suspension of zinc powder (2 g, 30.8 mmol) in THF (10 cm^3) and dipotassium hydrogen phosphate buffer (2 cm^3 of a 1 mol dm^{-3} solution) containing the bromocephalosporin **13** (R=CH_2CCl_3)* (2 g, 4.9 mmol) was agitated in an ultrasonic bath for 4 h at room temperature. The suspension was filtered and the zinc residues were washed with THF. The filtrate was partitioned between chloroform and dilute hydrochloric acid and the organic layer was separated and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield a white foam which was dissolved in THF and added dropwise to excess ethereal diazomethane at 0 °C. Excess diazomethane was removed by a stream of nitrogen and the solvent was removed under reduced pressure to yield an off-white solid which was purified by chromatography (chromatotron: silica: ether–hexane, 1:3) to yield two components. The first component proved to be the ester **4** (R=CH_2CHCl_2) which crystallised on trituration with diethyl ether; 210 mg, 14%; m.p. 97–99 °C; (Found, C, 40.2; H, 3.8; N, 4.9. $C_{10}H_{11}Cl_2NO_3S$ requires C, 40.6; H, 3.7; N, 4.7%); *m/z* 297 and 295 (M^+); λ_{max}(MeOH)/nm 263 (log ε 3.59); ν_{max}(KBr)/cm^{-1} 1780 (β-lactam) and 1720 (ester); δ (C^2HCl_3; 360 MHz) 2.12 (3 H, s, CH_3C=), 2.93 (1 H, d × d, *J* 2.16 and 15.6, 7-H), 3.21 and 3.55 (2 H, AB, *J* 18.3, CH_2S), 3.58 (1 H, d × d, *J* 15.6 and 5.03, 7-H), 4.63 (2 H, d × q, *J* 11.5, 6.5 and 5.5, OCH_2), 4.68 (1 H, d × d, *J* 5.0 and 2.2, NCHS) and 5.91 (1 H, d × d, *J* 6.5 and 5.5, $CHCl_2$).

The second component was the desired β-lactam **4**, (R=Me) which formed white needles on trituration with diethyl ether; 0.48 g, 46%; m.p. 111–113 °C; $[\alpha]_D^{22.5}$ + 117.5 (*c* 1, THF); (Found: C, 50.1; H, 5.2; N, 6.0. $C_9H_{11}NO_3S$ requires C, 50.7; H, 5.2; N, 6.6%); *m/z* 213 (M^+); ν_{max}(KBr)/cm^{-1} 1785 (β-lactam) and 1725 (ester); λ_{max}(MeOH)/nm 268 (log ε 4.07); δ_H (C^2HCl_3; 360 MHz) 2.08 (3 H, CH_3C=), 2.92 (1 H, d × d, *J* 2.5 and 15, 7-H), 3.17 and 3.51 (2 H, AB, *J* 18.5, CH_2S), 3.56 (1 H, d × d, *J* 5 and 15, 7-H), 3.85 (3 H, s, OCH_3) and 4.65 (1 H, d × d, *J* 5 and 2.5, NCHS); δ_C (C^2HCl_3; 90.55 MHz) 19.82 (C-3′), 31.80 (C-7), 44.93 (C-2), 48.85 (OCH_3), 52.53 (C-6), 123.14 (C-3), 127.77 (C-4) and 162.2 (C-8 + ester C=O).

Photolysis of Compound **4** (R=Me) *in Methanol*.—The β-lactam **4** (R=Me) (0.5 g, 2.3 mmol) was photolysed in dry degassed methanol (150 cm^3) at −10 °C under nitrogen with an external Phillips 125 W high pressure mercury arc lamp. After 20 h a new component had appeared by TLC (silica:ether–hexane, 3:1). The solvent was removed under reduced pressure without heating, to yield a pale oil. Chromatography (chromatotron: silica: ether–hexane, 1:3) separated the new component from unchanged starting material (48 mg). The product **14** crystallised from chloroform–hexane as colourless prisms; 22 mg, 4%; m.p. 130–132 °C; *m/z* (+ve CI, NH_3), 246 (M^+ + 1); ν_{max}(KBr)/cm^{-1} 1730 (ester) and 1660 (amide); δ_H(C^2HCl_3; 360 MHz) 1.87 (3 H, d, *J* 0.56, CH_3C=), 2.85 (2 H, d, *J* 3.6, CH_2C=O), 3.34 (3 H, s, OCH_3), 3.79 (3 H, s, OCH_3), 4.85 (1 H, t, *J* 3.6, CHO), 5.16 (1 H, m, *J* 1.4, olefinic) and 5.35 (1 H, s, olefinic); δ_C (C^2HCl_3; 90.55 MHz) 19.14 (CH_3), 40.52 (CH_2), 53.77 (OCH_3), 56.72 (OCH_3), 81.71 (CH), 116.68 (olefinic) and 168.66 (C=O).

Methyl 3-*Methyl*-7-*bromo*-8-*oxo*-5-*thia*-1-*azabicyclo*[4.2.0]*oct*-2-*ene*-2-*carboxylate* **13** (R=Me).—7-Aminodesacetoxycephalosporanic acid **21*** (2 g, 9.3 mmol) was dissolved in water at room temperature (100 cm^3) and concentrated hydrobromic acid (7 cm^3) was added, followed by sodium bromide (4 g, 39 mmol). Diethyl ether (80 cm^3) was added and the biphasic mixture was stirred at room temperature while sodium nitrite (1.3 g) was added portionwise. After two minutes, nitrogen evolution had ceased and the organic layer was separated, washed with brine and dried ($MgSO_4$). This solution was added dropwise to excess ethereal diazomethane at 0 °C, the unreacted diazomethane was removed under a stream of nitrogen and the solvent was removed under reduced pressure to yield a dark oil. Chromatography (chromatotron: silica: ether–hexane, 1:1) gave the required material as a yellow oil which was crystallised from chloroform–hexane to yield colourless prisms of the product; 580 mg, 21%; m.p. 96–97 °C; (Found: C, 37.2; H, 3.5; N, 4.9. $C_9H_{10}BrNO_3S$ requires C, 37.0; H, 3.4; N, 4.8%); *m/z* (+ve CI, NH_3), 294 and 292 (M^+ + 1); ν_{max}(KBr)/cm^{-1} 1790 (β-lactam) and 1720 (ester); δ_H (C^2HCl_3; 90 MHz) 2.16 (3 H, s, CH_3C=), 3.36 (2 H, AB, *J* 18, CH_2S), 3.87 (3 H, s, OCH_3), 4.69 (1 H, br s, 6-H) and 4.82 (1 H, br s, 7-H).

Methyl [7-^{2}H]-3-*Methyl*-8-*oxo*-5-*thia*-1-*azabicyclo*[4.2.0]*oct*-2-*ene*-2-*carboxylate* **20**.—A solution of the bromocephalosporin **13**, (R=Me) (100 mg, 0.34 mmol) in THF (2 cm^3) and dipotassium deuterium phosphate buffer (1 cm^3 of a 1 mol dm^{-3} solution) containing zinc powder (100 mg, 1.53 mmol) was stirred overnight at room temperature. The suspension was filtered and the zinc residues were washed with chloroform. The solution was partitioned between chloroform and dilute hydrochloric acid. The organic layer was separated and dried ($MgSO_4$) and the solvent was removed under reduced pressure to yield a pale yellow solid which was purified by chromatography (chromatotron: silica: ether–hexane, 3:1). The product was a white solid which was recrystallised from chloroform–hexane to give white needles; 56 mg, 76%; m.p. 94–97 °C; *m/z* (EI) 214 (M^+); δ_H (C^2HCl_3; 360 MHz), 2.09 (3 H, s, CH_3C=), 2.90 (*ca.* $\frac{1}{3}$H, s, 7-H), 3.18 (1 H, d, *J* 18.2, 2-H), 3.53 (1 H, d, *J* 18.2, 2-H), 3.55 (*ca.* $\frac{2}{3}$H, s, 7-H) 3.86 (3 H, s, OCH_3) and 4.66 (1 H, d, *J* 3.7, 6-H).

Photolysis of Compound **20**.—A solution of the [7-^{2}H]-cephalosporin **20** (60 mg, 0.28 mmol) was irradiated in dry methanol (45 cm^3) under nitrogen with a Phillips 125 W high pressure mercury arc lamp at room temperature for 10 h. TLC (silica: ethyl acetate) showed one major and one minor component in addition to some starting material. Separation was carried out using a sep-pak cartridge (silica:ether–hexane, 3:1) to yield the product **22** as the main fraction which crystallised from chloroform–hexane; 4.5 mg, 6%; m.p. 129–131 °C; *m/z* (+ve CI, NH_3), 247 (M^+ + 1); δ_H (C^2HCl_3, 360

* Obtained as a gift from ICI Pharmaceuticals PLC.

Table 1 X-Ray structure details

	1,3-Thiazine **14**	Tricyclic Lactone **25**
Formula	$C_{10}H_{15}NO_4S$	$C_{15}H_{21}NO_4S$
Mr	245.3	311.4
Crystal system, space group	monoclinic, $C2/c$	orthorhombic, $P2_12_12_1$
a	15.507(3)	7.318(2)
b	7.889(1)	13.883(2)
c	22.106(3)	14.752(2)
β	114.60(2)	90
U(Å^3), Z, D_{calc} (g cm^{-3})	2458.9, 8. 1.33	1498.7, 4, 1.38
μ(Mo-Kα) (cm^{-1})	2.6	2.3
F(000)	1040	664
Number of observed reflections [$I > \sigma(I)$]	929	912
Number of parameters	145	190
R	0.049	0.049
wR	0.064	0.062
(Δ/σ) max	0.1	0.01

Table 2 Fractional atomic co-ordinates ($\times 10^3$) of the 1,3-thiazine **14** with estimated standard deviations in parentheses

	x	y	z
S	2046.3(9)	4134.8(18)	2925.5(6)
N	2523(3)	3558(5)	4241(2)
O(1)	3094(3)	1047(4)	4704(2)
O(2)	3955(2)	3770(4)	3436(2)
O(3)	3753(2)	6047(4)	4573(2)
O(4)	3161(2)	7315(4)	3576(2)
C(1)	2302(3)	4946(7)	3757(2)
C(2)	2924(3)	2049(6)	4240(2)
C(3)	3141(4)	1516(7)	3665(2)
C(4)	3101(3)	2834(6)	3156(2)
C(5)	4146(4)	4728(8)	2954(3)
C(6)	1407(4)	5813(7)	3732(2)
C(7)	1449(4)	7435(9)	3937(3)
C(8)	546(4)	4738(11)	3546(4)
C(9)	3131(3)	6232(6)	3948(2)
C(10)	4529(4)	7251(8)	4783(3)

Table 3 Intramolecular distances (Å) and angles (°) of the 1,3-thiazine **14** with estimated standard deviations in parentheses

(*a*) Bond lengths

S–C(1)	1.828(3)	S–C(4)	1.815(4)
N–C(1)	1.468(4)	N–C(2)	1.344(4)
O(1)–C(2)	1.233(4)	O(2)–C(4)	1.414(4)
O(2)–C(5)	1.434(4)	O(3)–C(9)	1.324(4)
O(3)–C(10)	1.449(4)	O(4)–C(9)	1.200(4)
C(1)–C(6)	1.528(5)	C(1)–C(9)	1.551(5)
C(2)–C(3)	1.503(5)	C(3)–C(4)	1.515(5)
C(6)–C(7)	1.349(6)	C(6)–C(8)	1.487(6)

(*b*) Bond angles

C(1)–S–C(4)	97.1(1)	C(1)–N–C(2)	128.9(3)
C(4)–O(2)–C(5)	113.3(3)	C(9)–O(3)–C(10)	114.1(3)
S–C(1)–N	111.0(2)	S–C(1)–C(6)	107.9(2)
S–C(1)–C(9)	108.1(2)	N–C(1)–C(6)	107.0(3)
N–C(1)–C(9)	112.0(3)	C(6)–C(1)–C(9)	110.8(3)
N–C(2)–O(1)	120.4(3)	N–C(2)–C(3)	121.0(3)
O(1)–C(2)–C(3)	118.5(3)	C(2)–C(3)–C(4)	118.9(3)
S–C(4)–O(2)	113.4(2)	S–C(4)–C(3)	110.4(3)
O(2)–C(4)–C(3)	107.0(3)	C(1)–C(6)–C(7)	119.7(4)
C(1)–C(6)–C(8)	116.8(4)	C(7)–C(6)–C(8)	123.1(4)
O(3)–C(9)–O(4)	125.1(3)	O(3)–C(9)–C(1)	111.9(3)
O(4)–C(9)–C(1)	122.9(3)		

MHz) 1.89 (3 H, d, J 0.65, CH_3C=), 2.87 (1 H, m, CHD), 3.37 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 4.87 (1 H, d, J 2.1, C*H*OMe), 5.19 (1 H, q, J 1.3, olefinic), 5.37 (1 H, s, olefinic) and 6.65 (1 H, br s, NH).

Table 4 Fractional atomic co-ordinates ($\times 10^4$) of the tricyclic lactone **25** with estimated standard deviations in parentheses

	x	y	z
S	10 019(3)	6 777(1)	8 821(1)
N	6 701(6)	7 459(3)	8 337(3)
O(1)	4 255(6)	6 469(4)	7 856(4)
O(2)	4 557(6)	8 446(4)	6 685(3)
O(3)	7 030(6)	7 664(3)	6 223(3)
O(4)	7 999(6)	9 347(3)	8 896(3)
C(1)	7 698(9)	7 141(5)	9 138(4)
C(2)	6 362(10)	6 280(5)	9 211(5)
C(3)	5 492(8)	6 695(5)	8 356(5)
C(4)	7 154(8)	8 241(5)	7 726(4)
C(5)	9 164(8)	8 111(4)	7 364(4)
C(6)	10 551(8)	7 794(5)	8 082(4)
C(7)	8 915(9)	7 405(4)	6 542(4)
C(8)	6 060(9)	8 140(5)	6 843(4)
C(9)	8 874(10)	6 331(5)	6 723(4)
C(10)	9 870(10)	9 078(4)	7 028(4)
C(11)	6 748(9)	9 217(4)	8 159(4)
C(12)	4 863(10)	9 326(4)	8 603(5)
C(13)	5 220(11)	10 118(5)	9 291(5)
C(14)	7 223(10)	9 967(5)	9 568(4)
C(15)	10 137(11)	7 587(5)	5 740(5)

Table 5 Intramolecular distances (Å) and angles (°) of the tricyclic lactone **25** with estimated standard deviations in parentheses

(*a*) Bond lengths

S–C(1)	1.833(5)	S–C(6)	1.825(5)
N–C(1)	1.458(6)	N–C(3)	1.381(6)
N–C(4)	1.449(5)	O(1)–C(3)	1.209(6)
O(2)–C(8)	1.202(6)	O(3)–C(7)	1.501(5)
O(3)–C(8)	1.334(6)	O(4)–C(11)	1.432(5)
O(4)–C(14)	1.430(6)	C(1)–C(2)	1.547(7)
C(2)–C(3)	1.526(7)	C(4)–C(5)	1.575(6)
C(4)–C(8)	1.534(6)	C(4)–C(11)	1.528(6)
C(5)–C(6)	1.532(6)	C(5)–C(7)	1.569(6)
C(5)–C(10)	1.522(6)	C(7)–C(9)	1.516(6)
C(7)–C(15)	1.504(7)	C(11)–C(12)	1.535(7)
C(12)–C(13)	1.520(7)	C(13)–C(14)	1.537(8)

(*b*) Bond angles

C(1)–S–C(6)	97.9(2)	C(1)–N–C(3)	94.1(4)
C(1)–N–C(4)	128.1(3)	C(3)–N–C(4)	137.2(4)
C(7)–O(3)–C(8)	113.1(3)	C(11)–O(4)–C(14)	110.4(4)
S–C(1)–N	109.9(3)	S–C(1)–C(2)	113.0(3)
N–C(1)–C(2)	88.5(4)	C(1)–C(2)–C(3)	85.1(3)
N–C(3)–O(1)	131.9(5)	N–C(3)–C(2)	92.2(4)
O(1)–C(3)–C(2)	135.9(5)	N–C(4)–C(5)	109.8(3)
N–C(4)–C(8)	109.9(3)	N–C(4)–C(11)	111.1(3)
C(5)–C(4)–C(8)	100.9(3)	C(5)–C(4)–C(11)	115.1(4)
C(8)–C(4)–C(11)	109.5(4)	C(4)–C(5)–C(6)	114.6(3)
C(4)–C(5)–C(7)	103.0(3)	C(4)–C(5)–C(10)	109.0(4)
C(6)–C(5)–C(7)	115.6(3)	C(6)–C(5)–C(10)	104.7(4)
C(7)–C(5)–C(10)	109.8(3)	S–C(6)–C(5)	119.6(3)
O(3)–C(7)–C(5)	101.5(3)	O(3)–C(7)–C(9)	105.8(4)
O(3)–C(7)–C(15)	105.1(4)	C(5)–C(7)–C(9)	118.7(4)
C(5)–C(7)–C(15)	115.7(4)	C(9)–C(7)–C(15)	108.4(4)
O(2)–C(8)–O(3)	121.9(4)	O(2)–C(8)–C(4)	127.6(5)
O(3)–C(8)–C(4)	110.5(4)	O(4)–C(11)–C(4)	107.8(3)
O(4)–C(11)–C(12)	103.8(3)	C(4)–C(11)–C(12)	116.1(4)
C(11)–C(12)–C(13)	101.6(4)	C(12)–C(13)–C(14)	104.0(4)
O(4)–C(14)–C(13)	106.1(4)		

Photolysis of Compound **4** (R=Me) *in Liquid Ammonia–Ether.*—The β-lactam **4** (R=Me) (200 mg, 0.94 mmol) was dissolved in dry ether (50 cm^3) in a Hanovia photochemical reactor and cooled to −78 °C. Ammonia (*ca.* 100 cm^3) was distilled into the reactor and the whole system was purged with nitrogen. The solution was irradiated under nitrogen at −78 °C with a Phillips 125 W high pressure mercury immersion lamp

for 10 h. The ammonia was removed under a stream of nitrogen and the ether was removed under reduced pressure at 0 °C to yield a red oil. TLC (silica–ethyl acetate) showed one component in addition to some starting material. The product **24** was separated by chromatography (chromatotron: silica: ethyl acetate, 2 runs) to yield a pale oil which crystallised from chloroform–hexane; 5 mg, 3%; m.p. 175–177 °C; *m/z* 198 (M^+); ν_{max}(KBr)/cm^{-1} 3420 (NH), 1765 (β-lactam) and 1710 (amide); δ_H (C^2HCl_3; 360 MHz) 1.92 (3 H, d, *J* 0.85, CH_3), 3.00 (1 H, d × d, *J* 1.4 and 14.8, 7-H), 3.51 (1 H, d × d, *J* 4.2 and 14.8, 7-H), 4.61 (1 H, s, 4-H), 4.94 (1 H, d × d, *J* 1.1 and 4.0, 6-H) and 6.07 (1 H, d, *J* 0.65, olefinic).

Photolysis of Compound **4** (R=Me) *in Tetrahydrofuran–Acetone.*—The cephalosporin **4** (R=Me) (160 mg, 0.75 mmol) was irradiated with an external Phillips 125 W high pressure mercury arc lamp under nitrogen at −10 °C in a mixture of dry THF (120 cm^3) and dry acetone (30 cm^3) for 6 h. The solvent was removed under reduced pressure to yield an oil which was purified by chromatography (chromatotron: silica: 1st run: ether–hexane, 3:1, 2nd run: ether–hexane, 4:1) to yield one main fraction which recrystallised from cold dichloromethane as colourless needles of the product **25**; 18 mg, 8%; m.p. 106–108 °C; *m/z* (+ve CI, NH_3) 312 (M^+ + 1); ν_{max}($CHCl_3$)/cm^{-1} 1780 (β-lactam) and 1750 (lactone); δ_H (C^2HCl_3; 360 MHz) 1.32 and 1.40 (2 × 3 H, s, 2 × CH_3), 1.75 (3 H, s, CH_3), 1.80–2.00 (2 H, m, THF-β-CH_2), 2.05–2.02 and 2.35–2.4 (2 × 1 H, 2 × m, THF-β-CH_2), 2.60 (1 H, d, *J* 14.7, 2-H), 2.90 (1 H, d × d, *J* 14.7 and 1.9, 7-H), 3.43 (1 H, d × d, *J* 14.7 and 4.6, 7-H), 3.48 (1 H, d, *J* 14.7, 2-H), 3.5–3.6 and 3.7–3.8 (2 × 1 H, 2 × m, THF-α-CH_2), 4.08 (1 H, t, *J* 7.3, THF-α-CH) and 4.85 (1 H, d × d, *J* 1.9 and 4.5, 6-H); δ_C (C^2HCl_3; 90.55 MHz) 19.23 (3 × CH_3), 26.40 and 26.84 (THF-β-C), 34.46 (C-7) 39.0 (CO), 44.72 (C-3), 46.80 (CS), 52.35 (C-6), 67.96 (THF-α-CH_2), 79.90 (THF-α-CH) and 152.0 (2 × C=O).

X-*Ray Structure Determinations of the* 2-*Isopropenyl*-6-*methoxy*-4-*oxotetrahydrothiazine* **14** *and the Tricyclic Lactone* **25**.—Diffraction data were measured on an Enraf-Nonius CAD4 diffractometer. Cell dimensions were calculated from setting angles for 25 reflections with $\theta \simeq 15°$. Intensities for unique reflections were measured by a θ–2θ scan, of width $\Delta\theta = (0.8 + 0.35 \tan\theta)°$, and maximum scan time of one minute. Corrections were made for Lorentz and polarisation effects, but not for absorption. Reflections with $|F^2| > \sigma(F^2)$, where $\sigma(F^2) = \{\sigma^2(I) + (0.02I)^2\}^{\frac{1}{2}}/Lp$, were used in the refinement.

Non-hydrogen atoms were located by direct methods using MULTAN and refined with anisotropic thermal parameters by full matrix least squares. Hydrogen atoms were located on difference maps, except for those on C(8) in compound **14** which were omitted, and held fixed with B_{iso} = 6.0 Å^2. The weighting scheme was $w = \sigma^{-2}(F)$. Programs were from the Enraf-Nonius SDP package. Further details are given in Table 1. Fractional atomic co-ordinates for the thiazine **14** are given in Table 2 and for the lactone **25** in Table 4. Intramolecular distances and bond angles for the thiazine **14** are given in Table 3 and for the lactone **25** in Table 5. Tables of anisotropic thermal parameters and hydrogen atom co-ordinates are available from the CCDC.* Final structure factors are available from the authors.

* For full details of the CCDC deposition scheme see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1992, Issue 1.

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