Transformations using Benzyl 6-Isocyanopenicillanate

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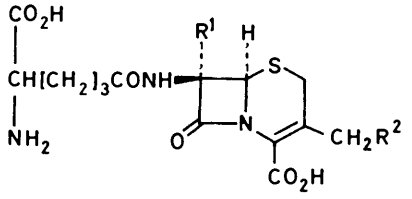
The preparation and C-6 epimerisation of benzyl 6α-isocyanopenicillanate is described. By utilising the activating influence of the isocyanide group and a subsequent conversion of this group into an amino-group under mild conditions, 6α-substituted penicillins were thereby prepared. Additionally, several novel rearrangements of these isocyanides are described.

THE cephamycins (1a—h), produced by various *streptomyces spp.*, were the third, naturally occurring group of β-lactam antibiotics to be reported.[1] These substances differed from the closely related naturally occurring



(1)

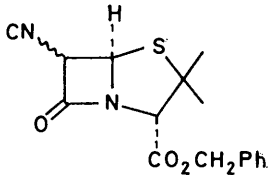
a; R^1 = OMe; R^2 = OCOC(OMe)=CH–C_6H_4–OSO_3H-4
b; R^1 = OMe; R^2 = OCOC(OMe)=CH–C_6H_4–OH-4
c; R^1 = OMe; R^2 = $OCONH_2$
d; R^1 = OMe; R^2 = OAc
e; R^1 = OMe; R^2 = OCOC(OMe)=CHC_6H_3–$(OH)_2$-3,4
f; R^1 = OMe; R^2 = SSO_3H
g; R^1 = OMe; R^2 = OH
h; R^1 = OMe; R^2 = H
j; R^1 = H; R^2 = OAc

cephalosporin C (1j) in the presence of a methoxy-group at C-7 in the nucleus, and also, except for (1d), in the nature of the C-3 substituent. Penicillins incorporating a methoxy-group at the equivalent position (C-6) have not been reported in nature.

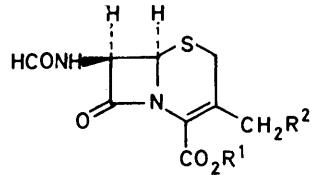
The recognition that the introduction of a methoxy-group into the cephalosporin nucleus at C-7 frequently resulted in an improvement in activity against many β-lactamase-producing Gram-negative bacilli, stimulated the development of methods for incorporating this and other groups into both cephalosporins and penicillins. A variety of procedures have now been described, which achieve this objective.[2] In our own work we have taken advantage of the activating influence of the isocyanide group [3] in order to introduce appropriate substitution into the penicillin nucleus at C-6 and preliminary accounts of this work have been reported.[4]

When a methylene chloride solution of benzyl 6β-formamidopenicillanate was treated with phosgene at −40 °C in the presence of triethylamine or *N*-methylmorpholine, a mixture of benzyl 6α-isocyanopenicillanate 6α-(2) and the 6β-epimer 6β-(2), in a ratio of 55 : 45, was obtained following chromatography. Fractional crystallisation provided the pure 6α-epimer, m.p. 87—89 °C. Similarly, treatment of the 7β-formamidocephalosporin esters (3a) and (3b) in the presence of triethylamine provided an epimeric mixture of the isocyanides (4a) † and (4b), respectively, in which the ratio of 7α- to 7β-epimers was approximately 1 : 1. In contrast use of *N*-methylmorpholine as base resulted, in each case, in the formation of a single epimer only, namely 7β-(4a) and 7β-(4b).‡

The epimerisation of isocyanides 6α-(2) and 7β-(4a) was studied by ^1H n.m.r. spectroscopy. In the spectrum of 6α-(2) in deuteriochloroform, the 5α and 6β protons appeared as doublets (J = 1.5 Hz) at δ 5.43 and 4.64

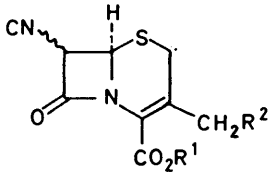


(2)

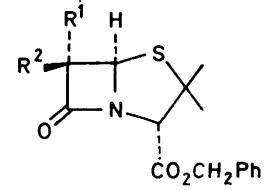


(3)

a; R^1 = Me; R^2 = H
b; R^1 = Bu^t; R^2 = OAc



(4)



(5)

a;
b; } R^1, R^2 as for (3)

a; R^1 = CH_2Ph; R^2 = NC
b; R^1 = CH_2Bz; R^2 = NC
c; R^1 = CH_2CO_2Me; R^2 = NC
d; R^1 = $[CH_2]_2CO_2CH_2Ph$; R^2 = NC
e; R^1 = $C(OH)Me_2$; R^2 = NC
f; R^1 = SMe; R^2 = NC
g; R^1 = OMe; R^2 = NC
h; R^1 = NC; R^2 = CH_2CO_2Me

respectively. Addition of triethylamine (*ca.* 0.1 equivalent) resulted in rapid equilibration (<5 min) to the same mixture of 6α- and 6β-isocyanides as obtained

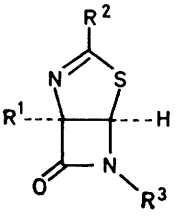
† We thank Dr. E. Hunt for the synthesis and spectroscopic details of compound (4a).

‡ Glaxo Laboratories Ltd., in German Offenlegungsschrift 2,337,105, 1972, disclose the synthesis of several 7-isocyanocephalosporins and their reaction with aldehydes.

above. This was indicated by the relative intensities of new doublets (J = 4.5 Hz) at δ 5.52 and 5.11, assigned to the 5α- and 6α-protons in 6β-(2). Similarly isocyanide 7β-(4a), having doublets (J = 4.5 Hz) at δ 5.00 and 5.28 for the 6α- and 7α-protons, was equilibrated (triethylamine, <10 min) to a mixture of 7α-(4a) and 7β-(4a) in a ratio of *ca.* 1 : 1. New doublets (J = 2 Hz) were seen at δ 4.66 and 4.91, assigned to the 6α and 7β protons in 7α-(4a). In addition to epimerisation at the C-7 position, a slower isomerisation of the double bond occurred, which appeared to reach equilibrium after 2 h, when the ratio of $\Delta^3 : \Delta^2$ isomers was 2 : 1 as determined by the integral for the C-2 methylene resonance. The high proportion of the β-epimers of (2) and (4) at equilibrium supports earlier conclusions that this depends, in part at least, on the steric requirement of the 6 (or 7) substituent.[5]

The base epimerisation of (2) suggested that the intermediate C-6 anion might be intercepted with appropriate electrophiles under mild conditions, thus providing potential intermediates for conversion into 6-substituted penicillins. Only non-β-lactam compounds resulted when isocyanide (2) was treated with n-butyl-lithium or sodium hydride at low temperature followed by attempted methylation with methyl iodide. However, when potassium carbonate, as a suspension in dimethylformamide, was used to form the anion and this was followed by more reactive halides such as benzyl bromide, phenacyl bromide, or methyl bromoacetate, acceptable yields of the corresponding isocyanides (5a—c) were obtained. Furthermore, benzyl acrylate led to the Michael adduct (5d) and if acetone was substituted for dimethylformamide as solvent and electrophile, isocyanide (5e) resulted. Of greater interest, as will become evident later, was the reaction of (2) with methyl methoxycarbonyl disulphide, which gave a good yield of the 6α-methylthio-isocyanide (5f).

These reactions were highly stereoselective,* the electrophile approaching the anion from the α-face and resulting in a 6α-substituted isocyanide. In the reaction with methyl bromoacetate a small yield of the 6α-isocyanide (5h) was also isolated. Our evidence for assigning structures (5a—f) to the major products of these reactions is substantial. Thus, in the ^{1}H n.m.r. spectrum of the 6α-benzyl derivative (5a), a 15% enhancement of the 5α-proton signal intensity was observed when the methylene resonance at δ 3.38 was irradiated, indicating that the 5α-proton was oriented *cis* with respect to the benzyl group. This was confirmed by a single crystal *X*-ray analysis of compound (5a), as detailed in the Experimental section. Further evidence for the 6α-orientation of the ingoing groups R^1 in the isocyanides (5a—f) came from their subsequent transformations to the thiazolines (6). Thus it was observed that the formation of isocyanide (5d) was always accompanied by a second, more polar compound, assigned the thiazoline structure (6c) on the basis of the physical data. The i.r. spectrum of (6c) showed no isocyanide band, but absorptions at 1 770 (β-lactam) and 1 725 cm^{-1} (br, saturated and unsaturated ester). The ^{1}H n.m.r. spectrum showed two 3H-singlets corresponding to the vinylic methyl groups and a doublet (J = 1.7 Hz) at δ 7.92 assigned to the doubly bonded thiazoline proton, coupled to the bridgehead proton at δ 5.54. Subsequently the thiazoline (6c) was shown to be formed from (5d) in high yield by stirring with potassium carbonate in dry dimethylformamide. Similar observations were made with the other isocyanides, although in the case of (5a), the use of sodium thiophenoxide as base, provided a cleaner conversion to the thiazoline (6a). The isopropylidene group in (6c) was readily removed [6] using potassium permanganate to provide (6j).



(6)

a; R^1 = CH_2Ph; R^2 = H
b; R^1 = CH_2CO_2Me; R^2 = H
c; R^1 = $[CH_2]_2CO_2CH_2Ph$; R^2 = H
d; R^1 = SMe; R^2 = H
e; R^1 = H; R^2 = Cl
f; R^1 = CH_2Ph; R^2 = Cl
g; R^1 = CH_2CO_2Me; R^2 = Cl
h; R^1 = SMe; R^2 = Cl
} R^3 = $Me_2C{=}CCO_2CH_2Ph$

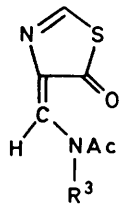
j; R^1 = $[CH_2]_2CH_2CO_2Ph$; R^2 = R^3 = H

Our attempts to introduce other C-6 substituents into (2) under similar or other conditions were unsuccessful. Using the potassium carbonate–dimethylformamide conditions no substitution products were isolated from attempted acylation (with acetic anhydride, ethyl formate), carboxylation (carbon dioxide, chloroformates, dialkyl carbonates, phenyl isocyanate), halogenation (bromine, t-butyl hypochlorite, 1,2-dibromoethane, *N*-bromosuccinimide), amination (*O*-aryl- or arylsulphonylhydroxylamines), sulphonation (arylsulphonyl fluoride), sulphenation (sulphenyl chlorides), or oxygenation (oxygen, peresters). Attempts to introduce specifically a 6α-methoxy-group into (2), thus providing isocyanide (5g), were also made. To our knowledge a reagent for methoxylating a carbanion has not been described. For our purposes dimethyl sulphite, methyl *o*-nitrophenyl sulphenate, and *N*-methoxypyridinium perchlorate were tried but without the desired effect.

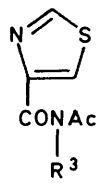
During the course of these unsuccessful attempts to introduce other C-6 substituents into (2), various rearrangements were observed. Thus attempted acetylation of (2), under the usual conditions using acetic anhydride, resulted in a slower reaction, from which a crystalline compound (7) was isolated in 35% yield. Structure (7) was supported by elemental analysis and

* For other stereospecific reactions, electrophilic and nucleophilic, at C-6 (C-7) in penicillin and cephalosporin derivatives, see ref. 2.

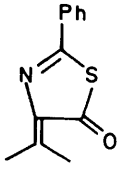
the presence of an M^+ ion at 358 indicating the incorporation of one acetyl group into (2). The i.r. spectrum showed the absence of isocyanide and β-lactam groups and contained a strong, unresolved band centred at 1 710 cm^{-1}, which was not readily assigned, but



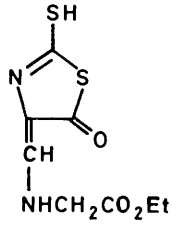
(7) R^3 as in (6a)



(8) R^3 as in (6a)



(9)

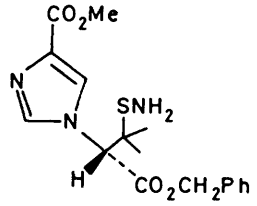


(10)

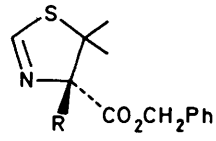
suggested the ester was now αβ-unsaturated. Additional bands at 1 640 (m) and 1 600 (s) supported the presence of C=C and probably C=N groupings. In the ^1H n.m.r. spectrum, three proton singlets at δ 1.79, 2.13, and 2.38 pointed to the presence of the $CH_3CON{-}C(=CMe_2){-}CO_2CH_2Ph$ unit, and doublets (J = 1.5 Hz) at δ 8.14 and 8.23 were the only other new resonances. These were assigned to the olefinic protons in (7) where 5-bond coupling of the observed order would not be unexpected.[7] The presence of an extended chromophore was indicated by strong absorptions in the u.v. spectrum at 272 and 340 nm, which ruled out a possible alternative structure, namely the thiazole (8). Further support for the thiazolone structure (7) came from the work of Bachi,[8] who quotes $\nu_{max.}$ 1 686 (C=O) and 1 616 cm^{-1} (C=N) for the related compound (9), and although no u.v. data is given in this work, Cook [9] quotes $\lambda_{max.}$ 245 and 337 nm for structure (10). Additional confirmation of structure (7) was afforded by the ^{13}C n.m.r. spectrum where resonances at δ 130.7 and 150.8 were assigned to the two olefinic CH carbons. The resonance at δ 193.7 is highly characteristic of a carbonyl group next to sulphur.[10] Mechanistic considerations (see later) suggested the configuration of the exocyclic double bond as shown.

When the isocyanides (2) were treated with t-butyl hypochlorite under the potassium carbonate–dimethylformamide conditions a low yield of the chlorothiazoline (6e) was obtained, the ^1H n.m.r. spectrum of which was characterised by a pair of doublets (J = 4 Hz) at δ 5.86 and 5.97, assigned to the ring methine protons.[11] Subsequently, the substituted isocyanides (5a), (5c), and (5f) were shown to undergo the same reaction in higher yield to give the chlorothiazolines (6f—h) respectively, where the remaining ring proton appeared as a singlet between δ 5.59—5.89. In (6e—h) the i.r. spectrum was characterised by bands at *ca.* 1 780 (β-lactam), *ca.* 1 720 (αβ unsaturated ester), and *ca.* 1 600 cm^{-1} (C=N). In the absence of base a methylene dichloride solution of the isocyanide (2) was shown to undergo oxidation with t-butyl hypochlorite to isocyanate [ν(NCO) 2 240 cm^{-1}].[12] Such a reaction presumably occurred concurrently under the basic conditions and might be the source of amine (21a), observed to be formed along with (6f).

Our attempts to introduce a 6α-amino-group into (2) using *O*-mesitylsulphonyl- or *O*-2,4-dinitrophenylhydroxylamine [13] under the potassium carbonate–dimethylformamide conditions were unrewarding. However a relatively clean reaction with the latter reagent took place in the presence of potassium carbonate using methanol as solvent, and provided the imidazole (11) in 42% yield. In the ^1H n.m.r. spectrum of this product, the *gem*-dimethyl protons appeared as a single broad line at δ 1.22 which, together with the 1H-singlet at δ 5.01, suggested that the fragment, $-S{-}C(Me)_2{-}CH{-}(CO_2CH_2Ph)N-$, was still present. The incorporation of an amino and a methoxy(carbonyl) group was evident from the broad, exchangeable 2H-resonance at δ 2.4 and the 3H-singlet at δ 3.89 respectively. Additionally a pair of 1H-doublets (J = 1.6 Hz) at δ 7.75 and 8.01 could only be assigned to two heteroaromatic protons.* An imidazole was indicated by the hypsochromic shift of the absorption observed in the u.v. spectrum of (11) in the presence of dilute hydrochloric acid.* Whilst the i.r. spectrum provided further evidence for structure (11), the mass spectrum showed only a weak M^+ ion, the measured ion at 314 corresponding to loss of the elements of $HSNH_2$.



(11)



(12)

a; R = OH
b; R = H

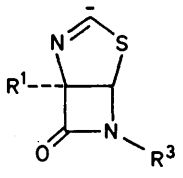
When a tetrahydrofuran solution of the isocyanides (2) was treated with n-butyl-lithium at −70 °C followed by dry oxygen, the only product isolated was the thiazoline (12a), in which oxygenation had occurred at C-3, with cleavage of the β-lactam ring.

A reaction of isocyanides of potential interest in the present context was their known thermal isomerisation

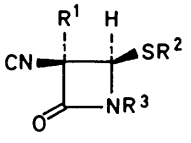
* H. R. Matthews and H. Rapoport, *J. Amer. Chem. Soc.*, 1973, **95**, 2297, quote $\lambda_{max.}$ 233 (MeOH) and 219 nm (0.1M-HCl) and δ 7.5, 7.7 (each d, J 1.4 Hz, 2- and 5-H) for 1-methyl-4-methoxycarbonylimidazole.

to cyanides.[14] When 6α-(2) was heated no evidence of any conversion into a cyanide was forthcoming (i.r.). Instead a slow conversion to a slightly more polar compound took place, which was identified as the thiazoline (12b). In the case of the 6α-benzyl isocyanide (5a) an i.r. study showed the formation of a cyanide [ν(CN) 2 260 cm^{-1}], but attempts to isolate the product proved unsuccessful.

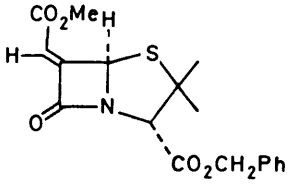
Mechanism of Reactions leading to the Thiazolines (6), *the Thiazolone* (7), *and the Imidazole* (11).—The most likely mechanism for the reaction, which gives rise to the thiazolines (6a—d), is one in which base abstraction of the C-3 proton in the corresponding isocyanides (5) initiates a β-elimination process, which is followed by trapping of the developing thiolate by the electrophilic isocyanide carbon. Protonation of the resulting carbanions (13) then gives (6a—d).* This represents yet a further case, in which such a thiolate is captured intramolecularly,† and since for this to occur the sulphur and isocyanide group must be *cis* to each other, the orientation of the groups at C-6 in (5) is confirmed. The same mechanism would hold for the formation of the corresponding chlorothiazolines (6e—h), *i.e.* the anion (13) now reacts with the electrophilic halogenating agent. However a further possibility suggests itself, namely that the initially formed thiolate undergoes an intermolecular reaction with the hypochlorite to give the sulphenyl chlorides (14a). Compounds (6e—h) then result following an α-addition reaction with the isocyanide group.[15] In the case of isocyanide (5c), an attempt was made to trap any (14a; $R^1 = CH_2CO_2Me$)



(13) R^3 as in (6a)



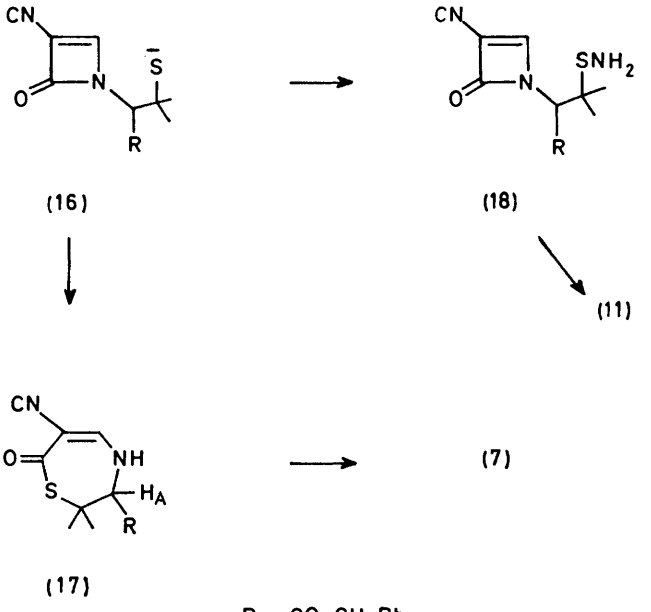
(14) R^3 as in (6a)



(15)

a; R^2 = Cl
b; R^2 = $NHPr^i$

by incorporating isopropylamine with the reaction mixture. Instead of the sulphenamide (14b) being isolated, the olefin (15) (27%) was obtained as a single geometric isomer, together with some (6b). No chloro-derivative (6g) was produced under these conditions. The most likely process leading to (15) is base-promoted loss of hydrogen isocyanide from (5c).‡ The above processes, therefore, are initiated by proton loss from C-3 in the isocyanides (2) and (5a—f). Processes initiated by proton loss from C-6 in the parent isocyanide



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(2) may account for the observed formation of the two products (7) and (11). Thus following proton loss from C-6, the enethiolate (16) (Scheme) could react intramolecularly to give the thiazepinone (17),§ or intermolecularly, *e.g.* with the aminating agent, to provide the sulphenamide, (18). The thiazolone (7) then arises from (17) following *N*-acetylation and a further β-elimination process, initiated by loss of H_A, which allows the developing thiocarboxylate to react ¶ at the isocyanide carbon atom once again. In the case of (18), methanolysis of the β-lactam provides for a reaction * between the isocyanide and the resulting enamine NH, thus leading to the imidazole (11).

Conversion of the Isocyanides (5a—f) *into* 6α-*Substituted Penicillins.*—In order to enter the 6α-substituted penicillin series, a mild method of converting the isocyanide group into (5a—f) was sought. The usual methods were considered too severe, and indeed aqueous hydrochloric acid rapidly transformed the isocyanides (5a, d, e) into hydrochlorides, formulated as the penillic acid salts (19a—c) respectively. In particular, the ^1H n.m.r. spectra of these compounds had resonances at

* For a discussion on this particular aspect of isocyanide chemistry, see U. Schöllkopf, ref. 3*b*.

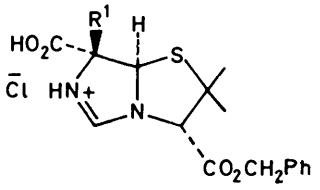
† For other examples of *intra*molecular and *inter*molecular trapping of thiolates from penicillin derivatives, see cited references by R. J. Stoodley, *Tetrahedron*, 1975, **31**, 2321.

‡ For other reactions involving loss of hydrogen isocyanide see K. Matsumoto, M. Suzuki, Y. Ozaki, and M. Miyoshi, *Agric. Biol. Chem.*, 1976, **40**, 2271.

§ For a discussion of thiazepinone formation from penicillin derivatives see p. 2336 of reference cited in footnote †.

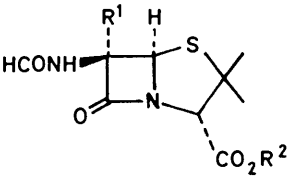
¶ This would be an expected reaction of isocyanides, see U. Schöllkopf, ref. 3*b*.

δ *ca.* 5.2 ($CHCO_2R$), δ 6.3 (NC*H*S), and δ 9.0 (N=C*H*).* These salts are presumably formed from the corresponding formamido-compounds (20a—c) following cyclisation in an analogous manner to that for penicillin.† Alter-



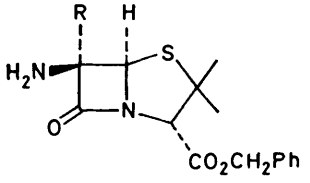
(19)

a; $R^1 = CH_2Ph$
b; $R^1 = [CH_2]_2CO_2CH_2Ph$
c; $R^1 = C(OH)Me_2$



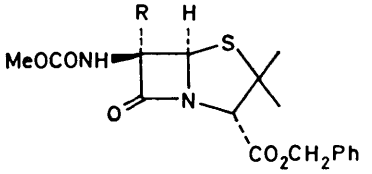
(20)

a;
b; R^1 as in (19a—c); $R^2 = CH_2Ph$
c;
d; $R^1 = CH_2Ph$; $R^2 = Na$
e; $R^1 = SMe$; $R^2 = CH_2Ph$



(21)

a; R = CH_2Ph
b; R = CH_2CO_2Me
c; R = $[CH_2]_2CO_2CH_2Ph$
d; R = SMe
e; R = OMe
f; R = OEt
g; R = N_3



(22)

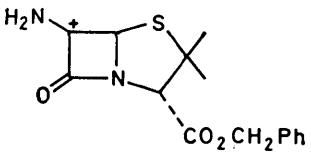
a; R = OMe
b; R = H

natively, acidolysis of the β-lactam ring in the starting isocyanides is followed by reaction of the isocyanide group with the thiazolidine NH to give the observed products. Excess of formic acid in chloroform smoothly converted the isocyanides (5a, d) into the formamides (20a, b) without rupture of the β-lactam ring, but these were of no further utility, except that hydrogenolysis of the benzyl protecting group in (20a) furnished the sodium salt (20d). A similar reaction with the isocyanide (5e) gave the impure formamide (20c).

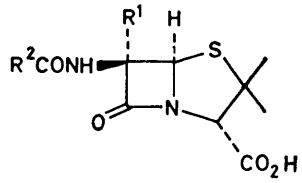
The reaction of the substituted isocyanides with one equivalent of toluene-*p*-sulphonic acid in chloroform conveniently took a third course. Thus the isocyanides (5a, c, d, f) all gave satisfactory yields of the amines (21a—d) respectively, isolated as their toluene-*p*-sulphonates,‡ though in the case of (5f) some of the corresponding formamide (20e) was also isolated. The reaction of the isocyanides (5b, e) under these conditions was more complicated.

Attempts were also made to convert the isocyanide (5f) directly into a 6α-alkoxy-amine [*e.g.* (21e)] or a derivative, from which (21e) could be liberated. Thus treatment of (5f) with mercuric acetate § in methanol provided the 6α-methoxyurethane (22a) in 59% yield. Under similar conditions thallic trinitrate * transformed the isocyanides (2) into the urethanes (22b) as a mixture of C-6 epimers. Clearly the urethane (22a) arises by way of an oxidation (to isocyanate) and a displacement (SMe to OMe) reaction. However, the exact sequence of events is in doubt. In tetrahydrofuran solution an i.r. study showed that the oxidation of the isocyanide (5f) to isocyanate was indeed rapid. Whilst this work was in progress, Jen *et al.*[16] described a superior method for converting the amine (21d) into the desired methoxy-derivative (21e), in which a solution of (21d) in methanol and dimethylformamide containing pyridine was treated with mercuric chloride. We extended this reaction and found that when the methanol was replaced by ethanol or a methylene dichloride solution of triethylammonium azide the corresponding 6α-substituted amines (21f) and (21g) were obtained in good yields. The presumed intermediate in these reactions is the carbonium ion (23), which is stabilised by the adjacent lone pair on the nitrogen atom.

Finally, acylation of the amines (21a—g) by appropriate side-chain acids, followed by removal of protecting groups, furnished a representative number of the 6α-

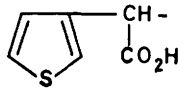


(23)



(24)

a; $R^1 = R^2 = CH_2Ph$
b; $R^1 = [CH_2]_2CO_2H$; $R^2 = CH_2Ph$
c; $R^1 = CH_2CO_2Me$
d; $R^1 = OMe$
e; $R^1 = OEt$
f; $R^1 = N_3$
} R^2 =



g; R^1 = SMe
h; R^1 = OMe
} R^2 = D-PhCH(NH_2)–

substituted penicillins. Details of the synthesis of the 6α-benzyl (24a) and 6α-carboxyethyl (24b) derivatives of benzylpenicillin, and the 6α-methoxycarbonylmethyl (24c), 6α-methoxy (24d), and 6α-ethoxy (24e) derivatives

* M. R. Bell, S. D. Clemans, R. Oesterlin, and J. A. Carlson, *J. Heterocyclic Chem.*, 1974, **11**, 823, quote similar shifts for a related penillic acid in trifluoroacetic acid. The observed $\lambda_{max.}$ (see Experimental section) also agree with that quoted for benzylpenillic acid, 235 nm (sh). See A. H. Livermore, F. H. Carpenter, R. W. Holley, and V. du Vigneaud, *J. Biol. Chem.*, 1948, **175**, 721.

† See F. P. Doyle and J. H. C. Nayler in 'Advances in Drug Research,' 1964, **1**, 1 and p. 2338 of the reference cited in footnote † on p. 2458 for a discussion on this point.

‡ Toluene-*p*-sulphonic acid had not previously been used for this process. For subsequent use, see I. Hoppe and U. Schöllkopf, *Chem. Ber.*, 1976, **109**, 482.

§ For use of these salts in converting isocyanides into urethanes see H. Sawai and T. Takizawa, *Tetrahedron Letters*, 1972, 4263 and F. Kienzle, *ibid.*, 1972, 1771.

of α-carboxy-3-thienylmethylpenicillin are described in the Experimental section. Also described is the preparation of the protected forms of 6α-azido-α-carboxy-3-thienylmethylpenicillin (24f) and 6α-methylthio-α-aminobenzylpenicillin (ampicillin) (24g) and the conversion of the latter compound into 6α-methoxyampicillin (24h) by the method of Spitzer and Goodson.[17] Antimicrobial activity of these and other 6α-substituted penicillins will be presented in our biological paper.*

EXPERIMENTAL

Reagents were of the highest grade. Solvents were dried and distilled before use. Thin layer chromatography on Merck Kieselgel plates containing F_{254} was used for routine assessment of purity and for following the progress of reactions. R_{F1} is quoted for system chloroform–acetone–acetic acid (7 : 7 : 1), R_{F2} for butan-1-ol–ethanol–water (4 : 2 : 4), and R_{F3} for ethyl acetate–light petroleum (b.p. 60—80°) (1 : 3). Plates were visualised by u.v., aqueous potassium permanganate, or ethanolic phosphomolybdic acid. Column chromatography was performed on Merck Kieselgel H. The eluant was generally combinations of ethyl acetate (5—80%) in light petroleum (b.p. 60—80 °C). Standard work-up conditions involved isolating the neutral component(s) from ethyl acetate solution by successive washings with aqueous 1M-hydrochloric acid, water, aqueous sodium hydrogencarbonate, water, and drying ($MgSO_4$). Toluene-*p*-sulphonates were converted into their free bases by washing a suspension of the salt in chilled ethyl acetate with a several fold excess of dilute aqueous sodium hydrogen carbonate and drying. I.r. and u.v. spectra were recorded for solutions in chloroform and ethanol respectively except as indicated. ^1H and ^{13}C N.m.r. spectra were recorded as solutions in deuteriochloroform with tetramethylsilane as internal standard except as indicated. M.p.s are uncorrected; DMF is *NN*-dimethylformamide, THF is tetrahydrofuran, and ether refers to diethyl ether.

Benzyl 6β-*Formamidopenicillanate*.—(a) *From benzyl* 6β-*aminopenicillanate*. A solution of benzyl 6β-aminopenicillanate (from 47.8 g, 0.1 mol of the toluene-*p*-sulphonate) in ethyl acetate (300 ml) was cooled to −20 °C and formic acid (98%, 3.8 ml, 0.1 mol) and *NN*-dicyclohexylcarbodi-imide (21 g, 0.1 mol) added. After 0.5 h at −10 to −15 °C and then 2.5 h at 0—5 °C, the urea was filtered off and the neutral product, which was sufficiently pure for the next step, was isolated in the usual way (yield 90%). A portion was chromatographed to give the title *formamide* as a colourless syrup, $\nu_{max.}$ (film) 3 300, 1 790, 1 745, and 1 680 cm^{-1}; δ 1.45, 1.64 (6 H, 2s, CH_3), 4.50 (1 H, s, 3-H), 5.22 (2 H, s, OCH_2), 5.54—5.90 (2 H, m, 5- and 6-H), 7.40 (5 H, s, Ph–H), and 8.24 (1 H, s, *H*CO) (Found: C, 57.3; H, 5.8; N, 8.2. $C_{16}H_{18}N_2O_4S$ requires C, 57.5; H, 5.4; N, 8.4%).

(b) *From sodium* 6β-*formamidopenicillanate*. A mixture of sodium 6β-formamidopenicillanate (2.7 g, 10 mmol), benzyl bromide (1.26 ml), and DMF (25 ml) were stirred together at 20 °C for 4 h. After the addition of ice–water and ether, the neutral product (86% yield) was isolated in the usual way. It was identical to that prepared in (a).

t-Butyl 7β-*Formamidocephalosporanate* (3b).—The compound was prepared from t-butyl 7β-aminocephalosporanate as in (a) above. Crystallisation of the crude product from propan-2-ol–cyclohexane provided the *formamide* (3b) (52%), m.p. 75 °C (decomp.); $\nu_{max.}$ 3 400, 1 785, 1 735sh, 1 720, 1 700, 1 640, and 1 510 cm^{-1}; $\lambda_{max.}$ 266 nm (ε 7 435); δ 1.53 (9 H, s, butyl-H), 2.08 (3 H, s, $OCOCH_3$), 3.51 (2 H, ABq, 2-H), 4.7—5.3 (3 H, m, OCH_2 and 6-H), 5.90 (1 H, dd, 7-H), 6.70 (1 H, d, N*H*), and 8.30 (1 H, s, *H*CO) (Found: C, 50.7; H, 5.8; N, 7.7. $C_{15}H_{20}N_2O_6S$ requires C, 50.6; H, 5.7; N, 7.9%).

Methyl 7β-*Formamidodeacetoxycephalosporanate* (3a).—A solution of 7β-formamidodeacetoxycephalosporanate (3.5 g, 14.5 mmol) in dry methanol (30 ml) was treated with a slight excess of diazomethane in ether. The *formamide* (3a) (2.5 g, 68%), m.p. 170—172 °C, was obtained after evaporation and crystallisation from MeOH–ether; $\nu_{max.}$ 3 380, 1 780, 1 720, and 1 695 cm^{-1}; $\lambda_{max.}$ 270 nm (ε 6 110); δ[$(CD_3)_2SO$] 2.10 (3 H, s, CH_3), 3.42 (2 H, ABq, 2-H), 3.80 (3 H, s, OCH_3), 5.05 (1 H, d, 6-H), 5.73 (1 H, dd, 7-H), 8.22 (1 H, s, *H*CO), and 8.90 (1 H, d, N*H*) (Found: C, 46.8; H, 4.6; N, 10.8; S, 12.8. $C_{10}H_{12}N_2O_4S$ requires C, 46.8; H, 4.7; N, 10.9; S, 12.5%).

Benzyl 6α- *and* 6β-*Isocyanopenicillanate* (2).—Crude benzyl 6β-formamidopenicillanate (30 g, 0.09 mol) was dissolved in dry methylene chloride (200 ml) containing triethylamine (30 ml, 0.21 mol) and treated at −45 ± 5 °C with a solution of phosgene (9 g, 0.09 mol) in methylene chloride (70 ml) during 10 min. After a further 0.75 h, the mixture was washed with water and dilute aqueous sodium hydrogencarbonate and the organic layer dried and evaporated. Chromatography furnished a mixture of the *isocyanides* (2) (14.7 g, 52%) as a pale yellow, semisolid mass. Trituration with dry ether followed by crystallisation from ether–light petroleum provided the pure 6α-*isocyanide*, m.p. 87—89 °C, as pale yellow needles; $[\alpha]_D^{20}$ 229° (*c* 0.43, MeOH); $\nu_{max.}$ 2 130, 1 795, 1 745, 1 305, 1 265, and 1 180 cm^{-1}; δ 1.38 (3 H, s, CH_3), 1.53 (3 H, s, CH_3), 4.54 (1 H, s, 3-H), 4.64 (1 H, d, *J* 1.5 Hz, 6-H), 5.22 (2 H, s, OCH_2), 5.43 (1 H, d, *J* 1.5 Hz, 5-H), and 7.38 (5 H, s, Ph–H). [In the mixture of isocyanides additional signals, assigned to the 6β-epimer, appeared at δ 1.45, 1.67 (s, CH_3), 4.58 (s, 3-H), 5.11 (d, *J* 4.5 Hz, 6-H), and 5.52 (d, *J* 4.5 Hz, 5-H)] (Found: C, 60.6; H, 5.1; N, 8.8. $C_{16}H_{16}N_2O_3S$ requires C, 60.8; H, 5.1; N, 8.9%).

Methyl 7β-*isocyanodeacetoxycephalosporanate* 7β-(4a).—The formamido-derivative (3a) (1.02 g, 4 mmol) was similarly transformed to the 7β-*isocyanide* (4a) (0.51 g, 54%), a colourless gum, using *N*-methylmorpholine, $\nu_{max.}$ 2 110, 1 785, and 1 720 cm^{-1}; δ 2.22 (3 H, s, CH_3), 3.41 (2 H, ABq, 2-H), 3.88 (3 H, s, OCH_3), and 5.00 and 5.28 (each 1 H, d, *J* 4.5 Hz, 6- and 7-H) (Found: M^+, 238.040 7. $C_{10}H_{10}N_2O_3S$ requires *M*, 238.041 2).

t-Butyl 7-*Isocyanocephalosporanate*, 7β-(4b) *and* 7α-(4b).—The formyl derivative (3b) (8.6 g, 24 mmol) was treated in the same way using triethylamine as base to furnish the *title isocyanides* (4b) (1.9 g, 24%) which were partially separated by chromatography. The 7β-*isocyanide* was a gum; $\nu_{max.}$ 2 140, 1 800, 1 730sh, 1 720, and 1 640 cm^{-1}; δ 1.54 (9 H, s, Bu–H), 2.09 (3 H, s, CH_3), 3.56 (2 H, ABq, 2-H), and 4.94 (d, *J* 5 Hz, 6- or 7-H), 5.00 (ABq, *J* 14 Hz, CH_2O), and 5.27 (d, *J* 5 Hz, 6- or 7-H) (4 H in all); $\lambda_{max.}$ 268 nm (ε 7 840) (Found: $M^+ - 56$, 282.028 8. $C_{11}H_{10}N_2O_5S$, $M - C_4H_8$ requires 282.031 1).

If *N*-methylmorpholine was the base in the above experiment the 7β-isocyanide (54%) was the sole product.

Benzyl 6α-*Benzyl*-6β-*isocyanopenicillanate* (5a).—The isocyanides (2) (9.0 g, 28.4 mmol) were dissolved in dry DMF (31 ml) and treated with powdered potassium carbonate (3.92 g) and benzyl bromide (3.5 ml) under nitrogen. After

* Some preliminary data has already been published (ref. 4).

3 h at 20 °C ice–water (50 ml) and ethyl acetate (150 ml) were added. The organic phase was separated, washed with water, dried, and evaporated. Chromatography of the residue provided the *isocyanide* (5a) (3.1 g, 27%), m.p. 114.5—116° (needles from cyclohexane); $[\alpha]_D^{22}$ +157.3° (*c* 1.08, methanol); $\nu_{max.}$ 2 120, 1 790, and 1 740 cm^{-1}; δ_H 1.40, 1.63 (6 H, 2s, CH_3), 3.38 (2 H, s, 6α-CH_2), 4.55 (1 H, s, 3-H), 5.18 (2 H, s, OCH_2), 5.39 (1 H, s, 5-H), and 7.4 (10 H, m, Ph–H); δ_C 25.8, 33.4 (2 CH_3), 40.4 (6α-CH_2), 64.9 (C-2), 67.6 (OCH_2), 69.9 and 70.6 (C-3 and C-5), 75.8 (2 lines) (C-6 and solvent), 128.0, 128.7, and 129.8 (aryl CH), 132.4 and 134.6 (aryl C), 165.0 (NC), 166.2 and 166.7 (2 CO) (Found: C, 67.7; H, 5.6; N, 6.6. $C_{23}H_{22}N_2O_3S$ requires C, 68.0; H, 5.5; N, 6.9%).

Measurement of n.O.e. in (5a).*—A degassed (N_2), filtered solution of (5a) in $CDCl_3$ was used. Spectra, with and

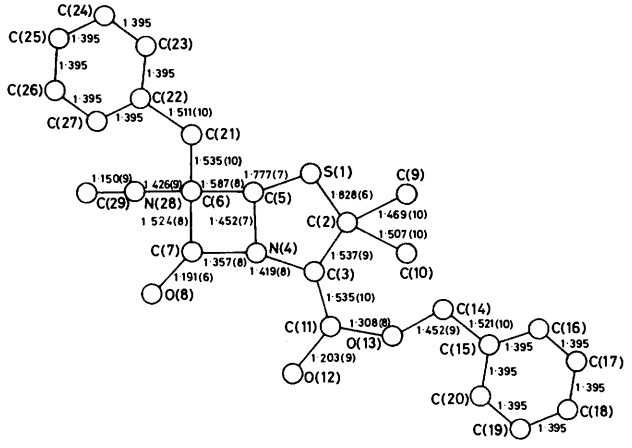


FIGURE 1 Bond distances for the isocyanide (5a) in Å

without saturation, were taken under similar operating conditions. The results are shown below:

Signal irradiated (δ)	Signal observed (δ)	n.O.e. (%)
3.38 (6α-CH_2)	5.39 (5α-H)	15
1.40 (2α-CH_3)	4.55 (3β-H)	<5
1.62 (2β-CH_3)	4.55 (3β-H)	20
ditto	5.39 (5α-H)	0

X-Ray Structure Determination of Compound (5a).—Crystals of (5a) were grown as white needles by slow evaporation from a solution containing 0.5 g of compound in chloroform (5 ml) and cyclohexane (30 ml). These crystals were found to be orthorhombic with $a = 5.871(14)$, $b = 16.554(14)$, $c = 21.547(30)$ Å, $D_m = 1\,305$ kg^{-3}. *X*-Ray intensities were obtained from Weissenberg photographs using Cu-K_α radiation $\lambda = 1.542$ Å and measured by the S.R.C. microdensitometer. The structure was solved by direct methods using the TANGEN programme of the *X*-Ray 70 system on the ICL 1906 A at the Atlas Computer Laboratory.

In the final refinement all non-hydrogen atoms except benzene carbons were refined anisotropically. Benzene carbon atoms were refined as rigid groups and hydrogen atoms inserted at their calculated positions constrained to ride on carbon atoms. The final conventional unweighted

* These measurements carried out by Dr. R. G. Alexander (B.P.R.D.) and Dr. R. A. Spragg (Perkin-Elmer, Beaconsfield, Bucks).

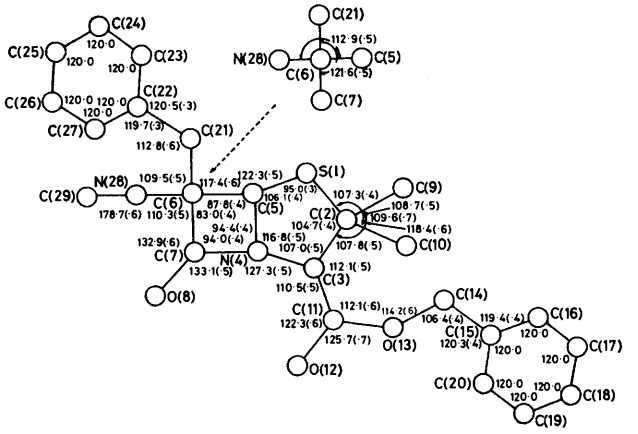


FIGURE 2 Bond angles (°) for the isocyanide (5a)

R factor for 1 494 unique reflections was 0.077. Full details of the structure determination with observed and calculated structure factors and the final atomic parameters are given by Girven.[18] Figures 1 and 2 show the bond distances and angles and Figure 3 shows the structure viewed along the *a* crystallographic axis.

The structure shows that there is no significant interaction between the isocyano-carbon of the penicillanate and either a hydrogen atom or an isocyano-group of another molecule since the nearest hydrogen atom to the isocyano-carbon is at a distance of 2.83 Å and the intermolecular N–C separation between isocyano-carbon and nitrogen is 4.39 Å. There are no other atoms in the structure significantly close to each other to indicate the possibility of hydrogen bonding. The deviation of N-4 from the plane of the lactam ring defined by C(3), C(5), and C(7) is 0.37 Å, which is comparable to that defined in the same manner for other active penicillins.[19] The conformation of the thiazolidine ring has the usual arrangement of one atom being significantly out of the plane defined by the remaining four atoms. In this compound C-3 is 0.45 Å below the plane

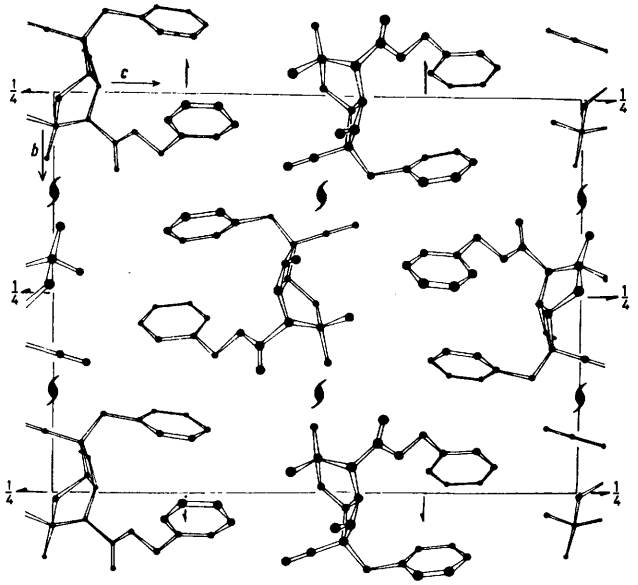


FIGURE 3 Structure of the isocyanide (5a) as viewed from the direction of the *a*-axis

defined by S(1), C(2), N(4), C(5). The isocyanide N–C bond length of 1.150 Å provided by this work is of some interest since no previous *X*-ray analysis of an isocyanide appears to have been carried out.*

Benzyl 6α-Benzoylmethyl-6β-isocyanopenicillanate (5b).—The isocyanides (2) (2.85 g, 9 mmol), DMF (10 ml), potassium carbonate (1.25 g), and phenacyl bromide (1.80 g, 1 equiv.) were stirred together as before for 4 h. Work-up and chromatography provided the *isocyanide* (5b) (0.41 g, 11%), m.p. 77—78 °C (cyclohexane), $\nu_{max.}$ 2 120, 1 795, and 1 740 cm^{-1}; δ 1.38 and 1.63 (6 H, 2s, CH_3), 3.29 (2 H, ABq, *J* 5 Hz, 6α-CH_2), 4.59 (1 H, s, 3-H), 5.19 (2 H, s, OCH_2), 5.48 (1 H, s, 5-H), and 7.4 (10 H, m, Ph–H) (Found: C, 65.8; H, 5.1; N, 6.4. $C_{24}H_{22}N_2O_4S$ requires C, 66.3; H, 5.1; N, 6.5%).

Benzyl 6β-Isocyano-6α-methoxycarbonylmethylpenicillanate (5c) *and the 6α-Isocyanide* (5h).—The isocyanide (2) (mainly 6α-isomer) (0.54 g, 1.7 mmol), DMF (3 ml), potassium carbonate (0.24 g), and methyl bromoacetate (0.16 ml, 1.7 mmol) were stirred together for 3 h at 0—5 °C under nitrogen. Work-up and chromatography as before provided first 6α-*isocyanide* (5h) (0.05 g, 7%) as a colourless oil, $\nu_{max.}$ 2 120, 1 795, and 1 745 cm^{-1}; δ 1.42 and 1.56 (6 H, 2s, CH_3), 3.10 (2 H, s, 6β-CH_2), 3.81 (3 H, s, OCH_3), 4.52 (1 H, s, 3-H), 5.28 (2 H, s, CH_2Ph), 5.73 (1 H, s, 5-H), and 7.47 (5 H, s, Ph–H) (Found: M^+, 388.110 3. $C_{19}H_{20}N_2O_5S$ requires *M*, 388.109 3). Continued elution of the column gave the 6β-*isocyanide* (5c) (0.29 g, 44%) as a colourless oil, $\nu_{max.}$ 2 130, 1 790, and 1 740 cm^{-1}; δ 1.41 and 1.64 (6 H, 2s, CH_3), 3.14 (2 H, ABq, *J* 17 Hz, 6α-CH_2), 3.77 (3 H, s, OCH_3), 4.57 (1 H, s, 3-H), 5.20 (2 H, s, CH_2Ph), 5.53 (1 H, s, 5-H), and 7.4 (5 H, s, Ph–H) (Found: M^+, 388.110 3. $C_{19}H_{20}N_2O_5S$ requires *M*, 388.109 3).

Benzyl 6α-Benzyloxycarbonylethyl-6β-isocyanopenicillanate (5d) *and* (1R,5R)-1-(2-*Benzyloxycarbonylethyl*)-6-(1-*benzyloxycarbonyl-2-methylprop*-1-*enyl*)-4-*thia*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-7-*one* (6c).—The isocyanides (2) (3.8 g, 12 mmol), DMF (18 ml), and benzyl acrylate (2.5 g, 1.3 equiv.) were stirred together with potassium carbonate (1.7 g) under nitrogen for 1.5 h at 20 °C, with monitoring by t.l.c. Work-up and chromatography as before provided, first, the *isocyanide* (5d) (2.8 g, 48%) as a colourless syrup, $\nu_{max.}$ 2 120, 1 790, and 1 740 cm^{-1}; δ 1.43 and 1.64 (6 H, 2s, CH_3), 2.3—2.8 (4 H, m, CH_2CH_2), 4.57 (1 H, s, 3-H), 5.17 and 5.22 (4 H, 2s, OCH_2), 5.34 (1 H, s, 5-H), and 7.36 (10 H, s, Ph–H); *m/e* (weak M^+ at 478) 288 (*M* − 190; Found: 288.108 2. $C_{16}H_{18}NO_2S$ requires 288.105 8).

Continued elution of the column provided the *thiazoline* (6c) (0.51 g, 9%) as a colourless oil; $\nu_{max.}$ 1 770 and 1 725 cm^{-1}; δ 1.89 and 2.28 (6 H, 2s, CH_3), 2.46 (4 H, m, CH_2–CH_2), 5.15 and 5.21 (4 H, 2s, CH_2Ph), 5.54 (1 H, d, *J* 1.7 Hz, C*H*), 7.3 (10 H, s, Ph–H), and 7.92 (1 H, d, *J* 1.7 Hz, N=C*H*) (Found: C, 65.6; H, 5.6; N, 5.5. $C_{26}H_{26}N_2O_5S$ requires C, 65.3; H, 5.5; N, 5.8%). If the reaction time for the preparation of (5d) was extended to 3.5 h a higher yield (51%) of the thiazoline (6c) was obtained at the expense of isocyanide (5d). If isocyanide (5d) (0.20 g) was stirred for 3.5 h in DMF (2 ml) containing potassium carbonate (0.06 g) work-up as before provided the same thiazoline (0.15 g, 75%).

Benzyl 6α-(1-Hydroxy-1-methylethyl)-6β-isocyanopenicillanate (5e).—The isocyanides (2) (7.2 g, 22.8 mmol) were dissolved in acetone (50 ml) and stirred under nitrogen with potassium carbonate (3.2 g) for 3.5 h at 20 °C. Water (20 ml) and ether (120 ml) were then added. The organic phase was separated, washed with water, dried, and evaporated. Chromatography provided the *isocyanide* (5e) (2.8 g, 34%) as a syrup, which crystallised on storage, m.p. 90—91 °C, after collection with light petroleum; $[\alpha]_D^{20}$ +149.9 (*c* 0.7, MeOH); $\nu_{max.}$ 2 120, 1 790, 1 740, 1 310, and 1 180 cm^{-1}; δ 1.42 (6 H, br, CH_3), 1.53 and 1.65 (6 H, 2s, thiazolidine –CH_3), 2.34 (1 H, br, exchanges with D_2O, O*H*), 4.58 (1 H, s, 3-H), 5.21 (2 H, s, CH_2Ph), 5.56 (1 H, s, 5-H), and 7.41 (5 H, s, Ph–H) (Found: C, 60.9; H, 6.1; N, 7.2. $C_{19}H_{22}N_2O_4S$ requires C, 60.9; H, 5.9; N, 7.5%).

Benzyl 6β-Isocyano-6α-methylthiopenicillanate (5f).—The isocyanides (2) (34 g, 0.11 mol), DMF (175 ml), potassium carbonate (14.9 g), and methyl methoxycarbonyl disulphide † (15.6 g, 1.1 equiv.) were stirred together for 2.5 h at 0—5 °C. Work-up and chromatography as before provided the *isocyanide* (5f) (21 g, 54%) as a syrup, which crystallised on triturating with light petroleum, m.p. 55—57 °C (from EtOH); $[\alpha]_D^{25}$ +197° (*c* 0.5; MeOH); $\nu_{max.}$ 2 110, 1 790, and 1 740 cm^{-1}; δ 1.43 and 1.63 (6 H, 2s, CH_3), 2.46 (3 H, s, SCH_3), 4.58 (1 H, s, 3-H), 5.21 (2 H, s, OCH_2), 5.36 (1 H, s, 5-H), and 7.38 (5 H, s, Ph–H) (Found: C, 56.5; H, 5.1; N, 7.8. $C_{17}H_{18}N_2O_3S_2$ requires C, 56.3; H, 5.0; N, 7.7%).

(1R,5R)-1-*Benzyl*-6-(1-*benzyloxycarbonyl-2-methylprop*-1-*enyl*)-4-*thia*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-7-*one* (6a).—The isocyanide (5a) (0.30 g, 0.74 mmol) was dissolved in DMF (2 ml) and stirred with sodium thiophenoxide (0.1 g) for 1 h at 20 °C. Ethyl acetate and water were added and the organic phase separated and dried. Chromatography of the residue provided the *thiazoline* (6a) (0.16 g, 54%); m.p. 111—114 °C, $\nu_{max.}$ 1 770 and 1 720 cm^{-1}; δ 1.70 and 2.20 (6 H, 2s, CH_3), 3.33 (2 H, s, CH_2Ph), 5.11 (2 H, ABq, *J* 13 Hz, CH_2O), 5.47 (1 H, d, *J* 1.5 Hz, 5-H), 7.2—7.4 (10 H, m and s, Ph–H), and 7.82 (1 H, d, *J* 1.5 Hz, N=C*H*) (Found: C, 66.6; H, 5.5; N, 6.6. $C_{23}H_{22}N_2O_3S{\cdot}0.5H_2O$ requires C, 66.5; H, 5.3; N, 6.7%).

(1S,5R)-6-(1-*Benzyloxycarbonyl-2-methylprop*-1-*enyl*)-1-*methylthio*-4-*thia*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-7-*one* (6d).—In a similar experiment to that producing the isocyanide (5f) and following the isolation of (5f) (33%), continued elution of the column provided the *thiazoline* (6d) (0.21 g, 27%) as a pale yellow solid, m.p. 78—81 °C; $\nu_{max.}$ 1 775 and 1 720 cm^{-1}; δ 1.88 and 2.21 (6 H, 2s, CH_3), 2.29 (3 H, s, SCH_3), 5.23 (2 H, s, OCH_2), 5.68 (1 H, d, *J* 1.4 Hz, C*H*), 7.41 (5 H, s, Ph–H), and 8.02 (1 H, d, *J* 1.7 Hz, N=C*H*) (Found: C, 56.8; H, 5.0; N, 7.8. $C_{17}H_{18}N_2O_3S_2$ requires C, 56.3; H, 5.0; N, 7.7%).

(1R,5R)-6-(1-*Benzyloxycarbonyl-2-methylprop*-1-*enyl*)-3-*chloro*-4-*thia*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-7-*one* (6e).—The isocyanides (2) (1.0 g, 3.2 mmol) were dissolved in DMF (3 ml) and treated at ice-bath temperature with potassium carbonate (0.44 g) and t-butyl hypochlorite (0.36 ml, 3.3 mmol). After 1.5 h, work-up and chromatography provided the *thiazoline* (6e) (0.17 g, 16%) as a pale yellow gum, $\nu_{max.}$ 1 775, 1 720, 1 625, 1 575, and 975 cm^{-1}; δ 1.98 and 2.29 (6 H, 2s, CH_3), 5.24 (2 H, s, OCH_2), 5.86 and 5.97 (each 1 H, d, *J* 4 Hz, C*H*), and 7.40 (5 H, s, Ph–H) (Found: Cl, 9.9. $C_{16}H_{15}ClN_2O_3S$ requires Cl, 10.1%). If the reaction with t-butyl hypochlorite is carried out in methylene chloride in the absence of K_2CO_3, i.r. analysis of

* Microwave studies of methyl isocyanide gave a value of 1.167 Å, quoted in ref. 3*a*, p. 3.

† Prepared according to G. Zumach and E. Kühle, *Angew. Chem. Internat. Edn.*, 1970, **9**, 54, b.p. 72—78 °C/15 mmHg.

the solution after 2 h shows *ca.* 50% conversion into the corresponding isocyanate ν_{NCO} 2 240 cm^{-1}.

(1R,5R)-6-(1-*Benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-1-*methoxycarbonylmethyl*-4-*thia*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-7-*one* (6g).—The isocyanide (5c) (0.50 g, 1.3 mmol), DMF (5 ml), potassium carbonate (0.19 g), and t-butyl hypochlorite (0.15 ml, 1.3 mmol) were stirred together for 1.5 h at 0—5 °C. Work-up and chromatography gave the *thiazoline* (6g) (0.22 g, 40%), m.p. 97—99 °C; $\nu_{max.}$ 1 780, 1 735, 1 710sh, 1 630, and 1 580 cm^{-1}; δ 1.98 and 2.32 (6 H, 2s, CH_3), 2.98 (2 H, ABq, *J* 17 Hz, CH_2), 3.70 (3 H, s, OCH_3), 5.19 (2 H, s, OCH_2), 5.89 (1 H, s, CH), and 7.40 (5 H, s, Ph–H) (Found: C, 53.7; H, 4.6; N, 6.5%; M^+, 422.070 4. $C_{19}H_{19}ClN_2O_5S$ requires C, 54.0; H, 4.5; N, 6.6%; *M*, 422.070 4).

(1R,5R)-1-*Benzyl*-6-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-3-*chloro*-4-*thia*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-7-*one* (6f).—In a similar manner the isocyanide (5a) (0.45 g, 1.1 mmol) reacted with t-butyl hypochlorite (0.12 ml) during 1.5 h, and furnished the *thiazoline* (6f) (0.28 g, 59%), m.p. 109—110.5 °C; $\nu_{max.}$ 1 780, 1 720, 1 580, 1 165, 1 005, and 955 cm^{-1}; δ 1.80 and 2.28 (6 H, 2s, CH_3), 3.33 (2 H, s, CH_2Ph), 5.12 (2 H, ABq, OCH_2), 5.59 (1 H, s, CH), and 7.3 (10 H, m and s, Ph–H) (Found: C, 62.5; H, 5.0; Cl, 8.1; N, 6.5. $C_{23}H_{21}ClN_2O_3S$ requires C, 62.6; H, 4.8; Cl, 8.1; N, 6.4%).

Also isolated from this reaction was the amine (21a) (0.04 g, 9%).

(1S,5R)-6-(1-*Benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-3-*chloro*-1-*methylthio*-4-*thia*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-7-*one* (6h).—Similarly the isocyanide (5f) (0.31 g, 0.85 mmol) reacted with t-butyl hypochlorite (0.1 ml) during 1.5 h at 0—5 °C and 0.5 h at 20 °C, to furnish the *thiazoline* (6h) (0.12 g, 36%), m.p. 105—106 °C; $\nu_{max.}$ 1 780, 1 720, 1 630, and 1 565 cm^{-1}; δ 1.96 (3 H, s, CH_3), 2.31 (6 H, 2s, CH_3 and SCH_3), 5.26 (2 H, s, OCH_2), 5.78 (1 H, s, CH), and 7.43 (5 H, s, Ph–H) (Found: C, 51.7; H, 4.3; N, 7.0. $C_{17}H_{17}ClN_2O_3S_2$ requires C, 51.4; H, 4.3; N, 7.1%).

(1R,5R)-1-(2-*Benzyloxycarbonylethyl*)-4-*thia*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-7-*one* (6j).—The thiazoline (6c) (1.0 g, 2.1 mmol) was dissolved in DMF (9 ml) and water (0.9 ml) and pyridine (0.49 ml) was added, followed at 0—5 °C with powdered potassium permanganate (0.50 g, 3.1 mmol) in portions during 0.5 h. After a further 1 h, brine (15 ml) and ethyl acetate (25 ml) were added. The organic phase was washed, dried, and evaporated. Chromatography of the residue provided the *thiazoline* (6j) (0.21 g, 35%), m.p. 77—78 °C (from EtOAc–light petroleum); $\nu_{max.}$ 3 420, 3 260, 1 780, and 1 735 cm^{-1}; δ 2.56 (4 H, m, CH_2), 5.14 (2 H, s, OCH_2), 5.23br (1 H, CH), 6.9br (1 H, NH), 7.36 (5 H, s, Ph–H), and 8.04br (1 H, N=CH) (Found: C, 58.2; H, 5.1; N, 9.6. $C_{14}H_{14}N_2O_3S$ requires C, 57.9; H, 4.9; N, 9.7%).

4-[N-*Acetyl*-N-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-*aminomethylene*]-2-*thiazolin*-5-*one* (7).—The isocyanides (2) (1.0 g, 3.2 mmol) were dissolved in DMF (4 ml) and treated with potassium carbonate (0.44 g), and acetic anhydride (0.33 ml, 3.5 mmol). After 20 h at 20 °C, ice–water was added and the product extracted into ethyl acetate. Chromatography of the dried extracts furnished the *thiazolinone* (7) (0.39 g, 35%) as colourless prisms, m.p. 124—126 °C (ethyl acetate–light petroleum), $\nu_{max.}$ 1 710br, 1 640, 1 600, 1 365, 1 340, 1 260, 1 160, 1 120, 1 075, 995, 905, and 815 cm^{-1}; $\lambda_{max.}$ 225sh, 272, and 340 nm (ε 8 270 and 14 690); δ_H 1.79 (3 H, s, CH_3), 2.13 (3 H, s, CH_3), 2.38 (3 H, s, CH_3CO), 5.19 (2 H, s, CH_2O), 7.29 (5 H, s, Ph–H), and 8.14 and 8.23 (each 1 H, d, *J* 1.5 Hz, CH); δ_C 21.0 (2 lines) and 23.1 (q, 3 CH_3), 66.5 (t, OCH_2), 125.2 (s, C-4 or Me_2C), 128.1 and 128.5 (3 lines, aromatic CH), 129.3 (s, C-4 or Me_2C), 130.7 (d, AcN–CH), 135.5 (s, aromatic C), 150.8 (d, C-2), 154.6 (s, olefinic C), 162.8 (s, amide CO), 171.0 (s, ester CO), and 193.7 (C-5) (Found: C, 60.4; H, 5.2; N, 8.0%; M^+, 358.097 6. $C_{18}H_{18}N_2O_4S$ requires C, 60.3; H, 5.1; N, 7.8%; *M*, 358.098 8).

(2R)-2-*Benzyloxycarbonyl*-1,1-*dimethyl*-2-(4-*methoxycarbonylimidazolyl*)*ethanesulphenamide* (11).—The isocyanides (2) (0.88 g, 2.8 mmol) were dissolved in dry methanol (9 ml) and treated at 0—5 °C with potassium carbonate (0.38 g) and *O*-2,4-dinitrophenylhydroxylamine (0.55 g, 2.8 mmol). A yellow suspension formed. After 1.5 h and the usual work-up, chromatography provided the *imidazole* (11) (0.42 g, 42%) as a pale yellow gum, $\nu_{max.}$ 3 380w, 1 740, 1 720sh, 1 605, 1 550, 1 325, 1 275, and 1 000 cm^{-1}; $\lambda_{max.}$ (EtOH) 231.5 (ε 12 200); $\lambda_{max.}$ (EtOH containing 1N-aq. HCl) 223sh nm (ε 11 400); δ 1.22 (6 H, 2s, CH_3), 2.4br (2 H, exchanges with D_2O, NH_2), 3.89 (3 H, s, OCH_3), 5.01 (1 H, s, 2-H), 5.22 (2 H, ABq, OCH_2), 7.40 (5 H, s, Ph–H), and 7.75 and 8.01 (each 1 H, d, *J* 1.6 Hz, imidazole –CH); *m/e* (weak M^+ at 363) 314 (28) (Found: 314.127 1; *M* − 49 $C_{17}H_{18}N_2O_4$ requires 314.126 7), 283 (9), 270 (7), 255 (5), 232 (metastable), 223 (8), 180 (16), 179 (14), 108 (base), 107 (96), and 91 (92).

(4S)-*Benzyl* 4-*Hydroxy*-5,5-*dimethyl*-2-*thiazoline*-4-*carboxylate* (12a).—The isocyanides (2) (1.45 g, 4.6 mmol) were dissolved in dry THF (12 ml) and treated at −70 °C under N_2 with n-butyl-lithium (2.1M; 2.3 ml, 4.6 mmol) and then flushed with dry oxygen for 0.75 h. After the usual work-up, the crude product was chromatographed to furnish the *thiazoline* (12a) (0.14 g, 12%), m.p. 130—132 °C (diethyl ether); $\nu_{max.}$ 3 200br, 1 735, 1 560, 1 460, 1 260, and 815 cm^{-1}; δ 1.33 (3 H, s, CH_3), 1.58 (3 H, s, CH_3), 4.74 (1 H, br, exchanges with D_2O, OH), 5.28 (2 H, s, OCH_2), 7.35 (5 H, s, Ph–H), and 8.18 (1 H, s, N=CH) (Found: M^+, 265.076 6. $C_{13}H_{15}NO_3S$ requires *M*, 265.077 3).

Benzyl 6-(*Methoxycarbonylmethylene*)*penicillanate* (15) *and* (1R,5R)-6-(1-*Benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-1-*methoxycarbonylmethyl*-4-*thia*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-7-*one* (6b).—The isocyanide (5c) (1.88 g, 4.8 mmol) was dissolved in DMF (20 ml) and treated at 0—5 °C with potassium carbonate (0.74 g), isopropylamine (0.41 ml, 4.8 mmol) and then t-butyl hypochlorite (0.55 ml, 4.8 mmol). After 2.3 h ice–water was added and the product extracted into ethyl acetate. Chromatography of the dried, extracts provided, first, the *olefin* (15) (0.46 g, 27%) as a colourless oil; $\nu_{max.}$ 1 785, 1 740, 1 710sh, 1 350, 1 295, 1 270, 1 185, and 830 cm^{-1}; $\lambda_{max.}$ (iso-octane) 218.5 nm (ε 14 020); δ_H 1.43 and 1.56 (6 H, 2s, CH_3), 3.81 (3 H, s, OCH_3), 4.60 (1 H, s, 3-H), 5.23 (2 H, s, OCH_2), 6.03 and 6.32 (each 1 H, s, 5- and vinyl-H), and 7.41 (5 H, s, Ph–H); δ_C[$(CD_3)_2SO$] 25.2 and 32.1 (q, 2-CH_3), 52.2 (q, OCH_3), 63.6 (s, C-2), 66.7 (t, OCH_2), 67.9 and 69.8 (both d, C-3 and C-5), 115.5 (d, =CH), 128.3 (d, aromatic CH), 135.0 (s, aromatic C), 155.5 (s, C-6), and 163.5, 165.5, and 166.7 (each s, 3 CO) (Found: M^+, 361.098 1. $C_{18}H_{19}NO_5S$ requires *M*, 361.098 4).

Continued elution of the column then gave the *thiazoline* (6b) (0.32 g, 17%), m.p. 80—83 °C (cyclohexane); $\nu_{max.}$ 1 770, 1 730, and 1 705sh cm^{-1}; δ 1.90 and 2.26 (6 H, 2s, CH_3), 3.05 (2 H, ABq, *J* 17 Hz, CH_2), 3.62 (3 H, s, OCH_3), 5.18 (2 H, s, OCH_2), 5.76 (1 H, d, *J* 1.6 Hz, CH), 7.37 (5 H,

s, Ph–H), and 7.95 (1 H, d, *J* 1.6 Hz, N=C*H*) (Found: C, 59.3; H, 5.3; N, 7.4. $C_{19}H_{20}N_2O_5S$ requires C, 58.8; H, 5.2; N, 7.2%).

Action of Heat on Isocyanides (2) *and* (5a).—(i) The isocyanides (2) (1.13 g) were refluxed under nitrogen in benzene (30 ml) for 23 h, after which the benzene was replaced by xylene and refluxing continued for 4 h. Examination by t.l.c. indicated a more polar component to be forming, but no cyanide band was evident in the i.r. spectrum. Filtration and chromatography provided recovered starting material and then the thiazoline (12b) (0.15 g, 17%) as a colourless gum which crystallised with time and was identical to that described by Firestone *et al.*[20]

(ii) When a mixture of the isocyanide (5a) (0.05 g) and Nujol (0.2 ml) was heated at 180—200 °C for 1 h under nitrogen, i.r. analysis indicated loss of the isocyanide band and the appearance of a new band corresponding to the cyanide (ν_{CN} 2 260 cm^{-1}).

Benzyl (2S,5R,6R)-6-(2-*Benzyloxycarbonylethyl*)-6-*carboxy*-4-*thia*-1,7-*diazabicyclo*[3.3.0]*oct*-7-*ene*-2-*carboxylate Hydrochloride* (19b).—The isocyanide (5d) (0.30 g, 0.62 mmol) was dissolved in ether (5 ml) and treated at 0—5 °C with 5N-aqueous hydrochloric acid (0.1 ml); the mixture was then vigorously shaken for 4 h. The colourless precipitate was collected and washed with ether to furnish the *hydrochloride* (19b) (0.15 g, 46%), m.p. 155—156 °C; $\nu_{max.}$ (Nujol) 2 600br, 1 743, 1 650, and 1 630 cm^{-1}; $\lambda_{max.}$ 230sh nm (ε 6 415); δ[$(CD_3)_2SO$] 1.44 (3 H, s, CH_3), 1.52 (3 H, s, CH_3), 2.27 (4 H, m, CH_2), 5.13 (2 H, s, OCH_2), 5.19 (1 H, s, C*H*), 5.28 (2 H, s, OCH_2), 6.26 (1 H, s, C*H*), 7.4 (10 H, 2s, Ph–H), and 9.00 (1 H, s, N=C*H*) (Found: C, 57.9; H, 5.7; Cl, 6.6; N, 5.4. $C_{26}H_{29}N_2O_6S$·HCl requires C, 58.5; H, 5.7; Cl, 6.6; N, 5.3%).

Benzyl (2S,5R,6R)-6-*Carboxy*-6-(1-*hydroxy*-1-*methylethyl*)-4-*thia*-1,7-*diazabicyclo*[3.3.0]*oct*-7-*ene*-2-*carboxylate Hydrochloride* (19c).—The isocyanide (5e) (0.41 g, 1.1 mmol) was treated similarly for 1 h to provide the *hydrochloride* (19c) (0.26 g, 55%), m.p. 146—148 °C (methanol–ether); $\nu_{max.}$ (Nujol) 3 340, 2 550br, 1 740, and 1 610 cm^{-1}; $\lambda_{max.}$ 233 nm (ε 7 025); δ[$(CD_3)_2SO$] 1.4 (12 H, 2s, CH_3), 5.14 (1 H, s, C*H*), 5.29 (2 H, s, OCH_2), 6.13 (1 H, s, C*H*), 7.42 (5 H, s, Ph–H), 9.12 (1 H, s, N=C*H*), and 9.8br (2 H, exchanges with D_2O, N*H* and CO_2H) (Found: C, 52.9; H, 5.9; Cl, 8.4; N, 6.5. $C_{19}H_{25}N_2O_5S$·HCl requires C, 53.1; H, 6.1; Cl, 8.3; N, 6.5%).

Benzyl (2S,5R,6R)-6-*Benzyl*-6-*carboxy*-4-*thia*-1,7-*diazabicyclo*[3.3.0]*oct*-7-*ene*-2-*carboxylate Hydrochloride* (19a).—The isocyanide (5a) (0.04 g) was treated similarly except acetone replaced ether as the solvent. The *hydrochloride* (19a) (0.03 g, 70%), m.p. 156—159 °C, was obtained as a colourless solid after dilution with ether; $\nu_{max.}$ 2 600br, 1 740, and 1 620 cm^{-1}; $\lambda_{max.}$ 233 nm (ε 7 870); δ[$(CD_3)_2SO$] 1.46, 1.58 (6 H, 2s, CH_3), 3.30 (2 H, s, CH_2), 5.17 (1 H, s, C*H*), 5.30 (2 H, s, OCH_2), 6.30 (1 H, s, C*H*), 7.4 (10 H, 2s, Ph–H), and 8.87 (1 H, s, N=C*H*) (Found: C, 59.2; H, 5.4; N, 5.8. $C_{23}H_{25}N_2O_4S$·HCl requires C, 59.8; H, 5.7; N, 6.1%).

Benzyl 6α-*Methoxy*-6β-*methoxycarbonylaminopenicillanate* (22a).—A solution of the isocyanide (5f) (0.98 g, 2.72 mmol) in dry methanol (30 ml) was treated at 20 °C with mercuric acetate (0.93 g, 2.99 mmol). After 35 min in all, ether (80 ml) was added, the mixture filtered, and the filtrates washed with water, dilute sodium hydrogencarbonate, and water, and then dried and evaporated. Chromatography of the residue gave the *urethane* (22a) (0.63 g, 59%) as a colourless oil; $\nu_{max.}$ 3 440, 3 300, 1 780, 1 745sh, 1 725, 1 495, 1 220, and 1 095 cm^{-1}; δ 1.38 (3 H, s, CH_3), 1.50 (3 H, s, CH_3), 3.51 (3 H, s, OCH_3), 3.74 (3 H, s, urethane CH_3), 5.20 (2 H, s, OCH_2), 5.54 (1 H, s, 5-H), 5.91br (1 H, N*H*), and 7.40 (5 H, s, Ph–H); δ_C[$(CD_3)_2SO$] 25.3, 31.9 (q, 2-CH_3), 51.6, 52.4 (q, OCH_3), 61.4 (s, C-2), 62.5 (t, OCH_2), 67.7 (d, C-3), 73.8 (d, C-5), 95.2 (s, C-6), 128 (d, aromatic *C*H), 134.6 (s, aromatic C), 154.0 (s, CO), and 166.3 (2 lines, s, 2 CO) (Found: M^+, 394.119 5. $C_{18}H_{22}N_2O_6S$ requires *M*, 394.119 2).

If the above reaction is carried out in dry THF at 0—5 °C, t.l.c. showed absence of starting material within 10 min. I.r. examination indicated the corresponding isocyanate to be present, ν_{NCO} 2 260 cm^{-1}.

Benzyl 6α- *and* 6β-*Methoxycarbonylaminopenicillanate* (22b).—The isocyanides (2) (1.0 g, 3.2 mmol), potassium carbonate (0.48 g) and thallic trinitrate (1.36 g, 3.5 mmol) were allowed to react in dry methanol (5 ml) for 0.5 h at 0—5 °C. After the usual work-up and chromatography the *urethanes* (22b) (0.50 g, 43%) were obtained as a colourless gum; $\nu_{max.}$ 3 430, 1 785, 1 735, 1 515, and 1 240 cm^{-1}; δ 1.39, 1.43, 1.58, and 1.63 (6 H, 4s, CH_3), 3.73 (3 H, s, OCH_3), 4.49, 4.54 (1 H, 2s, 3-H), 4.82, 4.98, 5.27, and 5.55 (2 H in all, 5- and 6-H), 5.21 (2 H, s, OCH_2), and 7.40 (5 H, s, Ph–H) (Found: C, 55.2; H, 5.7; N, 7.1. $C_{17}H_{20}N_2O_5S$ requires C, 56.0; H, 5.5; N, 7.7%).

Benzyl and Sodium 6α-*Benzyl*-6β-*formamidopenicillanate* (20a) *and* (20d).—The isocyanide (5a) (2.0 g, 4.9 mmol) was dissolved in chloroform (40 ml) to which formic acid (5 ml) was added at 0—5 °C. After being allowed to reach 20 °C during 2.3 h, the solution was evaporated to dryness. A solution of the residue in ether was washed with aqueous sodium hydrogencarbonate and water, and then dried and evaporated to furnish the *ester* (20a) (1.7 g, 80%), m.p. 85—87 °C (cyclohexane); $\nu_{max.}$ 3 300, 3 390, 1 780, 1 750, 1 690, and 1 495 cm^{-1}; δ 1.34, 1.51 (each 3 H, s, CH_3), 3.46 (2 H, ABq, 6α-CH_2), 4.42 (1 H, s, 3-H), 5.16 (2 H, s, OCH_2), 5.51 (1 H, s, 5-H), 6.30 (1 H, br, N*H*), 7.3 (10 H, 2s, Ph–H), and 8.13 (1 H, s, *H*CO) (Found: C, 65.1; H, 5.8; N, 6.4. $C_{23}H_{24}N_2O_4S$ requires C, 65.1; H, 5.7; N, 6.6%).

This ester (1.0 g, 2.4 mmol) was added to a prehydrogenated mixture of ethyl acetate (30 ml) and 10% Pd on charcoal (0.5 g). After hydrogenation had been carried out for 23 h the catalyst was filtered off, replaced by fresh, and the hydrogenation continued for a further 2 days. Finally the mixture was filtered and extracted with sufficient 0.5M-aqueous sodium hydrogen carbonate as to give pH 7, and the extracts evaporated and dried over P_2O_5 to furnish *penicillin salt* (20d) (0.61 g, 72%) as a hemihydrate; $\nu_{max.}$ (Nujol) 3 250, 1 770, 1 675, and 1 610 cm^{-1}; δ(D_2O) 1.50 and 1.55 (6 H, 2s, CH_3), 3.48 (2 H, s, 6α-CH_2), 4.23 (1 H, s, 3-H), 5.56 (1 H, s, 5-H), 3.38 (5 H, s, Ph–H), and 8.06 (1 H, s, *H*CO) (Found: C, 52.4; H, 5.1; N, 7.5. $C_{16}H_{17}N_2NaO_4S$·$0.5H_2O$ requires C, 52.7; H, 5.0; N, 7.7%).

Benzyl 6α-(2-*Benzyloxycarbonylethyl*)-6β-*formamidopenicillanate* (20b).—By the same procedure the isocyanide (5d) was transformed into the formamide (20b); $\nu_{max.}$ 3 400, 3 360, 1 780, 1 740, 1 700, and 1 180 cm^{-1}; δ 1.37, 1.53 (6 H, 2s, CH_3), 2.57 (4 H, m, CH_2), 4.44 (1 H, s, 3-H), 5.1, 5.18 (4 H, 2s, OCH_2), 5.45 (1 H, s, 5-H), 6.85br (1 H, N*H*), 7.35 (10 H, s, Ph–H), and 8.11br (1 H, *H*CO).

Benzyl 6β-*Formamido*-6α-(1-*hydroxy*-1-*methylethyl*)*penicillanate* (20c).—Similarly the isocyanide (5e) (1.75 g, 4.7 mmol) was converted into the formamide (20c) (58%), which contained *ca.* 15% of an unknown impurity, as judged by n.m.r. spectroscopy; $\nu_{max.}$ 3 380, 3 300, 1 780, 1 745, 1 680,

and 1 180 cm^{-1}; δ 1.33, 1.40, 1.56 (12 H, 3s, CH_3), 4.46 (1 H, s, 3-H), 4.75br (*ca.* 0.75 H, O*H*), 5.21 (2 H, s, OCH_2), 5.77 (1 H, s, 5-H), 7.16br (*ca.* 0.75 H, N*H*), 7.33 (5 H, s, Ph–H), and 8.06 (1 H, d, *H*CO).

Benzyl 6β-*Amino*-6α-*benzylpenicillanate* (21a).—A solution of the isocyanide (5a) (1.75 g, 4.33 mmol) in chloroform (50 ml) was stirred with toluene-*p*-sulphonic acid hydrate (0.83 g, 4.33 mmol) for 0.5 h at 20 °C. The solution was washed with aqueous sodium hydrogencarbonate, dried, and evaporated. A sample of the pure *amine* (21a), m.p. 99—101 °C was obtained by chromatography; $\nu_{max.}$ 3 360, 1 775, and 1 750 cm^{-1}; δ 1.40 and 1.58 (6 H, 2s, CH_3), 1.83 (2 H, s, exchanges with D_2O, NH_2), 3.24 (2 H, ABq, 6α-CH_2), 4.43 (1 H, s, 3-H), 5.17 (2 H, s, OCH_2), 5.39 (1 H, s, 5-H), and 7.29 and 7.39 (10 H, 2s, Ph–H) (Found: M^+, 396.150 9. $C_{22}H_{24}N_2O_3S$ requires *M*, 396.150 8).

The crude amine from the above experiment was dissolved in dry ether to which was added toluene-*p*-sulphonic acid (0.79 g); the corresponding *salt* (1.7 g, 68%), m.p. 164 °C (deco ɔ.), was precipitated, collected, and washed with ether (Found: C, 61.4; H, 6.0; N, 4.8. $C_{29}H_{32}N_2O_6S_2$ requires C, 61.2; H, 5.7; N, 4.9%).

Benzyl 6β-*Amino*-6α-*methoxycarbonylmethylpenicillanate* (21b).—In a similar fashion the isocyanide (5c) (0.68 g, 1.75 mmol) was converted into the *toluene*-p-*sulphonate* of the amine (21b) (0.55 g, 57%), m.p. 154—155 °C (ethanol–ether); $[\alpha]_D^{20}$ 110° (*c* 0.53, MeOH); $\nu_{max.}$ 2 700br, 1 790, and 1 740 cm^{-1}; δ[$(CD_3)_2SO$] 1.38 and 1.63 (6 H, 2s, CH_3), 2.28 (3 H, s, CH_3), 3.65 (3 H, s, OCH_3), 4.58 (1 H, s, 3-H), 5.23 (2 H, s, OCH_2), 5.54 (1 H, s, 5-H), and 7.0—8.1 (12 H, m, Ar–H and NH_3) (Found: C, 54.6; H, 5.4; N, 4.9. $C_{25}H_{30}N_2O_8S_2$ requires C, 54.5; H, 5.5; N, 5.1%).

Benzyl 6β-*Amino*-6α-(2-*benzyloxycarbonylethyl*)*penicillanate* (21c).—Similarly, the isocyanide (5d) (2.54 g, 5.3 mmol) was converted into the *free base* (21c) (56%) as a syrup; $\nu_{max.}$ 3 350, 1 770, 1 740, and 1 600 cm^{-1}; δ 1.40, 1.57 (6 H, 2s, CH_3), 1.82br (2 H, NH_2), 2.1—2.8 (4 H, m, CH_2), 4.43 (1 H, s, 3-H), 5.14 and 5.19 (4 H, 2s, OCH_2), 5.27 (1 H, s, 5-H), and 7.38 (10 H, s, Ph–H). The *toluene*-p-*sulphonate* was also obtained in a similar manner, m.p. 140 °C (decomp.) (ethyl acetate–ether) (Found: C, 58.6; H, 5.7; N, 4.0. $C_{32}H_{36}N_2O_8S_2 \cdot H_2O$ requires C, 58.3; H, 5.8; N, 4.2%).

Benzyl 6β-*Amino*-6α-*methylthiopenicillanate* (21d) *and Benzyl* 6β-*formamido*-6α-*methylthiopenicillanate* (20e).—Similarly, the isocyanide (5f) (3.61 g, 10 mmol) was treated during 1.5 h at 0—5 °C. The *toluene*-p-*sulphonate salt* of the amine (21d) (2.92 g, 56%), m.p. 136—138 °C (decomp.) (lit.,[16] m.p. 135 °C), was precipitated from ether in the same way; $\nu_{max.}$ 3 200—3 300br, 1 785, and 1 740 cm^{-1}; δ 1.30, 1.42 (6 H, 2s, CH_3), 2.37 (6 H, s, SCH_3 and aryl-CH_3), 4.53 (1 H, s, 3-H), 5.23 (2 H, s, OCH_2), 5.48 (1 H, s, 5-H), 7.1—8.0 (9 H, m, Ar–H), and 8.9br (3 H, NH_3) (Found: C, 52.6; H, 5.5; N, 5.0. $C_{23}H_{28}N_2O_6S_2$ requires C, 52.6; H, 5.4; N, 5.3%).

From the liquors, following chromatography, the *formamide* (20e) (0.39 g, 10%) was isolated as a pale yellow solid, m.p. 123—125 °C (Found: C, 53.7; H, 5.4; N, 7.2. $C_{17}H_{20}N_2O_4S_2$ requires C, 53.7; H, 5.3; N, 7.4%).

Benzyl 6β-*Amino*-6α-*methoxypenicillanate* (21e).—The amine (21e) was prepared from the amine (21d) according to the method of Jen *et al.*[16]

Benzyl 6β-*Amino*-6α-*ethoxypenicillanate* (21f).—If ethanol is substituted for the methanol in the method of Jen *et al.*,[16] the desired free *amine* (21f) (95% yield) was obtained as a gum, which was purified by chromatography; $\nu_{max.}$ 3 420, 1 775, and 1 745 cm^{-1}; δ 1.24 (3 H, t, CH_3CH_2), 1.40, 1.54 (6 H, 2s, CH_3), 2.30br (2 H, NH_2), 3.72 (2 H, m, OCH_2CH_3), 4.46 (1 H, s, 3-H), 5.18 (2 H, s, OCH_2), 5.35 (1 H, s, 5-H), and 7.36 (5 H, s, Ph–H) (Found: M^+, 350.133 2. $C_{17}H_{22}N_2O_4S$ requires *M*, 350.130 0).

Benzyl 6β-*Amino*-6α-*azidopenicillanate* (21g).—The free base (21d) (prepared from 1.05 g, 2 mmol of the salt) was dissolved in DMF (8 ml) and pyridine (0.38 ml, 4.8 mmol) at 0—5 °C and treated with a methylene chloride solution of triethylammonium azide (*ca.* 40 mmol, prepared by neutralising a solution of HN_3[21] with triethylamine), and then with mercuric chloride (0.54 g, 2 mmol) at −10 to −20 °C. After 12 min, the mixture was filtered and diluted with ether (200 ml). After washing with water, drying, and evaporation, the residue (0.6 g, 87%) was the essentially pure *amine* (21g), which was used immediately; $\nu_{max.}$ 3 310, 2 110, 1 780, and 1 740 cm^{-1}; δ 1.42 and 1.57 (6 H, 2s, CH_3), 2.7br (2 H, NH_2), 4.57 (1 H, s, 3-H), 5.27 (2 H, s, OCH_2), 5.43 (1 H, s, 5-H), and 7.50 (5 H, s, Ph–H).

6α-*Benzyl*-6β-*phenylacetamidopenicillanic Acid* (24a).—The free base (21a) (prepared from 1 mmol of the salt) was dissolved in methylene chloride (10 ml) and pyridine (0.16 ml, 2 mmol) and treated at 0—5 °C with phenylacetyl chloride (0.19 ml, 1.5 mmol). After 3 h, work-up and chromatography provided the *benzyl ester* of the title compound (0.45 g, 88%) as a frothy solid; $\nu_{max.}$ 3 380, 1 775, 1 750, 1 670, and 1 495 cm^{-1}; δ 1.32, 1.37 (6 H, 2s, CH_3), 3.45 (2 H, ABq, 6α-CH_2), 3.52 (2 H, s, PhCH_2), 4.38 (1 H, s, 3-H), 5.14 (2 H, s, OCH_2), 5.49 (1 H, s, 5-H), 6.1br (1 H, N*H*), and 7.2—7.5 (15 H, m, Ph–H) (Found: C, 70.6; H, 5.9; N, 5.3. $C_{30}H_{30}N_2O_4S$ requires C, 70.1; H, 5.9; N, 5.4%).

This ester (0.41 g, 0.79 mmol) was hydrogenolysed as for compound (20a) during 5 h. After filtration and evaporation the *acid* (24a) (0.32 g, 96%), m.p. 93—97 °C, crystallised on the addition of ether, and contained ether of crystallisation; $\nu_{max.}$ 3 380, 2 400—2 700, 1 775, 1 740, 1 720sh, 1 670, and 1 490 cm^{-1}; δ 1.43, 1.47 (6 H, 2s, CH_3), 3.4—3.6 (4 H, m, CH_2Ph), 4.32 (1 H, s, 3-H), 5.49 (1 H, s, 5-H), 6.22br (1 H, N*H*), 7.2—7.4 (10 H, m, Ph–H), and 8.04br (1 H, COO*H*). A satisfactory analysis was not obtained. The acid was homogeneous by t.l.c., R_{F2} 0.6.

6α-(2-*Carboxyethyl*)-6β-*phenylacetamidopenicillanic Acid* (24b).—The salt of the amine (21c) (1.84 g, 2.88 mmol), pyridine (0.58 ml), and phenylacetyl chloride (0.55 ml) were allowed to react in methylene chloride (28 ml) for 2.5 h at 0—5 °C. After work-up and chromatography as before, the *dibenzyl ester* of the title compound (0.98 g, 59%) was obtained as a clear, colourless oil; $\nu_{max.}$ 3 380, 1 775, 1 740, 1 675, and 1 495 cm^{-1}; δ 1.32, 1.37 (6 H, 2s, CH_3), 2.50 (4 H, m, CH_2), 3.56 (2 H, s, PhCH_2), 4.38 (1 H, s, 3-H), 5.09 and 5.18 (each 2 H, s, OCH_2), 5.43 (1 H, s, 5-H), 6.03br (1 H, N*H*), and 7.3—7.5 (15 H, m, Ph–H). Hydrogenolysis of this diester, as before, provided the *disodium salt* of acid (24b) as an amorphous solid; $\nu_{max.}$(KBr) 1 755, 1 660, 1 600, 1 490, and 1 400 cm^{-1} (Found: C, 50.7; H, 5.0; N, 5.6. $C_{19}H_{20}N_2Na_2O_6S$ requires C, 50.7; H, 4.5; N, 6.2%).

6β-(2-*Carboxythien*-3-*ylacetamido*)-6α-*methoxypenicillanate* (24d).—The amine (21e) [prepared from 10 mmol of the amine (21d) according to Jen *et al.*[16]] was dissolved in methylene chloride (100 ml) containing pyridine (1.3 ml,

16 mmol) and treated, under ice-cooling, with a solution of the acid chloride of monobenzylthien-3-ylmalonate (12.5 mmol), in the same solvent (25 ml). After 3 h ice–water was added and the neutral product isolated from ethyl acetate. After drying and evaporation of the solvent, the crude product (4.7 g) was chromatographed to furnish the *dibenzyl ester* of the title compound (24d) (2.83 g, 47%), as a colourless, frothy solid which was a mixture of diastereoisomers; $\nu_{max.}$ 3 250, 1 770, 1 635, 1 685, 1 495, 1 315, and 1 160 cm^{-1}; δ 1.33br (6 H, CH_3), 3.43, 3.48 (3 H, 2s, OCH_3), 4.47, 4.51 (1 H, 2s, 3-H), 4.86 (1 H, s, malonyl C*H*), 5.27, 5.32 (2 H, 2s, OCH_2), 5.63 (1 H, s, 5-H), 7.1—7.6 (13 H, m, Ar–H), 7.75br and 7.91br (1 H, N*H*) (Found: M^+, 594.152 8. $C_{30}H_{30}N_2O_7S_2$ requires *M*, 594.149 4). This diester (2.75 g. 4.6 mmol) was dissolved in ethanol (80 ml), water (20 ml), and 1.0M-sodium hydrogen carbonate solution (7 ml). The mixture was hydrogenolysed at s.t.p. for 1.5 h over 10% Pd on carbon (2.75 g). The catalyst was filtered off and the filtrates reduced in volume by evaporation to one third. More catalyst (1.3 g) was added and the reaction continued for 1.75 h, when the process was repeated a third time. Finally, filtration, evaporation of the ethanol, adjustment of the pH to 6.5 and freeze-drying provided the diastereoisomeric disodium salts of (24d) (1.63 g, 77%) as an amorphous solid; $\nu_{max.}$(KBr) 1 760, 1 670, 1 605, 1 500, and 1 365 cm^{-1}; δ (D_2O, HOD at 4.70) 1.33br (6 H, CH_3), 3.43, 3.52 (3 H, 2s, OCH_3), 4.24 (1 H, s, 3-H), 4.6 (partially obscured) (malonyl C*H*), 5.51 (1 H, s, 5-H), and 7.0—7.6 (3 H, m, thienyl-H). The material was homogeneous by t.l.c., R_{F1} 0.2. In the same way acylation of the appropriate amine (21) and hydrogenolysis provided the following compounds.

6β-(2-*Carboxythien*-3-*ylacetamido*)-6α-*methoxycarbonylmethylpenicillanic Acid* (24c).—The *dibenzyl ester* of the title compound (24c) (0.29 g, 67% yield) was obtained as a frothy solid from the amine (21b) (0.68 mmol); $\nu_{max.}$ 3 250, 1 780, 1 740br, 1 675, 1 500, 1 310, and 1 170 cm^{-1}; δ 1.36br (6 H, CH_3), 3.34 (2 H, ABq, 6α-CH_2), 3.68 (3 H, s, OCH_3), 4.52 (1 H, s, 3-H), 4.73 (1 H, s, malonyl C*H*), 5.30br (4 H, OCH_2), 5.54 (1 H, s, 5-H), and 7.1—7.8 (14 H, m, aryl-H and N*H*) (Found: M^+, 636. $C_{32}H_{32}N_2O_8S_2$ requires *M*, 636). The corresponding amorphous disodium salt (0.16 g, 74%) was obtained following hydrogenolysis of the above diester (0.44 mmol); $\nu_{max.}$(KBr) 1 765, 1 730sh, 1 660, 1 505, 1 365, and 1 210 cm^{-1}; δ(D_2O, HOD at 4.70) 1.34, 1.41 (6 H, 2s, CH_3), 3.31 (2 H, s, 6α-CH_2), 3.63, 3.68 (3 H, 2s, OCH_3), 4.22 (1 H, s, 3-H), 4.48, 4.53 (1 H, 2s, malonyl C*H*), 5.46, 5.48 (1 H, 2s, 5-H), and 7.0—7.6 (3 H, m, thienyl-H). This material was judged to be essentially pure by t.l.c. R_{F1} 0.4.

6β-(2-*Carboxythien*-3-*ylacetamido*)-6α-*ethoxypenicillanic Acid* (24e).—The *dibenzyl ester* of the title compound (24e) (0.54 g, 45%) was obtained as a gum from the amine (21f) (2 mmol); $\nu_{max.}$ 3 250, 1 775, 1 740, 1 690, 1 495, 1 320, and 1 160 cm^{-1}; δ 1.11, 1.15 (3 H, 2t, CH_2CH_3), 1.31br (6 H, s, CH_3), 3.67 (2 H, m, CH_2CH_3), 4.45, 4.49 (1 H, 2s, 3-H), 4.85 (1 H, s, malonyl C*H*), 5.26, 5.29 (4 H, 2s, CH_2Ph), 5.61 (1 H, s, 5-H), 7.1—7.6 (13 H, m, aryl-H), and 7.71br, 7.89br (1 H, N*H*) (Found: M^+, 608.164 6. $C_{31}H_{32}N_2O_7S_2$ requires *M*, 608.164 7).

The amorphous disodium salt (0.28 g, 75%) was isolated following hydrogenolysis of this diester (0.79 mmol); $\nu_{max.}$(KBr) 1 760, 1 670, 1 600, 1 495, and 1 370 cm^{-1}; δ(D_2O, HOD at 4.70) 1.07, 1.13 (3 H, 2t, CH_2CH_3), 1.27, 1.33 (6 H, 2s, CH_3), 3.70 (2 H, m, OCH_2), 4.23 (1 H, s, 3-H), 4.61 (partially obscured, malonyl –C*H*), 5.48 (1 H, s, 5-H), and 7.0—7.5 (3 H, m, thienyl-H). This material was judged to be essentially pure by t.l.c., R_{F1} 0.3.

6α-*Azido*-6β-(2-*carboxythienyl*-3-*ylacetamido*)*penicillanic Acid* (24f).—The dibenzyl ester of the title compound (24f) (0.57 g, 47%) was obtained as a gum from the amine (21g) (2 mmol); $\nu_{max.}$ 3 240, 2 110, 1 785, 1 740, 1 690, 1 495, 1 320, 1 260, and 1 170 cm^{-1}; δ 1.32, 1.40, 1.60 (6 H, 3s, CH_3), 4.51, 4.53 (1 H, 2s, 3-H), 4.86 (1 H, s, malonyl C*H*), 5.23, 5.31 (4 H, 2s, OCH_2), 5.59 (1 H, s, 5-H), 7.1—7.7 (13 H, m, aryl-H), and 8.05br (1 H, N*H*); *m/e* (no molecular ion), 562 (M − 43) ($C_{29}H_{27}N_5O_6S_2$ requires *M*, 605). The material was homogeneous by t.l.c., R_{F1} 0.9; R_{F3} 0.3.

6β-(D-2-*Aminophenylacetamido*)-6α-*methoxypenicillanic Acid* (24h).—A mixed anhydride was prepared from *N*-benzyloxycarbonyl-D-phenylglycine (1.14 g, 4 mmol) and ethyl chloroformate (4 mmol) in dry THF (8 ml), containing triethylamine (0.56 ml, 4 mmol) at −15 °C. After 10 min a solution of the toluene-*p*-sulphonate of the amine (21d) (2.10 g, 4 mmol) in dry THF (20 ml), containing triethylamine (4 mmol) was added during 3 min. The reaction was allowed to proceed during 10 min at −10 °C and 1.75 h at ice-bath temperature, when the bulk of the THF was evaporated and replaced by ethyl acetate. The neutral product was isolated in the usual way. Chromatography of the crude product provided recovered amine (21d) (29%) and then *benzyl* 6β-(D-2-*benzyloxycarbonylaminophenylacetamido*)-6α-*methylthiopenicillanate* (1.3 g, 52%) as an amorphous solid; $\nu_{max.}$ 3 270, 3 380, 1 770, 1 720sh, 1 700, 1 685, and 1 490 cm^{-1}; δ 0.97, 1.22 (6 H, 2s, CH_3), 2.24 (3 H, s, SCH_3), 4.34 (1 H, s, 3-H), 5.13, 5.19 (4 H, 2s, OCH_2), 5.50 (m, Ph–C*H*) and 5.56 (s, 5-H) (2 H in all), 6.2 (1 H, m, N*H*), and 7.3—7.5 (15 H, m, Ph–H) (Found: C, 62.1; H, 5.5; N, 6.6. $C_{32}H_{33}N_3O_6S_2$ requires C, 62.0; H, 5.4; N, 6.8%). A solution of this ester (1.17 g, 1.9 mmol) in methylene dichloride (25 ml) was treated at −70 °C with a methylene dichloride solution of chlorine (0.14 g). After 7 min methanol (4.7 ml) containing triethylamine (0.19 g) was added and the reaction allowed to proceed for 15 min at −70 °C and then 1.5 h at 0—5 °C. The solution was washed with water, dried, and evaporated. Chromatography of the residue provided the 6α-methoxyampicillin derivative (0.30 g, 26%) as an amorphous solid; $\nu_{max.}$ 3 360, 3 260, 1 770, 1 735, 1 690br, 1 490, 1 320, 1 260, and 1 220 cm^{-1}; δ 0.90, 1.21 (6 H, 2s, CH_3), 3.46 (3 H, s, OCH_3), 4.33 (1 H, s, 3-H), 5.13, 5.19 (4 H, 2s, OCH_2), 5.48 (1 H, d, PhC*H*), 5.60 (1 H, s, 5-H), 6.22 (1 H, d, N*H*), and 7.4br (15 H, Ph–H). Hydrogenolysis of this ester (0.25 g) in 20% aqueous ethanol (25 ml) was carried out for a total of 22 h at s.t.p. and 7 h at 50 lb/in², in the presence of 10% Pd–C (0.3 g initially and two further portions, at intervals, following filtration). After the addition of sodium hydrogencarbonate (1 equiv.) and removal of the ethanol, lyophilisation provided the sodium salt of 6α-methoxyampicillin (24h); $\nu_{max.}$(KBr) 1 760, 1 680, 1 600br, 1 520sh, 1 410, and 1 110 cm^{-1}; δ(D_2O, HOD at 4.70) 0.98, 1.35 (6 H, 2s, CH_3), 3.54 (3 H, s, OCH_3), 4.18 (1 H, s, 3-H), 5.54, 5.60 (2 H, 2s, 5-H and PhC*H*), and 7.50 (5 H, s, Ph–H).

If the reaction mixture was concentrated prior to the addition of the hydrogen carbonate the *title compound* (24h) precipitated as the crystalline hydrated zwitterion, m.p. 185 °C (decomp.) (Found: C, 51.7; H, 5.9; N, 10.1; S, 7.9. $C_{17}H_{21}N_3O_5S{\cdot}H_2O$ requires C, 51.4; H, 5.8; N, 10.6; S, 8.1%).

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