Transformations of Penicillins: Reactions of Penam *S*-Oxides with *N*-Chloro-*N*-sodiocarbamates [1]

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Penicillanate (*S*)-*S*-oxides reacted with ethyl *N*-chloro-*N*-sodiocarbamate to give 6α-ethoxyformamido-derivatives together with the corresponding 6-*epi*-penicillanate, an intermediate in the formation of the former product. The (*R*)-*S*-oxides reacted with *N*-chloro-*N*-sodiocarbamate to give 6α-alkoxyformamido-derivatives, together with 6,6-bis(alkoxyformamido)penam (*R*)-*S*-oxides, which were further transformed into cephalosporanates. Mechanisms for these substitution reactions are discussed.

THE ability of *N*-chloro-*N*-sodio-reagents derived from sulphonamides and carbamates to react as sources of (*a*) chloronium cation, and (*b*) amidate anions has been utilised [2] in an extensive range of transformations of penicillanates and secopenicillanates. In solution these reagents appear to exist as a complex mixture of species in equilibrium (Scheme 1). The *N*-chloro-species (or the

$$\begin{aligned} R\bar{N}Cl + H_2O &\rightleftharpoons RHNCl + {}^-OH \\ 2RNHCl &\rightleftharpoons RNCl_2 + RNH_2 \\ RNCl_2 + H_2O &\rightleftharpoons RNHCl + HOCl \\ RNHCl + H_2O &\rightleftharpoons RNH_2 + HOCl \\ RNH_2 + {}^-OH &\rightleftharpoons R\bar{N}H + H_2O \end{aligned}$$

SCHEME 1

hypochlorite species which may be present in alcohol or when hydrated reagents are used) are responsible for the chloronium cation reactions, and the nitrogen anion species act both as bases and nucleophiles.

We have demonstrated [2] significant differences between the reactions of *N*-chloro-*N*-sodiosulphonamides (*e.g.* chloramine T) and *N*-chloro-*N*-sodiocarbamates in penicillanate reactions. New penicillin-derived products from the reactions of the former reagents include β-lactam-fused thiadiazine ylides, oxazolinoazetidinones, 4-chloroazetidin-2-ones, and sulphimides. The latter group of reagents on the other hand afforded new and improved methods of directly functionalising C-6 of the penicillanates. In an extension of these investigations designed to further elucidate the reactivity of the penam system and to seek new analogues with potential antibiotic or β-lactamase-resistant properties, we have now examined the reactions of *N*-chloro-*N*-sodiocarbamates with certain penicillanate (*S*)- and (*R*)-*S*-oxides.

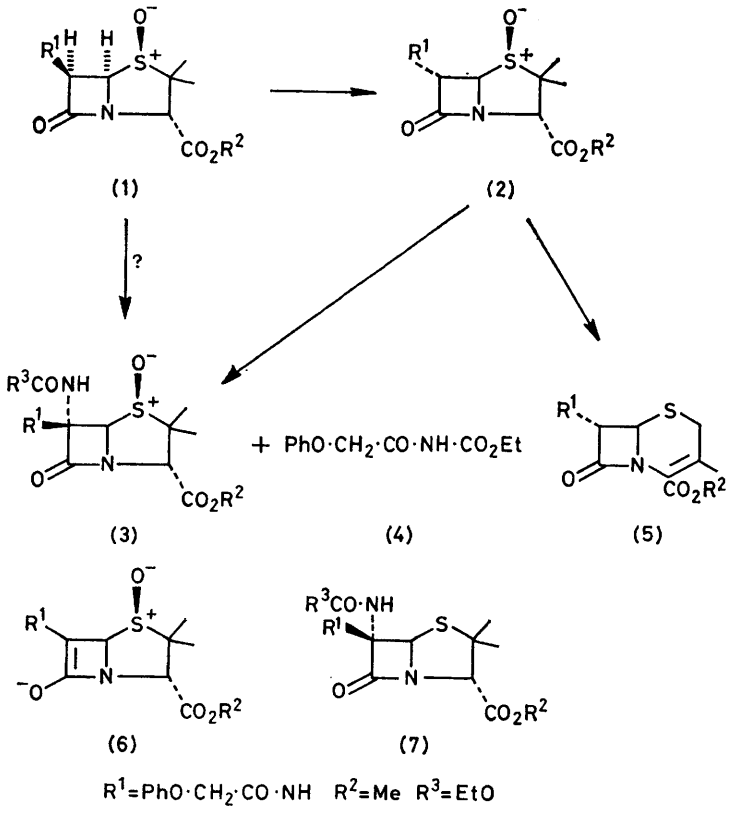
Reaction of (S)-S-*Oxides*.—Methyl (1*S*)-6β-phenoxyacetamidopenicillanate 1-oxide (**1**) was treated at room temperature with ethyl *N*-chloro-*N*-sodiocarbamate in methanol and in methanolic sodium borate, but in each case β-lactam cleavage occurred. With acetonitrile or dimethylformamide as solvent the reagent (4 mol. equiv.) gave a slow reaction which could not be made to go to completion. Chromatographic separation gave first ethyl(phenoxyacetyl)carbamate (**4**). Further elution gave the new 6β-ethoxyformamido-penam derivative (**3**). The elemental composition ($C_{20}H_{25}N_3O_8S$)

[1] Preliminary communication, D. H. Bremner, M. M. Campbell, and G. Johnson, *Tetrahedron Letters*, 1975, 2955.

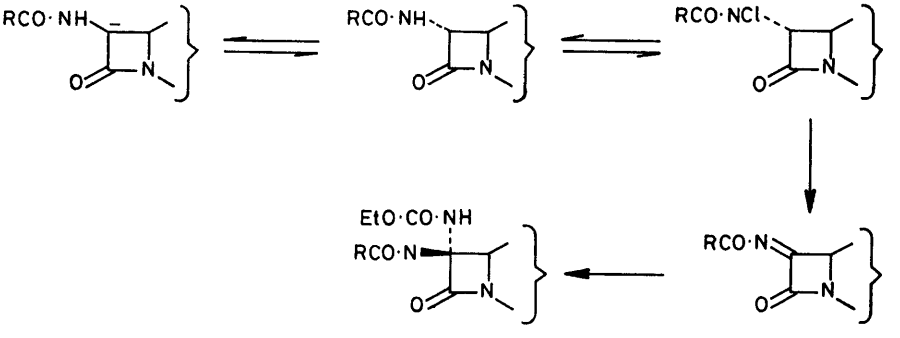
[2] M. M. Campbell, G. Johnson, A. F. Cameron, and I. R. Cameron, *J.C.S. Perkin I*, 1975, 1208; M. M. Campbell and G. Johnson, *ibid.*, pp. 1077, 1932; D. H. Bremner, M. M. Campbell, and G. Johnson, *J.C.S. Chem. Comm.*, 1976, 293; *J.C.S. Perkin I*, 1976, 1918.

indicated incorporation of an ethyl carbamate system, as was confirmed by the n.m.r. spectrum. Functionalisation at C-6 rather than C-5 was proved by the presence of the β-lactam proton signal as a sharp singlet (a C-6 proton signal would appear as a doublet because of coupling to the amide NH). The structure was confirmed by eluted was the 6-*epi*-penicillanate (*S*)-*S*-oxide (**2**), the structure of which was proved by comparison with the product of epimerisation of the 6β-amido-group of (**1**) by a standard method.[4] Ring expansion of the product (**2**) gave the *epi*-cephalosporanate (**5**).

It was suspected that the 6-*epi*-penicillanate (*S*)-*S*-



SCHEME 2



SCHEME 3

deoxygenation [3,4] to the known [2] 6α-ethoxyformamido-6β-phenoxyacetamidopenicillanate (**7**), whose structure has been proved by *X*-ray crystallography. Finally oxide (**2**), formed *via* the enolate (**6**), was an intermediate in the formation of the 6α-substituted (*S*)-*S*-oxide (**3**). This was demonstrated by treating (**2**) * under similar

* Oxidation of the penicillanates with iodobenzene dichloride [5] or with ozone [6] gave mixtures of (*S*)- and (*R*)-*S*-oxides which were separated chromatographically.

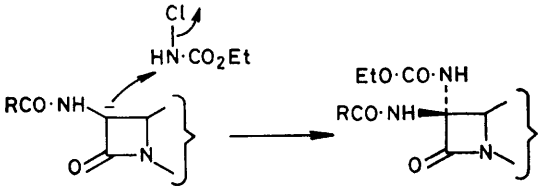
[3] R. R. Chauvette, P. A. Pennington, C. W. Ryan, R. D. G. Cooper, F. L. José, I. G. Wright, E. M. Van Heyningen, and G. W. Huffman, *J. Org. Chem.*, 1971, **36**, 1259.

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

[5] D. H. R. Barton, F. Comer, D. G. R. Grieg, P. G. Sammes, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *J. Chem. Soc.* (*C*), 1971, 3540.

[6] A. J. Vlietinck, E. Roets, H. Vanderhaeghe, and S. Toppet, *J. Org. Chem.*, 1974, **39**, 441.

conditions with *N*-chloro-*N*-sodiocarbamate and isolating the penam (3) from the reaction mixture. A plausible pathway for the formation of the 6α-substituted

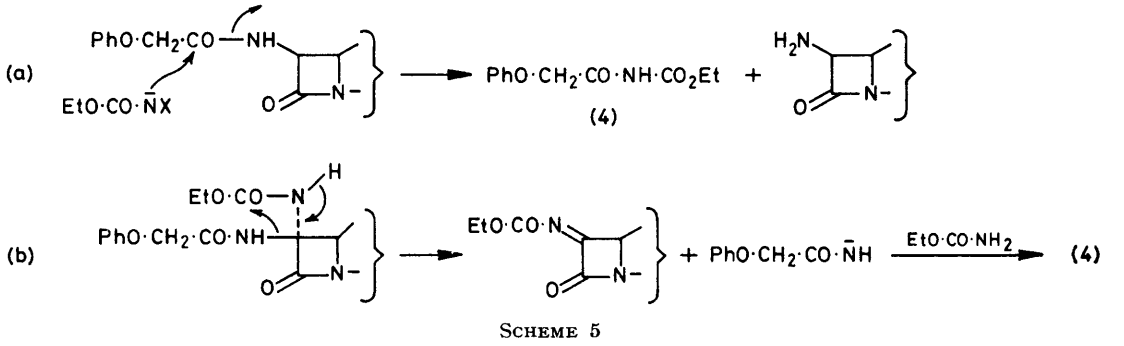


SCHEME 4

product therefore involves epimerisation at C-6 *via* a 6-anion, followed by *N*-chlorination and elimination of hydrogen chloride to give an acylimine (Scheme 3) and then 6α-substitution. We have recently suggested [2] a related reaction sequence; as before, we have not succeeded in trapping the intermediate 6-imine with water, methanol, or chloride, possibly because of the existence of an intimate reactant pair involving imine and amidate. For the present reaction it is further proposed that *N*-chlorination of the 6β-acylamino-sulphoxide (1) is sterically disfavoured because of the proximity of the sulphoxide group, and that following epimerization the *N*-chlorination–elimination step is facilitated. A reaction pathway involving epimerization of the 6β-phenoxyacetamido-group, followed by a re-epimerization, therefore contributes to the overall process. An alternative reaction pathway (Scheme 4) found no support in an attempted trapping reaction with acrylonitrile. Evidence is presented later for an acylimine type of intermediate. The formation of the phenoxyacetylcarbamate (4) [7] is possibly explained by attack of amidate anion on the amide carbonyl group, or by attack of phenoxyacetamidate on ethoxyformamide (Scheme 5).

Similar products were obtained, again in low yield, from reactions of *N*-chloro-*N*-sodiocarbamate with benzyl and 2,2,2-trichloroethyl penicillanate *S*-oxides.

Reactions of (R)-S-*Oxides*.—A reaction of ethyl *N*-chloro-*N*-sodiocarbamate with methyl 6β-phenoxyacetamidopenicillanate (*R*)-*S*-oxide (8) [6] gave as major product the 6,6-bis(ethoxyformamido)penam (*R*)-*S*-oxide (9) (Scheme 6). To our knowledge this is the first complete replacement of the 6-acylamino-group of a penicillanate



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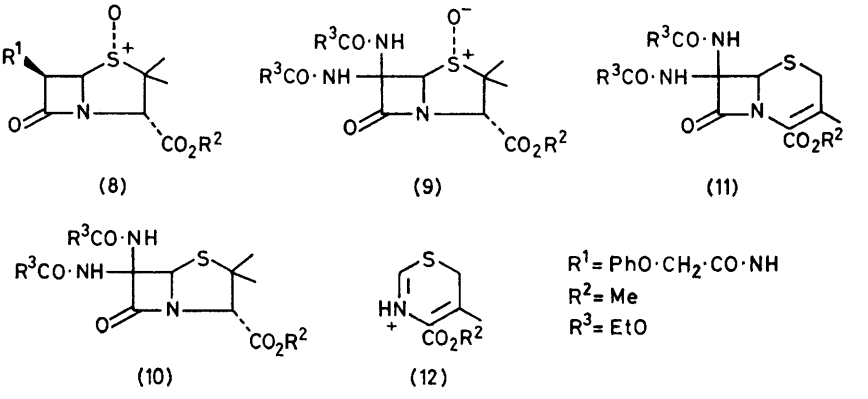


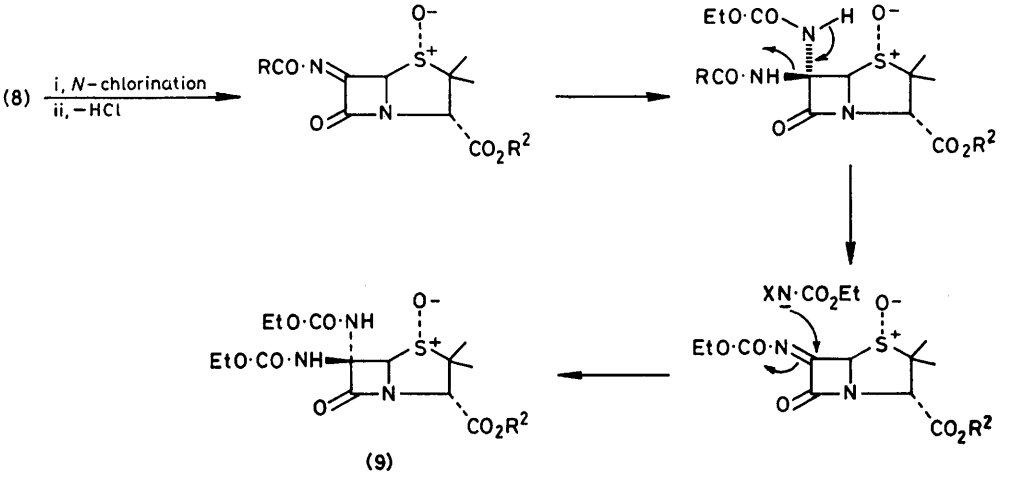
SCHEME 6

to be reported. The formation of (9) is best explained (Scheme 7) as involving two successive acylimine precursors. Introduction of the second ethoxyformamido-substituent must certainly involve an intermediate 6-acylimine. Deoxygenation gave the new 6,6-bis-(ethoxyformamido)penam (10), which when re-oxidized gave (9) as the sole sulphoxide product. (We have previously observed [2] that related 6,6-disubstituted penams gave both sulphoxides.) Benzyl 6α-phenoxyacetamido-penicillanate (*R*)-*S*-oxide reacted in a similar manner to (8); the corresponding trichloroethyl ester was exceedingly reactive, and gave a complex mixture of products.

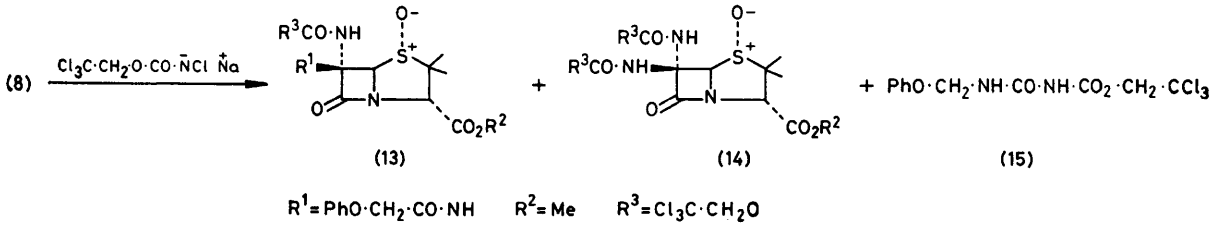
[7] S. Bellioni, *Ann. Chim.* (*Italy*), 1962, **52**, 187.

Ring expansion of the (*R*)-*S*-oxide (9) led to the new 6,6-disubstituted cephalosporanate (11), which was characterised by analytical and spectroscopic methods and contained an abundant thiazinium ion (12) in its mass spectrum.

It was of particular interest to extend this substitution method to the preparation of a 6,6-bis-(2,2,2-trichloroethoxyformamido)penam (*R*)-*S*-oxide because of its potential use in forming products derived from a 6,6-diamine, such as a 6-oxopenam.[8] Treatment of compound (8) with 2,2,2-trichloroethyl *N*-chloro-*N*-sodiocarbamate (Scheme 8) gave two β-lactam products, the minor being the 6α-formamido-derivative (13)



SCHEME 7



SCHEME 8

and the major the bis-compound (14). The urea (15) which was also isolated probably resulted from Hoffman rearrangement of a phenoxyacetamidate anion, followed by trapping of the resultant phenoxymethyl isocyanate by a trichloroethoxyformamidate anion, or by the *N*-chloro-anion.

Conclusions.—Penicillanates react with *N*-chloro-*N*-sodiocarbamates to yield 6α-substituted derivatives.[2] The (*S*)-*S*-oxide derivatives react similarly, but probably require epimerisation of the 6β-amide side chain prior to C-6 substitution. The (*R*)-*S*-oxides undergo 6,6-disubstitution. Differences in reactivity at C-6 due to the presence of an adjacent (*R*)- or (*S*)-*S*-oxide system have thus been discovered, and stereoselective reaction processes which depend upon the nature of the sulphoxide group have been proposed.

EXPERIMENTAL

General details are as described in earlier papers.[2] Mass measurements were performed on spectroscopically and chromatographically pure material unless otherwise stated.

Reaction of Methyl 6β-*Phenoxyacetamidopenicillanate* (S)-S-*Oxide* (1) *with Ethyl* N-*Chloro*-N-*sodiocarbamate.*—The sulphoxide (1) (5.0 g, 12.9 mmol) and ethyl *N*-chloro-*N*-sodiocarbamate (7.8 g, 52 mmol) in dimethylformamide (100 ml) were stirred at 0 °C for 1 h and then overnight at room temperature. The resultant yellow solution was poured into water and extracted twice with ethyl acetate; the extract was then washed with water and brine, dried ($MgSO_4$), and evaporated *in vacuo* to yield a yellow oil. Column chromatography afforded first ethyl phenoxyacetylcarbamate (4) [7] (0.50 g, 17%), m.p. 80—83° (from benzene), $\lambda_{max.}$ (KBr) 3 210 and 3 160 (NH), 1 760 (ester C=O), and 1 705—1 690 cm^{-1} (amide C=O), δ ($CDCl_3$) 1.30 (3 H, t, *J* 8 Hz, $CH_2{\cdot}CH_3$), 3.25 (2 H, q, *J* 8 Hz, $CH_2{\cdot}CH_3$), 4.75 (2 H, s, OCH_2), 6.80—7.45 (5 H, m, Ph), and 8.45br (1 H, s, NH exch.), M^+, 223. Further elution yielded *methyl* 6α-*ethoxyformamido*-6β-*phenoxyacetamidopenicillanate* (S)-S-*oxide* (3) (1.2 g, 22%) as an amorphous solid, $[\alpha]_D^{22}$ +193° (*c* 1.00 in $CHCl_3$), $\nu_{max.}$ (film) 3 280 (NH), 1 800 (β-lactam C=O), 1 755 (ester C=O), 1 730 (carbamate C=O), and 1 695 cm^{-1} (amide C=O), δ ($CDCl_3$) 1.24 (3 H, t, *J* 8 Hz, $CH_2{\cdot}CH_3$), 1.64 (6 H, s, 2 × Me), 3.80 (3 H, s, OMe), 4.10 (2 H, q, *J* 8 Hz, $CH_2{\cdot}CH_3$), 4.49 (2 H, s, OCH_2), 4.64 (1 H, s, 3-H), 5.10 (1 H, s, 5-H), 6.80—7.40 (6 H, m, Ph and NH), and 8.16br (1 H, s, NH exch.) (Found: M^+, 467.1368. $C_{20}H_{25}N_3O_8S$ requires

[8] Y. S. Lo and J. C. Sheehan, *J. Amer. Chem. Soc.*, 1972, **94**, 8253.

M, 467.1362). The final product eluted was methyl 6α-phenoxyacetamidopenicillanate (*S*)-*S*-oxide (2) (0.75 g, 15%), identical with an authentic sample. A similar reaction was achieved in acetonitrile.

Epimerisation of Methyl 6β-*Phenoxyacetamidopenicillanate* (S)-S-*Oxide* (1).—The sulphoxide (1) (3.42 g, 9.0 mmol) in anhydrous methylene chloride (45 ml) was stirred at room temperature with *NO*-bis(trimethylsilyl)acetamide (3 ml, 12 mmol) for 1 h. The mixture was cooled to 0 °C and 1,5-diazabicyclo[4.3.0]non-5-ene (1.2 ml, 9 mmol) in anhydrous methylene chloride (15 ml) was added. The solution was stirred for 10 min and 2N acetic acid (2 ml) was added. The organic solution was washed with water and brine, dried ($MgSO_4$), and evaporated *in vacuo* to yield a yellow-brown oil. Dry benzene (40 ml) was added; the precipitate was filtered off to give methyl 6α-phenoxyacetamidopenicillanate (*S*)-*S*-oxide (2) (2.35 g, 69%), m.p. 134—135°, $[\alpha]_D^{22}$ +177° (*c* 1.00 in $CHCl_3$), $\nu_{max.}$ (KBr) 3 300 (amide NH), 1 785 (β-lactam C=O), 1 755 (ester C=O), and 1 690 cm^{-1} (amide C=O), δ ($CDCl_3$) 1.23 (3 H, s, 2-Me), 1.68 (3 H, s, 2-Me), 3.80 (3 H, s, OMe), 4.48 (1 H, s, 3-H), 4.54 (2 H, s, PhO·CH_2), 5.14 (1 H, d, *J* 2 Hz, 5-H), 5.38 (1 H, dd *J* 8 and 2 Hz, H-6), 6.80—7.40 (5 H, m, Ph), and 7.84 (1 H, d, *J* 8 Hz, NH exch.) (Found: C, 53.5; H, 5.1; N, 7.2; S, 8.2. $C_{17}H_{20}N_2O_6S$ requires C, 53.7; H, 5.3, N, 7.4; S, 8.4%).

Methyl 7α-*Phenoxyacetamidoceph*-3-*em*-4-*carboxylate* (5).—The sulphoxide (2) (0.8 g, 2.1 mmol) was refluxed in pre-heated dimethylformamide–acetic anhydride (30 ml; 50 : 1) at 130 °C for 0.5 h. The vessel was cooled in ice and the solution reduced in volume *in vacuo*, then poured into water, and extracted with ethyl acetate (2 × 100 ml). The extracts were washed with water, aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and evaporated *in vacuo* to yield a dark oil. Some material crystallised out and was filtered off. The remaining oil was chromatographed on silica gel to yield the *ester* (5) (0.18 g, 24% combined yield), m.p. 162—163°, $[\alpha]_D^{22}$ −77° (*c* 1.0 in $CHCl_3$), $\lambda_{max.}$ 269 nm (ε 8 700), $\nu_{max.}$ (KBr) 3 320 (amide NH), 1 770 (β-lactam C=O), 1 730 (ester C=O), and 1 685 cm^{-1} (amide C=O), δ ($CDCl_3$) 2.05 (3 H, s, Me), 3.10 and 3.50 (2 H, ABq, *J* 18 Hz, 2-H), 5.0 (1 H, dd, *J* 8 and 2 Hz, 7-H), 6.70—7.50 (5 H, m, Ph), and 7.70 (1 H, d, *J* 8 Hz, NH exch.) (Found: M^+, 362.0942. $C_{17}H_{18}N_2O_5S$ requires *M*, 362.0937).

Reaction of Methyl 6α-*Phenoxyacetamidopenicillanate* (S)-S-*Oxide* (2) *with Ethyl* N-*Chloro*-N-*sodiocarbamate*.—To the sulphoxide (2) (0.5 g, 1.3 mmol) in acetonitrile (20 ml) was added ethyl *N*-chloro-*N*-sodiocarbamate (0.58 g, 4 mmol). The solution was stirred for 3 h at room temperature then poured into water and extracted with ethyl acetate (2 × 75 ml). The extract was washed with water, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was dissolved in benzene and the residual solid (0.3 g) [starting material (2)] was removed. The remaining material was chromatographed, yielding methyl 6α-ethoxyformamido-6β-phenoxyacetamidopenicillanate (*S*)-*S*-oxide (3) (0.1 g, 16%; corrected yield 39%), identical with that obtained in a previous reaction.

Reaction of Methyl 6β-*Phenoxyacetamidopenicillanate* (R)-S-*Oxide* (8) *with Ethyl*-N-*Chloro*-N-*sodiocarbamate*.—The (*R*)-*S*-oxide (8) (0.3 g, 0.8 mmol) in acetonitrile (15 ml) was stirred at room temperature with ethyl *N*-chloro-*N*-sodiocarbamate (0.35 g, 2.35 mmol) for 1.5 h. The mixture was diluted with ethyl acetate (100 ml), washed with water, dried ($MgSO_4$), and evaporated *in vacuo* to yield a yellow oil. Column chromatography yielded as a single product *methyl* 6,6-*bis*(*ethoxyformamido*)*penicillanate* (R)-S-*oxide* (9) (0.23 g, 70%) as an oil, $[\alpha]_D^{22}$ +136° (*c* 1.00 in $CHCl_3$), $\nu_{max.}$ (film) 3 300 (NH), 1 795 (β-lactam C=O), 1 745 (ester C=O), and 1 730—1 690 cm^{-1} (carbamate C=O), δ ($CDCl_3$) 1.28 (6 H, t, *J* 8 Hz, CH_2·CH_3), 1.34 (3 H, s, Me), 1.52 (3 H, 2, Me), 3.72 (3 H, s, OMe), 4.10 (4 H, dq, *J* 7 Hz, 2 × CH_2·CH_3), 4.48 (1 H, s, 3-H), 5.06 (1 H, s, 5-H), 6.88br (1 H, s, NH exch.), and 6.95br (1 H, s, NH exch.) (Found: M^+, 405.1206. $C_{15}H_{23}N_3O_8S$ requires *M*, 405.1206).

Methyl 7,7-*Bis*(*ethoxyformamido*)-3-*methylceph*-3-*em*-4-*carboxylate* (11).—The sulphoxide (9) (0.4 g, 0.99 mmol) was refluxed in dimethylformamide–acetic anhydride (50 : 1; 25 ml) at 130 °C for 0.5 h. The flask was cooled in ice and half the solvent was removed *in vacuo*. The residue was poured into water and extracted with ethyl acetate; the extract was washed with water and aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated *in vacuo* to give an oil. Chromatography afforded the *cephemcarboxylate* (11) as an oil (0.14 g, 36%), $[\alpha]_D^{22}$ +24° (*c* 0.25 in $CHCl_3$), $\lambda_{max.}$ 269 nm (ε 3 400), $\nu_{max.}$ (film) 3 300 (NH), 1 790 (β-lactam C=O), 1 750 (ester C=O), and 1 725—1 690 cm^{-1} (carbamate C=O), δ ($CDCl_3$) 1.30 (6 H, t, *J* 8 Hz, CH_2·CH_3), 2.25 (3 H, s, Me), 2.98 and 3.42 (2 H, ABq, *J* 16 Hz, 2-H), 3.80 (3 H, OMe), 4.15 (4 H, dq, *J* 8 Hz, CH_2·CH_3), 5.15 (1 H, s, 5-H), 6.25br (1 H, s, NH exch.), and 6.50br (1 H, s, NH exch.) (Found: M^+, 387.1079. $C_{15}H_{21}N_3O_7S$ requires *M*, 387.1100).

Deoxygenation of Methyl 6,6-*Bis*(*ethoxyformamido*)*penicillanate* (R)-S-*Oxide* (9) *with Phosphorus Tribromide*.—The sulphoxide (9) (0.48 g, 1.2 mmol) in dimethylformamide (30 ml) was stirred at ice temperature for 0.75 h with phosphorus tribromide (1.20 ml, *ca.* 10 mmol). The mixture was poured into aqueous sodium hydrogen carbonate, and extracted with ethyl acetate; the extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to give an oil. Chromatography yielded as the only product *methyl* 6,6-*bis*(*ethoxyformamido*)*penicillanate* (10) as an oil (0.35 g, 76%), $[\alpha]_D^{22}$ +81° (*c* 1.49 in $CHCl_3$), $\nu_{max.}$ (film) 3 300 (NH), 1 785 (β-lactam C=O), 1745 (ester C=O), and 1 720—1 690 cm^{-1} (carbamate C=O), δ ($CDCl_3$) 1.24 (6 H, dt, *J* 8 Hz, CH_2·CH_3), 1.46 (3 H, s, Me), 1.56 (3 H, s, Me), 3.72 (3 H, s, OMe), 4.10 (4 H, dq, *J* 8 Hz, CH_2·CH_3), 4.42 (1 H, s, 3-H), 5.54 (1 H, s, 5-H), 6.28br (1 H, s, NH exch.), and 6.60br (1 H, s, NH exch.) (Found: M^+, 389.1272. $C_{15}H_{23}N_3O_7S$ requires *M*, 389.1257.

Oxidation of Methyl 6,6-*Bis*(*ethoxyformamido*)*penicillanate* (10).—The ester (10) (0.3 g, 0.77 mmol) in methylene chloride (20 ml) at 0 °C was treated with *m*-chloroperbenzoic acid in methylene chloride (in portions) until t.l.c. showed complete removal of the starting material. The solution was washed with aqueous sodium disulphite, aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and evaporated *in vacuo* to yield an oil which was chromatographed on silica gel; the oily product (0.2 g, 72%) was identical with the sulphoxide (9).

Reaction of Benzyl 6β-*Phenoxyacetamidopenicillanate* (R)-S-*Oxide with Ethyl* N-*Chloro*-N-*sodiocarbamate*.—The (*R*)-*S*-oxide (0.5 g 1.14 mmol) in acetonitrile (15 ml) was stirred at room temperature with ethyl *N*-chloro-*N*-sodiocarbamate (0.48 g, 3.3 mmol) for 0.5 h. The mixture was extracted with ethyl acetate and the extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. Chromatography yielded *benzyl* 6,6-*bis*(*ethoxyformamido*)*penicillanate* (R)-S-*oxide* (0.35 g, 67%), as an oil, $[\alpha]_D^{22}$ +136° (*c* 1.00 in $CHCl_3$), $\nu_{max.}$ (film) 3 300 (NH), 1 800 (β-lactam C=O), 1 755 (ester

C=O), and 1 720—1 690 cm^{-1} (carbamate C=O), δ ($CDCl_3$) 1.25 (9 H, m, Me and CH_2·CH_3), 1.49 (3 H, s, Me), 4.12 (4 H, dq, *J* 8 Hz, CH_2·CH_3), 4.53 (1 H, s, 3-H), 5.11 (1 H, s, 5-H), 5.19 (2 H, s, CH_2Ph), 7.13br (2 H, s, NH exch.), and 7.3 (5 H, s, Ph) (Found: M^+, 481.1520. $C_{21}H_{27}N_3O_8S$ requires *M*, 481.1519.)

Reaction of Methyl 6β-*Phenoxyacetamidopenicillanate* (R)-S-*Oxide* (8) *with* 2,2,2-*Trichloroethyl* N-*Chloro*-N-*sodiocarbamate*.—The (*R*)-*S*-oxide (8) (1.1 g, 2.9 mmol) in dimethylformamide was stirred overnight with trichloroethyl *N*-chloro-*N*-sodiocarbamate (2.3 g, 9.2 mmol). The mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and evaporated *in vacuo* to yield an oil which was chromatographed. The early fractions were complex but the urea (15) was later obtained as a crystalline solid (0.2 g, 21%), m.p. 115—118°, $\nu_{max.}$ (KBr) 3 360 and 3 200 (NH), 1 750 (carbamate C=O), and 1 710 cm^{-1} (amide C=O), δ ($CDCl_3$) 4.72 (2 H, s, CH_2·CCl_3), 5.32 (2 H, d, *J* 8 Hz, CH_2·NH), 6.80—7.45 (5 H, m, Ph), 8.50br (1 H, t, *J* 9 Hz, NH exch.), and 8.85br (1 H, s, NH exch.), M^+, 340. The next component eluted was *methyl* 6,6-*bis*-(2,2,2-*trichloroethylethoxyformamido*)*penicillanate* (R)-S-*Oxide* (13), an amorphous solid (0.82 g, 47%), $[\alpha]_D^{22}$ +102° (*c* 0.95 in $CHCl_3$), $\nu_{max.}$ (film) 3 290 and 3 200 (NH), 1 802 (β-lactam C=O), 1 755 (ester C=O), and 1 745 cm^{-1} (carbamate C=O), δ ($CDCl_3$) 1.39 (3 H, s, Me), 1.55 (3 H, s, Me), 3.82 (3 H, s, OMe), 4.60 (1 H, s, 3-H), 4.75 (4 H, m, CH_2), 5.25 (1 H, s, 5-H), 7.40br (1 H, s, NH exch.), and 7.58br (1 H, s, NH exch.) (Found: M^+, 608.8872. $C_{15}H_{17}Cl_6N_3O_8S$ requires *M*, 608.8869.) The final compound eluted was *methyl* 6β-*phenoxyacetamido*-6α-(2,2,2-*trichloroethoxyformamido*)*penicillanate* (R)-S-*Oxide* (14), an oil (0.095 g, 6%), $[\alpha]_D^{22}$ +107° (*c* 0.79 in $CHCl_3$), $\nu_{max.}$ (film) 3 290 (NH), 1 800 (β-lactam C=O), 1 755 (ester C=O), 1 745 (carbamate C=O), and 1 690 cm^{-1} (amide C=O), δ ($CDCl_3$) 1.35 (3 H, s, Me), 1.50 (3 H, s, Me), 3.80 (3 H, s, OMe), 4.50 (1 H, s, 3-H), 4.53 (2 H, s, CH_2) 4.70 (2 H, s, CH_2·CCl_3), 5.18 (1 H, s, 5-H), 6.80—7.45 (5 H, m, Ph), 7.80 (1 H, s, amide NH), and 8.15br (1 H, s, carbamate NH) (Found: M^+, 569.0182. $C_{20}H_{22}Cl_3N_3O_8S$ requires *M*, 569.0194).

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