Preparation and Properties of Substituted 6β-Vinylpenicillanic Acids

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Routes to the title compounds are described, either using the selective addition of thiols to the known 6-allylidenepenicillanic acids or by the conjugate addition of Grignard derivatives, derived from 6,6-dibromopenicillanates, to substituted acrylates and acrylamides, followed by stereoselective reduction of the remaining 6-bromo-group to produce the 6β-substituted penicillanates. The 6β-derivatives containing the acryloyl side-chain were relatively unstable and readily underwent intramolecular rearrangement to the corresponding thiazepinones.

Most penicillins in use as antibiotics bear a 6β-acylamido substituent (1), a notable exception being mecillinam (2) in which an amidine group replaces the normal substituent.[1] Compared to the efforts made at varying the acyl group, relatively few studies have been made at replacing the 6β-amido group by other substituents, apart from the efforts of Sheehan and his group.[2] The discovery of new natural β-lactam antibiotics bearing widely differing side-chains as in the thienamycins,[3] has reawakened interest in possible variations of structure at this site. For such substitutions it is known that, whereas several types of structural variations are possible in highly strained, fused β-lactams, such as the penems and carbapenems, less reactive systems, such as the penicillanate structure (1), show a lower tolerance to chemical change. Presumably, penicillanic derivatives must attain greater residence times during interaction with the target enzymes than the more reactive systems and, during the interaction period, the 6β-substituent must be of a suitable size and be able to adopt an appropriate conformation to fit onto the enzyme surface.[4]

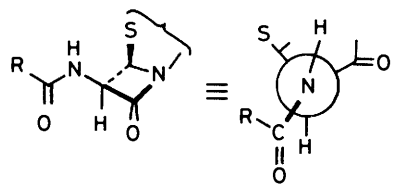
In order to investigate whether or not the 6β-acylamido-group can be replaced by substituents of a similar steric shape, we have prepared derivatives in which the amide group has been replaced by an olefinic bond. Such substitutions can be tolerated in peptides when the amide bond has mainly a structural role; the replacement is likely to be less successful when the amide group also has other roles involving either its dipolar nature or hydrogen bonding properties.[5]

The target structures were compounds (3)—(7), which may be compared to the standard penicillin structure (1). One would predict structure (4) to be less active than that of structure (3) if the preferred conformation adopted by (1) is as indicated in Figure 1 *a*.[6] The methyl group in (4) would be expected to interfere with the 6α-hydrogen atom thus disfavouring the conformation shown in Figure 1 *b*, whilst in compounds (3), (5), (6), and (7), the conformation indicated in Figure 1 *b* could be adopted. The nature and preferred conformation of the side-chain is known to be critical for enhancing the antibacterial properties of the β-lactam antibiotics.[7] Substitution into the double bond of the electron-withdrawing carbonyl group, as in compounds (5)—(7), should activate position 6, thus favouring rearrangements of the penicillanate nucleus after reaction with the target enzymes, for example, by the types illustrated in Scheme 1.

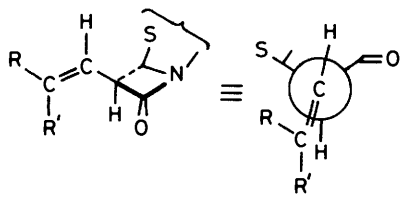
The route to compounds (3) and (4) involved initial nitrosation of the trichloroethyl ester of penicillin V (8) with dinitrogen tetroxide, followed by heating it, either in dichloromethane containing pyridine,[8] or, in better yield, without the pyridine, to give the 6-diazo-derivative (9). Using the method of Giddings *et al.*[9] the diazo-ester (9) could be treated with either substituted allylic sulphides or selenides. The allylidenes (15) and (16) were more readily prepared from the corresponding selenides (10) and (11), by oxidation with *m*-chloroperbenzoic acid at −5 °C followed by ready elimination of benzeneselenenic acid at room temperature. The allylidenes were unstable and rapidly formed polymers in the presence of air. The polymerisation probably involves free radicals since trituration with solvent ether also catalysed polymer formation. The reaction of the allylidenes with thiols was studied since these are free radical inhibitors which should inhibit such polymerisation whilst retaining the ability to add to the conjugated system. In this manner the addition of *p*-thiocresol could be effected to yield an epimeric mixture of 6-(3-*p*-tolylthioprop-1-enyl)-substituted penicillanates. Short reaction times gave mainly the 6β-isomer (12) but prolonged reaction times, aimed at securing completion of reaction, gave larger proportions of the 6α-epimer (13), presumably by

(1) X = RCONH
(2) X = $(CH_2)_6N.CH{:}N$

(3) R = 4-$MeC_6H_4SCH_2$; R′ = H
(4) R = 4-$MeC_6H_4SCH_2$; R′ = Me
(5) R = PhCO; R′ = H
(6) R = EtOCO; R′ = H
(7) R = Me_2NCO; R′ = H

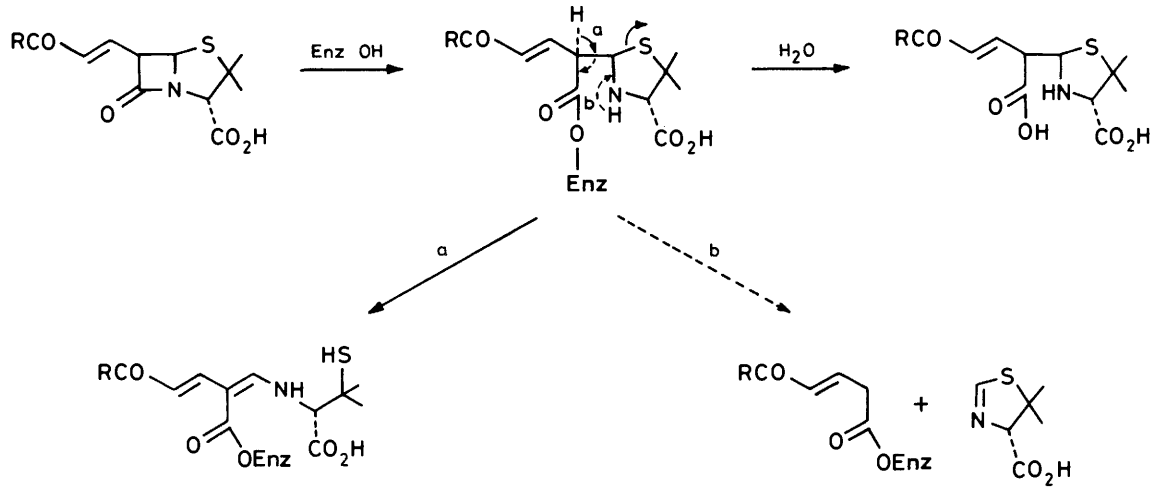


a

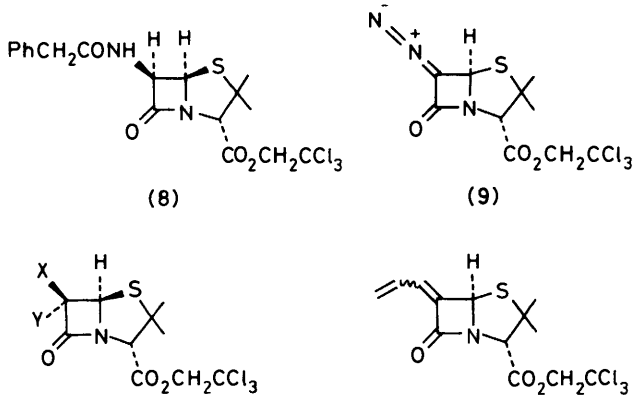


b

Figure 1.

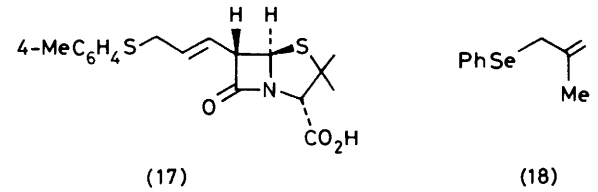


Scheme 1.



(8) (9)

(10) X = PhSe; Y = 
(11) X =  ; Y = PhSe
(15)(*E*)-isomer
(16) (*Z*)-isomer
(12) X = 4-$MeC_6H_4SCH_2CH{=}CH$; Y=H
(13) X = H; Y = 4-$MeC_6H_5SCH_2CH{=}CH$
(14) X = 4-$MeC_6H_4SCH_2C(Me){=}CH$-; Y=H



(17)

(18)

epimerisation of the kinetically favoured 6β-isomer. Deprotection of the 3-carboxylic acid group was effected by zinc dust in acetic acid [10] to afford the desired acid (3) and its epimer (17).

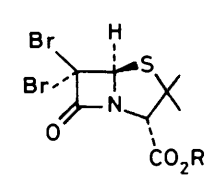
The addition of *p*-thiocresol to the allylidenes (15) and (16) involves a 1,6-addition process and results in the siting of a *trans*-double bond in the position normally associated with an amide group. (No sign of *cis*-olefin formation could be detected in the addition reaction.) The addition of other nucleophiles to the allylidene mixture was attempted, for example with sodium benzenesulphinate, but failed to give discrete products.

Preparation of the methylpropenyl derivatives (4) followed that of the allyl derivatives. Thus reaction of the methylallyl selenide (18) with the diazo-ester (9) produced a mixture of the 6-phenylseleno-6-methylpropenylpencillanates. Selective oxidation and elimination afforded the methylallylidenes to which was added *p*-thiocresol to give, mainly, the 6β-substituted derivative (14). Removal of the trichloroethyl group with zinc dust in acetic acid gave the acid (4).

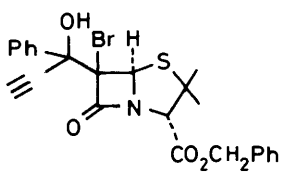
The route to the target compounds (5)—(7) commenced with the known ability of 6,6-dibromopenicillanate esters to form Grignard-like reagents at position 6 by exchange with methylmagnesium bromide.[11]

In an approach to compound (5) the attempted Michael addition between the magnesio-derivative obtained from benzyl 6,6-dibromopenicillanate (19) and propiolophenone only afforded a mixture of the 1,2-adducts (21) and a more indirect route to this target, using conjugated acetylenic synthons had to be adopted. Our approach required the development of reagents in which conjugate addition was preferred to direct attack at the activating group. Because of our current interest in vinylic sulphoxides,[12] in which eventual elimination of benzenesulphenic acid can be used to introduce a double bond into systems, reagents of the types (22)—(24) were preferred. The phenylsulphinyl group should shield the carbonyl formation from attack, thus helping to direct nucleophilic addition across the olefinic bond with subsequent controlled elimination of the sulphoxide group to generate the required double bond. The ketone (22) was prepared by addition of benzenesulphenic acid [13] to phenyl(ethynyl)-methanol, followed by oxidation of the hydroxy-sulphoxide with either manganese dioxide or pyridinium chlorochromate. The ketone (22) was unstable to storage and was therefore generated as required. The ester (23) and the amide (24) were prepared by the methods indicated in Schemes 2 and 3, respectively. Since this work was completed an alternative route to the ester (23) has been reported.[14]

Reaction of the Grignard reagent from (19) with 2-phenylsulphinyl-1-phenylprop-2-en-1-one (22) was successful, producing a mixture of the isomeric keto-sulphoxides (25). At this stage two possible reaction paths presented themselves, either pyrolysis, to eliminate benzenesulphenic acid and introduce the required double bond into the side-chain, followed by stereoselective reductive removal of the 6-bromo group, or the reverse procedure. The mildest procedure was necessary since we wished to avoid the intramolecular rearrangement of our target to the corresponding thiazepinone,



(19) R = CH_2Ph
(20) R = $CHPh_2$



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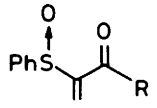
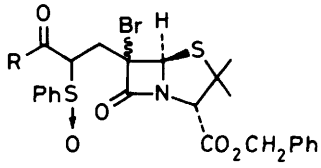
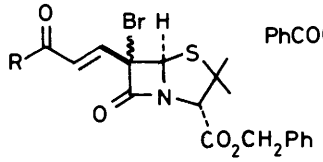


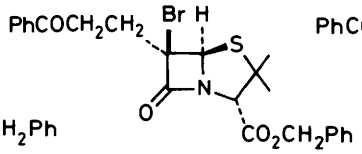
(22) R = Ph
(23) R = OEt
(24) R = NMe_2



(25) R = Ph
(26) R = OEt
(27) R = NMe_2



(31) R = Ph
(32) R = EtO
(33) R = Me_2N



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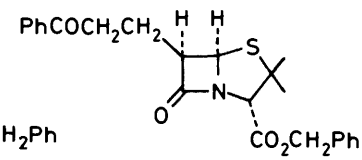

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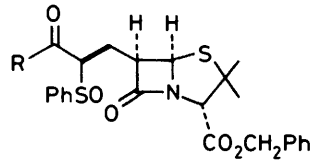
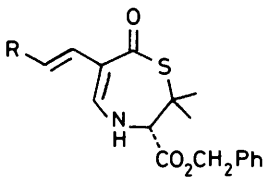
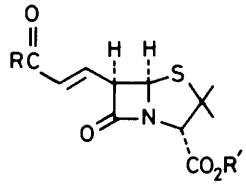


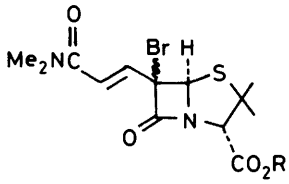
(36) R = Ph
(37) R = EtO
(38) R = Me_2N



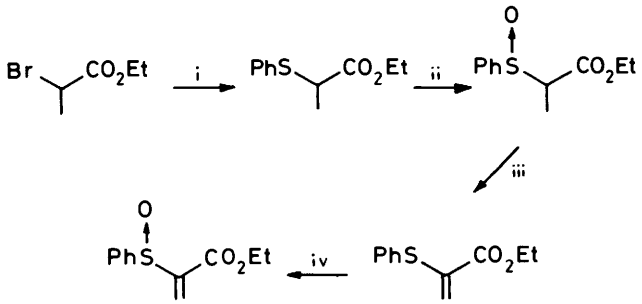
(28) R = Ph
(29) R = OEt
(30) R = NMe_2



(39) R = Ph; R′ = CH_2Ph
(40) R = EtO; R′ = CH_2Ph
(41) R = Me_2N; R′ = CH_2Ph
(42) R = Me_2N; R′ = $CHPh_2$



(43) R = $CHPh_2$



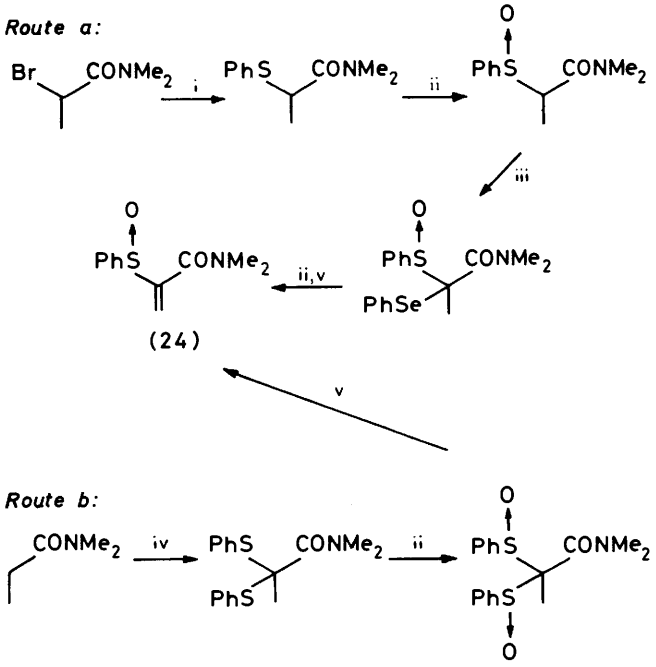
Scheme 2. *Reagents:* i, PhS^-Na^+; ii, $NaIO_4$; iii, Ac_2O, $MeSO_3H$; iv, *m*-Cl-perbenzoic acid

in this case (28), a process known to occur for 6-acylpenicillanates.[15] In the event, neither route was successful; pyrolysis of the mixture (25) gave the epimeric ketones (31) in good yield but attempted reduction of the 6-bromo group with tributyltin hydride [16] failed, producing instead a complex mixture of products in which only the saturated ketones (34) and (35) could be detected. Although prior reduction of the adducts (25) with tributyltin hydride was achieved, mainly producing the 6β-substituted penicillanate (36), thermolysis of the latter was unsuccessful, affording the unstable yellow thiazepinone (28) rather than the required ester of compound (2).

These observations suggested that the 6α-proton in the ester of (2) was too acidic, the system rearranging spontaneously to the thiazepinone. In order to moderate the acidity of the proton at position 6, a less electronegative conjugating influence was required. The next target was, therefore, the substituted acrylate ester (3), since ester groups are less activating than ketones. In order to introduce the appropriate side-chain the α-phenylsulphinylacrylate ester (23) was prepared by the route indicated (Scheme 3) and treated with the Grignard derivative from the benzyl ester (19) to give a mixture of the isomeric adducts (26). Further reactions were carried out either by prior reductive removal of the 6-bromo-group or prior elimination of benzenesulphenic acid. The former route, using tributyltin hydride as reductant, afforded a mixture of the products (37), of predominantly 6β-configuration. Thermolysis of this reduced ester (37) in refluxing toluene afforded the desired ester (39) contaminated with a little of the 6α-epimer and some of the corresponding thiazepinone (30). The alternative route, involving prior thermolysis of the adduct (26) to give (32), followed by reductive removal of the 6-bromo-group with tributyltin hydride, afforded a similar mixture of products but attempted purification of these mixtures by silica gel chromatography again afforded only the corresponding thiazepinone (29).

In a final attempt to obtain the target compounds, further moderation of the acidity of the 6α-hydrogen group of the penicillinate nucleus was aimed at by generating a conjugated amide. Reaction of the Grignard reagent derived from (19) with the α-phenylsulphinylacrylamide (24), prepared by either of two simple routes (Scheme 3), afforded the adducts (27).

Thermolysis of the sulphoxide adducts followed by re-



Scheme 3. *Reagents:* i, PhS^-Na^+; ii, *m*-Cl-perbenzoic acid; ii, PhSeCl; iv, PhSSPh, $NaNH_2$; v, heat

ductive removal of the bromine with tributyltin hydride gave the required amide (41). In this case, as anticipated, rearrangement to the corresponding thiazepinone (30) was a much slower process. By repeating the reactions on the benzylhydryl ester (20), the corresponding amide (42) was prepared. Removal of the benzhydryl protecting group, by use of trifluoroacetic acid and anisole, afforded some of the required target acid (7).

Biological assays on the potassium salts of the acids (3), (4), and (17) showed that of the three compounds the 6α-substituted derivative (17) was a very weak antibiotic. Compounds (3) and (4), however, both possessed antibacterial properties. For example, against a penicillin sensitive strain of *Staphylococcus aureus* the allyl derivative (3) showed 1/1600 the activity of penicillin G, whilst the methylpropenyl derivative (4) was, as expected, less active by a factor of 3. The amide (7) showed very weak antibacterial properties.*

The modest antibacterial properties exhibited by the penicillin analogues (3) and (4) demonstrate that the replacement of the side-chain amide group by a double bond is not intolerable. The poor activity of the amide (7) is believed to be associated with the deformity from planarity of the dimethylacrylamide group, thus preventing the side-chain from adopting a suitable conformation for entry into the active site.

Finally, it should be pointed out that conjugate additions to the α-phenylsulphinylacryloyl systems (22)—(24) should be general and allow the ready introduction of the β-substituted acryloyl groups into organic compounds.

Experimental

M.p.s were determined on a Kofler hot-stage apparatus. I.r. spectra were recorded with a Perkin-Elmer 297 spectrophotometer, either on film, or for solids, in $CHCl_3$ solution.

* We thank Dr. S. G. Waley and his colleagues, Sir William Dunn School of Pathology, University of Oxford, for the antibacterial results.

^1H N.m.r. spectra were recorded on either a Perkin-Elmer R32 (90 MHz) instrument or a Jeol FX90Q (90 MHz) spectrometer for solutions in deuteriochloroform (tetramethylsilane as internal reference). Mass spectra were recorded on a Kratos MS 25 instrument with accurate mass measurements being carried out on an AEI-Kratos MS9/50 instrument.

Thin-layer chromatography (t.l.c.) and short-column chromatography were carried out on Kieselgel GF_{254} (Merck). Solvents were generally distilled and dried before use. Light petroleum refers to the fraction of boiling range 40—60 °C. Solvent ratios are in volumes before mixing. Solutions were dried over anhydrous sodium sulphate. All reactions were carried out under an atmosphere of oxygen-free nitrogen.

2,2,2-Trichloroethyl 6α-Allyl-6β-phenylselenopenicillanate (10) *and Its Isomer* (11).—These compounds were prepared according to the method of Giddings *et al.*[9] A solution of the diazo-ester (9) (0.71 g) and allyl phenyl selenide [18] (0.43 g) in dichloromethane (25 ml) at room temperature was treated with copper(II) acetylacetonate (50 mg) for 20 min. Work-up afforded the title products (0.53 g, 51%). Further separation, by preparative t.l.c. gave two fractions. The less polar, minor component was trichloroethyl 6α-allyl-6β-phenylselenopenicillanate (10) (0.16 g, 15%), m.p. 104—106 °C (lit.,[9] m.p. 105—106 °C), δ 1.56 and 1.83 (3 H each, 2, Me_2C), 2.54 (2 H, br d, *J* 7 Hz, $CH_2CH{=}CH_2$), 4.65 (1 H, s, 3-H), 4.70 and 4.84 (2 H, ABq, *J* 12 Hz, CH_2CCl_3), 4.95—5.2 (2 H, m, $CH_2{=}CH$), 5.40 (1 H, s, 5-H), 5.75 (1 H, m, $CH{=}CH_2$), 7.25—7.5 (5 H, m, ArH).

The more polar, major component, was trichloroethyl 6β-allyl-6α-phenylselenopenicillanate (11) (0.38 g, 36%), m.p. 75—80 °C (lit.,[9] m.p. 80—81 °C), δ 1.48 and 1.62 (3 H each, s, Me_2C), 2.85 (2 H, m, $CH_2CH{=}CH_2$), 4.40 (1 H, s, 3-H), 4.52 and 4.74 (2 H, ABq, *J* 12 Hz, CH_2CCl_3), 5.14 and 5.30 (2 H, m, $CH_2{=}CH$), 5.34 (1 H, s, 5-H), 5.80 (1 H, m, $CH{=}CH_2$), 7.25—7.75 (5 H, m, ArH).

Preparation of Epimeric 2,2,2-Trichloroethyl 6-(3-p-Tolylthioprop-1-enyl)penicillanates (12) *and* (13).—An epimeric mixture of the 6-allyl-6-phenylselenopenicillanates (10) and (11) (0.79 g) was oxidised with *m*-chloroperbenzoic acid (0.34 g, 85%) in dichloromethane (25 ml) at −78 °C for 10 min before the temperature was allowed to rise to 0 °C; the mixture was then stirred for a further 1 h. The mixture was diluted with dichloromethane, washed with dilute aqueous sodium hydrogen carbonate and water, before being dried and filtered; solvent was then removed under reduced pressure. The allylidenes (15) and (16) so obtained as an unstable yellow oil [9] (0.77 g) were dissolved in ethanol (20 ml) and to the solution was added an ice-cold one of *p*-thiocresol (0.20 g) in ethanol (10 ml) containing triethylamine (1 drop). The mixture was stirred for 1 h, diluted with ether (200 ml), and the organic phase washed thoroughly with water. After drying, the organic extract was evaporated under reduced pressure and the residue chromatographed through silica gel, using EtOAc–light petroleum as eluant. The less polar component, isolated as an oil, was *2,2,2-trichloroethyl 6α-(3-p-tolylthioprop-1-enyl)penicillanate* (13) (0.10 g, 13%), $\nu_{max.}$ 1 770 and 960 cm^{-1}; δ 1.53 and 1.67 (3 H each, s, Me_2C), 2.32 (3 H, s, aromatic Me), 3.46 (2 H, d, *J* 7 Hz, CH_2S), 3.89 (1 H, dd, *J* 1, 7 Hz, 6-H), 4.58 (1 H, s, 3-H), 4.70 and 4.84 (2 H, ABq, *J* 12 Hz, CH_2CCl_3), 4.98 (1 H, d, *J* 1 Hz, 5-H), 5.4—5.9 (2 H, m, CH=CH), 7.08—7.24 (4 H, m, ArH) (Found: M^+, 493.1016, $C_{20}H_{22}{}^{35}Cl_3NO_3S_2$ requires *M*, 493.0106).

The more polar compound was the *6β-substituted epimer* (12) (0.20 g, 28%), isolated as an amorphous solid, $\nu_{max.}$

1 770 and 965 cm^{-1}; δ 1.55 and 1.65 (3 H each, s, Me_2C), 2.32 (3 H, s, aromatic Me), 3.50 (2 H, d, *J* 7 Hz, CH_2S), 4.24 (1 H, m, 6-H), 4.50 (1 H, s, 3-H), 5.4—6.0 (2 H, m, CH=CH), 5.44 (1 H, d, *J* 5 Hz, 5-H), 7.0—7.25 (4 H, m, ArH) (Found: M^+, 403.0106, $C_{20}H_{22}{}^{35}Cl_3NO_3S_2$ requires *M*, 493.0106).

The esters (12) and (13) were separately deprotected by stirring portions (0.20 g) in water–acetic acid (1 : 9) (10 ml) and zinc dust (2 g) at 0 °C for 3 h before being filtered onto ice–water, and extracted with dichloromethane. The organic extract was reduced in volume and ether added to it; the mixture was then basified with aqueous sodium hydrogen carbonate to pH 9.0 before reacidification and re-extraction into dichloromethane. The free acids were obtained in yields of 80—85% by this procedure. Samples of the acids were converted into their potassium salts, by exchange with potassium 2-ethylhexanoate, before antibacterial assay.

Synthesis of 6β-(3-p-*Tolylthio*-2-*methylprop*-1-*enyl*)*penicillanic Acid* (4).—2,2,2-Trichloroethyl 6-diazopenicillanate (9) (1.43 g) was treated with methylallyl phenyl selenide (18) (0.86 g) (prepared from benzeneselenol and methylallyl chloride) using copper(II) acetylacetonate (30 mg) as catalyst, and dichloromethane (100 ml) as solvent. After 30 min at room temperature, when N_2 evolution had ceased, the mixture was worked up in the manner described above, to yield a brown oil (2.30 g). Chromatography on silica gel afforded, as the less polar material, 2,2,2-*trichloroethyl* 6α-*methylallyl*-6β-*phenylselenopenicillanate* (0.27 g, 12%), m.p. 95—97 °C (EtOAc), $\nu_{max.}$ 1 760 and 1 640 cm^{-1}; δ 1.54 and 1.68 (3 H, each s, Me_2C), 1.82 (3 H, s, vinylic Me), 2.52 [2 H, br s, $CH_2C(Me)$], 4.62 (1 H, s, 3-H), 4.68 and 4.88 (1 H each, br s, CH_2=C), 4.66 and 4.80 (2 H, ABq, *J* 12 Hz, CH_2CCl_3), 5.50 (1 H, s, 5-H), and 7.3—7.8 (5 H, m, ArH); *m/z* 545, 543, 541, 539 (M^+), 366, 311, 292, 290, 252 (base peak), 114, 95, and 77 (Found: M^+ 540.9535. $C_{20}H_{22}{}^{35}Cl_3NO_3{}^{80}SeS$ requires *M*, 540.9551).

The more polar epimer, 2,2,2-*trichloroethyl* 6β-*methylallyl*-6α-*phenylselenopenicillanate* (0.65 g, 30%), had m.p. (EtOAc) 132—133 °C, $\nu_{max.}$ 1 760 and 1 640 cm^{-1}; δ 1.44 and 1.60 (3 H each, s, Me_2C), 1.80 (3 H, s, vinylic Me), 2.70 and 3.08 [2 H, ABq, *J* 16 Hz, $CH_2C(Me)$], 4.36 (1 H, s, 3-H), 4.90 (2 H, m, CH_2=C), 4.48 and 4.79 (2 H, ABq, *J* 12 Hz, CH_2CCl_3), 5.46 (1 H, s, 5-H), and 7.3—7.7 (5 H, m, ArH); *m/z* 545, 543, 541, 539 (M^+), 366, 311, 292, 290, 252 (base peak, 114, 95, and 77) (Found: M^+ 540.9533. $C_{20}H_{22}NO_3{}^{35}Cl_3{}^{80}SeS$ requires *M*, 540.9551).

A mixture of the selenides (0.37 g) was oxidised with *m*-chloroperbenzoic acid (150 mg, 85%), in dichloromethane (25 ml) at −78 °C. On warming the solution to room temperature the selenoxides decomposed smoothly to yield, after work-up, mainly one methylallylidene together with diphenyl diselenide. The ^1H n.m.r. spectrum of the mixtures showed δ 1.64 and 1.75 (3 H, each, s, Me_2C), 1.92 (3 H, s, vinylic Me), 4.64 (1 H, s, 3-H), 4.74 and 4.82 (2 H, ABq, *J* 12 Hz, CH_2CCl_3), 5.36 (2 H, br s, CH_2=C), 6.0 (1 H, br s), 6.70 (1 H, br s) and aromatic signals. The mixture was dissolved in ethanol (15 ml) and added dropwise, during 20 min, to a solution of *p*-thiocresol (0.10 g) in ethanol (5 ml) containing triethylamine (1 drop). After 30 min the solution was concentrated under reduced pressure and the residue dissolved in ether and extracted with brine before drying. The organic extract was chromatographed on silica with EtOAc–light petroleum (1 : 9) as eluant, to yield 2,2,2-trichloroethyl 6β-(3-*p*-tolylthio-2-methylprop-1-enyl)penicillanate (14) (0.19 g, 55%), as a pale yellow oil, $\nu_{max.}$ 1 770 cm^{-1}; δ 1.52 and 1.60 (3 H each, s, Me_2C), 1.82 (3 H, br s, vinylic Me), 2.28 (3 H, s, aromatic Me), 3.46 (2 H, br s, CH_2S), 4.36 (1 H, m, 6-H), 4.46 (1 H, s, 3-H), 4.68 and 4.80 (2 H, ABq, *J* 12 Hz, CH_2CCl_3), 5.38 (1 H, br d, *J* 9 Hz, 3′-H), 5.40 (1 H, d, *J* 4 Hz, 5-H), and 7.05—7.2 (4 H, m, ArH).

A sample of the acid (4) was obtained by deprotecting the ester with zinc dust in aqueous acetic acid by the method described above. The acid was immediately converted into the potassium salt by exchange with potassium 2-ethylhexanoate before a sample was sent for antibacterial assay.

2-*Phenylsulphinyl*-1-*phenylprop*-2-*en*-1-*one* (22).—1-Cyano-2-phenylsulphinylethane [13] (0.89 g, 5 mmol) and phenylethynylmethanol (0.66 g, 5 mmol) were heated in benzene (30 ml) at reflux for 16 h. The solvent was removed under reduced pressure and the residue filtered through silica to give a mixture of the diastereoisomeric alcohols, 1-phenyl-2-phenylsulphinylprop-2-en-1-ol (0.60 g, 46%) as a white solid, m.p. 92—102 °C, $\nu_{max.}$ 3 500—3 200br and 1 020 cm^{-1} (the mixture showed M^+ 258.07090; $C_{15}H_{14}O_2S$ requires M^+, 258.07145). The alcohol (0.30 g) was oxidised by shaking it in dry dichloromethane with activated manganese dioxide (1.00 g) for 9 h. After filtration and evaporation of solvent under reduced pressure the product was purified by p.l.c. on silica, using EtOAc–light petroleum (2 : 3) as eluant, to afford the unstable ketone (22) (0.11 g, 38%), $\nu_{max.}$ 1 660 and 1 050 cm^{-1}; δ 6.45 and 6.95 (1 H each, *J* 2 Hz, H_2C=C), 7.2—7.9 (10 H, m, ArH). The freshly prepared material was used directly in further reactions.

Ethyl 2-*Phenylsulphinylacrylate* (23).—To a solution of sodium thiophenoxide (39.6 g, 0.3 mol) in ethanol (250 ml) was added ethyl 2-bromopropionate (54.3 g, 0.3 mol) and the mixture heated to reflux for 6 h. The reaction mixture was evaporated under reduced pressure and the residue dissolved in ether (500 ml) and washed with 2M-NaOH and brine. The organic extract, after removal of solvent, afforded an oil (50.7 g, 81%) $\nu_{max.}$ ($CHCl_3$) 1 730 and 1 580 cm^{-1}; δ 1.12 (3 H, t, *J* 7 Hz, $MeCH_2$), 1.45 (3 H, d, *J* 7 Hz, *Me*CH), 3.82 (1 H, q, *J* 7 Hz, MeC*H*), 4.1 (2 H, q, *J* 7 Hz, MeCH_2), and 7.4 (5 H, m, ArH). This oil (42.0 g, 0.2 mol) was dissolved in methanol (400 ml) at 0 °C and oxidised with sodium periodate (46.7 g, 0.2 mol) dissolved in the minimum quantity of water. After 2 h the mixture was filtered and the filtrate concentrated under reduced pressure. The concentrate was dissolved in ether (400 ml), washed with brine, dried, and evaporated under reduced pressure to yield ethyl 2-phenylsulphinylpropionate as an oily mixture of diastereoisomers (40.7 g, 90%), $\nu_{max.}$ ($CHCl_3$) 1 730, 1 580, and 1 005 cm^{-1}.

To the sulphoxide ester (22.6 g, 0.1 mol) in dichloromethane (500 ml) under nitrogen at room temperature, was added acetic anhydride 11.1 ml) and methanesulphonic acid (0.89 ml). The solution was stirred for 24 h before being washed with water (2 × 20 ml), dried, and the solvent removed under reduced pressure. The residue was chromatographed through Florisil (500 g) using ether–light petroleum as eluant, to give ethyl 2-phenylthioacrylate as an oil (16.4 g, 80%), $\nu_{max.}$ ($CHCl_3$) 1 720 and 1 587 cm^{-1}; δ 1.23 (3 H, t, *J* 7 Hz, $MeCH_2$), 4.3 (2 H, q, *J* 7 Hz, CH_2), 5.3 and 6.35 (1 H each, s, CH_2=C), and 7.43 (5 H, m, ArH).

The acrylate ester (10.2 g, 0.05 mol) in dichloromethane (100 ml) was cooled to −78 °C before the addition of *m*-chloroperbenzoic acid (10.1 g, 85%, 0.05 mol) in dichloromethane (50 ml). The reaction mixture was stirred for 2 h before it was washed with aqueous sodium hydrogen carbonate and brine, dried and the solvent removed under reduced pressure. The residue was chromatographed through Florisil, using ether–light petroleum as eluant, to give the title ester [14] as an oil (10.7 g, 95%), $\nu_{max.}$ (film) 1 725, 1 620, 1 585, and 1 055 cm^{-1}; δ 1.15 (3 H, t, *J* 7 Hz, $MeCH_2$), 4.81 (2 H, q, *J* 7 Hz, $MeCH_2$), 6.83 and 6.9 (1 H each, s, CH_2=C), 7.4—7.95 (5 H, m, ArH).

N,N-*Dimethyl-2-phenylsulphinylacrylamide* (24).—Method (a). 2-Bromopropionic acid (15.3 g) was dissolved in freshly distilled thionyl chloride (10 ml) at room temperature. After 16 h the excess of the thionyl chloride was removed and the residue dissolved in ether (50 ml) before careful addition of an excess of dimethylamine dissolved in ether. After 30 min the mixture was washed with water and dilute HCl before it was dried and the solvent removed to yield the bromoamide (3.3 g). Thiophenol (2 ml) in a solution of sodium ethoxide (1 equiv.) in ethanol (20 ml) was added to a solution of the bromoamide in ethanol (10 ml) and the solution stirred at room temperature for 12 h before removal of solvent under reduced pressure and partitioning of the residue between ether and water. Work-up in the normal manner afforded the crude 2-phenylthiopropionamide (3.6 g). Oxidation of this material with *m*-chloroperbenzoic acid (3.7 g, 80%) in dichloromethane (10 ml) at −78 °C for 1 h afforded a mixture of the corresponding diastereoisomeric sulphoxides.

A sample of the sulphoxide mixture (0.60 g) in dry tetrahydrofuran (30 ml) was treated with potassium hydride (0.24 g) at 0 °C, with liberation of hydrogen as the anion formed and, after 30 min, with a solution of benzeneselenyl chloride (0.80 g) in tetrahydrofuran (20 ml), the temperature being kept at 0 °C. After addition was complete and the orange colour of the solution had been discharged, the solution was poured into ethyl acetate (50 ml) and washed with water, aqueous sodium hydrogen carbonate and water until neutral. The organic extract was dried, and the solvent removed under reduced pressure to yield the phenyl selenide as an oil (0.57 g). This material was dissolved in dichloromethane (30 ml) and oxidised with *m*-chloroperbenzoic acid (0.30 g, 80%) at −78 °C for 15 min before the mixture was allowed to warm to room temperature. Work-up in the normal manner afforded an oil which was chromatographed through silica, using EtOAc–light petroleum as eluant, to afford the *title sulphoxide* (0.18 g, 27% from the bromoamide), m.p. 93—96 °C, $\nu_{max.}$ 1 680 cm^{-1}; δ 2.57 and 2.78 (3 H each, s, NMe_2), 5.80 and 6.16 (1 H each, s, CH_2=C), 7.2 (5 H, ArH) (Found: C, 59.3; H, 5.75; N, 6.25; S, 14.3. $C_{11}H_{13}NO_2S$ requires C, 59.2; H, 5.8; N, 6.3; S, 14.35%).

Method (*b*). *N,N*-Dimethylpropionamide (4.11 g, 40 mmol) was dripped into a solution of freshly prepared sodamide (*ex.* Na, 1.87 g, 80 mg-atom) in liquid ammonia (100 ml) at −78 °C, followed by the addition of tetrahydrofuran (3 ml). The solution was warmed to reflux (−20 °C) for 0.5 h and then re-cooled to −78 °C before addition of diphenyl disulphide (20 g, 100 mmol); the mixture was then allowed to warm to reflux for 15 min when its colour faded. The ammonia was distilled off, water and concentrated HCl were added, and the organic material extracted into chloroform. The solution was washed with water, dried, and evaporated to produce an oil, which was filtered through silica using, initially, hexane and finally ether–hexane (2 : 3), to yield N,N-*dimethyl* 2,2-*bisphenylthiopropionamide* as a low-melting solid (70 g, 54%), m.p. 10—18 °C, δ 1.51 (3 H, s, Me), 3.35 (6 H, s, NMe_2), and 7.0—7.4 (10 H, ArH) (Found: C, 64.35; H, 6.1; N, 4.5; S, 20.3. $C_{17}H_{19}NOS_2$ requires C, 64.35; H, 6.0; N, 4.4; S, 20.2%).

The bisphenylsulphenylamide (5.35 g, 17 mmol) was treated with *m*-chloroperbenzoic acid (5.82, 34 mmol) in chloroform (100 ml) at 0 °C. The crude product solution was extracted with aqueous sodium hydrogen carbonate, dried, and then heated to reflux for 3 h before chromatography through silica using EtOAc–light petroleum as eluant. The major fraction was the desired sulphoxide (24) (1.5 g, 22% from the unsubstituted propionamide), m.p. 93—96 °C.

Reaction of the Dibromide (19) *with Propiolophenone*.—To a solution of benzyl 6,6-dibromopenicillanate [19] (0.47 g, 1 mmol) in tetrahydrofuran (15 ml) at −78 °C was added, dropwise, an ethereal solution of methylmagnesium bromide (1M; 1.0 ml). The clear solution was stirred under nitrogen at −78 °C for 25 min before addition of a solution of propiolophenone (0.14 g, 1.08 mmol) in tetrahydrofuran (6 ml). After a further 30 min, the reaction was quenched with saturated aqueous ammonium chloride and diluted with ether; the combined organic extract was washed with water and brine before being dried. After removal of the solvent the residue was chromatographed through silica gel to produce two major fractions identified as diastereoisomers of benzyl 6-bromo-6-(1-hydroxy-1-phenylprop-2-ynyl)penicillanate (21). The largest fraction was the less polar material (0.26 g, 52%) and this was isolated as a white solid, $\nu_{max.}$ 3 570, 3 300, 1 785, and 1 745 cm^{-1}; δ 1.30 and 1.52 (3 H each, s, Me_2C), 2.80 (1 H, s, H·C≡C), 4.36 (1 H, s, 3-H), 4.46 (1 H, s, exchangeable with D_2O, OH), 5.04 (2 H, s, CH_2Ph), 5.75 (1 H, s, 5-H), and 7.3—7.5 (10 H, ArH). The more polar fraction (0.04 g, 9%), isolated as a white foam, showed δ 1.44 and 1.76 (3 H, each s, Me_2C), 2.90 (1 H, s, HC≡C), 4.62 (1 H, s, 3-H), 5.0 (1 H, s, exchangeable with D_2O, H), 5.22 (2 H, s, CH_2Ph), 5.82 (1 H, s, 5-H), and 7.36—7.9 (10 H, m, ArH).

Reaction of the Dibromide (19) *with* 2-*Phenylsulphinyl*-1-*phenylprop*-2-*en*-1-*one* (22).—To the magnesio-derivative of benzyl 6,6-dibromopenicillanate (0.45 g), prepared as described above, in tetrahydrofuran solution (15 ml), was added dropwise at −78 °C, a solution of the sulphoxide (22) (0.26 g) in tetrahydrofuran (6 ml). After 75 min the reaction was quenched with saturated aqueous ammonium chloride and diluted with ethyl acetate (50 ml). After work-up in the usual manner the reaction afforded an off-white foam, which consisted mainly of the diastereoisomeric adducts (25), $\nu_{max.}$ 1 785, 1 745, 1 675, and 1 050 cm^{-1}. The crude product was dissolved in anhydrous benzene (50 ml) and heated to reflux for 1.5 h before removal of the solvent and chromatography of the product through silica gel, using EtOAc–light petroleum as eluant. This afforded a mixture of diastereoisomeric benzyl 6-bromo-6-(3-oxo-3-phenylprop-1-enyl)penicillanates (31) (0.39 g, 79%), $\nu_{max.}$ 1 785, 1 745, 1 670, and 1 615 cm^{-1}. Chromatographic separation of a sample by analytical h.p.l.c. (SiO_2) afforded two products, the minor material was assigned the 6α-bromo-configuration and showed δ 1.38 and 1.48 (3 H each, s, Me_2C), 4.50 (1 H, s, 3-H), 5.18 (2 H, s, CH_2Ph), 5.70 (1 H, s, 5-H), 7.08 (1 H, d, *J* 16 Hz, CH=CH), 7.35—8.0 (11 H, m, vinylic and aromatic H). The major fraction, assigned the 6β-bromo-configuration, showed δ 1.40 and 1.68 (3 H each, s, Me_2C), 4.60 (1 H, s, 3-H), 5.18 (2 H, s, CH_2Ph), 5.50 (1 H, s, 5-H), and 7.35—8.0 (12 H, m, vinylic and aromatic H).

Attempted Reduction of the Vinylic Ketones (31).—A sample of the ketone mixture (31) (0.175 g) in anhydrous benzene (3 ml) was heated with tributyltin hydride (0.14 g) for 45 min before addition of a further quantity of the hydride (0.15 g) and heating for a further 45 min. Chromatographic separation of the complex mixture of products afforded, amongst other materials, products assigned as the fully reduced ketone, benzyl 6β-(3-oxo-3-phenylpropyl)penicillanate (35) (20 mg) as an oil, $\nu_{max.}$ 1 785, 1 745, and 1 685 cm^{-1}; δ 1.42 and 1.63 (3 H each, s, Me_2C), 2.28 (2 H, q, *J* 7 Hz, CH_2CH$_2$CO), 3.15 (2 H, t, *J* 7 Hz, CH_2CO), 3.70 (1 H, m, 6-H), 4.44 (1 H, s, 3-H), 5.20 (2 H, s, CH_2Ph), 5.48 (1 H, d, *J* 4 Hz, 5-H), 7.35—8.0 (10 H, ArH), and the dihydro-compound (34) (30 mg) as an oil, $\nu_{max.}$ 1 785, 1 745, and 1 685 cm^{-1}; δ 1.38 and 1.62 (3 H each, s, Me_2C), 2.75 (2 H, m), 3.35 (2 H, m), 4.50 (1 H, s, 3-H), 5.18 (2 H, s, CH_2Ph), 5.36 (1 H, s, 5-H), and 7.35—8.0

(10 H, m, ArH). These compounds were not further characterised.

Reduction of the Adducts (25).—Freshly chromatographed material (27 mg) in ether (1 ml) was treated with tributyltin hydride (0.2 ml) for 2 days at room temperature. The solvent was removed and the residue partitioned between acetonitrile and light petroleum, the heavier layer being washed several times with more light petroleum. Chromatography of the acetonitrile extract through silica gel, using EtOAc–benzene as eluant, gave benzyl 6β-(2-phenylsulphinyl-3-oxo-3-phenylpropyl)penicillanate (36) (12 mg) as a solid foam and as a mixture of diastereoisomers, $\nu_{max.}$ 1 770, 1 745, 1 670, and 1 050 cm^{-1}. Pyrolysis of this sulphoxide in refluxing toluene for 30 min gave, principally, the unstable thiazepinone (29), $\nu_{max.}$ ($CHCl_3$) 3 380, 3 270, 1 735, 1 645, 1 595, and 1 550 cm^{-1}; δ 1.43 and 1.50 (3 H each, s, Me_2C), 4.46 (1 H, br d, became a singlet on exchange with D_2O), 5.16 (2 H, s, C*H*Ph), 7.2—8.0 (14 H, aromatic, amide and vinylic H). With time the thiazepinone rapidly decomposed to a complex mixture of more polar compounds.

Reaction of the Dibromide (19) *with Ethyl 2-Phenylsulphinylacrylate* (23).—Freshly prepared ethereal methylmagnesium bromide (1M; 2.2 ml) was added dropwise to a solution of the dibromide (1.06 g, 2 mmol) in tetrahydrofuran (15 ml) at −78 °C. After 20 min, ethyl 2-phenylsulphinylacrylate (0.45 g, 2 mmol) in tetrahydrofuran (8 ml) was injected. The solution was stirred at <78 °C for a further 30 min before it was quenched with saturated aqueous ammonium chloride and diluted with ethyl acetate (75 ml). The organic phase was washed with water and brine and then dried. Removal of the solvent under reduced pressure afforded, as a pale yellow foam (1.21 g), a diastereoisomeric mixture of benzyl 6-bromo-6-(2-phenylsulphinyl-2-ethoxycarbonylethyl)penicillanates (26). The crude product was used directly in subsequent reactions.

The crude product (0.65 g) was heated in anhydrous toluene (25 ml) at reflux for 1 h before removal of the solvent under reduced pressure and chromatography of the residue through silica gel, using EtOAc–light petroleum (1 : 9) as eluant, to produce an epimeric mixture of benzyl 6-bromo-6-(2-ethoxycarbonylvinyl)penicillanates (32) (0.25 g, 50%), as a yellow oil, $\nu_{max.}$ 1 785, 1 750, 1 720, and 1 655 cm^{-1}; its ^1H n.m.r. spectrum indicated a 1 : 4 ratio of two major components.

Reduction of the Acrylate (32).—The epimeric mixture (0.152 g) was dissolved in anhydrous benzene and tributyltin hydride (0.09 g) added together with a catalytic amount of azobisisobutyronitrile (AIBN) (1 mg). The solution was heated to 105 °C for 1 h before being cooled and the solvent removed under reduced pressure; the product was partitioned between acetonitrile and hexane. After washing of the acetonitrile layer with more hexane (× 5), the solvent was removed to yield an oil which was separated on silica gel by h.p.l.c. (EtOAc–hexane, 1 : 5) to give in order of elution the following: *benzyl 6α-(1-ethoxycarbonylvinyl)penicillanate* (17 mg, 14%), as a pale yellow oil, $\nu_{max.}$ 1 780, 1 750, 1 720, and 1 655 cm^{-1}; δ 1.28 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.40 and 1.63 (3 H, each s, Me_2C), 3.96—4.34 (3 H, m, superimposed on a q, *J* 7 Hz), 4.53 (1 H, s, 3-H), 5.18 (2 H, s, CH_2Ph), 5.23 (1 H, d, *J* 1.5 Hz, 5-H), 6.06 (1 H, dd, *J* 16, 1 Hz, C*H*=CH), 7.0 (1 H, dd, *J* 16, 8, Hz, CH=C*H*), and 7.35 (5 H, m, ArH) (Found: M^+, 389.12969. $C_{20}H_{23}NO_5S$ requires *M*, 398.12968); *benzyl 6β-(2-ethoxycarbonylvinyl)pencillanate* (40) (10 mg, 8%), as a pale yellow oil, $\nu_{max.}$ ($CHCl_3$) 1 780, 1 745, 1 720, and 1 655 cm^{-1}; δ 1.30 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.42 and 1.60 (3 H each, s, Me_2C), 4.30 (3 H, q, *J* 7 Hz, MeCH_2), 4.40 (1 H, m, 6-H), 4.46 (1 H, s, 3-H), 5.18 (2 H, s, CH_2Ph), 5.50 (1 H, d, *J* 4 Hz, 5-H), 6.14 (1 H, dd, *J* 16, 1 Hz, C*H*=CH), 6.94 (1 H, dd, *J* 16, 8 Hz, CH=C*H*), and 7.35 (5 H, m, ArH) (Found: M^+, 389.12969. $C_{20}H_{23}NO_5S$ requires *M*, 389.129684); the *thiazepinone* (29) (64 mg, 52%), as a pale yellow foam, $\nu_{max.}$ ($CHCl_3$) 3 390, 3 300, 1 740, 1 690, and 1 600 cm^{-1}; δ 1.24 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.40 and 1.50 (3 H each, s, Me_2C), 4.14 (2 H, q, *J* 7 Hz, MeCH_2), 4.43 (1 H, br d, *J* 5 Hz, becomes br s on D_2O exchange), 5.20 (2 H, s, CH_2Ph), 6.20 (1 H, d, *J* 17 Hz, C*H*=CH), 7.0—7.4 (7 H, m, 1 exchangeable), and 7.38 (1 H, d, *J* 17 Hz, CH=C*H*) (Found: M^+, 389.12969. $C_{20}H_{23}NO_5S$ requires *M*, 389.12968).

Reduction of the Adducts (26).—The crude adducts (0.60 g) were reduced with tributyltin hydride in benzene, with AIBN as catalyst, in the manner described above. The product was chromatographed through silica gel, using EtOAc–light petroleum mixtures as eluant, to produce a mixture of epimers of benzyl 6β-(2-ethoxycarbonyl-2-phenylsulphinylvinyl)-penicillanate (37) (0.15 g, 28%) as a colourless foam, $\nu_{max.}$ 1 780 and 1 750 cm^{-1}. Thermolysis of the ester (37) (52 mg) in anhydrous toluene at 100 °C for 30 min led cleanly to the 6β-substituted penicillanate (40), as determined by the ^1H n.m.r. spectrum of the crude product. However, attempts to purify the product by either column chromatography or t.l.c. caused its extensive conversion into the thiazepinone (29). The ester was also unstable in aqueous methanolic solutions hence preventing purification by reverse-phase chromatography.

Reaction of the Dibromide (19) *with* N,N-*Dimethyl-2-phenylsulphinylacrylamide* (24).—Freshly prepared ethereal methylmagnesium bromide was treated with the dibromide (19) (0.36 g) in the manner described above and the tetrahydrofuran solution was cooled to −70 °C before addition of the amide (0.18 g) in tetrahydrofuran (5 ml). After 0.5 h at −70 °C the temperature was raised to −60 °C for 1 h before quenching of the reaction with saturated aqueous ammonium chloride; the mixture was then extracted with ethyl acetate, the extract dried, and the solvent removed under reduced pressure. The residue was chromatographed through silica gel, using EtOAc–light petroleum (1 : 4) as eluant, to afford recovered starting dibromide (0.16 g) and a mixture of the diastereoisomeric sulphoxide adducts (27) (0.27 g, 57%). Thermolysis of the sulphoxides (0.25 g) in toluene for 1 h at 100 °C and work-up in the normal manner afforded a mixture of the amides (33) (0.19 g, 95%), as a colourless foam, $\nu_{max.}$ 1 785, 1 745, 1 680, and 1 640 cm^{-1}; the *major isomer* showed δ 1.39 and 1.50 (3 H each, s, Me_2C), 3.03 and 3.10 (3 H each, s, NMe_2), 4.51 (1 H, s, 3-H), 5.22 (2 H, s, CH_2Ph), 5.71 (1 H, s, 5-H), 6.15 (1 H, d, *J* 16 Hz, CH=CH), and 7.0—7.4 (6 H, m) (Found: M^+, 466.05626. $C_{20}H_{23}{}^{79}BrN_2O_4S$ requires 466.05623).

Reduction of the Acrylamide (33).—The amides (72 mg) were reduced with tributyltin hydride (51 mg) in the normal manner, using [$^2H_6$]benzene as solvent and monitoring the reduction by ^1H n.m.r. spectroscopy. After 16 h at 0 °C and 1 min at 90 °C the reaction was adjudged to be complete. Partitioning between acetonitrile and hexane gave, as a crude product, the amide (41) which showed a signal at δ 5.5 (1 H, d, 5-H), indicating the 6β-isomer (41) to be the major product. This material was not purified further.

Preparation of the Acid (7).—Benzylhydryl 6,6-dibromopenicillanate [20] (20) (0.575 g) in tetrahydrofuran (20 ml) at −78 °C was treated with freshly prepared methylmagnesium bromide (2.4M solution in ether; 0.6 ml). After 15 min a

solution of the sulphoxide amide (24) (0.32 g) in tetrahydrofuran (8 ml) was slowly added. After a further 30 min at −78 °C the solution was quenched with saturated aqueous ammonium chloride and the product extracted with EtOAc. After drying and removal of solvent the residue was heated in toluene (15 ml) under reflux for 30 min. After work-up the residue was chromatographed through silica (10 g) using EtOAc–light petroleum as eluant, to yield, as mainly one stereoisomer, the adduct (43) (0.55 g, 84%). The mixture showed $\nu_{max.}$ 1 780, 1 740, and 1 640 cm^{-1}; and principal peaks at δ 1.24 and 1.50 (3 H each, s, MeC_2), 3.01 and 3.05 (3 H each, s, Me_2N), 4.5 (1 H, s), 5.72 (1 H, s), 6.93 (3 H, m), and 7.1—7.4 (10 H, m, ArH).

The bromo esters (43) (0.10 g) in anisole (1 ml) were cooled to 0 °C and trifluoroacetic acid (3 ml) added at 0 °C. After 10 min the solvents were rapidly removed under reduced pressure at <20 °C. The residue was dissolved in chloroform (10 ml) and extracted with aqueous sodium hydrogen carbonate (5% w/v; 10 ml). The aqueous phase was washed with chloroform before re-acidification with phosphoric acid and extraction into chloroform (2 × 10 ml). The extract was then dried and evaporated to yield the *acid* (44) (68 mg, 99%), m.p. (MeOH) 176—178 °C, δ 1.54 (6 H, s, Me_2C), 3.04 and 3.13 (3 H each, s, Me_2N), 4.48 (1 H, s, 3-H), 4.60 (1 H, s, exchanged with D_2O), 5.71 (1 H, s, 5-H), and 6.90 (2 H, br s, CH=CH) (Found: C, 41.0; H, 4.25; N, 7.35; S, 8.5; Br, 21.3. $C_{13}H_{17}BrN_2O_4$ requires C, 41.4; H, 4.5; N, 7.4; S, 8.5; Br, 21.2%).

A sample of the acid (44) (0.12 g) was reduced with tributyltin hydride (0.185 g, 3 equiv.) in benzene (4 ml) and methanol (1 ml) at 60 °C for 12 min. The solution was evaporated to small bulk and partitioned between hexane and acetonitrile. The polar phase was washed with hexane (3×) before evaporating it under reduced pressure to afford the crude acid (50 mg). A portion of this material was sent for biological assay. A further portion was purified by reverse-phase h.p.l.c. using water–methanol–acetic acid (70 : 30 : 0.5) as solvent to afford pure material (single compound by t.l.c.).

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