Transformations of Penicillins: New Methods of Formation and Reactions of 6,6-Disubstituted Penams and 7,7-Disubstituted Cephems [1]

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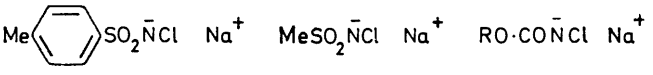
The reactions of penicillanate esters with ethyl or trichloroethyl *N*-chloro-*N*-sodiocarbamate gave 6α-ethoxyformamido and 6α-trichloroethoxyformamido-6β-acylaminopenicillanates, respectively. The 6α-trichloroethoxyformamido-group was transformed in certain penicillanates into a 6α-amino-group. 7β-Acylamino-7α-ethoxyformamidodeacetoxycephalosporanates were formed from the appropriate 6,6-disubstituted penicillanate *S*-oxides. The reaction of the 6,6-disubstituted penicillanates with phosgene led to a 1-ethoxycarbonyl-2-oxo-3-phenoxyacetyl-1,3-diazetidine-4-spiro-6'-penicillanate.

RECENT studies [2] of the reactions of penicillanates and secopenicillanates with *N*-chloro-*N*-sodiotoluene-*p*-sulphonamide (1) revealed several different reaction modes. The β-lactam products obtained stemmed from initially formed *S*-chlorosulphonium species which underwent subsequent transformations affording, among other products, (*a*) sulphoxides, (*b*) sulphimides, (*c*) oxazolinoazetidinones, and (*d*) thiadiazine *S*-imides. Related products have also been obtained from the corresponding reactions of *N*-chloro-*N*-sodiomethanesulphonamide (2).[3]



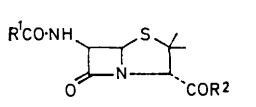
(1) (2) (3) R = Et (4) R = $Cl_3C \cdot CH_2$

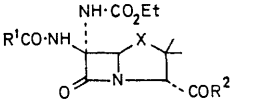
We have extended these investigations to evaluate the scope and limitations of *N*-chloro-*N*-sodio-reagents in the structural modification of penicillins, with the objectives of discovering new reaction pathways which preserve intact the biologically important β-lactam ring, and of transforming penicillins into analogues with potential antibiotic activity. Thus, the group of reagents including ethyl and trichloroethyl *N*-chloro-*N*-sodiocarbamate [(3) and (4)] was chosen for further study because of potential reactivity differences, relative to chloramine T (1), involving (*a*) the availability of the chloronium ion (*i.e.* the susceptibility of the *N*-chloro-group to attack by a nucleophilic centre in the penam) and (*b*) the basicity and nucleophilicity of the alkoxyformamido-species present in equilibrium in the reaction solution. We report that the reagents (3) and (4) undergo reactions totally different from those encountered with the related *N*-chloro-*N*-sodiosulphonamides.[2]

Preparation of the N-*Chloro*-N-*sodiocarbamates.*—*N*-Chloro-*N*-sodiocarbamates and related compounds have been prepared by several groups.[4,5] We have prepared the ethyl and trichloroethyl esters (3) and (4) by a modification of the Swern route.[4] An ice-cold, dry methanolic solution of the appropriate carbamate was treated with an equimolar quantity of t-butyl hypochlorite and sodium hydroxide. Evaporation and filtration afforded the salt, which was washed with dry ether, and stored under anhydrous conditions. Elemental analysis indicated the absence of water of hydration. (Formamide thus treated did not give *N*-chloro-*N*-sodioformamide. Also, several batches of methyl *N*-chloro-*N*-sodiocarbamate underwent spontaneous and rapid exothermic decomposition.)

Reactions of Ethyl N-*Chloro*-N-*sodiocarbamate* (3) *with Penicillanates.*—Ethyl *N*-chloro-*N*-sodiocarbamate (3) caused β-lactam cleavage of the penicillanates (5)—(7) and the penicillamide (8) in protic solvents such as methanol and ethanol. This is in marked contrast to the chloramine T reactions [2] which proceeded smoothly in alcohols, affording intact β-lactam products, and reflects the unexpectedly basic nature of the reagent (3) in such solvents.

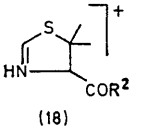
In acetonitrile suspension, however, the penams (5)—(8) reacted with an excess of the carbamate (3) at different rates [(7) > (8) > (5) > (6)], affording β-lactam products. For example, methyl 6β-phenoxyacetamidopenicillanate (5) gave, after chromatography, a crystalline solid (89%) † of composition $C_{20}H_{25}N_3SO_7$, indicating





	R^1	R^2
(5)	PhO·CH_2	OMe
(6)	$Cl_3C \cdot CH_2$	O·CH_2Ph
(7)	PhO·CH_2	O·CH_2CCl_3
(8)	PhCH_2	NHBu^t

	R^1	R^2	X
(9)	PhO·CH_2	OMe	S
(10)	CCl_3CH_2	O·CH_2Ph	S
(11)	PhCH_2	O·CH_2CCl_3	S
(12)	PhCH_2	NHBu^t	S
(13)	PhO·CH_2	OH	S
(14)	PhO·CH_2	OMe	SO(*R*,*S*)
(15)	PhCH_2	NHBu^t	SO(*R*)
(16)	PhO·CH_2	O·CH_2CCl_3	SO(*R*,*S*)
(17)	PhO·CH_2	O·CH_2CCl_3	SO_2



(18)

incorporation of one ethoxyformamido-group. Substitution at C-6, as in structure (9), rather than at C-5 was strongly suggested from the spectroscopic data: in the i.r. spectrum peaks at 1 780, 1 740, 1 725, and 1 680 cm^{-1} indicated β-lactam, ester, formamido- and phenoxy-

† All yields take into account recovered starting material.

[1] Preliminary communication, M. M. Campbell and G. Johnson, *J.C.S. Chem. Comm.*, 1975, 479.

[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, 1212.

[3] M. M. Campbell and G. Johnson, unpublished results.

[4] See, for example, T. A. Foglia and D. Swern, *J. Org. Chem.*, 1966, **31**, 3625; D. Saika and D. Swern, *ibid.*, 1968, **33**, 4548; S. C. Czapf, H. Gottlieb, G. F. Whitfield, and D. Swern, *ibid.*, 1973, **38**, 2555; G. F. Whitfield, H. S. Beilan, D. Saika, and D. Swern, *ibid.*, 1974, **39**, 2148; W. Traube and H. Gockel, *Ber.* 1923, 384, 1951; P. Chabrier, *Compt. rend.*, 1942, 362; C. Bachand, H. Driguez, J. M. Paton, D. Tanchard, and J. Lessard, *J. Org. Chem.*, 1974, **39**, 3136.

[5] Fr. P. 974,085/1951.

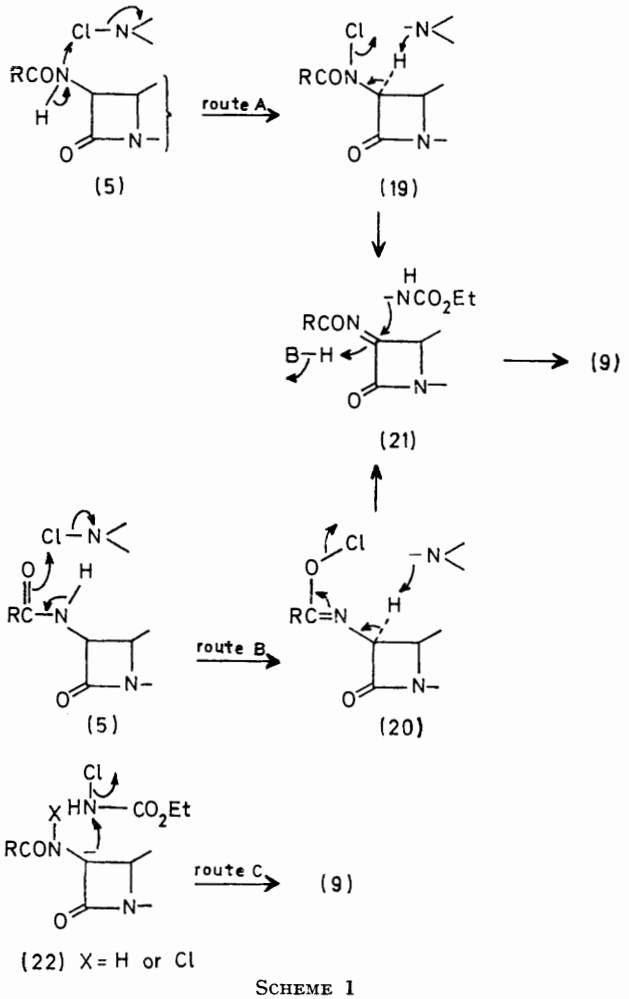
acetamido-groups, respectively; the n.m.r. spectrum ($CDCl_3$) showed signals for two amide protons at τ 2.0 and 3.75 which were only slowly exchanged in D_2O–D_2SO_4, a sharp singlet at 4.32 for a β-lactam proton at C-5 (a proton at C-6 would have coupled with the amide NH), a singlet at 5.54 (H-3), and signals for *gem*-dimethyl, phenoxyacetamido-, ethoxyformamido-, and methoxycarbonyl groups; the mass spectrum contained as the base peak the cation (18; R^2 = Me), formed by retro-[2 + 2] cleavage of the β-lactam ring. The detailed stereochemistry as shown in formula (9) has been rigorously defined by *X*-ray crystallography.[6]

Similar products (10)—(12) with corresponding spectroscopic properties were obtained in good yield from the penicillanates (6) and (7) and from the penicillamide (8). A common feature of particular diagnostic value in the series was the mass spectral fragment (18).

One mechanism which accounts for the formation of these 6,6-disubstituted penams is shown in Scheme 1. Initial *N*-chlorination (route A) of the phenoxyacetamido-group of (5), giving (19), followed by 1,2-elimination of HCl by ethoxyformamide anion, would yield the 6-acylimine (21). Alternatively, initial *O*-chlorination (route B) of (5), followed by 1,4-elimination of HCl from the imidoyl hypochloride (20) may be invoked. Nucleophilic addition to the α-face * of the resulting acylimine (21) by a further ethoxyformamido-species would then produce the 6,6-disubstituted product (9).

It was not possible to trap the postulated imine (21) with water, or with methanol, and it is also significant that no 6α-chloro-products were formed in spite of the presence of chloride ion. Added sodium azide inhibited the reaction. Firestone *et al.*[7] have shown that 6-acylimines undergo ready addition of nucleophiles such as water or alcohols. This may indicate in the ethyl *N*-chloro-*N*-sodiocarbamate reaction a strongly solvated ethoxyformamide–acylimine reactant pair, or a different mechanism (route C) in which a C-6 anion (22) is formed and then attacks an *N*-chloro-species with elimination of chloride ion. We do not favour this last course, since a C-6 anion might also be expected to attack the electrophilic chlorine with formation of a 6-chloro-product. In addition, attempts to intercept a C-6 anion with, for example, acrylonitrile, were unsuccessful.

Variation of solvent resulted in significant differences in yields of products (9)—(12). For example, in dimethylformamide high yields were obtained, whereas in formamide no reaction occurred, possibly owing to *N*-chloro-transfer between solvent and reagent, or reaction to give an allophanate.[5] In the reactions of the penams (5)—(8) in acetonitrile or dimethylformamide, traces of



SCHEME 1

polar β-lactam by-products were not characterized, although it was shown that they did not result from further reaction of the products (9)—(12) with ethyl *N*-chloro-*N*-sodiocarbamate.

The free carboxylic acid (13) † required for antibiotic screening was prepared by treating the trichloroethyl ester (7) with zinc–dimethylformamide–acetic acid.[8]

The sulphoxides (14)—(16) were readily formed by the action of *m*-chloroperbenzoic acid[9] on compounds (5), (7), and (8). The sulphoxides (14) and (16) thus prepared were inseparable mixtures of *R*- and *S*-isomers, indicating that the direction of attack of the incoming oxidant was being influenced by both phenoxyacetamido- and the ethoxyformamido-groups. It is well established[9] that the 6β-amidopenicillanates undergo stereoselective β-oxidation giving mainly *S*-sulphoxide because

* There is ample precedent for nucleophilic addition to a 6-iminopenicillanate formed *in situ*.[7]

† Inactive against a range of organisms.

[6] A. F. Cameron, J. McElhatton, M. M. Campbell, and G. Johnson, unpublished results.

[7] A particularly relevant example is described by R. A. Firestone and B. G. Christensen, *J. Org. Chem.*, 1973, **38**, 1436; see also G. A. Koppel and R. E. Koehler, *J. Amer. Chem. Soc.*, 1973, **95**, 2403; W. H. W. Lunn and E. V. Mason, *Tetrahedron Letters*, 1974, 1311; G. A. Koppel and R. E. Koehler, *ibid.*, 1973, 1943; J. E. Baldwin, F. J. Urban, R. D. G. Cooper, and F. L. Jose, *J. Amer. Chem. Soc.*, 1975, **95**, 2401; Y. S. Lo and J. C. Shechan, *J. Org. Chem.*, 1975, **40**, 191; W. A. Spitzer and T. Goodson, *Tetrahedron Letters*, 1973, 273.

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

[9] R. D. G. Cooper, P. V. De Marco, J. C. Cheng, and N. D. Jones, *J. Amer. Chem. Soc.*, 1969, **91**, 1408; R. D. G. Cooper, P. V. De Marco, and D. O. Spry, *ibid.*, p. 1528.

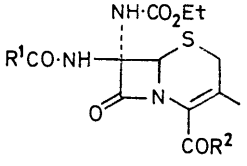
of hydrogen bonding. The penicillamide (8) afforded only one sulphoxide (15), tentatively assigned *R*-stereochemistry, since hydrogen bonding of oxidant to the 3α-t-butylcarbamoyl group may assist the 6α-ethoxyformamido-group in directing the oxidation. Molecular models indicate that the bulk of the t-butylcarbamoyl group should not interfere with this process. Treatment of the trichloroethyl ester (7) with an excess of oxidant led rapidly to the sulphone (17).

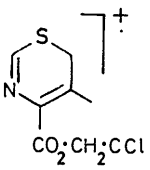
Treatment of the mixed sulphoxides (16) with dimethylformamide–acetic anhydride at 130 °C [8] gave, following rapid short-path column chromatography, the expected 7,7-disubstituted deacetoxycephalosporanate (23) in 50% yield as an amorphous solid [$\nu_{max.}$ 1 790 and 1 730—1 670 cm^{-1}; $\lambda_{max.}$ 265 nm (ε 6 800); τ 2.00 and 3.20 (amide protons slowly exchanged in D_2O–D_2SO_4), 4.83 (single uncoupled β-lactam proton), and 7.10 (ABq, *J* 15 Hz, geminal methylene protons), and signals for vinylic methyl, trichloroethyl, ethoxyformamido-, and phenoxyacetamido-groups]. An intense peak corresponding to the thiazine cation (25) appeared in the mass spectrum.

De-esterification of (23) in dimethylformamide–acetic anhydride [8] gave the free carboxylic acid (24) † in 78% yield. The spectroscopic characteristics were similar to those of (23). No molecular ion was observed in the mass spectrum, but an accurate mass measurement of the ion of highest *m/e* value ($M - CO_2$) was satisfactory. The major fragmentation processes are shown in Scheme 2.

We hoped to utilize this route to 6α(or 7α)-ethoxyformamidopenams (or cephems) in the synthesis of amino-analogues. However, the conventional hydrolysis procedures for converting ethoxyformamido- into amino-groups would be too severe for β-lactams. Accordingly, the introduction of the 6α-amino-unit *via* 6β-trichloroethoxyformamido-substitution was investigated.

Reactions of Trichloroethyl N-*Chloro*-N-*sodiocarbamate* (4) *with Penicillanates.*—Methyl 6β-phenoxyacetamidopenicillanate (5) reacted at room temperature in dimethylformamide with 2 mol. equiv. of the carbamate

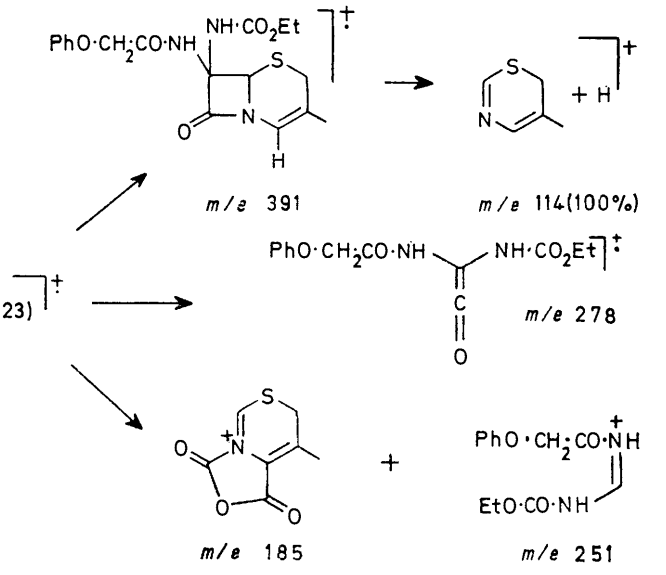




	R^1	R^2
(23)	PhO·CH_2	Cl_3C·CH_2O
(24)	PhO·CH_2	OH

(25)

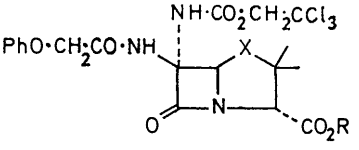
(4) to give starting material and a product of identical R_F value on t.l.c. Oxidation of the mixture with *m*-chloroperbenzoic acid preferentially converted the starting material (5) into its *S*-oxide,[9] allowing chromatographic separation of the product (82%), characterized as the methyl 6β-phenoxyacetamido-6α-trichloroethoxyformamidopenicillanate (26). Again, a thiazoline cation



SCHEME 2

(18; R^2 = OMe) formed the base peak in the mass spectrum.

In acetonitrile as solvent the reaction was slower, and in addition to (26) (39%) the known oxazolinoazetidinone



	R	X
(26)	Me	S
(27)	CH_2CCl_3	S
(31)	CH_2CCl_3	SO(*R*,*S*)

(30) [10] was isolated in 43% yield. Isolation of (30) provided the one instance in this study of a product which resulted from an *S*-chlorosulphonium precursor (28) [2] (Scheme 3). Bond cleavage between S and C-5 in (28) affords the intermediate oxazoline sulphenyl chloride (29), and elimination leads to (30). The trichloroethyl group in the reagent (4) facilitates *S*-chlorosulphonium ion formation and subsequent thiazolidine ring cleavage and elimination, providing competition with the *N*-chlorination and 1,2-elimination pathways (Scheme 1) which predominate in dimethylformamide.

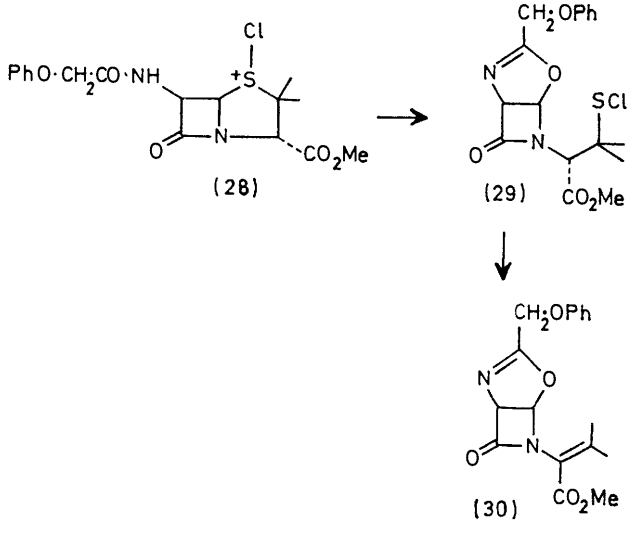
In a similar reaction in dimethylformamide, the carbamate (4) transformed the trichloroethyl penicillanate (7) into the 6α-trichloroethoxyformamido-derivative (27) [isolated after removing starting material by oxidation as above, together with the *R*- and *S*-sulphoxides (31)]. The benzylpenicillanate (6) reacted slowly with the carbamate (4), giving no 6α-substitution and affording only β-lactam-cleaved products.

† Same footnote as on page 1919.

[10] References cited within ref. 2.

Removal of the trichloroethoxycarbonyl group in (26) was effected both with zinc–dimethylformamide–acetic acid [8] and with zinc–methanol–acetic acid. After extraction of acids with sodium hydrogen carbonate, a low yield of neutral products was obtained. A combination of selective oxidation and column chromatography revealed that the neutral constituents had been (*a*) methyl phenoxyacetamidopenicillanate (5) [which had been carried through in trace quantities from the preparation of (26)], (*b*) 6α-dichloroethoxyformamido-6β-phenoxyacetamidopenicillanate (32) [formed by partial reduction of the trichloroethoxyformamido-group of (26)], and (*c*) the desired 6α-amino-6β-phenoxyacetamidopenicillanate (33) (20%), obtained as an oil, identified by spectroscopic data and high resolution mass measurement. The amine (33) was not readily extracted into aqueous acetic acid from organic solvents.

Acidification of the hydrogen carbonate extracts from the reaction of (26) yielded as the major product (38%)



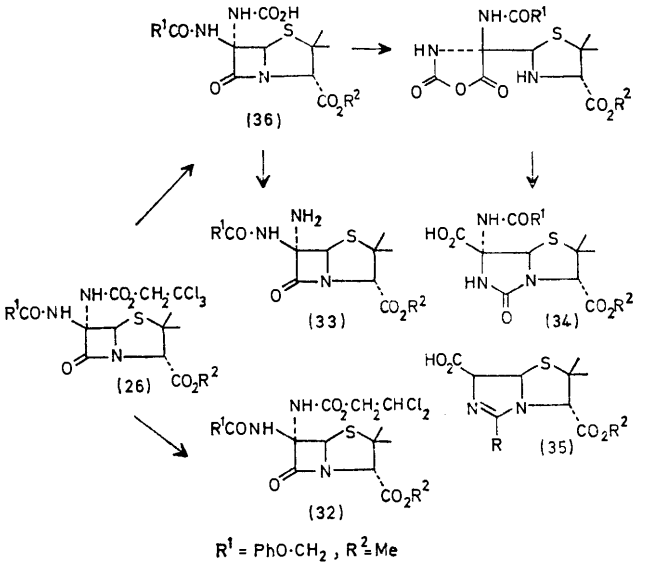
SCHEME 3

the penillic acid (34), possibly formed (Scheme 4) from a carbamic acid (36) which, as well as decarboxylating to give (33), undergoes intramolecular cyclizations to the anhydride, and thence to the penillic acid (34). It can reasonably be assumed that C-6 of (26) retains its chirality throughout the reaction sequence, and that the absolute stereochemistry at C-6 in (34) is *R* as depicted.

Whereas the known penillic acids (35) are readily formed by carboxylation of 6β-aminopenicillanic acid,[11] the 6α-amino-6β-phenoxyacetamidopenicillanate (33) underwent no reaction with carbon dioxide.

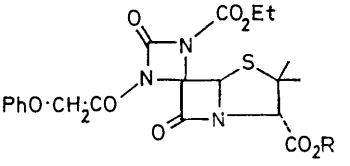
Satisfactory conditions have yet to be developed for the de-esterification and deformylation of trichloroethyl 6β-phenoxyacetamido-6α-trichloroethoxyformamidopenicillanate (27) to a 6α-amino-3α-carboxylic acid.

Transformation of 6,6-Disubstituted Penams into Spiro-β-lactams.—It was apparent that the 6,6-disubstituted penams were of potential value for the construction of

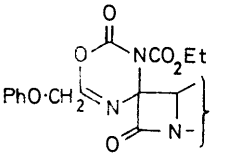


SCHEME 4

spiro-linked heterocyclic systems at C-6.* Treatment of the 6α-ethoxyformamidopenicillanate (9) —78 °C in dry tetrahydrofuran with 2 mol. equiv. of phenyllithium followed by an excess of phosgene afforded a yellow oil which was shown by t.l.c. to contain a complex mixture. Dissolution in ether gave in low yield (19%) a solid, $C_{21}H_{23}N_3O_8S$, showing intense i.r. absorption at 1 858 cm^{-1}, together with β-lactam (1 800 cm^{-1}) and ester and amide absorptions. No OH or NH bands were present. The n.m.r. spectrum was similar to that of (9) with the notable absence of the two amide proton signals. The spiro-structure (37) rather than one of the alternative ring-systems such as (40) or (41) is tentatively assigned.



(37) R = Me
(38) R = CH_2CCl_3
(39) R = H



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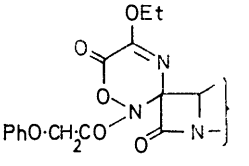

(41)

* Spiro-β-lactams have been prepared by other routes.[12]

[11] F. R. Batchelor, D. Gazzard, and J. H. C. Nayler, *Nature*, 1961, **191**, 910; D. A. Johnson and G. A. Hardcastle, *J. Amer. Chem. Soc.*, 1961, **23**, 3534.

[12] R. Reiner and P. Zeller, *Helv. Chim. Acta*, 1968, 1905; G. H. Rasmusson, G. F. Reynolds, and G. E. Arth, *Tetrahedron Letters*, 1973, 145; G. A. Koppel and R. E. Koehler, *ibid.*, p. 1943.

Similarly, the spiro-diazetidinone (38) was prepared from compound (11) in 16% yield. This trichloroethyl derivative was de-esterified,[8] yielding 1-ethoxycarbonyl-2-oxo-3-phenoxyacetyl-1,3-diazetidine-4-spiro-6′-penicillanic acid (39).*

Conclusions.—Many recent patents and publications describe methods of introducing functional groups at C-6 [7,12,13] in the penam nucleus and at C-7 of the cephems. The present paper describes a simple and economical method of inserting amino- and related functional groups at these positions.† These exploratory studies also provide potential precursors for the construction of a range of penam and cephem β-lactam-fused spiro-heterocycles.

EXPERIMENTAL

General details are as reported in previous papers.[2] Elemental compositions assigned on the basis of high resolution mass measurement were of chromatographically pure material. All yields take into account recovered starting material. For compounds marked with an asterisk, physical data are available as Supplementary Publication No. SUP 21791 (2 pp.).‡

Preparation of Ethyl N-*Chloro*-N-*sodiocarbamate* (3).—Two procedures were employed: (*a*) the method of Saika and Swern; [4] and (*b*) addition to an ice-cold solution of ethyl carbamate (4.5 g, 50 mmol) in dry methanol (40 ml) of t-butyl hypochlorite (5.4 g, 50 mmol), followed by stirring for 15 min, and dropwise addition of a dry methanolic solution of sodium hydroxide (2.0 g, 50 mmol); the solvent was then evaporated off *in vacuo* and the white solid residue filtered off and washed with dry ether to give the carbamate (3) (8.90 g).

Preparation of Trichloroethyl N-*Chloro*-N-*sodiocarbamate* (4).—Trichloroethyl carbamate [15] was treated as above, giving, as a white crystalline solid which oxidized moist starch–iodide paper, the carbamate (4), $\nu_{max.}$ (KBr) 1 650, 1 450, 1 285, 1 120, 1 065, 1 047, 985, 830, 765, and 700 cm^{-1}.

Reaction of the Carbamate (3) *with Methyl* 6β-*Phenoxyacetamidopenicillanate* (5).—To a stirred solution of the penicillanate (5) (2.0 g, 5.5 mmol) in acetonitrile (50 ml) was added the carbamate (3) (2.4 g, 16.5 mmol). The reaction was continued till t.l.c. indicated completion, and the solution was filtered through Celite, diluted with ethyl acetate, washed twice with brine, dried ($MgSO_4$), and concentrated *in vacuo* to yield a yellow syrup (3.0 g). Chromatography gave starting material (0.9 g) and *methyl* 6α-*ethoxyformamido*-6β-*phenoxyacetamidopenicillanate* (9) (1.3 g, 89%), m.p. 140—140.5°, $[\alpha]_D^{22}$ +56° (*c* 1.18 in $CHCl_3$), $\nu_{max.}$ (KBr) 3 300 (amide NH), 1 776 (β-lactam C=O), 1 740 (ester C=O), 1 726 (carbamoyl C=O), and 1 680 cm^{-1} (amide C=O), τ 8.78 (3 H, t, *J* 8 Hz, OCH_2CH_3), 8.64 and 8.57 (each 3 H, s, *gem*-Me_2), 6.25 (3 H, s, OMe), 5.9 (2 H, q, *J* 8 Hz, OCH_2CH_3), 5.54 (1 H, s, 3-H), 5.48 (2 H, s, $PhOCH_2$), 4.32 (1 H, s, 5-H), 3.51br (1 H, s, NH; concentration- and solvent-dependent; exchanged in D_2O–D_2SO_4), 3.2—2.5 (5 H, m, aromatic), and 2.07br (1 H, s, NH, exchanged in D_2O–D_2SO_4) (Found: C, 53.25; H, 5.7; N, 9.2; S, 7.05%; M^+, 451.1383. $C_{20}H_{25}N_3O_7S$ requires C, 53.3; H, 5.55; N, 9.3; S, 7.1%; *M*, 451.1413).

Similarly prepared from the penams (6)—(8) were *benzyl* 6α-*ethoxyformamido*-6β-*trichloroethoxyformamidopenicillanate* (10) * (52%), *trichloroethyl* 6α-*ethoxyformamido*-6β-*phenylacetamidopenicillanate* (11) * (88%), and 6α-*ethoxyformamido*-6β-*phenylacetamido*-N-*t-butylpenicillanamide* (12)* (80%).

6α-*Ethoxyformamido*-6β-*phenoxyacetamidopenicillanic Acid* (13).—A solution of the penicillanate (11) (0.20 g, 0.35 mmol) in dimethylformamide–glacial acetic acid (4 ml; 25 : 7.5 v/v) at 0 °C was stirred with zinc dust (0.25 g) for 1.5 h, then filtered and diluted with ethyl acetate (40 ml). The ethyl acetate solution was washed twice with water and once with sodium hydrogen carbonate solution. The aqueous hydrogen carbonate layer was acidified and extracted with ethyl acetate and the extract was washed with water, dried ($MgSO_4$), and evaporated *in vacuo* to yield the *penicillanic acid* (13) * (0.13 g, 82%) as a foam.

Oxidation of Methyl 6α-*Ethoxyformamido*-6β-*phenoxyacetamidopenicillanate* (5) *with* m-*Chloroperbenzoic Acid.*—To a solution of the penicillanate (5) (0.2 g, 0.45 mmol) in dry methylene chloride at 0 °C was added dropwise a solution in methylene chloride of *m*-chloroperbenzoic acid until t.l.c. indicated completion of the reaction. The solution was washed with aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated *in vacuo* to yield an inseparable 1 : 1 mixture of *methyl* 6α-*ethoxyformamido*-6β-*phenoxyacetamidopenicillanate* (R)- *and* (S)-S-*oxides* (14) (0.208 g) as an oil, $\nu_{max.}$ (film) 3 280 (amide NH), 1 800 (β-lactam C=O), 1 760 and 1 730 (esters C=O), 1 690 (amide C=O), 1 220 (esters C=O), and 1 060 cm^{-1} (S=O). Isomer (a) showed τ 8.80 (3 H, t, *J* 8 Hz, OCH_2CH_3), 8.80 and 8.38 (each 3 H, s, *gem*-Me_2), 6.21 (3 H, s, OMe), 5.89 (2 H, q, *J* 8 Hz, OCH_2CH_3), 5.49 (2 H, s, $PhCH_2$), 5.35 (1 H, s, 3-H), 4.89 (1 H, s, 5-H), 3.30—2.50 (6 H, m, aromatic and NH), 1.80br (1 H, s, NH); isomer (b) showed τ 8.80 (3 H, t, *J* 8 Hz, OCH_2CH_3), 8.70 and 8.50 (each 3 H, s, *gem*-Me_2), 6.21 (3 H, s, OMe), 5.89 (2 H, q, *J* 8 Hz, OCH_2CH_3), 5.49 (1 H, s, 3-H), 5.48 (2 H, s, $PhOCH_2$), 4.80 (1 H, s, 5-H), 3.25—2.40 (6 H, m, aromatic and NH), and 1.75 (1 H, s, NH) [Found (for mixture), M^+, 467.1354. $C_{20}H_{25}N_3O_8S$ requires *M*, 467.1362].

6α-*Ethoxyformamido*-6β-*phenylacetamido*-N-*t-butylpenicillanamide* (R)-S-*oxide* (15) * (52%) and a mixture of *trichloroethyl* 6α-*ethoxyformamido*-6β-*phenoxyacetamidopenicillanate* (R)- *and* (S)-S-*oxides* (16) * (82%) were prepared similarly from the penam derivatives (8) and (6), respectively.

Trichloroethyl 6α-*Ethoxyformamido*-6β-*phenoxyacetamidopenicillanate* SS-*Dioxide* (17).—A solution of the ester (11) (1.67 g, 2.94 mmol) in dry methylene chloride at 0 °C was stirred with *m*-chloroperbenzoic acid (1.0 g, 5.85 mmol) till t.l.c. indicated complete reaction. Chromatography afforded, as the least polar product, the *sulphone* (17) (0.74 g, 40%) as an oil, $[\alpha]_D^{23}$ +119° (*c* 0.94 in $CHCl_3$), $\nu_{max.}$ (film) 3 250 (amide NH), 1 812 (β-lactam C=O), 1 775 and 1 730 (ester C=O), and 1 680 cm^{-1} (amide C=O), τ 8.80 (3 H, t, *J* 7 Hz, OCH_2CH_3), 8.50 and 8.40 (each 3 H, s, *gem*-Me_2), 5.89 (2 H, q, *J* 7 Hz, OCH_2CH_3), 5.40 (2 H, s, $PhOCH_2$), 5.40 (1 H, s, 3-H), 5.36 (1 H, d, *J* 12 Hz, CH_aCCl_3), 4.98 (1 H, d, *J* 12 Hz, CH_bCCl_3), 3.30—2.50 (5 H, m, aromatic), and 2.45br

* Inactive against a range of organisms.

† For a preliminary account of the reactions of alkyl *N*-chloro-*N*-sodiocarbamates with secopenicillanates and penicillanate *S*-oxides see ref. 14.

‡ For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S Perkin I*, 1975, Index issue.

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(1 H, s, NH) (Found: M^+, 599.0262. $C_{21}H_{24}{}^{35}Cl_3N_3O_9S$ requires M, 599.0298). The more polar products were the sulphoxide esters (16).

Conversion of the Mixed Oxides (16) *into Trichloroethyl* 7α-*Ethoxyformamido*-7β-*phenoxyacetamidodeacetoxycephalosporanate* (23).—The oxides (16) (0.50 g, 0.86 mmol) in dry dimethylformamide (25 ml) and acetic anhydride (0.50 g) were stirred in a preheated oil-bath at 130 °C for 35 min, then cooled, and the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate and washed with dilute aqueous sodium hydrogen carbonate and then water, dried ($MgSO_4$), and evaporated to yield a dark oil (0.44 g). Rapid chromatography gave, as the major product, the *deacetoxycephalosporanate* (23) as an oil (0.20 g, 38%), $[\alpha]_D^{22}$ +23° (*c* 1.95 in $CHCl_3$), $\nu_{max.}$ (film) 3 300 (amide NH), 1 790 (β-lactam C=O) and 1 730vbr cm^{-1} (esters and amide C=O), $\lambda_{max.}$ (EtOH) 265 (ε 6 800) and 272 nm (6 300), τ 8.79 (3 H, t, *J* 7 Hz, OCH_2CH_3), 7.7 (3 H, s, 3-CH_3), 7.25 (1 H, d, *J* 15 Hz, 2-H_a), 6.95 (1 H, d, *J* 15 Hz, 2-H_b), 5.93 (2 H, q, *J* 7 Hz, OCH_2CH_3), 5.46 (2 H, s, $PhOCH_2$), 5.16 (2 H, s, CH_2CCl_3), 4.82 (1 H, s, 6-H), 3.30—2.50 (6 H, m, aromatic and NH), and 2.00br (1 H, s, NH) (Found: M^+, 565.0212. $C_{21}H_{22}{}^{35}Cl_3N_3O_7S$ requires M, 565.0245.)

7α-*Ethoxyformamido*-7β-*phenoxyacetamidodeacetoxycephalosporanic Acid* (24).—A solution of the trichloroethyl ester (23) (0.20 g, 0.36 mmol) in dimethylformamide–glacial acetic acid (4 ml; 25 : 7.5 v/v) at 0 °C was stirred with zinc dust (0.20 g) for 1.5 h, filtered, diluted with ethyl acetate, and washed twice with water. The ethyl acetate solution was extracted with aqueous sodium hydrogen carbonate, which was then acidified. Extractions with ethyl acetate gave the *acid* (24) (0.12 g, 78%) as an oil, $[\alpha]_D^{22}$ +28° (*c* 2.2 in $CHCl_3$), $\nu_{max.}$ (film) 3 300 (amide NH), 1 785 (β-lactam C=O), and 1 720br cm^{-1} (ester, amide, and acid C=O), $\lambda_{max.}$ (EtOH) 215 (ε 12 600), 265 (7 200), and 272 nm (6 100), τ 8.78 (3 H, t, 7 Hz, OCH_2CH_3), 7.72 (3 H, s, 3-CH_3), 7.25 (1 H, d, *J* 16 Hz, 2-H_a), 6.95 (1 H, d, 16 Hz, 2-H_b), 5.77 (2 H, q, *J* 7 Hz, OCH_3CH_3), 5.40 (2 H, s, $PhOCH_2$), 4.82 (1 H, s, 6-H), 3.30—2.50 (6 H, m, aromatic and NH), 1.78br (1 H, s, NH), and —0.40br (1 H, s, CO_2H) [Found: $(M - CO_2)^+$, 391.1206. $C_{18}H_{21}N_3O_5S$ requires $(M - CO_2)$, 391.1206].

Reaction of Methyl 6β-*Phenoxyacetamidopenicillanate* (5) *with Trichloroethyl* N-*Chloro*-N-*sodiocarbamate* (4).—To a solution (15 ml) of the ester (5) (1 g, 2.75 mmol) in acetonitrile was added the carbamate (4) (1.40 g, 5.5 mmol). After stirring for 2.5 h, t.l.c. indicated the presence of several products and starting material. The solution was diluted with ethyl acetate and washed twice with water, dried ($MgSO_4$), and concentrated *in vacuo*. The resultant syrup was chromatographed, giving as an inseparable mixture the starting material and a product, and as a more polar component (1*S*,5*R*)-3-phenoxymethyl-6-(2-methyl-1-methoxycarbonylprop-1-enyl)-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-en-7-one (30) (0.10 g, 42.5%), identified by comparison with an authentic sample.

The mixed components, including starting material, were treated in methylene chloride solution with *m*-chloroperbenzoic acid, added dropwise (in methylene chloride) until t.l.c. indicated complete reaction of the major component. The solution was washed with aqueous sodium hydrogen carbonate and then water, dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography of the resultant syrup gave *methyl* 6β-*phenoxyacetamido*-6α-*trichloroethoxyformamidopenicillanate* (26) (0.154 g, 39%) as an oil, $[\alpha]_D^{22}$ +57° (*c* 1.22 in $CHCl_3$), $\nu_{max.}$ (film) 3 300 (amide NH), 1 793 (β-lactam C=O), 1 750 (ester C=O), and 1 690 cm^{-1} (amide C=O), τ 8.60 and 8.54 (each 3 H, s, *gem*-Me_2), 6.20 (3 H, s, OMe), 5.46 (1 H, s, 3-H), 5.41 (2 H, s, OCH_2CCl_3), 5.26 (2 H, s, $PhOCH_2$), 4.21 (1 H, s, 5-H), 3.20—2.50 (6 H, m, aromatic and NH), and 1.88br (1 H, s, NH) (Found: M^+, 553.0216. $C_{20}H_{22}{}^{35}Cl_3N_4O_7S$ requires M, 553.0244). The more polar constituent was eluted and shown by comparison with an authentic sample to be methyl 6β-phenoxyacetamidopenicillanate (*S*)-*S*-oxide (14), derived by oxidation of starting material.

The reaction of the ester (5) (3.0 g, 8.25 mmol) in dimethylformamide (30 ml) with the carbamate (4) (7.50 g, 26.5 mmol) over 3 h and oxidative separation as described above gave the product (26) (2.40 g, 82%) and the (*S*)-sulphoxide (14). No oxazolinoazetidinone (30) was detected.

Removal of the Trichloroethoxyformyl Group in 6β-*Phenoxyacetamido*-6α-*trichloroethoxyformamidopenicillanate* (26).—A solution of the penicillanate (26) (0.50 g, 0.90 mmol) in methanol–glacial acetic acid (25 ml; 25 : 75 v/v) at 0 °C was stirred for 2 h with zinc dust (0.50 g), filtered, diluted with ethyl acetate, washed with aqueous sodium hydrogen carbonate and water, and dried ($MgSO_4$). Evaporation *in vacuo* gave an oil (0.17 g). In a parallel reaction in dimethylformamide–glacial acetic acid (26) (1.0 g, 1.81 mmol), treatment with zinc dust (1.0 g) and work-up as above gave an oil (0.31 g) identical in composition with the oil obtained from the methanol–glacial acetic acid–zinc reaction. The neutral products from each reaction were combined, as were the hydrogen carbonate extracts.

Column chromatography of the combined neutral products gave as the most polar constituent *methyl* 6α-*amino*-6β-*phenoxyacetamidopenicillanate* (33) (0.20 g, 20%) as an oil, $[\alpha]_D^{22}$ +109° (*c* 0.85 in $CHCl_3$), $\nu_{max.}$ (film) 3 320 (amide and amine NH), 1 795 (β-lactam C=O), 1 750 (ester C=O) and 1 685 cm^{-1} (amide C=O), τ 8.63 and 8.60 (each 3 H, s, *gem*-Me_2), 7.20br (2 H, s, NH), 6.26 (3 H, s, OMe), 5.55 (1 H, s, 3-H), 5.49 (2 H, s, $PhOCH_2$), 4.55 (1 H, s, 5-H), 3.20—2.45 (5 H, m, aromatic), and 2.13br (1 H, s, NH) (Found: M^+, 379.1198. $C_{17}H_{21}N_3O_5S$ requires M, 379.1202).

The less polar constituents were obtained as an inseparable mixture. Oxidation with *m*-chloroperbenzoic acid removed starting material (5) which had been carried through in trace quantities, and allowed chromatographic isolation of *methyl* 6α-(ββ-*dichloroethoxyformamido*)-6β-*phenoxyacetamidopenicillanate* (32) (0.09 g),obtained from diethyl ether–petroleum as crystals, m.p. 117.5—118°, $[\alpha]_D^{22}$ +83.4° (*c* 0.42 in $CHCl_3$), $\nu_{max.}$ (film) 3 280 (amide NH), 1 783 (β-lactam C=O), 1 740 (ester C=O), and 1 690 cm^{-1} (amide C=O), τ 8.60 and 8.55 (each 3 H, s, *gem*-Me_2), 6.20 (3 H, s, OMe), 5.57 (2 H, d, *J* 6 Hz, OCH_2CHCl_2), 5.49 (1 H, s, 3-H), 5.42 (2 H, s, $PhOCH_2$), 4.26 (1 H, s, 5-H), 4.16 (1 H, t, *J* 6 Hz, OCH_2CHCl_2), 3.20—2.60 (6 H, m, aromatic and NH), and 1.96br (1 H, s, NH) (Found: M^+, 519.0637. $C_{20}H_2{}^{35}Cl_2N_3O_7S$ requires M, 519.0634).

Acidification of the combined hydrogen carbonate extracts with dilute sulphuric acid and extraction with ether gave (2S,-5R,6S)-2-*methoxycarbonyl*-3,3-*dimethyl*-8-*oxo*-6-*phenoxyacetamido*-4-*thia*-1,7-*diazabicyclo*[3.3.0]*octane*-6-*carboxylic acid* (34) (0.44 g, 38%), which was recrystallized from acetone–diethyl ether; m.p. 186—187°, $[\alpha]_D^{22}$ +207° (*c* 0.54 in Me_2CO), $\nu_{max.}$ (KBr), 3 490 3 200, and 3 040 (amide and acid NH and OH), and 1 765, 1 750, 1 730, and 1 665 cm^{-1} (ester, amide, and carboxylic C=O), τ 8.61 and 8.56 (each 3 H, s,

gem-Me_2), 6.24 (3 H, s, OMe), 5.45br (3 H, s, 3-H and PhOCH_2), 4.23 (1 H, 5-H), 3.20—2.60 (5 H, m, PhOCH_2), 1.58br (1 H, s, NH), and 0.60br (1 H, s, CO_2H) (Found: C, 51.05; H, 5.0; N, 9.62; S, 7.95. $C_{18}H_{21}O_7N_3S$ requires C, 51.0; H, 4.95; N, 9.95; S, 7.55%).

Conversion of Methyl 6α-Ethoxyformamido-6β-phenoxyacetamidopenicillanate (9) *into the Spiropenicillanate* (37).—To a solution of the ester (9) (0.50 g, 1.1 mmol) in dry tetrahydrofuran (20 ml) at −78 °C was added phenyl-lithium (0.19 g, 2.2 mmol) in benzene–diethyl ether. The solution was stirred for 5 min, and phosgene was bubbled through. Nitrogen was bubbled through to remove phosgene, and an excess of triethylamine was added. The solution was partitioned between ethyl acetate and water, and the organic phase was dried ($MgSO_4$) and concentrated *in vacuo*, giving a yellow oil containing several constituents (t.l.c.). Crystallization from diethyl ether gave *methyl 1-ethoxycarbonyl-2-oxo-3-phenoxyacetyl-1,3-diazetidine-4-spiro-6′-penicillanate* (37) (0.10 g, 19%) as a cream-coloured solid, m.p. 201—203° (from benzene–diethyl ether) $[\alpha]_D^{22}$ +103° (*c* 1.0 in $CHCl_3$), $\nu_{max.}$ (KBr) 1 858vs (spiro C=O), 1 800s (β-lactam C=O), and 1 750 cm^{-1} (ester and amide C=O), τ 8.66 (3 H, t, *J* 7 Hz, OCH_2CH_3), 8.50 and 8.24 (each 3 H, s, *gem*-Me_2), 6.22 (3 H, s, OMe), 5.65 (2 H, q, *J* 7 Hz, OCH_2CH_3), 5.35 (1 H, s, 3-H), 5.02 (2 H, s, PhOCH_2), 4.10 (1 H, s, 5-H), and 3.20—2.50 (5 H, m, aromatic) (Found: M^+, 477.1206. $C_{21}H_{23}N_3O_8S$ requires *M*, 477.1206.)

The Trichloroethyl Spiropenicillanate (38).—Trichloroethyl 6α-ethoxyformamido-6β-phenoxyacetamidopenicillanate (11) (2.00 g, 3.5 mmol) in ether (50 ml) at −60 °C was treated with phenyl-lithium (0.60 g, 7.0 mmol) in benzene–ether. After stirring for 5 min an excess of phosgene was bubbled through the solution, which after a further 5 min was poured onto aqueous sodium hydrogen carbonate. The organic layer was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give a yellow oil shown by t.l.c. to contain several constituents. *Rapid* chromatography afforded, apart from starting material, *trichloroethyl 1-ethoxycarbonyl-2-oxo-3-phenoxyacetyl-1,3-diazetidine-4-spiro-6′-penicillanate* (38) (0.35 g, 16%), which crystallized from the ethyl acetate–petroleum chromatographic fractions and was recrystallized from ether; m.p. 176—178°, $[\alpha]_D^{22}$ +99° (*c* 1.45 in $CHCl_3$), $\nu_{max.}$ (KBr) 1 855vs (spiro C=O), 1 795s (β-lactam C=O), and 1 780, 1 755, and 1 730 cm^{-1} (ester and amide C=O), τ 8.65 (3 H, t, *J* 7.5 Hz, OCH_2CH_3), 8.40 and 8.20 (each 3 H, s, *gem*-Me_2), 5.63 (2 H, q, *J* 7.5 Hz, OCH_2CH_3), 5.22 (3 H, s, 3-H and CH_2CCl_3), 5.03 (2 H, s, PhOCH_2), 4.10 (1 H, s, 5-H), and 3.25—2.50 (5 H, m, aromatic) (Found: M^+, 593.0189. $C_{22}H_{22}{}^{35}Cl_3N_3O_9S$ requires *M*, 593.0193).

1-Ethoxycarbonyl-2-oxo-3-phenoxyacetyl-1,3-diazetidine-4-spiro-6′-penicillanic Acid (39).—A solution of the trichloroethyl ester (38) (0.09 g, 0.15 mmol) in dimethylformamide–glacial acetic acid at 0 °C was stirred with zinc dust (0.13 g) for 1.75 h, filtered, diluted with ethyl acetate, washed (× 3) with water, dried ($MgSO_4$), and concentrated *in vacuo*. Crystallization from diethyl ether–benzene gave the *penicillanic acid* (39) (0.054 g, 77%), m.p. 91—93° (from diethyl ether), $[\alpha]_D^{22}$ +94° (*c* 0.27 in $CHCl_3$), $\nu_{max.}$ (KBr) 1 860vs (spiro C=O), 1 790s (β-lactam C=O), and 1 750 cm^{-1} (ester, amide, and acid C=O), τ 5.61 (2 H, q, *J* 7 Hz, OCH_2CH_3), 5.35 (1 H, s, 3-H), 4.98 (2 H, s, PhOCH_2), 4.06 (1 H, s, 5-H), 3.20—2.50 (5 H, m, aromatic), and 1.90br (1 H, s, CO_2H) (Found: M^+, 463.1049. $C_{20}H_{21}N_3O_8S$ requires *M*, 463.1049).

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