Alkylation of Penicillanates: Aspects of the Chemistry of Penicillanate Sulphonium Salts

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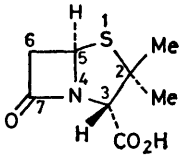
Methyl (6*S*)-6-chloro-, (6*S*)-6-phthalimido-, and 6,6-dibromo-penicillanates (4)—(6) have been converted into sulphonium salts (7)—(12) using trimethyloxonium tetrafluoroborate, methyl fluorosulphonate, and triethyloxonium tetrafluoroborate. Methyl 6,6-dibromo-1-methylpenicillanate tetrafluoroborate (9) was assigned the 1α-configuration on the basis of an n.O.e. experiment. Treatment of sulphonium salts (7)—(12) with sodium carbonate gives the corresponding methyl 2-[(2*R*)-2-alkylthio-4-oxoazetidin-1-yl)-3-methylbut-2-enoates (22)—(25) in high yield. Methanolysis of methyl (6*S*)-6-chloro-1-methylpenicillanate tetrafluoroborate (7) ‡ gives a mixture of methyl (2*S*)-2-[(2*S*,3*R*)-3-chloro-2-methoxy-4-oxoazetidin-1-yl]-3-methyl-3-methylthiobutanoate (29), its C-2′ epimer (30), and methyl (2*S*)-2-[(2*R*)-2-chloro-3,3-dimethoxypropionamido]-3-methyl-3-methylthiobutanoate (32), whereas treatment with sodium carbonate in methanol gives methyl (2*S*)-2-(*trans*-2-chloro-*cis*-2-methoxycarbonylvinylamino)-3-methyl-3-methylthiobutanoate (36). Similar reactions were observed with ethanol. A sulphonium salt could not be isolated from the reaction between methyl (6*R*)-6-phthalimidopenicillanate (3) and trimethyloxonium tetrafluoroborate, but treatment of the mixture with anhydrous sodium carbonate gave a mixture of methyl 3-methyl-2-[(2*R*,3*R*)- and -[(2*S*,3*R*)-2-methylthio-4-oxo-3-phthalimidoazetidin-1-yl]-but-2-enoates (39) and (46). Complex product mixtures were obtained from the reaction between methyl (6*R*)-6-phenylacetamidopenicillanate (2) and trimethyloxonium tetrafluoroborate.

THE chemistry of penicillins has been intensively investigated in recent years.[1] During this time, many rearrangements of derivatives of penicillanic acid (1) have been discovered, and put to good use in the preparation of penicillin analogues.[2] Some of these re-

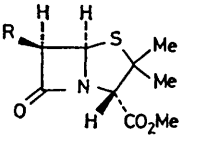


(1)

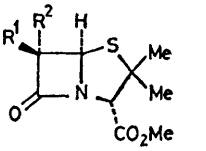
arrangements are initiated by electrophilic attack on the sulphur atom of the thiazolidine ring, the electrophilic attack being followed by sulphur–C(2) cleavage,[3] or by sulphur–C(5) cleavage.[4] However despite this interesting chemistry, no simple sulphonium salts derived from penicillanates have been prepared or isolated. We describe the preparation of some simple penicillanate sulphonium salts, together with a brief investigation into their chemistry.[5]

Preparation of Penicillanate Sulphonium Salts.—Preliminary attempts to methylate methyl 6β-phenylacetamido- and methyl 6β-phthalimido-penicillanates (2) and (3) using a variety of methylating agents ($AgClO_4$–MeI, methyl fluorosulphonate, trimethyloxonium tetrafluoroborate, dimethoxycarbenium tetrafluoroborate) gave complex product mixtures that could not be characterized. It was thought that the lack of success in these alkylations could be due to the presence of bulky 6β-substituents, and so it was decided to investigate the alkylation of some simple 6α-substituted penicillanates first of all. Methyl 6α-chloro- and methyl 6α-phthalimido-penicillanates (4) and (5) were chosen for study,[6,7] together with methyl 6,6-dibromopenicillanate (6),[8] a readily available 6,6-disubstituted penicillanate.

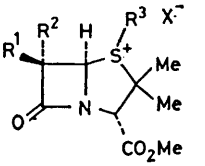
It was found that the simple penicillanates (4)—(6) could be converted into their *S*-methylsulphonium salts (7)‡—(11) by treatment with trimethyloxonium tetra-



(2) R = $PhCH_2CONH$
(3) R = phthalimido



(4) R^1 = H, R^2 = Cl
(5) R^1 = H, R^2 = phthalimido
(6) R^1 = R^2 = Br



(7) R^1 = H, R^2 = Cl, R^3 = Me; X = BF_4
(8) R^1 = H, R^2 = phthalimido, R^3 = Me; X = BF_4
(9) R^1 = R^2 = Br, R^3 = Me; X = BF_4
(10) R^1 = H, R^2 = Cl, R^3 = Me; X = FSO_3
(11) R^1 = H R^2 = phthalimido, R^3 = Me; X = FSO_3
(12) R^1 = H, R^2 = Cl, R^3 = Et; X = BF_4

fluoroborate in nitromethane at 20 °C for several hours, or by treatment with methyl fluorosulphonate in refluxing dichloromethane for several days. Methyl 6α-chloropenicillanate (4) was also converted into its *S*-ethylsulphonium salt using triethyloxonium tetrafluoroborate in dichloromethane. The reaction in this case is quite slow; after 40 h at 20 °C only 40% of the *S*-ethylsulphonium salt (12) had separated out of solution, but

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‡ Systematic name: (6*S*)-6-chloro-2-methoxycarbonyl-3,3,4-trimethyl-7-oxo-4-thionin-1-azabicyclo[3.2.0]heptane tetrafluoroborate.

since little starting material remained, the reaction was not continued.

The sulphonium salts (7)—(12) were isolated as crystalline solids, soluble in nitromethane, but insoluble in non-polar solvents. The crude products were sufficiently pure for most synthetic purposes, and samples of tetrafluoroborates (7), (9), and (12) were obtained analytically pure by recrystallization. The 6α-chloro- and 6,6-dibromo-penicillanate tetrafluoroborates (7), (9), and (12) are quite stable, and samples have been stored for months at 0 °C without significant decomposition. In contrast the 6α-phthalimidopenicillanate tetrafluoroborate (8), and the fluorosulphonates (10) and (11) are less stable, and decompose in the atmosphere after several hours at 20 °C.

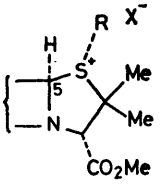
The structures assigned to sulphonium salts (7)—(12) are consistent with their spectroscopic data. The fluorosulphates (10) and (11) and the corresponding tetrafluoroborates (7) and (8), have identical ^{1}H n.m.r. spectra. The ^{1}H n.m.r. spectra of the *S*-methylsulphonium salts (7)—(11) resemble those of the starting materials, except for the downfield shift of all peaks consistent with the introduction of an electron deficient centre, and the presence of an additional 3H singlet at δ 3.2—3.4, due to the *S*-methyl group. The ^{1}H n.m.r. spectrum of the *S*-ethylsulphonium salt (12) is very similar to that of the *S*-methylsulphonium salt (7) except for the presence of a 3 H triplet at δ 1.64 and a 2 H quartet at δ 3.78 instead of the 3 H singlet at δ 3.28. The 6α-chloro- and 6α-phthalimido-penicillanate sulphonium salts all had H(5)–H(6) coupling constants of *ca.* 2 Hz, consistent with the presence of a *trans*-substituted β-lactam.[9]

The formation of sulphonium salts from penicillanates (4)—(6) was accompanied by a shift of the β-lactam carbonyl stretching absorption in the i.r. to higher frequencies. For example, the β-lactam carbonyl stretching absorption occurs at 1 785 cm^{-1} for methyl 6α-chloropenicillanate (4), and at 1 810 cm^{-1} for methyl 6α-chloro-1-methylpenicillanate tetrafluoroborate (7), a shift of 25 cm^{-1}.

This shift is not unexpected in view of the known sensitivity of the β-lactam carbonyl stretching frequency to the state of the thiazolidine sulphur; shifts to shorter wavelengths have been recorded on oxidation of penicillanates to sulphoxides and sulphones.[10]

Sulphonium Salt Configuration.—In principle, alkylation of penicillanates on sulphur can lead to either 1α- or 1β-sulphonium salts (13) and (14). In practice, only one sulphonium salt could be detected in the crude product mixtures by ^{1}H n.m.r. for all of the alkylations described above. Therefore, either these alkylations are particularly stereoselective, or subsequent equilibration of the primary products is giving rise to one final isomer.

Asymmetric sulphonium salts are usually configurationally stable at room temperature, and do not lose their asymmetry by simple 'umbrella' inversion.[11] Therefore any room temperature equilibration of isomeric penicillanate sulphonium salts must occur *via* a different mechanism from this. One possible process is equilibration *via* an azetidinium cation (15). However the asymmetry at C(5) would be lost in this process, and although the subsequent ring-closure should be stereoselective at C(5) as well as at the sulphur, it is unlikely that such an equilibration would lead to the exclusive formation of one isomer in all cases.[12] Moreover the sulphonium salts would be expected to be particularly sensitive to moisture if equilibration with an azetidinyl cation (15) was occurring during their preparation, and



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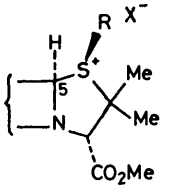

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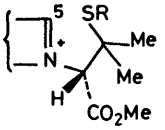

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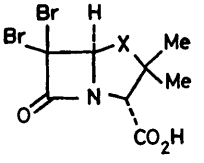
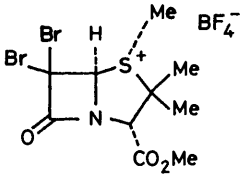


(16) X = –S–

(17) X = 

(18) X = 



(19)

this was not found to be the case, except for sulphonium salts prepared from methyl 6β-phthalimidopenicillanate (3) (see below). Finally when methylation of methyl 6α-phthalimidopenicillanate (5) in [^{2}H$_3$]nitromethane was followed by ^{1}H n.m.r., clean conversion of starting penicillanate into sulphonium salt was observed; no short-lived intermediates were detected. Therefore it is likely that these alkylations are stereoselective, and that the observed formation of one sulphonium salt in each case is not due to subsequent equilibration of the initially formed stereoisomers.

In general oxidation of penicillanates by peracids proceeds stereoselectively to give more of the (1*S*)-sulphoxide by attack of peracid on the β-face of the molecule.[13] However a bulky β-substituent at C(6), which cannot hydrogen-bond to the approaching peracid, reverses this stereoselectivity because of steric hindrance, and the (1*R*)-sulphoxide becomes the major product.[14] In particular, oxidation of 6,6-dibromopenicillanic acid (16) gives a 91 : 9 mixture of (1*R*)- and (1*S*)-sulphoxides (17) and (18).[15] Since alkylation should be subject to similar steric control, methylation of methyl 6,6-dibromopenicillante (6) would be expected to give predominantly the 1α-methylsulphonium salt (19).

This stereoselectivity has been confirmed by an n.O.e.

experiment. Molecular models show that for a 1-methylpenicillanate sulphonium salt, a 1α-methyl group is *ca.* 3.0 Å from H(5), whereas a 1β-methyl group is >3.5 Å from H(5), irrespective of the conformation of the thiazolidine ring. Therefore an enhancement of the ^{1}H n.m.r. signal due to H(5) would be expected on irradiation of the *S*-methyl group for a 1α- but not for a 1β-sulphonium salt. It was found that irradiation of the *S*-methyl group of methyl 6,6-dibromo-1-methylpencillanate tetrafluoroborate (9) gave a 20(±5)% increase in the integration of the signal due to H(5) so confirming that sulphonium salt (9) was the 1α-isomer (19).

Furthermore, comparison of the ^{1}H n.m.r. spectra of sulphonium salts (7)—(12) suggests that they all have the same configuration at sulphur. This is shown in detail in the Table. [In the Table, the assignments to H(5) and H(6) of the sulphonium salts were made on the basis of deuteriation at C(6); see Experimental section for details.] The Table shows that the chemical shifts induced on alkylation of 6α-chloro- and 6α-phthalimidopenicillanates (4) and (5) closely correspond to those induced on alkylation of 6,6-dibromopenicillanate (6). In particular the signals for H-5 are all shifted by 0.6—0.7, and the 2α-methyl group is always deshielded more than the 2β-methyl group. It is difficult to assign configurations to the sulphonium salts solely on the basis of the chemical shifts induced by alkylation, because of the possibility of conformational changes. However the similarity of the chemical shifts induced on formation of the different sulphonium salts does suggest that all the sulphonium salts have the same configuration at sulphur, *i.e.* the *S*-alkyl group has the α-orientation.

^{1}H N.m.r. chemical shifts on *S*-methylation [a]

Starting penicillanate	Sulphonium salt(s)	H(6) [b]			H(5) [b]			H(3) [b]			2α-Me [b]			2β-Me [b]		
		S	S$^+$	Δδ	S	S$^+$	Δδ	S	S$^+$	Δδ	S	S$^+$	Δδ	S	S$^+$	Δδ
(4)	(7), (10)	4.87	5.80	0.93	5.31	5.96	0.65	4.54	5.11	0.57	1.46	1.86	0.40	1.59	1.86	0.27
(4)	(12)	4.87	5.82	0.95	5.31	5.93	0.62	4.54	5.09	0.55	1.46	1.87 1.89	0.41 0.43	1.59	1.89 1.87	0.30 0.28
(5)	(8), (11)	5.30	6.16	0.86	5.53	6.24	0.71	4.60	5.18	0.58	1.46	1.90 1.94	0.44 0.48	1.65	1.94 1.90	0.29 0.25
(6)	(9)				5.80	6.42	0.62	4.59	5.13	0.54	1.45	1.84 1.93	0.39 0.48	1.61	1.93 1.84	0.32 0.23

[a] Chemical shifts (δ) in CD_3NO_2. [b] Assignments for penicillanates made by analogy with the literature (ref. 1, p. 332). H(5) and H(6) assignments for penicillanate sulphonium salts made on the basis of deuteriation at C(6) (see Experimental section for details).

As sulphoxidation of 6α-chloro- and 6α-phthalimidopenicillanates (4) and (5) gives selectively the (1*S*)-sulphoxide,[15,16] it is surprising that alkylation gives exclusively the 1α-alkylsulphonium salt, and so these stereochemical assignments should be regarded as tentative. However for the 6α-phthalimidopenicillanate sulphonium salt (8), irradiation of the *S*-methyl group caused a 20% increase in the integration of H(5) in its ^{1}H n.m.r. spectrum, which is consistent with the *S*-methyl group being in the 1α-orientation.

Reactions of the Sulphonium Salts.—During the characterization of the penicillanate sulphonium salts (7)—(12), attempts were made to record their ^{1}H n.m.r. spectra in [$^2H_6$]dimethyl sulphoxide. However in this solvent the sulphonium salts decompose within seconds to give products that could not be characterized. (^{1}H N.m.r. spectra were eventually obtained in [$^2H_3$]nitromethane.) Similar products were obtained on hydrolysis of the sulphonium salts; for example, addition of one drop of water to a solution of methyl 6α-chloro-1-methylpenicillanate tetrafluoroborate (7) in [$^2H_3$]nitromethane initiated a reaction that could be followed by n.m.r. After 2 h, the spectrum of the sulphonium salt had disappeared, and had been replaced by peaks at δ 1.38 (6 H, s), 2.05 (3 H, s), 3.79 (3 H, s), and 4.55 (1 H, d, *J* 8.5 Hz), together with other peaks integrating for less than one proton. However, attempts to isolate the major component of this mixture by column chromatography were unsuccessful. When the 6α-chlorosulphonium salt (7) was suspended in water, and the mixture stirred vigorously, it took 90 min to dissolve. Extraction of the product into dichloromethane gave a product mixture which had a ^{1}H n.m.r. spectrum similar to that recorded above, but again attempts to characterize the major component of this mixture were unsuccessful.

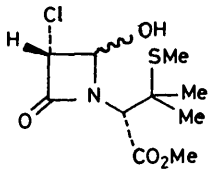
The ^{1}H n.m.r. spectra of these hydrolysis products were not always reproducible, but it appeared that the $CH(CO_2Me)\cdot CMe_2SMe$ unit was present. By analogy with the methanolysis results discussed below, hydroxyazetidinone intermediates (20) are probably involved in these reactions, and decompose *via* β-lactam cleavage. Such hydroxyazetidinones have been postulated as intermediates in the formic acid-catalysed hydrolysis of chloroazetidinones (21), which also gave products that could not be characterized.[17]

Penicillanate rearrangements initiated by electrophilic attack on sulphur, generally continue by sulphur–C(2) cleavage, or by sulphur–C(5) cleavage. Having isolated sulphonium salts (7)—(12), it was of interest to examine their chemistry, to see whether such thiazolidine ring cleavages could be observed.

It was found that treatment of solutions of the penicillanate sulphonium salts (7)—(12) in nitromethane at room temperature, with anhydrous sodium carbonate, gave excellent yields of the corresponding secopenicillanates (22)—(25). Indeed it is unnecessary to isolate the sulphonium salts; addition of anhydrous sodium carbonate to the alkylation product mixtures gives the

secopenicillanates in high yield. However it is not possible to react the starting penicillanate with alkylating agent and sodium carbonate at the same time, because the sodium carbonate destroys the alkylating agent before alkylation is complete.

Structures were assigned to secopenicillanates (22)—(25) on the basis of their spectroscopic data, and, for the dibromo compound (24), by comparison with the literature data.[18] A sample of the *trans*-phthalimidosecopenicillanate (23) was prepared by base-catalysed epimerization of the *cis*-isomer (39) (see below).



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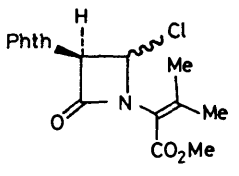

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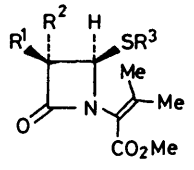
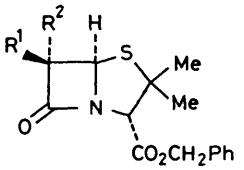
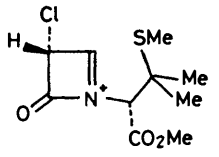




(22) R^1 = H, R^2 = Cl, R^3 = Me
(23) R^1 = H, R^2 = phthalimido, R^3 = Me
(24) R^1 = R^2 = Br, R^3 = Me
(25) R^1 = H, R^2 = Cl, R^3 = Et
(26) R^1 = Ph_3CNH, R^2 = H
(27) R^1 = R^2 = Br



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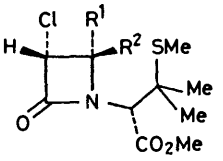
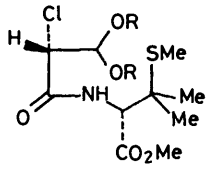
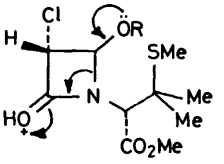


(29) R^1 = OMe, R^2 = H
(30) R^1 = H, R^2 = OMe
(31) R^1 = H, R^2 = OEt



(32) R = Me
(33) R = Et



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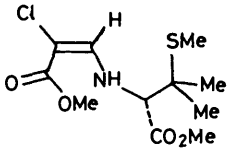

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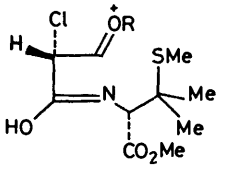

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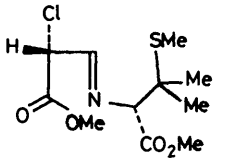

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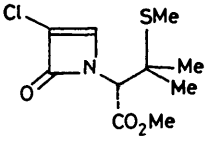


(38)

This procedure for the preparation of secopenicillanates can be compared with that of Clayton.[18,19] In this latter procedure, 6β-triphenylmethylamino- and 6,6-dibromo-penicillanates (26) and (27) are treated with a reactive alkyl halide in the presence of sodium hydride. The mechanism of this reaction has not been clarified. There is no reaction between the alkyl halides and the penicillanates in the absence of base, nor is there any reaction between the base and the penicillanates in the absence of alkyl halide. Activation of H(3) by the carboxylate group is important, and it has been suggested that removal of H(3) initiates a concerted β-elimination–alkylation process, the details of which are obscure. In our secopenicillanate preparation, the free sulphonium salt is formed, and is treated with base in a discrete second step. Preparatively Clayton's procedure has wider application, since our procedure is severely limited by the substituents that can be tolerated at C(6), and by the need for very reactive alkylating agents. Nevertheless, for the preparation of simple secopenicillanates, our procedure is extremely efficient.

Next we considered cleavage of the sulphur–C(5) bond of the penicillanate sulphonium salts. Heterolytic cleavage of this bond would give rise to azetidinyl cations, *e.g.* the 6α-chloropenicillanate tetrafluoroborate (7) should generate azetidinyl cation (28). Such azetidinyl cations are well established intermediates in β-lactam chemistry.[4]

When the 6α-chloropenicillanate tetrafluoroborate (7) was suspended in anhydrous methanol at room temperature, and the mixture stirred vigorously, it took 5 h to dissolve. Brief treatment of the solution so obtained with anhydrous sodium carbonate, gave a mixture of three products that were separated by column chromatography, and identified as the *cis*- and *trans*-methoxyazetidinones (29) and (30), together with the ring-opened dimethoxy acetal (32) (isolated yields 26, 43, and 16%, respectively). Similar behaviour was observed with ethanol. In this case treatment of the 6α-chloropenicillanate tetrafluoroborate (7) with ethanol at 50 °C for 4 h, followed by brief treatment with anhydrous sodium carbonate, gave the *trans*-ethoxyazetidinone (31) (28%), together with the diethoxy acetal (33) (69%).

Structures were assigned to these products on the basis of their spectroscopic data. In particular, the coupling for the β-lactam protons in the *cis*-substituted azetidinone (29) was 4.0 Hz, whereas that for the *trans*-substituted azetidinones (30) and (31) was <1 Hz.[9]

The formation of these solvolysis products is consistent with the participation of azetidinyl cation (28). Methanolysis was faster than ethanolysis, although both reactions were slower than hydrolysis, *i.e.* the rate of solvolysis increases with the polarity of the solvent. The stereoselectivity of methanolysis and ethanolysis is

consistent with azetidinyl cation participation since azetidinyl cation (28) would be expected to capture solvent from both sides of the β-lactam ring with a preference for capture on the opposite side to the chlorine substituent, as was observed.

The acetal products (32) and (33) are formed by further solvolysis of the alkoxyazetidinone products. During formation of the alkoxyazetidinones (29)—(31), one equivalent of acid is released. This acid catalyses β-lactam cleavage of the alkoxyazetidinones, as shown in formula (34), to give oxonium ions (35), which capture solvent to give the acetal products. Acid catalysed cleavage of alkoxyazetidinones has been observed before.[20]

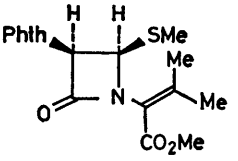
In an attempt to prevent this secondary acid-catalysed β-lactam cleavage, the reaction of 6α-chloropenicillanate tetrafluoroborate (7) with methanol was investigated in the presence of anhydrous sodium carbonate. However under these conditions, a new product was the major product of the reaction, and was identified as the *cis*-acrylate (36), isolated in 50% yield.

Acrylate (36) was identified on the basis of its spectroscopic data. In particular, the ^{1}H n.m.r. spectrum showed a vinylic proton as a doublet at δ 7.5 (*J* 14 Hz), a broad NH peak, and a second doublet at δ 3.87 (*J* 10 Hz). On addition of D_2O, the NH peak disappeared, and the two doublets collapsed to singlets. The *cis*-geometry was assigned to acrylate (36) on the basis of its u.v. spectrum which had a maximum at 275 nm (ε 11 000). The intensity of this band is more consistent with a *cis*-acrylate structure than with a *trans*-acrylate structure.[21]

Several mechanisms can be suggested for the formation of acrylate (36). Perhaps in methanol, under basic conditions, the sulphonium salt (7) undergoes β-lactam cleavage to give imine (37) which isomerizes to acrylate (36). Alternatively, perhaps the azetidinyl cation (28) is still involved, but this, under basic conditions, suffers proton loss to give azetinone (38), or β-lactam cleavage to give imine (37). Methanolysis of azetinone (38) would give the *cis*-acrylate (36) directly, and would explain the selective formation of the *cis*-isomer.

Alkylation of Methyl 6β-Phthalimidopenicillanate.—Methyl 6β-phthalimidopenicillanate (3) was treated with a slight excess of trimethyloxonium tetrafluoroborate in [$^2H_3$]nitromethane, and the reaction followed by ^{1}H n.m.r. After 90 min at 20 °C little starting material remained, and peaks were observed that were consistent with the presence of two penicillanate sulphonium salts. Doublets were observed at δ 5.85 and 6.0 (*J* 2 Hz), and at δ 6.1 and 6.38 (*J* 4.5 Hz), suggesting that one of the sulphonium salts had a *cis*-substituted β-lactam and the other a *trans*-substituted β-lactam. However this reaction mixture was extremely sensitive. Nothing could be induced to crystallize out of solution, and evaporation of the solvent led to the formation of an extremely complicated mixture of products that could not be characterized.

Subsequently it was found that if an excess of anhydrous sodium carbonate was added to the alkylation mixture 2.5 h after the initial addition of trimethyloxonium tetrafluoroborate, and the basic mixture stirred at room temperature, a simpler mixture of products could be obtained that was amenable to column chromatography. Separation of the products in this way, led to the isolation of a mixture of two β-lactam-containing products (ratio 2.5 : 1; 30% combined yield). Recrystallization of this mixture gave a pure sample of the *cis*-phthalimidosecopenicillanate (39) identified by comparison with a

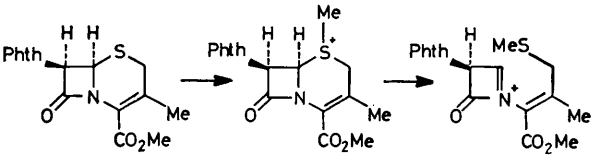


(39)

Phth = phthalimido

sample prepared by an established route.[22] The minor product was not obtained pure, but its ^{1}H n.m.r. spectrum was identical with that of the *trans*-phthalimidosecopenicillanate (23).

It has been reported that alkylation of methyl 7β-phthalimidocephalosporanate (40) by methyl fluoro-

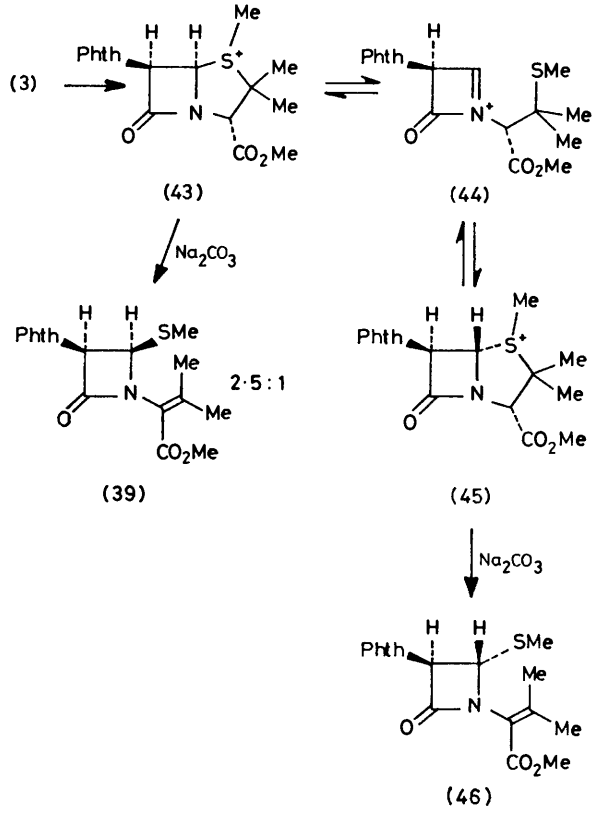


(40) (41)

(42)

sulphonate gives the rearranged sulphonium salt (42).[23] It was suggested that this rearrangement proceeds *via* a ring-opening–ring-closing process involving azetidinyl cation (41). By analogy with this result, it is likely that the minor product of our alkylation–elimination of methyl 6β-phthalimidopenicillanate (3) is the *trans*-phthalimido-secopenicillanate (46), formed as shown in the Scheme. It is suggested that the 6β-phthalimidopencillanate tetrafluoroborate is unstable, and undergoes spontaneous sulphur–C(5) bond cleavage to generate azetidinyl cation (44). In the absence of nucleophiles, this recyclizes to give the C(5) epimeric sulphonium salt (45), which is the *trans*-substituted penicillanate salt observed by ^{1}H n.m.r. Addition of base traps both penicillanate sulphonium salts (43) and (45), to give secopenicillanates (39) and (46). The spontaneous formation of the azetidinyl cation (44) under the alkyl-

ation conditions, is consistent with the increased instability of these sulphonium salts towards isolation since traces of moisture would be expected to initiate immediate decomposition to non-characterizable pro-



SCHEME

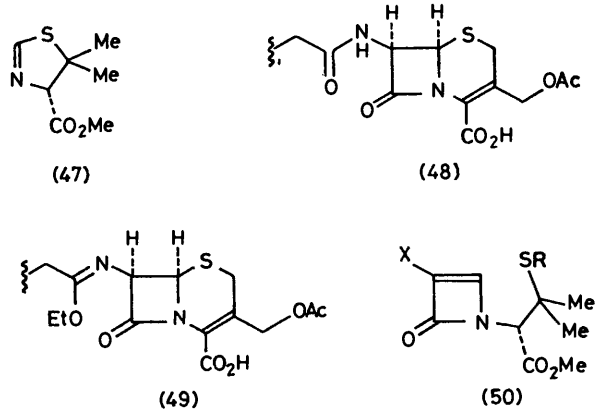
ducts. One attempt was made to slow down the rate of azetidinyl cation formation in this system by using a mixture of dichloromethane and nitromethane as reaction solvent, but it still proved to be impossible to isolate any sulphonium salt.

Attempted Alkylation of Methyl 6β-Phenylacetamidopenicillanate.—Several attempts were made to methylate methyl 6β-phenylacetamidopenicillanate (2) using trimethyloxonium tetrafluoroborate under conditions that had been successful for the alkylation of the simpler penicillanates (4)—(6), but mixtures of products were obtained. Even in the presence of anhydrous sodium carbonate, the starting penicillanate (2) disappeared within 10 min, far faster than would have been expected if the desired alkylation was taking place, and rapid work-up gave mixtures of products that were not reproducible. From one run, the ^1H n.m.r. spectrum suggested that a small amount of thiazoline (47) was present, but attempts to isolate a pure sample were unsuccessful. No peak attributable to S^+Me was present.

It has been reported that treatment of the cephalosporin C derivative (48) with triethyloxonium tetrafluoroborate gives a low yield of imino-ether (49).[24] This was then hydrolysed to 7-aminocephalosporanic acid. However we were unable to isolate any analogous imino-ether, or products derived from its hydrolysis, from the reactions of methyl 6β-phenylacetamido-penicillanate (2) with trimethyloxonium tetrafluoroborate. During a brief investigation into the use of dimethoxycarbenium tetrafluoroborate a small amount of methyl phenylacetate was isolated, and so some side-chain cleavage had occurred in this case.

Conclusions.—6α-Substituted and 6,6-disubstituted penicillanates (4)—(6) have been converted into penicillanate sulphonium salts (7)—(12). However attempts to isolate 6β-substituted penicillanate sulphonium salts were unsuccessful, although methyl 6β-phthalimidopenicillanate tetrafluoroborate (43) was generated in solution, and products derived by its base-induced fragmentation isolated.

Two reasons can be suggested for the relative instability of 6β-substituted penicillanate sulphonium salts. Perhaps steric hindrance between a bulky 6β-substituent and the thiazolidine ring favours azetidinium cation formation, the azetidinium cation then being destroyed by adventitious moisture. The isolation of a small amount of the *trans*-phthalimidosecopenicillanate (46) from alkylation–elimination of methyl 6β-phthalimidopenicillanate (3) is consistent with this explanation. Alternatively, perhaps rapid abstraction of the 6α-proton accompanied by a *trans*-elimination to give an azetinone intermediate (50) is responsible for the instability of 6β-substituted penicillanate sulphonium salts. It is known that abstraction of 6α-protons from 6β-substituted penicillanates is faster than removal of 6β-protons from the isomeric 6α-substituted penicillanates.[25]



Probably both factors are involved. Attempts to isolate the 6β-substituted penicillanate sulphonium salts are probably thwarted by decomposition *via* the azetidinium ion pathway. Attempts to prepare secopenicillanate by treatment of 6β-substituted penicillanate sulphonium salts with base, are probably inefficient because of competing azetinone formation.

The chemistry of penicillanate sulphonium salts (7)—(12) has been briefly explored. Treatment with base gives the corresponding secopenicillanates (22)—(25), and alcoholysis gives alkoxyazetidinones, *e.g.* (29)—(31).

EXPERIMENTAL

M.p.s were recorded on a Kofler hot-stage apparatus. I.r. and u.v. spectra were recorded on a Perkin-Elmer 257 spectrophotometer, and on a Pye–Unicam SP 8000 spectrophotometer, respectively. N.m.r. spectra were measured on Perkin-Elmer R12B and Brucker HFX 90 spectrometers. Mass spectra were determined on an A.E.I. MS 30 mass spectrometer. A Perkin-Elmer 141 polarimeter was used for optical activity measurements.

Silica gel pre-coated plates (Merck GF_{254}) were used for analytical t.l.c. Short-column chromatography was used for preparative purposes using Hopkin and Williams silica gel for t.l.c. (20—50 mesh; MFC without binder).

All solvents were dried and distilled before use. In particular, nitromethane and dichloromethane were distilled from phosphorus pentaoxide.

Methyl 6,6-*Dibromopenicillanate* (6).—A solution of dinitrogen tetraoxide (9.0 g) in dichloromethane (50 ml) was added to a solution of methyl (6*R*)-6-phenylacetamidopenicillanate (2) (12 g) and anhydrous sodium acetate (8.5 g) in dichloromethane (50 ml) at 0 °C, and the mixture stirred for 60 min before being poured into aqueous sodium hydrogencarbonate (9 g in 150 ml). The organic phase was separated, and the aqueous phase extracted with dichloromethane (2 × 75 ml). The combined organic phases were washed with water, dried ($MgSO_4$), and a small sample concentrated to give methyl (6R)-6-(*N*-nitrosophenylacetamido)penicillanate as an oil, $\nu_{max.}$ ($CHCl_3$) 3 030, 1 790, 1 745, and 1 530 cm^{-1}, δ($CDCl_3$) 1.41 and 1.69 (each 3 H, s, CH_3), 3.69 (3 H, s, OCH_3), 4.41 (2 H, s, CH_2Ph), 4.52 (1 H, s, H-3), 5.31 and 5.55 (each 1 H, d, *J* 4 Hz, H-5 and -6), and 7.2 (5 H, s, C_6H_5).

Anhydrous pyridine (4 ml) was added to the rest of the *N*-nitrosoamide solution, and the mixture heated under reflux for 3 h.[26] The reaction mixture was then washed with water, 5% aqueous sodium hydrogencarbonate, and water again, dried ($MgSO_4$), and concentrated to give *methyl* 6-*diazopenicillanate* (8.8 g) as an oil, still contaminated with a little pyridine, $\nu_{max.}$ (CCl_4) 2 085, 1 755, 1 270, 1 240, and 1 210 cm^{-1}, δ($CDCl_3$) 1.40 and 1.60 (each 3 H, s, CH_3), 3.69 (3 H, s, OCH_3), 4.32 (1 H, s, H-3), and 6.10 (1 H, s, H-5), together with peaks attributable to pyridine.

The impure methyl 6-diazopenicillanate was dissolved in carbon tetrachloride (200 ml), and bromine (8 g) in carbon tetrachloride (50 ml) added at 0 °C.[27] After being stirred for 30 min, the mixture was filtered and concentrated *in vacuo* to give a brownish red residue (5 g) that was chromatographed on silica and recrystallized to give methyl 6,6-dibromopenicillanate (6) (930 mg), m.p. 99—100 °C (lit.,[8] 100—101 °C).

Methyl (6S)-6-*Phthalimidopenicillanate* (5).—Methyl (6*R*)-6-phthalimidopenicillanate (3) (7 g) and diazabicyclononene (0.4 g) were dissolved in anhydrous dichloromethane (100 ml), and the mixture stirred for 1 h at 20 °C. The mixture was then diluted with dichloromethane, washed with dilute aqueous acetic acid and water, dried ($MgSO_4$), and concentrated *in vacuo*. Recrystallization (acetone–light petroleum) gave methyl (6*S*)-6-phthalimidopenicillanate (5) (5.0 g), m.p. 182—183 °C (lit.,[7,28] 183 °C).

Methyl (6S)-6-*Chloro*-1-*methylpenicillanate Tetrafluoroborate* (7).—A solution of methyl (6*S*)-6-chloropenicillanate (4) (1.07 g) [6] in anhydrous nitromethane (5 ml) was added to trimethyloxonium tetrafluoroborate (0.77 g) under nitrogen. The mixture was stirred at 20 °C for 16 h during which time the sulphonium salt (0.99 g) crystallized out of solution. Recrystallization from anhydrous nitromethane gave *methyl* (6S)-6-*chloro*-1-*methylpenicillanate tetrafluoroborate* (7), m.p. 152—152.5 °C, $[\alpha]_D$ +105° (0.027M in CH_3NO_2), $\nu_{max.}$ (Nujol) 1 810, 1 750, and 1 050 cm^{-1}, δ(CD_3NO_2) 1.86 (6 H, s, 2 × CH_3), 3.28 (3 H, s, SCH_3), 3.94 (3 H, s, OCH_3), 5.11 (1 H, s, H-3), 5.80 (1 H, d, *J* 1.5 Hz, H-6), and 5.96 (1 H, d, *J* 1.5 Hz, H-5) (Found: C, 34.25; H, 4.3; N, 4.1; Cl, 9.85; S, 9.35. $C_{10}H_{15}BClF_4NO_3S$ requires C, 34.15; H, 4 3; N, 4.0; Cl, 10.1; S, 9.1%).

In a separate reaction methyl (6*S*)-6-chloropenicillanate (4) (1.03 g) was treated with trimethyloxonium tetrafluoroborate (0.74 g) in nitromethane (10 ml) as described above, but after 16 h at 20 °C the reaction mixture was simply concentrated *in vacuo* to leave the sulphonium salt (7) as a pale yellow solid (1.57 g), better than 95% pure as judged by ^1H n.m.r.

Methyl (6S)-1-*Methyl*-6-*phthalimidopenicillanate Tetrafluoroborate* (8).—A solution of methyl (6*S*)-6-phthalimidopenicillanate (5) (0.36 g) in anhydrous nitromethane (2 ml) was added to trimethyloxonium tetrafluoroborate (0.165 g) under nitrogen. After being stirred for 6 h at 20 °C, the mixture was concentrated *in vacuo* to leave a brown foam which was triturated with dichloromethane to give the crude sulphonium salt (8) (0.413 g). This was recrystallized from anhydrous nitromethane to give methyl (6*S*)-1-methyl-6-phthalimidopenicillanate tetrafluoroborate (8), m.p. 157—158 °C, $[\alpha]_D$ +100° (0.012M in CH_3NO_2), $\nu_{max.}$ (Nujol) 1 805, 1 725, 1 065, and 720 cm^{-1}, δ(CD_3NO_2) 1.90 and 1.94 (each 3 H, s, 2 × CH_3), 3.23 (3 H, s, SCH_3), 3.97 (3 H, s, OCH_3), 5.18 (1 H, s, H-3), 6.16 (1 H, d, *J* 2 Hz, H-6), 6.24 (1 H, d, *J* 2 Hz, H-5), and 7.96 (4 H, s, aromatic H).

Methyl 6,6-*Dibromo*-1-*methylpenicillanate Tetrafluoroborate* (9).—A solution of methyl 6,6-dibromopenicillanate (6) (0.7 g) in anhydrous nitromethane (3 ml) was added to trimethyloxonium tetrafluoroborate (0.44 g) under nitrogen. After being stirred for 16 h at 20 °C, the mixture was concentrated *in vacuo*, and the residue triturated with dichloromethane to give the crystalline sulphonium salt (9) (0.63 g). Recrystallization from nitromethane gave *methyl* 6,6-*dibromo*-1-*methylpenicillanate tetrafluoroborate* (9), m.p. 130—131 °C, $[\alpha]_D$ +62° (0.013M in CH_3NO_2), $\nu_{max.}$ 1 810, 1 740, and 1 070 cm^{-1}, δ(CD_3NO_2) 1.84 and 1.93 (each 3 H, s, 2 × CH_3), 3.30 (3 H, s, SCH_3), 3.89 (3 H, s, OCH_3), 5.13 (1 H, s, H-3), and 6.42 (1 H, s, H-5) (Found: C, 25.3; H, 3.0; N, 3.1. $C_{10}H_{14}Br_2BF_4NO_3S$ requires C, 25.3; H, 2.95; N, 2.95%).

Methyl (6S)-6-*Chloro*-1-*methylpenicillanate Fluorosulphonate* (10).—A solution of methyl (6*S*)-6-chloropenicillanate (4) (1.0 g) and methyl fluorosulphonate (0.35 ml) in dichloromethane (5 ml) was heated under reflux under dry nitrogen for three days. During this time a brown, crystalline solid (1.15 g) separated out of solution. This was filtered off, washed with anhydrous dichloromethane, and recrystallized (nitromethane) to give methyl (6*S*)-6-chloro-1-methylpenicillanate fluorosulphonate (10), m.p. 95—96 °C $[\alpha]_D$ +88° (0.037M in CH_3NO_2), $\nu_{max.}$ (Nujol) 1 808, 1 745, 1 280, 1 076, and 724 cm^{-1}, δ(CD_3NO_2) 1.86 (6 H, s, 2 × CH_3), 3.29 (3 H, s, SCH_3), 3.94 (3 H, s, OCH_3), 5.11 (1 H, s, H-3), 5.81 (1 H, d, *J* 1.5 Hz, H-6), and 5.95 (1 H, d, *J* 1.5 Hz, H-5). A satisfactory analysis could not be obtained for this compound since on standing at room temperature, even *in vacuo* (0.01 mmHg), it decomposed to give a glassy solid.

Methyl (6S)-1-*Methyl*-6-*phthalimidopenicillanate Fluorosulphonate* (11).—A solution of methyl (6*S*)-6-phthalimido-

penicillanate (1.0 g) and methyl fluorosulphonate (0.25 ml) in dichloromethane (5 ml) was heated under reflux under nitrogen for 3 days. During this time a brown solid (0.81 g) separated out of solution. This was filtered off, washed with anhydrous dichloromethane, and recrystallized (nitromethane–dichloromethane, 2 : 5), to give methyl (6*S*)-1-methyl-6-phthalimidopenicillanate fluorosulphonate (11), m.p. 156 °C, $[\alpha]_D$ +63° (0.127M in CH_3NO_2), $\nu_{max.}$ (Nujol) 1 805, 1 728, 1 270, 1 072, and 722 cm^{-1}, $\delta(CD_3NO_2)$ 1.90 and 1.94 (each 3 H, s, 2 × CH_3), 3.24 (3 H, s, SCH_3), 3.98 (3 H, s, OCH_3), 5.18 (1 H, s, H-3), 6.16 (1 H, d, *J* 2 Hz, H-6), 6.25 (1 H, d, *J* 2 Hz, H-5), and 7.97 (4 H, s, aromatic H).

Methyl (6S)-6-*Chloro*-1-*ethylpenicillanate Tetrafluoroborate* (12).—A solution of methyl (6*S*)-6-chloropenicillanate (1.09 g) and triethyloxonium tetrafluoroborate (3.32 g) in anhydrous dichloromethane (10 ml) was stirred at 20 °C for 40 h under dry nitrogen. During this time crystals (0.62 g) separated out. These were filtered off, washed with dichloromethane, and recrystallized from nitromethane–dichloromethane (1 : 5) to give *methyl* (6S)-6-*chloro*-1-*ethylpenicillanate tetrafluoroborate* (12), m.p. 139—140 °C, $[\alpha]_D$ +191° (0.006 8M in CH_3NO_2), $\nu_{max.}$ (Nujol) 1 810, 1 746, and 1 040 cm^{-1}, $\delta(CD_3NO_2)$ 1.64 (3 H, t, *J* 8 Hz, CH_2CH_3), 1.86 and 1.89 (each 3 H, s, 2 × CH_3), 3.78 (2 H, q, *J* 8 Hz, CH_2CH_3), 3.93 (3 H, s, OCH_3), 5.09 (1 H, s, H-3), 5.82 (1 H, d, *J* 1.5 Hz, H-6), and 5.93 (1 H, d, *J* 1.5 Hz, H-5) (Found: C, 36.0; H, 4.75; Cl, 9.45; N, 3.85; S, 8.6. $C_{11}H_{17}BClF_4NO_3S$ requires C, 36.15; H, 4.7; Cl, 9.7; N, 3.85; S, 8.75%).

Methyl 2-[(2R,3S)-3-*Chloro*-2-*methylthio*-4-*oxoazetidin*-1-*yl*]-3-*methylbut*-2-*enoate* (22).—(a) Crude methyl (6*S*)-6-chloro-1-methylpencillanate tetrafluoroborate (7) (1.57 g) was prepared as described above, and dissolved in anhydrous nitromethane (25 ml). Anhydrous sodium carbonate (3 g) was added, and the mixture was stirred at 20 °C under nitrogen for 3 h before being filtered, and concentrated *in vacuo* to give secopenicillanate (22) (1.14 g). The crude product, which was greater than 95% pure by ^1H n.m.r., was distilled to give *methyl* 2-[(2R,3S)-3-*chloro*-2-*methylthio*-4-*oxoazetidin*-1-*yl*]-3-*methylbut*-2-*enoate* (22), as an oil, b.p. 160 °C at 0.05 mmHg, $[\alpha]_D$ +23° (0.004 6M in $CHCl_3$), $\nu_{max.}$ 1 770, 1 725, 1 630, 1 230, 1 090, and 830 cm^{-1}, $\delta(CDCl_3)$ 2.0 (3 H, s, SCH_3), 2.17 and 2.27 [each 3 H, s, $=C(CH_3)_2$], 3.80 (3 H, s, OCH_3), 4.68 (1 H, d, *J* 2 Hz, H-3′), and 5.02 (1 H, d, *J* 2 Hz, H-2′); *m/e* 263, 265 (M^+), 249, 251 ($M^+ - CH_2$), 232, 234 ($M^+ - OCH_3$), and 228 ($M^+ - Cl$) (Found: C, 45.55; H, 5.55; Cl, 13.5; N, 5.4; S, 12.0. $C_{10}H_{14}ClNO_3S$ requires C, 45.55; H, 5.35; Cl, 13.45; N, 5.3; S, 12.15%).

(b) Crude methyl (6*S*)-6-chloro-1-methylpenicillanate fluorosulphonate (10) (0.7 g) was dissolved in anhydrous nitromethane (15 ml) and anhydrous sodium carbonate (2.1 g) added. The mixture was stirred under dry nitrogen for 1 h, and concentrated to give the secopenicillanate (22) (0.48 g) identical (^1H n.m.r., i.r., m.s., t.l.c.) with the sample prepared above.

Methyl 3-*Methyl*-2-[(2R,3S)-2-*methylthio*-4-*oxo*-3-*phthalimidoazetidin*-1-*yl*]*but*-2-*enoate* (23).—(a) A solution of methyl (6*S*)-6-phthalimidopenicillanate (0.5 g) and trimethyloxonium tetrafluoroborate (0.21 g) in anhydrous nitromethane (5 ml) was stirred under nitrogen at 20 °C for 6 h. Anhydrous sodium carbonate (0.52 g) was added to the orange-red solution, and the mixture stirred for a further 16 h. Concentration *in vacuo* gave a pale brown foam (0.4 g) which was recrystallized (acetone–hexane) to give *methyl* 3-*methyl*-2-[(2R,3S)-2-*methylthio*-4-*oxo*-3-*phthalimidoazetidin*-1-*yl*]*but*-2-*enoate* (23), m.p. 175—177 °C, $[\alpha]_D$ +147° (0.003 1M in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 1 765, 1 720, 1 630, 1 103, and 1 090 cm^{-1}, $\delta(CDCl_3)$ 2.11 (3 H, s, SCH_3), 2.18 and 2.29 [each 3 H, s, $=C(CH_3)_2$], 3.84 (3 H, s, OCH_3), 5.36 (1 H, d, *J* 2.5 Hz, H-3′), 5.47 (1 H, d, *J* 2.5 Hz, H-2′), and 7.8 (4 H, m, aromatic H); *m/e* 374 (M^+) and 219 [base peak, $M^+ - Me_2C{=}C(CO_2Me)NCO$] (Found: C, 57.6; H, 4.95; N, 7.5; S, 8.7. $C_{18}H_{18}NO_5S$ requires C, 57.75; H, 4.85; N, 7.5; S, 8.55%). This material was identical (^1H n.m.r., i.r., m.p.) with a sample prepared by epimerization of the *cis*-phthalimidosecopenicillanate (39).[22]

(b) A crude sample of methyl (6*S*)-1-methyl-6-phthalimidopenicillanate fluorosulphonate (11) (86 mg) was dissolved in anhydrous nitromethane, anhydrous sodium carbonate (120 mg) was added, and the mixture was stirred under nitrogen for 2 h at 20 °C. The mixture was filtered, and concentrated *in vacuo* to give the *trans*-phthalimidosecopenicillanate (23) (65 mg), identical with the sample prepared above.

Methyl 2-[(2R)-3,3-*Dibromo*-2-*methylthio*-4-*oxoazetidin*-1-*yl*]-3-*methylbut*-2-*enoate* (24).—Methyl 6,6-dibromo-1-methylpenicillanate tetrafluoroborate (9) (0.58 g) was dissolved in nitromethane (3 ml), anhydrous sodium carbonate (1 g) added, and the mixture stirred at 20 °C for 16 h. Filtration and concentration of the filtrate *in vacuo* gave methyl 2-[(2*R*)-3,3-dibromo-2-methylthio-4-oxoazetidin-1-yl]-3-methylbut-2-enoate (24) (0.4 g), identified by comparison of its ^1H n.m.r. and its i.r. spectra with those reported in the literature.[18]

Methyl 2-[(2R,3S)-3-*Chloro*-2-*ethylthio*-4-*oxoazetidin*-1-*yl*]-3-*methylbut*-2-*enoate* (25).—Anhydrous sodium carbonate (330 mg) was added to a solution of methyl (6*S*)-6-chloro-1-ethylpenicillanate tetrafluoroborate (12) (340 mg) in nitromethane (3 ml), and the mixture stirred under nitrogen for 16 h at 20 °C. Filtration and concentration of the filtrate *in vacuo* gave an oil which was purified by column chromatography on silica (20 g) (eluted with ethyl acetate–hexane, 1 : 4) to give *methyl* 2-[(2R,3S)-3-*chloro*-2-*ethylthio*-4-*oxoazetidin*-1-*yl*]-3-*methylbut*-2-*enoate* (25) (213 mg), as an oil homogeneous by t.l.c., $\nu_{max.}$ ($CHCl_3$) 1 780, 1 720, and 1 630 cm^{-1}, $\delta(CDCl_3)$ 1.28 (3 H, t, *J* 7.3 Hz, CH_2CH_3), 1.99 and 2.29 (each 3 H, s, 2 × CH_3), 2.64 (2 H, q, *J* 7.3 Hz, CH_2CH_3), 3.79 (3 H, s, OCH_3), 4.66 (1 H, d, *J* 1.8 Hz, H-3′), and 5.03 (1 H, d, *J* 1.8 Hz, H-2′); *m/e* 277, 279 (M^+) and 122, 124 [base peak, $M^+ - Me_2C{=}C(CO_2Me)NCO$] (Found: C, 47.3; H, 5.95; Cl, 12.95; N, 4.9; S, 11.75. $C_{11}H_{16}ClNO_3S$ requires C, 47.6; H, 5.8; Cl, 12.75; N, 5.05; S, 11.55%).

Hydrolysis of Methyl (6S)-6-*Chloro*-1-*methylpenicillanate Tetrafluoroborate* (7).—Sulphonium salt (7) (0.8 g) was suspended in water (25 ml), and the mixture stirred vigorously for 90 min. The solution obtained was extracted into dichloromethane (4 × 25 ml), and the dichloromethane extracts dried ($MgSO_4$), and concentrated to give an oil (0.41 g), mainly one product by t.l.c., $\nu_{max.}$ 3 320, 1 740, 1 670, and 1 210 cm^{-1}, $\delta(CDCl_3)$ 1.35 (6 H, s, 2 × CH_3), 2.02 (3 H, s, SCH_3), and 3.75 (3 H, s, OCH_3) together with minor peaks at 4.46, 4.60, 5.0, and 7.0—8.0. Chromatography on silica (40 g; eluted with ethyl acetate–hexane, 2 : 3) gave an oil (0.25 g) whose ^1H n.m.r. and i.r. spectra closely resembled those of the crude product. Attempts to induce crystallization were unsuccessful.

Methanolysis of Methyl (6S)-6-*Chloro*-1-*methylpenicillanate Tetrafluoroborate*.—(a) Sulphonium salt (7) (405 mg) was

suspended in anhydrous methanol (4 ml), and the mixture stirred vigorously for 5 h during which time the sulphonium salt dissolved. Anhydrous sodium carbonate (250 mg) was added, and the mixture was stirred for a further 15 min. Filtration and concentration *in vacuo* gave an oil (320 mg) which was shown to consist of three major components by t.l.c. (ethyl acetate–hexane, 1 : 2). These three components were separated by column chromatography on silica gel (40 g). The first product off the column was identified as *methyl* (2S)-2-[(2R,3R)-3-*chloro*-2-*methoxy*-4-*oxoazetidin*-1-*yl*]-3-*methyl*-3-*methylthiobutanoate* (30) (144 mg), an oil, homogeneous by t.l.c., $\nu_{max.}$ 1 787, 1 740, 1 220, 1 103, 995, 915, and 760 cm^{-1}, $\delta(C_6D_6)$ 1.38 and 1.41 (each 3 H, s, 2 × CH_3), 1.80 (3 H, s, SCH_3), 2.99 and 3.21 (each 3 H, s, OCH_3), 4.16 (1 H, d, *J* 0.8 Hz, H-3′), 4.62 (1 H s, $CHCO_2CH_3$), and 5.05 (1 H d, *J* 0.8 Hz, H-2′); *m/e* 295, 297 (M^+), 264, 266 ($M^+ - OCH_3$), 248, 250 ($M^+ - SCH_3$), 236, 238 ($M^+ - CO_2CH_3$), 144 [M^+ – CO·CHCl·CH(OCH$_3$)N], and 89 (base peak) (Found: M^+, 295.064 9. $C_{11}H_{18}ClNO_4S$ requires *M*, 295.064 6).

The second product off the column was identified as *methyl* (2S)-2-[(2S,3R)-3-*chloro*-2-*methoxy*-4-*oxoazetidin*-1-*yl*]-3-*methyl*-3-*methylthiobutanoate* (29) (87 mg), a solid recrystallized from ether–hexane, m.p. 107 °C, $\nu_{max.}$ (Nujol) 1 760, 1 740, 1 274, 1 180, and 1 115 cm^{-1}, $\delta(CDCl_3)$ 1.43 (6 H, s, 2 × CH_3), 2.07 (3 H, s, SCH_3), 3.47 and 3.73 (each 3 H, s, OCH_3), 4.38 (1 H, s, $CHCO_2CH_3$), 4.99 (1 H, d, *J* 4 Hz, H-3′), and 5.3 (1 H, d, *J* 4 Hz, H-2′); *m/e* 295, 297 (M^+), 264, 266 ($M^+ - OCH_3$), 248, 250 ($M^+ - SCH_3$), 236, 238 ($M^+ - CO_2CH_3$), 144 [M^+ – CO·CHCl·CH(OCH$_3$)N], and 89 (base peak) (Found: C, 44.65; H, 6.15; Cl, 11.95; N, 4.75; S, 10.65. $C_{11}H_{18}ClNO_4S$ requires C, 44.65; H, 6.15; Cl, 12.0; N, 4.75; S, 10.85%).

The third product off the column was identified as *methyl* (2S)-2-[(2R)-2-*chloro*-3,3-*dimethoxypropionamido*]-3-*methyl*-3-*methylthiobutanoate* (32) (60 mg), a solid recrystallized from ether–hexane, m.p. 72—73 °C, $\nu_{max.}$ (Nujol) 3 280, 1 735, 1 650, 1 540, 1 205, 1 112, and 1 067 cm^{-1}, $\delta(CDCl_3)$ 1.35 (6 H, s, 2 × CH_3), 2.03 (3 H, s, SCH_3), 3.45 and 3.48 (each 3 H, s, OCH_3), 3.72 (3 H, s, CO_2CH_3), 4.38 (1 H, d, *J* 4.5 Hz, H-2′), 4.53 (1 H, d, *J* 8 Hz, H-2), 4.70 (1 H, d, *J* 4.5 Hz, H-3′), and 7.4br (1 H, s, NH); *m/e* 327, 329 (M^+), 296, 298 ($M^+ - OCH_3$), 268, 270 ($M^+ - CO_2CH_3$), 239, 241 [$M^+ - CH_2C(SCH_3)CH_3$], 204 [M^+ – CHCl·CH(OCH$_3$)$_2$], and 89 (base peak) (Found: M^+, 327.090 7. $C_{12}H_{22}ClNO_5S$ requires *M*, 327.090 8).

(b) Sulphonium salt (7) (100 mg) and anhydrous sodium carbonate (50 mg) were suspended in anhydrous methanol (1 ml), and the mixture stirred under nitrogen for 5 h. Filtration and concentration *in vacuo* gave an oil (82 mg) which was chromatographed on silica gel (6 g) (ethyl acetate–light petroleum 1 : 4) to give *methyl* (2S)-2-(trans-2-*chloro*-cis-2-*methoxycarbonylvinylamino*)-3-*methyl*-3-*methylthiobutanoate* (36) (40 mg), as an oil, homogeneous by t.l.c., $\nu_{max.}$ 3 390, 3 050, 1 740, 1 700, 1 630, 1 254, 1 170, 1 137, 1 062, 920, and 755 cm^{-1}, $\delta(CDCl_3)$ 1.33 (6 H, s, 2 × CH_3), 2.04 (3 H, s, SCH_3), 3.73 and 3.76 (each 3 H, s, OCH_3), 3.87 (1 H, d, *J* 10 Hz, $CHCO_2CH_3$), 5.5br (1 H, s, exchanges with D_2O, NH), and 7.5 (1 H, d, *J* 14 Hz, =CHN); *m/e* 295, 297 (M^+), 264, 266 ($M^+ - OCH_3$), 260 (M^+ – Cl), 248, 250 ($M^+ - SCH_3$), 236, 238 ($M^+ - CO_2CH_3$), 207, 209 [$M^+ - CH_2C(SCH_3)CH_3$], and 89 (base peak) (Found: M^+, 295.064 6. $C_{11}H_{18}ClNO_4S$ requires *M*, 295.064 5).

Ethanolysis of Methyl (6S)-6-*Chloro*-1-*methylpenicillanate Tetrafluoroborate* (7).—Sulphonium salt (7) (0.99 g) was suspended in anhydrous ethanol (4 ml) and the mixture stirred under nitrogen for 4 h at 45—50 °C. Anhydrous sodium carbonate (0.5 g) was added, and the mixture stirred for 15 min, before being filtered and concentrated *in vacuo* to leave a semi-solid residue. T.l.c. showed that this residue was a mixture of two components. These were separated by column chromatography on silica gel (70 g), eluted with ethyl acetate–hexane, 1 : 3. The first product off the column was identified as *methyl* (2S)-2-[(2R,3R)-3-*chloro*-2-*ethoxy*-4-*oxoazetidin*-1-*yl*]-3-*methyl*-3-*methylthiobutanoate* (31) (240 mg), an oil, homogeneous by t.l.c., $\nu_{max.}$ 1 775, 1 735, 1 175, 1 100, 1 018, and 910 cm^{-1}, $\delta(C_6D_6)$ 0.90 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.41 and 1.43 (each 3 H, s, 2 × CH_3), 1.81 (3 H, s, SCH_3), 3.22 (3 H, s, OCH_3), 3.2—3.7 (2 H, m, CH_2CH_3), 4.18 (1 H, d, *J* 0.9 Hz, H-3′), 4.65 (1 H, s, $CHCO_2CH_3$), and 5.11 (1 H, d, *J* 0.9 Hz, H-2′); *m/e* 309, 311 (M^+) and 89 (base peak) (Found: C, 46.6; H, 6.65; N, 4.65; Cl, 11.4; S, 10.2. $C_{12}H_{20}ClNO_4S$ requires C, 46.55; H, 6.45; N, 4.5; Cl, 11.45; S, 10.35%).

The second product off the column was identified as *methyl* (2S)-2-[(2R)-2-*chloro*-3,3-*diethoxypropionamido*]-3-*methyl*-3-*methylthiobutanoate* (33) (690 mg), recrystallized from ether–hexane, m.p. 73 °C, $\nu_{max.}$ (Nujol) 3 300, 1 740, 1 650, 1 545, 1 210, and 1 060 cm^{-1}, $\delta(CDCl_3)$ 1.22 and 1.27 (each 3 H, t, *J* 7 Hz, 2 × CH_2CH_3), 1.36 and 1.39 (each 3 H, s, CH_3), 2.07 (3 H, s, SCH_3), 3.5—4.2 (4 H, m, 2 × CH_2), 3.76 (3 H, s, OCH_3), 4.38 (1 H, d, *J* 3.5 Hz, H-2′), 4.58 (1 H, d, *J* 8.5 Hz, $CHCO_2CH_3$), 4.86 (1 H, d, *J* 3.5 Hz, H-3′), and 7.3br (1 H, d, *J* 8.5 Hz, NH); *m/e* 355, 357 (M^+) and 89 (base peak) (Found: C, 47.35; H, 7.45; Cl, 10.0; N, 3.8; S, 9.15. $C_{14}H_{26}ClNO_5S$ requires C, 47.25; H, 7.3; Cl, 10.0; N, 3.95; S, 9.0%).

Methyl (6S)-6-*Chloro*-6-*deuterio*-1-*methylpenicillanate Tetrafluoroborate*.—Lithium isopropylcyclohexylamide (prepared from 1.75 ml of 2.4N-n-butyl-lithium) in tetrahydrofuran (2.75 ml) was added to a solution of methyl (6*S*)-6-chloropenicillanate (4) (0.8 g) in tetrahydrofuran (4 ml) containing deuterium oxide (1 ml), at 0 °C under nitrogen. The mixture was stirred for 1 h, and allowed to warm to room temperature. The solution was then added to dichloromethane, and the dichloromethane extract washed with dilute aqueous acetic acid and water, and dried ($MgSO_4$). Concentration *in vacuo*, and recrystallization from methanol–water, gave a sample of methyl (6*S*)-6-chloropenicillanate (4) whose n.m.r. spectrum indicated 34% deuteriation at C(6). A sample of this partially deuteriated methyl (6*S*)-6-chloropenicillanate (4) (125 mg) was alkylated using trimethyloxonium tetrafluoroborate (89 mg) in nitromethane (1.5 ml) to give a sample of the partially deuteriated sulphonium salt (7), $\delta(CD_3NO_2)$ 1.86 (6 H, s, 2 × CH_3), 3.28 (3 H, s, SCH_3), 3.94 (3 H, s, OCH_3), 5.11 (1 H, s, H-3), 5.80 (0.6 H, d, H-6), and 5.96 (1 H, m, H-5).

Methyl (6S)-6-*Deuterio*-1-*methyl*-6-*phthalimidopenicillanate Tetrafluoroborate*.—Lithium isopropylcyclohexylamide (prepared from 1.75 ml of 2.4N-n-butyl-lithium) in tetrahydrofuran (2.76 ml) was added to a solution of methyl (6*R*)-6-phthalimidopenicillanate (1.0 g) in tetrahydrofuran (15 ml) containing deuterium oxide (1.2 ml) at 0 °C under nitrogen. The mixture was allowed to warm to 20 °C, and stirred for 2 h before being quenched with dilute aqueous acetic acid and extracted into dichloromethane. The dichloromethane extract was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give a mixture (510 mg) of deuteriated (6*S*)- and undeuteriated (6*R*)-6-phthalimidopenicillanates (5) and (3) [ratio 1 : 1 (^1H n.m.r.)]

This mixture was dissolved in chloroform (100 ml), diazabicyclononene (50 mg) added, and the mixture stirred for 16 h at 20 °C. Work-up as usual gave methyl (6*S*)-6-phthalimidopenicillanate (5) (500 mg), 50% deuteriated at C(6) (^{1}H n.m.r.). A pure sample was obtained by recrystallization from acetone–hexane. A sample of methyl (6*S*)-6-phthalimidopenicillanate (5) (50 mg), 50% deuteriated at C(6), was methylated using trimethyloxonium tetrafluoroborate (28 mg) in nitromethane (0.5 ml), to give a sample of partially deuteriated sulphonium salt (8), δ(CD_3NO_2) 1.90 and 1.94 (each 3 H, s, 2 × CH_3), 3.23 (3 H, s, SCH_3), 3.97 (3 H, s, OCH_3), 5.18 (1 H, s, H-3), 6.16 (0.5 H, d, *J* 2 Hz, H-6), 6.24 (1 H, m, H-5), and 7.96 (4 H, s, aromatic H).

Attempted Methylation of Methyl (6R)-6-*Phenylacetamidopenicillanate* (2).—Trimethyloxonium tetrafluoroborate (0.77 g) in anhydrous nitromethane (15 ml) was added to a mixture of methyl (6*R*)-6-phenylacetamidopenicillanate (2) (1.57 g) and anhydrous sodium carbonate (0.78 g) under nitrogen, and the mixture stirred at 20 °C for 10 min. The mixture was then quenched by the addition of ice–water (50 g), stirred for 15 min, and extracted into dichloromethane (2 × 50 ml). The dichloromethane extracts were washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give a pale brown oil (1.01 g). This oil was shown to contain several products by t.l.c. Repeated attempts to isolate a pure product by column chromatography were unsuccessful.

Methylation of Methyl (6R)-6-*Phthalimidopenicillanate* (3). *Isolation of Methyl* 3-*Methyl*-2-[(2R,3R)- and 3-*Methyl*-2-[(2S,3R)-2-*methylthio*-4-*oxo*-3-*phthalimidoazetidin*-1-*yl*]-*but*-2-*enoates* (39) *and* (46).—Methyl (6*R*)-6-phthalimidopenicillanate (3) (1.19 g) and trimethyloxonium tetrafluoroborate (0.6 g) were dissolved in nitromethane, and the mixture stirred at 20 °C for 2.5 h under nitrogen. Anhydrous sodium carbonate was then added, and the mixture stirred for a further 16 h at 20 °C before being filtered, and concentrated *in vacuo* to give a pale brown oil (0.85 g). This oil was chromatographed on silica gel (60 g) (elution with ethyl acetate–hexane, 3 : 7) to give a mixture (260 mg) of secopenicillanates (39) and (46) (ratio 2.5 : 1). Crystallization of this mixture gave a sample of the pure *cis*-phthalimidosecopenicillanate (39) (100 mg), identical with an authentic sample [22] by ^{1}H n.m.r., i.r., t.l.c., optical activity, and m.s. The minor component of the mixture was not obtained pure, but was identified by comparison of the ^{1}H n.m.r. spectrum of the mixture with that of the *trans*-phthalimidosecopenicillanate (23) prepared earlier.

In a separate experiment, an attempt was made to observe methyl (6*R*)-1-methyl-6-phthalimidopenicillanate tetrafluoroborate (43) directly by ^{1}H n.m.r. Methyl (6*R*)-6-phthalimidopenicillanate (3) (360 mg) and trimethyloxonium tetrafluoroborate (160 mg) were dissolved in [$^2H_3$]nitromethane, and the mixture stirred at 20 °C under nitrogen. Samples were removed at intervals for ^{1}H n.m.r. analysis. After 90 min little starting material remained, but peaks were observed attributable to sulphonium salts, δ(CD_3NO_2) 1.8, 1.84, 1.97, and 2.24 (each 3 H, s, CH_3), 3.06 and 3.08 (each 3 H, s, SCH_3), 3.9 and 3.92 (each 3 H, s, OCH_3), 5.03 (2 × 1 H, s, H-3 of each isomer), 5.85 and 6.0 (each 1 H, d, *J* 2 Hz, H-5 and -6), 6.1 and 6.38 (each 1 H, d, *J* 4.5 Hz, H-5 and -6), and 7.84 (2 × 4 H, m, aromatic H of each isomer). The ^{1}H n.m.r. data are consistent with the mixture containing the sulphonium salts (43) and (45) in 1 : 1 ratio, and would appear to be quite clean at this stage. However on concentration *in vacuo*, a complex product mixture was obtained with a poorly defined ^{1}H n.m.r. spectrum.

We thank Professor C. B. Reese for drawing our attention to this problem and the S.R.C. for support (to P. M. D.). We also thank the School of Pharmacy (University of London) for mass spectra and accurate mass determinations and Mrs. E. Summers for 90-MHz n.m.r. spectra. We are indebted to Beecham Pharmaceuticals for a generous gift of starting material.

[9/290 *Received*, 26*th February*, 1979]

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