Transformations of Penicillins and Cephalosporins: Reactions of Chlorosulphonyl Isocyanate with Penams, Cephems, and Azetidin-2-ones

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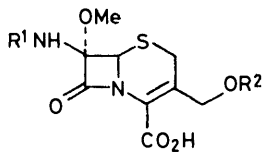
Benzyl 6β-phthalimidopenicillanate reacted with chlorosulphonyl isocyanate to give a thiazolo[3,2-*c*]pyrimidine derivative by ring expansion of the β-lactam. The trimethylsilyl derivative of 2,2,2-trichloroethyl 6β-phenoxyacetamidopenicillanate gave two isomeric thiazolo[3,2-*c*]pyrimidine derivatives. Methyl 3-methyl-7β-phenoxyacetamidoceph-3-em carboxylate gave a pyrimido[6,1-*b*][1,3]thiazine derivative. (3*R*,4*R*)-3-Phthalimido-1-(1-benzyloxycarbonyl-2-methylprop-1-enyl)-4-methylthioazetidin-2-one did not give a corresponding β-lactam ring expansion product, but gave epimeric 4-chloro-products by replacement of the 4-methylthio-group. 4-Acetoxyazetidin-2-one reacted with chlorosulphonyl isocyanate to give an *N*-allophanoyl derivative.

CHLOROSULPHONYL ISOCYANATE [1] (CSI) reacts with an extensive series of organic functional groups, effecting a wide range of transformations. It undergoes nucleophilic additions at either the chlorosulphonyl or the isocyanate function with, for example, alcohols, amines, thiols, carboxylic acids and will also react with electron-rich aromatic and heteroaromatic compounds. Enolizable ketones may be converted into β-ketonitriles,[2] and

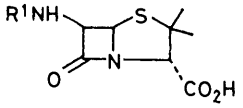
[1] R. Graf, *Angew. Chem. Internat. Edn.*, 1968, **7**, 172; J. K. Rasmussen and A. Hassner, *Chem. Rev.*, 1976, **76**, 389; W. A. Szabo, *Aldrichimica Acta*, 1977, **10**, 23.

[2] J. K. Rasmussen and A. Hassner, *Synthesis*, 1973, 682.

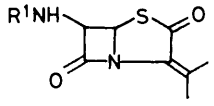
also into oxathiazinone, 1,3-oxazine, and uracil derivatives.[3] CSI also reacts with olefins to give azetidin-2-ones,[4] with imines to give triazindiones,[1] and with conversion of cephamycin derivatives (1) into the carbamates (2),[6] and the transformation of the penicillanic acid (3) into the anhydropenicillin (4).[7] A patent [5] describes



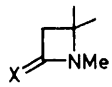
(1) R^2 = H
(2) R^2 = $CONH_2$



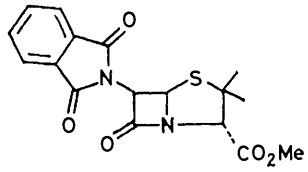
(3) R^1 = trityl



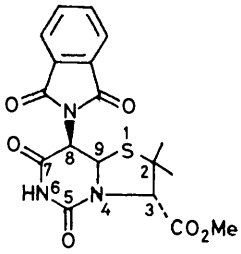
(4) R^1 = trityl



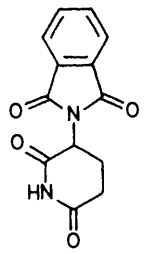
(5) X = O
(6) X = NSO_2Cl



(7)



(8)



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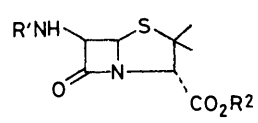
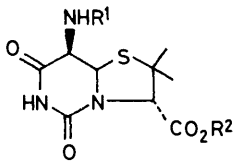


(10) R^1 = $PhO{\cdot}CH_2{\cdot}CO$, R^2 = $CH_2{\cdot}CCl_3$



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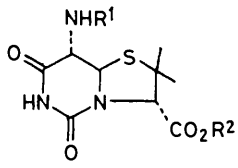

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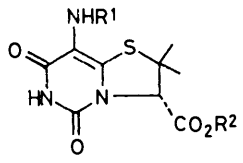
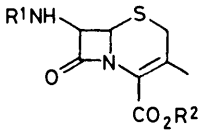
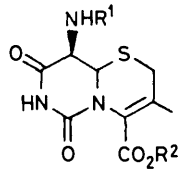


(13) R^1 = acyl, R^2 = NCO



(14) R^1 = $PhO{\cdot}CH_2{\cdot}CO$, R^2 = Me



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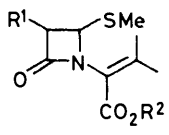
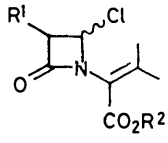
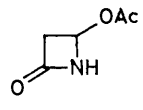


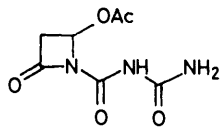
(16) R^1 = phthalimido, R^2 = $PhCH_2$
(18) R^1 = trityl, R^2 = $PhCH_2$



(17) R^1 = phthalimido, R^2 = $PhCH_2$
(19a,b) R^1 = trityl, R^2 = $PhCH_2$



(20)



(21)

certain *NN*-disubstituted amides with replacement of the carbonyl group by the chlorosulphonylimino-group by a [2 + 2] cycloaddition–cycloreversion sequence.[5]

Specific uses of CSI in β-lactam chemistry include the conversion of azetidin-2-ones (5) into the chlorosulphonylimino-analogues (6). We now describe a new group of reactions of CSI with penams, cephems, and azetidin-2-ones.

Methyl 6β-phthalimidopenicillanate (7) reacted readily with excess of CSI at room temperature in methylene

[3] K. Clauss and H. Jensen, *Angew. Chem. Internat. Edn.*, 1973, **12**, 869; J. K. Rasmussen and A. Hassner, *J. Org. Chem.*, 1973, **38**, 2114.
[4] N. S. Isaacs, *Chem. Soc. Rev.*, 1976, **5**, 181; K. Clauss, D. Grimm, and G. Prossel, *Annalen*, 1974, 539; J. R. Malpass and N. J. Tweddle, *J.C.S. Perkin I*, 1977, 874.
[5] G.P. 1,444,718/1963.
[6] G.P. 2,264,651/1974.
[7] H. Faubl, *J. Org. Chem.*, 1976, **41**, 3048.

chloride–ether. Reductive work-up with aqueous sodium metabisulphite (to remove the chlorosulphonyl group) and chromatography gave (8) (37%). In the ^1H n.m.r. spectrum coupling between H-8 and -9 (6 Hz) could be compared with the *cis*-coupling (4 Hz) between H-5 and -6 in (7). The ^{13}C n.m.r. spectrum was also

patented reaction [10] of penicillanate *S*-oxides with acyl isocyanates to give the 8,9-didehydro-analogues (13) which are schistosomicidal agents. De-esterification of of (11) and (12) gave the carboxylic acids which were not significantly active as antibiotics.

The 7β-phenoxyacetamidocephem ester (14) was

TABLE 1

Compound (11)	[Eu(fod)$_3$] : [substrate] 0.049	0.078	0.127	0.144	Gradient	Intercept (δ)	Correlation coefficient
	Chemical shift (δ)						
2a-Me	1.66	1.65	1.66	1.66	0.36	1.61	0.72
2b-Me	1.51	1.52	1.54	1.56	0.63	1.47	0.98
3-H	4.74	4.81	4.89	4.94	2.28	4.61	0.99
6-H	9.95	10.18	10.46	10.54	7.79	9.41	0.96
8-H	5.14			5.84	6.77	4.85	
9-H	5.49	5.50	5.52	5.56	0.43	5.48	0.86

in accord with structure (8), the presence of five carbonyl groups eliminating certain other possibilities. The structural similarity of (8) to thalidomide (9) is of interest, and this reaction type may therefore allow access to a range of analogues of central nervous system depressant drugs.

observed to react with CSI (without prior silylation), but refluxing di-isopropyl ether was needed, whereas the penicillanates reacted at room temperature. The elemental composition indicated incorporation of an HNCO moiety, and spectroscopic analysis suggested the pyrimido[6,1-*b*]thiazine structure (15). Only one isomer

TABLE 2

Compound (12)	[Eu(fod)$_3$] : [substrate] 0.03	0.06	0.09	0.13	Gradient	Intercept (δ)	Correlation coefficient
	Chemical shift (δ)						
2a-Me	1.72	1.74	1.77	1.80	0.92	1.68	0.99
2b-Me	1.56	1.61	1.66	1.70	1.52	1.52	0.99
3-H	4.97	5.11	5.30	5.44	5.24	4.80	0.99
6-H	8.97	9.04	9.14	9.24	3.21	8.84	0.99
8-H	5.33	5.45	5.70	5.78	7.33	4.98	0.99
9-H	5.62	5.78	5.97	6.09	5.11	5.46	0.99

In a similar reaction, trichloroethyl 6β-phenoxyacetamidopenicillanate (10) was first trimethylsilylated to protect the 6β-amide (probably as the imidate trimethylsilyl derivative). Reaction *in situ* with CSI, treatment with metabisulphite, and chromatography gave two major non-polar reaction products, shown to be the C-8 phenoxyacetamido-epimers (11) and (12). The ^1H coupling constants between H-8 and -9 in (11) (4 Hz) suggested *cis*-orientation, whereas the corresponding coupling in (12) (11 Hz) was in accord with *trans*-orientation. Lanthanide shift studies (Tables 1 and 2) confirmed these stereochemical assignments.* Consideration of the relative rates of shift of H-8 and -9 in each isomer, as a function of the molar ratio of shift reagent, showed that H-9 is *trans* to the phenoxyacetamido-group in the less polar isomer (11), and *cis* in the more polar isomer (12). The isomerism at C-8 in (11) and (12) probably occurred during the silylation process.[8] The mechanism of the β-lactam ring expansion is unclear, but precedent exists in the reaction of thiocyanic acid with penicillins to give a related 5-thiouracil,[9] and in a

was formed, in contrast to the reaction of (10), H-9 and -10 being tentatively assigned *cis*-stereochemistry.

The reaction of CSI with monocyclic azetidinones such as (16) was of interest because of the possibility of formation of 2-imino analogues [5] by a [2 + 2] cycloaddition–cycloreversion sequence, and also because of possible ring-expansion to give substituted uracils. Additionally, reaction at the 4-methylthio-group was envisaged. 3β-Phthalimidosecopenicillanate (16) was therefore refluxed in di-isopropyl ether with CSI, giving almost quantitatively a mixture of 4-chloroazetidin-2-ones (17), with *cis* : *trans* ratio of 2 : 3 ($J_{3,4cis}$ 4, $J_{3,4trans}$ 1.2 Hz). The mechanism could involve a 'Type 3' [1] reaction of the chlorosulphonyl group (Scheme). Other mechanisms involving initial attack by the methylthio-group on the isocyanate moiety of CSI can, however, be envisaged. It was not possible to separate the isomeric 4-chloroazetidin-2-ones (17), and the absolute stereochemistries at C-3 and -4 were therefore not assigned. The 3β-tritylaminoazetidin-2-one (18) when subjected to a similar CSI reaction did not give the corresponding 4-

* References to the use of lanthanide shift reagents with amides are cited by Malpass *et al.* within ref. 4.

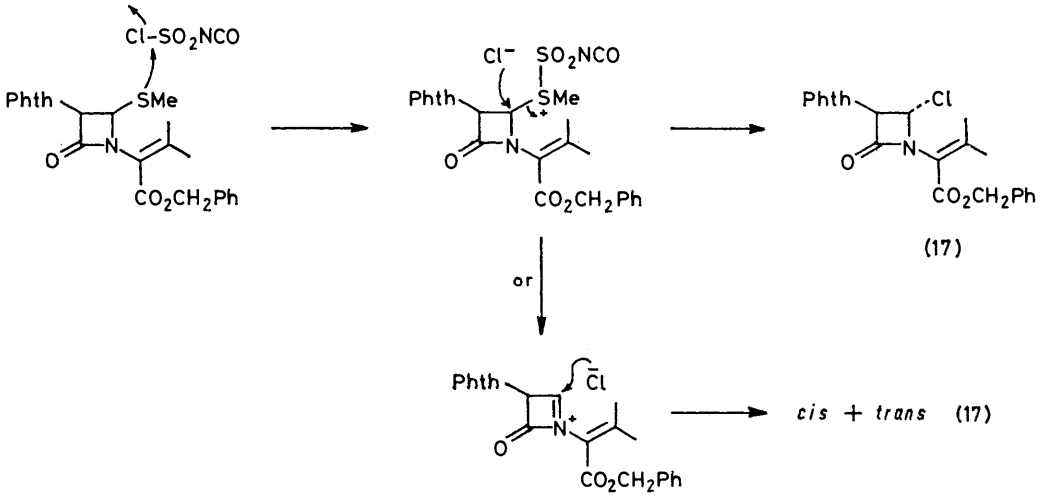
[8] P. Claes, A. Vlietinck, E. Roets, H. Vanderhaeghe, and S. Toppet, *J.C.S. Perkin I*, 1973, 932.

[9] H. T. Clarke, J. R. Johnson, and R. Robinson, 'The Chemistry of Penicillins,' Princeton University Press, 1949, p. 307.

[10] U.S.P. 3,850,933/1974.

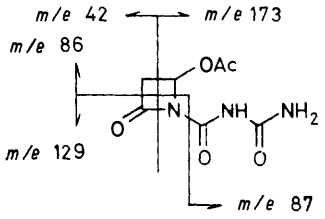
chloroazetidin-2-ones, but gave an inseparable mixture.*

4-Acetoxyazetidin-2-one (20) has recently received much attention in the synthesis of analogues of the β-lactam antibiotics.[3,11] When (19) was treated in ether with CSI and the resultant product treated with aqueous sodium metabisulphite (to hydrolyse chlorosulphonyl groups), a β-lactam product of elemental composition $C_7H_9N_3O_5$ was obtained, suggesting incorporation of two isocyanate units. The ^1H n.m.r. spectrum was



SCHEME

characteristic of a 4-acetoxyazetidin-2-one, and, together with the ^{13}C n.m.r. spectrum indicated structure (21) rather than alternative uracil-based structures. The mass spectral fragmentation modes were also in accord with this structure (Figure). A related reaction



which has been reported [12] involved the addition of a single chlorosulphonyl isocyanate unit to the NH group of an azetidin-2-one.

Reactions of chlorosulphonyl isocyanate with penicillanates and cephalosphoranates therefore lead to two relatively unusual fused uracil ring systems, thiazolo-[3,2-*c*]pyrimidines and pyrimido[6,1-*b*][1,3]thiazines. 4-Methylthioazetidin-2-ones, however, do not undergo β-lactam ring expansion under similar reaction conditions, but give instead 4-chloroazetidin-2-ones by a different reaction pathway. 1-Unsubstituted azetidin-2-ones give by a third reaction mode nitrogen adducts which may be of use in the synthesis of analogues of the β-lactam antibiotics.

* The 3β-tritylaminoazetidin-2-one could, however, be converted into a separable mixture (5 : 1) of *cis*- and *trans*-4-chloroazetidin-2-ones (19) in good yield by the reaction of (dichloroiodo)benzene (see Experimental section).

EXPERIMENTAL

General details are as reported previously.

Reaction of Methyl 6β-Phthalimidopenicillanate (7) *with Chlorosulphonyl Isocyanate.*—Methyl phthalimidopenicillanate (2 g, 5.55 mmol) in dry dichloromethane was added to chlorosulphonyl isocyanate (0.83 g, 0.5 ml, 6 mmol) in dry diethyl ether (1 ml) with stirring at room temperature. After 1.5 h a further portion of chlorosulphonyl isocyanate (6 mmol) was added, and after 3 h the mixture was diluted with chloroform (50 ml) and aqueous sodium metabisulphite added. The aqueous layer was extracted with further portions of chloroform and the combined chloroform extracts dried ($MgSO_4$), evaporated *in vacuo*, and chromatographed to give, as a solid which melted with decomposition over a wide temperature range, (3R,8R,8aR)-*methyl 2,2-dimethyl-5,7-dioxo-8-phthalimidoperhydrothiazolo-*[3,2-c]*pyrimidine-3-carboxylate* (8) (0.85 g, 37%), $[\alpha]_D^{20}$ +15° (*c* 1.2 $CHCl_3$), $\nu_{max.}$ (KBr) 3 350 (NH), 1 780 and 1 725 (phthalimido C=O), and 1 715 cm^{-1} (amide =O), δ_H ($CDCl_3$) 1.38 and 1.33 (each 3 H, s, CMe_2), 3.80 (3 H, s, CO_2Me), 4.62 (1 H, s, 3-H), 5.02 (1 H, d, *J* 6 Hz, 8-H), 6.87 (1 H, d, *J* 6 Hz, 9-H), 7.85 (4 H, m, phthalimide), and 8.37br (1 H, s, NH), δ_C ($CDCl_3$) 169.18, 167.48, 166.94, 165.28 and 150.48 (each, C=O), 134.68 (d), 131.34 (s), 131.26 (s), 124.09 (d), and 123.81 (d) (phthalimido carbons), 70.08 (d, C-8), 63.20 (d, C-9), 52.89 (s, C-2), 52.45 (q, CO_2Me), 50.75 (d, C-3), and 33.22 and 26.03 p.p.m. (each q, CMe_2) (Found: M^+, 403.083 8. $C_{18}H_{17}N_3O_6S$ requires *M*, 403.083 8), *m/e* 403 (M^+, 8%), 344 (15), 289 (35), 256 (100), 174 (65), and 116 (60).

Reaction of 2,2,2-Trichloroethyl 6β-Phenoxyacetamidopenicillanate (10) *with Chlorosulphonyl Isocyanate.*—*NO*-Bis(trimethylsilyl)acetamide (2.5 g, 12.3 mmol) was added

[11] A. K. Mukerjee and R. C. Srivasta, *Synthesis*, 1973, 327; H. W. Schnabel, D. Grimm, and H. Jensen, *Annalen*, 1974, 477; D. Bormann, *ibid.*, 1974, 1391; A. G. Brown, D. F. Corbett, and T. T. Howarth, *J.C.S. Chem. Comm.*, 1977, 359.

[12] R. Graf, ref. 1, p. 178.

to (10) (6 g, 12.2 mmol) in dry dichloromethane (50 ml) and stirred for 2 h at room temperature under nitrogen. Chlorosulphonyl isocyanate (3.57 g, 2.2 ml, 25.3 mmol) was added to the solution at 0°, stirred for 5 min, and the mixture allowed to come to room temperature and stirred for a further 1.5 h. The solution was shaken with concentrated aqueous sodium metabisulphite and the dichloromethane solution dried ($MgSO_4$). Column chromatography yielded a mixture of two isomeric compounds, followed by a second pair of products of greater polarity.

The first pair of products was rechromatographed to yield first (3R,8R,8aR)-2,2,2-*trichloroethyl* 2,2-*dimethyl*-5,7-*dioxo*-8-*phenoxyacetamidoperhydrothiazolo*[3,2-c]*pyrimidine*-3-*carboxylate* (11) (1.1 g, 17%), m.p. 113.5—114°, $[\alpha]_D^{22}$ +2.6° (*c* 1.17 $CHCl_3$), $\nu_{max.}$ (KBr) 3 300br and 3 200br (amide NH), 1 750 (ester C=O), 1 720 and 1 700 (amide C=O), and 1 430 cm^{-1}, δ_H [C_6D_6–CD_3COCD_3 (1 : 1)] 1.72 and 1.59 (each 3 H, s, CMe_2), 4.73 (2 H, s, CH_2CCl_3), 4.82 (2 H, s, PhOCH_2), 4.97 (1 H, s, 3-H), 5.32 (1 H, dd, *J* 9.5 and 4 Hz, 8-H), 5.83 (1 H, d, *J* 4 Hz, 9-H), 7.25 (5 H, m, Ph), 8.59 (1 H, d, *J* 9.5 Hz, side chaim amide), and 9.92 (1 H, s, ring NH) (Found: M^+, 523.015 2. $C_{19}H_{20}{}^{35}Cl_3N_3O_6S$ requires *M*, 523.013 9), *m/e* 523 (M^+, 2), 489 (7), 449 (9), 372 (18), 348 (12), 290 (20), 234 (13), 185 (55), and 151 (100%) (Found: C, 43.7; H, 3.7; N, 8.0. $C_{19}H_{20}Cl_3N_3O_6S$ requires C, 43.5; H, 3.8; N, 8.0%). The isomer (12) (0.45 g, 17%), (3R,8S,8aR)-2,2,2-*trichloroethyl* 2,2-*dimethyl*-5,7-*dioxo*-8-*phenoxyacetamidoperhydrothiazolo*-[3,2-c]*pyrimidine*-3-*carboxylate*, was then obtained as an amorphous solid, $[\alpha]_D^{22}$ +23° (*c* 1.075 $CHCl_3$), $\nu_{max.}$ (KBr) 3 400—3 200 (unresolved NH), 1 750 (ester C=O), 1 710 (unresolved amide C=O), and 1 440 cm^{-1}, δ_H [C_6D_6–CD_3COCD_3 (1 : 1)] 1.58 and 1.42 (each 3H, s, CMe_2), 4.46 (2 H, s, CH_2CCl_3), 4.75 (2 H, s, PhOCH_2), 4.89 (1 H, s, 3-H), 5.10 (1 H, dd, *J* 9 and 11 Hz, 8-H), 5.80 (1 H, d, *J* 11 Hz, 9-H), 7.4—6.7 (5 H, m, PhO), 8.08 (1 H, d, *J* 9 Hz, side chain NH), and 9.67 (1 H, s, ring NH) (Found: M^+, 523.011 3. $C_{19}H_{20}{}^{35}Cl_3N_3O_6S$ requires *M*, 523.013 9), *m/e* 523 (2%), 449 (3), 372 (6), 348 (5), 290 (8), 262 (4), 261 (8), 198 (18), and 151 (100%). Mixed fractions containing (11) and (12) (0.55 g) were also obtained.

100 MHz N.m.r. spectra were measured for (11) and (12) with varying molar ratios of $Eu(fod)_3$ to substrate. The chemical shift of each proton was plotted against the molar ratio of $Eu(fod)_3$ and the gradient of each plot calculated, allowing assignment of stereochemistry.

The second isomeric pair of products were not separated by chromatography, but were obtained as a mixture (0.4 g, 6%), $\nu_{max.}$ (KBr) 1 800 cm^{-1} (Found M^+, 523.013 0. Calc. for $C_{19}H_{20}{}^{35}Cl_3N_3O_6S$: *M*, 523.013 9.)

De-esterification of (11) *and* (12).—Ester (11) (0.17 g, 0.32 mmol) in dimethylformamide–glacial acetic acid (25 : 7.5) (11 ml) was stirred for 2 h at 0° with zinc dust (0.53 g, 8.1 mmol). The mixture was filtered, diluted with ethyl acetate, and washed with water. The organic layer was dried ($MgSO_4$), evaporated, and the residue crystallized from chloroform to give the carboxylic acid, m.p. 125° (decomp.), $[\alpha]_D^{22}$ +6.8° (*c* 1.03 $CHCl_3$), $\nu_{max.}$ (KBr) 3 600—2 700 (CO_2H), 3 300 and 3 200 (NH), and 1 750—1 650br (C=O), $\delta(CDCl_3)$ 1.67 and 1.55 (each 3 H, s, CMe_2), 4.70 (2 H, s), 4.83 (1 H, s), 5.1 (1 H, dd), 5.84 (1 H, d), 7.7—6.9 (5 H, m, PhO), 8.35 (1 H, d, *J* 9 Hz, side chain NH), and 9.58 (1 H, s, ring NH), *m/e* 393 (M^+, 4%), 347 (8), 319 (10), 261 (30), 160 (40), and 132 (30%).

Similarly prepared was the isomeric carboxylic acid, m.p. *ca.* 125° (decomp.), $[\alpha]_D^{22}$ +82° (*c* 1.24 $CHCl_3$), $\nu_{max.}$ (KBr) 3 600—2 700br (CO_2H), 3 350 and 3 200 (NH), and 1 730 and 1 700 cm^{-1} (C=O), $\delta(CDCl_3)$ 1.71 and 1.51 (each 3 H, s, CMe_2), 4.58 (2 H, s, PhOCH_2), 4.71 (1 H, s, 3-H), 4.98 (1 H, dd, *J* 9 and 12 Hz), 5.64 (1 H, d, *J* 12 Hz), 7.50—6.85 (5 H, m, Ph), 8.05 (1 H, d, *J* 9 Hz, side chain NH), and 9.40 (1 H, s, ring NH), *m/e* 393 (M^+, 3%), 375 (7), 349 (6), 315 (70), 261 (60), and 243 (11%).

Reaction of Methyl 3-*Methyl*-7β-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* (14) *with Chlorosulphonyl Isocyanate*.—Methyl ester (14) (0.2 g, 0.48 mmol) and *NO*-bis(trimethylsilyl)acetamide (0.19 g, 1.40 mmol) were stirred with chlorosulphonyl isocyanate (0.06 g, 0.4 mmol) at room temperature, but did not react after 2.5 h. Reflux led to a complex mixture.

The reaction was repeated, adding chlorosulphonyl isocyanate (0.114 g, 0.07 ml, 0.8 mmol) dropwise to (14) (0.122 g, 0.29 mmol) in dry di-isopropyl ether (25 ml) under nitrogen. After refluxing for 3 h the solution was washed with aqueous sodium metabisulphite, extracted with chloroform (2 × 50 ml) and ethyl acetate (50 ml), and the combined extracts dried ($MgSO_4$), evaporated, and chromatographed. Following a second column chromatography (9R,9aR)-*methyl* 7,8,9,9a-*tetrahydro*-3-*methyl*-6,8-*dioxo*-10-*phenoxyacetamido*-2H,6H-*pyrimidino*[6,1-b][1,3]-*thiazine*-4-*carboxylate* (15) (0.076 g, 56%) was obtained as an oil, $\nu_{max.}$ (film) 3 400, 3 240, 1 760, 1 740, and 1 590 cm^{-1}, $\delta(CDCl_3)$ 2.18 (3 H, s, 3-Me), 2.96 (2 H, ABq, *J* 15 Hz, 2-H), 3.68 (3 H, s, OMe), 4.92 (1 H, d, *J* 3 Hz, 10-H), 5.08 (3 H, m, 1-H and PhOCH_2), 6.5—5.9br (1 H, s, NH), 7.34—6.8 (6 H, m), and 9.10br (1 H, s, NH) (Found: M^+, 405.099 0. $C_{18}H_{19}N_3O_6S$ requires M^+, 405.099 5), *m/e* 405 (M^+, 9%), 373 (5), 371 (5), 312 (10), 261 (8), 234 (28), 171 (20), and 141 (60).

Reaction of (3R,4R)-3-*Phthalimido*-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*methylthioazetidin*-2-*one* (16) *with Chlorosulphonyl Isocyanate*.—Benzyl ester (16) (0.06 g, 0.13 mmol) was refluxed with excess of chlorosulphonyl isocyanate in di-isopropyl ether–dichloromethane (1 : 1) and the reaction monitored by t.l.c. until after 8 h the starting material had been consumed. After washing the solution with aqueous sodium metabisulphite, drying ($MgSO_4$), evaporation, and repeated column chromatography the chloro-compounds (17) (0.058 g, 98%) were obtained as an inseparable mixture and identified by mass spectrometry and spectroscopic analysis of the mixture.

Reaction of (18) *with* (*Dichloroiodo*)*benzene*.—The tritylaminosecopenicillanate (18) (0.76 g, 1.35 mmol) in dry pyridine (6 ml) was cooled to 0° and (dichloroiodo)benzene (1.07 g, 4.05 mmol) added with stirring. After 15 min water (1 ml) was added dropwise to the cooled solution (−15°) and after a further 15 min ethyl acetate (20 ml) was added. The organic solution was washed four times with brine and with aqueous copper sulphate, dried ($MgSO_4$), and evaporated to give a brown oil (1.40 g). Column chromatography gave the *trans*-chloride (19a) (0.07 g) as a solid, $[\alpha]_D^{22}$ +30°, m.p. 65°, $\nu_{max.}$ (KBr) 3 315, 1 780, and 1 730—1 710 cm^{-1}, $\delta(CDCl_3)$ 8.30 (20 H, m), 5.14 (2 H, s, PhCH_2), 4.76 (1 H, d, *J* 1 Hz, 4-H), 4.33br (1 H, dd, *J* 10 and 1 Hz, 3-H), 3.60 (1 H, d, *J* 10 Hz, NH), and 2.28 and 1.92 (each 3 H, s, CMe_2) (Found: M^+, 550.202 2. $C_{34}H_{31}ClN_2O_3$ requires M^+, 550.202 7). The *cis*-chloride (19b) was obtained as a solid (0.40 g), $[\alpha]_D^{22}$ +40°, m.p. 67° (decomp.), $\nu_{max.}$ (KBr) 1 775 and 1 725 cm^{-1}, $\delta(CDCl_3)$ 7.20—7.60 (2 H, m), 5.09 (2 H, s, PhCH_2), 4.45 (1 H, dd, *J* 4 and 10 Hz,

3-H), 3.17 (1 H, d, *J* 4 Hz, 4-H), and 2.25 and 1.98 (each 3 H, s, CMe_2) (Found: C, 73.9; H, 6.0; N, 4.9; Cl, 6.3. $C_{34}H_{31}ClN_2O_3$ requires C, 74.1; H, 5.6; N, 5.1; Cl, 6.5%.)

Reaction of 4-Acetoxyazetidin-2-one (20) *with Chlorosulphonyl Isocyanate*.—The acetate (20) (0.25 g, 1.94 mmol) in dry ether (20 ml) was purged with dry nitrogen and then chlorosulphonyl isocyanate (0.55 g, 0.34 ml, 3.88 mmol) added dropwise at room temperature. After stirring at room temperature for 10 min, and then refluxing for 10 min, the solution was cooled and aqueous sodium metabisulphite (1% solution, 50 ml) added dropwise. Vigorous reaction preceded precipitation of crystals which were filtered, washed with cold, dry ether, and dried to give (21) (0.13 g), m.p. 157.5—160°, $\nu_{max.}$ (KBr) 3 400, 3 280, 3 180, 1 800, 1 750, 1 730, 1 690, and 1 610 cm^{-1}, δ_H ([$^2H_6$]DMSO) 7.3br, 6.4br, and 5.3br (each 1 H, NH), 6.69 (1 H, dd, *J* 2 and 4 Hz, 4-H), 3.41 (1 H, dd, *J* 4 and 16 Hz, 3-H_{cis}), and 2.96 (1 H, dd, *J* 2 and 16 Hz, 3-H_{trans}), δ_C ([$^2H_6$]DMSO) 169.43, 164.61, 149.05, and 141.19 (each C=O), 73.58 (C-4), 40.64 (C-3), and 20.7 p.p.m. (C-6) {*cf.* 4-acetate (19), δ_C ([$^2H_6$]DMSO) 171.20 (C-2, s), 166.09 (*C*OMe, s), 73.13 (C-4, d), 44.98 (C-3, d), and 20.78 (CO*M*e, q)} (Found: C, 38.4; H, 4.4; N, 19.3. $C_7H_9N_3O_5$ requires C, 38.7; H, 4.2; N, 19.5%), *m/e* 215 (M^+).

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