Studies on Lactams. Part XLII.[1] A Stereoselective Synthesis of Some α-Amido-β-lactams

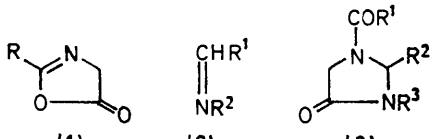
By Ajay K. Bose, M. S. Manhas,* H. P. S. Chawla, and B. Dayal, Department of Chemistry and Chemical Engineering, Stevens Institute of Technology, Hoboken, New Jersey 07030, U.S.A.

N-Alkoxycarbonyl derivatives of glycine have been shown to be useful intermediates for the stereoselective synthesis of β-lactams. These compounds, in the form of acid chloride or mixed anhydride, give β-lactams when treated with imines in the presence of triethylamine. Monocyclic β-lactams and penam analogues are formed in 10—20% yield whereas cepham analogues are obtained in 60—70% yield. In some instances, imidazolidinones were formed instead of β-lactams. The protecting group can be removed under mild conditions without scission of the four-membered ring, to give α-amino-β-lactams.

We report here the details of the synthesis [2] of some α-amido-β-lactams by condensation of benzoyloxycarbonylglycyl chloride with imines, and the extension of this approach to a variety of products of this type.

The use of α-azidoacyl chlorides for the formation of α-azido-β-lactams from acyclic and cyclic imines [3] and thioimidates [4] was initiated some years ago, and has been applied to the total synthesis of 6-*epi*-penicillin V methyl ester.[5] Other laboratories have utilized azidoacetyl chloride for the total synthesis of penicillins,[6] cephalosporins,[7,8] and analogues. The mechanism and the steric course of the reaction are not well understood.[9] Often mixtures of *cis*- and *trans*-β-lactams are obtained. A synthesis with better steric control was therefore desirable. Furthermore, azidoacetyl chloride may decompose explosively during purification by distillation under reduced pressure. An alternative to the azido-group as the progenitor of an amino- or amido-group was thus an attractive goal.[10]

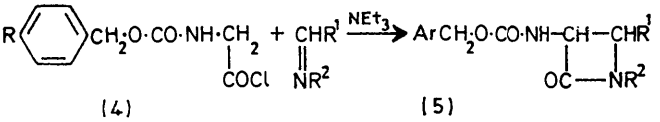
Direct synthesis of α-phenoxyacetamido-β-lactams from imines appeared impractical. An azlactone is formed when attempts are made to prepare the acid chloride from an α-acylamino-acid. The reaction of azlactones (1) with imines (2) has been reported to produce imidazolidinones (3) rather than β-lactams.[11]



(1) (2) (3)

The use of *N*-protected glycyl chlorides, *e.g.* (4a or b), carrying protecting groups which can be easily cleaved under mild acidic conditions to generate an amino-function, appeared promising. It is known that β-lactams are more stable under acidic than under basic conditions. Hitherto there has been only a limited and unsuccessful attempt [12] to construct a β-lactam from benzyloxycarbonylglycyl chloride and an imine. Our efforts have been more successful.

α-Amido-β-lactams.—One-step synthesis of 3-amido-azetidin-2-ones of type (5) was achieved by the reaction of an acid chloride of type (4) with an imine in the

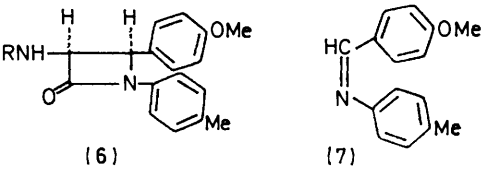


(4) (5)

a; R = H

b; R = NO_2

presence of triethylamine. For example, benzyloxycarbonylglycyl chloride (4a), prepared *in situ*, and



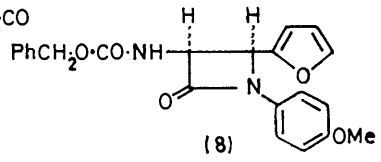
(6) (7)

a; R = $PhCH_2O\cdot CO$

b; R = *p*-$NO_2C_6H_4\cdot CH_2O\cdot CO$

c; R = H

d; R = $PhO\cdot CH_2CO$



(8)

N-*p*-anisylidene-*p*-toluidine (7) gave the *cis*-β-lactam (6a) in 15% yield. Similarly, the *p*-nitro-derivative (4b) gave the β-lactam (6b) in 8% yield, and the β-lactam (8) was prepared by the same method (22% yield).

The same approach was successful for the synthesis of bicyclic β-lactams. The thiazoline (11) gave an 11% yield of the 6-amidopenam (12). The yield was much

[1] Part XLI, A. K. Bose, J. C. Kapur, and M. S. Manhas, *Synthesis*, 1974, 891.

[2] Preliminary report, A. K. Bose, H. P. S. Chawla, B. Dayal, M. S. Manhas, *Tetrahedron Letters*, 1973, 2503.

[3] A. K. Bose and B. Anjaneyulu, *Chem. and Ind.*, 1966, 903.

[4] A. K. Bose, B. Dayal, H. P. S. Chawla, and M. S. Manhas, *Tetrahedron Letters*, 1972, 2823.

[5] A. K. Bose, G. Spiegelman, and M. S. Manhas, *J. Amer. Chem. Soc.*, 1968, **90**, 4506.

[6] (*a*) P. Claes, A. Vlietinck, H. Vanderhaege, and S. Toppet, *J.C.S. Perkin I*, 1973, 932; (*b*) R. A. Firestone, N. S. Maciejewicz, R. W. Ratcliffe, and B. G. Christensen, *J. Org. Chem.*, 1974, **39**, 437.

[7] R. W. Ratcliffe and B. G. Christensen, *Tetrahedron Letters*, 1973, 4649, 4653.

[8] J. A. Edwards, A. Guzman, R. Johnson, P. J. Beeby, and J. H. Fried, *Tetrahedron Letters*, 1974, 2031.

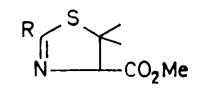
[9] A. K. Bose, Y. H. Chiang, and M. S. Manhas, *Tetrahedron Letters*, 1972, 4091.

[10] See also (*a*) J. C. Sheehan and G. D. Laubach, *J. Amer. Chem. Soc.*, 1951, **73**, 4752, 4756; (*b*) J. C. Sheehan and E. J. Corey, *ibid.*, p. 4756.

[11] C. W. Bird, *Tetrahedron Letters*, 1964, 609.

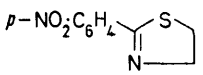
[12] J. C. Sheehan and E. J. Corey, *Org. Reactions*, 1957, **9**, 388.

greater when a dihydrothiazine (13) was used as the imine component; the 7-amidoacephams (14a and b)

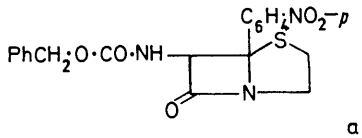


(9) R = Ph
(10) R = H

(13)
a; R = Ph
b; R = *p*-$NO_2C_6H_4$



(11)



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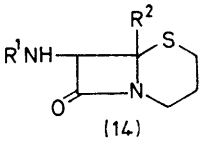
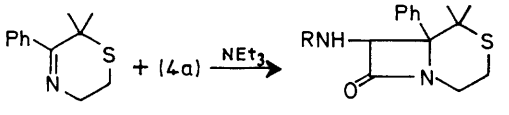


(14)

	R^1	R^2
a;	$PhCH_2O\cdot CO$	Ph
b;	$PhCH_2O\cdot CO$	*p*-$NO_2C_6H_4$
c;	$PhO\cdot CH_2\cdot CO$	Ph
d;	$PhO\cdot CH_2\cdot CO$	*p*-$NO_2C_6H_4$
e;	$PhO\cdot CH_2\cdot CO$	*p*-$NH_2C_6H_4$
f;	$Bu^tO\cdot CO$	Ph
g;	$Bu^tO\cdot CO$	*p*-$NO_2C_6H_4$

were obtained in 60—70% yield. The greater ease of formation of 7-substituted cephams than of 6-substituted penams from imines has been observed with other acid chlorides.[7,8] The imine (15) and the glycyl chloride (4a) gave a high yield of a bicyclic β-lactam (16a) prepared earlier by a different method.[13]



(15) (16)

a; R = $PhCH_2O\cdot CO$
b; R = $PhO\cdot CH_2CO$

t-Butoxycarbonylglycine was a convenient substitute for (4a and b). Because the preparation of t-butoxycarbonylglycyl chloride did not appear practicable, the free acid was converted into the mixed carbonic acid anhydride (17) with isobutyl chloroformate. Reactions of the anhydride with the imines (13a and b) gave satisfactory yields of the cephams (14f and g).

$$Bu^tO\cdot CO\cdot NH\cdot CH_2CO\cdot O\cdot CO_2Bu^i$$

(17)

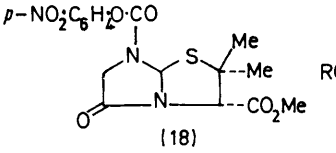
α-Amino-β-lactams.—The protecting groups from the α-amido-β-lactams could be removed under mild conditions without ring cleavage. Catalytic hydrogenation, commonly used for removing a benzyloxycarbonyl group, is known to be without effect on the β-lactam ring. Treatment of (6a and b) with hydrobromic acid in acetic acid led readily to the 3-aminoazetidin-2-one (6c) hydrobromide in very high yield. Acylation of (6c) with phenoxyacetyl chloride gave the 3-phenoxyacetamidoazetidin-2-one (6d). The t-butoxycarbonyl groups from (14f and g) were removed in high yield by treatment with either trifluoroacetic acid or hydrobromic acid in acetic acid. Acylation of the products with phenoxyacetyl chloride provided the 7-phenoxyacetamidocephams (14c and d).

Stereochemistry of β-Lactam Formation.—β-Lactam formation from imines often leads to *trans*-[14] or mixtures of *cis*- and *trans*-products.[13] The synthesis described here led to a single isomer in each case. In the ^1H n.m.r. spectra of the monocyclic azetidin-2-ones the 3-H and 4-H signals were superposed on other signals, making it difficult to deduce the stereochemistry from the size of the coupling constant. However use of the shift reagent Eu(fod)$_3$ enabled $J_{3,4}$ to be evaluated as 5 Hz, indicative of *cis*-stereochemistry.[13,14]

The ^1H n.m.r. spectrum of the 3-phenoxyacetamidoazetidin-2-one (6d) was simplified by deuterium exchange of the amide proton with $NaDCO_3$ solution; the quartet for H-3 and H-4 with J 5.5 Hz established the *cis*-stereochemistry. The related β-lactams (6a—c) must also be *cis* since no epimerization is involved.

The stereochemistry of the 6-aminopenam and 7-amidocepham derivatives synthesized could not be determined from their ^1H n.m.r. spectra. On the basis of analogy it is likely that these bicyclic β-lactams have the amide side chain *trans* to the sulphur atom.[15]

Attempted Penicillin Synthesis.—As a further application of the new synthesis, the possibility of preparing a penicillin in one step was investigated. The reaction of *p*-nitrobenzyloxycarbonylglycyl chloride with the thiazoline ester (10) in the presence of triethylamine proceeded in 80% yield to give a product which had the expected molecular weight (mass spectrum). The i.r. and ^1H n.m.r. spectra indicated, however, that the product was the bicyclic imidazolidinone (18). The rearrangement



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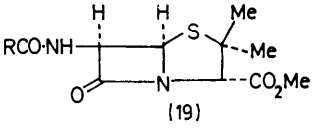

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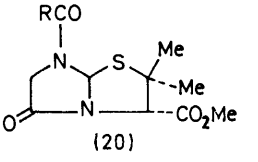
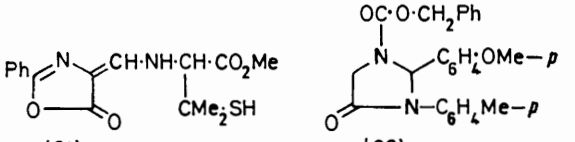


(20)

of the penicillin (19) to penillonic acid (20) is known to take place readily.[11,16]

[13] A. K. Bose, V. Sudarsanam, B. Anjaneyulu, and M. S. Manhas, *Tetrahedron*, 1969, **25**, 1191, and subsequent papers in this series.
[14] H. B. Kagan, J. J. Basselier, and J. L. Luche, *Tetrahedron Letters*, 1964, 941.
[15] A. K. Bose, M. S. Manhas, J. S. Chib, H. P. S. Chawla, and B. Dayal, *J. Org. Chem.*, 1974, **39**, 2877.
[16] 'The Chemistry of Penicillin,' ed. H. T. Clarke, J. R. Johnson, and R. Robinson, Princeton University Press, Princeton, New Jersey, 1949.

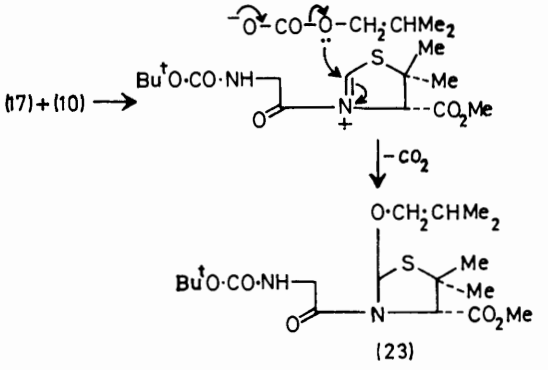
In view of the fact that the thiazoline (10) gave a poor yield of a bicyclic β-lactam in the reaction with azidoacetyl chloride,[5] it is unlikely that a penicillin (19) is formed first in the reaction of (10) with *p*-nitrobenzyloxycarbonylglycyl chloride and that this rearranges to the penillonic acid derivative (20). The product (18) is probably formed directly in place of the penicillin by an alternative route. Jansen and Robinson [17] have shown the ready formation of methyl phenylpenicillenate (21) and methyl phenylpenillonate (20; R = Ph) from (1; R = Ph) and the thiazoline (10) under different sets of experimental conditions. However, *N*-benzyloxycarbonylglycyl chloride is not known to form an oxazolone. Further studies are required to establish the pathway to (18) and to explain the difference between the thiazolines (9)—(11) in their reactivity towards *N*-benzyloxycarbonylglycyl chloride. In this context, it is interesting that the imidazolidinone (22) was the product of the reaction of *p*-anisylidene-*p*-toluidine (7) with benzyloxycarbonylglycine and phosphoryl chloride in dimethylformamide under the conditions used by Ziegler and his co-workers [18] for β-lactam synthesis. Previous workers had reported the formation of this type of compound from (4a) and *N*-benzylideneaniline.[12]



(21)

(22)

Condensation of the t-butoxycarbonylglycyl derivative (17) with the imine (10) did not give the expected penicillin. The product was devoid of a β-lactam ring as indicated by the absence of i.r. absorption at 1 770—1 780 cm^{-1}. The n.m.r. spectrum showed the presence of an isobutyl group. Two structures (23) and (24) appeared plausible. The presence of only three i.r. bands in the carbonyl region combined with elemental

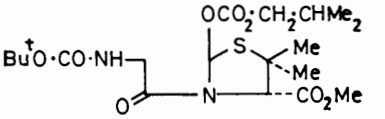


(23)

SCHEME

and mass spectral analysis ruled out the latter (24). The n.m.r. spectrum was fully consistent with structure (23), the formation of which may be envisaged as shown in the Scheme.

Conclusions.—Our observations demonstrate that protected glycine derivatives of types (4) and (17) can be used for the synthesis of α-amido-β-lactams from various imines. The mechanism and the conditions



(24)

promoting side reactions have not been established. The formation of *cis*-β-lactams from Schiff bases, although in low yield, is of preparative interest. The yield of penam derivatives is low. However this one step method is of practical value for preparing 7-amidocepham derivatives such as (14).

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer Infracord spectrophotometer. ^1H N.m.r. spectra were recorded on a Varian A-60A spectrometer operating at 60 MHz with Me_4Si as internal standard. Mass spectra were recorded on a Hitachi–Perkin-Elmer RMU-7 spectrometer at 70 eV by use of an all-glass inlet system.

cis-3-*Benzyloxycarbonylamino*-4-p-*methoxyphenyl*-1-p-*tolylazetidin*-2-*one* (6a).—To a vigorously stirred suspension of benzyloxycarbonylglycine (4.18 g, 0.02 mol) in anhydrous ether (250 ml) cooled to 0 °C was added phosphorus pentachloride (4.17 g, 0.02 mol). After 0.5 h, when a clear solution had been obtained, a mixture of *p*-methoxybenzylidene-*p*-toluidine (4.50 g, 0.02 mol) and triethylamine (10.1 g, 0.1 mol) in anhydrous ether (100 ml) was added dropwise over 2 h. The mixture was stirred at 0—5 °C for an additional 3 h. Ether was distilled off and the residue was dissolved in dichloromethane. The solution was washed successively with water, aqueous sodium hydrogen carbonate, and water again and then dried ($MgSO_4$) and evaporated. The residue was chromatographed over Florisil [benzene–hexane (1 : 1) as eluant]. Crystallization from benzene gave the β-*lactam* (1.28 g, 15%), m.p. 177—178°; $\nu_{max.}$ (Nujol) 3 310 (NH), 1 760 (β-lactam C=O), and 1 695 cm^{-1} (NH·CO_2); τ ($CDCl_3$) 2.60—3.2 (13 H, m), 4.60—4.85 (3 H, m), 5.03 (2 H, s), 6.24 (3 H, s), and 7.73 (3 H, s) (Found: C, 72.4; H, 6.0; N, 6.9. $C_{25}H_{24}N_2O_4$ requires C, 72.1; H, 5.8; N, 6.75%).

cis-4-p-*Methoxyphenyl*-3-p-*nitrobenzyloxycarbonylamino*-1-p-*tolylazetidin*-2-*one* (6b).—This was prepared from *p*-nitrobenzyloxycarbonylglycine and *p*-anisylidene-*p*-toluidine as described for (6a) in 8% yield; m.p. 207°; $\nu_{max.}$ (Nujol) 3 310 (NH), 1 758 (β-lactam C=O), and 1 697 cm^{-1} (NH·CO_2); τ [$(CD_3)_2SO$] 2.06—2.20 (2 H, m), 2.89—3.40 (10 H, m), 4.83—5.17 (5 H, m), 6.32 (3 H, s), and 7.82 (3 H, s).

cis-4-p-*Methoxyphenyl*-3-*phenoxyacetamido*-1-p-*tolylazetidin*-2-*one* (6d).—A solution of the β-lactam (6a) (0.416 g, 0.001 mol) and 32% hydrogen bromide in acetic acid (4 ml) was stirred at room temperature. After evolution of carbon dioxide ceased, the mixture was stirred for 10 min more. An excess of anhydrous ether was added. 3-Amino-4-*p*-methoxyphenyl-1-*p*-tolylazetidin-2-one (6c)

[17] A. B. Jansen and R. Robinson, *Monatsh.*, 1967, **98**, 1017.
[18] E. Ziegler, T. Wimmer, and H. Mittelbach, *Monatsh.*, 1968, **99**, 2128.

hydrobromide precipitated out and afforded crystals (0.32 g, 86%), m.p. 152° (from ethanol–ether); $\nu_{max.}$ (Nujol) 3 452 (NH_2) and 1 754 cm^{-1} (β-lactam C=O).

To a suspension of the amine (6c) hydrobromide (0.30 g, 0.0008 mol) in dichloromethane (50 ml) was added triethylamine (3 ml) followed dropwise by phenoxyacetyl chloride (0.15 g, 0.0009 mol) and the mixture was stirred at room temperature for 6 h. After washing with aqueous sodium hydrogen carbonate, the solution was washed with water, dried ($MgSO_4$), and evaporated. Crystallization of the residue from benzene provided the *product* (6d) (0.28 g, 84%), m.p. 206—207°; $\nu_{max.}$ (Nujol) 3 321 (NH), 1 769 (β-lactam C=O), and 1 678 cm^{-1} (CONH); τ ($CDCl_3$) 2.65—3.50 (14 H, m, aromatic and CONH), 4.23 (1 H, dd, *J* 5.5 and 9.0 Hz, H-3; converted into a doublet *J* 5.5 Hz, on equilibration with $NaDCO_3$ solution), 4.66 (1 H, d, *J* 5.5 Hz, H-4), 5.58 and 5.88 (2 H, ABq, *J* 11.5 Hz, O·CH_2·CO), 6.26 (3 H, s, OCH_3), and 7.72 (3 H, s, CH_3); M^+ 416 (Found: C, 72.4; H, 5.8; N, 6.8. $C_{25}H_{24}N_2O_4$ requires C, 72.1; H, 5.8; N, 6.75%).

cis-3-*Benzyloxycarbonylamino*-4-(2-*furyl*)-1-p-*methoxyphenylazetidin*-2-*one* (8).—This β-*lactam* was obtained essentially by the procedure described for (6a) from benzyloxycarbonylglycine and furfurylidene-*p*-anisidine in 22% yield; m.p. 175°; $\nu_{max.}$ (Nujol) 3 295 (NH), 1 757 (β-lactam C=O), and 1 690 cm^{-1} (NH·CO_2); τ ($CDCl_3$) 2.60—3.65 (12 H, m), 4.45—4.67 (3 H, m), 4.95 (2 H, s), and 6.27 (3 H, s) (Found: C, 67.55; H, 5.35; N, 7.6. $C_{22}H_{20}N_2O_5$ requires C, 67.35; H, 5.15; N, 7.15%).

6-*Benzyloxycarbonylamino*-5-p-*nitrophenylpenam* (12).—The *penam* was prepared from benzyloxycarbonylglycyl chloride and 2-*p*-nitrophenyl-Δ^2-thiazoline [19] in the presence of triethylamine as described for (6a) in 11% yield; m.p. 150°; $\nu_{max.}$ (Nujol) 3 205 (NH), 1 788 (β-lactam CO), and 1 689 cm^{-1} (NH·CO_2); τ ($CDCl_3$) 1.93 (2 H, d, *J* 9 Hz, H *ortho* to NO_2), 2.52—2.82 (7 H, m, aromatic H), 4.30 (1 H, d, *J* 9.0 Hz, NH·CO_2), 4.67 (1 H, d, *J* 9.0, H-6), 5.08 (2 H, s, $PhCH_2$·O), 5.52—5.81 (1 H, m, H-3), 6.5—7.0 (3 H, m, H-3 and -2) (Found: C, 54.1; H, 5.85; N, 11.4. $C_{17}H_2N_3O_5S$ requires C, 53.8; H, 5.6; N, 11.05%).

7-*Benzyloxycarbonylamino*-6-*phenylcepham* (14a).—To a solution of benzyloxycarbonylglycyl chloride [from benzyloxycarbonylglycine (4.18 g) and phosphorus pentachloride (4.17 g)] in anhydrous ether was added a mixture of 5,6-dihydro-2-phenyl-4*H*-1,3-thiazine [20] (3.54 g, 0.02 mol) and triethylamine (10.1 g, 0.1 mol) in ether. After stirring at room temperature for 16 h the mixture was worked up in the usual manner and the residue chromatographed over Florisil with benzene–dichloromethane as eluant to furnish the *cepham* (14a) (4.4 g, 60%); m.p. 124—125°; $\nu_{max.}$ (Nujol) 3 300 (NH), 1 761 (β-lactam C=O), and 1 715 cm^{-1} (NH·CO_2); τ ($CDCl_3$) 2.5—2.7 (10 H, m), 4.69 (2 H, s), 5.06 (2 H, s), 5.71—6.06 (1 H, m), 6.66—7.41 (3 H, m), and 8.0—8.30 (2 H, m) (Found: C, 65.35; H, 5.4; N, 7.6. $C_{20}H_{20}N_2O_3S$ requires C, 65.2; H, 5.45; N, 7.6%).

7-*Phenoxyacetamido*-6-*phenylcepham* (14c).—7-Amino-6-phenylcepham hydrobromide was obtained in 70% yield by treatment of (14a) with hydrogen bromide in acetic acid under the conditions described earlier; $\nu_{max.}$ (Nujol) 3 390 (NH_2) and 1 748 cm^{-1} (β-lactam C=O).

Treatment of 7-amino-6-phenylcepham with phenoxyacetyl chloride gave the amide (14c) [13] (85%); m.p. 151—152°; $\nu_{max.}$ (Nujol) 3 289 (NH), 1 754 (β-lactam C=O), and 1 684 cm^{-1} (amide C=O); τ ($CDCl_3$) 2.31—3.56 (11 H, m), 4.49 (1 H, d, *J* 9 Hz), 5.69—6.01 (2 H, ABq, *J* 15 Hz), 6.61—7.50 (3 H, m), and 7.90—8.40 (2 H, m); M^+ 368.

7-*Benzyloxycarbonylamino*-6-p-*nitrophenylcepham* (14b).—This *cepham* was prepared by the reaction of benzyloxycarbonylglycyl chloride and 5,6-dihydro-2-*p*-nitrophenyl-4*H*-1,3-thiazine [13] in 68% yield; m.p. 176—177°; $\nu_{max.}$ (Nujol) 3 268 (NH), 1 773 (β-lactam C=O), and 1 684 cm^{-1} (NH·CO_2); τ ($CDCl_3$) 2.12 (2 H, d, *J* 9.0 Hz), 2.58—3.05 (7 H, m), 4.40 (1 H, d, *J* 8 Hz), 4.92 (1 H, d, *J* 8 Hz; singlet after equilibration with $NaDCO_3$ solution), 5.24 (2 H, s), 5.83—6.18 (1 H, m), 6.83—7.54 (3 H, m), and 8.04—8.32 (2 H, m) (Found: C, 58.3; H, 4.9; N, 9.85. $C_{20}H_{19}N_3O_5S$ requires C, 58.1; H, 4.65; N, 10.15%).

6-p-*Nitrophenyl*-7-*phenoxyacetamidocepham* (14d).—Treatment of (14b) with 32% hydrogen bromide in acetic acid gave 7-amino-6-*p*-nitrophenylcepham acetate; m.p. 179—181°; $\nu_{max.}$ (Nujol) 3 226 (NH_2), 1 767 (β-lactam C=O), and 1 712 (AcO^-; disappeared on addition of a drop of morpholine); τ (D_2O) 1.53 (2 H, d, *J* 8.5 Hz), 1.97 (2 H, d, *J* 8.5 Hz), 4.81 (1 H, s), 5.50—5.89 (1 H, m), 6.32—6.60 (1 H, m), 7.05—7.30 (2 H, m), 7.85 (3 H, s), and 7.87—8.17 (2 H, m).

Reaction of phenoxyacetyl chloride with 7-amino-6-*p*-nitrophenylcepham acetate in the presence of triethylamine gave the *cepham* (14d) (75%); m.p. 174—175°; $\nu_{max.}$ (Nujol) 3 236 (NH), 1 786 (β-lactam C=O), and 1 667 cm^{-1} (amide C=O); M^+ 413 (Found: C, 58.35; H, 5.0; N, 9.9. $C_{20}H_{19}N_3O_5S$ requires C, 58.1; H, 4.65; N, 10.15%).

6-p-*Aminophenyl*-7-*phenoxyacetamidocepham* (14e).—A solution of 6-*p*-nitrophenyl-7-phenoxyacetamidocepham (14d) (1.24 g, 0.003 mol) in ethyl acetate (200 ml) was hydrogenated over Adams catalyst at 45 lb in^{-2} for 8 h. The catalyst was filtered off and the filtrate concentrated. The residue was crystallized from benzene–hexane to give the *cepham* (14e) (0.92 g, 82%); m.p. 154—155°; $\nu_{max.}$ (Nujol) 3 356, 3 236 (NH_2, amide NH), 1 757 (β-lactam C=O), and 1 684 cm^{-1} (amide C=O); *m/e* 383 (M^+), 232 (M^+ — PhO·CH_2·CO·NH), 192 ([2-*p*-aminophenyl-5,6-dihydro-4*H*-1,3-thiazine]$^+$), and 107 ($PhOCH_2^+$) (Found: C, 62.8; H, 5.75; N, 11.2. $C_{20}H_{21}N_3O_3S$ requires C, 62.65; H, 5.5; N, 10.95%).

6-*Phenyl*-7-*t*-*butoxycarbonylaminocepham* (14f).—To a suspension of t-butoxycarbonylglycine (3.50 g, 0.02 mol) and triethylamine (2.02 g, 0.02 mol) in anhydrous tetrahydrofuran (200 ml), cooled to −10 °C, was added dropwise isobutyl chloroformate (2.73 g, 0.02 mol) and the mixture was stirred for 30 min till the solution became clear. A mixture of 5,6-dihydro-2-phenyl-4*H*-1,3-thiazine (2.66 g, 0.015 mol) and triethylamine (1.52 g, 0.015 mol) in tetrahydrofuran (100 ml) was then added over 2 h. The mixture was stirred for a further 2 h at −10 °C and then at room temperature for 10 h. Tetrahydrofuran was removed by distillation under reduced pressure and the residue was taken up in dichloromethane. The solution was washed with aqueous sodium hydrogen carbonate followed by water, dried ($MgSO_4$), and evaporated. The crude solid so obtained was crystallized from dichloromethane–hexane to give the *cepham* (14f) (3.2 g, 64%); m.p. 134—135°; $\nu_{max.}$ (Nujol) 3 344 (NH), 1 761 (β-lactam C=O), and 1 712 cm^{-1} (NH·CO); τ ($CDCl_3$) 2.25—2.68 (5 H, m), 4.6 (1 H, d, *J* 9 Hz), 5.67—6.0 (1 H, m), 6.50—7.40 (3 H, m), 7.92—8.30 (2 H, m), and 8.73 (9 H, s) (Found: C, 60.95; H, 6.45; N, 8.55. $C_{17}H_{22}N_2O_3S$ requires C, 61.05; H, 6.65; N, 8.4%).

7-*Phenoxyacetamido*-6-*phenylcepham* (14c).—The cepham

[19] G. L. Schmir, *J. Amer. Chem. Soc.*, 1965, **87**, 2743.
[20] A. Lawson and C. E. Searle, *J. Chem. Soc.*, 1964, 788.

(14f) (1.67 g, 0.005 mol) was stirred with 32% hydrogen bromide in acetic acid (5 ml) at room temperature. After the evolution of carbon dioxide had ceased, the mixture was stirred for another 10 min. An excess of anhydrous ether was added, the 7-amino-6-phenylcepham hydrobromide which precipitated was taken up in dichloromethane, and triethylamine (0.5 g, 0.005 mol) was added, followed by phenoxyacetyl chloride (0.85 g, 0.005 mol). The mixture was stirred at room temperature for 6 h, washed with aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated. The residue was crystallized from dichloromethane–hexane to give the cepham (14c) (1.25 g, 68%), m.p. 151—152°.[13]

6-p-*Nitrophenyl*-7-*t-butoxycarbonylaminocepham* (14g).—The *cepham* (14g) was obtained in 60% yield from t-butoxycarbonylglycine and 5,6-dihydro-2-*p*-nitrophenyl-4*H*-1,3-thiazine [13] by the procedure described for (14f); m.p. 195°; $\nu_{max.}$ (Nujol) 3 300, 1 767, and 1 712 cm^{-1}; τ ($CDCl_3$) 1.66 (2 H, d, *J* 9 Hz), 2.25 (2 H, d, *J* 9 Hz), 4.76 (2 H), 5.60—5.96 (1 H, m), 6.60—7.39 (3 H, m), 7.90—8.20 (2 H, m), and 8.71 (9 H) (Found: C, 54.0; H, 5.85; N, 11.4. $C_{17}H_{21}N_3O_5S$ requires C, 53.85; H, 5.6; N, 11.1%).

6-p-*Nitrophenyl*-7-*phenoxyacetamidocepham* (14d).—This was synthesized in 65% yield by treating (14g) with hydrogen bromide in acetic acid followed by phenoxyacetyl chloride in the presence of triethylamine as described for (8d); m.p. 174—175°. It was identical (mixed m.p., i.r., and n.m.r.) with the compound obtained from (6c).

7-*Benzyloxycarbonylamino*-5,5-*dimethyl*-6-*phenyl*-4-*thia*-1-*azabicyclo*[4.2.0]*octan*-8-*one* (16a).—The β-lactam (16a) was prepared by condensation of benzyloxycarbonylglycyl chloride and 5,6-dihydro-2,2-dimethyl-3-phenyl-1,4-thiazine [13] in 65% yield; m.p. 178°; $\nu_{max.}$ (Nujol) 3 289 (NH), 1 745 (β-lactam C=O), and 1 712 cm^{-1} (NHCO); τ ($CDCl_3$) 2.62—2.75 (10 H, m), 4.72 (2 H), 4.79 and 5.03 (2 H, ABq, *J* 12.5 Hz), 5.70—6.05 (1 H, m), 6.27—7.56 (3 H, m), and 8.20 (3 H, s) (Found: C, 66.4; H, 6.0; N, 6.85. $C_{22}H_{24}N_2O_3S$ requires C, 66.65; H, 6.0; N, 7.05%).

5,5-*Dimethyl*-7-*phenoxyacetamido*-6-*phenyl*-4-*thia*-1-*azabicyclo*[4.2.0]*octan*-8-*one* (16b).—The amine hydrobromide obtained by treating (16a) with hydrogen bromide in acetic acid [m.p. 196—197°; $\nu_{max.}$ (Nujol) 3 333 (NH_2) and 1 754 cm^{-1} (β-lactam C=O)] was treated with phenoxyacetyl chloride and triethylamine to give the *product* (16b) in 68% overall yield; m.p. 173—174°; [13] $\nu_{max.}$ (Nujol) 3 247 (NH), 1 773 (β-lactam C=O), and 1 661 cm^{-1} (amide C=O); τ ($CDCl_3$) 2.52—3.45 (11 H, m), 4.29 (1 H, d, *J* 10 Hz), 5.52 (2 H, s), 5.48—7.57 (4 H, m), 8.09 (3 H, s), and 8.72 (3 H, s); M^+ 396.

Methyl 3,3-*Dimethyl*-6-(p-*nitrobenzyloxycarbonyl*)-8-*oxo*-4-*thia*-1,6-*diazabicyclo*[3.3.0]*octane*-2-*carboxylate* (18).—To a refluxing solution of *p*-nitrobenzyloxycarbonyl chloride [21] (5.45 g, 0.002 mol) and methyl 5,5-dimethyl-Δ²-thiazoline-4-carboxylate [5] (3.46 g, 0.002 mol) in anhydrous dichloromethane (500 ml) was added dropwise a solution of triethylamine (2.02 g, 0.02 mol) in dichloromethane over 6 h and the mixture was refluxed for another 20 h. Dichloromethane was removed by distillation under reduced pressure and the residue was treated with anhydrous tetrahydrofuran. Triethylamine hydrochloride was filtered off and the filtrate was concentrated. The residue was crystallized from benzene–hexane to give the product (18) (6.52 g, 80%), m.p. 127—128°; $\nu_{max.}$ (Nujol) 1 745, 1 730, and 1 701 cm^{-1}; τ($CDCl_3$) 1.81 (2 H, d, *J* 9 Hz, H *ortho* to NO_2), 2.50 (2 H, d, *J* 9 Hz, H *meta* to NO_2), 2.96 (1 H, s, H-5), 4.72 (2 H, s, CH_2O), 5.15 (1 H, s, H-3), 5.65 and 5.95 (2 H, ABq, *J* 15 Hz), 6.21 (3 H, s, OCH_3), 8.47 (3 H, s, 3-Me), and 8.53 (3 H, s, 3-Me); M^+ 409.

1-*Benzyloxycarbonyl*-2-p-*methoxyphenyl*-3-p-*tolylimidazolidin*-4-*one* (22).—To anhydrous dimethylformamide (40 ml) cooled in an ice-bath was slowly added, with stirring, phosphoryl chloride (4.89 g, 0.03 mol), followed dropwise by a mixture of benzyloxycarbonylglycine (4.18 g, 0.02 mol) and *p*-anisylidene-*p*-toluidine (4.5 g, 0.02 mol) in dimethylformamide (15 ml). The mixture was stirred at room temperature for 15 h, poured onto cold water, and extracted with dichloromethane. The extract was washed repeatedly with water, dried ($MgSO_4$), and evaporated. Trituration with ethanol provided a solid which on crystallization from dichloromethane–hexane gave the product (22) (4.95 g, 59%), m.p. 132°; $\nu_{max.}$ (Nujol) 1 695 and 1 681 cm^{-1}; τ ($CDCl_3$) 2.66—3.28 (13 H, m, aromatic), 3.55 (1 H, s, H-2), 4.76 and 5.0 (2 H, ABq, *J* 12 Hz, N·CH_2·CO), 5.63 (2 H, s, CO_2·CH_2), 6.26 (3 H, s, OCH_3), and 7.77 (3 H, s, CH_3); M^+ 416.

2-*Isobutyloxy*-4-*methoxycarbonyl*-5,5-*dimethyl*-3-*t-butoxycarbonylglycylthiazolidine* (23).—A mixture of t-butoxycarbonylglycine (4.37 g, 0.025 mol) and triethylamine (2.5 g, 0.02 mol) in tetrahydrofuran (250 ml) was treated at −10 °C with isobutyl chloroformate (3.40 g, 0.025 mol). A mixture of methyl 5,5-dimethyl-Δ²-thiazoline-4-carboxylate (3.46 g, 0.025 mol) and triethylamine (2.02 g, 0.002 mol) in tetrahydrofuran (100 ml) was then added dropwise. After stirring at room temperature for 10 h, the mixture was filtered and concentrated under vacuum. Chromatography over Florisil with benzene as eluant gave the *product* (23) (4.4 g, 54.5%), m.p. 134—135°; $\nu_{max.}$ (Nujol) 3 367 (NH), 1 724 (CO_2Me), 1 692 (NH·CO_2), and 1 642 cm^{-1} (amide C=O); τ ($CDCl_3$) 3.62 (1 H, s, H-2), 4.66br (1 H, d, NH), 5.27 (1 H, s, H-4), 5.82 (2 H, d, *J* 5 Hz, NH·CH_2·CO; singlet after deuteriation with $NaDCO_3$ solution), 6.20 (3 H, s, OCH_3), 6.59—6.79 (2 H, m, O·CH_2), 7.81—8.17 (1 H, m, CH_2·$CHMe_2$), 8.23 (3 H, s, 5-CH_3), 8.52 (9 H, s, CMe_3), 8.60 (3 H, s, 5-CH_3), and 9.03 (6 H, d, *J* 6 Hz) (Found: C, 53.35; H, 8.1; N, 6.9; S, 8.0. $C_{18}H_{32}N_2O_6S$ requires C, 53.45; H, 8.0; N, 6.95; S, 7.9%).

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[21] F. H. Carpenter and D. T. Gish, *J. Amer. Chem. Soc.*, 1952, **74**, 3818.