Transformations of Penicillin. Part 8.† Preparation of 2-Acetylceph-3-em Derivatives from Carboxy-protected Penicillin *S*-Oxides

By **Maria J. V. de Oliveira Baptista, Anthony G. M. Barrett,* Derek H. R. Barton,* Moopil Girijavallabhan, Richard C. Jennings, John Kelly, Vasiliki J. Papadimitriou, John V. Turner,** and **Norman A. Usher,** Chemistry Department, Imperial College, London SW7 2AY

Carboxylic acids were protected by formation of acylhydrazine or acylhydrazone derivatives. The influence of *N*-substitution on the ease of carboxylic acid regeneration by oxidation under mild conditions is described. Such hydrazine derivatives have been applied in protecting the 3- and 4-carboxy-functions of substituted penicillins and deacetoxycephalosporins. Penicillin G *S*-oxide, protected as the *N'*-diphenylmethylene-*N*-methylhydrazide, was converted into the novel 2-acetyldeacetoxycephalosporin G. The sulphenic acid from pyrolysis of the protected penicillin *S*-oxide was trapped with n-propyl isopropenyl ether to give the 1,2-secopenicillin enol ether derivative. Mercury(II)-nitrate-catalysed hydrolysis gave the corresponding 4-(acetylmethylthio)azetidin-2-one. Ozonolysis of the azetidinone isopropenyl function gave the derived diketone. This on 1,5-diazabicyclo-[4.3.0]non-5-ene-catalysed cyclisation and subsequent dehydration gave the novel protected 2-acetyldeacetoxycephalosporin G.

The protection of carboxylic acids *via* formation of dihydro-heteroaromatic amides is described. Mild oxidation of these derivatives gave the corresponding heteroaromatic amides, which were readily hydrolysed, regenerating the carboxylic acids.

Attention is directed to the use of fluoride anion as a base in penicillin and cephalosporin chemistry.

β-LACTAM derivatives are the most widely used antibiotics. The search for improved antibiotic derivatives of penam (1) and cepham (2) has stimulated the development of new synthetic routes to β-lactams. Since the classical total synthesis of 6-aminopenicillanic acid (3a) by Sheehan,[1] several elegant syntheses have been described. Woodward *et al.*[2] prepared 3-acetoxymethylcephems (4a) from L-cysteine *via* the thiazolidine (5). The key intermediate (5) was, however, more conveniently prepared in several steps from the penicillanic acid (3a). Recently biomimetic routes to penicillins and cephalosporins have been described. Kishi and his co-workers have prepared the 7-methoxy- (4b) [3] and 7-methyl- (4c) [4] cephalosporins from a masked dipeptide precursor. The key step involved a double cyclisation of the thioamide (6) to give the β-lactam (7a). Evaporation of a solution of the derived bromide (7b) in dichloromethane gave 7α-methoxycephem (4b) in 40% yield. Baldwin has reported [5] a stereocontrolled total synthesis of the penicillin (3b). The β-lactam unit was prepared *via* cyclisation of the dipeptide thiazolidine (8) with sodium hydride. The cycloaddition of azidoketens and 6*H*-1,3-thiazine derivatives has been applied in an important total synthesis of cephalosporins.[6] Recent developments in β-lactam antibiotic chemistry are summarised in a review by Sammes.[7]

Since penicillin G (3c) is a cheap starting material, the transformation of the penam (1) into the cepham (2) system constitutes an attractive route to novel cephalosporins. Such an approach conserves the β-lactam unit with correct chirality at C-5 and C-6. On heating the sulphoxide (9) the thiazolidine ring opens giving the sulphenic acid (10).[8] This reactive intermediate can be trapped by reaction with ' soft ' nucleophiles, for example vinyl ethers,[9] keten acetals,[9] thiols,[10] and arenesulphinic acids,[11] or ' soft ' electrophiles, *e.g.* acetylene-mono- or -di-carboxylic esters,[9] to give sulphide (11) or sulphoxide (12) derivatives, respectively (Scheme 1). If the sulphide (11) is ozonolysed it should be possible by suitable choice of nucleophile to cyclise the derived oxo-sulphide (13) and thus to prepare novel 2-substituted cephalosporins (14) (Scheme 2). The final step is the regeneration of the acid function in the cephem (14).

† Part 7, ref. 12

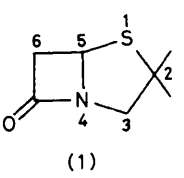
[1] J. C. Sheehan and K. R. Henery-Logan, *J. Amer. Chem. Soc.*, 1962, **84**, 2983.
[2] R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbrüggen, *J. Amer. Chem. Soc.*, 1966, **88**, 852.
[3] S. Nakatsuka, H. Tanino, and Y. Kishi, *J. Amer. Chem. Soc.*, 1975, **97**, 5008.
[4] S. Nakatsuka, H. Tanino, and Y. Kishi, *J. Amer. Chem. Soc.*, 1975, **97**, 5010.
[5] J. E. Baldwin, M. A. Christie, S. B. Haber, and L. I. Kruse, *J. Amer. Chem. Soc.*, 1976, **98**, 3045.
[6] R. W. Ratcliffe and B. G. Christensen, *Tetrahedron Letters*, 1973, 4645, 4649, 4653; R. A. Firestone, N. S. Maciejewicz, R. W. Ratcliffe, and B. G. Christensen, *J. Org. Chem.*, 1974, **39**, 437.
[7] P. G. Sammes, *Chem. Rev.*, 1976, **76**, 113.
[8] R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, 1969, **91**, 1401.
[9] I. Ager, D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, G. H. Hewitt, B. E. Looker, A. Mowatt, C. A. Robson, and W. G. E. Underwood, *J.C.S. Perkin I*, 1973, 1187.
[10] R. D. Allan, D. H. R. Barton, M. Girijavallabhan, P. G. Sammes, and M. V. Taylor, *J.C.S. Perkin I*, 1973, 1182.
[11] R. D. Allan, D. H. R. Barton, M. Girijavallabhan, and P. G. Sammes, *J.C.S. Perkin I*, 1974, 1456.

The carboxy-protecting group chosen must: (i) be stable to mild acids, bases, oxidising agents, and ozone; (ii) disfavour conjugation of the βγ-double bond with the carbonyl group in (11); (iii) be bulky to favour formation of the sulphenic acid (10) from the sulphoxide (9); [12] (iv) disfavour enolisation of the β-oxo-derivative (13); and (v) be removable under mild specific conditions.

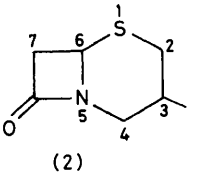
Penicillin G *S*-oxide (9a) can be conveniently protected as the *NN'*-di-isopropylhydrazide (9b).[13] Since the α-proton of a hydrazide is less acidic than that of an ester criteria (ii) [12] and (iv) are fulfilled. The di-isopropylhydrazide group is bulky, stable to mild acid, mild base, and ozone [12] and is readily removed by oxidation.[13] However, since ozonolysis of the sulphoxide (15a) gave the pyrazolinone (16) *via* cyclisation of the ketone (15b),[12] N' of the protecting hydrazide group must be disubstituted.

The present paper describes the search for a suitable protecting group in which N' is disubstituted and the application of this group in the synthesis of our original target compound (14).

In order to select a suitable protecting group, the oxidative regeneration of benzoic acid from various hydrazide derivatives was examined. Reaction of benzoyl chloride or benzoic anhydride, the substituted hydrazine or hydrazone, and triethylamine in THF gave the *N'N'*-dialkylhydrazides (17), *NN'N'*-trialkylhydrazides (18), and *N'*-methylenehydrazides (19a—c). Reductive methylation of the hydrazone (19f) gave the hydrazide (18e). Since benzophenone methylhydrazone (20a) was



(1)



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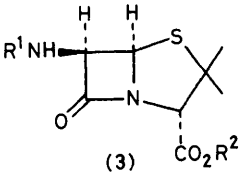
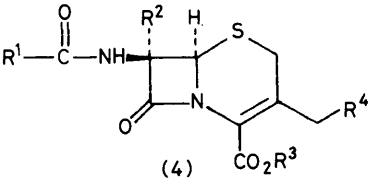


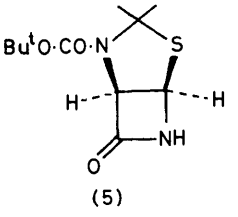
(3)

a; $R^1 = R^2 = H$
b; $R^1 = PhCO, R^2 = Me$
c; $R^1 = PhCH_2 \cdot CO, R^2 = H$



(4)

a; R^1 variable, $R^2 = R^3 = H, R^4 = OAc$
b; $R^1 = R^3 = Me, R^2 = OMe, R^4 = H$
c; $R^1 = 4\text{-}MeO \cdot C_6H_4, R^2 = R^3 = Me, R^4 = H$



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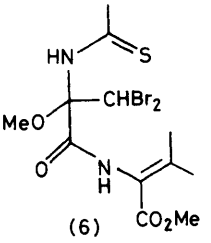

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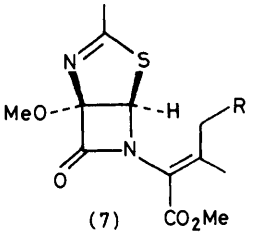
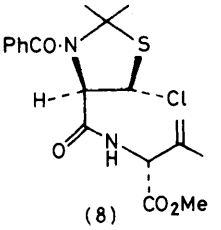


(7)

a; R = H
b; R = Br



(8)

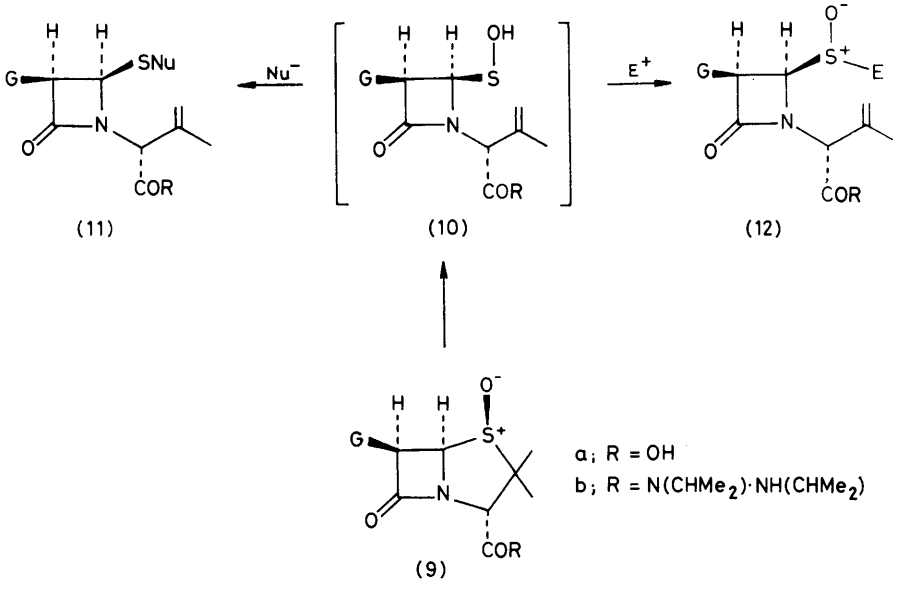
* G = $PhCH_2CONH$ here and in all subsequent formulae.

[12] Part 7, D. H. R. Barton, I. H. Coates, P. G. Sammes, and C. M. Cooper, *J.C.S. Perkin I*, 1974, 1459.

[13] D. H. R. Barton, M. Girijavallabhan, and P. G. Sammes, *J.C.S. Perkin I*, 1972, 929.

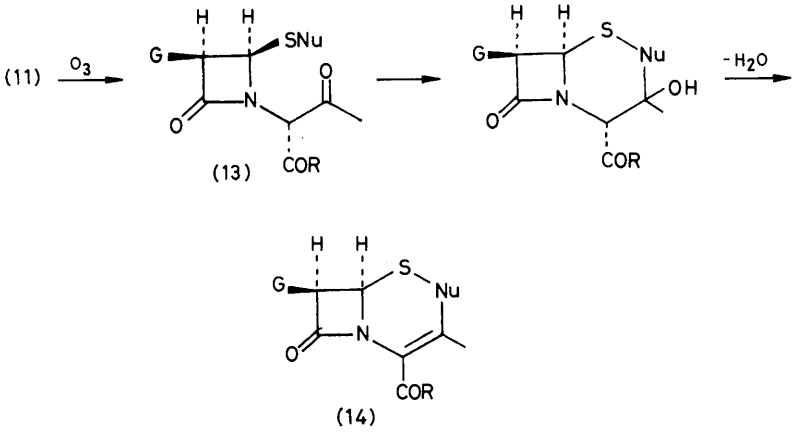
unstable (see below), *N*-benzoyl-*N*-methyl-*N'*-diphenylmethylenehydrazine (19d) was more conveniently prepared by methylation of the hydrazone (19a) with iodomethane–sodium hydride.

The results of oxidation of the benzoylhydrazines are summarised in Table 1. The *N'N'*-dimethylhydrazide (17a) gave poor yields of benzoic acid on oxidation with lead tetra-acetate in the absence of water. That the oxadiazolones (21a and b) were the major products suggested that the oxidation proceeded *via* intermediates isolated oxadiazolones (21a and b), respectively. Highest yields of benzoic acid were obtained *via* oxidation with lead tetra-acetate, active manganese dioxide,[14] or sodium nitrite in aqueous acetic acid. Benzoic acid was also regenerated in high yield from the *N'N'*-di-isopropyl-



SCHEME 1

hydrazide (17b) or *N'N'*-dibenzylhydrazide (17c) on reaction with lead tetra-acetate in aqueous acetic acid. Oxidation of the hydrazide (17c) in the absence of water gave the diphenyloxadiazole (24). Presumably after oxidative debenzylation the intermediate (17e) was



SCHEME 2

(23a), (17d), and subsequently (23b). The cation (23a or b) was either intercepted by nucleophilic attack giving benzoic acid, or cyclised giving the oxadiazoline (22a or b). Presumably, subsequent oxidation gave the oxidised further to the cation (25) *via* the hydrazone (19h), which cyclised giving the product (24).[15]

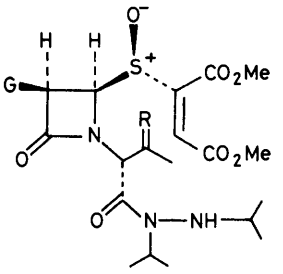
Protection of a carboxylic acid *via* the trialkylhydrazide was examined, since the proton α to the carbonyl

[14] J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1952, 1094.

[15] R. O. C. Norman, R. Purchase, C. B. Thomas, and J. B. Aylward, *J.C.S. Perkin I*, 1972, 1692; M. Milone and E. Borello, *Gazzetta*, 1951, **81**, 677.

group (in the β-lactam series) should be less enolisable than the *N*-unsubstituted analogue. This reduction in enolisability would further prevent ready conjugation of the βγ-double bond in the intermediate (11). As a model the oxidation of the *NN'N'*-trialkylhydrazides (18b, c, and e) were investigated. Benzoic acid was regenerated rapidly in high yield on oxidation with lead tetra-acetate. The oxidations probably proceeded by dealkylation [15] *via*, for example, the cation (18d), giving the hydrazide (18a) (Scheme 3). Consistent with this hypothesis, the aryl-hydrazide (18f) gave both benzoic acid and 4-anisaldehyde on oxidation with lead tetra-acetate. Alternatively, benzoic acid was regenerated in high yield on oxidation of the hydrazide (18f) with selenium dioxide.

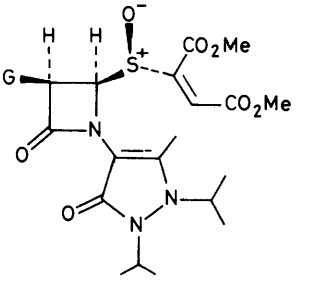
Oxidation with dichlorodicyanobenzoquinone, however, gave poor yields of benzoic acid. Even in the presence of powerful acylating agents, the hydroquinone dibenzoate (26a) was the major product. This surprising result merits more detailed mechanistic study.



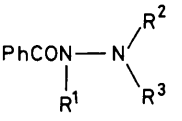
(15)

a ; R = CH_2

b ; R = O



(16)



(17) R^1 = H

a; R^2 = R^3 = Me

b; R^2 = R^3 = Me_2CH

c; R^2 = R^3 = $PhCH_2$

d; R^2 = Me, R^3 = $AcO{\cdot}CH_2$

e; R^2 = H, R^3 = $PhCH_2$

f ; R^2 = H, R^3 = $C_6H_4{\cdot}OMe-4$

(18) R^1 = alkyl

a; R^1 = R^2 = Me, R^3 = H

b; R^1 = R^2 = R^3 = Me

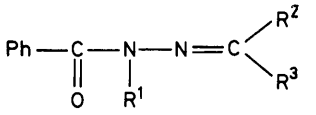
c; R^1 = R^2 = R^3 = $PhCH_2$

d; R^1 = R^2 = Me, R^3 = CH_2: ; cation

e; R^1 = R^2 = Me, R^3 = $CH_2{\cdot}C_6H_4{\cdot}NMe_2-4$

f; R^1 = Me, R^2 = Ph, R^3 = $CH_2{\cdot}C_6H_4{\cdot}OMe-4$

g; R^1 = Me, R^2 = R^3 = H



(19)

a; R^1 = H, R^2 = R^3 = Ph

b; R^1 = H, R^2 = R^3 = $C_6H_4{\cdot}OMe-4$

c; R^1 = H, R^2 = R^3 = $C_6H_4{\cdot}NMe_2-4$

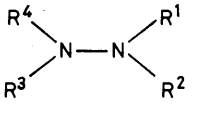
d; R^1 = Me, R^2 = R^3 = Ph

e; R^1 = Me, R^2 = H, R^3 = $C_6H_4{\cdot}OMe-4$

f; R^1 = Me, R^2 = H, R^3 = $C_6H_4{\cdot}NMe_2-4$

g; R^1 = R^2 = Me, R^3 = C_6H_4Cl-4

h; R^1 = R^2 = H, R^3 = Ph



(20)

a; R^1R^2 = Ph_2C, R^3 = Me, R^4 = H

b; R^1R^2 = $(4-MeO{\cdot}C_6H_4)_2C$, R^3 = Me, R^4 = H

c; R^1R^4 = H, R^2 = $CF_3{\cdot}CO$, R^3 = $C_6H_4{\cdot}OMe-4$

d; R^1R^2 = $4-ClC_6H_4{\cdot}CMe$, R^3 = Me, R^4 = H

e; R^1R^2 = $4-Me_2N{\cdot}C_6H_4{\cdot}CH$, R^3 = Me

f; R^1 = Ph, R^2 = $4-MeO{\cdot}C_6H_4{\cdot}CH_2$, R^3 = R^4 = H

g; R^1 = Ph, R^2 = $4-MeO{\cdot}C_6H_4{\cdot}CH_2$, R^3R^4 = CH_2

h; R^1 = Ph, R^2 = $4-MeO{\cdot}C_6H_4{\cdot}CH_2$, R^3 = Me, R^4 = H

i; R^1R^2 = $(4-Me_2N{\cdot}C_6H_4)_2C$, R^3 = R^4 = H

j; R^1 = H, R^2 = R^3 = Me, R^4 = $CH_2{\cdot}C_6H_4{\cdot}OMe-4$

k; R^1 = H, R^2 = R^3 = Me, R^4 = $OC{\cdot}C_6H_4{\cdot}OMe-4$

The potential nucleophilicity of N′ in acylhydrazines can be reduced by formation of the derived hydrazones (19) with aromatic aldehydes or ketones. Such protecting groups are bulky and should confer easy crystallisability (desirable in penicillin derivatives). As a model system the regeneration of benzoic acid from the benzoylhydrazones (19a—c) was investigated. Oxidation of the benzophenone hydrazone (19a) with sodium periodate, selenium dioxide, or chromium trioxide gave benzoic acid in good yield. Oxidation with manganese dioxide or lead tetra-acetate gave lower yields. However, if the hydrazone was first hydrolysed with dilute aqueous acid the presumed intermediate (27a), on oxidation with manganese dioxide, gave benzoic acid in 96% yield. The oxidation of acylhydrazones under anhydrous conditions has been suggested to proceed as in

TABLE 1

Oxidation of benzoylhydrazines

Substrate	Reaction conditions *	Isolated product(s)
Dimethylhydrazide [34] (17a)	$Pb(OAc)_4$ (5 equiv.), pyridine (5 equiv.), benzene, 1h	Benzoic acid (38%) Oxadiazolone (21a) (28%) Oxadiazolone (21b) (25%)
	$Pb(OAc)_4$ (5 equiv.), pyridine (5 equiv.), H_2O (5 equiv.), benzene, 1 h	Benzoic acid (65%)
	$Pb(OAc)_4$ (5 equiv.), pyridine (5 equiv.), Et_2NH (2 equiv.), benzene, 1 h	Benzoic acid (75%)
	$Pb(OAc)_4$ (20 equiv.), aqueous 60% AcOH, 30 min	Benzoic acid (95%)
	MnO_2 (20 equiv.), aqueous 60% AcOH, 30 min	Benzoic acid (85%)
	$NaNO_4$ (4 equiv.), aqueous 60% AcOH, 30 min	Benzoic acid (80%)
Di-isopropylhydrazide (17b)	$Pb(OAc)_4$ (20 equiv.), aqueous 60% AcOH, 30 min	Benzoic acid (94%)
	MnO_2 (20 equiv.), aqueous 60% AcOH, 30 min	Benzoic acid (87%)
Dibenzylhydrazide [a] (17c)	$Pb(OAc)_4$ (20 equiv.), aqueous 60% AcOH, 30 min	Benzoic acid (95%)
	$Pb(OAc)_4$ (5 equiv.), pyridine (5 equiv.), benzene, 1 h	Benzoic acid (19%), 2,5-diphenyloxadiazole [15] (24) (31%)
Trimethylhydrazide (18b)	$Pb(OAc)_4$ (20 equiv.), aqueous 60% AcOH, 30 min	Benzoic acid (94%)
	$Pb(OAc)_4$ (4 equiv.), $CF_3{\cdot}CO_2H$, 7 15 min,	Benzoic acid (98%)
Tribenzylhydrazide (18c)	$Pb(OAc)_4$ (20 equiv.), aqueous 60% AcOH, 15 h	Benzoic acid (53%)
Arylhydrazide (18e)	$Pb(OAc)_4$ (20 equiv.), aqueous 60% AcOH, 45 min	Benzoic acid (53%)
Arylhydrazide (18f)	$Pb(OAc)_4$ (4 equiv.), pyridine (4 equiv.), CH_2Cl_2 or PhH, 2 days	Benzoic acid (75%), 4-anisaldehyde (92%)
	$Pb(OAc)_4$ (6 equiv.), aqueous 60% AcOH, 2 days	Benzoic acid (73%)
	SeO_2 (3 equiv.), H_2SO_4 (2.5 equiv.), H_2O–dioxan (1 : 5), 1 h	Benzoic acid (90%)
Hydrazone (19a) [16]	$Pb(OAc)_4$ (20 equiv.), aqueous 60% AcOH, 30 min	Benzoic acid (30%)
	MnO_2 (20 equiv.), aqueous 60% AcOH, 30 min	Benzoic acid (49%)
	CrO_3 (12 equiv.), AcOH–H_2O–Me_2CO (1 : 2 : 4), 15 min	Benzoic acid (85%), benzophenone † (86%)
	SeO_2 (3 equiv.), H_2SO_4 (2.5 equiv.), H_2O–dioxan (1 : 5), 1 h	Benzoic acid (75%), benzophenone † (95%)
	$NaIO_4$ (2.5 equiv.), H_2SO_4 (2.5 equiv.), H_2O–dioxan (1 : 5), 1 h	Benzoic acid (90%), benzophenone † (72%)
	Conc. HCl–THF (1 : 8), 5 min; neutralised with Na_2CO_3; MnO_2 (3.5 equiv.), AcOH, 10 min (' one pot ')	Benzoic acid (96%)
Hydrazone (19b) [37]	$Pb(OAc)_4$ (5 equiv.), pyridine (10 equiv.), CH_2Cl_2, 35 min	Benzoic acid (71%)
	$Pb(OAc)_4$ (20 equiv.), aqueous 60% AcOH, 30 min	Benzoic acid (65%)
	$NaIO_4$ (2.5 equiv.), H_2SO_4 (2.5 equiv.), H_2O–dioxan (1 : 5), 1 h	Benzoic acid (73%), 4,4′-dimethoxybenzophenone † (45%)
Hydrazone (19c)	$Pb(OAc)_4$ (5 equiv.), pyridine (10 equiv.), CH_2Cl_2, 35 min	Benzoic acid (71%)
	$Pb(OAc)_4$ (20 equiv.), aqueous 60% AcOH, 30 min	Benzoic acid (65%)
	$NaIO_4$ (2.5 equiv.), H_2SO_4 (2.5 equiv.), H_2O–dioxan (1 : 5), 1 h	Benzoic acid (53%)
Hydrazone (19d)	MnO_2 (20 equiv.), aqueous 60% AcOH, 2 days	Benzoic acid (90%), benzophenone † (61%)
	$NaIO_4$ (2.5 equiv.), H_2SO_4 (1.5 equiv.), H_2O–dioxan (1 : 5), 30 min	Benzoic acid (85%), benzophenone (69%)
	m-4-$MeC_6H_4{\cdot}SO_3H$ in H_2O–THF (1 : 4), 5 min; neutralised with $NaHCO_3$; MnO_2 (20 equiv.), aqueous 60% AcOH, 30 min (' one pot ')	Benzoic acid (95%)
	m-4-$MeC_6H_4SO_3H$ in H_2O–THF (1 : 4), 30 min; added to $NaIO_4$ (4 equiv.) in H_2O–THF (1 : 4), dilute solution, 50 min ‡	Benzoic acid (100%)
	m-4-$MeC_6H_4{\cdot}SO_3H$ in H_2O–THF (1 : 4), 20 min; solid $NaIO_4$ (2.5 equiv.), 10 min (' one pot ') ‡	Benzoic acid (40%), *N*-methylbenzamide (60%)
	m-4-$MeC_6H_4{\cdot}SO_3H$ in H_2O–THF (1 : 4), 20 min; solid $NaNO_2$ (5 equiv.), 30 min, 0 °C (' one pot ')	Benzoic acid (78%)
Hydrazone [b] (19e)	m-4-$MeC_6H_4{\cdot}SO_3H$, THF–H_2O (4 : 1), 1 h; $NaIO_4$ (2.5 equiv.), 20 min	Benzoic acid (95%), 4-methoxybenzaldehyde † (86%)
Hydrazone (19g)	m-4-$MeC_6H_4{\cdot}SO_3H$, THF–H_2O (4 : 1), 5 min	*N*-benzoyl-*N*-methylhydrazine (18g) (60%), 4′-chloroacetophenone † (77%)

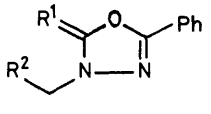
* Reactions carried out at room temperature unless stated to the contrary. † Isolated as the 2,4-dinitrophenylhydrazone. ‡ See Experimental.

[a] A. N. Kost and R. S. Sagitullin, *Zhur. obshchei Khim.*, 1957, **27**, 3338. [b] A. Michaelis and E. Hadanck, *Ber.*, 1908, **41**, 3288.

Scheme 4.[16] Presumably interception of the cation (28a) with water gave benzoic acid and benzophenone. Alternatively, hydrolysis giving the hydrazine (27a) and benzophenone may have preceded oxidation. Oxidation of the 4,4'-disubstituted hydrazones (19b and c) also gave benzoic acid.

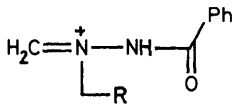
The introduction of an *N*-methyl substitutent in acylhydrazones will both increase the size of the protecting group and decrease the enolisability of the proton α to the carbonyl group (in penicillins). Benzoic acid was recovered from the model hydrazones (19d and e) on oxidation with manganese dioxide, sodium periodate, or sodium nitrite in dilute aqueous acid. Quantitative recovery was obtained on dilute acid-catalysed hydrolysis prior to oxidation with sodium periodate in dilute solution. That hydrolysis of the hydrazone (19f) gave the acylhydrazine (18g) suggested the intermediacy of (18g), formed in the rate-determining step, in the regeneration of benzoic acid. The formation of *N*-methylbenzamide on oxidation of the hydrazine (18g) with sodium periodate in concentrated solution suggested the formation of the tetra-azene (29).[17]

Having completed these model studies, we examined the chemistry of penicillin derivatives protected as hydrazides (Table 2). Reaction of the sulphoxide acid

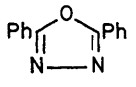


(21) $R^1 = O$
a; $R^2 = H$
b; $R^2 = OAc$

(22) $R^1 = H_2$
a; $R^2 = H$
b; $R^2 = OAc$



(23)
a; R = H
b; R = AcO



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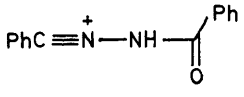
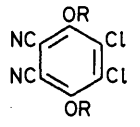
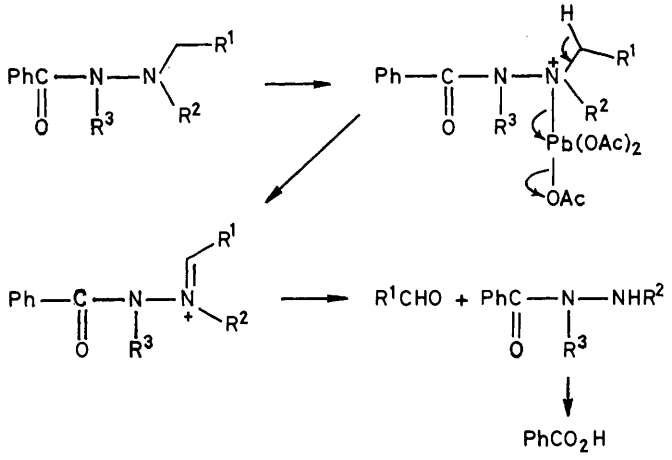


(25)



(26)
a; R = PhCO
b; R = H



SCHEME 3

(9a) with triethylamine and ethyl or isopropyl chloroformate in tetrahydrofuran gave the mixed anhydrides (30a and b), respectively. *In situ* reaction with the substituted hydrazine gave the derived protected penicillins (31a —d). Use of the more hindered isopropyl mixed anhydride (30b) reduced the amount of alkoxycarbonylhydrazine [of type (32)] side product.

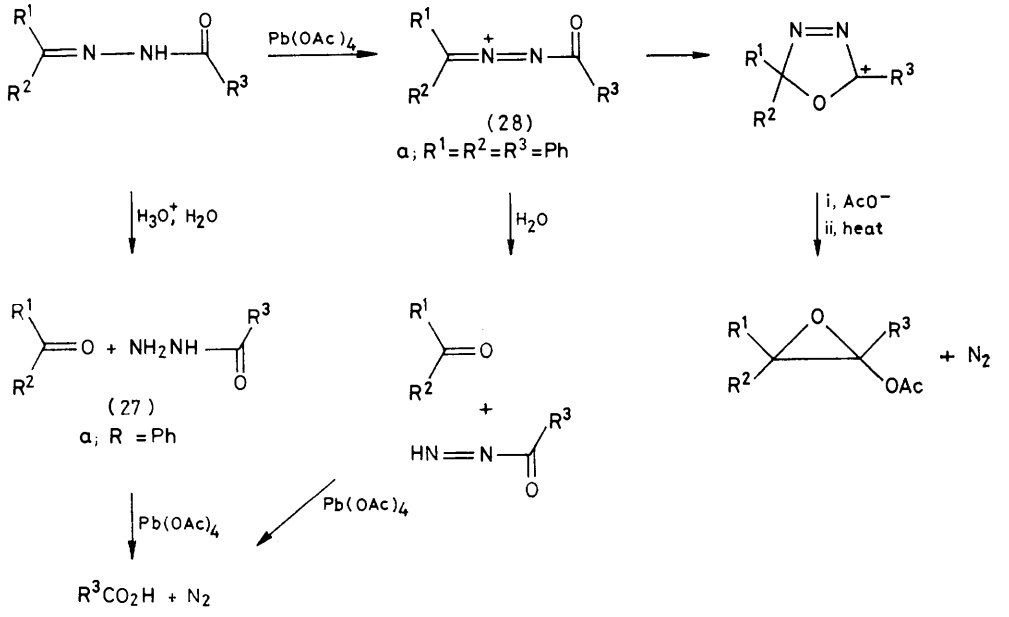
The results of oxidation of β-lactam hydrazine derivatives are summarised in Table 2. Oxidation of the *N'N'*-di-isopropylhydrazide (31a) by lead tetra-acetate gave only a modest recovery of the acid (9a). The trimethylhydrazide (31d) did not react or gave non-β-lactam products, with lead tetra-acetate, manganese dioxide, mercury(II) oxide, chromium trioxide, or dichlorodicyanobenzoquinone. Oxidation of (31d) with cerium(IV) ammonium nitrate in aqueous acetonitrile and acetic acid or nitric acid at −10 °C gave a high recovery of the acid (9a). Dealkylation, presumably *via* the cation (31k) giving the hydrazone (31l), was confirmed by the n.m.r. spectrum before complete reaction. Surprisingly, the hydrazone (31l) was oxidised at a lower rate than the trimethylhydrazide (31d) (t.l.c., n.m.r.). Since oxidation of trialkylhydrazides proceeds *via* initial *N'*-dealkylation, replacement of an *N'*-methyl by a 4-methoxybenzyl group should stabilise the intermediate cation (31m) and thus facilitate regeneration of the acid (9a). Consistent with this hypothesis, oxidation of the hydrazide (31c) with lead tetra-acetate gave the acid (9a), although the

[16] R. W. Hoffmann, and H. J. Luthardt, *Tetrahedron Letters*, 1966, 411; 1967, 3501; *Chem. Ber.*, 1968, **101**, 3851.

[17] J. S. Pizey, ' Synthetic Reagents,' Wiley, New York, 1974, vol. 1, p. 298.

trimethylhydrazide (31d) did not react. However, oxidation of the hydrazide (31b) with lead tetra-acetate gave no β-lactam products.

(33a) by reaction of the derived mixed anhydride (33b) with trimethylhydrazine. Oxidation of the cephem sulphide (33d) with cerium(IV) ammonium nitrate at



SCHEME 4

Reduction of the penicillin *S*-oxide trimethylhydrazide (31d) with phosphorus tribromide in dimethylformamide gave the sulphide (31n). This less stable β-lactam (31n) —20 °C gave no β-lactam products. Presumably the enamide system and/or the dihydrothiazine ring were more readily oxidised than the trimethylhydrazide

TABLE 2

Oxidation of β-lactam hydrazine derivatives

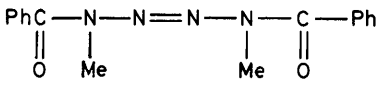
Substrate	Reaction conditions	Isolated products
Di-isopropylhydrazide (31a)	$Pb(OAc)_4$ (20 equiv.), aqueous 60% AcOH, 30 min	Penam acid (9a (46%)
	MnO_2 (20 equiv.), aqueous 60% AcOH, 30 min	No β-lactam products
Arylhydrazide (31c)	$Pb(OAc)_4$ (4 equiv.), pyridine (4 equiv.), CH_2Cl_2, 3 days	Penam acid (9a) (33%)
	$Pb(OAc)_4$ (6 equiv.), aqueous 60%, 2 days	Penam acid (9a) (31%)
	DDQ (4 equiv.), CH_2Cl_2, 36 h	Starting material (31c) and non-β-lactam products
Trimethylhydrazide (31d)	Cerium(IV) ammonium nitrate (5 equiv.), MeCN–aq. 0.5M-HNO_3 (5 : 4), −10 °C, 170 min	Hydrazine (31l) (33%), starting material (31d) (33%)
	Cerium(IV) ammonium nitrate (10 equiv.), MeCN–AcOH–H_2O (5 : 4 : 4), 20 h, −10 °C	Acid (9a) (>90%)
Hydrazone (31e)	$Pb(OAc)_4$ (20 equiv.), aqueous 60% AcOH, 30 min	Acid (9a) (51%)
	SeO_2 (3 equiv.), H_2SO_4 (2.5 equiv.), H_2O–dioxan (1 : 5), 1 h	Acid (9a) (70%)
	M-4-MeC_6H_4·SO_3H in THF–H_2O (4 : 1), 5 min; $NaIO_4$ (2.5 equiv.), 5 min (' one pot ')	Acid (9a (47%)
Hydrazone (31f)	SeO_2 (3 equiv.), H_2SO_4 (2.5 equiv.), H_2O–dioxan (1 : 5) 1 h	Acid (9a) (85%)
Hydrazone (31g)	SeO_2 (3 equiv.), H_2SO_4 (2.5 equiv.), H_2O–dioxan (1 : 5), 1 h	Acid (9a) (84%)
Hydrazone (31i)	SeO_2 (3 equiv.), H_2SO_4 (2.5 equiv.), H_2O–dioxan (1 : 5), 1.5 days	Impure acid (91), (20%)
	$NaIO_4$ (2.5 equiv.), H_2SO_4 (2.5 equiv.), H_2O–dioxan (1 : 5), 3 days	Acid (9a) (62%), 4,4'dimethoxybenzophenone † (47%)
Hydrazone (33e)	M-4-MeC_6H_4·SO_3H in THF–H_2O (4 : 1), 10 min; neutralised with $NaHCO_3$; MnO_2 (3 equiv.), aqueous 60% AcOH, 15 min	Acid (33a) (46%)

† Isolated as 2,4-dinitrophenylhydrazone.

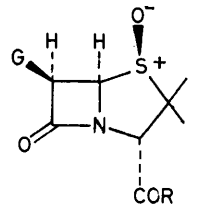
did not survive reaction with cerium(IV) ammonium nitrate at −17 °C. As a model system, ceph-3-em trimethylhydrazide (33d) was prepared from ceph-3-em

function. The 3-chlorocepham *S*-oxide (34b) (see below) was unchanged after treatment with cerium(IV) ammonium nitrate at room temperature.

Since benzoic acid was recovered in high yield from its derived substituted *N'*-methylenehydrazides, the corresponding penam hydrazones (31e—j) were examined.

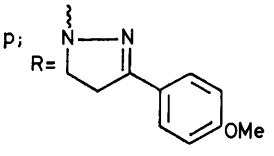


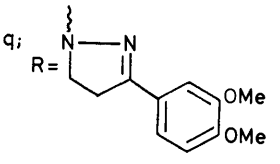
(29)

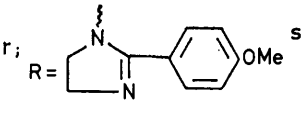


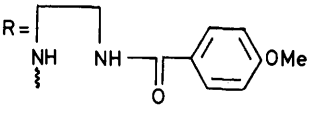
(30) a; R = EtO·CO·O
b; R = Me_2CH·O·CO·O

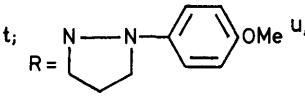
(31) a; R = $NHN(CHMe_2)_2$
b; R = NMe·NMe·CH_2·C_6H_4·OMe-4
c; R = NMe·NPh·CH_2·C_6H_4·OMe-4
d; R = NMe·NMe_2
e; R = NH·N:CPh_2
f; R = NH·N:$C(C_6H_4$·OMe-4$)_2$
g; R = NH N:$C(C_6H_4$·NMe_2-4$)_2$
h; R = NMe·N:CPh_2
i; R = NMe·N:$C(C_6H_4$·OMe-4$)_2$
j; R = NMe·N=CHC_6H_4-4-OMe
k; R = NMe·$\overset{+}{N}$Me:CH_2
l; R = NMe·N:CH_2
m; R = NMe·$\overset{+}{N}R^1$:CR^2
n; R = NMe·NMe_2; 1-deoxy
o; R = N:$\overset{+}{N}(C_6H_4R^1)_2$

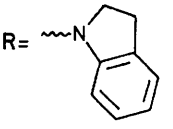
p; 

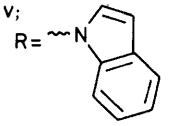
q; 

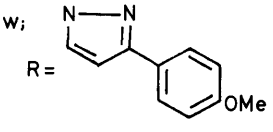
r; 

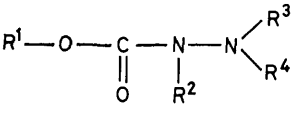
s; 

t; 

u; 

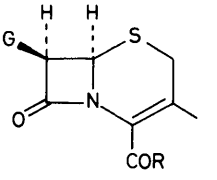
v; 

w; 

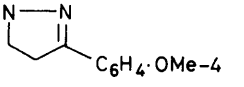


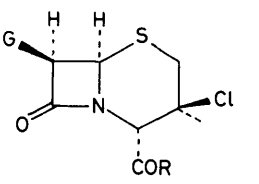
(32)

Reactions of the anhydrides (30a and b) with the substituted hydrazones gave the derived *N*-methylenehydrazides. Benzophenone *N*-methylhydrazone (20a) was prepared from diazo(diphenyl)methane and methylmagnesium iodide.[18] Alternatively, a prolonged reaction of methylhydrazine hydrogen sulphate, triethylamine, and benzophenone or 4,4'-dimethoxybenzophenone gave the derived *N*-methylhydrazones (20a and b).



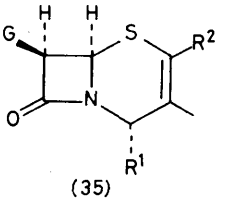
(33)

a; R = OH
b; R = O·CO_2Et
c; R = Cl
d; R = NMe·NMe_2
e; R = NMe·N:CPh_2
f; R = NMe·NH_2
g; R = 
h; R = Me



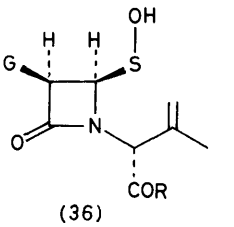
(34)

a; R = NMe·NMe_2
b; R = NMe·NMe_2; *S*-oxide
c; R = NH·N$(CHMe_2)_2$
d; R = NMe·N:CPh_2
e; R = NH·N:CPh_2



(35)

a; R^1 = CO·NMe·N:CPh_2, R^2 = H
b; R^1 = H, R^2 = COMe
c; R^1 = CO·NMe·N:CPh_2, R^2 = COMe



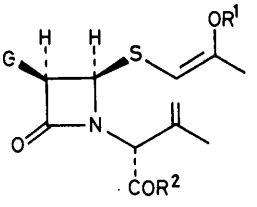
(36)

a; R = NH·N:CPh_2
b; R = N$(CHMe_2)$·NH$(CHMe_2)$
c; R = NMe·N:CPh_2

Both compounds were unstable. Thus the acylhydrazones (31h and i) were obtained only in modest yield by using freshly prepared benzophenone or 4,4'-dimethoxybenzophenone methylhydrazone (20a or b). The acylhydrazone (31h), however, was more conveniently prepared in high yield by methylation of the hydrazone (31e) with iodomethane and potassium carbonate in acetone. Reaction of 4-anisaldehyde with methylhydrazine and subsequently with the mixed anhydride (30a) gave the derived acylhydrazone (31j). The cephem acid chloride (33c) prepared from the cephem (33a) and oxalyl chloride [19] gave both ceph-3-em and ceph-2-em hydrazides, (33e) and (35a), on reaction with benzophenone methylhydrazone.

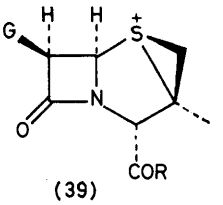
[18] G. H. Coleman, H. Gilman, C. E. Adams, and P. E. Pratt, *J. Org. Chem.*, 1938, **3**, 99.
[19] C. F. Murphy and R. E. Koehler, *J. Org. Chem.*, 1970, **35**, 2429.

Oxidation of the parent penam hydrazone (31e) with lead tetra-acetate, selenium dioxide, or sodium periodate in the presence of aqueous acid gave a moderate recovery of the acid (9a). The dimethoxy- (31f) and bisdimethylamino- (31g) derivatives give a more stable intermediate



(37)

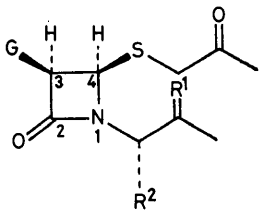
a; $R^1 = Bu^n$, $R^2 = NH{\cdot}N(CHMe_2)_2$
b; $R^1 = Bu^n$, $R^2 = NMe{\cdot}NMe_2$
c; $R^1 = Pr^n$, $R^2 = N(CHMe_2){\cdot}NH(CHMe_2)$
d; $R^1 = Pr^n$, $R^2 = NMe{\cdot}N{:}CPh_2$
e; $R^1 = Bu^n$, $R^2 = NH{\cdot}N{:}CPh_2$



(39)

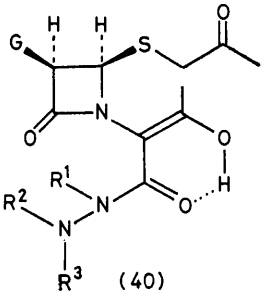
a; $R = NH{\cdot}N(CHMe_2)_2$
b; $R = NMe{\cdot}NMe_2$

should not compete with hydrazone hydrolysis. The acylhydrazone (33e) was treated with 1M-toluene-4-sulphonic acid in aqueous tetrahydrofuran. Since the carbonyl group of the cephem hydrazone (33e) was much less hindered than that of the penam hydrazone



(38) $R^1 = CH_2$
a; $R^2 = CO{\cdot}NH{\cdot}N(CHMe_2)_2$
b; $R^2 = CO{\cdot}NMe{\cdot}NMe_2$
c; $R^2 = CO{\cdot}NH{\cdot}N{:}CPh_2$
d; $R^2 = CO{\cdot}NMe{\cdot}N{:}CPh_2$

(41) $R^1 = O$
a; $R^2 = CO{\cdot}NMe{\cdot}NMe_2$
b; $R^2 = CO{\cdot}NMe{\cdot}N{:}CPh_2$
c; epimer of (41b) α to hydrazide
d; $R^2 = H$



(40)

a; $R^1 = H, R^2 = R^3 = CHMe_2$
b; $R^1 = R^2 = R^3 = Me$
c; $R^1 = H, R^2\ R^3 = Ph_2C$

cation (31o). Consistent with this hypothesis, the acid (9a) was recovered in higher yield from oxidation of the derivatives (31f and g) with selenium dioxide.

N-Acyl-*N*-methyl-*N'*-methylenehydrazines must be first hydrolysed to the derived hydrazine and aldehyde or ketone before oxidation can take place. Thus recovery of a penicillin requires that the hydrazone must be hydrolysed more readily than the β-lactam. The β-lactam of the hydrazone (31h) did not survive the required prolonged hydrolysis. However, the dimethoxy-derivative (31i) rapidly gave a good recovery of the acid (9a) on hydrolysis and subsequent oxidation with sodium periodate oxidation. The less reactive hydrazone (31j) gave only starting material and non-β-lactam products.

Deacetoxycephalosporins (33) are stable to M-toluene-4 sulphonic acid even at reflux.[20] Thus β-lactam cleavage (31h) (owing to the *gem*-dimethyl substituents), hydrolysis took place rapidly giving the hydrazide (33f). Subsequent oxidation with manganese dioxide gave the cephem acid (33a) in satisfactory yield.

Concurrent with the investigation of protecting groups, we examined transformations in the projected deacetoxycephalosporin synthesis. Interception of the sulphenic acid [of type (36)] with an alkyl isopropenyl ether should on mild acidic hydrolysis give the derived methyl ketone [of type (38)]. On heating with n-butyl isopropenyl ether in dioxan and tetrahydrofuran in the presence of the catalyst aluminium chloride, the *N'N'*-di-isopropylhydrazide (31a) gave the vinyl ether (37a).

[20] B. G. Jackson, Belg. P. 746,860; 'Cephalosporins and Penicillins Chemistry and Biology,' ed. E. H. Flynn, Academic Press, New York, 1972, p. 240.

Hydrolysis *in situ* with aqueous 20% orthophosphoric acid gave the derived ketone (38a). The structure (38a) was supported by spectral data, especially the presence of only one vinylic methyl signal in the n.m.r. spectrum. Since the hydrazide α-hydrogen atom is less acidic than an ester α-hydrogen atom the βγ-double bond did not migrate into conjugation with the hydrazide function in the ketone (38a). Spectral data suggested that the minor product of the reaction was the chlorocepham (34c), presumably produced by interception of the episulphonium ion (39a) with chloride anion.

Subsequent ozonolysis of the ketone (38a) in dichloromethane in the presence of toluene-4-sulphonic acid resulted in selective oxidation of the terminal double bond to give the enol (40a). That the product existed in the enol (40a) form was supported by spectral data [especially $\lambda_{max.}$ 260 nm (ε 7 500)].

Since the enol (40a) is not suitable for cyclisation, the carboxy-protecting group must be replaced by a group that disfavours such enol formation. *N*-Alkylation of the hydrazide should destabilise the enol [of type (40)] by introducing steric congestion between the *N*-alkyl group and the β-lactam.

On heating under reflux in dioxan and tetrahydrofuran containing aluminium chloride as a catalyst, the trimethylhydrazide (31d) and n-butyl isopropenyl ether gave the enol ether (37b). Formulation as (37b) was was consistent with the i.r. (1 670 cm^{-1}) and n.m.r. spectra. Hydrolysis with aqueous 10% orthophosphoric acid gave the desired ketone (38b) in high yield. The composition of the product was in accord with analysis and the mass spectrum. The i.r. (925 cm^{-1}) and n.m.r. (only one vinylic methyl signal at τ 8·1) spectra supported formulation as the βγ-olefin (38b). In addition the chlorocepham (34a) was a minor product. Refluxing the enol ether (37b) and aluminium chloride in tetrahydrofuran gave the chlorocepham (34a), presumably formed *via* the episulphonium ion (39b). The structure (34a) was in accord with spectral data and was confirmed by oxidation with sodium periodate to the derived crystalline sulphoxide (34b).

Ozonolysis of oxo-olefin (38b) in dichloromethane containing toluene-4-sulphonic acid at −70 °C gave a single product in high yield. The n.m.r. spectrum showed the loss of the terminal double bond and signals for two acetyl methyl groups (τ 7.78 and 8.0) and the proton α to the hydrazide (τ 4.4). Since the i.r. spectrum showed the absence of sulphoxide and the presence of two non-enolised ketone groups (1 710 and 1 700 cm^{-1}), the product was formulated as the diketone (41a); the enol (40b) was not formed.

Generation of the anion α to sulphur in the sulphide (41a) should readily bring about cyclisation to the 3-hydroxycepham system (42a). Subsequent dehydration would give the novel protected 2-acylceph-3-em (43a). During this work Lattrell and Lohaus [21] reported the formation of the cephems (33 h) and (35b) on cyclisation of the diketone (41d). The latter product (35b) readily isomerised to the ceph-3-em (43e). The diketone (41d) was prepared by total synthesis.

The dioxo-sulphide (41a) was readily cyclised on reaction with 1,5-diazabicyclo[4.3.0]non-5-ene in hexamethylphosphoramide or Triton B in dimethylformamide to give the 3-hydroxycepham (42a) as a crystalline solid. Formation of the cepham (42a) was consistent with analytical figures, retention of the β-lactam system (1 770 cm^{-1}; τ 3.1 and 4.5—4.7), and replacement of an acetyl methyl (τ 8.0) by a methyl group (τ 8.6) geminal to OH (3 500—3 400 cm^{-1}; τ 5.9). The cepham sulphide (42a) consisted largely of one isomer (n.m.r.) and was stable to chromatography. Reactions of the cepham (42a) with diverse dehydration reagents resulted in no change or gave complex mixtures of non-β-lactam products. That dehydration was difficult suggested that the hydroxy-substituent was both very hindered and probably β. Attempted dehydration *via syn*-elimination with 4-nitrophenyl isothiocyanate, dicyclohexylcarbodi-imide, and copper(II) chloride [22] or phenyl isocyanate in dry tetrahydrofuran under reflux was unsuccessful.

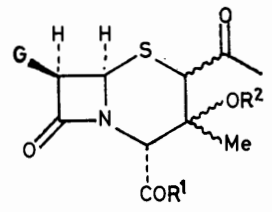
The acetate (42b) was prepared in good yield by acylation of the cepham (42a) with acetic trifluoroacetic anhydride and anhydrous potassium fluoride as base. The acetate (42b) on refluxing in dimethylformamide containing anhydrous lithium fluoride or in benzene containing anhydrous potassium fluoride and 18-crown-6 gave a single β-lactam product. The u.v. spectrum [$\lambda_{max.}$ 262 nm (ε 6 000)] suggested formation of the required ceph-3-em (43a). This was supported by spectral data indicating an acetyl methyl (τ 7.75), a vinylic methyl (τ 8.2), a single proton α to sulphur (τ 6.05), and the αβ-unsaturated hydrazide (1 685 and 1 665 cm^{-1}). Both analytical data and the mass spectrum confirmed that the product was the cephem (43a).

At this stage the unsuitability of the trimethylhydrazide function for the protection of ceph-3-em (33d) systems became apparent. Oxidation with cerium(IV) ammonium nitrate gave only non-β-lactam products. Clearly trisubstituted hydrazides satisfy all the criteria for a protecting group except that the grouping cannot be removed under oxidation conditions which are certain to leave the rest of the molecule intact. For this reason hydrazide protecting groups with N' 'temporarily' disubstituted as the hydrazone derivative were examined, as already adumbrated above. Mild acidic hydrolysis would give the readily oxidisable unsubstituted arylhydrazine, thus regenerating the carboxylic acid.

Synthesis of the cepham acid (43b) from the benzophenone acylhydrazone (31e) was examined. Trapping of the derived sulphenic acid (36a) with n-butyl isopropenyl ether gave, on acidic hydrolysis, the expected oxo-sulphide (38c). The product yield was reduced by partial concomitant hydrolysis of the hydrazone, giving benzophenone and a polar unidentified product. Again spectral data supported formulation as the βγ-unsatur-

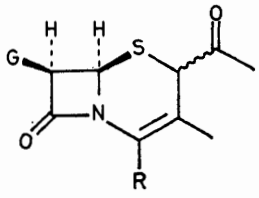
[21] R. Lattrell and G. Lohaus, *Annalen*, 1974, 870.

[22] N. H. Andersen, R. M. Carlson, E. J. Corey, J. Paust, E. Vedejs, I. Vlattas, and R. E. K. Winter, *J. Amer. Chem. Soc.*, 1968, **90**, 3245.



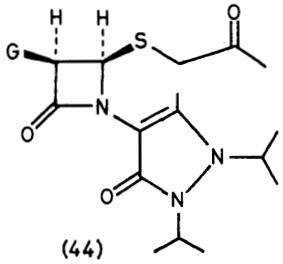
(42)

a; R^1 = NMe·NMe_2, R^2 = H
b; R^1 = NMe·NMe_2, R^2 = MeCO
c; R^1 = NMe·N:CPh_2, R^2 = H; 3β-*O*- substituent, 2α-acetyl substituent
d; R^1 = NMe·N:CPh_2, R^2 = CO·CF_3; 3β-*O*- substituent, 2α-acetyl substituent

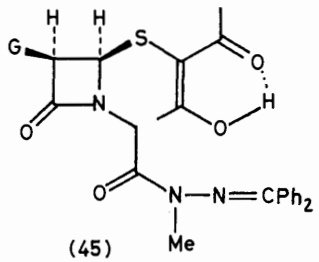


(43)

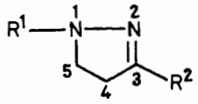
a; R = CO·NMe·NMe_2
b; R = CO_2H; 2α-acetyl substituent
c; R = CO·NMe·N:CPh_2; 2α-acetyl substituent
d; R = CO·NMe·NH_2; 2α-acetyl substituent



(44)



(45)



(46)

a; R^1 = PhCO, R^2 = Ph
b; R^1 = PhCO, R^2 = C_6H_4·OMe-4
c; R^1 = PhCO, R^2 = $C_6H_3(OMe)_2$-3,4
d; R^1 = PhCO, R^2 = C_6H_4·OMe-4; 4,5-didehydro
e; R^1 = PhCO, R^2 = $C_6H_3(OMe)_2$-3,4; 4,5-didehydro
f; R^1 = PhCO, R^2 = H
g; R^1 = C_6H_4·OMe-4, R^2 = H
h; R^1 = H, R^2 = Ph
i; R^1 = H, R^2 = C_6H_4·OMe-4
j; R^1 = H, R^2 = $C_6H_3(OMe)_2$-3,4

ated hydrazide (38c). Ozonolysis in dichloromethane solution in the presence of pyridine [23] gave a high yield of a single product. Ozonolysis in the absence of pyridine gave no identified products. The intense u.v. absorption of the product [$\lambda_{max.}$ 259 nm (ε 16 300)] suggested formation of the enol hydrazide (40c). This was confirmed by other spectral data and an intense purple colour with ethanolic iron(III) chloride. Clearly

[23] G. Slomp, jun., and J. L. Johnson, *J. Amer. Chem. Soc.*, 1958, **80**, 915.

in order to prevent enol (40) formation the hydrazide *N* must, as already stated, be alkylated.

The sulphenic acid (36b) derived from the *NN'*-diisopropylhydrazide (9b) was also trapped with 2-propoxypropene to give the derived enol ether (37c). The synthesis was not continued because of anticipated (see above) pyrazolinone (44) formation. However, since the *NN'*-di-isopropylhydrazide function is readily removable, the enol ether (37c) should lend itself to alternate transformations.

At this stage the cephem (33a) was shown to be regenerated on oxidation of the derived *N*-acyl-*N*-methylbenzophenone hydrazone (33e). Such a protecting group should ensure that the intermediate diketone (41) is more stable than the derived enol (40), since the acyl nitrogen is alkylated. On refluxing in dioxan and tetrahydrofuran, the sulphenic acid (36c) derived from the hydrazone (31h) was efficiently trapped with 2-propoxypropene giving the enol ether (37d) in high yield. If the catalyst aluminium chloride was added in small portions as the reaction proceeded, formation of the chlorocepham (34d) was suppressed completely. Again spectral data confirmed the stability of the βγ-unsaturated acylhydrazone (37d). However, on reaction of the enol ether (37d) with phosphoric, oxalic, tartaric, phthalic, or benzoic acid in aqueous tetrahydrofuran both enol ether and hydrazone (partial) functions were hydrolysed. Since enol ethers undergo mercury(II)-catalysed transetherification,[24] hydrolysis of the enol ether (37d) catalysed by mercury(II) salts was examined. Reaction with mercury(II) nitrate in aqueous acetonitrile gave the oxo-olefin (38d) in high yield. Mercury(II) acetate or chloride in aqueous tetrahydrofuran or acetonitrile gave incomplete hydrolysis. Presumably the reaction involves a hydroxymercuration–demercuration sequence.

Subsequent ozonolysis of the oxo-olefin (38d) in dichloromethane in the presence of pyridine as a moderator [23] gave the diketone as a mixture of epimers (41b and c). Absence of a peak at 265 nm in the u.v. spectrum, other spectral data, and the absence of colour with iron(III) chloride showed that the enol form was not favoured. Crystallisation gave the major isomer (41b) as an analytically pure compound. The minor epimer (41c) was obtained on chromatography. Assignment of stereochemistry followed from the optical rotation. Both the oxo-olefin (38d) and the major epimer (41b) had large negative rotations; the epimer (41c) was dextrorotatory. Ozonolysis of the oxo-olefin (38d) gave consistently better yields on the 2—3 mmol scale. Some benzophenone was produced in larger scale reactions.

A mixture of the epimeric ketones (41b and c) was treated with a catalytic amount of diazabicyclononene. In hexamethylphosphoramide solution an equilibrium between starting material and a single product was established in 5 h. Reaction in pyridine or tetrahydrofuran and hexamethylphosphoramide (4 : 1) was much slower and gave lower yields of the product. Chromatography afforded the stable cepham (42c) in 86% yield (allowing for recovered starting material). The formation of the cepham (analysis) as a single epimer (42c) was consistent with spectral data and t.l.c. behaviour. Since the related cepham (42a) was difficult to dehydrate, the hydroxy-group is probably *syn* to the C-4 proton and therefore β. The acetyl group in the cepham (42c) would be expected to take up the less hindered α-configuration, thus minimising steric congestion with the 6β-phenylacetamido-group. Formulation of stereochemistry, however, must be regarded as tentative. In the cyclisation, prolonged reaction, especially in the presence of an excess of diazabicyclononene, gave a new product. The u.v. spectrum [$\lambda_{max.}$ 289 nm (ε 12 000)] and orange colour with ethanolic iron(III) chloride suggested the formation of an enolised β-diketone. Confirmation of the product as the enol (45) followed from the n.m.r. spectrum. The initial cyclisation of the diketone (41b and c) gave 3-hydroxycepham (42c) as the kinetic product. Thermodynamic control gave eventually the enol (45). Presumably formation of the derived diazabicyclononene salt of the enolised β-diketone system provides the required driving force.

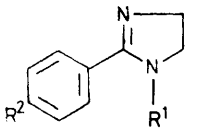
N-Acyl-*N*-methylbenzophenone hydrazones are more hindered than the corresponding acyltrimethylhydrazines. This was reflected in difficulty in acylating the 3-hydroxy-function of the cepham (42c). An attempted reaction with acetic trifluoroacetic anhydride in the presence of potassium fluoride in dichloromethane gave only starting material. Addition of triethylamine, diazabicyclononene, or 4-dimethylaminopyridine, or reaction in pyridine or benzene solution at room temperature, or on reflux, gave starting material or resulted in decomposition. However, reaction of the cepham (42c) and trifluoroacetic anhydride in dichloromethane gave a single less polar product (t.l.c.). The product, presumably the trifluoroacetate (42d), on reaction with diazabicyclononene *in situ* gave the required cephem (43c) in 71% yield (allowing for recovered starting material). The structural assignment was based on analytical and mass and other spectral data. Although the cephem chromophore was masked by the hydrazone chromophore, the 2-acetyl ketone was not conjugated ($\nu_{max.}$ 1 710 cm^{-1}; τ 7.7). This was supported by the n.m.r. signal at τ 5.98, consistent with a proton α to both sulphur and a ketonic carbonyl and inconsistent with the 4β-hydrogen atom in the alternate ceph-2-em (35c) (expected at τ *ca.* 4). Confirmation of the cephem structure (43c) follows from analogy with the cephem trimethylhydrazide (43a).

The cephem hydrazone (43c) was rapidly hydrolysed in M-toluene-4-sulphonic acid to give a polar intermediate, presumably the hydrazide (43d). Oxidation *in situ* with sodium periodate gave a carboxylic acid. Spectral data showed the presence of the β-lactam (1 785 cm^{-1}; τ 4.28 and 5.22), an αβ-unsaturated carboxylic acid (3 500—2 500 and 1 710 cm^{-1}), an unconjugated methyl ketone (1 710 cm^{-1}; τ 7.65), an intact phenylacetamide (3 400, 1 690, and 1 505 cm^{-1}; τ 2.72, 3.08, and 6.42), and

[23] H. Yuki, K. Hatada, and K. Nagata, *Bull. Soc. Chem. Japan*, 1970, **43**, 1817.

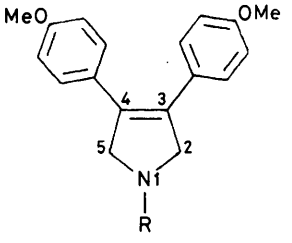
a vinylic methyl group (τ 7.95). Analytical data and the u.v. spectrum [$\lambda_{max.}$ 265 nm (ε 4 800)] confirmed that the product was the projected deacetoxycephalosporin (43b). The molecular ion was absent in the mass spectrum; the highest mass ion (330 m.u.) resulted from loss of carbon dioxide. The biological activity of the cephem (43b) is under investigation by Glaxo Research.

Other syntheses of novel 2- and 3-substituted cephalanhydride or benzoyl chloride with triethylamine and the appropriate heterocyclic amines gave the corresponding benzoylpyrazolines (46a—c), the imidazoline (47a), and the pyrazolidine (49a). The structures of the *N*-acyl heterocycles were consistent with spectral and analytical data. The mixed anhydrides (30a) and (33b) derived from penicillin G *S*-oxide (9a), and deacetoxycephalosporin (33a) gave the corresponding *N*-acyl



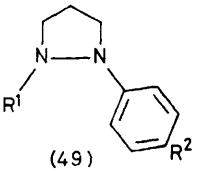
(47)

a; R^1=PhCO, R^2=H
b; R^1=H, R^2=MeO



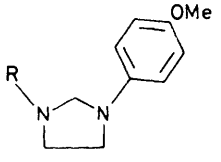
(48)

a; R=PhCO
b; R=PhCO; 2,5-didehydro
c; R=H; 2,5-didehydro
d; R=H



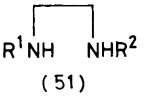
(49)

a; R^1=PhCO, R^2=H
b; R^1=PhCO, R^2=OMe
c; R^1=H, R^2=OMe; 2,3,4,5-tetradehydro
d; R^1=H, R^2=OMe
e; R^1=CF_3CO, R^2=OMe
f; R^1=EtO_2C, R^2=OMe
g; R^1=R^2=H



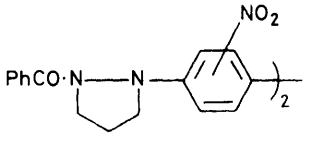
(50)

a; R=PhCO
b; R=H

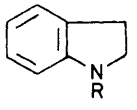


(51)

a; R^1=R^2=PhCO
b; R^1=H, R^2=OC·C_6H_4·OMe-4
c; R^1=H, R^2=C_6H_4·OMe-4

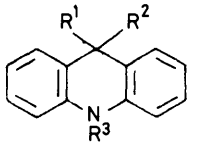


(52)



(53)

a; R=PhCO·
b; R=PhCO; 2,3-didehydro
c; R=EtO_2C
d; R=H



(54)

a; R^1=R^2=H, R^3=PhCO
b; R^1 R^2=O, R^3=PhCO
c; R^1=R^2=R^3=H; 9,10-didehydro
d; R^1 R^2=O, R^3=H

osporins have recently been described, but by methods different from those that we report here.[25-27]

The cleavage of an acyl–nitrogen bond can be facilitated by decreasing electron density on the nitrogen. This, in hydrazides, is achieved by oxidation to intermediates such as the cation (28a). If the nitrogen forms part of a potential aromatic ring, aromatisation will increase the acyl electrophilicity. The application of such 'latent' heteroaromaticity in carboxy-group protection is described herein. Reaction of benzoic heterocycles on reaction with the heterocyclic amines. The corresponding urethanes (49f) and (53c) accompanied the β-lactam derivatives. Formulations of the β-lactam derivatives were consistent with analytical and spectral data. Since *N*-(4-methoxyphenyl)pyrazolidine (49d) was air-sensitive, the *N'*-benzoyl derivative (49b) was prepared from *N*-benzoyl-*N'*-(4-methoxyphenyl)hydrazine (17f), sodium hydride, and 1,3-dibromopropane. An analogous reaction with the trifluoroacetylhydrazine (20c) gave the pyrazolidine (49e). Hydrolysis and subsequent reaction with the penam anhydride (30a) gave the pyrazoline (46g) derived from oxidation of the

[25] T. Kamiya, T. Teraji, M. Hashimoto, O. Nakaguchi, and T. Oku, *J. Amer. Chem. Soc.*, 1976, **98**, 2342.
[26] D. H. Bremner and M. M. Campbell, *J.C.S. Chem. Comm.*, 1976, 538.
[27] J. H. C. Nayler, N. F. Osborne, M. J. Pearson, and R. Southgate, *J.C.S. Perkin I*, 1976, 1615.

intermediate pyrazolidine (49d), the ethoxycarbonyl-pyrazolidine (49f), and the required penam pyrazolidine (31t).

Results of oxidations of the acyl latent heteroaromatic compounds are summarised in Table 3. Oxidations by lead tetra-acetate or cerium(IV) ammonium nitrate of the benzoylpyrazolines (46a—c) all gave high yields of benzoic acid. The intermediate pyrazoles (46d and e) were isolated from oxidations with lead tetra-acetate in the absence of water. Only oxidation with cerium(IV) ammonium nitrate gave a moderate recovery of β-lactam acid (9a) from the penicillin pyrazolines (31p and q).

TABLE 3

Oxidations of ' latent ' heteroaromatic compounds

Substrate	Reaction conditions	Product(s)
Acyl pyrazoline (46a)	$Pb(OAc)_4$ (3 equiv.), H_2O–$CF_3{\cdot}CO_2H$–HOAc (3 : 10 : 20), 18 h	Benzoic acid (95%)
Acyl pyrazoline (46b)	$Pb(OAc)_4$ (2 equiv.), pyridine (2 equiv.), CH_2Cl_2, reflux, 4.5—7 h	Pyrazole (46d) (99%)
	$Pb(OAc)_3$ (3 equiv.), H_2O–$CF_3{\cdot}CO_2H$–HOAc(3 : 10 : 20), 2.5 h	Benzoic acid (98%)
	Cerium(IV) ammonium nitrate (2.5 equiv.), H_2O–HOAc–MeCN (1 : 1 : 2), 2.5 h, −20 °C	Benzoic acid (91%)
Acyl pyrazoline (46c)	$Pb(OAc)_4$ (2 equiv.), pyridine (2 equiv.), CH_2Cl_2, reflux, 4.5—7 h	Pyrazole (46e) (100%)
	$Pb(OAc)_4$ (3 equiv.), H_2O–$CF_3{\cdot}CO_2H$–HOAc (3 : 10 : 20), 2.5 h	Benzoic acid (92%)
Penam acylpyrazoline (31p)	$Pb(OAc)_4$ (3 equiv.), H_2O–$CF_3{\cdot}CO_2H$–HOAc (3 : 10 : 20), 2.5 h	Low yield of β-lactam
	Cerium(IV) ammonium nitrate (2.5 equiv.), H_2O–HOAc–MeCN (1 : 1 : 3), 2 h, −20 °C; aqueous 20% H_3PO_4 in dioxan, 24 h	Acid (9a) (62%)
Penam acylpyrazoline (31q)	$Pb(OAc)_4$ (3 equiv.), H_2O–$CF_3{\cdot}CO_2H$–HOAc (3 : 10 : 20), 2.5 h	Low yield of β-lactam
	Cerium(IV) ammonium nitrate (2.5 equiv.), H_2O–HOAc–MeCN (1 : 1 : 3), 2 h, −20 °C; aqueous 20% H_3PO_4 in dioxan, 24 h	Acid (9a) (24%)
Acyl imidazoline [a] (47a)	SeO_2 (3 equiv.), dioxan, reflux, 4 h	Benzoic acid (64%), *NN'*-dibenzoylethyl-enediamine (51a) [b] (18%)
Penam acylimidazoline (31r)	SeO_2 (2 equiv.), dioxan, 2.5 days	Acid (9a) (69%), amide (31s) (5%)
Δ^3-Pyrroline (48a)	SeO_2 (3 equiv.), dioxan, reflux, 2.5 h	Pyrrole (48b) (85%)
Pyrrole (48b)	Aqueous 20% H_3PO_4–dioxan (1 : 1), 24 h	No reaction
	NaCN (5 equiv.), H_2O–MeCN–THF (5 : 5 : 7), 48 h	Benzoic acid (93%)
	DNB–THF–H_2O (1 : 15 : 3), 10 min	Benzoic acid (95%)
Pyrazolidine (49a)	Cerium ammonium nitrate (1.7 equiv.), AcOH–H_2O–MeCN (2 : 1 : 2), −20 °C, 24 h	Dimer (52) (71%)
	$Pb(OAc)_4$, CH_2Cl_2; SeO_2, H_2O, dioxan; SeO_2, dioxan; $Hg(OAC)_2$, CH_2Cl_2; or $Tl(OAc)_3$, CH_2Cl_2	No reaction
Pyrazolidine (49b)	Cerium(IV) ammonium nitrate (1.1 equiv.), AcOH–H_2O–MeCN (2 : 1 : 2), −20 °C, 24 h	1-Benzoyl-Δ^2-pyrazoline (46f) (40%)
	DDQ (2 equiv.), CH_2Cl_2, 16 h	Hydroquinone dibenzoate (26a) (68%), pyrazole (49c) [c] (88%)
	DDQ (2 equiv.), NaOAc (4 equiv.), HOAc–CH_2Cl_2 (2 : 5), 3 days	No benzoic acid, hydroquinone dibenzoate (26a) (t.l.c.)
	DDQ (2 equiv.), LiSCN (1.3 equiv.), PhH, 3 days	No benzoic acid, hydroquinone dibenzoate (26a) (t.l.c.)
Imidazolidine (50a)	$Pb(OAc)_4$ (4 equiv.), pyridine (4 equiv.), CH_2Cl_2, 2 days	Benzoic acid (46%)
	MnO_2 (20 equiv.) PhH, 36 h	No reaction
N-Benzoylindoline (53a) [d]	DDQ (3 equiv.), PhH, 2 days; or reflux 3 h	*N*-Benzoylindole (53b) [e] (100%)
	$Pb(OAc)_4$, pyridine, CH_2Cl_2; $Pb(OAc)_4$, 50% aqueous AcOH; cerium(IV) ammonium nitrate, H_2O–MeCN–AcOH (1 : 2 : 2); SeO_2, H_2O, dioxan; NCS, Et_3N, CH_2Cl_2; or MnO_2, CH_2Cl_2	No reaction, or mixture of indoline (53a), indole (53b), and side products
N-Benzoylindole (53b)	Aqueous 20% H_3PO_4–dioxan 1.1, 16 h	No reaction
	M-4-$MeC_6H_4{\cdot}SO_3H$ in H_2O–THF (1 : 4), 6 h	Benzoic acid (35%)
	2N-NaOH in EtOH, 3 h	Benzoic acid (99%)
Penam indoline (31u)	DDQ (3.5 equiv.), CH_2Cl_2, reflux 4 h, 12 h room temperature	Indole (31v) (40%) and starting material
N-Benzoyl-9,10-dihydro-acridine (54a) [47]	$Pb(OAc)_4$ (2.75 equiv.), CH_2Cl_2, 24 h	*N*-Benzoyl-9-acridone (54b) [48] (99%)
	MnO_2 (6 equiv.), THF–HOAc–H_2O (4 : 1 : 1), 4 days	Starting material (54a) (48%), acridone (54b) (15%), benzoic acid (30%), acridine (54c) [c] (32%)
	SeO_2 (1.5 equiv.), dioxan, reflux, 7 h	Acridine (54c) [c] (97%), benzoic acid (97%)
	DDQ (1.3 equiv.), PhH, 16 h	Acridine (54c) [c] (86%), hydroquinone dibenzoate (26a) (61%), benzoic acid (5%)
N-Benzoyl-9-acridone (54b)	Aqueous 20% H_3PO_4–dioxan (3 : 5), 16 h; aqueous 5% $NaHCO_3$, 16 h	No reaction
	N-NaOH, 1 h	Benzoic acid (90%), 9-acridone (54d) (92%)

[a] A. Marxer, *J. Amer. Chem. Soc.*, 1957, **79**, 467. [b] S. R. Aspinall, *J. Org. Chem.*, 1941, **6**, 895. [c] J. D. Kendall and G. F. Duffin, B.P. 797,144 (*Chem. Abs.*, 1959, **53**, 4984). [d] G. M. Bennet and M. M. Hafez, *J. Chem. Soc.*, 1941, 652. [e] ' Heilbron's Dictionary of Organic Compounds,' Eyre and Spottiswoode. London, 1965.

Again the cephem analogue (33g) did not survive treatment with cerium(IV) ammonium nitrate.

Benzoic acid and penicillin G *S*-oxide (9a), respectively, were recovered from oxidation of the imidazolines (47a) and (31r) with selenium dioxide. Acid-catalysed hydrolysis accompanied oxidation, giving the *NN'*-diacylethylenediamine derivatives (51a) and (31s), respectively. The structures of the diamides followed from spectral data and identity with synthetic materials. Monoacylation of ethylenediamine with methyl anisate and subsequent reaction with anhydride (30a) gave the diamide (31s), identical with the minor product from the imidazolidine (31r) oxidation.

Reduction of the substituted pyrrole (48c) with zinc–hydrochloric acid and subsequent benzoylation gave the Δ^3-pyrroline derivative (48a). Oxidation with selenium dioxide gave the derived acylpyrrole (48b). Hydrolysis of this pyrrole (48b) required conditions incompatible with β-lactams. As a protecting group, Δ^3-pyrroline derivatives were not examined further.

Since *N*-acyl-*N'*-arylpyrazolidines are equivalent to dialkylarylhydrazides, oxidations of the acylpyrazolidines (49a and b) and (31t) were examined. The parent phenyl derivative (49a) did not react with several oxidising agents (see Table 3), but cerium(IV) ammonium nitrate gave a new product, $C_{32}H_{28}N_6O_6,0.5H_2O$ (analysis and mass spectrum). The i.r. spectrum showed the presence of *N*-benzoyl functions (1 655 cm^{-1}) and aryl nitro-groups (1 520 and 1 330 cm^{-1}). The pyrazolidine ring was intact (τ 5.8—6.1, 6.1—6.8, and 7.5—8.0) and the molecule contained six aromatic protons (excluding those in two benzoyl groups). These data are consistent with the product being the dinitrated dimer (52). Presumably dimerisation of the pyrazolidine (49a) radical cation, proton loss, and subsequent nitration would give the dimer (52). The pyrazolidine methoxy-analogue (49b) gave polymeric material and 1-benzoyl-Δ^2-pyrazoline (46f). Oxidation with dichlorodicyanobenzoquinone did not give any benzoic acid; the pyrazole (49c) and the substituted hydroquinone dibenzoate (26a) were both formed. Addition of sodium acetate or lithium isothiocyanate did not intercept any reactive benzoylating agent. No β-lactam products were obtained from the reaction of dichlorodicyanobenzoquinone and the penicillin pyrazolidine (31t). Benzoic acid was, however, recovered in modest yield on oxidation of the imidazolidine (50a) with lead tetra-acetate.

N-Benzoylindoline (53a) gave a quantitative yield of *N*-benzoylindole (53b) on oxidation with dichlorodicyanobenzoquinone. This indole (53b) was hydrolysed slowly in *m*-toluene-4-sulphonic acid giving a low recovery of benzoic acid. Alkaline hydrolysis, however, gave a high yield of benzoic acid. Oxidation of the penicillin indoline (31u) with the quinone gave a slow partial conversion into a product, probably the indole (31v). Since *N*-benzoylindole (53b) was not hydrolysed under conditions compatible with penicillins, further study was not undertaken. Oxidation of *N*-benzoyl-9,10-dihydroacridine (54a) with selenium dioxide gave excellent yields of benzoic acid and the acridine (54c). Oxidation with lead tetra-acetate gave *N*-benzoyl-9-acridone (54b). This derivative, however, required hydrolysis conditions incompatible with β-lactam stability to regenerate benzoic acid. Oxidation with manganese dioxide gave a mixture of *N*-benzoyl-9-acridone (54b), benzoic acid, and acridine (54c) in low yields; dichlorodicyanobenzoquinone gave acridine (54c) in high yields, benzoic acid as a minor product, and the substituted hydroquinone dibenzoate (26a).

Although not yet applied to synthesis, we have demonstrated that the protection of a carboxylic acid by formation of an *N*-acyl latent heteroaromatic system is viable.

In conclusion, we have shown the utility of acyldialkyl- and trialkyl-hydrazine and acylhydrazone derivatives for protecting carboxylic acids. Excellent recovery of the acid was obtained in some cases on mild oxidation. Such protecting groups have been applied to penicillin and cephalosporin derivatives. The novel 2-acetyldeacetoxycephalosporin (43b) has been synthesised from penicillin G *S*-oxide (9a) by protecting the carboxy-group as the *N'*-diphenylmethylene-*N*-methylhydrazide derivative (31h). Protection of carboxylic acids by formation of 'latent' heteroaromatic amide derivatives has been applied to both benzoic acid and penicillin G *S*-oxide (9a).

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. Unless otherwise stated, i.r., u.v., and n.m.r. spectra were determined for solutions in chloroform, ethanol, and deuteriochloroform (tetramethylsilane reference), respectively. Optical rotations were recorded for solutions in chloroform. Column and preparative thin-layer chromatography (p.l.c.) were carried out on Merck Kieselgel 60 and GF_{254}, respectively. Light petroleum refers to the fraction with b.p. 40—60 °C. Solutions were dried over anhydrous Na_2SO_4. *NN*-Dibenzylhydrazine [28,29] and *NNN'*-tribenzylhydrazine [30] were prepared by standard procedures.

N-[1-(4-*Chlorophenyl*)*ethylidene*]-N'-*methylhydrazine* (20d).—4'-Chloroacetophenone (2.0 g), methylhydrazine (2.0 g), and sulphuric acid (1 drop) in ethanol (10 ml) were heated to reflux for 20 min. After cooling, benzene (100 ml) was added, and the solution washed with water (3 × 20 ml) and dried. Evaporation gave the crude hydrazine (20d) (1.7 g, 71%), m.p. 35—40° (decomp.) (from EtOH–light petroleum), τ 2.3—2.9 (4 H, m, aryl H), 5.0br (1 H, NH), 6.99 (3 H, s, NMe), and 8.05 (3 H, s, CMe). The compound was used without further purification to prepare acyl derivatives.

N-*Diphenylmethylene*-N'-*methylhydrazine* (20a).—Benzophenone (5.0 g), methylhydrazinium hydrogen sulphate (16 g), and triethylamine (11 g) in ethanol (50 ml) and water (10 ml) were heated to reflux (8 h), cooled, and stored for 2 weeks. Chloroform (180 ml) was added and the solution washed with water (3 × 30 ml) and dried. Evaporation gave the crude hydrazone (20a) as an unstable oil, τ 2.0—

[28] H. Zimmer, L. F. Audrieth, M. Zimmer, and R. A. Rowe, *J. Amer. Chem. Soc.*, 1955, **77**, 790.

[29] M. Busch and B. Weiss, *Ber.*, 1900, **33**, 2701.

[30] J. Kenner and J. Wilson, *J. Chem. Soc.*, 1927, 1108.

2.8 (aryl-H), 5.0br (NH), and 7.07 (s, NMe). This product was alternatively prepared by Coleman's procedure.[18]

N-[*Bis*-(4-*methoxyphenyl*)*methylene*]-N′-*methylhydrazine* (20b).—The reaction of 4,4′-dimethoxybenzophenone and methylhydrazinium hydrogen sulphate gave the crude hydrazone (20b) as an oil, τ 2.2—3.5 (m, aryl-H), 5.0br (NH), 6.3 (m,OMe), and 7.05 (s, NMe).

Preparation of N-*Substituted Benzoylhydrazines*.—Benzoyl chloride (1 mol. equiv.), the appropriate substituted hydrazine and trimethylamine (1 mol. equiv.) in tetrahydrofuran (THF) were stirred at room temperature for 10 min. The mixture was evaporated and the residue in ethyl acetate was washed with aqueous 1% phosphoric acid, aqueous 5% sodium hydrogen carbonate, and brine. Evaporation and crystallisation gave N-*benzoyl*-NN′N′-*trimethylhydrazine* (18b) (79%), m.p. 87—88° (from light petroleum), $\nu_{max.}$ (Nujol) 1 642 cm^{-1}, τ 2.2—2.8 (5 H, m, aryl H), 6.96 (3 H, s, NMe), and 7.51 (6 H, s, NMe_2) (Found: C, 67.3; H, 8.0; N, 16.0. $C_{10}H_{14}N_2O$ requires C, 67.4; H, 7.9; N, 15.7%); *N*-benzoyl-*NN′N*-tribenzylhydrazine (18c) (72%), m.p. 111—112° (from PhH) (lit.,[31] 181°), $\nu_{max.}$ (Nujol) 1 640 cm^{-1}, τ 2.0—3.4 (20 H, m, aryl-H), 5.0—6.4 (6 H, m, aryl-CH_2) (Found: C, 82.7; H, 6.4; N, 6.8. Calc. for $C_{28}H_{26}N_2O$: C, 82.7; H, 6.5; N, 6.9%); N-*benzoyl*-N′N′-*di-isopropylhydrazine* (17b) (38%), m.p. 142—143° (from PhH), $\nu_{max.}$ 3 280, 1 655, and 1 535 cm^{-1}, τ 2.4—2.7 (5 H, m, aryl H), 3.5br (1 H, s, NH), 6.81 (2 H, septet, *J* 6 Hz, CH), and 8.78 (12 H, d, *J* 6 Hz, CMe_2) (Found: C, 70.9; H, 9.15; N, 12.85. $C_{13}H_{20}N_2O$ requires C, 70.85; H, 9.15; N, 12.7%); or N-*benzoyl*-N′-[1-(4-*chlorophenyl*)*ethylidene*]-N-*methylhydrazine* (19g) (60%), m.p. 125—126° (from PhH–light petroleum), $\nu_{max.}$ 1 630 and 826 cm^{-1}, $\lambda_{max.}$ 251 (ε 18 200) and 303 nm (4 500), τ 2.2—2.8 (9 H, m, aryl-H), 6.62 (3 H, s, NMe), and 7.76 (3 H, s, CMe) (Found: C, 67.0; H, 5.6; Cl, 12.3; N, 10.0. $C_{16}H_{15}ClN_2O$ requires C, 67.0; H, 5.3; Cl, 12.4; N, 9.8%).

N-*Benzoyl*-N′-4-*dimethylaminobenzyl*-NN′-*dimethylhydrazine* (18e).—*N*-Benzoyl-*N*′-4-dimethylaminomethylidene-*N*-methylhydrazine (19f) (60%), prepared as for (19h) from the hydrazone (20e),[32] was obtained as orange crystals, m.p. 153—154° (from PhH–light petroleum). Hydrochloric acid (6N) was added dropwise over 4 h to the arylhydrazone (19f) (0.50 g), formalin (37%; 0.5 ml), Bromocresol Green (2 mg), and sodium cyanoborohydride (0.67 g) in methanol (20 ml) to maintain a yellow colour. The mixture was stirred overnight and evaporated; the residue in ethyl acetate was washed with 6N-hydrochloric acid, brine, dried, and evaporated to give the *hydrazine* (18e) (447 mg, 84%) as an oil, $\nu_{max.}$ 2 830 and 1 625 cm^{-1}, τ 2.67 (5 H, s, C_6H_5), 3.47 (4 H, m, C_6H_4), 6.45br (2 H, s, aryl-CH_2), 7.00 (3 H, s, CONMe), 7.20 (6 H, s, NMe_2), and 7.60 (3 H, s, NMe) (Found: C, 72.5; H, 7.7; N, 14.1. $C_{18}H_{23}N_3O$ requires C, 72.7; H, 7.8; N, 14.1%).

N-(4-*Methoxybenzyl*)-N-*phenylhydrazine* (20f).—The reaction of phenylhydrazine with sodamide and 4-methoxybenzyl bromide[33] gave the hydrazine (20f) (92%), m.p. 149°, τ 2.7—3.2 (9 H, m, aryl-H), 5.5 (2 H, s, aryl-CH_2), 6.2 (3 H, s, OMe), and 6.6—6.8br (2 H, m, NH_2).

N-(4-*Methoxybenzyl*)-N′-*methyl*-N-*phenylhydrazine* (20h).—*N*-(4-Methoxybenzyl)-*N*-phenylhydrazine (20f) (10 g) and formalin (10 ml) were heated to reflux for 15 min. Removal of half the solvent and cooling gave *N*-(4-methoxybenzyl)-*N*′-methylene-*N*-phenylhydrazine (20 g) (9.5 g, 91%), m.p. 51° (from MeOH), τ 2.7—3.4 (9 H, m, aryl H), 3.8—4.0 (2 H, m, N=CH_2), 5.1 (2 H, s, aryl CH_2), and 6.3 (3 H, s, OMe). The hydrazine (20g) (6 g) and lithium aluminium hydride (2.5 g) in diethyl ether (150 ml) were stirred for 2 h at room temperature. Ethyl acetate was added, followed by aqueous sodium hydroxide. The organic phase was washed with water, dried (KOH), and evaporated to give the hydrazine (20h) (5.8 g, 96%) as an oil, τ 2.8—3.4 (9 H, m, aryl-H), 5.5 (2 H, s, aryl-CH_2), 6.3 (3 H, s, OMe), and 7.3 (3 H, s, NMe).

N-*Benzoyl*-N′-(4-*methoxybenzyl*)-N-*methyl*-N′-*phenylhydrazine* (18f).—The *benzoylhydrazine* (18f) (82%) prepared in the usual way was obtained as white crystals, m.p. 128° (from PhH), $\nu_{max.}$ 1 640 cm^{-1}, τ 2.6—3.5 (14 H, m, aryl-H), 5.5—5.7 (2 H, s, aryl-CH_2), 6.2 (3 H, s, OMe), and 6.8 (3 H, s, NMe) (Found: C, 76.2; H, 6.5; N, 8.0. $C_{22}H_{22}N_2O_2$ requires C, 76.3; H, 6.35; N, 8.1%).

N-*Benzoyl*-N′-[*bis*-(4-*dimethylaminophenyl*)*methylene*]*hydrazine* (19c).—The *benzoylhydrazone* (19c) (84%), prepared from the hydrazone (20i) and benzoic anhydride, was obtained as white crystals, m.p. 204—205° (from EtOAc), $\nu_{max.}$ (Nujol) 3 350, 1 685, and 1 510 cm^{-1}, τ 2.0—3.5 (14 H, m, aryl-H and NH), 7.00, and 7.20 (12 H, 2s, NMe_2) (Found: C, 74.3; H, 6.7; N, 14.4. $C_{24}H_{16}N_4O$ requires C, 74.6; H, 6.8; N, 14.5%).

N-*Benzoyl*-N′-*diphenylmethylene*-N-*methylhydrazine* (19d).—The hydrazine (19a)[16] (10 g) in anhydrous benzene (20 ml) and THF (30 ml) was added to sodium hydride (1.2 g) in THF (100 ml) under nitrogen, followed after 30 min by iodomethane (7.1 g). After stirring overnight ethanol was added and the mixture evaporated. The residue in benzene (100 ml) was washed with water, dried, and evaporated to give the *hydrazide* (19d) (8.5 g, 81%), m.p. 66.5—67° (from Et_2O–light petroleum), $\nu_{max.}$ ($CHBr_3$) 1 630 cm^{-1}, $\lambda_{max.}$ 243 (ε 18 000), and 311 nm (4 800), τ 2.3—3.0 (15 H, m, aryl-H), and 6.93 (3 H, s, CONMe), *m/e* 314 (M^+), 237, 200, 194, 165, and 77 (Found: C, 80.4; H, 5.8; N, 8.9. $C_{21}H_{18}N_2O$ requires C, 80.2; H, 5.8; N, 8.9%).

Oxidation of N′-*Benzoyl*-NN-*dimethylhydrazine* (17a).—Lead tetra-acetate (3.72 g) in dry benzene (400 ml) was added to *N*′-benzoyl-*NN*-dimethylhydrazine[34] (17a) (275 mg) and pyridine (662 mg) in dry benzene (20 ml). After 1 h, aqueous 10% sodium disulphite (50 ml) was added and the mixture stirred for 10 min. Excess of aqueous sodium hydrogen carbonate was added and the mixture filtered through Celite. Normal work-up[13] gave benzoic acid (78 mg, 38%). A repeat oxidation of the dimethylhydrazide (17a) (600 mg) gave, in the neutral fraction, a 1 : 1 mixture of oxadiazoline (21a and b) (426 mg). Crystallisation from benzene–light petroleum gave 3-*acetoxymethyl*-5-*phenyl*-1,3,4-*oxadiazol*-2(3H)-*one* (21b), m.p. 132—133°, $\nu_{max.}$ (Nujol) 1 785 and 1 745 cm^{-1}, $\lambda_{max.}$ 260 nm (ε 9 900), τ 2.0—2.7 (5 H, m, aryl-H), 6.52 (2 H, s, N·CH_2), and 7.87 (3 H, s, COMe) (Found: C, 56.1; H, 4.3; N, 12.0. $C_{11}H_{10}N_2O_4$ requires C, 56.4; H, 4.3; N, 12.0%); and as a third crop crystals of 3-*methyl*-5-*phenyl*-1,3,4-*oxadiazol*-2(3H)-*one* (21a), m.p. 97.5—98.5°, $\nu_{max.}$ 1 775 cm^{-1}, τ 2.0—2.8 (5 H, m, aryl-H) and 6.53 (3 H, s, NMe) (Found: C, 61.6; H, 4.8; N, 15.9. $C_9H_8N_2O_2$ requires C, 61.4; H, 4.6; N, 15.9%).

Oxidation of the Hydrazide. (19d).—Toluene-4-sulphonic acid (0.95 g) in water (1 ml) was added to the hydrazide (19d) (314 mg) in THF (4 ml). After 30 min the solution with

[31] S. Goldschmidt and V. Voeth, *Annalen*, 1924, **435**, 265.
[32] R. L. Hinman, *J. Org. Chem.*, 1960, **25**, 1775.
[33] L. F. Audrieth, J. R. Weisiger, and H. E. Carter, *J. Org. Chem.*, 1941, **6**, 417.
[34] R. L. Hinman, *J. Amer. Chem. Soc.*, 1956, **78**, 1645.

THF (2 × 2 ml) was added *drop by drop* over 30 min with stirring to sodium periodate (0.86 g) in THF (20 ml) and water (5 ml). THF was removed under vacuum after 20 min and the residue worked up by the normal method [13] to give benzoic acid (122 mg, 100%). Inverse addition of solid sodium periodate gave benzoic acid (40%) and *N*-methylbenzamide (60%).

(1S,3S,5R,6R)-2,2-*Dimethyl*-3-(N'N'-*di-isopropylcarbazoyl*)-6-*phenylacetamidopenam* 1-*Oxide* (31a).—Reaction of the anhydride (30a) and *NN*-di-isopropylhydrazine gave the *hydrazide* (31a) (55%), m.p. 176—178° (from EtOAc), $[\alpha]_D^{25}$ +200° (*c* 2.0), $\nu_{max.}$ 3 400, 1 780, and 1 680 cm^{-1}, τ 2.78 (5 H, s, aryl-H), 4.0 (1 H, dd, *J* 10 and 4 Hz, 6-H), 5.14 (1 H, d, *J* 4 Hz, 5-H), 5.46 (1 H, s, 3-H), 6.44 (2 H, s, aryl-CH_2), 6.7 (2 H, m, C*H*Me_2), 8.22 (3 H, s, 2-Me), 8.78 (3 H, s, 2-Me), and 8.9 and 9.02 (12 H, 2d, CH*Me*$_2$) (Found: C, 58.9; H, 7.1; N, 12.4; S, 7.1. $C_{22}H_{32}N_4O_4S$ requires C, 58.9; H, 7.2; N, 12.5; S, 7.1%).

(3R,4R)-4-(*Acetylmethylthio*)-1-[1-(N'N'-*di-isopropylcarbazoyl*)-2-*methylprop*-2-*enyl*]-3-*phenylacetamidoazetidin*-2-*one* (38a).—The hydrazide (31a) (2.5 g) and aluminium chloride (50 mg) in dry THF (20 ml), dioxan (80 ml), and n-butyl isopropenyl ether (10 ml) were heated to reflux under nitrogen for 7.5 h. After cooling aqueous 20% v/v orthophosphoric acid (15 ml) was added, followed after 14 h by ethyl acetate (200 ml). The solution was washed with brine (2 × 50 ml), aqueous 5% sodium hydrogen carbonate (2 × 30 ml), and brine (50 ml) again, and dried. Evaporation and chromatography (eluant $CHCl_3$) gave the chlorocepham (34c) (0.29 g, 12%), $\nu_{max.}$ 3 450, 3 300, 1 760, and 1 680 cm^{-1}, τ 2.6 (5 H, s, aryl-H), 4.3 (1 H, m, 7-H), 4.75 (1 H, m, 6-H), 5.2 (1 H, s, 4-H), 5.65 and 7.3 (2 H, ABq, *J* 14 Hz, 2-H), 6.3 (2 H, s, aryl-CH_2), 6.8 (2 H, m, C*H*Me_2), 8.02 (3 H, s, 3-Me), and 8.9 and 9.04 (12 H, d, CH*Me*$_2$), *m/e* 468/466 (M^+); and (eluant EtOAc) the oxo-sulphide (38a) (1.25 g, 45%) as a foam, $\nu_{max.}$ 3 400, 3 300, 1 755, and 1 680 cm^{-1}, τ 2.74 (5 H, s, aryl-H), 4.72—5.18 (5 H, m), 6.38 (3 H, s, aryl-CH_2), 6.46—7.26 (4 H, m, CH_2·CO, C*H*Me_2), 7.86 (3 H, s, MeCO), 8.12 (3 H, s, C=CMe), and 8.78—9.26 (12 H, d, CH*Me*$_2$), *m/e* 488 (M^+), 473, 430, and 398.

(3R,4R)-4-(*Acetylmethylthio*)-1-[1-(N'N'-*di-isopropylcarbazoyl*)-2-*hydroxyprop*-1-*enyl*]-3-*phenylacetamidoazetidin*-2-*one* (40a).—Ozonised oxygen was bubbled through the oxo-sulphide (38a) (0.31 g) and anhydrous toluene-4-sulphonic acid (0.11 g) in dichloromethane (15 ml) at −78 °C until reaction was complete (t.l.c.; 20 min). Dichloromethane (20 ml) was added and the solution washed with aqueous 10% potassium iodide and 10% potassium thiosulphate (10 ml), aqueous 5% sodium hydrogen carbonate (10 ml) and water (10 ml), and dried. Evaporation gave the enol (40a) as foam, $\nu_{max.}$ 3 350, 1 780, 1 680, and 1 630 cm^{-1}, $\lambda_{max.}$ 260 nm (ε 7 500), τ 2.75 (5 H, s, aryl-H), 5.05 (1 H, d, *J* 4 Hz, 4-H), 5.32 (1 H, dd, *J* 8 and 4 Hz, 3-H), 6.38 (2 H, s, aryl-CH_2), 6.6—7.2 (2 H, m, C*H*Me_2), 6.85 (2 H, s, CH_2·CO), 7.85 (3 H, s, MeCO), 8.08 [3 H, s, *Me*C(OH)=C)], 8.95 and 9.05 (12 H, d, CH*Me*$_2$).

(1S,3S,5R,6R)-2,2-*Dimethyl*-6-*phenylacetamido*-3-(NN'N'-*trimethylcarbazoyl*)*penam* 1-*Oxide* (31d).—Reaction of the mixed anhydride (30a) and trimethylhydrazine gave the *hydrazide* (31d) (51%), m.p. 76—82° (from $CHCl_3$), $[\alpha]_D^{20}$ −140° (*c* 2.0), $\nu_{max.}$ 3 400, 1 780, 1 680, and 1 510 cm^{-1}, τ 2.75 (5 H, s, aryl-H), 2.80 (1 H, d, *J* 10 Hz, NH), 4.05 (1 H, dd, *J* 10 and 4 Hz, 6-H), 4.4 (1 H, s, 3-H), 4.98 (1 H, d, *J* 4 Hz, 5-H), 6.42 (2 H, s, aryl CH_2), 7.07 (3 H, s, NMe), 7.42 (6 H, s, NMe_2), 8.35 (3 H, s, 2-Me), and 8.75 (3 H, s, 2-Me) (Found: C, 45.5; H, 5.1; Cl, 20.5; N, 10.6; S, 6.1. $C_{19}H_{26}N_4O_4S,CHCl_3$ requires C, 45.7; H, 5.2; Cl, 20.2; N, 10.7; S, 6.1%).

Oxidation of the Trimethylhydrazide (31d).—Cerium(IV) ammonium nitrate (1.2 equiv.) in 0.5M-nitric acid or 50% aqueous acetic acid (4 ml) was added over 20 min to the trimethylhydrazide (31d) (131 mg) in acetonitrile (5 ml) at −10 °C. After 2.5 h stirring, dichloromethane (50 ml) was added and the solution washed with brine to neutrality, dried, and evaporated to give a 1 : 1 mixture (n.m.r.) of the hydrazone (31l) and starting material (31d) (86 mg). Reaction of the trimethylhydrazide (31d) with cerium(IV) ammonium nitrate (10 equiv.) at −10 °C for 20 h gave the acid (9a) (>90%), identical with an authentic sample.

(3S,5R,6R)-2,2-*Dimethyl*-6-*phenylacetamido*-3-(NN'N'-*trimethylcarbazoyl*)*penam* (31n).—Phosphorus tribromide (4.8 g) was added over 5 min to the sulphoxide (31d) (4.8 g) in dry dimethylformamide (DMF) (70 ml) at −5 °C. After 10 min ice (200 g) and water (100 ml) were added, and after 5 min more the mixture was extracted with ethyl acetate (3 × 200 ml). The organic phase was washed with brine (100 ml), dried, and evaporated to give the *sulphide* (31n) (1.25 g, 25%), m.p. 84—86° (from EtOAc), $[\alpha]_D^{25}$ +100° (*c* 1.0), $\nu_{max.}$ (Nujol) 3 330, 3 290, 1 780, 1 732, 1 680, 1 650, and 1 510 cm^{-1}, τ 2.68 (5 H, s, aryl-H), 3.37br (1 H, d, *J* 10 Hz, NH), 4.42 (3 H, m, 3-, 5-, and 6-H), 6.37 (2 H, s, aryl-CH_2), 7.10 (3 H, s, NMe), 7.45 (6 H, s, NMe_2), 8.57 (6 H, s 2-Me), and peaks due to solvate (0.5 mol. equiv.) [Found: C, 58.0; H, 6.7; N, 13.0; S, 7.6. $C_{19}H_{26}N_4O_3S,0.5(C_4H_8O_2)$ requires C, 58.0; H, 7.0; N, 12.9; S, 7.4%].

(3R,4R)-4-(*Acetylmethylthio*)-1-[2-*methyl*-1-(NN'N'-*trimethylcarbazoyl*)*prop*-2-*enyl*]-3-*phenylacetamidoazetidin*-2-*one* (38b).—The penam trimethylhydrazide (31d) (20g) in dry dioxan–THF (250 ml; 7 : 1) and n-butyl isopropenyl ether (48 g) were heated under nitrogen. Anhydrous aluminium chloride (400 and 150 mg) was added on reflux commencing and after 1 h, respectively. After a further 45 min the solution was cooled to 0 °C and a sample (10 ml) worked up to give the enol ether (37b), $\nu_{max.}$ 3 400, 1 780, 1 680, 1 670, 1 520, and 925 cm^{-1}, τ 2.7 (5 H, s, aryl H), 3.0 (1 H, d, *J* 10 Hz, NH), 4.1—5.4 (6 H, m, vinyl H, N·CHCO, 3-H, and 4-H), 6.4 (2 H, s, aryl-CH_2), 7.1 (3 H, s, NMe), 7.5 (6 H, 2s, NMe_2), 8.1br (6 H, 2s, vinyl Me), and n-butyl resonances. The bulk solution was diluted with acetone (160 ml) and aqueous 10% phosphoric acid (80 ml) added. After 18 h stirring, ethyl acetate–diethyl ether (400 ml; 4 : 1) was added, and the solution washed with brine, dried, and evaporated. Chromatography (eluant CH_2Cl_2–EtOAc, 9 : 1) gave the *oxo-olefin* (38b) (13.2 g, 78%) as a gum, $[\alpha]_D^{20}$ −137° (*c* 1.0), $\nu_{max.}$ 3 400, 1 760, 1 660, 1 520, and 925 cm^{-1}, τ 2.7 (5 H, m, aryl-H), 3.5 (1 H, m, NH), 4.5 (3 H, m, N·CHCO, 3-H, and 4-H), 5.0 (2 H, m, vinyl H), 6.3 (2 H, s, aryl-CH_2), 6.7 (2 H, s, SCH_2), 7.1 (3 H, s, NMe), 7.5 and 7.6 (6 H, 2s, NMe_2), 7.9 (3 H, s, COMe), and 8.1 (3 H, s, vinyl Me), *m/e* 446 (M^+) (Found: C, 59.1; H, 6.9; N, 12.6; S, 7.35. $C_{22}H_{30}N_4O_4S$ requires C, 59.2; H, 6.8; N, 12.55; S, 7.2%); and the less polar chlorocepham (34a) (5%).

(6R,7R)-3-*Chloro*-3-*methyl*-7-*phenylacetamido*-4-(NN'N'-*trimethylcarbazoyl*)*cepham* (34a).—The enol ether (37b) (223 mg) in dry THF (25 ml) was heated to reflux, and aluminium chloride (50 mg) was added. After 1½ h ethyl acetate (50 ml) was added, and the solution washed to neutrality with brine and evaporated to give the crude chlorocepham (34a) as a gum, τ 2.7 (5 H, m, aryl-H), 3.1 (1 H, d, *J* 10 Hz, NH), 4.1 (1 H, s, 4-H), 4.4 (1 H, dd, *J* 10 and 4 Hz, 4-H), 4.8 (1 H,

d, *J* 4 Hz, 6-H), 6.0 (1 H, d, *J* 14 Hz, 2-H), 6.4 (2 H, s, aryl-CH_2), 7.1 (4 H, s, d, *J* 14 Hz, NMe and 2-H), 7.5 (6 H, 2s, NMe_2), and 8.4 (3 H, s, 3-Me).

(6R,7R)-3-*Chloro*-3-*methyl*-7-*phenylacetamido*-4-(NN'N'-*trimethylcarbazoyl*)*cepham* 1-*Oxide* (34b).—Sodium periodate (290 mg) in water (2 ml) was added to the chlorocepham (34a) (523 mg) in THF (20 ml). After 2 days at 5 °C the *sulphoxide* (34b) (330 mg, 57%) was filtered off; m.p. 129.5—130.5° (from wet EtOAc), $[\alpha]_D^{21}$ −65° (*c* 0.9), $\nu_{max.}$ ($CHBr_3$) 3 680, 3 600, 1 775, 1 685, 1 655, 1 505, 1 050, and 1 040 cm^{-1}, τ 2.64 (6 H, m, aryl-H and N-H), 4.20 (2 H, m, 4-H and 7-H), 5.05 (1 H, d, *J* 4 Hz, 6-H), 5.86 [1 H, d, *J* 12 Hz, S(O)CH], 6.34 (2 H, s, aryl-CH_2), 6.4 [1 H, m, S(O)CH], 7.08 (3 H, s, NMe), 7.43 and 7.50 (6 H, 2s, NMe_2), and 8.32 (3 H, s, 3-Me) (Found: C, 48.5; H, 5.9; Cl, 7.5; N, 11.45; S, 6.7. $C_{19}H_{25}ClN_4O_4S,1.5H_2O$ requires C, 48.8; H, 5.7; Cl, 7.6; N, 11.95; S, 6.9%).

(3R,4R)-4-(*Acetylmethylthio*)-1-[2-*oxo*-1-(NN'N'-*trimethylcarbazoyl*)*propyl*]-3-*phenylacetamidoazetidin*-2-*one* (41a).—Ozonised oxygen was passed through the oxo-olefin (38b) (2.5 g) and toluene-4-sulphonic acid (100 mg) in dichloromethane at −70 °C until the solution was permanently pale blue. The solution was purged with nitrogen and washed [aqueous KI–$Na_2S_2O_3$–$NaHCO_3$ (5% each in brine, 3 × 50 ml), brine (50 ml)], dried, and evaporated to leave the diketone (41a) (2.3 g, 92%) as an orange foam, $\nu_{max.}$ 3 400, 1 780, 1 710, 1 700, and 1 520 cm^{-1}, τ 2.7 (5 H, s, aryl-H), 3.4 (1 H, m, NH), 4.4 (1 H, s, N·CHCO), 4.7 (2 H, m, 3-H and 4-H), 6.4 (2 H, s, aryl-CH_2), 6.7 (2 H, m, S·CH_2CO), 7.1 (3 H, s, NMe), 7.4, 7.6 (6 H, 2s, NMe_2), 7.7 (3 H, s, COMe), and 8.0 (3 H, s, COMe).

(6R,7R)-2-*Acetyl*-3-*hydroxy*-3-*methyl*-7-*phenylacetamido*-4-(NN'N'-*trimethylcarbazoyl*)*cepham* (42a).—Cyclisation of the diketone (41a) (2.3 g) with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (0.6 g) in hexamethylphosphoramide (HMPT) (10 ml) for 18 h, work-up, and chromatography (eluant CH_2Cl_2–EtOAc, 22 : 3, 4 : 1) gave the *cepham* (42a) (1.6 g, 69%), m.p. 163—165° (from $CHCl_3$–CCl_4), $[\alpha]_D^{20}$ +108° (*c* 1.0), $\nu_{max.}$ 3 500—3 400, 1 770, 1 710, 1 680, and 1 500 cm^{-1}, τ 2.8 (5 H, s, aryl-H), 3.1br (1 H, d, *J* 9 Hz, NH), 4.5—4.7 (3 H, m, 2-, 6-, and 7-H), 4.9 (1 H, s, 4-H), 5.9 (1 H, m, OH), 6.4 (2 H, s, aryl-CH_2), 7.1 (3 H, s, NMe), 7.5 (6 H, 2s, NMe_2), 7.7 (3 H, s, COMe), 8.6 (3 H, s, 3-Me), and 8.8 (s, minor isomer, 3-Me) (Found: C, 56.5; H, 6.2; N, 12.75; S, 7.35. $C_{21}H_{28}N_4O_5S$ requires C, 56.25; H, 6.25; N, 12.5; S, 7.15%). The cepham (42a) (50%) was alternatively prepared by cyclisation of the diketone (41a) with an excess of Triton B in DMF for 12 h at room temperature.

(6R,7R)-3-*Acetoxy*-2-*acetyl*-3-*methyl*-7-*phenylacetamido*-4-(NN'N'-*trimethylcarbazoyl*)*cepham* (42b).—Anhydrous potassium fluoride (500 mg) was added, with cooling, to the cepham (42a) (200 mg) in acetic anhydride (3 ml) and trifluoroacetic anhydride (0.7 ml). After 2 h stirring, ethyl acetate (30 ml) was added and the solution stirred with aqueous 3% phosphoric acid (14 ml) for 2 h. Work-up gave the acetate (42b) (208 mg, 95%), $\nu_{max.}$ 3 400, 1 765, 1 735, 1 705, 1 690, 1 660, and 1 495 cm^{-1}.

(6R,7R)-2-*Acetyl*-3-*methyl*-7-*phenylacetamido*-4-(NN'N'-*trimethylcarbazoyl*)*ceph*-3-*em* (43a).—The acetate (42b) (100 mg) and anhydrous lithium fluoride in dry DMF (2 ml) were heated to reflux for 1 h. Work-up with ethyl acetate and brine gave the *ceph*-3-*em* (43a) as a foam, $[\alpha]_D^{20}$ −90° (*c* 1.0), $\nu_{max.}$ 3 400, 1 760, 1 710, 1 685, and 1 665 cm^{-1}, $\lambda_{max.}$ 262 nm (6 000), τ 2.9 (5 H, s, aryl-H), 3.2 (1 H, d, *J* 9 Hz, NH), 4.5 (1 H, dd, *J* 9 and 4 Hz, 7-H), 5.2 (1 H, d, *J* 4 Hz, 6-H), 6.05 (1 H, s, 2-H), 6.4 (2 H, s, aryl-CH_2), 7.1 (3 H, s, NMe), 7.6 (6 H, 2s, NMe_2), 7.75 (3 H, s, COMe), and 8.2 (3 H, s, 3-Me), *m/e* 430 (M^+) (Found: C, 58.75; H, 5.9; N, 12.95; S, 7.4. $C_{21}H_{26}N_4O_4S$ requires C, 58.6; H, 6.1; N, 13.0; S, 7.45%).

The acetate (42b) (200 mg), 18-crown-6 (100 mg), and anhydrous potassium fluoride (700 mg) in benzene (8 ml) were heated to reflux for 45 min. Chromatography gave the cephem (43a).

(6R,7R)-3-*Methyl*-7-*phenylacetamido*-4-(NN'N'-*trimethylcarbazoyl*)*ceph*-3-*em* (33d).—The *ceph*-3-*em* (33d) (400 mg, 68%), prepared *via* the mixed anhydride (33b), was obtained as a pale yellow foam, $[\alpha]_D^{25}$ +354° (*c* 1.0), $\nu_{max.}$ 3 400, 1 770, 1 680, and 1 510 cm^{-1}, τ 2.35 (1 H, d, *J* 9 Hz, NH), 2.71 (5 H, s, aryl-H), 4.40 (1 H, dd, *J* 9 and 4.5 Hz, 7-H), 5.08 (1 H, d, *J* 4.5 Hz, 6-H), 6.43 (2 H, s, aryl-CH_2), 6.78 (1 H, d, *J* 13 Hz, S·CH), 7.0—7.4 (1 H, m, S·CH), 7.11 (3 H, s, NMe), 7.57 (6 H, s, NMe_2), and 8.25 (3 H, s, 3-Me) (Found: C, 58.4; H, 6.2; N, 13.9; S, 7.8. $C_{19}H_{24}N_4O_3S$ requires C, 58.7; H, 6.2; N, 14.4; S, 8.25%).

Oxidation of the Trimethylhydrazide (33d).—Cerium(IV) ammonium nitrate (0.3M in 50% aqueous acetic acid; 8.5 ml, 10 equiv.) was added to the trimethylhydrazide (33d) (97 mg) in acetonitrile at −20 °C. After 18 h work-up gave non-β-lactam products.

N-4-*Methoxybenzyl*-NN'-*dimethylhydrazine* (20j).—4-Methoxybenzoic anhydride (5.45 g) in dichloromethane (60 ml) was added with stirring over 30 min to *NN'*-dimethylhydrazine (2.8 g) and triethylamine (6.49 g) in ethyl acetate (50 ml) and light petroleum (50 ml) at −20°. The mixture was diluted with ethyl acetate (50 ml) and washed with aqueous sodium hydrogen carbonate (4 × 50 ml) and brine (50 ml), dried, and evaporated to give *N*-4-methoxybenzoyl-*NN'*-dimethylhydrazine (20k) (2.95 g, 79%) as an oil, $\nu_{max.}$ 3 600—3 200, 2 840, and 1 620 cm^{-1}, τ 2.3—3.3 (4 H, m, aryl-H), 4.5—5.5br (1 H, m, NH), 6.15 (3 H, s, OMe), 6.78 (3 H, s, CONMe), and 7.32 (3 H, s, NMe), *m/e* 194 (M^+). The hydrazide (20k) (2.95 g) in dry dioxan (50 ml) was added dropwise with stirring to lithium aluminium hydride (1.15 g) in diethyl ether (100 ml) while refluxing was maintained. After 30 min, water was added and the solution filtered, dried, and evaporated to give the hydrazine (20j) (2.44 g, 89%) as an oil, $\nu_{max.}$ (film) 3 400br, 2 830, 1 610, 1 510, and 825 cm^{-1}, τ 2.6—3.3 (4 H, m, aryl-H), 6.22 (3 H, s, OMe), 6.35 (2 H, s, aryl-CH_2), 7.43 (3 H, s, CH_2NMe), and 7.62 (3 H, s, NMe).

(1S,3S,5R,6R)-3-(N'-4-*Methoxybenzyl*-NN'-*dimethylcarbazoyl*)-2,2-*dimethyl*-6-*phenylacetamidopenam* 1-*Oxide* (31b).—Reaction of the acid (9a) (3.91 g) and the hydrazine (20j) (2.0 g) *via* the anhydride (30a) gave the *hydrazide* (31b) (1.22 g, 39%), m.p. 154.5—156° (from EtOAc), $[\alpha]_D^{25}$ +41° (*c* 1.0), $\nu_{max.}$ (Nujol) 3 320, 1 785, 1 690, 1 660, and 1 510 cm^{-1}, τ 2.65 (5 H, s, C_6H_5), 2.5—3.3 (4 H, m, C_6H_4), 4.0 (1 H, m, 6-H), 4.16 (1 H, s, 3-H), 4.93 (1 H, d, *J* 5 Hz, 5-H), 6.17 (3 H, s, OMe), 6.2br (2 H, s, aryl-CH_2N), 6.4 (2 H, s, $PhCH_2$), 6.96 (3 H, s, CONMe), 7.53 (3 H, s, NMe), 8.40 (3 H, s, 2-Me), and 8.73 (3 H, s, 2-Me) (Found: C, 60.8; H, 6.4; N, 10.9; S, 6.4. $C_{26}H_{31}N_4O_5S$ requires C, 60.9; H, 6.3; N, 10.9; S, 6.2%).

(1S,3S,5R,6R)-3-[N'-(4-*Methoxybenzyl*)-N-*methyl*-N'-*phenylcarbazoyl*]-2,2-*dimethyl*-6-*phenylacetamidopenam* 1-*Oxide* (31c) —The *hydrazine* (31c) (72%) prepared in the usual way, was obtained as crystals, m.p. 88—89° (from PhH–light petroleum), $\nu_{max.}$ 3 400, 1 798, and 1 672 cm^{-1}, τ 2.6—3.4 (14 H, m, aryl-H), 6.2 (3 H, s, OMe), and 7.1 (3 H, s,

NMe) (Found: C, 64.35; H, 5.95; N, 9.2; S, 5.5. $C_{31}H_{34}N_4O_5S$ requires C, 64.8; H, 5.9; N, 9.75; S, 5.55%).

(1S,3S,5R,6R)-3-(N′-*Diphenylmethylenecarbazoyl*)-2,2-*dimethyl*-6-*phenylacetamidopenam* 1-*Oxide* (31e).—Reaction of benzophenone hydrazone (2.8 g) and the acid (9a) (5.0 g) *via* the anhydride (30a) gave the *hydrazone* (31e) (6.1 g, 81%) as a pale yellow foam, $[\alpha]_D^{20}$ +155° (*c* 1.05), $\nu_{max.}$ 3 350, 1 795, 1 685, and 1 510 cm^{-1}, $\lambda_{max.}$ 288 nm (ε 20 300), τ 2.0—3.0 (16 H, m, aryl-H and NH), 3.16 and 4.37 (1 H, 2dd, *J* 10 and 5 Hz, 6-H), 4.17 and 5.51 (1 H, 2s, 3-H), 4.93 and 5.17 (1 H, 2d, *J* 5 Hz, 5-H), 6.42 and 6.47 (2 H, 2s, aryl-CH_2), 8.23 and 8.29 (3 H, 2s, Me), and 8.76 and 8.83 (3 H, 2s, Me), *m/e* (M^+ absent) 494, 476, 450, 360, 202, and 165 (100%) (Found: C, 65.85; H, 5.45; N, 10.45. $C_{29}H_{28}N_4O_4S$ requires C, 65.85; H, 5.35; N, 10.6%).

(1S,3S,5R,6R)-3-{N′-[(*Bis*-4-*methoxyphenyl*)*methylene*]*carbazoyl*}-2,2-*dimethyl*-6-*phenylacetamidopenam* 1-*Oxide* (31f).—The acid (9a) (2.74 g) and 4,4′-dimethoxybenzophenone hydrazone [35] (2.0 g) on reaction *via* compound (30a) gave the hydrazone (31f) (2.96 g, 53%) as a white foam, $[\alpha]_D^{21}$ +101° (*c* 0.9), $\nu_{max.}$ 3 380, 3 290, 1 800, 1 690, and 1 510 cm^{-1}, τ 2.0—3.5 (14 H, m, NH and aryl-H), 3.92 and 4.27 (1 H, 2-dd, *J* 10 and 5 Hz, 6-H), 4.12 and 5.47 (1 H, 2s, 3-H), 4.91 and 5.30 (1 H, 2d, *J* 5 Hz, 5-H), 6.10 and 6.18 (6 H, 2s, MeO), 6.40 and 6.43 (2 H, 2s, aryl-CH_2), 8.12 and 8.25 (3 H, 2s, 2-Me), and 8.75 (3 H, 2s, 2-Me).

(1S,3S,5R,6R)-3-{N′-[(*Bis*-4-*dimethylaminophenyl*)*methylene*]*carbazoyl*}-2,2-*dimethyl*-6-*phenylacetamidopenam* 1-*Oxide* (31g).—Reaction of the acid (9a) (3.7 g) and 4,4′-bisdimethylaminobenzophenone hydrazone [35] (3.0 g) *via* the anhydride (30a) gave the *hydrazide* (31g) (2.6 g, 40%), m.p. 177.5—179° (from EtOAc), $[\alpha]_D^{25}$ +130° (*c* 0.7), $\nu_{max.}$ 3 380, 3 300, 1 810, 1 690, 1 615, and 1 500 cm^{-1}, τ 2.3—3.6 (14 H, m, aryl-H and NH), 3.93 and 4.33 (1 H, 2dd, *J* 10 and 5 Hz, 6-H), 5.14 and 5.51 (1 H, 2s, 3-H), 4.93 and 5.38 (1 H, 2d, *J* 5 Hz, 5-H), 6.42br (2 H, s, aryl-CH_2), 7.00 (12 H, m, NMe_2), 8.20 and 8.25 (3 H, 2s, 2-Me), and 8.74 and 8.81 (3 H, 2s, 2-Me) (Found: C, 64.2; H, 6.0; N, 13.9; S, 5.3. $C_{33}H_{38}N_6O_4S$ requires C, 64.5; H, 6.2; N, 13.7; S, 5.2%).

(3R,4R)-4-(*Acetylmethylthio*)-1-[1-(N′-*diphenylmethylenecarbazoyl*)-2-*methylprop*-2-*enyl*]-3-*phenylacetamidoazetidin*-2-*one* (38c).—The hydrazide (31e) (8.36 g) and n-butyl isopropenyl ether (17.0 g) in dry dioxan (90 ml) and THF (10 ml) were heated to reflux under nitrogen. Anhydrous aluminium chloride (10 mg) was added at 45 min intervals. After 6 h the usual work-up gave the crude enol ether (37e), $\nu_{max.}$ 3 300, 1 760, and 1 680 cm^{-1}. The crude product in dioxan (100 ml) and orthophosphoric acid (10%; 60 ml) was stirred overnight. Work-up as before and chromatography gave benzophenone (700 mg, 26%), (6*R*,7*R*)-3-chloro-4-(*N*′-diphenylmethylenecarbazoyl)-3-methyl-7-phenylacetamidocepham (34e) (610 mg, 8%), $[\alpha]_D^{21}$ +240° (*c* 1.0), $\nu_{max.}$ 3 400, 3 300, 1 770, and 1 680 cm^{-1}, τ 1.47 (1 H, s, NNH), 2.2—3.0 (15 H, m, aryl-H), 3.22 (1 H, d, *J* 9 Hz, NH), 3.96 (1 H, s, 4-H), 4.37 (1 H, dd, *J* 9, 4 Hz, 7-H), 4.69 (1 H, d, *J* 4 Hz, 6-H), 6.09 and 7.32 (2 H, ABq, *J* 16 Hz, S·CH_2), and 8.25 (3 H, s, 3-Me); and the sulphide (38c) (5.04 g, 59%), $[\alpha]_D^{21}$ −136° (*c* 0.9), $\nu_{max.}$ 3 400, 3 300, 1 770, 1 715, and 1 685 cm^{-1}, τ 1.55 (1 H, s, NNH), 2.2—3.2 (16 H, m, aryl-H and NH), 4.26 (1 H, s, CH·CONN), 4.57 (2 H, m, 3-H and 4-H), 4.87 (2 H, m, C=CH_2), 6.38 (2 H, s, aryl-CH_2), 6.80 (2 H, s, S·CH_2), 7.91 (3 H, s, COMe), and 7.95 (3 H, s, CMe).

[35] H. H. Szmant and C. McGinnis, *J. Amer. Chem. Soc.*, 1950, **72**, 2890; N. Latif, I. Zeid, and B. Hoggog, *J. Heterocyclic Chem.*, 1968, **5**, 831.

(3R,4R)-4-(*Acetylmethylthio*)-1-[1-(N′-*diphenylmethylenecarbazoyl*)-2-*hydroxyprop*-1-*enyl*]-3-*phenylacetamidoazetidin*-2-*one* (40c).—The sulphide (38c) (300 mg) and pyridine (0.5 ml) in dichloromethane (80 ml) were treated with ozonised oxygen at 78 °C to give, after normal work-up, the enol hydrazide (40c) (242 mg, 80%), $[\alpha]_D^{24}$ −54° (*c* 0.15), $\nu_{max.}$ 3 400s, 3 300s (NH), 3 500—3 100br (OH), 1 775, and 1 680 cm^{-1}, $\lambda_{max.}$ 259 (ε 16 300) and 338 nm (14 000), τ 2.0—3.0 (15 H, m, aryl-H), 3.5—5.5br (3 H, m, 3-H, 4-H, and N·CH-CONN), 6.4br (2 H, s, aryl-CH_2), 4.6—4.9 (2 H, m, S·CH_2), 7.9 (3 H, s, SCH_2·CO*Me*), and 7.95 [3 H, m, C=C(OH)*Me*].

(1S,3S,5R,6R)-3-[N′-*Bis*-(4-*methoxyphenyl*)*methylene*-N-*methylcarbazoyl*]-2,2-*dimethyl*-6-*phenylacetamidopenam* 1-*Oxide* (31i).—Reaction of the acid (9a) (1.5 g) and 4,4′-dimethoxybenzophenone methylhydrazone (70% pure; 1.5 g) *via* the anhydride (30a) and chromatography gave the hydrazide (31i) (1.19 g, 46%), as a foam, $[\alpha]_D^{21}$ +101° (*c* 0.9), $\nu_{max.}$ 3 350, 1 785, 1 670, and 1 060 cm^{-1}, τ 2.3—3.3 (14 H, m, aryl-H and NH), 4.00 (1 H, dd, *J* 11 and 5 Hz, 6-H), 4.32 (1 H, s, 3-H), 4.95 (1 H, d, *J* 5 Hz, 5-H), 6.13 (3 H, s, OMe), 6.17 (3 H, s, OMe), 6.45 (2 H, s, aryl-CH_2), 7.25 (3 H, s, NMe), 8.37 (3 H, s, 2-Me), and 8.68 (3 H, s, 2-Me).

(1S,3S,5R,6R)-3-[N′-(4-*Methoxyphenyl*)*methylene*-N-*methylcarbazoyl*]-2,2-*dimethyl*-6-*phenylacetamidopenam* 1-*Oxide* (31j).—Reaction of the acid (9a) (4.3 g) and 4-methoxybenzaldehyde methylhydrazone [36] (2.0 g) *via* the anhydride (30a) gave after chromatography the *hydrazide* (31j) (3.36 g, 55%), m.p. 161—162° (from PhH–EtOAc), $[\alpha]_D^{25}$ −100° (*c* 1.0), $\nu_{max.}$ (Nujol) 1 795, 1 690, 1 040, and 845 cm^{-1}, τ 2.21 (1 H, s, aryl-CH=), 2.2—3.2 (5 H, m, C_6H_4 and NH), 2.65 (5 H, m, C_6H_5), 3.91 (1 H, dd, *J* 10 and 4 Hz, 6-H), 3.95 (1 H, s, 3-H), 4.89 (1 H, d, *J* 4 Hz, 5-H), 6.14 (3 H, s, OMe), 6.40 (2 H, s, aryl-CH_2), 6.58 (3 H, s, NMe), 8.47 (3 H, s, 2-Me), and 8.95 (3 H, s, 2-Me) (Found: C, 60.4; H, 5.7; N, 11.3; S, 6.5. $C_{25}H_{28}N_4O_5S$ requires C, 60.5; H, 5.7; N, 11.3; S, 6.5%).

(3R,4R)-1-[1-(NN′-*Di-isopropylcarbazoyl*)-2-*methylprop*-2-*enyl*]-3-*phenylacetamido*-4-(2-*propoxyprop*-1-*enylthio*)*azetidin*-2-*one* (37c).—Reaction of the sulphoxide (9b) [13] and 2-propoxypropene [37] gave the crude *enol ether* (37c) (220 mg). Purification by p.l.c. (developing solvent EtOAc) gave a white foam (80 mg, 36%), $[\alpha]_D^{20}$ −117° (*c* 1.1), $\nu_{max.}$ 3 400, 1 765, 1 660, and 1 510 cm^{-1}, τ 2.69 (5 H, s, aryl-H), 4.6 (3 H, m, CONH, 3-H, and 4-H), 5.0 (2 H, m, C=CH_2), 5.5—7.0 (3 H, m, NH, 2 × C*H*Me_2), 6.42 (2 H, s, aryl-CH_2), 6.60 (2 H, s, S·CH_2), 7.90 (3 H, s, $COCH_3$), 8.12 (3 H, s, vinyl Me), and 8.5—9.2 (12 H, m, CH*Me*$_2$) (Found: C, 60.9; H, 7.3; N, 11.4; S, 6.7. $C_{25}H_{36}N_4O_4S$ requires C, 61.4; H, 7.4; N, 11.5; S, 6.6%).

(6R,7R)-4-(N′-*Diphenylmethylene*-N-*methylcarbazoyl*)-3-*methyl*-7-*phenylacetamidoceph*-3-*em* (33e).—Pyridine (1.8 g) and the crude hydrazone (20a) (3.5 g, containing 1 mol. equiv.) were added to the acyl chloride (33c) [19] (3.0 g) in THF (100 ml) at −20 °C. After warming to room temperature, ethyl acetate (200 ml) was added and the solution washed with aqueous 1% phosphoric acid (2 × 30 ml) and brine (2 × 30 ml), dried and evaporated. Chromatography gave (eluant $CHCl_3$–PhMe, 1 : 1) the *ceph*-2-*em* (35a) (380 mg, 9%) as a foam, $[\alpha]_D^{22}$ +190° (*c* 1.1), $\nu_{max.}$ ($CHBr_3$) 3 390, 1 760, 1 670, 1 660, and 1 510 cm^{-1}, $\lambda_{max.}$ 288 nm (ε 15 100), τ 2.3—2.8 (15 H, m, aryl-H), 3.64 (1 H, d, *J* 9 Hz, NH), 3.46 (1 H, s, S·CH=), 4.11 (1 H, s, 4-H), 4.38 (1 H, dd, *J* 9 and 4.5 Hz, 7-H), 4.65 (1 H, d, *J* 4.5 Hz, 6-H), 6.39 (2 H, s, aryl-CH_2),

[36] R. H. Wiley and G. Irick, *J. Org. Chem.*, 1959, **24**, 1925.
[37] H. P. Crocker and R. H. Hall, *J. Chem. Soc.*, 1955, 2052.

7.26 (3 H, s, NMe), and 8.19 (3 H, s, 3-Me) (Found: C, 68.45; H, 5.4; N, 10.65. $C_{30}H_{28}N_4O_3S$ requires C, 68.65; H, 5.4; N, 10.7%); a mixture of the ceph-2-em (35a) and the ceph-3-em (33e) (600 mg); and the *ceph-3-em* (33e) (2.59 g, 58%), $[\alpha]_D^{21}$ −40° (*c* 1.0), $\nu_{max.}$ ($CHBr_3$) 3 400, 1 764, 1 680, 1 660, and 1 510 cm^{-1}, τ 2.4—2.8 (15 H, m, aryl-H), 3.84 (1 H, d, *J* 10 Hz, NH), 4.36 (1 H, dd, *J* 10 and 4.5 Hz, 7-H), 5.11 (1 H, d, *J* 4.5 Hz, 6-H), 6.39 (2 H, s, aryl-CH_2), 6.57 and 6.79 (2 H, m, S·CH_2), 7.10 (3 H, s, NMe), and 8.12 (3 H, s, 3-Me), *m/e* 524 (M^+) (Found: C, 68.35; H, 5.4; N, 10.6%).

(6R,7R)-3-*Methyl*-4-(N-*methylcarbazoyl*)-7-*phenylacetamidoceph*-3-*em* (33f).—The cephem (33e) (524 mg) and toluene-4-sulphonic acid monohydrate (1.9 g) in THF (8 ml) and H_2O (2 ml) were stirred for 10 min. Brine (20 ml) and ethyl acetate (20 ml) were added and the organic phase was extracted with M-toluene-4-sulphonic acid (10 ml). Excess of sodium hydrogen carbonate and sodium chloride (to saturate) were added to the combined aqueous phase, and the solution was extracted with chloroform (4 × 30 ml). The chloroform solution was washed with water (10 ml), dried, and evaporated to give the *hydrazide* (33f) (245 mg, 74%) as a white foam, $[\alpha]_D^{21}$ −33° (*c* 0.9), $\nu_{max.}$ ($CHBr_3$) 3 412, 3 300, 1 766, 1 684, 1 670, and 1 508 cm^{-1}, $\lambda_{max.}$ 259 (ε 8 100), τ 2.66 (5 H, m, aryl-H), 3.39 (1 H, d, *J* 10.5 Hz, NH), 4.28 (1 H, m, 7-H), 5.07 (1 H, d, *J* 4.5 Hz, 6-H), 6.48 and 6.96 (2 H, ABq, *J* 18 Hz, S·CH_2), 6.42 (2 H, s, aryl-CH_2), 6.88 (3 H, s, NMe), and 8.30 (3 H, s, 3-Me), *m/e* 360 (M^+).

Oxidation of the Hydrazide (33f).—Oxidation of the hydrazide (33f) from the cephem (33e) (390 mg), without isolation, with manganese dioxide (260 mg) in acetic acid (5 ml) gave on normal work-up [13] the carboxylic acid (33a) (112 mg, 46%), identical with an authentic sample.

(1S,3S,5R,6R)-3-(N′-*Diphenylmethylene*-N-*methylcarbazoyl*)-2,2-*dimethyl*-6-*phenylacetamidopenam* 1-*Oxide* (31h).—Triethylamine (15.9 g), isopropyl chloroformate (19.3 g), and (after 1 h) *N*-diphenylmethylene-*N*′-methylhydrazine [18] (35 g; 70% pure) were added in sequence to (1*S*)-6β-phenylacetamidopenicillanic acid 1-oxide (9a) (55 g) in THF (800 ml) at 0 °C under nitrogen. After 1 h stirring the solvent was removed *in vacuo* and the residue in ethyl acetate washed with water, aqueous sodium hydrogen carbonate, and brine. Evaporation and chromatography (eluant CH_2Cl_2–EtOAc) gave the *hydrazone* (31h) (42 g, 49%) as a foam. Crystallisation from EtOAc–light petroleum gave white needles, m.p. 113.5—115°, $[\alpha]_D^{16}$ −34° (*c* 0.96), $\nu_{max.}$ 3 380, 1 780, and 1 675br cm^{-1}, $\lambda_{max.}$ 235.5 (ε 16 700) and 300 nm (8 400), τ 2.62 (16 H, m, aryl-H and NH), 3.98 (1 H, dd, *J* 4.5 and 10.5 Hz, 6-H), 4.18 (1 H, s, 3-H), 4.95 (1 H, d, *J* 4.5 Hz, 5-H), 6.43 (2 H, s, aryl-CH_2), 7.25 (3 H, s, NMe), 8.4 (3 H, s), and 8.72 (3 H, s), *m/e* (M^+ absent) 524, 492, 210, 165, and 105 (Found: C, 66.45; H, 5.4; N, 10.55. $C_{30}H_{30}N_4O_4S$ requires C, 66.4; H, 5.55; N, 10.3%).

Methylation of the Hydrazone (31e).—Iodomethane (0.36 ml) in dry acetone (3 ml) was added with stirring to the hydrazone (31e) (1.46 g) in acetone (8 ml) containing anhydrous potassium carbonate (0.6 g). After 30 h, ethyl acetate (40 ml) was added and the mixture filtered and evaporated to give the methyl derivative (31 h) (1.33 g, 91%) as white needles, m.p. 114—115° (from EtOAc–light petroleum).

(3R,4R)-1-[1-(N′-*Diphenylmethylene*-N-*methylcarbazoyl*)-2-*methylprop*-2-*enyl*]-3-*phenylacetamido*-4-(2-*propoxyprop*-1-*enylthio*)*azetidin*-2-*one* (37d).—The sulphoxide (31h) (3 g) in dioxan (20 ml), THF (5 ml), and 2-propoxypropene [38] (6 ml) was heated to reflux under nitrogen. Portions of anhydrous aluminium chloride (*ca.* 2 mg) were added at 30 min intervals. After 2 h the solvent was removed under vacuum and the residue in EtOAc washed with aqueous sodium hydrogen carbonate, and brine, dried, and evaporated to give the crude enol ether (37d) (3.9 g) as a brown oil. Chromatography (eluant CH_2Cl–EtOAc 4 : 1) gave the *enol ether* (37d) (1.87 g) as a foam, $[\alpha]_D^{22}$ −295° (*c* 0.11), $\nu_{max.}$ 3 400, 1 762, and 1 675 cm^{-1}, τ 2.67 (15 H, m, aryl-H), 3.55 (1 H, d, *J* 10 Hz, NH), 4.3 (1 H, s, N·CHCO), 4.4 (1 H, m, 3-H), 4.7 (1 H, m, 4-H), 4.9 (2 H, m, C=CH_2), 5.45 (1 H, s, S·CH), 6.35 (2 H, s, aryl-CH_2), 6.5 (2 H, m, O·CH_2), 7.3 (3 H, s, NMe), 8.1 [3 H, s, C=C(OPr)CH_3], 8.15br (3 H, s, MeC=C), 8.1—8.8 (2 H, m, OCH_2·CH_2), and 9.1br (3 H, t, CH_2·CH_3), *m/e* (M^+ absent) 583, 493, 291, 255, 209, and 165 (100%). The crude product (not normally isolated) was leached with boiling light petroleum and used directly in the next step.

(3R,4R)-4-(*Acetylmethylthio*)-1-[1-N′-*diphenylmethylene*-N-*methylcarbazoyl*)-2-*methylprop*-2-*enyl*]-3-*phenylacetamidoazetidin*-2-*one* (38d).—Mercury(II) nitrate (50 mg) was added to the enol ether (37d) (1.05 g) in acetonitrile (35 ml) and water (7 ml). After stirring for 2½ h the solution was diluted with EtOAc, filtered through Celite, washed with water, and brine, dried, and evaporated. Chromatography (eluant CH_2Cl_2–EtOAc, 9 : 1) gave the *ketone* (38d) (850 mg, 87%) as a pale yellow foam, $[\alpha]_D^{21}$ −317° (*c* 0.11), $\nu_{max.}$ 1 765, 1 715sh, and 1 670br cm^{-1}, $\lambda_{max.}$ 305 nm (ε 9 000), τ 2.4—2.7 (15 H, m, aryl-H), 3.48br (1 H, NH), 4.24 (1 H, s, N·CH·C=), 4.4—4.6 (2 H, m, 3-H and 4-H), 4.88br and 4.97br (2 H, C=CH_2), 6.34 (2 H, s, aryl-CH_2), 6.78 (2 H, s, S·CH_2·CO), 7.28 (3 H, s, NMe), 7.86 (3 H, s, $COCH_3$), and 8.17 (3 H, s, C=CMe), *m/e* 582 (M^+), 524, 491, 319, 291, 209, and 165 (100%) (Found: C, 67.8; H, 5.9; N, 9.7; S, 5.5. $C_{33}H_{34}N_4O_4S$ requires C, 68.0; H, 5.9; N, 9.6; S, 5.5%). Hydrolysis of the enol ether (37d) with 0.1M-orthophosphoric acid in THF–H_2O (2 : 1) during 5 h at room temperature resulted in concomitant hydrazone cleavage. Benzoic, phthalic, tartaric, or oxalic acid (0.1M) catalysed hydrolysis at reflux or at room temperature also gave benzophenone.

(3R,4R)-4-(*Acetylmethylthio*)-1-[1-(N′-*diphenylmethylene*-N-*methylcarbazoyl*)-2-*oxopropyl*]-3-*phenylacetamidoazetidin*-2-2-*one* (41b *and* c).—The olefin (38d) (0.95 g) in dichloromethane (70 ml) and pyridine (1.5 ml) was treated at −78 °C with ozonised oxygen until a permanent pale blue colour was observed. The solution was purged with nitrogen, warmed to room temperature, and washed with aqueous potassium iodide (5%)–sodium thiosulphate (5%), aqueous sodium hydrogen carbonate, and brine. Evaporation and chromatography (eluant CH_2Cl_2–EtOAc, 9 : 2) gave *diketone* (940 mg, 99%) as a mixture of stereoisomers (41b and c). Crystallisation from EtOAc–light petroleum gave the major isomer (41b) as white needles, m.p. 141.5—143°, $[\alpha]_D^{23}$ −244° (*c* 1.01), $\nu_{max.}$ 1 775, 1 725, and 1 675 cm^{-1}, $\lambda_{max.}$ 303 nm (ε 7 300), τ 2.6br (15 H, m, aryl-H), 3.1 (1 H, d, *J* 9 Hz, NH), 3.95 (1 H, s, NCHCO), 4.2—4.8 (2 H, m, 3-H and 4-H), 6.26 (2 H, s, s, aryl-CH_2), 6.6 (2 H, s, S·CH_2), 7.25 (3 H, s, NMe), 7.72 (3 H, s, MeCO), and 7.85 (3 H, s, SCH_2·CO*Me*), *m/e* (M^+ absent) 541, 450, 210, and 165 (100%) (Found: C, 65.65; H, 5.6; N, 9.45. $C_{32}H_{32}N_4O_5S$ requires C, 65.7; H, 5.5; N, 9.6%). P.l.c. on silica (developed in EtOAc–light

[38] K. von Auwers and P. Heimke, *Annalen*, 1927, **458**, 186.

petroleum, 7 : 3) gave the minor isomer (41c) as an oil, $[\alpha]_D^{23}$ +24° (*c* 1.01), τ 4.25 (1 H, s, NCHCO) and 6.75 (2 H, s, S·CH_2).

(6R,7R)-2-*Acetyl*-4-(N′-*diphenylmethylene*-N-*methylcarbazoyl*)-3-*hydroxy*-3-*methyl*-7-*phenylacetamidocepham* (42c).—DBN (25 μl) was added to the diketone mixture (41b and c) (700 mg) in HMPT (15 ml). The mixture was stirred for 5 h under N_2, then diluted with EtOAc, and washed with aqueous 4% phosphoric acid (4 × 10 ml), water (3 × 10 ml), and brine (3 × 10 ml). Evaporation and chromatography (eluant CH_2Cl_2–EtOAc, 9 : 1) gave the *cepham* (42c) (370 mg, 53%) as a foam, $[\alpha]_D^{21}$ +208° (*c* 0.88), $\nu_{max.}$ 3 405s, 3 100—3 500br, 1 775, 1 730, and 1 675 cm^{-1}, $\lambda_{max.}$ 243.5 (ε 19 500) and 305.5 nm (7 800), τ 2.7br (15 H, aryl-H), 3.55br (1 H, d, *J* 9 Hz, NH), 4.45 (3 H, m, 6-H, 7-H, and NCHCO), 5.22 (1 H, s, S·CH), 5.3 (1 H, s, exch.D_2O, OH), 6.45 (2 H, s, aryl-CH_2), 7.3 (3 H, s, NMe), 7.65 (3 H, s, COMe), and 8.5br (3 H, s, *Me*COH), *m/e* (M^+ absent) 450, 287, 241, 210, and 165 (100%) (Found: C, 65.95; H, 5.6; N, 9.4. $C_{32}H_{32}N_4O_5S$ requires C, 65.7; H, 5.5; N, 9.6%); and (eluant CH_2Cl_2–EtOAc, 9 : 1) the cepham (42c) contaminated by starting material (41b and c) (270 mg, 39%).

(3R,4R)-4-(1-*Acetyl*-2-*hydroxyprop*-1-*enylthio*)-1-(N′-*diphenylmethylene*-N-*methylcarbazoylmethyl*)-3-*phenylacetamidoazetidin*-2-*one* (45).—The diketone mixture (41b and c) (259 mg), DBN (700 mg), and HMPT (5 ml) were stirred for 2 h. Usual work-up and p.l.c. (developing solvent EtOAc) gave the enol (45) (58 mg, 20%) as a gum, $\nu_{max.}$ ($CHBr_3$) 3 380, 1 760, 1 670, and 1 510 cm^{-1}, $\lambda_{max.}$ 240 (ε 17 700) and 289 nm (12 000), τ 2.4—2.7 (15 H, m, aryl-H), 3.37 (1 H, d, *J* 9 H , NH), 4.39 (1 H, dd, *J* 9 and 5 Hz, 3-H), 4.91 (1 H, d, *J* 5 Hz, 4-H), 5.10 and 5.75 (2 H, ABq, *J* 18 Hz, N·CH_2), 6.33 (2 H, s, aryl-CH_2), 7.29 (3 H, s, NMe), and 7.74 (6 H, s, COMe).

(6R,7R)-2-*Acetyl*-4-(N′-*diphenylmethylene*-N-*methylcarbazoyl*)-3-*methyl*-7-*phenylacetamidoceph*-3-*em* (43c).—The cepham (42c) (150 mg) in dichloromethane (freshly distilled from P_4O_{10}; 3 ml) and trifluoroacetic anhydride (1 ml) was stirred at 0 °C under argon for 3 h 40 min. Volatile materials were removed under vacuum at 0 °C and the residue was dissolved in dichloromethane (3 ml). DBN (freshly distilled from sodium; 80 μl) in dichloromethane (0.5 ml) was added dropwise and the solution stirred at 0 °C for 45 min. The solution was diluted with ethyl acetate, washed with aqueous 5% phosphoric acid, water, and brine, dried, and evaporated. P.l.c. on silica (developed in EtOAc–light petroleum, 1 : 1) gave (in order of increasing polarity) starting material (42c) (18 mg, 13%) and the ceph-3-em (43c) (95 mg, 65%) as a foam, $[\alpha]_D^{23}$ −248° (*c* 0.22), $\nu_{max.}$ 1 775 and 1 710, $\lambda_{max.}$ 210 (ε 19 800), 244 (15 400), and 304 nm (6 500), τ 2.65 (15 H, aryl-H), 3.33br (1 H, d, *J* 9 Hz, NH), 6.5 (1 H, dd, *J* 9 and 4.5 Hz, 7-H), 5.25 (1 H, d, *J* 4.5 Hz, 6-H), 5.98 (1 H, s, S·CH), 6.45 (2 H, s, aryl-CH_2), 7.1 (3 H, s, NMe), 7.7 (3 H, s, COMe), and 8.28 (3 H, s, C=CMe), *m/e* 566 (M^+), 312, 210, and 165 (100%) (Found: C, 67.8; H, 5.35; N, 9.85. $C_{32}H_{30}N_4O_4S$ requires C, 67.8; H, 5.35; N, 9.9%).

(6R,7R)-2-*Acetyl*-3-*methyl*-7-*phenylacetamidoceph*-3-*em*-4-*carboxylic Acid* (43b).—Toluene-4-sulphonic acid (0.25 g) was added to the cephem (43c) (90 mg) in THF (1 ml) and water (0.25 ml). After 35 min stirring the solution with THF (2 × 1 ml) was added *drop by drop* over 20 min to sodium periodate (37.4 mg) in THF (12 ml) and water (3 ml). After a subsequent 10 min sodium hydrogen carbonate (150 mg) and aqueous 10% sodium thiosulphate (to remove iodide) were added. THF was removed under vacuum and the residue diluted with water (30 ml) and extracted with dichloromethane (20 ml and 6 × 10 ml). Aqueous 5% orthophosphoric acid was added (to pH 2.5) and the solution extracted with ethyl acetate (30 ml and 6 × 10 ml). The dried extract was evaporated and chromatographed (eluant EtOAc) to give the *carboxylic acid* (43b) (35 mg, 59%) as a white amorphous solid, $[\alpha]_D^{22}$ −93° (*c* 0.103), $\nu_{max.}$ (CH_2Cl_2) 3 400s, 3 500—2 500br, 1 785, 1 710, 1 690, 1 635sh, and 1 505 cm^{-1}, $\lambda_{max.}$ 265 nm (ε 4 800), τ 2.72 (5 H, m, aryl-H), 3.08 (1 H, d, *J* 9 Hz, NH), 3.37 (2—3 H, m, CO_2H and H_2O), 4.28 (1 H, dd, *J* 9 and 4.5 Hz, 7-H), 5.22 (1 H, d, *J* 4.5 Hz, 6-H), 5.88 (1 H, s, 2-H), 6.42 (2 H, s, aryl-CH_2), 7.65 (3 H, s, COMe), and 7.95 (3 H, s, 3-Me), *m/e* 330, 328, 312, 287, and 159; a sample purified by p.l.c. on silica (developed in Me_2CO–$CHCl_3$–AcOH, 50 : 50 : 7.5) was obtained as a white amorphous solid (Found: C, 55.25; H, 4.8; N, 7.4; S, 8.3. $C_{18}H_{18}N_2O_5S,H_2O$ requires C, 55.1; H, 5.15; N, 7.15; S, 8.15%).

1-*Benzoyl*-3-*phenyl*-Δ²-*pyrazoline* (46a).—3-Phenyl-Δ²-pyrazoline (46h) [38] (0.73 g) was added to benzoic anhydride (1.13 g) and triethylamine (0.56 g) in dry THF (6 ml) under nitrogen at 0 °C. After warming to room temperature the solvent was removed and the residue in benzene washed with aqueous 10% orthophosphoric acid, aqueous 5% sodium hydrogen carbonate, and brine, and dried. Evaporation gave 1-*benzoyl*-3-*phenyl*-Δ²-*pyrazoline* (46a) (1.27 g, 85%), m.p. 80.5—81.5° (from Et_2O), $\nu_{max.}$ (Nujol) 1 628 cm^{-1}, $\lambda_{max.}$ 223 (ε 15 500) and 301 nm (25 000), τ 1.9—2.9 (10 H, m, aryl-H), 5.6—6.1 (2 H, t, *J* 10 Hz, N·CH_2), and 6.7—7.2 (2 H, t, *J* 10 Hz, N=C–CH_2), *m/e* 250 (M^+) (Found: C, 76.75; H, 5.5; N, 11.05. $C_{16}H_{14}N_2O_4$ requires C, 76.8; H, 5.65; N, 11.2%).

1-*Benzoyl*-3-(4-*methoxyphenyl*)-Δ²-*pyrazoline* (46b).—The *pyrazoline* (46b) (88%), prepared as for (46a), was obtained as crystals, m.p. 110—112°, $\nu_{max.}$ 1 615br, 1 575, 1 455, and 1 440 cm^{-1}, $\lambda_{max.}$ 223 (ε 14 500), 303sh (25 100), and 308 nm (25 700), τ 2.1—3.2 (9 H, m, aryl-H), 5.8 (2 H, t, *J* 10 Hz, N·CH_2), 6.2 (3 H, s, OMe), and 6.8 (2 H, t, *J* 10 Hz, N=C–CH_2) (Found: C, 72.65; H, 5.8; N, 9.9. $C_{17}H_{16}N_2O_2$ requires C, 72.8; H, 5.75; N, 10.0%).

1-*Benzoyl*-3-(3,4-*dimethoxyphenyl*)-Δ²-*pyrazoline* (46c).—The *pyrazoline* (46c) (67%), prepared as for (46a), was obtained as white crystals, m.p. 119.5—120.5° (from EtOAc–Et_2O), $\nu_{max.}$ 1 622br and 1 572 cm^{-1}, $\lambda_{max.}$ 220 (ε 13 000), 292sh (11 500), 304sh (15 000), and 316 nm (18 000), τ 1.9—3.3 (8 H, m, aryl-H), 5.8 (2 H, t, *J* 10 Hz, CH_2), 6.2 (6 H, s, MeO), and 6.8 (2 H, t, *J* 10 Hz, CH_2), *m/e* 310 (M^+), 205, 105, and 77 (Found: C, 69.7; H, 5.65; N, 9.15. $C_{18}H_{18}N_2O_3$ requires C, 69.65; H, 5.85; N, 9.05%).

(1S,3S,5R,6R)-3-[3-(4-*Methoxyphenyl*)-Δ²-*pyrazolin*-1-*ylcarbonyl*]-2,2-*dimethyl*-6-*phenylacetamidopenam* 1-*Oxide* (31p).—Reaction of the pyrazoline (46i) [39] (2.1 g) and the mixed anhydride (30a) derived from the acid (9a) (3.5 g) gave the *pyrazoline* (31p) (4.3 g, 84%), m.p. 182—184.5° (from CH_2Cl_2–EtOAc), $[\alpha]_D^{25}$ −10° (*c* 1.0), $\nu_{max.}$ 3 400, 1 795, 1 670, 1 615, and 1 520 cm^{-1}, τ 2.4—3.0 (10 H, m, aryl-H and NH), 4.0 (1 H, dd, *J* 10 and 5 Hz, 6-H), 4.3 (1 H, s, 3-H), 4.9 (1 H, d, *J* 5 Hz, 5-H), 6.2 (5 H, s, t, OMe and CON·CH_2), 6.5 (2 H, s, aryl-CH_2), 6.8 (2 H, t, *J* 10 Hz, N=C–CH_2), 8.4 (3 H, s, 2-Me), and 8.8 (3 H, s, 2-Me) (Found: C, 61.2; H, 5.4; N, 11.0; S, 6.2. $C_{26}H_{28}N_4O_5S$ requires C, 61.4; H, 5.55; N, 11.0; S, 6.3%).

[39] A. N. Kost and V. V. Ershov, *Zhur. obshchei Khim.*, 1957, **27**, 1072.

(1S,3S,5R,6R)-3-[3-(3,4-*Dimethoxyphenyl*)-Δ²-*pyrazolin*-1-*ylcarbonyl*]-2,2-*dimethyl*-6-*phenylacetamidopenam* 1-*Oxide* (31q).—Reaction of the pyrazoline (46j) [40] (1.7 g) and the mixed anhydride (30a) derived from the acid (9a) (1.92 g) gave the *pyrazoline* (31q) (1.63 g, 61%), m.p. 174—176° (from EtOAc–light petroleum), $[\alpha]_D^{23}$ +109 (*c* 1.0), $\nu_{max.}$ (CH_2Cl_2) 3 372, 1 788, 1 665, and 1 520 cm^{-1}, $\lambda_{max.}$ 225 (ε 16 600), 287.5sh (18 200), 298sh (22 000), 315 (24 600), and 325sh nm (19 000), τ 2.7 (5 H, s, C_6H_5), 2.8—3.3 (4 H, m, C_6H_3 and NH), 4.0 (1 H, dd, *J* 10 and 5 Hz, 6-H), 4.3 (1 H, s, 3-H), 4.9 (1 H, d, *J* 5 Hz, 5-H), 6.1 (8 H, s, t, MeO and CON·CH_2), 6.4 (2 H, s, aryl-CH_2), 6.8br (2 H, t, *J* 10 Hz, N=C–CH_2), 8.2 (3 H, s, 2-Me), and 8.7 (3 H, s, 2-Me), *m/e* 520 (M^+ − 18), 488, 347, 329, and 314 (Found: C, 60.2; H, 5.65; N, 10.1; S, 5.75. $C_{27}H_{30}N_4O_6S$ requires C, 60.2; H, 5.6; N, 10.4; S, 5.95%).

(6R,7R)-4-[3-(4-*Methoxyphenyl*)-Δ²-*pyrazolin*-1-*ylcarbonyl*]-3-*methyl*-7-*phenylacetamidoceph*-3-*em* (33g).—The *pyrazoline* (33g) (65%), prepared in the usual way, was obtained as crystals, m.p. 198—200° (from CH_2Cl_2–Et_2O), $[\alpha]_D^{25}$ +106° (*c* 1.0 in CH_2Cl_2–MeOH, 20 : 1), $\nu_{max.}$ 3 400, 1 770, 1 675, 1 625, and 1 610 cm^{-1}, τ 2.4—3.0 (9 H, m, aryl-H), 3.5 (1 H, d, *J* 10 Hz, NH), 4.3 (1 H, dd, *J* 10 and 4 Hz, 7-H), 5.0 (1 H, d, *J* 4 Hz, 6-H), 5.9br (2 H, t, *J* 10 Hz, CON·CH_2), 6.2 (3 H, s, OMe), 6.4 (4 H, s, t, aryl-CH_2 and N=C–CH_2), and 8.1 (3 H, s, 2-Me) (Found: C, 63.8; H, 5.4; N, 11.2; S, 6.6. $C_{26}H_{26}N_4O_4S$ requires C, 63.7; H, 5.3; N, 11.4; S, 6.5%).

Oxidation of Acylpyrazolines with Lead Tetra-acetate.—The pyrazoline, lead tetra-acetate (2 equiv.), and pyridine (2 equiv.) in dichloromethane were heated to reflux for 4½—7 h. Work-up in the usual way gave 1-*benzoyl*-3-(4-*methoxyphenyl*)*pyrazole* (46d) (99%), m.p. 76—77° (from MeOH–Et_2O–light petroleum), $\nu_{max.}$ (Nujol) 1 690 and 1 615 cm^{-1}, $\lambda_{max.}$ 243.5 (ε 14 400), 290 (10 200), and 309 nm (11 200), τ 1.65 and 3.3 (2 H, ABq, *J* 3 Hz), 1.7—3.2 (9 H, m, aryl-H), and 6.2 (3 H, s, OMe) (Found: C, 73.25; H, 5.2; N, 10.05. $C_{17}H_{14}N_2O_2$ requires C, 73.35; H, 5.05; N, 10.05%); or 1-*benzoyl*-3-(3,4-*dimethoxyphenyl*)*pyrazole* (46e) (100%), m.p. 105—105.5° (from Et_2O), $\nu_{max.}$ (Nujol) 1 691 and 1 607 cm^{-1}, $\lambda_{max.}$ 245 (ε 16 200) and 316 nm (11 000), τ 1.7—3.1 (8 H, m, C_6H_5 and C_6H_3), 1.6 and 3.3 (2 H, ABq, *J* 3 Hz, pyrazole-H), and 6.1 (6 H, s, MeO), *m/e* 308 (M^+), 105, and 77 (Found: C, 69.95; H, 5.5; N, 9.0. $C_{18}H_{16}N_2O_3$ requires C, 70.1; H, 5.25; N, 9.1%).

Oxidation of the Penam Acylpyrazoline (31p).—Cerium(IV) ammonium nitrate (0.6 mmol) in 50% aqueous acetic acid (2 ml) was added over 15 min to the pyrazoline (31p) (126 mg) in acetonitrile (3 ml) at −20 °C. After 2 h dichloromethane (20 ml) was added and the solution washed with brine (to neutrality), dried, and evaporated to give the crude pyrazole (31w) as a foam, $\nu_{max.}$ 3 400, 1 800, 1 730, 1 680, and 1 610 cm^{-1}, τ 1.7 (1 H, d, *J* 3 Hz, pyrazole-H), 2.2 (2 H, d, *J* 9 Hz, aryl-H), 2.7br (6 H, s, C_6H_5 and NH), 3.1 (3 H, 2d, *J* 9 and 3 Hz, pyrazole-H and aryl-H), 3.9 (2 H, m, 3- and 6-H), 4.9 (1 H, d, *J* 4 Hz, 5-H), 6.2 (3 H, s, OMe), 6.4 (2 H, s, aryl-CH_2), 8.2 (3 H, s, 2-Me), and 8.8 (3 H, s, 2-Me). The crude pyrazole (31w) (80 mg) in dioxan (5 ml) containing aqueous 20% orthophosphoric acid (3 ml) was stirred for 24 h. Normal work-up gave the acid (9a) (35 mg, 62%) and unchanged pyrazoline (31p) (<20%).

(1S,3S,5R,6R)-3-[2-(4-*Methoxyphenyl*)-Δ²-*imidazolin*-1-*ylcarbonyl*]-2,2-*dimethyl*-6-*phenylacetamidopenam* 1-*Oxide* (31r).—Reaction of the anhydride (30a) and 2-(4-methoxyphenyl)-Δ²-imidazoline (47b) [41] gave the *acylimidazoline* (31r) (96%), m.p. 101.5—103° (from MeOH), $\nu_{max.}$ 3 340, 1 785, and 1 675 cm^{-1}, τ 2.8 (5 H, m, C_6H_5), 2.5—3.25 (4 H, m, C_6H_4), 4.0—4.3 (1 H, dd, *J* 10 and 4 Hz, 6-H), 5.1 (1 H, d, *J* 4 Hz, 5-H), 5.2 (1 H, s, 3-H), 5.7—6.1br (4 H, m, 2 × CH_2), 6.2 (3 H, s, OMe), 6.5 (2 H, s, aryl-CH_2), 8.5 (3 H, s. s, 2-Me), and 8.8 (3 H, s, 2-Me), *m/e* 508 (M^+) (Found: C, 60.15; H, 6.0; N, 10.0; S, 5.8. $C_{26}H_{28}N_4O_5S,CH_3OH$ requires C, 60.0; H, 6.0; N, 10.35; S, 5.95%).

N-(4-*Methoxybenzoyl*)*ethylenediamine* (51b).—Methyl anisate (13 g) and dry ethylenediamine (15.7 ml) were heated in a sealed tube for 24 h at 100 °C. The orange oil in benzene was extracted with water. After saturation with sodium chloride the aqueous phase was extracted repeatedly with chloroform. Evaporation gave the amide (51b) (11 g, 72%), as an oil, $\nu_{max.}$ 3 450 and 1 625 cm^{-1}, τ 2 25—3.5 (4 H, ABq, *J* 8 Hz, aryl-H), 6.35 (3 H, s, OMe), 6.5—6.95 (2 H, t, *J* 6 Hz, CH_2), 7.1—7.45 (2 H, t, *J* 6 Hz, CH_2), and 8.7 (2 H, s, exch. D_2O, NH_2).

(1S,3S,5R,6R)-3-[2-(4-*Methoxybenzamido*)*ethylcarbamoyl*]-2,2-*dimethyl*-6-*phenylacetamidopenam* 1-*Oxide* (31s).—The *amide* (31s) (95%) prepared from the acid (9a) (2.03 g) and *N*-(4-methoxybenzoyl)ethylenediamine (51b) (1.13 g) *via* the anhydride (30a), was obtained as a foam, $\nu_{max.}$ 3 310, 1 790, and 1 660 cm^{-1}, τ 2.7 (5 H, m, C_6H_5), 2.1—3.4 (4 H, m, C_6H_4), 3.9—4.3 (1 H, dd, *J* 10 and 4 Hz, 6-H), 5.2 (1 H, d, *J* 4 Hz, 5-H), 5.5 (1 H, s, 3-H), 6.2 (3 H, s, OMe), 6.2—7.0br (6 H, aryl-CH_2 and N·$[CH_2]_2$·N), 8.3 (3 H, s, 2-Me), and 8.9 (3 H, s, 2-Me), *m/e* 508 (M^+ − 18) (Found: C, 59.25; H, 6.0; N, 10.6; S, 5.6. $C_{26}H_{30}N_4O_6S$ requires C, 59.3; H, 5.75; N, 10.65; S, 6.1%).

3,4-*Bis*-(4-*methoxyphenyl*)-Δ³-*pyrroline* (48d).—3,4-Bis-(4-methoxyphenyl)pyrrole (48c) [42] (1.55 g) and zinc dust (3.3 g) in ethanol (30 ml) and 20% hydrochloric acid (25 ml) were heated to reflux for 4 h. The mixture was filtered and evaporated and the residue in dichloromethane washed with aqueous 5% sodium hydroxide and brine, dried, and evaporated to give the pyrroline (48d) (1.43 g, 92%), τ 2.75—3.35 (8 H, m, aryl-H), 5.8 (4 H, s, 2- and 5-H), and 6.1 (6 H, s, OMe), *m/e* 279 (M^+), 221, 165, 140, and 105. The *hydrochloride* was obtained as white needles, m.p. 224.5—225.5° (from MeOH–Et_2O–light petroleum) (Found: C, 68.3; H, 6.6; N, 4.45. $C_{18}H_{19}ClNO_2$ requires C, 68.05; H, 6.35; N, 4.4%).

1-*Benzoyl*-3,4-*bis*-(4-*methoxyphenyl*)-Δ³-*pyrroline* (48a).—Reaction of benzoyl chloride, triethylamine, and the pyrroline (48d) gave the *benzoylpyrroline* (48a) (87%), m.p. 141—142.5° (from EtOAc–light petroleum), $\nu_{max.}$ (Nujol) 1 650 cm^{-1}, $\lambda_{max.}$ 237 (ε 25 000) and 282.5 nm (15 000), τ 2.3—3.5 (13 H, m, aryl-H), 5.2 (2 H, d, *J* 3.5 Hz), 5.4 (2 H, d, *J* 3.5 Hz), and 6.3 (6 H, s, OMe), *m/e* 385 (M^+), 280, and 105 (Found: C, 78.0; H, 5.85; N, 3.55. $C_{25}H_{23}NO_3$ requires C, 77.9; H, 6.0; N, 3.65%).

Oxidation of 1-*Benzoyl*-3,4-*bis*-(4-*methoxyphenyl*)-Δ³-*pyrroline* (48a).—The pyrroline (48a) (52 mg) and selenium dioxide (45 mg) in dioxan (2 ml) were heated to reflux for 2.5 h. Normal work-up gave 1-*benzoyl*-3,4-*bis*-(4-*methoxyphenyl*)*pyrrole* (48b) (44 mg, 85%), m.p. 126—127° (from MeOH–Et_2O–light petroleum), $\nu_{max.}$ 1 685, 1 615, and 1 372 cm^{-1}, $\lambda_{max.}$ 238 (ε 23 000), 289 (11 000), and 305sh nm

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[41] P. Oxley and W. F. Short, *J. Chem. Soc.*, 1947, 497.

[42] M. Friedman, *J. Org. Chem.*, 1965, **30**, 859.

(9 500), τ 2.1—3.3 (15 H, m, aryl-H) and 6.2 (6 H, s, OMe), *m/e* 383 (M^+), 278, 105, and 77 (Found: C, 78.55; H, 5.75; N, 3.7. $C_{25}H_{21}NO_3$ requires C, 78.3; H, 5.5; N, 3.65%).

1-*Benzoyl*-2-*phenylpyrazolidine* (49a).—1-Phenylpyrazolidine (49g) [43] (2.88 g), benzoyl chloride (2.5 ml), and triethylamine (4.1 ml) in THF (25 ml) at 0 °C for 12 h gave the *pyrazolidine* (49a) (3.1 g, 63%), m.p. 90—91.5°, $\nu_{max.}$ (Nujol) 1 654 cm^{-1}, $\lambda_{max.}$ 235 (ε 11 000) and 265 nm (2 100), τ 2.2—3.35 (10 H, m, aryl-H), 5.8—6.4br (2 H, t, *J* 6 Hz, 5-H), 6.4—7.0br (2 H, t, *J* 6 Hz, 3-H), and 7.7—8.4 (2 H, q, *J* 6 Hz, 4-H), *m/e* 252 (M^+), 147, 105, and 77 (Found: C, 76.25; H, 6.45; N, 10.9. $C_{16}H_{16}N_2O$ requires C, 76.15; H, 6.4; N, 11.1%).

1-*Benzoyl*-2-(4-*methoxyphenyl*)*pyrazolidine* (49b).—*N*-Benzoyl-*N'*-(4-methoxyphenyl)hydrazine (17f) [44] (0.48 g) in dry THF (4 ml) and (after gas evolution had ceased) 1,3-dibromopropane (0.41 g) in THF (5 ml) were added to sodium hydride (48 mg) in THF (5 ml) under nitrogen. The mixture was heated to reflux (4 h), the THF evaporated off, and the residue in dichloromethane washed with aqueous 10% orthophosphoric acid, aqueous 5% sodium hydrogen carbonate, and brine, dried, and evaporated to give the *pyrazolidine* (49b) (0.47 g, 83%), m.p. 139.5—140.5°, $\nu_{max.}$ (Nujol) 1 639 cm^{-1}, $\lambda_{max.}$ 232 (ε 13 000) and 285 nm (2 100), τ 2.2—3.3 (9 H, m, aryl-H), 5.85—6.2 (2 H, t, *J* 6 Hz, 5-H), 6.2 (3 H, s, OMe), 6.45—7.0 (2 H, t, *J* 6 Hz, 3-H), and 7.65—8.3 (2 H, q, *J* 6 Hz, 4-H), *m/e* 282 (M^+), 177, 121, 105, and 77 (Found: C, 72.45; H, 6.5; N, 10.0. $C_{17}H_{18}N_2O_2$ requires C, 72.3; H, 6.45; N, 9.9%).

N-(4-*Methoxyphenyl*)-N'-*trifluoroacetylhydrazine* (20c).—Refluxing ethyl trifluoroacetate (3.1 g) and 4-methoxyphenylhydrazine [45] (3.0 g) in 95% ethanol (20 ml) for 4 h, evaporation, and chromatography (eluant hexane) gave the *hydrazine* (20c) (3.05 g, 60%), m.p. 93.5—94°, $\nu_{max.}$ (Nujol) 3 305, 3 254, 1 726, 1 708, and 1 172 cm^{-1}, $\lambda_{max.}$ 233 (ε 5 400) and 287 nm (1 500), τ 3.2 (4 H, s, aryl-H) and 6.2 (3 H, s, OMe), *m/e* 234 (M^+), 137, and 122 (Found: C, 46.05; H, 3.95; N, 11.95. $C_9H_9F_3N_2O_2$ requires C, 46.15; H, 3.85; N, 11.95%).

1-(4-*Methoxyphenyl*)-2-*trifluoroacetylpyrazolidine* (49e).—Reaction of the hydrazine (20c), sodium hydride, and 1,3-dibromopropane gave the *pyrazolidine* (49e) (90%), m.p. 117—118.5° (from MeOH), $\nu_{max.}$ 1 690 and 1 153 cm^{-1}, $\lambda_{max.}$ 230 (ε 11 000) and 287 nm (1 500), τ 3.1 (4 H, s, aryl-H), 6.2 (3 H, s, OMe), 5.65—7.0br (4 H, 2 t, *J* 8 Hz, 3- and 5-H), and 7.65—8.35 (2 H, q, *J* 8 Hz, 4-H), *m/e* 274 (M^+), 177, 134, and 121 (Found: C, 52.55; H, 4.85; N, 10.35. $C_{12}H_{13}F_3N_2O_2$ requires C, 52.55; H, 4.8; N, 10.2%).

(1S,3S,5R,6R)-3-[2-(4-*Methoxyphenyl*)*pyrazolidin*-1-*ylcarbonyl*]-2,2-*dimethyl*-6-*phenylacetamidopenam* 1-*Oxide* (31t).—1-(4-Methoxyphenyl)-2-trifluoroacetylpyrazolidine (49e) (0.67 g) and aqueous 40% sodium hydroxide (6 ml) in methanol (10 ml) were heated to reflux under argon for 1 h. The mixture was evaporated and the residue, in dichloromethane was washed with brine, dried, and evaporated to give the crude pyrazolidine (49d). The pyrazolidine (49d) and the anhydride (30a) gave (after p.l.c.) 1-(4-*methoxyphenyl*)-Δ^2-*pyrazoline* (46g) (70 mg, 16%), m.p. 76.5—77° (from MeOH), $\lambda_{max.}$ 240 (ε 6 500) and 282 nm (9 300), τ 2.9—3.3 (4 H, m, aryl-H), 3.35br (1 H, t, *J* 9 Hz, 3-H), 6.4 (3 H, s, OMe), 6.4—6.85 (2 H, t, *J* 9 Hz, 5-H), and 7.1—7.6 (2 H, t, *J* 9 Hz, 4-H), *m/e* 176 (M^+), 161, 134, 121, and 77 (Found: C, 68.25; H, 7.0; N, 15.8. $C_{10}H_{12}N_2O$ requires C, 68.15; H, 6.85; N, 15.9%); *ethyl* 2-(4-*methoxyphenyl*)*pyrazolidine*-1-*carboxylate* (49f) (29%), m.p. 56—57° (from light petroleum), $\nu_{max.}$ 1 685 and 1 125 cm^{-1}, $\lambda_{max.}$ 235 (ε 8 900) and 293 nm (1 300), τ 2.9—3.45 (4 H, m, aryl-H), 5.85 (2 H, q, *J* 7 Hz, O·C*H*$_2$·CH$_3$), 6.25 (3 H, s, OMe), 6.3—6.8 (4 H, 2 t, *J* 6 Hz, 3- and 5-H), 7.8—8.4 (2 H, m, 4-H), and 8.8 (3 H, t, *J* 7 Hz, O·CH$_2$·C*H*$_3$), *m/e* 250 (M^+) and 177 (Found: C, 62.15; H, 7.15; N, 11.4. $C_{13}H_{18}N_2O_3$ requires C, 62.35; H, 7.25; N, 11.2%); and the *pyrazolidine* (31t) (64%) as a foam, $[\alpha]_D^{25}$ +110° (*c* 1.0), $\nu_{max.}$ 3 375, 1 791, and 1 666 cm^{-1}, $\lambda_{max.}$ 226 (ε 13 000) and 289 nm (1 600), τ 2.65—3.0 (5 H, m, C_6H_5), 3.2 (4 H, m, C_6H_4), 4.2 (1 H, dd, *J* 9.4 Hz, 6-H), 4.7 (1 H, s, 3-H), 5.0 (1 H, d, *J* 4 H , 5-H), 6.2—7.2br (4 H, 2 t, *J* 6 Hz, 3'- and 5'-H), 6.25 (3 H, s, OMe), 6.5 (2 H, s, aryl-CH$_2$), 8.0 (2 H, m, 4'-H), and 8.8 (6 H, s, 2-Me), *m/e* 492 (M^+ − 18), 460, 360, 315, 301, 287, 177, and 91 (Found: C, 61.2; H, 6.05; N, 10.9; S, 6.05. $C_{26}H_{30}N_4O_5S$ requires C, 61.15; H, 5.9; N, 10.95; S, 6.3%).

Oxidation of 1-*Benzoyl*-1-*phenylpyrazolidine* (49a).—Oxidation of the pyrazolidine (49a) with cerium(IV) ammonium nitrate (1.7 equiv.) in acetonitrile–acetic acid–water (2 : 1 : 2) at −20 °C for 24 h gave the *pyrazolidine dimer* (52) (71%), m.p. 250—252°, $\nu_{max.}$ (Nujol) 1 655, 1 520, and 1 330 cm^{-1}, $\lambda_{max.}$ 222 (ε 30 000), 266 (23 000), and 296.5 nm (23 000), τ 2.0—3.0 (16 H, m, aryl-H), 5.8—6.1 (4 H, t, *J* 7 Hz, aryl-N·CH$_2$), 6.1—6.8 (4 H, t, *J* 7 Hz, PhCON·CH$_2$), and 7.5—8.0 (4 H, q, *J* 7 Hz, CH$_2$·C*H*$_2$·CH$_2$), *m/e* 592 (M^+), 487, 471, 437, 349, 333, 266, 122, 105, and 77 (Found: C, 63.8; H, 4.7; N, 13.65. $C_{32}H_{28}N_6O_6$,0.5H_2O requires C, 63.85; H, 4.85; N, 13.95%).

2,3-*Dichloro*-5,6-*dicyanohydroquinone Dibenzoate* (26a).—2,3-Dichloro-5,6-dicyanohydroquinone (26b), benzoyl chloride (2 equiv.), and triethylamine (2 equiv.) in THF gave the *dibenzoate* (26a) (95%), m.p. 252—253°, $\nu_{max.}$ (Nujol) 1 765 cm^{-1}, τ 1.7—2.8 (m, aryl-H), *m/e* 441/439/437 (M^+), 228, and 105 (Found: C, 60.15; H, 2.65; N, 6.45. $C_{22}H_{10}Cl_2N_2O_4$ requires C, 60.45; H, 2.3; N, 6.4%).

1-*Benzoyl*-3-(4-*methoxyphenyl*)*imidazolidine* (50a).—Formaldehyde was bubbled through 1-(4-methoxyphenyl)-ethylenediamine (51c) [46] (1.6 g) in dry benzene (15 ml) for 20 min. Filtration and evaporation gave 1-(4-methoxyphenyl)imidazolidine (50b) (1.35 g, 79%), m.p. 78° (from PhH), $\nu_{max.}$ 2 816 cm^{-1}, τ 5.1 (1 H, s, NH), 5.9 (2 H, s, N·CH$_2$·N), 6.2 (3 H, s, OMe), and 6.4—7.0 (4 H, m, N·CH$_2$·CH$_2$·N). Benzoylation of the imidazolidine (50b) gave the *benzoyl derivative* (50a) (71%), m.p. 131° (from PhH), $\nu_{max.}$ 1 625 cm^{-1}, τ 5.0—5.6br (2 H, m, N·CH$_2$·N) and 5.9—6.7 (7 H, m, OMe and N·CH$_2$·CH$_2$·N) (Found: C, 72.4; H, 6.45; N, 9.95. $C_{17}H_{18}N_2O_2$ requires C, 72.35; H, 6.4; N, 9.95%).

(1S,3S,5R,6R)-3-(*Indolin*-1-*ylcarbonyl*)-2,2-*dimethyl*-6-*phenylacetamidopenam* 1-*Oxide* (31u).—Indoline (53d) and the mixed anhydride (30a) gave [after chromatography (eluant $CHCl_3$–EtOAc, 1 : 1)] *ethyl indoline*-1-*carboxylate* (53c) (76%), m.p. 45—45.5° (from light petroleum), $\nu_{max.}$ (Nujol) 1 706 and 1 600 cm^{-1}, $\lambda_{max.}$ 240 (ε 15 000), 247sh (13 000), 281 (2 500), and 288.5 nm (2 100), τ 2.2—3.4 (4 H, m, aryl-H), 5.6—6.0 (2 H, q, *J* 6 Hz, O·C*H*$_2$·CH$_3$), 5.95—6.4 (2 H, t, *J* 8 Hz, 2-H), 6.8—7.35 (2 H, t, *J* 8 Hz, 3-H), and 8.4—8.85 (3 H, t, *J* 6 Hz, O·CH$_2$·C*H*$_3$), *m/e* 191

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(M^+), 163, 132, 118, and 91 (Found: C, 68.9; H, 6.75; N, 7.3. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.85; N, 7.3%); and (eluant EtOAc) the *indoline* (31u) (23%), m.p. 127—128° (from CCl_4), $[\alpha]_D^{25}$ +107 (*c* 1.0), $\nu_{max.}$ (Nujol) 3 300, 1 785, and 1 675 cm^{-1}, $\lambda_{max.}$ 257 (ε 14 000), 262sh (14 000), 280 (7 900), and 286.5sh nm (7 100), τ 1.5—3.1 (9 H, m, aryl-H and NH), 3.8—4.2 (1 H, dd, *J* 9 and 4 Hz, 6-H), 4.65 (1 H, d, *J* 4 Hz, 5-H), 5.1 (1 H, s, 3-H), 5.4—5.8 (2 H, t, *J* 7 Hz, 2′-H), 6.35 (2 H, s, aryl-CH_2), 6.55—7.0 (2 H, t, *J* 8 Hz, 3′-H), 8.3 (3 H, s, 2-Me), and 8.6 (3 H, s, 2-Me), *m/e* 437, 433, 405, and 401 (Found: C, 55.45; H, 4.95; Cl, 13.2; N, 7.85; S, 6.0. $C_{24}H_{25}N_3O_4S,0.5CCl_4$ requires C, 55.7; H, 4.75; Cl, 13.4; N, 7.95; S, 6.05%).

Oxidation of the Indoline (31u).—Refluxing the indoline (31u) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (3 equiv.) in dichloromethane for 4 h gave the crude penam indole (31v) (40%), τ 2.4 (1 H, d, *J* 3 Hz, indole 2-H), 2.5—3.0 (10 H, m, aryl-H and NH), 3.35 (1 H, d, *J* 3 Hz, indole 3-H), 3.8—4.1 (1 H, dd, *J* 9 and 4 Hz, 6-H), 4.5 (1 H, s, 3-H), 4.9 (1 H, d, *J* 4 Hz, 5-H), 6.4 (2 H, s, aryl-CH_2), 8.3 (3 H, s, 2-Me), and 8.6 (3 H, s, 2-Me).

Oxidation of N-*Benzoyl*-9,10-*dihydroacridine* (54a).—Oxidation of benzoyldihydroacridine (54a) [47] with lead tetra-acetate (2.75 equiv.) in dichloromethane for 24 h gave, on work-up, *N*-benzoyl-9-acridone (54b) (99%), m.p. 174.5—175.5° (from EtOAc–light petroleum) (lit.,[48] 198—200°), $\nu_{max.}$ 1 714 and 1 635 cm^{-1}, $\lambda_{max.}$ 248 (ε 50 000), 258sh (35 000), 285 (3 500), and 379 nm (7 200), τ 1.54 (1 H, d, *J* 2 Hz, aryl-H), 1.62 (1 H, d, *J* 2 Hz, aryl-H), and 2.20—3.03 (11H, m, aryl-H), *m/e* 299 (M^+), 195, 105, and 77 (Found: C, 80.0; H, 4.35; N, 4.55. Calc. for $C_{20}H_{13}NO_2$: C, 80.25; H, 4.4; N, 4.7%).

We thank Glaxo Research Ltd. for their generous funding of Parts 1—8 of this series. We also thank Professor P. G. Sammes (City University) who kindly advised us in the initial stages of the work described here. One of us (M. J. V. de O. B.) thanks the Gulbenkian Foundation for financial support.

[6/2271 *Received*, 14*th December*, 1976]

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